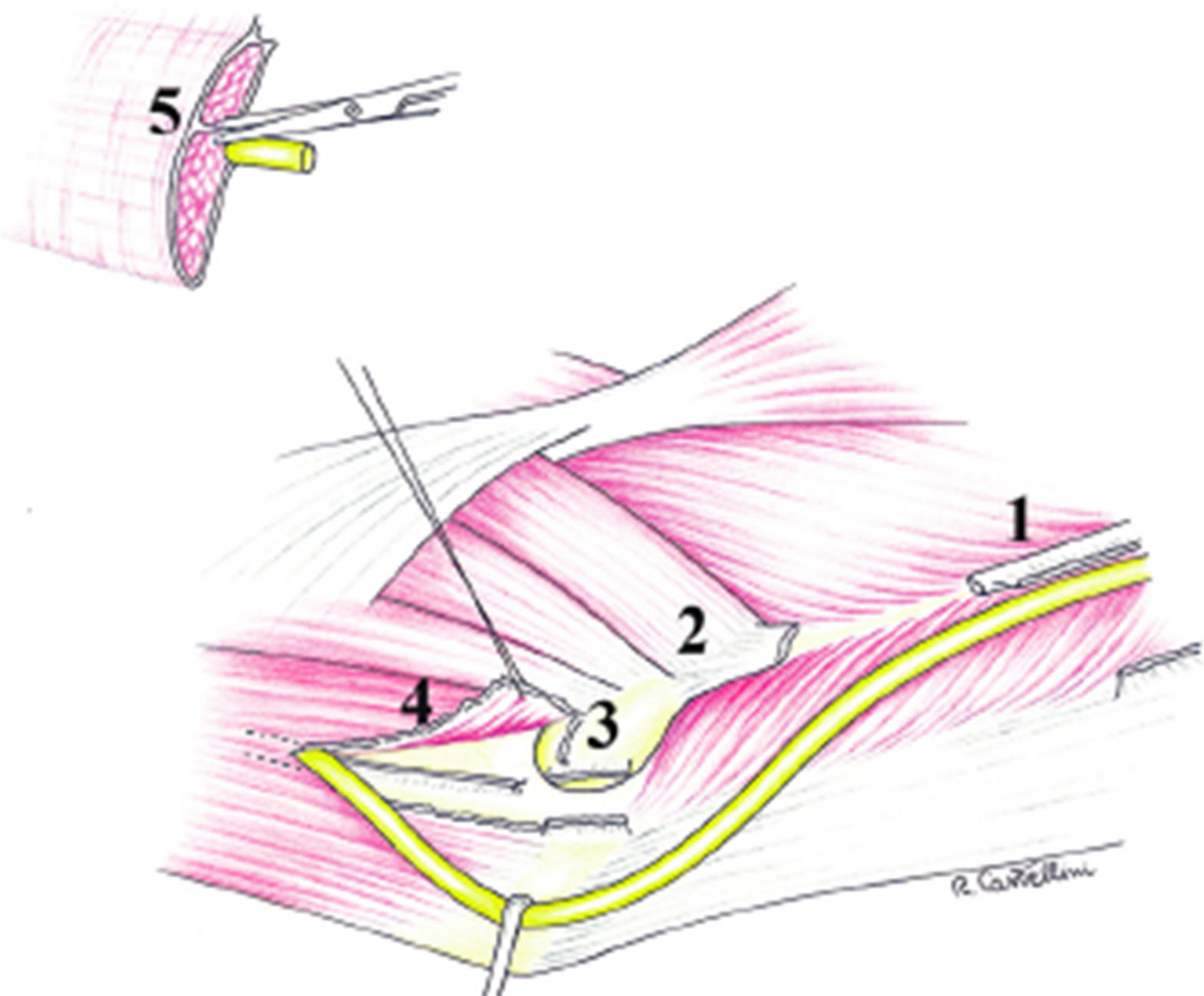


Plastic and Aesthetic Research

PAR



EDITORIAL BOARD

Editor-in-Chief

Raúl González-García (Spain)

Associate Editors

Charles E. Butler (USA)
Yi-Lin Cao (China)
Wen-Guo Cui (China)
Rui Fernandes (USA)
Raymund E. Horch (Germany)
Zhi-Qi Hu (China)
Pedro Infante-Cossio (Spain)
Hua Jiang (China)
Francesca Toia (Italy)
Anna Zampetti (UK)

Editorial Board Members

Syed Sayeed Ahmed (India)
Gururaj Arakeri (India)
Taina Broth (Sweden)
Fabio Caviggioli (Italy)
Chang-Cheng Chang (Taipei, China)
Ravi Kumar Chittoria (India)
Peter D. Costantino (USA)
Salvatore D'Arpa (Belgium)
Francesco M. Egro (USA)
Hamdy Elkhatib (State of Qatar)
Francesca Romana Grippaudo (Italy)
Thomas Haffner (Germany)
Umar Daraz Khan (UK)
Ruben Yap Kannan (UK)
Charles Yuen Yung Loh (UK)
Raman C. Mahabir (USA)
Ramesh Omranipour (Iran)
Raffaele Rauso (Italy)
Salah Rubayi (USA)
Gennaro Selvaggi (Sweden)
Jon Ver Halen (USA)
You-Bin Wang (China)
Alex K. Wong (USA)
Bin Yang (China)
Da-Ping Yang (China)
Cheng-Gang Yi (China)

Language Editors

Francesco M. Egro (USA)

Editorial Staffs

Min-Jie Zhang (China)
Huan-Liang Wu (China)
Cai-Hong Wang (China)

GENERAL INFORMATION

About the Journal

Plastic and Aesthetic Research (PAR), ISSN 2349-6150 (Online), ISSN 2347-9264 (Print), is a peer-reviewed online journal with print on demand compilation of articles published. The journal's full text is available online at www.parjournal.net. The journal allows free access (Open Access) to its contents and permits authors to self-archive final accepted version of the articles on any OAI-compliant institutional/subject-based repository. The journal focuses on plastic and aesthetic surgery, and the coverage extends to other basic and clinical studies related to plastic surgery, including microsurgery, laser treatment, orthopaedic surgery, psychology, social ethics, *etc.* The journal is indexed by Google Scholar, EBSCO, Hinari, Eurasian Scientific Journal Index (ESJI), Root Indexing, JournalTOCs, JournalGuide, CNKI, Wanfang Data, J-Gate, DRJI, SHERPA/RoMEO, ResearchBib, Chaoxing "Domain" Publishing Platform, Cite Factor, and Worldcat.

Information for Authors

Manuscripts should be prepared in accordance with Author Instructions.

Please check www.parjournal.net/pages/view/author_instructions for details.

All manuscripts should be submitted online at www.editorialmanager.com/par.

Copyright

The entire contents of the *PAR* are protected under international copyrights. The journal, however, grants to all users a free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, perform and display the work publicly and to make and distribute derivative works in any digital medium for any reasonable purpose, subject to proper attribution of authorship and ownership of the rights. The journal also grants the right to make small numbers of printed copies for their personal use under the Creative Commons Attribution 4.0 License.

Copyright is reserved by © The Author(s) 2015.

Permissions

For information on how to request permissions to reproduce articles/information from this journal, please visit www.parjournal.net.

Disclaimer

The information and opinions presented in the journal reflect the views of the authors and not of the journal or its Editorial Board or the Publisher. Publication does not constitute endorsement by the journal. Neither the *PAR* nor its publishers nor anyone else involved in creating, producing or delivering the *PAR* or the materials contained therein, assumes any liability or responsibility for the accuracy, completeness, or usefulness of any information provided in the *PAR*, nor shall they be liable for any direct, indirect, incidental, special, consequential or punitive damages arising out of the use of the *PAR*. *PAR*, nor its publishers, nor any other party involved in the preparation of material contained in the *PAR* represents or warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such material. Readers are encouraged to confirm the information contained herein with other sources.

Partner Affiliation/Society

Italian Federation of Aesthetic Medicine (FIME)

Contacts

E-mail: par_editor001@parjournal.net

Website: www.parjournal.net

Published by

OAE Publishing Inc.

245 E Main Street ste115, Alhambra, CA 91801, USA

Website: www.oaepublish.com

CONTENTS

- 1 Liposuction for chronic medical diseases and noncosmetic conditions: review of the literature**
Hamdy Abuelhassan El-Khatib
Plast Aesthet Res 2015;2:1-6 <http://dx.doi.org/10.4103/2347-9264.149362>
- 2 Surgical pitfalls with custom-made porous hydroxyapatite cranial implants**
Bruno Zanotti, Angela Verlicchi, Roberto Stefini, Attilio Carlo Salgarelli, Nicola Zingaretti, Pier Camillo Parodi, Casadei Matteo, Massimo Robiony
Plast Aesthet Res 2015;2:7-11 <http://dx.doi.org/10.4103/2347-9264.149364>
- 3 Patient-centric dose equivalency pilot study of incobotulinumtoxin a (xeomin) vs. abobotulinumtoxin a (dysport) in the treatment of glabellar frown lines**
Jonathan Bank, Nicole A. Phillips, Laurie A. Casas
Plast Aesthet Res 2015;2:12-16 <http://dx.doi.org/10.4103/2347-9264.149366>
- 4 Effect of neoadjuvant chemotherapy on skin-sparing mastectomy and breast reconstruction modalities in 409 patients**
Sameh Goubran, Jon Ver Halen
Plast Aesthet Res 2015;2:17-21 <http://dx.doi.org/10.4103/2347-9264.149369>
- 5 Primary contraction of skin grafts: a porcine preliminary study**
Alexander Bogdanov Berezovsky, Vasileios A. Pagkalos, Eldad Silberstein, Yaron Shoham, Lior Rosenberg, Yuval Krieger
Plast Aesthet Res 2015;2:22-26 <http://dx.doi.org/10.4103/2347-9264.149372>
- 6 Composite augmentation phalloplasty: personal experience after 275 patients**
Juan Monreal
Plast Aesthet Res 2015;2:27-33 <http://dx.doi.org/10.4103/2347-9264.149374>
- 7 Preliminary stages before nasal reconstruction using forehead flap: restoring perinasal subunits and nostril patency**
Victor Diniz de Pochat, Fernando César Câmara de Oliveira, Felipe Simões da Rocha Mata, Marcelo Sacramento Cunha, Nivaldo Alonso, José Valber Lima Meneses
Plast Aesthet Res 2015;2:34-37 <http://dx.doi.org/10.4103/2347-9264.149377>
- 8 Primary repair of ear laceration with wedge resection**
Bhupinder Singla, Inderjit Chawla, Prasant Gautam, Anupam Goyal, Jalaj Rath
Plast Aesthet Res 2015;2:38-39 <http://dx.doi.org/10.4103/2347-9264.149378>
- 9 Diode and Nd:YAG laser in a case of refractory acne keloidalis nuchae**
Ravi Kumar Chittoria, Devi Prasad Mohapatra, Friji Meethale Thiruvoth, Dinesh Kumar, Arjun Asokan, Vijayaraghavan Nandhagopal
Plast Aesthet Res 2015;2:40-42 <http://dx.doi.org/10.4103/2347-9264.149380>

- 10 Temporary ectopic hand implantation**
Xu Zhang, Hong-Wei Zhu
Plast Aesthet Res 2015;2:43-46 <http://dx.doi.org/10.4103/2347-9264.149381>
- 11 Surgical treatment of synovial-collagen disorders of the hand**
H. Kirk Watson, Purnell Traverso, Lois Carlson, Daniel Mastella, Ronit Wollstein
Plast Aesthet Res 2015;2:47-50 <http://dx.doi.org/10.4103/2347-9264.153192>
- 12 A survey of analgesic and anti-inflammatory drug prescription for oral implant surgery**
Rahul Datta, Yasmin Grewal, Jaspreet Singh Batth, Amandeep Singh
Plast Aesthet Res 2015;2:51-55 <http://dx.doi.org/10.4103/2347-9264.153194>
- 13 Heel pad avulsion injury: an approach with hyperbaric oxygen therapy**
Pradeoth Korambayil Mukundan, Prashanth Varkey Ambookan
Plast Aesthet Res 2015;2:56-62 <http://dx.doi.org/10.4103/2347-9264.153200>
- 14 Simultaneous expander and deep inferior epigastric perforator reconstruction: indications and alloderm sling technique for protecting the anastomosis**
Elizabeth Stirling Craig, Ajul Shah, Sarah Persing, Jeffrey Salomon, Stefano Fusi
Plast Aesthet Res 2015;2:63-68 <http://dx.doi.org/10.4103/2347-9264.153201>
- 15 Soft tissue defects of eyelid and malar region: an experience with the McGregor flap**
Pradeoth Korambayil Mukundan, Prashanth Varkey Ambookan, Vinoth Kumar Dilliraj
Plast Aesthet Res 2015;2:69-72 <http://dx.doi.org/10.4103/2347-9264.153202>
- 16 Aneurysmal bone cyst of the maxilla rare presentation with radiological and pathological correlation**
Bharat Bhushan Sharma, Priya Ramchandran, Sandeep Sharma, Shweta Sharma
Plast Aesthet Res 2015;2:73-75 <http://dx.doi.org/10.4103/2347-9264.153203>
- 17 A novel approach to achieve breast symmetry in a single-stage procedure**
Benedetto Longo, Rosaria Laporta, Marco Pagnoni, Fabio Santanelli di Pompeo
Plast Aesthet Res 2015;2:76-78 <http://dx.doi.org/10.4103/2347-9264.153204>
- 18 A rare case of bilateral absence of distal ulnar artery**
Jung Ho Lee, Rock Kuen Ju, Young Joon Jun, Young Jin Kim
Plast Aesthet Res 2015;2:79-80 <http://dx.doi.org/10.4103/2347-9264.153205>
- 19 Inferior dermoglandular flap for autologous breast remodeling following explantation of breast implants in ptotic breasts: a case report and literature search**
Umar Daraz Khan
Plast Aesthet Res 2015;2:81-84 <http://dx.doi.org/10.4103/2347-9264.153206>
- 20 Isolated tibial nerve injury: a rare presentation**
Rahul Krishnarao Patil, Prashant Verkey, Harshal Patil, Deepesh Manoharan
Plast Aesthet Res 2015;2:85-87 <http://dx.doi.org/10.4103/2347-9264.153207>

- 21 **Pseudoangiomatous squamous cell carcinoma: a challenge for pathologists and plastic surgeons**
Dimitrios Kanakopoulos, Evgenios Evgeniou, Panayiotis A. Dimitriadis, Mahendra Kulkarni
Plast Aesthet Res 2015;2:88-90 <http://dx.doi.org/10.4103/2347-9264.153208>
- 22 **Reconstruction of palate with buccal fat pad secondary to resection of desmoplastic ameloblastoma**
Bhimappa Mallappa Rudagi, Manjunatha Reddy Bandral, Reshma Hammannawar, Pritish Harish Padgavankar
Plast Aesthet Res 2015;2:91-94 <http://dx.doi.org/10.4103/2347-9264.153209>
- 23 **Straight line closure for correction of congenital isolated bilateral macrostomia**
Narendra S. Mashalkar, Naren Shetty
Plast Aesthet Res 2015;2:95-97 <http://dx.doi.org/10.4103/2347-9264.153210>
- 24 **Hemifacial microsomia: management of the vertical ramus compartment**
Maurice Yves Mommaerts
Plast Aesthet Res 2015;2:99-106 <http://dx.doi.org/10.4103/2347-9264.157097>
- 25 **Neurovascular plexus theory for “escape pain phenomenon” in lower third molar surgery**
Gururaj Arakeri, Mandeep Gill Sagoo, Peter A. Brennan
Plast Aesthet Res 2015;2:107-110 <http://dx.doi.org/10.4103/2347-9264.157098>
- 26 **Role of topical heparin in the management of burns: experience in a district government hospital of Karnataka in South India**
Ashish Gupta, Thangam J. Verghese, Priyanka Gupta, Ashok K. Gupta
Plast Aesthet Res 2015;2:111-114 <http://dx.doi.org/10.4103/2347-9264.157100>
- 27 **Fat injection to correct contour deformities of the reconstructed breast: a single surgeon experience**
Youssef Tahiri, Jonathan Kanevsky, Joshua Vorstenbosch, James Lee, Karl Schwarz
Plast Aesthet Res 2015;2:115-119 <http://dx.doi.org/10.4103/2347-9264.157103>
- 28 **Use of the multiplane internal mastopexy for ptosis correction revision-augmentation mammoplasty**
Umar Daraz Khan, Muhammad Riaz
Plast Aesthet Res 2015;2:120-126 <http://dx.doi.org/10.4103/2347-9264.157104>
- 29 **A guiding oblique osteotomy cut to prevent bad split in sagittal split ramus osteotomy: a technical note**
Gururaj Arakeri, Peter A. Brennan
Plast Aesthet Res 2015;2:127-129 <http://dx.doi.org/10.4103/2347-9264.157105>
- 30 **Hyperbaric oxygen therapy and surgical delay improve flap survival of reverse pedicle flaps for lower third leg and foot reconstruction**
Pradeoth Mukundan Korambayil, Prashanth Varkey Ambookan
Plast Aesthet Res 2015;2:130-137 <http://dx.doi.org/10.4103/2347-9264.157107>

- 31 **Rupture of the flexor carpi radialis tendon secondary to trauma: case report and literature review**
Jonathan Kanevsky, Dino Zammit, Jean-Paul Brutus
Plast Aesthet Res 2015;2:138-139 <http://dx.doi.org/10.4103/2347-9264.157108>
- 32 **Aesthetic rehabilitation of a patient with an anterior maxillectomy defect, using an innovative single-step, single unit, plastic-based hollow obturator**
Vishwas Bhatia, Garima Bhatia
Plast Aesthet Res 2015;2:140-143 <http://dx.doi.org/10.4103/2347-9264.157110>
- 33 **Use of tensor fascia lata flap for reconstruction of the defect created following inguinal block dissection in a case of carcinoma penis: a case report and brief review of literature**
Amitabh Jena, Banoth Manilal, Sriharsha Haranadh, Rashmi Patnayak
Plast Aesthet Res 2015;2:144-146 <http://dx.doi.org/10.4103/2347-9264.157111>
- 34 **Preface to special issue on “Peripheral Nerve Repair and Regeneration”**
Francesca Toia
Plast Aesthet Res 2015;2:147-148 <http://dx.doi.org/10.4103/2347-9264.160876>
- 35 **Clinical neurophysiology and imaging of nerve injuries: preoperative diagnostic work-up and postoperative monitoring**
Andrea Gagliardo, Francesca Toia, Francesco Maggi, Alessio Vincenzo Mariolo, Michele Cillino, Francesco Moschella
Plast Aesthet Res 2015;2:149-155 <http://dx.doi.org/10.4103/2347-9264.160877>
- 36 **Painful scar neuropathy: principles of diagnosis and treatment**
Pierluigi Tos, Alessandro Crosio, Pierfrancesco Pugliese, Roberto Adani, Francesca Toia, Stefano Artiaco
Plast Aesthet Res 2015;2:156-164 <http://dx.doi.org/10.4103/2347-9264.160878>
- 37 **The management of neuropathic pain from neuromas in the upper limb: surgical techniques and future directions**
Tereze Laing, Aftab Siddiqui, Manu Sood
Plast Aesthet Res 2015;2:165-170 <http://dx.doi.org/10.4103/2347-9264.160879>
- 38 **Neuropathic pain after bilateral sagittal split osteotomy: management and prevention**
Jimoh Olubanwo Agbaje, Ivo Lambrichts, Reinhilde Jacobs, Constantinus Politis
Plast Aesthet Res 2015;2:171-175 <http://dx.doi.org/10.4103/2347-9264.160880>
- 39 **Recalcitrant cubital tunnel syndrome**
Adolfo Vigasio, Ignazio Marcoccio, Eleonora Morandini
Plast Aesthet Res 2015;2:176-182 <http://dx.doi.org/10.4103/2347-9264.160881>
- 40 **Vascularized nerve “grafts”: just a graft or a worthwhile procedure?**
Salvatore D’Arpa, Karel Etienne Yvonne Claes, Filip Stillaert, Britt Colebunders, Stan Monstrey, Phillip Blondeel
Plast Aesthet Res 2015;2:183-194 <http://dx.doi.org/10.4103/2347-9264.160882>

- 41 **Nerve transfers of the forearm and hand: a review of current indications**
Paolo Sassu, Katleen Libberecht, Anders Nilsson
Plast Aesthet Res 2015;2:195-201 <http://dx.doi.org/10.4103/2347-9264.160887>
- 42 **Sensory protection to enhance functional recovery following proximal nerve injuries: current trends**
Boa Tram Nghiem, Ian C. Sando, Yaxi Hu, Melanie G. Urbanchek, Paul S. Cederna
Plast Aesthet Res 2015;2:202-207 <http://dx.doi.org/10.4103/2347-9264.156982>
- 43 **“Babysitting” procedures in proximal nerve trunk injuries: two case reports and a review**
Michele R. Colonna, Antonio Russo, Mariarosaria Galeano, Gabriele Delia, Giorgio E. Pajardi, Francesco Stagno d’Alcontres
Plast Aesthet Res 2015;2:208-212 <http://dx.doi.org/10.4103/2347-9264.160888>
- 44 **Tissue-engineered constructs for peripheral nerve repair: current research concepts and future perspectives**
Alba C. de Luca, Wassim Raffoul, Francesco Giacalone, Maddalena Bertolini, Pietro G. di Summa
Plast Aesthet Res 2015;2:213-219 <http://dx.doi.org/10.4103/2347-9264.160889>
- 45 **Endoscopic telemicrosurgery or minimally invasive robotically-assisted microsurgery for peripheral nerve repair**
Satoshi Ichihara, Sybille Facca, Frédéric Bodin, Sarah Hendriks, André Gay, Philippe Liverneaux
Plast Aesthet Res 2015;2:220-225 <http://dx.doi.org/10.4103/2347-9264.158860>
- 46 **Nerve regeneration in vascularized composite allotransplantation: current strategies and future directions**
Anirudh Arun, Nicholas B. Abt, Sami Tuffaha, Gerald Brandacher, Angelo A. Leto Barone
Plast Aesthet Res 2015;2:226-235 <http://dx.doi.org/10.4103/2347-9264.158853>
- 47 **Limited access dressing and wound infection**
Pramod Kumar
Plast Aesthet Res 2015;2:237-238 <http://dx.doi.org/10.4103/2347-9264.158856>
- 48 **Assessment of the histological state of the healing wound**
Akriti Gupta, Pramod Kumar
Plast Aesthet Res 2015;2:239-242 <http://dx.doi.org/10.4103/2347-9264.158862>
- 49 **Role of angiogenesis and angiogenic factors in acute and chronic wound healing**
Thittamaranahalli Muguregowda Honnegowda, Pramod Kumar, Echalasara Govindarama Padmanabha Udupa, Sudesh Kumar, Udaya Kumar, Pragna Rao
Plast Aesthet Res 2015;2:243-249 <http://dx.doi.org/10.4103/2347-9264.165438>
- 50 **Current concepts in the physiology of adult wound healing**
Friji Meethale Thiruvoth, Devi Prasad Mohapatra, Dinesh Kumar, Sivakuma Ravi Kumar Chittoria, Vijayaraghavan Nandhagopal
Plast Aesthet Res 2015;2:250-256 <http://dx.doi.org/10.4103/2347-9264.158851>

- 51 Effect of limited access dressing on surface pH of chronic wounds**
Pramod Kumar, Thittamaranahalli Muguregowda Honnegowda
Plast Aesthet Res 2015;2:257-260 <http://dx.doi.org/10.4103/2347-9264.165449>
- 52 Computer assessment of the composition of a generic wound by image processing**
Rohit Nayak, Pramod Kumar, Ramesh R. Galigekere
Plast Aesthet Res 2015;2:261-265 <http://dx.doi.org/10.4103/2347-9264.165444>
- 53 A comparative study to evaluate the effect of limited access dressing on diabetic ulcers**
Thittamaranahalli Muguregowda Honnegowda, Pramod Kumar, Krishnananda Prabhu, Ashwini Kumar, Pragna Rao, E G Padmanabha Udupa, Shobha Kamath, Antony Sylvan D' Souza, Krishna Kishore Mahato
Plast Aesthet Res 2015;2:266-271 <http://dx.doi.org/10.4103/2347-9264.165448>
- 54 Histopathological study of chronic wounds modulated by intermittent negative pressure therapy under limited access dressing**
Thittamaranahalli Muguregowda Honnegowda, Pramod Kumar, Rekha Singh, Swarna Shivakumar, Pragna Rao, Hemanth K. Prasad, Sudesh Kumar, Udaya Kumar, Echalasara Govindarama Padmanabha Udupa
Plast Aesthet Res 2015;2:272-276 <http://dx.doi.org/10.4103/2347-9264.156993>
- 55 Role of jet force technology in wound management**
Vijayaraghavan Nandhagopal, Ravi Kumar Chittoria, Devi Prasad Mohapatra, Friji Meethale Thiruvoth, Dinesh Kumar Shivakumar, Arjun Ashokan
Plast Aesthet Res 2015;2:277-281 <http://dx.doi.org/10.4103/2347-9264.165441>
- 56 Acellular micronized extracellular matrix and occlusive dressings for open fingertip injuries**
Stephanie E. Dreifuss, Ronit Wollstein, Stephen F. Badylak, Peter J. Rubin
Plast Aesthet Res 2015;2:282-283 <http://dx.doi.org/10.4103/2347-9264.156994>
- 57 Corticosteroid - an uncertainty in management of sepsis**
Kanica Yashi
Plast Aesthet Res 2015;2:284-285 <http://dx.doi.org/10.4103/2347-9264.165442>
- 58 Morphometry of subcutaneous fat lobules of the abdomen and its implication in obesity**
Arvind K Pandey, Pramod Kumar, Kodavoor Shrinivas Aithal, Rama Kotian Sushma, Antony Sylvan D'Souza
Plast Aesthet Res 2015;2:286-289 <http://dx.doi.org/10.4103/2347-9264.165443>
- 59 Ectrodactyly - ectodermal dysplasia - cleft lip/palate syndrome: a rare entity**
Samrat Sabhlok, Sobhan Mishra, Ramanupam Tripathy, Deepthi Mony
Plast Aesthet Res 2015;2:290-293 <http://dx.doi.org/10.4103/2347-9264.165446>
- 60 A massive dentigerous cyst of the mandible in a young patient: a case report**
Gururaj Arakeri, Kirthi Kumar Rai, Hosadurga Rudraswami Shivakumar, Shahanavaj I Khaji
Plast Aesthet Res 2015;2:294-298 <http://dx.doi.org/10.4103/2347-9264.165439>

- 61 **A simple postoperative oral physiotherapy aid for edentulous patients with oral submucous fibrosis**
Ankita Vastani, Anisha Maria, Nishant Chourasia, Ambika Shrivastava Gupta
Plast Aesthet Res 2015;2:299-300 <http://dx.doi.org/10.4103/2347-9264.165447>
- 62 **Lift of cheek and neck: technical notes**
Maurice Yves Mommaerts
Plast Aesthet Res 2015;2:301-308 <http://dx.doi.org/10.4103/2347-9264.169502>
- 63 **Peripheral nerve injuries**
Katerina Anesti, Paul Caine
Plast Aesthet Res 2015;2:309-310 <http://dx.doi.org/10.4103/2347-9264.169500>
- 64 **Free deep inferior epigastric perforator flap after abdominal liposuction: reconsidering a contraindication**
Peter James Mankowski, Jonathan Kanevsky, Anne-Sophie Lessard, Teanoosh Zadeh
Plast Aesthet Res 2015;2:311-314 <http://dx.doi.org/10.4103/2347-9264.169504>
- 65 **Nasal dorsal aesthetic lines and rhinoplasty technical tricks**
Alexander Kutubidze
Plast Aesthet Res 2015;2:315-319 <http://dx.doi.org/10.4103/2347-9264.169495>
- 66 **Cost-effectiveness of one-stage versus two-stage breast reconstruction in the United Kingdom**
Isabel Teo, Iman A. Azmy
Plast Aesthet Res 2015;2:320-325 <http://dx.doi.org/10.4103/2347-9264.169494>
- 67 **First-year experience of a new skin bank in Brazil**
Alysson Rogerio Matioski, Clóvis Rodrigo Guimarães Braz Pereira da Silva, Diogo Rodrigues da Silva Cunha, Luiz Henrique Auerswald Calomeno, Marisa Roma Herson, Flávia Thaiana Bonato, Marcelus Vinícios Araujo Nigro
Plast Aesthet Res 2015;2:326-331 <http://dx.doi.org/10.4103/2347-9264.169496>
- 68 **Synergistic effect of hyperbaric oxygen preconditioning and hydrogen-rich saline in ameliorating rat flap ischemia/reperfusion injury**
Yi-Ding Xiao, Yun-Qi Liu, Ming-Zi Zhang, You-Bin Wang, Yi-Fang Liu, Xue-Mei Ma
Plast Aesthet Res 2015;2:332-339 <http://dx.doi.org/10.4103/2347-9264.169499>
- 69 **Tissue engineering using mesenchymal stem cell with periosteal wrap for bone defect repair in rabbits**
Trung-Hau Lê Thua, Dang-Nhat Pham, Khanh-Linh Lê, Minh-Tuan Lê, Quang-Ton-Quyen Nguyen, Phan-Huy Nguyen, Ngoc-Vu Tran, Ngoc-Luong Nguyen, Willy Boeckx, Albert Demey
Plast Aesthet Res 2015;2:340-345 <http://dx.doi.org/10.4103/2347-9264.169497>
- 70 **Transfer of upper trapezius with clavicular segment for restoration of shoulder movements following injury to the brachial plexus**
Neeraj Kant Agrawal
Plast Aesthet Res 2015;2:346-349 <http://dx.doi.org/10.4103/2347-9264.169503>

- 71 High pressure paint gun injury of the index finger: a case report**
Memet Yazar, Zeliha Gül, Ali Can Günenç, Sevgi Kurt Yazar, Erol Kozanoğlu
Plast Aesthet Res 2015;2:350-352 <http://dx.doi.org/10.4103/2347-9264.169498>
- 72 Lacrimal sac rhinosporidiosis**
Laxmi Kanta Mishra, Sanjeev Gupta, Surya Kanta Pradhan, Manas R. Baisakh
Plast Aesthet Res 2015;2:353-356 <http://dx.doi.org/10.4103/2347-9264.169501>

Liposuction for chronic medical diseases and noncosmetic conditions: review of the literature

Hamdy Abuelhassan El-Khatib

Department of Plastic and Hand Surgery, Alkhor Hospital, Hamad Medical Corporation, Doha 00974, Qatar.

Address for correspondence: Dr. Hamdy Abuelhassan El-Khatib, Department of Plastic and Hand Surgery, Alkhor Hospital, Hamad Medical Corporation, Doha 00974, Qatar. E-mail: hamdya24@yahoo.com

ABSTRACT

The purpose of this systematic literature review was to evaluate the safety of liposuction techniques and to identify the cosmetic and noncosmetic application of liposuction. Liposuction can be used to improve the quality-of-life in patients with disabling medical conditions in addition to its use for cosmetic rejuvenation. An online search of the Cochrane Library, MEDLINE, Embase, and SciELO were conducted. Forty-seven original articles reported from 1982 to February 2014 were included in this review. The articles reported on the use as well as the limitations of liposuction for treatment of noncosmetic and disabling medical conditions. The criteria used for selection of articles were: large sample size and originality. The case reports were excluded. There was a broad agreement about the applicability and the efficacy of the liposuction for treatment of these chronic medical conditions, such as multiple systemic lipomatosis, dercum's disease, chronic lymphedema, and axillary hyperhidrosis. Literatures review confirmed that Liposuction technique has provided significant and stable cure for these chronic medical conditions. Liposuction is the most frequent esthetic procedure for adipose tissue reduction and treatment of lipedema worldwide. Apart from esthetic indications, liposuction can also be used to treat chronic medical diseases and noncosmetic conditions.

Key words:

Liposuction, noncosmetic indications, lipomatosis

INTRODUCTION

Five thousand years ago, the ancient Egyptian mummification methods were based on removal of all internal organs and subcutaneous fat except the heart, they used the liposuction technique via a small hole to aspirate the whole body contents.^[1] The traditional dry liposuction technique was introduced more than 50 years ago. The term liposculpture was introduced by Teimouria and Fisher^[2] and Fournier and Otteni^[3] who advocated also the criss-cross technique.

Illouz^[4] developed the wet tumescent liposuction that helped in standardization and refinement of this technique in 1977. Field,^[5] an American dermatologist, started the procedure in USA using the Fischer's suction machine. The first American liposuction course was taught 1982 by Dolsky *et al.*^[6]

In 1987, Klein^[7] developed a formula of 0.05% lidocaine, 1:1,000,000 epinephrine, and 10 mL of bicarbonate and a liter of normal saline. The Klein formula allowed large liposuction to be done under local anesthesia and provided patient a painless 24 h postoperatively.

Zocchi in 1992,^[8] presented a revolutionary body contouring technique based using ultrasound energy. This allows selective destruction of lipocytes by means of cavitation and elimination of the fluid fraction (fatty acids). The ultrasound waves stimulate the collagen in deep dermis and initiate lifting of the skin.

In 1992, Apfelberg^[9] described the use of laser assisted lipolysis. Laser-assisted liposuction uses laser energy lasers heat the fat, turning it semi-soft and making it

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.149362

easier to remove via liposuction, and helps to tighten the skin. There is no scientific evidence demonstrating the advantage of this technique over the ultrasound assisted liposuction or the traditional liposuction.

Blugerman *et al.*^[10] described a novel technique using radiofrequency assisted liposuction. Radio frequency is a form electro-magnetic energy similar to microwave. The process involves passing radio frequency energy through tissue to heat up fat cell and making it easier to remove via liposuction and helps to tighten the skin. This procedure was well-tolerated, safe, and efficient in the removal of a moderate volume of fat. Paul *et al.*^[11] reported three-dimensional skin tightening with this procedure and proposed a mechanism of tissue tightening.

The Water-Jet assisted liposuction is a new technique that uses fan-shaped jet of tumescent solution to anaesthetize the area for liposuction. Sasaki^[12] used this technique in 2011 on 41 patients. The amount of instilled tumescent fluid, lidocaine dosage, and aspiration volumes appeared to be safe, with minimal blood loss in small and moderate volume liposuction cases, and have emphasized on efficacy and safety of the technique.

ADIPOSE TISSUE DISEASES

El-Khatib^[13] has used the wet technique to treat the lower part of the body with unusual fat distribution that is clinically characterized by massive symmetric and diffuse fat deposition in the trochanters, groins, buttocks, hips, and lower extremities; it contrasts sharply with the normal fat distribution in the upper part of the body. The massive lipomatoses of the lower body can be classified into 3 types: type 1, the familial symmetric lipomatosis (Simon's syndrome) that affects the groins, trochanters, hips, buttocks, and thighs [Figure 1]; type 2, the bilateral peritrochanteric familial lipomatoses [Figure 2]; and type 3, the unilateral peritrochanteric lipomatosis. The adipose tissue diseases are often accompanied by psychological depression due to their disturbed body image. The traditional liposuction is the treatment of choice for these esthetic deformities. The surgical removal of the localized fatty deposit results in unacceptable cosmetic outcome.

MULTIPLE SYSTEMIC LIPOMATOSIS

Multiple Symmetrical Lipomatosis, also known as benign symmetric lipomatosis or Madelung's disease and Lanois-Bensaude syndrome are metabolic conditions characterized by the growth of fatty masses around the face, back of the head, neck, upper arms, abdomen, back and upper leg in a very specific distribution [Figure 3]. Unlike the usual lipoma, these benign fatty masses are not enclosed in a membranous. Due to this characteristic and symmetrical appearance, these conditions are often dismissed as simple obesity.

Bassetto *et al.*^[14] used the ultrasound-assisted liposuction to treat multiple systemic lipomatosis. He compared the traditional lipectomy and the ultrasound-assisted liposuction and concluded that the ultrasound liposuction



Figure 1: Simon syndrome. (a) Preoperative and (b) one-year postliposuction treatment



Figure 2: Peritrochantric lipomatosis. (a) Preoperative and (b) 18 months postliposuction



Figure 3: Madelung's disease. (a) Preoperative anterior and (b) posterior photos

is preferable due to a reduction of blood loss and reduction of effort produced by surgeon.

DERCUM'S DISEASE

Decrum's disease is characterized by the presence of the painful condition, sleep disturbance, memory impairment,

shortness of breath, constipation, and fatigue. As reported by Hansson *et al.*, Dercum's disease is classified into: generalized diffuse adiposity, generalized nodular adiposity [Figure 4], localized nodular adiposity, and juxta-articular adiposity.^[15,16]

Hansson traditionally treated 53 patients with Dercum's disease that had been operated on with liposuction. As controls, 58 nonoperated subjects with Dercum's disease and 41 obese abdominoplasty patients were followed for 5 years. Hansson suggested that liposuction might alleviate pain in patients with Dercum's disease. However, it is difficult to determine whether the effect is due to the actual surgery or to other factors.

Women are more affected by this condition and, it usually presents in ages between of 30 and 50 years. The differential diagnosis for this condition includes: familial lipomatosis, multiple symmetric lipomatosis, adipose tissue tumors, panniculitis, lipedema, and fibromyalgia. Dercum's disease is diagnosed based on patient's history and the physical findings. There are no specific laboratory tests for this disease.

The treatment strategies for this condition are mostly based on case reports. Treatment of Dercum's disease is usually targeted towards pain relief rather than lipoma removal.^[17] Currently, there is a lack of scientific data on the use of integrative therapies for the treatment or prevention of Dercum's disease.

De Silva and Earley^[18] used liposuction in the treatment of two patients with juxta-articular adiposis dolorosa (Dercum's disease), and recommended liposuction as an effective, has a low morbidity and is well-tolerated by the elderly.

SUBCUTANEUS LIPOMAS

A lipoma is a benign tumor composed of adipose tissue. It is the most common benign soft tissue tumor. Lipomas are often soft to the touch, mobile, and painless. Many lipomas are small (under 1 cm diameter) but can enlarge to sizes greater than 6 cm. They are commonly found in adults from 40 to 60 years of age, but can also be found in younger adults and children.

Al-basti and El-Khatib^[19] successfully reported the treatment of subcutaneous capsulated giant (more than 10 cm diameter) and moderate (5 cm to 10 cm diameter) sized lipomas by traditional liposuction. The capsule was extracted surgically by the end of the procedure from

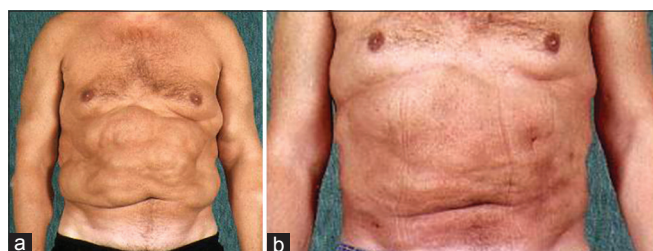


Figure 4: Dercum's disease. (a) Preoperative anterior and (b) 19 months postliposuction

the same small incision used for liposuction. There was no recurrence, and the cosmetic outcome was highly satisfactory.

POSTTRAUMATIC LIPOMAS

The pathogenetic link between soft tissue trauma and formation of lipomas remains controversial. A proposed mechanism is the prolapse of adipose tissue through the fascia defect resulting from direct impact. An alternate explanation is the formation of adipose tissue as a result of preadipocyte differentiation and proliferation mediated by cytokine release following trauma and hematoma formation.

Aust *et al.*^[20] used the simple excision method in 22 cases and used the liposuction method in 1 case and recommend both techniques.

CHRONIC LYMPHEDEMA

In chronic lymphedema, there is a physiological imbalance of blood flow and lymphatic drainage. The decreased lymphatic drainage results in impaired clearance of lipids and deposition of fat in subcutaneous tissue.

Lymphedema may be inherited (primary) or caused by injury to the lymphatic vessels (secondary). It is most frequently seen after lymph node dissection, surgery, and/or radiation therapy, most notably in the treatment for breast cancer. In many patients with cancer, this condition does not develop until months or even years after therapy have concluded. Lymphedema may also be associated with trauma or conditions that inhibit the lymphatic system function. In tropical areas, a common cause of secondary lymphedema is filariasis, a parasitic infection. It can also be caused by cellulitis as it compromises lymphatic drainage.

While the exact cause of primary lymphedema is still unknown, it occurs due to poorly developed or missing lymph nodes or channels. Lymphedema may be present at birth, develop at the onset of puberty (praecox), or in adulthood (tarda). Lower-limb primary lymphedema is most common in men, occurring in one or both legs. Secondary lymphedema affects both men and women. In women, it is most prevalent in upper limb after breast cancer surgery and lymph node dissection. It occurs on the same side as surgery. Cancer treatment is the most common cause of secondary lymphedema in western countries. Between 38% and 89% of breast cancer patients suffer from lymphedema due to axillary lymph node dissection and/or radiation.^[21-23] Unilateral lymphedema occurs in up to 41% of patients after gynecologic cancer.^[24] For men, a 5-66% incidence of lymphedema has been reported in patients treated with radical removal of lymph glands.

The first report of use of liposuction to reduce the size of lymphedema of the extremity was published by O'Brien *et al.*^[25] and Brorson.^[26] Developed a pressure-measuring device to optimize compression treatment of lymphedema

and evaluation of change in garment pressure with simulated wear and tear, was added to the liposuction technique in order to enhance the outcome.

In 2008, National Institute for Health and Clinical Excellence published guideline on indications and patients' selection for liposuction.

Brorson *et al.*^[27] used absence of pitting, failure of conservative treatment, absence of wounds and cancer as criteria for liposuction for treatment of lymphedema of upper extremity due to ablative surgery for breast cancer.

Literatures review concluded that liposuction demonstrated significant and stable reduction of both upper and lower limbs lymphedema. The technique is also reliable in the treatment of both the acquired and congenital lymphedema.

AXILLARY HYPERHIDROSIS

Axillary hyperhidrosis, also known as underarm sweating, involves extreme sweat production in the axillary region. This condition is not controlled by deodorants and other odor controlling medication. Axillary hyperhidrosis can occur by itself or associated with hyperhidrosis of other regions of the body.

Over-stimulating of sympathetic nervous system is the main cause of this condition. This has a direct relation to the emotional well-being of the person and environmental stimuli such as stress and anxiety.

Traditional surgical procedure has many disadvantages such as scarring, longer wound healing, complex wound dressing, and limited range of motion for shoulders after surgery.

Seo *et al.*^[28] studied 43 patients who underwent superficial liposuction with curettage for axillary hyperhidrosis and found that 31 patients (72.1%) showed excellent to good results. The most common postoperative complication was transient ecchymosis that spontaneously regressed in 1-2 weeks. Focal skin necrosis, induration, and hematoma or seroma were each noted in 4, 3 and 1 patient, respectively. All these conditions resolved with proper dressing. The preoperative histological findings included increase in size and number of apocrine glands in cross-section view, and the postoperative specimen showed absence of subcutaneous tissue, including apocrine and eccrine glands, and destruction of sweat glands.

Seo *et al.*^[28] used the tumescent superficial liposuction with curettage of the subdermal tissues for treatment of axillary bromhidrosis and concluded that this technique is an effective and safe.

Ottomann *et al.*^[29] studied reported a total of 88 patients, 47 patients underwent a tumescent liposuction curettage (TLC) (liposuction combined with curettage), and 41 patients received intradermal Botox injections. The effect of both treatments on the quality-of-life was assessed using a specific hyperhidrosis questionnaire

and was correlated with sweat volumes measured by gravimetry. Follow-up after 6 months showed significantly improved sweat volumes of 52 ± 41 mg/min of TLC patients versus 78 ± 87 mg/min in the Botox group. Ninety-one percent of TLC group and 98% of Botox group were satisfied with the result. Both methods were superior to the traditional surgical methods in terms of efficacy and complication rates. Both Botox and TLC improved the quality-of-life.

POSTABLATIVE SURGERY

Use of autologous fat grafting for reconstruction is still controversial because of its safety and efficacy. Liposuction is considered an ideal harvesting method for fat graft [Figure 5].

Coleman^[30] advocated a unique method for harvesting fat graft. General anesthesia can be used for removal of large volume of fat although local anesthesia is most commonly used. The preferred donor sites are the abdomen, the inner thigh, the lateral thigh, and the lower back.

Fifteen or twenty-six centimetre two hole Coleman harvesting cannula with a blunt tip and dull distal openings is placed near the end of the cannula, and it is twisted onto a 10 mL Luer-Lok syringe. The combination of negative pressure and the cannula motion through the fatty tissue allows aspiration of adipose tissue. The recommended centrifugation of the lipoaspirate is 3,000 revolutions per minute for 3 min. The middle layer contains fat cells that can be used as a fat graft.

Another technique is "The one-step harvesting modification" described by Lazzeri *et al.*^[31] It is a useful and time-saving method for high-volume replacement fat graft. This is an atraumatic, low-negative-pressure drain method that helps to preserves any viable lipocytes for transfer. The manual method using a Luer-Lok syringe is also similar and better than the continuous active suction machine liposuction.

Claro *et al.*^[32] studied articles regarding autologous liposuctioned fat grafting of female breast, with a description of clinical complications, radiographic changes, and local breast cancer recurrence.

Claro found that there were few complications reported in the literature; there was no evidence of interference with follow-up for breast cancer posttreatment although oncologic safety remains unclear.

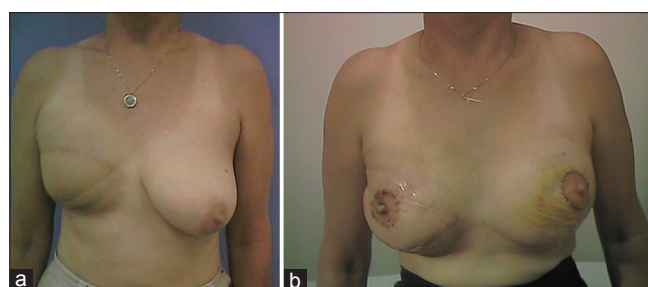


Figure 5: Lipofilling assisted latissimus dorsi flap for right breast reconstruction. (a) Preoperative and (b) two weeks postoperative

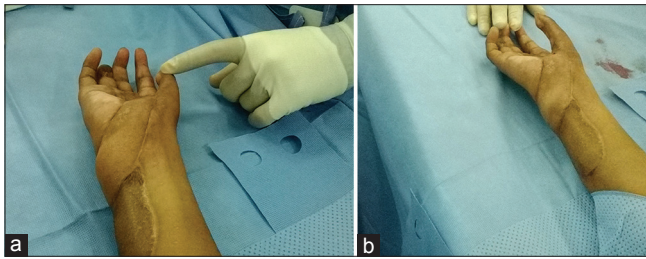


Figure 6: Right-hand reconstruction using perforator muscle skin flap. (a) Six months postoperative and (b) immediate postliposuction images

POSTIRRADIATED SKIN

Radiation dermatitis results from prolonged exposure of skin to ionizing radiation.^[33] It can be seen in patients receiving radiation therapy, with or without adjuvant chemotherapy.^[34]

Inflammation of the skin after exposure to the radiotherapy (radiodermatitis) can be classified to three specific types of radiodermatitis: acute radiodermatitis, chronic radiodermatitis, and eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy. Radiation therapy can also cause radiation skin cancer.

Radiodermatitis can be successfully treated by implantation of fat graft harvested from liposuction. The lipofilling procedure was first performed by Coleman.^[35-37]

After radiation treatment, breast reconstruction with an implant carries a high risk of failure and complication. Clinical and experimental studies have demonstrated that adipose tissue graft (lipofilling) in the irradiated area enhances skin atrophy. Sarfati *et al.*^[38,39] reported the use of lipofilling to the irradiated skin before the implant breast reconstruction. Safarai claimed that the lipofilling will decrease the risk of breast Implant exposure.

DEBULKING OF FLAPS

Patients often complain about an enlarged or bulky appearance after fasciocutaneous and myocutaneous flap reconstruction.

Conventional liposuction can be used to debulk the skin flap without fear of tissue necrosis [Figure 6].

Single-stage debulking of flaps using suction-assisted lipectomy combined with skin excision is a safe and reliable procedure with results comparable to conventional multistaged surgical techniques. In 2010, Reuben *et al.*^[40] reported on the efficacy and safety of power assisted suction lipectomy for debulking fasciocutaneous flaps in upper and lower extremity. Reuben operated on 16 lower extremity flaps of 15 patients and recommended the use of liposuction as an adjunct in debulking and contouring skin flaps.

Hallock^[41-43] reported successful use of traditional liposuction for debulking perforator muscle flaps, and free flaps elsewhere.

Overall, literature review [Table 1] showed good outcomes for suction-assisted lipectomy as an adjuvant procedure

Table 1: Summary of references

Chronic disease	Number of patients	Author
Dercum's disease	114	Hansson <i>et al.</i> ^[16]
	2	De Silva and Earley ^[18]
Subcutaneous lipomas	16	Al-Basti and El-Khatib ^[19]
Posttraumatic lipomas	23	Aust <i>et al.</i> ^[20]
Lymphoedema	200	Kissin <i>et al.</i> ^[22]
	136	Segerström <i>et al.</i> ^[23]
	54	Werngren-Elgström and Lidman ^[24]
	134	O'Brien <i>et al.</i> ^[25]
	N/A	Brorson ^[26]
Axillary hyperhidrosis	88	Ottomann <i>et al.</i> ^[29]
	43	Seo <i>et al.</i> ^[28]
Postablative reconstruction	An online review of 60 articles, 4601 patients	Claro Jr <i>et al.</i> ^[32]
	17	Coleman ^[35]
	N/A	Lazzeri <i>et al.</i> ^[31]
Radiodermatitis	N/A	Bernier <i>et al.</i> ^[34]
	68	Sarfati <i>et al.</i> ^[38]
Debulking of flaps	16 flaps in 15 patients	Reuben <i>et al.</i> ^[40]
	8 flaps in 7 patients	Hallock ^[41]
Multiple systemic-lipomatosis	N/A	Bassetto <i>et al.</i> ^[14]
		El-Khatib ^[13]

N/A: Not available

for recontouring bulky skin flaps. Most papers recommend debulking three months after initial procedure.

COMPLICATIONS OF LIPOSUCTION

Severe complications have been reported and include necrotizing fasciitis,^[44] toxic shock syndrome,^[45] perforation of inner organs,^[46] and pulmonary embolism.^[47] These complications were mostly due to inappropriate patient selection, use of excessive local anesthesia during mega-liposuction (tumescent technique) and inadequate postoperative surveillance based on literature review, the complication rate usually reflects a lack of medical experience.

Liposuction has gained popularity and has become the most frequent esthetic procedure for adipose tissue reduction and treatment of lipedema. Liposuction is also a suitable treatment for chronic medical conditions like lymphedema, benign adipose tissue diseases, radiodermatitis, re-contouring skin flaps from previous procedures and breast reconstruction. This intervention is not without risks and requires extensive knowledge and training to prevent irreversible medical or esthetic complications.

REFERENCES

- Charlotte B. Exploring funerary, beliefs and mummification. In: Charlotte B, editor. The Ancient Egyptians for Dummies. England: John Wiley and Sons; 2011. p. 189.
- Teimourian B, Fisher JB. Suction curettage to remove excess fat for body contouring. *Plast Reconstr Surg* 1981;68:50-8.
- Fournier PF, Otteni FM. Lipodissection in body sculpturing: the dry procedure. *Plast Reconstr Surg* 1983;72:598-609.

4. Illouz YG. History and current concepts of lipoplasty. *Clin Plast Surg* 1996;23:721-30.
5. Field LM. The dermatologist and liposuction-a history. *J Dermatol Surg Oncol* 1987;13:1040-1.
6. Dolsky RL, Newman J, Fetzek JR, Anderson RW. Liposuction. History, techniques, and complications. *Dermatol Clin* 1987;5:313-33.
7. Klein JA. The tumescent technique. Anesthesia and modified liposuction technique. *Dermatol Clin* 1990;8:425-37.
8. Zocchi M. Ultrasonic liposculpturing. *Aesthetic Plast Surg* 1992;16:287-98.
9. Apfelberg D. Laser-assisted liposuction may benefit surgeons, patients. *Clin Laser Mon* 1992;10:193-4.
10. Blugerman G, Schavelzon D, Paul MD. A safety and feasibility study of a novel radiofrequency-assisted liposuction technique. *Plast Reconstr Surg* 2010;125:998-1006.
11. Paul M, Blugerman G, Kreindel M, Mulholland RS. Three-dimensional radiofrequency tissue tightening: a proposed mechanism and applications for body contouring. *Aesthetic Plast Surg* 2011;35:87-95.
12. Sasaki GH. Water-assisted liposuction for body contouring and lipoharvesting: safety and efficacy in 41 consecutive patients. *Aesthet Surg J* 2011;31:76-88.
13. El-Khatib HA. Unusual distribution of the lower body fatty tissue: classification, treatment, and differential diagnosis. *Ann Plast Surg* 2008;61:2-8.
14. Bassetto F, Scarpa C, De Stefano F, Busetto L. Surgical treatment of multiple symmetric lipomatosis with ultrasound-assisted liposuction. *Ann Plast Surg* 2014;73:559-62.
15. Hansson E, Svensson H, Brorson H. Liposuction may reduce pain in Dercum's disease (adiposis dolorosa). *Pain Med* 2011;12:942-52.
16. Hansson E, Svensson H, Brorson H. Review of Dercum's disease and proposal of diagnostic criteria, diagnostic methods, classification and management. *Orphanet J Rare Dis* 2012;7:23.
17. Lange U, Oelzner P, Uhlemann C. Dercum's disease (Lipomatosis dolorosa): successful therapy with pregabalin and manual lymphatic drainage and a current overview. *Rheumatol Int* 2008;29:17-22.
18. De Silva M, Earley MJ. Liposuction in the treatment of juxta-articular adiposis dolorosa. *Ann Rheum Dis* 1990;49:403-4.
19. Al-basti HA, El-Khatib HA. The use of suction-assisted surgical extraction of moderate and large lipomas: long-term follow-up. *Aesthetic Plast Surg* 2002;26:114-7.
20. Aust MC, Spies M, Kall S, Jokuszies A, Gohritz A, Vogt P. Posttraumatic lipoma: fact or fiction? *Skinmed* 2007;6:266-70.
21. Brorson H, Ohlin K, Olsson G, Svensson B, Svensson H. Controlled compression and liposuction treatment for lower extremity lymphedema. *Lymphology* 2008;41:52-63.
22. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 1986;73:580-4.
23. Segerström K, Bjerle P, Graffman S, Nyström A. Factors that influence the incidence of brachial oedema after treatment of breast cancer. *Scand J Plast Reconstr Surg Hand Surg* 1992;26:223-7.
24. Werngren-Elgström M, Lidman D. Lymphoedema of the lower extremities after surgery and radiotherapy for cancer of the cervix. *Scand J Plast Reconstr Surg Hand Surg* 1994;28:289-93.
25. O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg* 1990;85:562-72.
26. Brorson H. Liposuction in arm lymphedema treatment. *Scand J Surg* 2003;92:287-95.
27. Brorson H, Hansson E, Jense E, Freccero C. Development of a pressure-measuring device to optimize compression treatment of lymphedema and evaluation of change in garment pressure with simulated wear and tear. *Lymphat Res Biol* 2012;10:74-80.
28. Seo SH, Jang BS, Oh CK, Kwon KS, Kim MB. Tumescent superficial liposuction with curettage for treatment of axillary bromhidrosis. *J Eur Acad Dermatol Venereol* 2008;22:30-5.
29. Ottomann C, Blazek J, Hartmann B, Muehlberger T. Liposuction curettage versus Botox for axillary hyperhidrosis. A prospective study of the quality of life. *Chirurg* 2007;78:356-61.
30. Coleman SR. Structural fat grafts: the ideal filler? *Clin Plast Surg* 2001;28:111-9.
31. Lazzeri D, Giannotti G, Colizzi L. One-step fat harvesting method in lipofilling. *Plast Reconstr Surg* 2009;124:e459-60.
32. Claro FJ, Figueiredo JC, Zampar AG, Pinto-Neto AM. Applicability and safety of autologous fat for reconstruction of the breast. *Br J Surg* 2012;99:768-80.
33. William J, Berger T, Elston D. Andrews' diseases of the skin. *Clin Dermatol* 2005;10:789-90.
34. Bernier J, Bonner J, Vermorken JB, Bensadoun RJ, Dummer R, Giralt J, Kornek G, Hartley A, Mesia R, Robert C, Segalier S, Ang KK. Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. *Ann Oncol* 2008;19:142-9.
35. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. *Clin Plast Surg* 1997;2:347-67.
36. Coleman SR. Structural fat grafting: more than a permanent filler. *Plast Reconstr Surg* 2006;118:S108-20.
37. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2007;119:775-85.
38. Sarfati I, Ihrat T, Duvernay A, Nos C, Clough KB. Autologous fat grafting to the postmastectomy irradiated chest wall prior to breast implant reconstruction: a series of 68 patients. *Ann Chir Plast Esthet* 2013;58:35-40.
39. Sarfati I, Ihrat T, Kaufman G, Nos C, Clough KB. Adipose-tissue grafting to the post-mastectomy irradiated chest wall: preparing the ground for implant reconstruction. *J Plast Reconstr Aesthet Surg* 2011;64:1161-6.
40. Reuben CM, Bastidas N, Sharma S. Power-assisted suction lipectomy of fasciocutaneous flaps in the extremities. *Ann Plast Surg* 2010;65:60-5.
41. Hallock GG. Conventional liposuction-assisted debulking of muscle perforator flaps. *Ann Plast Surg* 2004;53:39-43.
42. Hallock GG. Liposuction for debulking free flaps. *J Reconstr Microsurg* 1986;2:235-9.
43. Hallock GG. Defatting of flaps by means of suction-assisted lipectomy. *Plast Reconstr Surg* 1985;76:948-52.
44. González Alana I, Marin de la Cruz D, Palao Doménech R, Barret Nérin JP. Necrotizing fasciitis after liposuction. *Acta Chir Plast* 2007;49:99-102.
45. Di Candia M, Malata CM. Aesthetic and functional abdominal wall reconstruction after multiple bowel perforations secondary to liposuction. *Aesthetic Plast Surg* 2011;35:274-7.
46. Holm C, Mühlbauer W. Toxic shock syndrome in plastic surgery patients: case report and review of the literature. *Aesthetic Plast Surg* 1998;22:180-4.
47. Zeidman M, Durand P, Kundu N, Doumit G. Fat embolism after liposuction in Klippel-Trenaunay syndrome. *J Craniofac Surg* 2013;24:1319-21.

How to cite this article: El-Khatib HA. Liposuction for chronic medical diseases and noncosmetic conditions: review of the literature. *Plast Aesthet Res* 2015;2:1-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 20-05-2014; **Accepted:** 08-10-2014

Surgical pitfalls with custom-made porous hydroxyapatite cranial implants

Bruno Zanotti¹, Angela Verlicchi², Roberto Stefini³, Attilio Carlo Salgarelli⁴, Nicola Zingaretti⁵, Pier Camillo Parodi⁵, Casadei Matteo⁶, Massimo Robiony⁶

¹Department of Neurosurgery, University Hospital S. Maria della Misericordia, 33100 Udine, Italy.

²Neurology Unit, Free University of Neuroscience "Anemos", 42124 Reggio Emilia, Italy.

³Department of Neuroscience, Neurosurgery Unit, University of Brescia, 25123 Brescia, Italy.

⁴Department of Head and Neck Surgery, Unit of Maxillofacial Surgery, Modena and Reggio Emilia University, 41124 Modena, Italy.

⁵Department of Plastic and Reconstructive Surgery, University Hospital S. Maria della Misericordia, 33100 Udine, Italy.

⁶Department of Maxillo-Facial Surgery, University Hospital S. Maria della Misericordia, 33100 Udine, Italy.

Address for correspondence: Prof. Massimo Robiony, Department of Maxillo-Facial Surgery, University Hospital S. Maria della Misericordia, 33100 Udine, Italy. E-mail: massimo@robiony.it

ABSTRACT

Aim: Cranioplasty implants are used primarily in cases of surgical cranial decompression following pathological elevations of intracranial pressure. Available bone substitutes include porous hydroxyapatite (HA) and polymethylmethacrylate. Whichever material is used, however, prosthetic cranial implants are susceptible to intra- and postsurgical complications and even failure. The aim of this study was to investigate such occurrences in HA cranioplasty implants, seeking not only to determine the likely causes (whether correlated or not with the device itself) but also, where possible, to suggest countermeasures. **Methods:** We analyzed information regarding failures or complications reported in postmarketing surveillance and clinical studies of patients treated worldwide with custom-made HA cranial implants (Custom Bone Service Fin-Ceramica Faenza, Italy) in the period 1997-2013. **Results:** The two most common complications were implant fractures (84 cases, 2.9% of the total fitted) and infections (51 cases, 1.77%). **Conclusion:** Although cranioplasties are superficial and not difficult types of surgery, and use of custom-made implants are often considered the "easy" option from a surgical perspective, these procedures are nonetheless plagued by potential pitfalls. If performed well they yield more than satisfactory results from the points of view of both the patient and surgeon, but lack of appropriate care can open the door to numerous potential sources of failure, which can compromise-even irreparably-the ability to heal.

Key words:

Cranial, cranioplasty, custom-made, hydroxyapatite, implants

INTRODUCTION

Cranioplasty implants, whether of autologous bone or biocompatible bone substitutes, are used primarily in cases of surgical cranial decompression following pathological elevations of intracranial pressure. These implants play

roles in restoring both function and aesthetics, and thus, consideration of a custom-made solution as a first choice is in the best interest of the patient. Available bone substitutes include porous hydroxyapatite (HA), which favors regeneration (biomimetism) as well as reconstruction, and polymethylmethacrylate (PMMA), which should be reserved for severe cases of psychiatric disturbance, violent institutionalized patients, epileptics with frequent falling episodes, and the terminally ill.^[1] Whichever material is used, however, prosthetic cranial implants are susceptible to intra- and postsurgical complications and even failure. The aim of this study was to investigate such occurrences in HA cranioplasty implants, seeking not only to determine the likely

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.149364

causes (whether correlated or not with the device itself) but also, where possible, to suggest countermeasures.

METHODS

We analyzed information regarding failures or complications reported in postmarketing surveillance and clinical studies of patients treated worldwide with custom-made HA cranial implants (Custom Bone Service Fin-Ceramica Faenza, Italy) during the period of 1997-2013. This analysis was possible due to an agreement between the relevant parties in the context of an academic study. No sensitive information was collected during the research, which was limited to the processing of data regarding adverse events according to the biomedical device surveillance norms in force (MEDDEV-2).^[2] Statistical interpretation of the data was performed using IBM SPSS (V19; Chicago, United States).

RESULTS

In the study period, 2877 custom-made HA devices were implanted and all adverse events that arose were collated [Table 1]. The two most common complications were implant fractures (84 cases, 2.9% of the total fitted) and infections (51 cases, 1.77%). Of the fractures, 36 (1.25%) occurred postimplant (within 12 months of surgery, delayed fracture) and 48 (1.66%) occurred during the surgery itself (early fractures). A back-up was used to replace the primary implant in 43 of these cases. Fractures were not correlated with the size of the cranial defect. A correlation was noted between the occurrence of infection and the implantation site: frontoparietotemporal in 25 cases (49% of total infections), frontal-bifrontal in 17 (33.3%) temporoparietal in 6 (11.8%) and parietal in 3 (5.9%) [Table 2]. However, data analysis did not reveal a statistically significant difference regarding implantation site (Chi-square test; $P = 0.1694$; odds ratio = 1.65) [Table 3]. A further correlation between the time elapsed after surgery and the onset of infection was noted: less than 6 months in 32 (62.8%) cases, 6 months to 1 year in 3 cases (5.8%), and more than 1 year in 16 cases (31.4%). Analyzing data for the first postoperative year, it was observed that most infections occurred between 3 and 6 months (23 infections, 45%). It was also noted that infections were more common in cases of cranial trauma.

DISCUSSION

Delayed posttraumatic prosthesis fracture (36/2877) occurred with an incidence three-fold higher than that seen in normal population (3.5-4.5/1000). The incidence of a second cranial trauma also seemed to be greater than in normal population (2/1000), presumably due to the clinical and neurological effects of the underlying primary pathology. However, there was no discernable correlation between fracture and defect size, so other issues need to be examined, most likely the severity of the head trauma that fractured the skull or surgical error stemming from a lack of careful planning, positioning,

Table 1: Indicators for failure of HA cranioplasty implants

Errors	Complications
Incongruous size or shape	Infection
Breakage	Fistula
Dislocation/mobilization	Fluid collection: extracranial and/or extradural
	Subdural hematic suffusion
	Skin ischemia/necrosis/decubitus
	Lack of osteomimesis
HA: Hydroxyapatite	

Table 2: Correlation between the anatomical location of the prosthesis and the incidence of infection

Implantation site	Number of cases (n = 2877) (%)	Cases of infections (n) (%)	Rates in total infections (n = 51) (%)
Fontoparietotemporal	1588 (55)	25 (1.57)	49
Frontal-bifrontal	548 (19)	17 (3.10)	33.3
Parietal	231 (8)	3 (1.30)	5.9
Temporoparietal	491 (17)	6 (1.22)	11.8
Occipital	29 (1)	-	-

Table 3: Chi-square test to compare the infections implant rates of two groups

Group	Infected implants	Implants without infection	Total
Group 1	42	2094	2136
Group 2	9	742	751
Total	51	2836	2887

Group 1: the HA cranioplasty implant takes relationship with frontal sinus (frontal, frontoparietotemporal and bifrontal); Group 2: the HA cranioplasty implant does not take relationship with frontal sinus (parietotemporal, parietal, temporal and occipital). The Chi-square test revealed no significant difference between the two groups ($P = 0.1694$; OR 1.65). OR: Odds ratio; HA: Hydroxyapatite

or fixing of the implant. Regarding the planning, design, and validation phase, the relevant persons (manufacturing technician and surgeon) should pay particular attention to the following critical steps if such occurrences are to be avoided: verification of suitable implant thickness and uniformity of the density distribution of the prosthesis (micro- and macro-pores and interconnection channels), ensuring that the prosthesis perimeter engages the bone margin at all points, the latter being a type of ledge upon which the implant should rest snugly all round, thereby spreading the forces evenly. Thus, the prosthesis, in addition to possessing suitable curvature, should be tailored to fit the cranial lacuna precisely and without breaks. Indeed, if this does not occur, in addition to a lack of osteointegration, the laws of mechanics dictate that weaker areas with less resistance will arise. Regarding early fracture (i.e. during surgery), if one implant breaks, it could be due to manufacturing/design error, but if both the primary and back-up devices break, surgical error is the more likely cause because the possibility of a structural defect affecting two separate blocks of HA is remote.

Infections were more frequent in trauma patients, not surprisingly, because these represent the greater portion of the population in which custom-made HA cranial

implants are indicated. The incidence of infection was 1.77%, a finding comparable to that reported for titanium implants (1.18%) and slightly better than that for PMMA prostheses (5.48%).^[3-7] Of the infections, 73% occurred during the 1st year after fitting, confirming that infection risk is higher in the postsurgical period. That being said, cranioplasty implants fitted in the frontal sinus or mastoid can lead to airway fistulas and to acute secondary infections that may arise at any time during the life of the patient, even many years after surgery.^[8,9] Infections were found to occur with particular frequency in cases of large cranial implants (frontoparietotemporal), or those in the vicinity of the paranasal sinuses (frontal/bifrontal).^[10] This could be due to at least two distinct factors: (1) skin coverage is often insufficient in cases of large implants, due to tissue atrophy arising from the surgical approach itself (sectioning of large arterial blood vessels during the incision) and/or the time interval between craniotomy and reconstruction, which can predispose a patient to cutaneous lesions or ulcers that allow pathogenic agents to invade the prosthesis; and (2) poor occlusion of the sinuses, in cases of frontal or bifrontal cranioplasty, which effectively leaves the door open to any invading pathogen. Moreover, the sometimes precarious clinical and neurological conditions of trauma patients may reduce their immune responses. A first statistical analysis of the data (Chi-square test) did not reveal a difference between infection rates of HA implants that either take or do not take relationship with the frontal sinus [Table 3]. Despite this finding, further in-depth, studies are warranted to clarify a potential correlation between infection rates and implant sites.

In almost all cases of infection, it is advisable to cleanse the wound and remove the prosthesis to avoid intradural propagation and the consequent severe risk as well as prolonged hospitalization of the patient.^[8,11] Indeed, in cases in which back-up devices have been used to replace removed primary implants, infection rates are relatively low, presumably due to the fact that these patients have already been administered appropriate antibiotic treatment and have been scheduled for prompt re-intervention without undue waiting times. Nevertheless, the need for implant removal should be evaluated on a case-by-case basis, because in certain cases conservation is possible.^[12] Indeed, we recently managed to salvage an infected HA cranial implant by administering suitable antibiotic treatment over the course of a few months. This experience showed that if the dura mater appears intact, and if the pathogen can be isolated, identified, and targeted with appropriate antibiotics, it is possible to opt for conservative treatment provided that careful monitoring is implemented, which should include regular blood tests and serial scintigraphy with labeled leukocytes. It should not be forgotten that as long ago as 1948, 25% of infected synthetic implants were salvaged by means of antibiotic therapy and curettage.^[8]

The relationship between the timing of surgery and infection lead us to believe that this would be less frequent if the cranioplasty was performed within the

first 3 months or after 6 months. The time between 3 and 6 months is associated with the highest risk of complications, both infectious and otherwise.

Another complication arising from cranioplasty is the dislocation/mobilization of the implant, which can be caused by poor planning, design and/or validation, and errors in the surgical procedure. Thus, this type of occurrence is largely preventable if a few simple precautionary steps are taken during the craniotomy itself, such as use of the jigsaw technique and beveling the cranial defect edge [Figures 1 and 2]. Furthermore, in cases of large lacunas requiring more than one implant, these should be shaped so that their juncture mimics the natural sutures of the skull and features slanted-S edges [Figure 3]. Other precautions include avoiding anchoring the prosthesis to the temporal muscle; this muscle should instead be positioned over the implant, which should be equipped with sufficient holes for anchorage [Figure 4].^[13]

Attempts should also be made to prevent the formation of a fluid fistula, which can severely slow or impede cicatrisation and osteomimesis. The main cause of fistulas is adhesion between the dura mater, temporal muscle, and galea.^[14] Such scarring adhesions can prolong subsequent surgery times, cause excessive blood loss, and increase the probability of an inadvertent lesion to the dura mater or cerebral cortex due to the difficult techniques required for their dissection.^[15] Nevertheless, these events can be averted by placing an inert, nonresorbable membrane, such as a super-thin (0.1 mm) sheet of expanded polytetrafluoroethylene (ePTFE; e.g. Preclude



Figure 1: "Puzzle" technique. The perimeters of cranioplasty must be characterized by extroflexions to prevent slips and dislocations

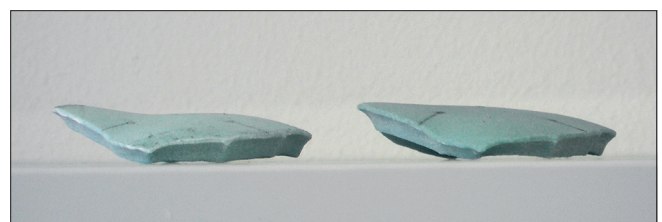


Figure 2: Forehead cranioplasty. The edges have an inclination of 45° to prevent the sinking of the cranioplasty. Male forehead profile on the left; female forehead profile on the right

Peritoneal Membrane, W.L. Gore and Associates. Inc.), between the dura and the soft tissues, especially at the site of the temporal muscle.^[16]

Extradural and extracranial pooling of fluid and subdural hematoma are less frequent events in cranioplasties. The former can usually be resolved by prompting parenchymal re-expansion (if viable) or by increasing the number of dural suspension points and maintaining subcutaneous drainage for a longer period of time. Adhesion of the scalp to the cranial implant can be promoted by anchoring the latter to the galea fascia using sutures.

The soft tissues overlying the cranioplasty implant can also be subject to ischemia, necrosis, and/or decubitus, and it is thus vital that cutaneous trophism and irrigation is carefully evaluated in the presurgical phase. Moreover, a surgical approach should be planned taking into account not only aesthetic concerns (such as avoiding the incision encroaching below the hairline and using the Simpson technique) but also seeking to avoid damage to the main arterial trunks and temporal muscle.^[13,17] In difficult cases featuring a paucity of viable soft tissue, cranioplasty implant fitting could necessitate the use of cutaneous expanders. Another useful surgical aid for improving cutaneous trophism is dermal matrix (INTEGRA Dermal Regeneration Template Single Layer film) [Figure 5].^[18] Such matrices promote mesenchymal hist induction and hist oconduction, serving to guide the formation of normal dermal tissue. The collagen and glucosaminoglycans of these matrices provide structural support for the infiltrating fibroblasts, macrophages, lymphocytes, and capillaries that form the neurovascular network. In covering the implant, these networks favor the development of better blood irrigation, important not only for cutaneous tropism but also for the invasion of the porous HA of the cranial implant by the organic bone matrix, promoting osteoconduction and osteointegration of the prosthesis. The scalp is not only necessary for implant coverage but it also supplies nutrients and immune system components. Together with the dura, it also aids in the osteomimesis process of the cranioplasty implant.

Indeed, another possible cause of HA cranial implant failure is lack of osteomimesis. If there is poor contiguity between the implant and the skull margin, osteoblast migration is compromised. To avoid this and to ensure the accurate design of the implant (which must fit perfectly along the entire border of its cranial housing), the surgeon must take certain factors into account during the surgery itself. In particular, the skull defect borders must be cleared completely of any scarring or inflammatory matrix, the dura on the border of the internal plate must be delaminated, and the craniectomy border drilled delicately. In addition, no material should be placed between the bone and implant, with the exception of HA granules or calcium phosphate paste [Figure 6]. Indeed, it has been demonstrated that more osteointegration occurs on a rough surface.^[19] A prime concern of the surgeon, however, should be that the continuum is controlled and that the tissue exposed to drilling is adequately cooled.



Figure 3: "Italic S" technique. If the cranioplasty involves the use of more pieces faced between them, the contact surfaces must not be linear. This prevents slips and dislocations

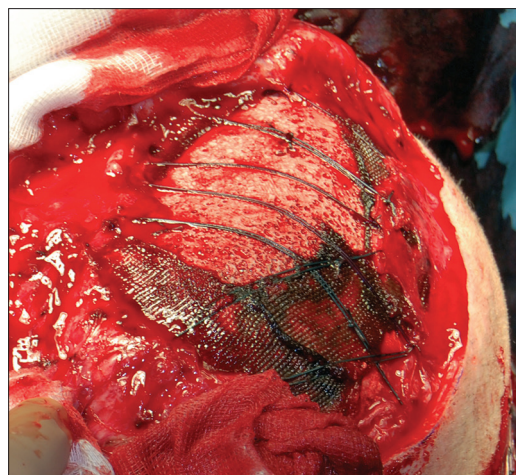


Figure 4: In the pterional area, the anchorage of the temporalis muscle should not be done on the cranioplasty, but must override it, with traction to the sagittal line

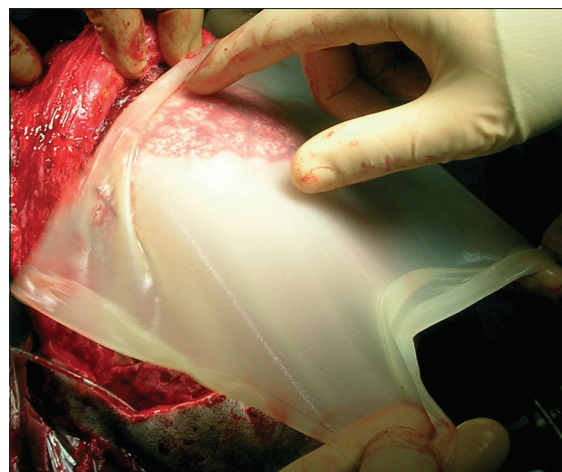


Figure 5: The trophism of the skin overlying the cranioplasty is important for the osteomimesis and for the prevention of infections. The trophism of the skin may improve by using dermal matrix placed between cranioplasty and subcutaneous tissue

In fact, the threshold for damage to osteocytes is as low as 47 °C.^[20] That being said, the limited clinical success of osteomimesis could also be explained by a lack of vascularization, which is affected by the tropism of the

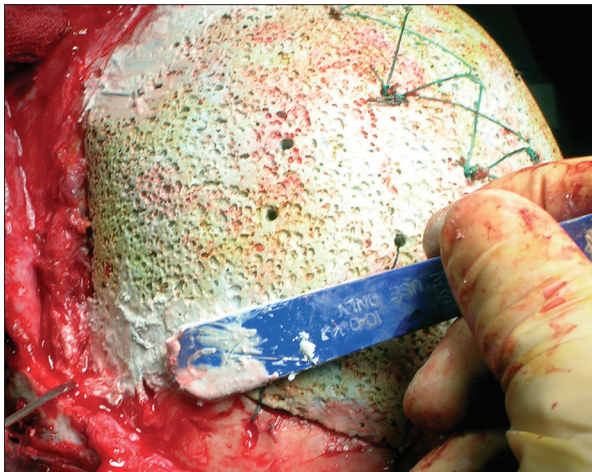


Figure 6: The solutions of continuous between cranioplasty and be must be filled with moldable pastes of calcium phosphate. This promotes osteointegration and increases the primary resistance of the cranioplasty thanks to optimal bone perimeter support (curb)

overlying skin, a critical process during bone growth and repair.^[21]

In general, it appears that the majority of adverse events in cranioplasties are ascribable to human error, on the part of the manufacturer or the surgeon. Indeed, poor design or lack of adequate preparation is responsible for almost all custom-made HA cranioplasty implant failures. For this reason, a continuous exchange of information among surgeons and implant manufacturing technicians is essential, and should go some way to ensuring the continued success of this procedure.

REFERENCES

1. Nataloni A. The biomimetism to medical device quality. *Riv Med* 2005;11:133-4.
2. Guidelines on a Medical Devices Vigilance System. MEDDEV 2.12-1 rev. 6 - December 2009, European Commission; DG Enterprise and Industry. Available from: http://www.ec.europa.eu/health/medical-devices/files/meddev2_12_1-rev_6-12-2009_en.pdf. [Last cited on 2014 Dec 5].
3. Eufinger H, Wehmöller M. Individual prefabricated titanium implants in reconstructive craniofacial surgery: clinical and technical aspects of the first

- 22 cases. *Plast Reconstr Surg* 1998;102:300-8.
4. Joffe J, Harris M, Kahugu F, Nicoll S, Linney A, Richards R. A prospective study of computer-aided design and manufacture of titanium plate for cranioplasty and its clinical outcome. *Br J Neurosurg* 1999;13:576-80.
5. Agner C, Dujovny M, Park H. Delayed minimally invasive cranioplasty. *Minim Invasive Neurosurg* 2003;46:186-90.
6. Chiarini L, Figurelli S, Pollastri G, Torcia E, Ferrari F, Albanese M, Nocini PF. Cranioplasty using acrylic material: a new technical procedure. *J Craniomaxillofac Surg* 2004;32:5-9.
7. Lee SC, Wu CT, Lee ST, Chen PJ. Cranioplasty using polymethyl methacrylate prostheses. *J Clin Neurosci* 2009;16:56-63.
8. White JC. Late complications following cranioplasty with alloplastic plates. *Ann Surg* 1948;128:743-54.
9. Gürbüz MS, Celik O, Berkman MZ. Infection of cranioplasty seen twenty years later. *J Korean Neurosurg Soc* 2012;52:498-500.
10. De Bonis P, Frassanito P, Mangiola A, Nucci CG, Anile C, Pompucci A. Cranial repair: how complicated is filling a "hole"? *J Neurotrauma* 2012;29:1071-6.
11. Zanotti B, Cramaro A. Notes of surgical procedure. *Riv Med* 1995;11:153-60.
12. Johnson PJ, Robbins DL, Lydiatt WM, Moore GF. Salvage of an infected hydroxyapatite cement cranioplasty with preservation of the implant material. *Otolaryngol Head Neck Surg* 2000;123:515-7.
13. Zanotti B, Verlicchi A, Robiony M, Parodi PC. Surgical calvarial demolition and reconstruction: procedure, implants and results. *Top in Med* 2010;16:1-19.
14. Kim H, Sung SO, Kim SJ, Kim SR, Park IS, Jo KW. Analysis of the factors affecting graft infection after cranioplasty. *Acta Neurochir (Wien)* 2013;155:2171-6.
15. Chun HJ, Yi HJ. Efficacy and safety of early cranioplasty, at least within 1 month. *J Craniofac Surg* 2011;22:203-7.
16. Zanotti B, Ius T. Surgery: useful to know. *Riv Med* 2005;11:185-7.
17. Zanotti B, Verlicchi A. Craniectomy decompressive. In: Zanotti B, Verlicchi A, Parodi PC, editors. *Cranioplastica Terapeutica*. Trento: New MAGAZINE edizioni; 2013. p. 37-46.
18. Cordaro ER, Calabrese S, Faini GP, Zanotti B, Verlicchi A, Parodi PC. Method to thicken the scalp in calvarian reconstruction. *J Craniofac Surg* 2011;22:598-601.
19. Albrektsson T, Wennerberg A. Oral implant surfaces: part I - review focusing on topographic and chemical properties of different surfaces and *in vivo* responses to them. *Int J Prosthodont* 2004;17:536-43.
20. Dolan EB, Haugh MG, Tallon D, Casey C, McNamara LM. Heat-shock-induced cellular responses to temperature elevations occurring during orthopaedic cutting. *J R Soc Interface* 2012;9:3503-13.
21. Szpalski C, Barr J, Wetterau M, Saadeh PB, Warren SM. Cranial bone defects: current and future strategies. *Neurosurg Focus* 2010;29:e8.

How to cite this article: Zanotti B, Verlicchi A, Stefini R, Salgarelli AC, Zingaretti N, Parodi PC, Matteo C, Robiony M. Surgical pitfalls with custom-made porous hydroxyapatite cranial implants. *Plast Aesthet Res* 2015;2:7-11.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 25-06-2014; **Accepted:** 17-08-2014

Patient-centric dose equivalency pilot study of incobotulinumtoxin a (xeomin) vs. abobotulinumtoxin a (dysport) in the treatment of glabellar frown lines

Jonathan Bank¹, Nicole A. Phillips², Laurie A. Casas¹

¹Department of Surgery, Section of Plastic and Reconstructive Surgery, University of Chicago Medical Center, Chicago, IL 60026, USA.

²Department of Surgery, Division of Plastic Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA.

Address for correspondence: Dr. Laurie A. Casas, Department of Surgery, Section of Plastic and Reconstructive Surgery, University of Chicago Medical Center, Chicago, IL 60026, USA. E-mail: lcasas@casas.md

ABSTRACT

Aim: Incobotulinumtoxin A (xeomin) has been proposed as an alternative to abobotulinumtoxin A (dysport) and onabotulinumtoxin A (Botox) in the treatment of glabellar frown lines. A recent study is comparing abobotulinumtoxin A and onabotulinumtoxin A revealed equivalent efficacy with a dose conversion ratio of 2.5:1. We sought to establish effectiveness and dosing equivalency of incobotulinumtoxin A vs. abobotulinumtoxin A. **Methods:** Inclusion criteria for this pilot study included patients of a single surgeon (LAC) who had previously received a constant dose of abobotulinumtoxin A over at least four consecutive treatment sessions for the previous 12 months to achieve an 85-90% elimination of dynamic glabellar frown lines. The primary outcome sought dose comparison between established maintenance abobotulinumtoxin A dosing and incobotulinumtoxin A first-time dosing. A 2:1 conversion (abobotulinumtoxin A: incobotulinumtoxin A) was chosen in most patients. Secondary outcomes were patient-reported onset of effect, physician-assessed effect at 10-12 weeks, pain associated with administration, and patient perceived need for re-treatment at 2 weeks. **Results:** A total of 32 subjects were included. The mean dose of incobotulinumtoxin A was 17.1 units (± 6.1 , the median dose 20 units). The mean dose of abobotulinumtoxin A was 27.6 (± 11.7 , the median dose 27.5 units). The mean difference in treatment units was -10.5 (95% confidence interval, $P < 0.001$). Among 30 patients who reported effect onset, the median was 8.5 days, with a range of 1-14. At 10-12 weeks, muscle paralysis was assessed to be 69.2% (± 27.3), vs. 90.3% (± 1.8) with abobotulinumtoxin A ($P < 0.001$). The majority of patients rated pain of administration as equal or greater to that of abobotulinumtoxin A (63% and 22%, respectively). Three patients (9%) required re-treatment at 2 weeks with abobotulinumtoxin A due to lack of effective treatment with incobotulinumtoxin A. Abobotulinumtoxin A re-treatment was chosen by the patient. **Conclusion:** We found incobotulinumtoxin A at 17.1 (± 6.1) units to be less effective than abobotulinumtoxin A at 27.6 (± 11.7) units in the treatment of glabellar frown lines at 10-12 weeks postadministration. Dosing was less predictable than dosing associated with abobotulinumtoxin A treatment. Larger,

randomized controlled trials are indicated to further delineate these differences and to clarify whether this difference from previously published incobotulinumtoxin A dosing may have been due to the small sample size.

Key words:

Abobotulinumtoxin A, glabellar frown lines, incobotulinumtoxin A, rhytids

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.149366

INTRODUCTION

Neurotoxin injection accounted for more than a third of all nonsurgical cosmetic procedures performed in the United States in 2012.^[1] Abobotulinumtoxin A (aboBTX-A, dysport) and onabotulinumtoxin A (onaBTX-A, Botox) are currently the most commonly used preparations of *Clostridium botulinum* toxin in the treatment of glabellar frown lines. Composed of high-molecular weight protein complexes unique to the various formulations, each of these neuromodulators has a slightly different pharmacokinetic profile.^[2] The protein complex is also thought to play a role in the immunogenicity of these therapeutic agents, influencing tolerance to drug effect and clinical response over time.^[3]

Abobotulinumtoxin A (aboBTX-A, dysport) is a type A botulinum toxin approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity.^[4] The toxin exists in a protein complex approximately 500 kDa in size. Incobotulinumtoxin A (incoBTX-A, Xeomin), a recently approved form of botulinum toxin type A, is also indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.^[5] IncoBTX-A differs from the other neuromodulators, including onaBTX-A and aboBTX-A, in its formulation as a purified toxin-free of complexing proteins. This formulation, in theory, renders incoBTX-A less immunogenic than the other forms of botulinum toxin A currently available, permitting reproducible effects on repeat injections.

Although a calculated unit conversion between alternative neurotoxin preparations cannot be directly derived due to differing manufacturing processes, the separate bacterial strains involved, and the variations in size of the associated complexing proteins,^[2,6,7] a published clinical study as well as the senior author's clinical experience has shown that a reliable conversion rate between aboBTX-A (dysport) and onaBTX-A (Botox) is 2.5:1.^[8] In addition, several studies have concluded that a 1:1 equivalency exists between onaBTX-A (Botox) and incoBTX-A (Xeomin).^[9,10]

In our practice since 2010, the majority of patients treated with neuromodulators receive aboBTX-A. Given the potentially promising immunogenic profile of incoBTX-A,^[11] we were interested in determining the correct dosage of this neuromodulator among our patient population. Due to the uncertainty regarding conjectural conversion between the three neurotoxin preparations, we sought to establish effectiveness and dosing equivalency of incoBTX-A versus aboBTX-A within a consecutive series of 32 patients previously treated with aboBTX-A for temporary reduction in glabellar dynamic wrinkles.

METHODS

We conducted a prospective pilot study at a single surgeon center, with all injections performed by the senior

author. The study included patients that had previously received at least four consecutive treatments of aboBTX-A at 4-month intervals at a stable dose, achieving 85-90% elimination of dynamic glabellar frown lines, and who had expressed satisfaction with at least four consecutive aboBTX-A treatments. Patient satisfaction with aboBTX-A treatment was defined by the patient's decision not to return for re-treatments before the planned redosing interval of 4-month. The study was approved by the review board of University of Chicago Medical Center.

Primary outcomes of this pilot study were patient perceived clinical effectiveness at 2 weeks (defined as an 85-90% decrease in muscle activity) and percentage of muscle activity at 3 months per surgeon assessment. The planned conversion rate was 2:1 (aboBTX-A: incoBTX-A) using the established aboBTX-A dosage for each patient to determine an initial incoBTX-A dose. However, we permitted dose adjustment per the physician's assessment at the time of incoBTX-A injection. The incoBTX-A dose was dispersed into the corrugator and procerus muscles for each patient; injection patterns were based on diagrams reviewed in the electronic medical record, documenting the injection points used during prior aboBTX-A treatments.

Secondary outcomes were examined via patient questionnaires that asked subjects to report on the onset of effect after incoBTX-A injection, the pain of injection versus their recollection of pain on aboBTX-A injections, the perceived duration of effect, and their overall satisfaction with the treatment session. Patients who were not satisfied with their initial treatment dosage were asked to return for re-treatment at 2 weeks. All patients were seen in follow-up at 10-12 weeks. At this time, glabellar and procerus activity were assessed by the treating surgeon, and the patient's perception of the treatment was recorded.

Demographic and clinical characteristics were summarized using frequency counts and percentages for categorical variables and median and range for continuous variables. Residual muscle activity at 4-month following at least four abobotulinumtoxin A treatment sessions was compared to muscle activity with one incobotulinumtoxin A treatment session at 10-12 weeks using a paired *t*-test.

RESULTS

A total of 32 subjects were included. The majority of patients were female (40-71 years old) and most had received aboBTX-A consistently for over 2 years [Table 1]. The mean dose of incoBTX-A administered was 17.1 units (\pm 6.1, median dose 20 units). The mean treatment dose of aboBTX-A administered was 27.6 (\pm 11.7, median dose 27.5 units). The mean difference in treatment units was -10.5 (95% confidence interval, P < 0.001) [Table 2]. Among 30 patients who reported effect onset of the one incoBTX-A treatment, the median result was 8.5 days, with a range of 1-14 days [Table 1].

Twenty-nine out of 32 patients (91%) reported satisfactory treatment effect at 2 weeks, 3 patients (9%) requested

re-treatment at 2 weeks with aboBTX-A due to perceived lack of effective treatment with incoBTX-A. During follow-up with the treating surgeon at 10-12 weeks, muscle paralysis was assessed to be 69.2% (\pm 27.3), vs. 90.3% (\pm 1.8) in an equivalent time period with aboBTX-A ($P < 0.001$) [Table 2]. With regard to perceived pain on injection, 62% of patients reported equivalent pain between the two treatments, 22% of patients reported more pain with the incoBTX-A injection, 9% had less pain with incoBTX-A, and 6% were unable to reliably recall. Overall satisfaction with incoBTX-A treatment was confirmed by 22 out of 32 patients among the study group (68%) at 2 weeks; this increased to 25/32 (78%) at 3 months. The most commonly cited reasons for dissatisfaction were related to the longevity and magnitude of incoBTX-A's effect.

At 10-12 weeks following incoBTX-A treatment, the percentage of muscle activity was recorded by the senior surgeon in light of the dose ratio of aboBTX-A: incoBTX-A administered. Of the subjects that received an incoBTX-A dose at a ratio of 1.5-2.5:1, only 40% had a clinical result that was considered equivalent to the original four aboBTX-A treatment dose results. A total of 16% of patients had effects that were less than expected for the hypothesized ratio. Some patients (38%) received relatively more incoBTX-A (ratio of 0.5-1.5:1), due to clinical evaluation that the dose should be higher than 2:1 of the original aboBTX-A dose. Among this study group, 16% resulted in muscle attenuation that was greater than

perceived with the aboBTX-A dose, whereas 22% had a less than expected response. Six percent of patients had a lesser response while receiving a relatively lower dose (ratio of 2.5-3:1) [Figure 1].

DISCUSSION

Injection of botulinum toxin type A was the most commonly performed cosmetic procedure in the United States in 2012, with over 4 million treatments reported for the year.^[1] Together with other injectable products, treatment with botulinum toxin type A accounted for approximately 2 billion dollars of United States spending in 2012. The rising number of minimally-invasive cosmetic procedures being performed, with a 10% increase in such procedures noted from 2011 to 2012, signals the long-term impact that injection of botulinum toxin type A and other nonsurgical procedures will have on the future of aesthetic practices.

Reported overall patient satisfaction rates with botulinum toxin type A treatments are high^[7,12] and are largely related to the onset, duration, and efficacy of treatment.^[7] Given the tremendous impact of neuromodulator therapy and the importance of patient satisfaction as a key outcome, it is essential for practitioners to understand the optimal treatment dose, re-treatment interval, and expected outcomes associated with the various botulinum toxin A preparations available today.

Multiple clinical studies have demonstrated the safety, efficacy and tolerability of aboBTX-A since its Food and Drug Administration (FDA) approval in 2009 for the treatment of glabellar frown lines.^[13-16] A prospective, randomized control split-face trial comparing aboBTX-A with onaBTX-A found no significant differences between treatment effects on muscle activity or wrinkle appearance, onset and duration of treatment effect, or diffusion characteristics of the two neurotoxins.^[8] Although one clinical trial is comparing onaBTX-A with aboBTX-A indicated lower rates of patient satisfaction among patients treated with aboBTX-A,^[17] satisfaction rates with aboBTX-A treatments were high among our patient population. All our patients had previously received at least four consecutive treatments of aboBTX-A at 4-month intervals at a stable dose and had continued to achieve 85-90% elimination of dynamic glabellar frown lines at this dose with a reported high patient satisfaction rate.

Free of complexing proteins, incoBTX-A is unique among the botulinum toxin preparations currently available. The subtraction of these inactive or denatured protein

Table 1: Patient demographics

Total patients	32
Median age in years (range)	56 (40-71)
Number female (%)	29 (91)
Length of abobotulinumtoxin A use (years), <i>n</i> (%)	
< 2	6 (19)
> 2	26 (81)
Median abobotulinumtoxin A dose in glabella (SD)	27.6 (\pm 11.7)
Median incobotulinumtoxin A dose in glabella (SD)	17.1 (\pm 6.1)
Average conversion rate	1.6:1
Glabella re-treatment, <i>n</i> (%) (patient request)	
No	29 (91)
Yes	3 (9)
Pain versus abobotulinumtoxin A, <i>n</i> (%)	
(patient recall of abobotulinumtoxin A: questionnaire following incobotulinumtoxin A treatment)	
Equal	20 (63)
Greater	7 (22)
Less	3 (9)
Can't remember	2 (6)

SD: Standard deviation

Table 2: Dose comparisons

	Incobotulinumtoxin A	Abobotulinumtoxin A	Mean difference (SD) (95% CI)	<i>P</i> *
Dose in the glabella	17.1 (6.1)	27.6 (11.7)	-10.5 (8.6)	< 0.001
	20	27.5	(-13.6, -7.4)	
Percentage of activity in glabella at 10-12 weeks (per surgeon evaluation)	69.2 (27.3)	90.3 (1.8)	-21.1 (27.0)	< 0.001
	70	90	(-30.8, -11.4)	

*Numbers in table are mean (SD) and median unless otherwise specified, difference calculated as incobotulinumtoxin A: abobotulinumtoxin A, *P* value from paired t-test. SD: Standard deviation, CI: Confidence interval

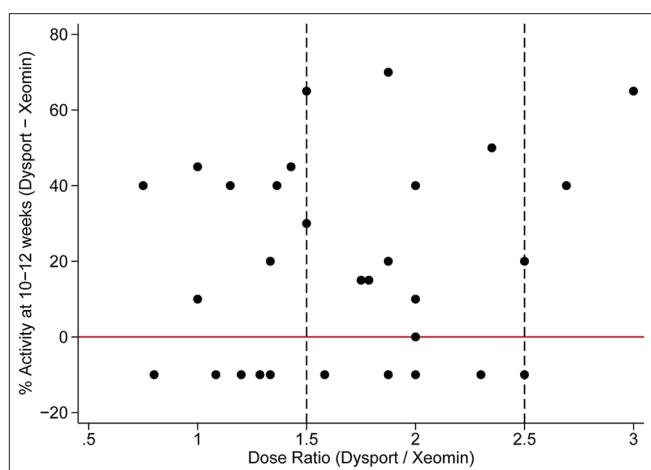


Figure 1: Neuromodulator dose ratio vs. muscle activity (percent) at 10-12 weeks

complexes theoretically results in a lower antigen load, decreasing the chance that the subject will develop neutralizing antibodies to treatment over time that could result in diminished clinical efficacy.^[11,18] IncoBTX-A received FDA approval for the treatment of glabellar frown lines in 2011, and a phase III clinical trial conducted that same year confirmed its efficacy for this indication, in accordance with FDA-mandated scoring criteria.^[19] One comparative trial of onabotulinumtoxin A and incoBTX-A reported overall high rates of patient satisfaction with both treatments and no statistically significant difference in satisfaction rates between the two neuromodulators.^[20] A noninferiority trial comparing incoBTX-A with onabotulinumtoxin A found similar efficacy, safety, and patient satisfaction profiles between the two treatments at a 1:1 dosing ratio.^[10] No head-to-head trials comparing incoBTX-A with abobotulinumtoxin A have been published to date.

As such, our pilot study aimed to determine a dosing equivalency of incoBTX-A vs. aboBTX-A that would result in similar clinical effectiveness and patient satisfaction among 32 patients previously treated with aboBTX-A for at least four treatments over 1 year. At ratios believed to anticipate equivalent results based on prior dose comparison studies,^[8-10] we found that no precise ratio could be determined.

Among the patients who reported effect onset with incoBTX-A treatment, the median result was 8.5 days, longer than the median onset of effect with aboBTX-A treatment reported in the literature of 3 days.^[21,22]

Limitations of our study include its small sample size, larger studies are warranted to better establish dose equivalency between aboBTX-A and incoBTX-A. IncoBTX-A injections were performed without cost to the patient, and this may have affected patient satisfaction rates. Secondary outcomes were determined through the use of a patient questionnaire. Recall bias may have affected our patients' ability to compare the pain of incoBTX-A injection compared with aboBTX-A injection which had occurred several months prior, and patient-reported onset and duration of effect may not be the most accurate means available of recording these results. However,

given the elective nature of treatment to improve patient cosmesis, we believe that the patient report, while inherently biased, is still an acceptable method of outcome assessment.

In conclusion, the pilot study did not establish a dose equivalency between incobotulinumtoxin A (xeomin) vs. abobotulinumtoxin A (dysport) in the treatment of dynamic glabellar frown lines in 32 consecutive patients who previously reported treatment success with abobotulinumtoxin A for at least 1 year at 4-month intervals. By combining the analysis of both the patient-reported results and the objective evaluation of dynamic glabellar muscle activity at 10-12 weeks following one treatment session with incoBTX-A, we found that using incoBTX-A at 17.1 (\pm 6.1) units was less predictable than using aboBTX-A at 27.6 (\pm 11.7) units. In comparison to aboBTX-A, the majority of our patients also reported lower satisfaction rates with incoBTX-A treatment; this difference was attributed to longer onset to treatment effect, increased pain on injection, and shortened duration of effect. Larger, prospective, randomized controlled studies are warranted to better establish dose equivalency between abobotulinumtoxin A and incobotulinumtoxin A.

REFERENCES

1. Cosmetic surgery national data bank: statistics 2012. *Aesthet Surg J* 2013;33: S1-21.
2. Klein AW, Carruthers A, Fagien S, Lowe NJ. Comparisons among botulinum toxins: An evidence-based review. *Plast Reconstr Surg* 2008;121:e413-22.
3. Dressler D, Wohlfahrt K, Meyer-Rogge E, Wiest L, Bigalke H. Antibody-induced failure of botulinum toxin a therapy in cosmetic indications. *Dermatol Surg* 2010;36 Suppl 4:2182-7.
4. Ipsen Biopharmaceuticals, Medicis Aesthetics. Medication Guide Dysport (dis-port) (abobotulinumtoxinA) Injection. 2012. Available from: http://www.pi.medicis.us/medication_guide/dysport.pdf. [Last accessed on 2014 Jul 10].
5. Merz Pharmaceuticals, Merz Aesthetics. Medication Guide Xeomin (zeo-min) (incobotulinumtoxinA) for Injection, for Intramuscular Use. 2011. Available from: <http://www.xeominaesthetic.com/EM00674-XEOMIN-Medication-Guide.pdf>. [Last accessed on 2014 Jul 10].
6. Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport): clinical indications and practice guide. *Aesthet Surg J* 2009;29:S72-9.
7. Flynn TC. Botulinum toxin: examining duration of effect in facial aesthetic applications. *Am J Clin Dermatol* 2010;11:183-99.
8. Michaels BM, Csank GA, Ryb GE, Eko FN, Rubin A. Prospective randomized comparison of onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport) in the treatment of forehead, glabellar, and periorbital wrinkles. *Aesthet Surg J* 2012;32:96-102.
9. Freeman SR, Cohen JL. New neurotoxins on the horizon. *Aesthet Surg J* 2008;28:325-30.
10. Sattler G, Callander MJ, Grabowitz D, Walker T, Bee EK, Rzany B, Flynn TC, Carruthers A. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. *Dermatol Surg* 2010;36 Suppl 4:2146-54.
11. Lorenc ZP, Kenkel JM, Fagien S, Hirmand H, Nestor MS, Sclafani AP, Sykes JM, Waldorf HA. Incobotulinumtoxin A (Xeomin): background, mechanism of action, and manufacturing. *Aesthet Surg J* 2013;33:S18-22.
12. Fagien S, Carruthers JD. A comprehensive review of patient-reported satisfaction with botulinum toxin type a for aesthetic procedures. *Plast Reconstr Surg* 2008;122:1915-25.
13. Kane MA, Brandt F, Rohrich RJ, Narins RS, Monheit GD, Huber MB, Reloxin Investigational Group. Evaluation of variable-dose treatment with a new U.S. Botulinum Toxin Type A (Dysport) for correction of moderate to severe glabellar lines: results from a phase III, randomized, double-blind, placebo-controlled study. *Plast Reconstr Surg* 2009;124:1619-29.
14. Baumann L, Brandt FS, Kane MA, Donofrio LM. An analysis of efficacy data

from four phase III studies of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J* 2009;29:S57-65.

15. Rubin M, Dover J, Maas C, Nestor M. An analysis of safety data from five phase III clinical trials on the use of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J* 2009;29:S50-6.
16. Carruthers JD, Lowe NJ, Menter MA, Gibson J, Eadie N, Botox Glabellar Lines II Study Group. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. *Plast Reconstr Surg* 2003;112:1089-98.
17. Lowe PL, Patnaik R, Lowe NJ. A comparison of two botulinum type a toxin preparations for the treatment of glabellar lines: double-blind, randomized, pilot study. *Dermatol Surg* 2005;31:1651-4.
18. Prager W. Differential characteristics of incobotulinumtoxin A and its use in the management of glabellar frown lines. *Clin Pharmacol* 2013;5:39-52.
19. Carruthers A, Carruthers J. Commentary: long-term treatment of glabellar rhytides using onabotulinumtoxin. *Dermatol Surg* 2011;37:929-30.
20. Prager W, Huber-Vorländer J, Taufig AZ, Imhof M, Kühne U, Weissberg R, Kuhr LP, Rippmann V, Philipp-Dormston WG, Proebstle TM, Roth C,

Kersch M, Ulmann C, Pavicic T. Botulinum toxin type A treatment to the upper face: retrospective analysis of daily practice. *Clin Cosmet Invest Dermatol* 2012;5:53-8.

21. Moy R, Maas C, Monheit G, Huber MB, Reloxin Investigational Group. Long-term safety and efficacy of a new botulinum toxin type A in treating glabellar lines. *Arch Facial Plast Surg* 2009;11:77-83.
22. Brandt F, Swanson N, Baumann L, Huber B. Randomized, placebo-controlled study of a new botulinum toxin type a for treatment of glabellar lines: efficacy and safety. *Dermatol Surg* 2009;35:1893-901.

How to cite this article: Bank J, Phillips NA, Casas LA. Patient-centric dose equivalency pilot study of incobotulinumtoxin a (xeomin) vs. abobotulinumtoxin a (dysport) in the treatment of glabellar frown lines. *Plast Aesthet Res* 2015;2:12-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 24-07-2014; **Accepted:** 28-09-2014

Effect of neoadjuvant chemotherapy on skin-sparing mastectomy and breast reconstruction modalities in 409 patients

Sameh Goubran¹, Jon Ver Halen^{2,3,4}

¹Department of Plastic Surgery, University of Tennessee Health Science Center, Memphis, TN 38103, USA.

²Department of Surgery, Division of Plastic, Reconstructive, and Hand Surgery, Baptist Memorial Healthcare Corporation, Memphis, TN 38120, USA.

³Department of Surgery, Vanderbilt-Ingram Cancer Center, Nashville, TN 37232, USA.

⁴Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN 38105, USA.

Address for correspondence: Dr. Jon Ver Halen, Division of Plastic and Reconstructive Surgery, Baptist Cancer Center, Vanderbilt Ingram Cancer Center, St. Jude Children's Research Hospital, 3268 Duke Circle, TN 38139, USA. E-mail: jpverhalen@gmail.com

ABSTRACT

Aim: While skin-sparing mastectomy (SSM) can be performed in patients with stage II-III breast cancer, the impact of neoadjuvant chemotherapy (NAC) on SSM rates and reconstructive modalities in these patients is not known. **Methods:** Between January 2007 and December 2009, 409 immediate breast reconstructions (IBRs) were performed in patients with Stage II-III breast cancer. Data were collected on preoperative, operative, and postoperative factors. **Results:** There was a statistically significant relationship between clinical stage of disease and the utilization of SSM or non-SSM ($P < 0.0001$). Seventy-five percent of all patients with stage II disease and 50% of patients with stage III disease underwent SSM; similarly, 75.5% of patients with stage II and 49.1% of patients with stage III disease who received NAC underwent SSM with immediate reconstruction, in spite of having a greater proportion of stage III patients ($P < 0.01$). In addition, patients who received NAC followed by SSM with IBR had larger tumors (mean, 3.5 cm vs. 3.1 cm, $P < 0.001$). The type of IBR, and size of skin defect was significantly affected by whether the patient underwent SSM or non-SSM ($P = 0.001$, $P < 0.01$, respectively). **Conclusion:** We are increasingly considering NAC to be an important tool to potentially reduce the morbidity of mastectomy, including the need to resect breast skin, which can subsequently enhance reconstructive outcomes in patients with clinical stage II and III breast cancer. Specifically, our data suggest that NAC patients with stage II and III breast cancer and larger tumors can reliably and safely undergo SSM in nearly half of cases, thus improving reconstructive outcomes and patient well-being.

Key words:

Immediate breast reconstruction, neoadjuvant chemotherapy, review, skin-sparing mastectomy

INTRODUCTION

The increased use of neoadjuvant chemotherapy (NAC) has altered the therapeutic management of patients with clinical stage II and III breast cancer. For patients with large breast

tumors, NAC has been shown to significantly reduce tumor size in $> 90\%$ of cases, thus increasing the proportion of patients eligible for breast conservation surgery (BCS).^[1] Conversely, in women undergoing mastectomy for early-stage breast cancer, skin-sparing mastectomy (SSM) followed by immediate breast reconstruction (IBR) has been shown to result in acceptable oncologic and esthetic outcomes and good patient satisfaction.^[2-5] There is increasing evidence that NAC followed by SSM and postmastectomy radiation therapy results in favorable long-term local control and survival rates.^[6,7] It is generally accepted that NAC does not increase complication rates after SSM and IBR but that NAC patients undergo IBR and delayed breast reconstruction with decreased frequency.^[8,9] However, it is unclear whether

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.149369

the use of NAC increases the likelihood that patients with stage II and III breast cancer will receive SSM with immediate reconstruction, or if it changes the use of reconstructive modality.

Given the clear preference for skin-preserving mastectomy with IBR in the majority of patients undergoing mastectomy, the interaction of these therapeutic options and their impact on outcomes needs to be elucidated.^[10-13] In light of the advantages of NAC on improving breast conservation rates, if applied to patients undergoing mastectomy, it could both allow for more skin preservation and improve the reconstructive options that can be offered to these patients.^[14,15] For patients with clinical stage II-III breast cancer who would otherwise not be candidates for SSM, conversion from non-SSM to SSM allows reconstructive surgeons to optimize outcomes due to the preservation of the three-dimensional skin envelope, the key component of an aesthetically acceptable breast reconstruction.

The purpose of this study was to compare the clinical characteristics and outcomes of patients with large primary and locally advanced breast cancer (stages II and III) with or without NAC and IBR after mastectomy. Objectives of this study were to determine the impact of NAC and other clinical factors on the rate of SSM and the choice of the reconstructive modality in these patients.

METHODS

We searched the plastic surgery, breast surgical oncology and breast medical oncology databases for patients with stage II-III breast cancer who underwent IBR. We excluded patients whose records lacked information about the type of primary surgery or whether the patient had received NAC. All patients were treated at the same tertiary referral center. American Joint Committee on Cancer clinical disease stage, patient demographic information, and the side of the affected breast were recorded for all patients. Data were collected from clinic notes, patient charts, operative reports, and prospectively entered plastic surgery, medical oncology, and breast surgical oncology databases.

For statistical analyzes, patients who underwent IBR were separated into two groups: patients who underwent SSM and patients who underwent non-SSM. Clinical and pathological data were tabulated for each of these groups. For comparison of all categorical variables, Chi-square analysis or Fisher's exact test (when sample sizes were small) was used. For continuous variables, Student's *t*-test or the rank sum test (when variances from comparison groups were not equal) was used. All *P* values were two-tailed, and we considered *P* ≤ 0.05 to be significant. Stata statistical software (StataSE 10, StataCorp LP, College Station, TX) was used for all statistical analyzes.

RESULTS

We identified 409 patients with stage II-III breast cancer who met study criteria for inclusion. Table 1 shows the clinical characteristics of patients who underwent SSM vs.

those who underwent non-SSM. There was a statistically significant relationship between clinical stage of disease and the utilization of SSM or non-SSM (*P* < 0.0001). Seventy-five percent of patients with stage II disease and 50% of patients with stage III disease underwent SSM. Tumor size also had a significant impact on the utilization of SSM (*P* = 0.017): patients who underwent SSM had a mean tumor size of 3.1 cm (range, 0.5-14 cm) vs. a mean tumor size of 3.9 cm (range, 0.8-20 cm) for patients who underwent non-SSM. The authors found a significant difference in the size of excised skin in non-SSM vs. SSM patients (56.2 cm² vs. 22.3 cm², *P* < 0.01). As a consequence of the need to replace breast skin, the type of IBR was significantly affected by whether the patient underwent SSM or non-SSM (*P* = 0.001). Fifty-one-point-four percent of SSM patients ultimately had implant-based reconstruction, 41.4% had autologous reconstruction, and only 7.2% had a latissimus dorsi flap plus a breast implant, vs. 36.8%, 44.4%, and 18.8% for non-SSM patients, respectively.

Despite the findings that 57.8% of the SSM patients received NAC and 69.5% of the patients who had NAC underwent SSM, NAC was not shown to have a significant impact on whether a patient underwent SSM or non-SSM (*P* = 0.3). Table 2 compares the clinical characteristics of SSM and non-SSM patients who underwent NAC. Similar to the listing in Table 1 (which includes all study participants), 75.5% of patients with stage II and 49.1% of patients with stage III disease who received NAC underwent SSM

Table 1: Comparisons of clinical characteristics between patients who underwent SSM and patients who did not (n = 409)

Characteristics	Non-SSM (n = 117)	SSM (n = 292)	P
Age			
Mean	48.1	47.3	0.4
Median (range)	47 (29-76)	48 (23-75)	
Race			
White	89 (29.1)	217 (70.9)	0.7
Other	28 (27.2)	75 (72.8)	
Clinical TNM stage			
Stage II	87 (24.9)	262 (75.1)	< 0.0001
Stage III	30 (50.0)	30 (50.0)	
Tumor size (cm)			
Mean	3.9	3.1	0.017*
Median (range)	3 (0.8-20)	2.9 (0.5-14)	
Neoadjuvant chemotherapy			
No	43 (25.9)	123 (74.1)	0.3
Yes	74 (30.4)	169 (69.6)	
Year of surgery			
2007	20 (32.3)	42 (67.7)	0.7
2008	35 (29.9)	82 (70.1)	
2009	62 (27.0)	168 (73.0)	
Reconstruction type			
Tissue expander followed by implant	43 (36.8)	150 (51.4)	0.001
Autologous	52 (44.4)	121 (41.4)	
Latissimus dorsi flap	22 (18.8)	21 (7.2)	

Data are shown as n (%). *Rank sum test. SSM: Skin-sparing mastectomy, TNM: Tumor node metastasis

Table 2: Comparisons of clinical characteristics of patients who received neoadjuvant chemotherapy with or without SSM (n = 243)

Characteristics	Non-SSM (n = 74)	SSM (n = 169)	P
Age			
Mean	46.8	45.8	0.4
Median (range)	47 (29-69)	47 (25-75)	
Race			
White	53 (29.0)	130 (71.0)	0.4
Other	21 (35.0)	39 (65.0)	
Clinical TNM stage			
Stage II	46 (24.5)	142 (75.5)	< 0.0001
Stage III	28 (50.9)	27 (49.1)	
Tumor size (cm)			
Mean	4.6	3.5	0.025*
Median (range)	4 (0.8-20)	3 (0.5-14)	
Year of surgery			
2007	15 (36.6)	26 (63.4)	0.3
2008	23 (34.3)	44 (65.6)	
2009	36 (26.7)	99 (73.3)	
Reconstruction type			
Tissue expander followed by implant	20 (27.0)	92 (54.4)	< 0.0001
Autologous	34 (46.0)	67 (39.6)	
Latissimus dorsi flap	20 (27.0)	10 (5.9)	

Data are shown as n (%). *Rank sum test. SSM: Skin-sparing mastectomy, TNM: Tumor node metastasis

with immediate reconstruction ($P < 0.0001$). Among the patients who received NAC, the mean clinical tumor size for the patients who underwent SSM was 3.5 cm (range, 0.5-14 cm) compared with 4.6 cm (range, 0.8-20 cm) for those who underwent non-SSM ($P = 0.025$). Of the patients who received NAC followed by SSM, 54.4% had implant-based reconstruction, 39.6% had autologous tissue flap reconstruction only, and 5.9% had a latissimus dorsi myocutaneous flap plus a breast implant, vs. 27%, 46%, and 27% for non-SSM patients, respectively.

Figure 1 displays by year the percentages of patients with stage II and III disease who underwent SSM, with or without NAC. In the latter years of this study, a statistically significant increase occurred in the percentage of patients with both stage II and III disease who underwent SSM with immediate reconstruction. This increase in SSM with immediate reconstruction was most notable in patients with stage III disease, especially between the time periods 2007 and 2009.

DISCUSSION

In this report, we present our experience with patients with clinical or pathological Stage II and III breast cancer who underwent IBR. We found that approximately 75% of patients with stage II disease and about half of patients with stage III disease underwent SSM. Patients who received NAC followed by SSM with IBR had larger clinical tumors than those who did not. More than half of these patients ultimately had implant-based reconstruction, without the need for additional skin from either a

latissimus dorsi flap or other autologous tissue flap. Immediate reconstruction with an autologous tissue flap was affected by the availability of the breast skin envelope as seen in the significantly increased utilization of flaps in non-SSM as opposed to SSM patients. Preservation of the breast skin envelope thus appeared most beneficial for immediate reconstruction with a tissue expander followed by an implant.

Although the use of NAC was not associated with an increase in the use of SSM and IBR (71.4% in all patients, vs. 69.5% in NAC patients, $P = 0.3$), it was associated with the choice of reconstruction ($P < 0.0001$). NAC had a moderate effect on the proportion of patients who underwent implant-based or autologous tissue flap reconstruction, and a larger proportional difference in patients who underwent reconstruction with a latissimus dorsi flap plus breast implant. The authors suspect that less breast skin was sacrificed during mastectomies in the NAC cohort, resulting in this difference. However, while fewer SSM patients who had NAC had a latissimus dorsi flap plus breast implant than those who did not have NAC (5.9% vs. 7.2%), this finding was not statistically significant ($P = 0.765$, Chi-square).

While one purpose of NAC is to facilitate the conversion of mastectomy to BCS, the authors hypothesized that in patients with locally-advanced breast cancer (i.e. stage II and III) it can also reduce the morbidity of mastectomy by converting patients who would otherwise receive non-SSM to SSM. There was a significantly higher percentage of Stage III breast cancer patients in the NAC cohort (22.6% vs. 14.7%, $P < 0.05$). NAC patients furthermore had larger tumors on average (3.5 cm, vs. 3.1 cm for non-neoadjuvant patients), potentially allowing the use of SSM in more patients who would otherwise not be candidates. Additionally, a greater percentage of SSM patients who had NAC had implant-based breast reconstruction than those who did not have NAC, which may indicate that more mastectomy skin was preserved at the time of SSM. Indeed, the authors found a significant difference in the size of excised skin in non-SSM vs. SSM patients (56.2 cm² vs. 22.3 cm², $P < 0.01$). It is our current practice to reconstruct non-SSM patients with either a latissimus dorsi flap + implant or autologous tissue, thus highlighting the role of mastectomy skin preservation in shaping reconstructive choices.

Breast conservation surgery has become an integral part of the management of breast cancer patients. It provides effective locoregional management and reduces the negative psychosocial impact related to mastectomy.^[16,17] Its oncologic safety is now documented; it does not increase local or distant recurrence, nor does it adversely affect disease-free or overall survival. Furthermore, there is no significant delay in detection of cancer recurrence.^[18-21] However, many patients still require mastectomies as standard treatment for breast cancer.^[8,22,23] Many institutions have adopted the use of NAC to facilitate the conversion of mastectomy to breast-conserving surgery or inoperable tumors to operable tumors in women with locally advanced breast

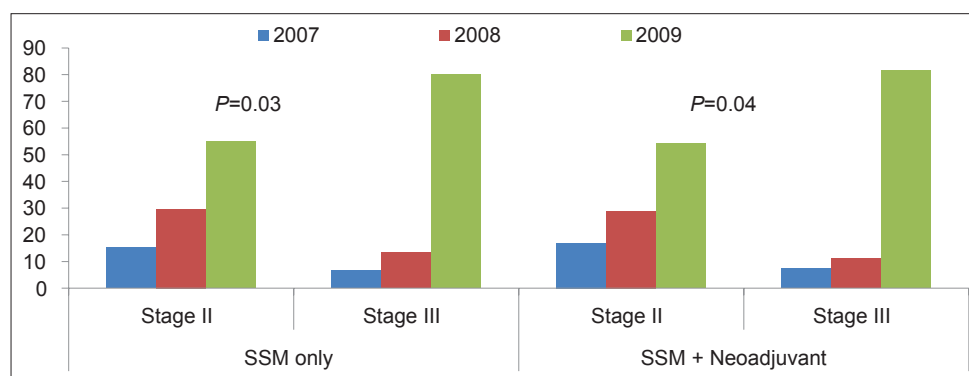


Figure 1: Percentage of patients receiving skin-sparing mastectomy (SSM) only or SSM with neoadjuvant chemotherapy, vs. stage of breast cancer, for years 2007-2009

cancer.^[7] In patients with skin involvement or frank T4b disease, NC has enabled an opportunity for SSM in patients where skin involvement regresses clinically.^[20] However, little has been studied regarding the effects of NAC on IBR. Patients who receive IBR have better esthetic results, better psychosocial outcomes, and lower costs of surgery compared to patients who undergo delayed reconstruction or no reconstruction.^[24] In these patients, SSM has clear advantages over non-SSM in that it preserves the breast's three dimensional architecture. Furthermore, many studies have shown that SSM with IBR does not increase local or distant recurrence, demonstrating the oncological safety of this technique.^[2,18] IBR after mastectomy is now routinely recommended for selected patients according to the National Comprehensive Cancer Network Guidelines.^[19] Compared with non-SSM, SSM is far superior as regards cosmetic outcomes and is expected to remarkably reduce the emotional trauma due to the sense of loss of a breast that is perceived by the patient just after surgery.^[25]

Although there have been some studies on the usefulness of SSM in locally advanced breast cancer,^[21,26] its application is still debated. It is commonly approved that local control, prognosis, and risk of complications are the same for SSM and NSSM, at least in stages 0, I, and II. SSM is still considered to be contraindicated for inflammatory breast cancer and breast cancer with skin invasion.^[25] So far, no study had addressed the issue of the influence of clinical characteristics on the type of breast reconstruction, especially for patients with advanced breast cancer. We found similar utilization of reconstructive modalities between non-NAC and NAC cohorts, despite the increased rate of stage III patients in the NAC cohort. The authors argue that NAC facilitates higher stage patients to undergo SSM-IBR, thus optimizing care in these patients.

Previous reports have documented a decreased receipt of breast reconstruction in NAC patients. Hu *et al.* revealed that recipients of neoadjuvant therapy are less likely to undergo immediate reconstruction, even after controlling for age, disease stage, and receipt of radiotherapy.^[27] They assumed that, the average NAC recipient has a 28% chance of undergoing immediate reconstruction compared with 40% for the average patient who receives only adjuvant chemotherapy. These neoadjuvant

recipients, however, are not more likely to progress to delayed reconstruction. Only younger age and lower BMI seem to predict delayed reconstruction among patients who do not undergo immediate reconstruction.^[27] Conversely, some patients undergoing NAC may develop treatment fatigue and may be unwilling to undergo elective breast reconstruction.^[28]

There are a number of limitations of our study. Since tissue expansion with two-stage reconstruction can be used for patients short of breast skin, a more logical comparison assessing the impact of NAC on SSM-IBR would evaluate direct-to-implant, one-stage implant reconstruction. Since we were only beginning to use this technique at the time of the study, there were not sufficient patients in the study cohort to examine this subject. In addition, our comparison of breast skin specimens (as noted above) makes this examination unnecessary. Direct comparison between NAC and non-NAC groups was confounded because tumor size was statistically larger in the NAC group (3.5 cm vs. 3.1 cm for SSM patients), and there was a statistically higher proportion of stage III patients in the NAC cohort. Patient cohort size did not permit us to confine statistical analysis only to patients with tumors larger than 3.5 cm or stage III patients. In addition, most patients with stage III disease already receive NAC, thus confounding this relationship. Of note, the authors found an increasing percentage of patients undergoing SSM over the course of the study, most notably in Stage III breast cancer patients [Figure 1]. While this is certainly multifactorial in nature, the use of NAC is a likely contributor to this phenomenon. However, a full analysis of this relationship is beyond the scope of this article.

Thus, far NAC has mainly been considered by medical oncologists as a predictor of response to chemotherapy and by breast surgeons as a means to increase eligibility for partial mastectomy instead of mastectomy. However, its use to reduce the morbidity of mastectomy in patients with Stage II and III breast cancer, including the need to resect breast skin and subsequently enhance reconstructive outcomes, is an intriguing possibility. In this large single-center study, we found that NAC did not statistically increase the use of SSM, but did affect the types of reconstruction used. Further work will help elucidate the role of NAC in IBR.

REFERENCES

- Prati R, Minami CA, Gornbein JA, Debruhl N, Chung D, Chang HR. Accuracy of clinical evaluation of locally advanced breast cancer in patients receiving neoadjuvant chemotherapy. *Cancer* 2009;115:1194-202.
- Monrighal E, Dauplat J, Gimbergues P, Le Bouedec G, Peyronie M, Achard JL, Chollet P, Mouret-Reynier MA, Nabholz JM, Pomel C. Mastectomy with immediate breast reconstruction after neoadjuvant chemotherapy and radiation therapy. A new option for patients with operable invasive breast cancer. Results of a 20 years single institution study. *Eur J Surg Oncol* 2011;37:864-70.
- Alderman AK, Kuhn LE, Lowery JC, Wilkins EG. Does patient satisfaction with breast reconstruction change over time? Two-year results of the Michigan Breast Reconstruction Outcomes Study. *J Am Coll Surg* 2007;204:7-12.
- Hu ES, Pusic AL, Waljee JF, Kuhn L, Hawley ST, Wilkins E, Alderman AK. Patient-reported aesthetic satisfaction with breast reconstruction during the long-term survivorship Period. *Plast Reconstr Surg* 2009;124:1-8.
- Lee C, Sunu C, Pignone M. Patient-reported outcomes of breast reconstruction after mastectomy: a systematic review. *J Am Coll Surg* 2009;209:123-33.
- Fernández-Frías AM, Aguilar J, Sánchez JA, Merck B, Piñero A, Calpena R. Immediate reconstruction after mastectomy for breast cancer: which factors affect its course and final outcome? *J Am Coll Surg* 2009;208:126-33.
- Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, Margolese RG, Hoehn JL, Vogel VG, Dakhil SR, Tamkus D, King KM, Pajon ER, Wright MJ, Robert J, Paik S, Mamounas EP, Wolmark N. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol* 2008;26:778-85.
- Song J, Zhang X, Liu Q, Peng J, Liang X, Shen Y, Liu H, Li H. Impact of neoadjuvant chemotherapy on immediate breast reconstruction: a meta-analysis. *PLoS One* 2014;9:e98225.
- Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev* 2007;CD005002. Doi: 10.1002/14651858.CD005002.pub2.
- Yedibela S, Elad L, Wein A, Dimmler A, Merkel S, Hohenberger W, Meyer T. Neoadjuvant chemotherapy does not increase postoperative complication rate after resection of colorectal liver metastases. *Eur J Surg Oncol* 2005;31:141-6.
- Turner II, Russell GB, Blackstock AWW, Levine EA. Impact of neoadjuvant therapy on postoperative complications in patients undergoing resection for rectal adenocarcinoma. *Am Surg* 2004;70:1045-9.
- Valenti V, Hernandez-Lizoain JL, Baixauli J, Pastor C, Aristu J, Diaz-Gonzalez J, Beunza JJ, Alvarez-Cienfuegos JA. Analysis of early postoperative morbidity among patients with rectal cancer treated with and without neoadjuvant chemoradiotherapy. *Ann Surg Oncol* 2007;14:1744-51.
- Milman S, Kim AW, Warren WH, Liptay MJ, Miller C, Basu S, Faber LP. The incidence of perioperative anastomotic complications after sleeve lobectomy is not increased after neoadjuvant chemoradiotherapy. *Ann Thorac Surg* 2009;88:945-50.
- Mehrara BJ, Santoro TD, Arcilla E, Watson JP, Shaw WW, Da Lio AL. Complications after microvascular breast reconstruction: experience with 1195 flaps. *Plast Reconstr Surg* 2006;118:1100-9.
- Mitchem J, Herrmann D, Margenthaler JA, Aft RL. Impact of neoadjuvant chemotherapy on rate of tissue expander/implant loss and progression to successful breast reconstruction following mastectomy. *Am J Surg* 2008;196:519-22.
- Foster JA, Abdolrasulnia M, Doroodchi H, McClure J, Casebeer L. Practice patterns and guideline adherence of medical oncologists in managing patients with early breast cancer. *J Natl Compr Canc Netw* 2009;7:697-706.
- Al-Ghazal SK, Sully L, Fallowfield L, Blamey RW. The psychological impact of immediate rather than delayed breast reconstruction. *Eur J Surg Oncol* 2000;26:17-9.
- Taylor CW, Horgan K, Dodwell D. Oncological aspects of breast reconstruction. *Breast* 2005;14:118-30.
- NCCN.org. 2012 NCCN clinical practice guidelines in oncology: breast cancer. Ver. 1. 2012. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. [Last accessed on 2014 Oct 23].
- Prabhu R, Godette K, Carlson G, Losken A, Gabram S, Fasola C, O'Regan R, Zelnak A, Torres M. The impact of skin-sparing mastectomy with immediate reconstruction in patients with Stage III breast cancer treated with neoadjuvant chemotherapy and postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 2012;82:e587-93.
- Lim W, Ko BS, Kim HJ, Lee JW, Eom JS, Son BH, Lee TJ, Ahn SH. Oncological safety of skin sparing mastectomy followed by immediate reconstruction for locally advanced breast cancer. *J Surg Oncol* 2010;102:39-42.
- Langstein HN, Cheng MH, Singletary SE, Robb GL, Hoy E, Smith TL, Kroll SS. Breast cancer recurrence after immediate reconstruction: patterns and significance. *Plast Reconstr Surg* 2003;111:712-20.
- Agrawal A, Grewal M, Sibbering DM, Courtney CA. Surgical and oncological outcome after skin-sparing mastectomy and immediate breast reconstruction. *Clin Breast Cancer* 2013;13:478-81.
- Mustonen P, Lepistö J, Papp A, Berg M, Pietiläinen T, Kataja V, Harna M. The surgical and oncological safety of immediate breast reconstruction. *Eur J Surg Oncol* 2004;30:817-23.
- Kinoshita S, Nojima K, Takeishi M, Imawari Y, Kyoda S, Hirano A, Akiba T, Kobayashi S, Takeyama H, Uchida K, Morikawa T. Retrospective comparison of non-skin-sparing mastectomy and skin-sparing mastectomy with immediate breast reconstruction. *Int J Surg Oncol* 2011;2011:876520.
- Foster RD, Esserman LJ, Anthony JP, Hwang ES, Do H. Skin-sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. *Ann Surg Oncol* 2002;9:462-6.
- Hu YY, Weeks CM, In H, Dodgion CM, Golshan M, Chun YS, Hassett MJ, Corso KA, Gu X, Lipsitz SR, Greenberg CC. Impact of neoadjuvant chemotherapy on breast reconstruction. *Cancer* 2011;117:2833-41.
- Medina-Franco H, Vasconez LO, Fix RJ, Heslin MJ, Beenken SW, Bland KI, Urist MM. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. *Ann Surg* 2002;235:814-9.

How to cite this article: Goubran S, Ver Halen J. Effect of neoadjuvant chemotherapy on skin-sparing mastectomy and breast reconstruction modalities in 409 patients. *Plast Aesthet Res* 2015;2:17-21.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 01-08-2014; **Accepted:** 27-10-2014

Primary contraction of skin grafts: a porcine preliminary study

Alexander Bogdanov Berezovsky, Vasileios A. Pagkalos, Eldad Silberstein, Yaron Shoham, Lior Rosenberg, Yuval Krieger

Department of Plastic and Reconstructive Surgery, Soroka University Medical Center, Ben Gurion University of the Negev, P.O. 151, Beer-Sheva 84101, Israel.

Address for correspondence: Dr. Vasileios A. Pagkalos, Division of Plastic and Reconstructive Surgery, Soroka University Medical Center, Ben-Gurion University of the Negev, P.O. Box 151, Beer-Sheva 84101, Israel. E-mail: pagkalos_v@yahoo.gr

ABSTRACT

Aim: Skin grafting is a common clinical practice for plastic surgeons, yet primary contraction of these grafts is a neglected topic. This study was designed to investigate primary contraction and introduce the shape of skin graft as a possible factor that modifies primary contraction behavior, using porcine models. **Methods:** In the first series, full-thickness skin grafts (FTSGs) and split-thickness skin grafts (STSGs) were compared. In a second series, how the shape of the skin graft affected the degree of contraction was examined. **Results:** The mean percentage of FTSG shrinkage was 12.04%, and the median was 12.18%. The mean percentage of STSG shrinkage was 6.87%, and the median was 5%. Circle-shaped and square-shaped FTSGs showed mean/median graft shrinkage of 5.83%/6.93% and 4.15%/3.75%, respectively. In STSGs, the circle-shaped and square-shaped grafts had mean/median graft shrinkage of 1.07%/0% and 0.31%/0%, respectively. **Conclusion:** Our preliminary report revealed an expected greater shrinkage of FTSGs compared with STSGs. Furthermore, in a limited number of specimens, the shape of the skin graft seemed to affect the primary contraction of the STSGs.

Key words:

Animal model, full-thickness skin graft, primary skin contraction, split-thickness skin graft

INTRODUCTION

Wound contraction is a normal physiological phenomenon reducing the area of a skin defect and therefore expediting its closure. This contraction is based on scar contraction and myofibroblast activity; all originate from granulation tissue that develops during the 1st week of the inflammatory process, part of the normal wound-healing course. The application of skin grafts to fresh skin defects has been proven to reduce wound contraction and hypertrophic scarring compared with full-thickness wounds that have been left to granulate and heal by secondary intention alone.^[1,2] However, skin grafts can also

contract, resulting in a compromised esthetic outcome and restricted mobility of the joints involved.

Skin graft contraction occurs in two stages: primary and secondary contraction. Primary contraction refers to the immediate reduction in size of the skin graft, directly after it has been harvested from its donor site. Primary contraction is due to passive recoil of the elastin fibers in the dermis and is, therefore, dependent upon the thickness of the graft. Full-thickness skin grafts (FTSGs) contain large volumes of elastin-containing dermis and consequently exhibit the greatest degree of primary contraction. Due to the reduced volume of dermis included, split-thickness skin grafts (STSGs) exhibit less contraction, whereas pure epidermal grafts do not contract.^[3] Secondary contraction is due to a wound bed contraction. This secondary contraction reduces both the size of the graft at the interface with its recipient bed and the circumference of the graft at its periphery.^[1,4] Traditionally, it is accepted that the degree of secondary contraction is inversely related to the thickness of the graft of FTSGs to minimize the extent of secondary contraction.^[5] Studies have shown that a granulating recipient bed, burn size, young age

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.149372

of the patient, anatomical area and grafting over mobile tissues may prompt skin graft contraction.^[1,5-7]

Skin grafting is a major element of reconstructive surgery. It is, therefore, important that every aspect of its practice is thoroughly investigated and evaluated. Primary contraction was first described and assessed by Davis and Kitlowski in 1931.^[3] The authors of that pioneering study used human specimens, a practice that has some limitations regarding the number, size and shape of skin grafts. Furthermore, although > 80 years have elapsed, there have not been any studies that further looked further into the development and cause of primary contraction. In this preliminary *in vivo* porcine study, we assessed the degree of primary skin graft contraction and investigated whether the shape of skin grafts affects the degree of contraction.

METHODS

The study was conducted at an accredited animal research facility (CRO, Lahav Research Institute, Lahav, Israel) following national and institutional guidelines for the care and use of laboratory animals.^[8] The animals were anesthetized female domestic pigs (Susscrofa), weighing approximately 30 kg. The study was approved by the Institutional Animal Care and Use Committee.

The study consisted of two parts. In the first part, we compared the contraction of FTSGs and STSGs. Four animals participated in the study, and a total of 67 specimens of skin grafts were harvested from the back of the pigs, 41 and 26 of FTSGs and STSGs, respectively.

For the study of the FTSG contraction, circles of 4 cm diameter were drawn with a permanent marker on the skin of each pig [Figure 1]. The area of the circles marked was calculated using the formula: $\text{area} = \pi r^2$, where r = radius of the circle and $\pi = 3.14$, resulting in the area value of 12.56 cm². The skin was excised with a No. 15-blade in a

circle shape and meticulously defatted. The FTSGs were placed on a flat surface 15 min after skin graft harvesting to facilitate complete primary contraction; their diameter was measured in 3 axes (with an axis-to-axis angle of 120°) and the average diameter was used to calculate the radius of the circle [Figure 1]. The mean value of the diameter was computed, and the surface was again calculated using the formula: $\text{area} = \pi r^2$.

For the study of STSG contraction, a rectangle stripe of 4 cm height and 40 cm width was drawn with a permanent marker on the pig. Additional lines were drawn vertically to produce 10 squares of equal 4 cm sides [Figure 1]. The area of each square was calculated using the formula: $\text{area} = s^2$, where s = side of the square and the initial area value of 16 cm² were recorded. All STSGs were harvested with a dermatome adjusted to 0.014 inch skin thickness, corresponding to moderate to thick skin grafts. The stripe was cut into squares according to our drawings, and the grafts were placed on a flat surface and left there for 15 min before measuring [Figure 1]. Due to the primary contraction, the initial squares changed into rectangles. Each side of the contracted STSGs was, therefore, measured, and the surface was calculated using the formula: $\text{area} = h \times w$, where h = height and w = width.

In the second part, we examined whether the shape of the skin graft affected the degree of contraction. For that purpose, we took a total of 27 specimens, harvested from the back of a single pig [Figure 2]. Nine of these specimens were circle-shaped FTSGs, 6 were square-shaped FTSGs, 8 circle-shaped STSGs and 4 square-shaped STSGs. The harvesting and calculation of the area of FTSGs and that of square-shaped STSGs were made in the same way as in the first stage of our study, with the initial surface area being 12.56 cm² and 16 cm² for the circle- and square-shaped specimens, respectively. For harvesting circle-shaped STSGs, we used a dermatome to create a “skin belt” graft, which was subsequently cut into a circle-shaped skin graft with scissors. All STSGs were harvested with a dermatome adjusted to 0.014 inch skin thickness [Figure 2].

Statistical analysis was performed using Microsoft Excel 2003® (Microsoft, Redmond, Washington, USA) and SPSS® version 14 (IBM-SPSS Inc., New York, USA). Statistical tests used Pearson’s Chi-square test and Student’s *t*-test.

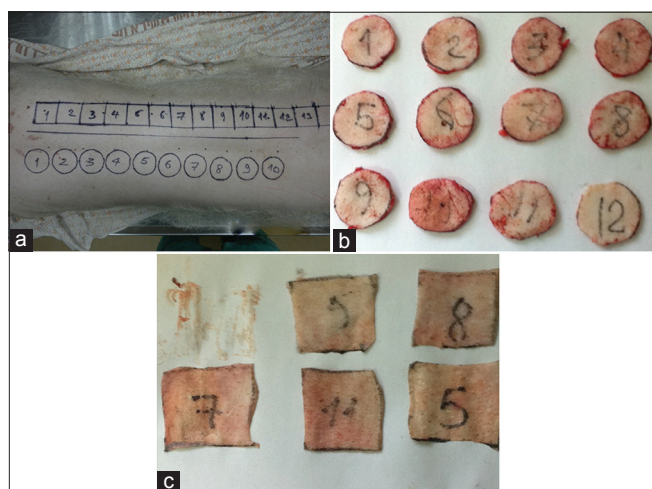


Figure 1: First part of study. (a) Skin grafts marked on the back of the animal. Circles are drawn with a permanent marker for the full-thickness skin grafts (FTSGs) and squares for the split-thickness skin grafts (STSGs). (b) Full-thickness skin grafts after excision and defatting. (c) STSGs after excision

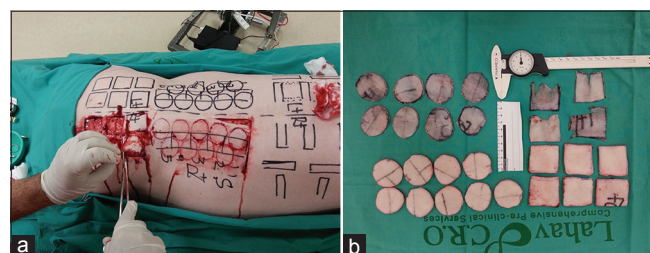


Figure 2: Second part of study. (a) Investigation of possible relation of shape of skin graft with degree of primary contraction. Circle- and square-shaped skin grafts excised from the back of a single animal. (b) Circle- and square-shaped full-thickness skin grafts and split-thickness skin grafts after excision

RESULTS

In the first part of the study, comparison was made between the contractions of FTSGs and STSGs. The initial surface area of the FTSG specimens was 12.56 cm². After excision and defatting, the area values of the contracted skin grafts ranged from 12.6 cm² (0% shrinkage) to 9.3 cm² (25.6% shrinkage). The mean area value of the FTSGs after primary contraction was 11.1 cm² and the median was 11.0 cm². The mean percentage of graft shrinkage was 12.0% and the median was 12.2% [Table 1]. The initial surface area of the STSG specimens was 16 cm². After harvesting with the dermatome, the area values of the contracted skin grafts ranged from 16 cm² (0% shrinkage, 1 specimen recorded) to 13.30 cm² (17% shrinkage). The mean area value of the STSGs after primary contraction was 14.9 cm² and the median was 15.2 cm². The mean percentage of graft shrinkage was 6.9% and the median was 5.0% [Table 1]. FTSGs presented greater primary contraction than STSGs at a statistically significant level ($P = 0.0011$) [Table 1].

In the second part, the role of the skin graft shape on primary skin contraction was investigated. The initial surface area of the circle-shaped specimens of both FTSGs and STSGs was 12.6 cm² and the initial surface area of the square-shaped specimens was 16.0 cm². After excision and defatting, the circle-shaped FTSGs had a calculated surface range from 12.3 cm² (2.0% shrinkage) to 11.3 cm² (9.8% shrinkage). The mean area value of the circle-shaped FTSGs was 11.8 cm² and the median was 11.7 cm². In this group, the mean percentage of graft shrinkage was 5.8% and the median was 6.9% [Table 2]. On the other hand, the square-shaped FTSGs ranged from 15.6 cm² (2.5% shrinkage) to 14.8 cm² (7.4% shrinkage). The mean area value of the square-shaped FTSGs was 15.3 cm² and the median was 15.4 cm². In the square-shaped FTSGs group, the mean percentage of graft shrinkage was 4.2% and the median was 3.8% [Table 2].

The comparison of primary contraction values between square- and circle-shaped FTSG specimens was not statistically significant ($P = 0.14$). The circle-shaped STSG specimens demonstrated a primary contraction ranging from 12.6 cm² (0% shrinkage) to 11.9 cm² (5.0% shrinkage). The mean area value of the circle-shaped STSGs was 12.4 cm² and the median was 12.6 cm². In the circle-shaped STSGs group, the mean percentage of graft shrinkage was 1.1% and the median was 0% [Table 2]. The square-shaped specimens showed primary contraction ranging from 16.0 cm² (0% shrinkage) to 15.8 cm² (1.3% shrinkage). The mean and median area values of the square-shaped STSGs were both 16.0 cm². In the square-shaped STSGs group, the mean percentage of graft shrinkage was 0.31% and the median was 0% [Table 2]. The different shrinkage rates between square- and circle-shaped STSG specimens were not statistically significant ($P = 0.33$).

DISCUSSION

Skin graft contraction is a common problem resulting in significant morbidity with restriction of joint mobility and cosmetic complications, often requiring multiple corrective operations. Secondary contraction has received the most research emphasis due to the fact that it is clinically more important than primary contraction. Secondary contraction often results in severe effects on body function or patient appearance. Studies on the cellular activity underlying skin graft contraction support a most probable theory that the contraction occurs secondary to the differentiation of fibroblasts to myofibroblasts with expression of α -actin filament bundles which exert an inward pull on the wounds edges.^[1,9,10] The myofibroblasts have contractile properties similar to smooth muscle cells and organize their actin cytoskeleton along the lines of greatest skin tension.^[1,11] As the myofibroblasts are adherent both to one another and to the fibronectin-rich wound bed, the entire mass of granulation tissue contracts.^[1] Keratinocytes may also

Table 1: First part of the study: comparison between contraction of FTSGs and STSGs

Skin graft type	Initial area value (cm ²)	Mean area value after primary contraction (cm ²)	Mean percentage of area value of FTSG to the initial area value (%)	Mean percentage of shrinkage (%)	SD	P t-test FTSG versus STSG
FTSG	12.56	11.5	87.96	12.04	0.069	0.0011
STSG	16	14.9	93.13	6.87	0.052	

FTSG: Full thickness skin graft, STSG: Split thickness skin graft, SD: Standard deviation

Table 2: Second part of the study: evaluation of the role of shape of skin graft in primary skin contraction

Skin graft type	Initial area value (cm ²)	Mean area value after primary contraction (cm ²)	Mean percentage of area value of FTSG to the initial area value (%)	Mean percentage of shrinkage (%)	SD	P t-test circle versus square
FTSG						
Circle shaped FTSGs	12.56	11.5	87.96	12.04	0.069	0.0011
Square shaped FTSGs	16	14.9	93.13	6.87	0.052	
STSG						
Circle shaped STSGs	12.56	11.83	94.17	5.83	0.021	0.142
Square shaped STSGs	16	15.34	95.85	4.15	0.016	

FTSG: Full-thickness skin graft, STSG: Split-thickness skin graft, SD: Standard deviation

play a distinct role at the early stages of contraction, since studies have shown that keratinocytes are capable of inducing collagen gel contraction *in vitro*.^[12-15] The actinfilament organization within keratinocytes at the wound margin appears to be responsible for the epidermal “purse-string phenomenon”.^[14] In addition, cytokines and growth factors such as transforming growth factor- β 1, insulin-like growth factor and fibroblast growth factors have also been found to play a major role in secondary contraction.^[15] Unlike secondary contracture, which is the result of a prolonged biological process, primary skin graft contraction is mainly an immediate physical change in graft dimensions mediated by the tough fibrous layer of the dermis, which is primarily composed of collagens, glycosaminoglycans and elastins.

Davis and Kitlowski^[3] were the first to study the primary contraction of skin grafts. The authors used skin grafts from patients of various age and donor sites and recorded the percentage of skin contracture in relation to the thickness of the graft. Their results showed that, regarding the “whole thickness skin grafts” (FTSGs), the mean amount of shrinkage was 43.6% with little variations according to the donor site. The “half thickness skin grafts” (mid thickness split thickness STSGs) were presented with a mean shrinkage of 24.86% and the “thick Ollier-Thiersch grafts” (small grafts with thinner periphery and thicker-centered STSGs) with a mean shrinkage of 11.26% and 11.95% for abdominal and thigh donor sites, respectively. The very thin “true Ollier-Thiersch grafts” (thin thickness STSGs) demonstrated a greatly reduced primary contraction of 1.24%.^[3] According to the authors, the shrinkage observed was in direct relation to the amount of dermis included in the harvested skin grafts. Using specimens from humans, however, had the limitation that the grafts and their donor sites could not be standardized according to the site, size and shape of the examined grafts. Homogeneity of the samples was further compromised due to variables like gender and age of the studied subjects.

Other authors had previously referred to the etiology of skin graft contraction, coming to the conclusion that the network of elastic fibers of the dermis is responsible for its ability to stretch under the movement of the underlying tissues, as well as for the shrinkage of the skin graft.^[16] In Ragnell’s study on the secondary contracting tendency of free skin grafts, the elasticity of circular pieces of rabbit skin was estimated using a manometer device. The author concluded that rabbit skin presented uniform elasticity, but no further studies on primary skin graft contraction were performed.^[16]

Skin is a very complex, integrated, dynamic organ that has many functions. In mammals, the primary functions of the skin include insulation and temperature regulation, although the role of the skin as an endocrine organ and a critical component of the immune system cannot be ignored.^[17] Species differences in all of these functions may dramatically alter skin behavior regarding its mechanical characteristics or drug absorption. When barrier, pelage, vascular, endocrine and immunological properties are considered *en masse*, pigskin is very similar

to human skin.^[17] Pigskin resembles human skin in both structure and function, having similar sparse hair coating, a relatively thick epidermis, similar turnover kinetics, lipid composition, carbohydrate biochemistry, lipid biophysical properties, and – what is most relevant to the present study – a similar arrangement of dermal collagen and elastic fibers.^[9,18] All these similarities establish the pig to be an essential model in cutaneous research. Since *in vivo* experiments on primary skin grafts would require grafts of different shapes, minimum dimensions of 2 or 3 cm, symmetrical locations of the grafts and suitable controls, human experimental material is not available.

In our study, the skin grafts were harvested from pigs, resulting in standardized specimens in terms of size, shape and location of the donor site and at the same time, skin behavior close to that of human skin. The substantial differences between our results and the results reported by Davis and Kitlowski,^[3] however, point out the different primary contraction behavior of human and porcine skin. Although similar in many ways, different thicknesses and possibly different elastic properties between human and porcine skin may lead to different contraction behaviors of skin grafts. Furthermore, the rate of primary skin contraction probably depends on donor site characteristics. Clinical experience shows that skin harvested from the backs of patients presents limited contraction when compared with skin grafts from other sites. Furthermore, there was one specimen from the STSG group of the first part of the study that surprisingly showed 0% shrinkage. Since 0% primary skin contraction before is rather unusual, we believe that this behavior was related to a specific donor site and will be further investigated in upcoming studies. Another possible reason for such a discrepancy in skin graft shrinkage could be technical difficulties: harvesting very thin skin grafts with small amounts of dermis may have been responsible for graft contraction.

The mean percentage of primary skin graft contraction has found to be different in the two parts of the study, with mean values for both FTSG and STSG contraction showing inconsistencies between the study series. These unexpected differences were probably due to the small number of specimens in the second part, which did not yield statistically significant results. Furthermore, the use of only one animal in the second part of the study may have magnified the role of biological variation, a matter that will be further investigated in future larger studies.

To the best of our knowledge, primary skin contraction in relation to the shape of the skin graft has never been investigated before. In our study the mean graft shrinkage was 5.8% and 4.2% in circle-shaped and square-shaped FTSGs, respectively [Table 2]. The difference was more notable in the STSGs, where the circle-shaped specimens showed graft shrinkage of 1.1%, whereas the square-shaped present a mere 0.31% [Table 2]. The difference recorded could be due to the relation of the line of contraction with the skin tension lines. Square specimens have one contraction vector that runs parallel to the direction of the skin tension lines, whereas the round-shaped specimens have multiple contraction

vectors positioned at various angles to the skin tension lines. Theoretically, the projection of the skin tension lines to the radii of the circle-shaped specimens could possibly add to their total graft shrinkage. Due to the small number of specimens, however, further studies should be conducted in order to determine potential statistically significant findings.

Mean percentage of primary contraction for square STSGs was found to be 3.8 times higher than round STSGs (4.2% and 11% for square and circular STSGs, respectively). The recorded difference for the FTSGs, however, is not that prodigious. Since this is only a preliminary report with a small number of specimens involved, we believe that future studies will help to clarify the issue.

Limitations regarding human specimens necessitate the use of animal models; further studies are required in order to investigate whether pigskin is suitable for the study of primary graft contraction. The study cohort is limited and a larger series for all arms is needed for a better understanding of these phenomena.

Skin grafts are widely used and any information regarding their characteristics is valuable. Our preliminary report reveals an expected increased shrinkage of FTSGs compared to STSGs and in a limited number of specimens, the shape of the skin graft seems to affect primary contraction of the STSGs. Although it is difficult to dramatically change the shape of skin grafts, if this feature is ultimately found to alter primary contraction, the results could possibly be applied in clinical practice.

REFERENCES

- Harrison CA, MacNeil S. The mechanism of skin graft contraction: an update on current research and potential future therapies. *Burns* 2008;34:153-63.
- Walden JL, Garcia H, Hawkins H, Crouchet JR, Traber L, Gore DC. Both dermal matrix and epidermis contribute to an inhibition of wound contraction. *Ann Plast Surg* 2000;45:162-6.
- Davis J, Kitlowski E. The immediate contraction of cutaneous grafts and its cause. *Arch Surg* 1931;23:954-65.
- Hinshaw JR, Miller ER. Histology of healing split-thickness, full-thickness autogenous skin grafts and donor sites. *Arch Surg* 1965;91:658-70.
- Corps BV. The effect of graft thickness, donor site and graft bed on graft shrinkage in the hooded rat. *Br J Plast Surg* 1969;22:125-33.
- Jones T, McDonald S, Deitch EA. Effect of graft bed on long-term functional results of extremity skin grafts. *J Burn Care Rehabil* 1988;9:72-4.
- Davies DM. Plastic and reconstructive surgery. Scars, hypertrophic scars, and keloids. *Br Med J (Clin Res Ed)* 1985;290:1056-8.
- Kilkenny C, Browne W, Cuthill IC, Emerson M, Altman DG, NC3Rs Reporting Guidelines Working Group. Animal research: reporting *in vivo* experiments: the ARRIVE guidelines. *Br J Pharmacol* 2010;160:1577-9.
- Tomasek JJ, Haaksma CJ. Fibronectin filaments and actin microfilaments are organized into a fibronexus in Dupuytren's diseased tissue. *Anat Rec* 1991;230:175-82.
- Welch MP, Odland GF, Clark RA. Temporal relationships of F-actin bundle formation, collagen and fibronectin matrix assembly, and fibronectin receptor expression to wound contraction. *J Cell Biol* 1990;110:133-45.
- Petroll WM, Cavanagh HD, Barry P, Andrews P, Jester JV. Quantitative analysis of stress fiber orientation during corneal wound contraction. *J Cell Sci* 1993;104:353-63.
- Denefle JP, Lechaire JP, Zhu QL. Cultured epidermis influences the fibril organization of purified type I collagen gels. *Tissue Cell* 1987;19:469-78.
- Souren JM, Ponc M, van Wijk R. Contraction of collagen by human fibroblasts and keratinocytes. *In Vitro Cell Dev Biol* 1989;25:1039-45.
- Brock J, Midwinter K, Lewis J, Martin P. Healing of incisional wounds in the embryonic chick wing bud: characterization of the actin purse-string and demonstration of a requirement for Rho activation. *J Cell Biol* 1996;135:1097-107.
- Wang YB, Ogawa Y, Kakudo N, Kusumoto K. Survival and wound contraction of full-thickness skin grafts are associated with the degree of tissue edema of the graft bed in immediate excision and early wound excision and grafting in a rabbit model. *J Burn Care Res* 2007;28:182-6.
- Ragnell A. The secondary contracting tendency of free skin grafts; an experimental investigation on animals. *Br J Plast Surg* 1952;5:6-24.
- Monteiro-Riviere NA, Riviere JE. The pig as a model for human skin research. In: Swindle M, Bouchard GF, editors. *Swine in Biomedical Research: Update on Animal Models*. Auxvasse: Sinclair Research Center; 2005. p. 17-22.
- Monteiro-Riviere N. Comparative anatomy, physiology, and biochemistry of mammalian skin. Boca Raton: CRC Press; 1991. p. 3-71.

How to cite this article: Berezovsky AB, Pagkalos VA, Silberstein E, Shoham Y, Rosenberg L, Krieger Y. Primary contraction of skin grafts: a porcine preliminary study. *Plast Aesthet Res* 2015;2:22-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 24-04-2014; **Accepted:** 28-10-2014

Composite augmentation phalloplasty: personal experience after 275 patients

Juan Monreal

Consultant Plastic Surgeon, Hospital Moncloa, Avenida de Valladolid, 83, 28008 Madrid, Spain.

Address for correspondence: Dr. Juan Monreal, Londres, 54-1ºD, Torrejon de Ardoz, 28850 Madrid, Spain. E-mail: juanmonreal@gmail.com

ABSTRACT

Aim: To report the author's experience in augmentation phalloplasty by studying a retrospective series of patients who underwent fat grafting for girth enhancement or a composite technique based on suspensory ligament release plus fat grafting performed simultaneously. **Methods:** The author analyzed retrospectively the outcomes of 275 augmentation phalloplasty procedures performed in 259 patients until November 2013. Of these, 127 correspond to girth augmentation with fat grafting and 148 to composite augmentation phalloplasty (girth augmentation with fat grafting and length improvement by suspensory ligament release). In 16 patients girth and length enhancement were performed in two separate procedures. **Results:** Of this 259 patients, 87 underwent postoperative follow-up for at least 12 months and 160 patients underwent follow-up for at least 6 months. The average increase in circumference at 6 months was 1.7 cm (1.57 cm at 12 months) and the average increase in length of 3.2 cm (3.1 cm at 12 months). Twenty-two patients showed minor complications that were treated without sequelae and without influencing the final result. **Conclusion:** By judicious use of currently available techniques, it is possible to achieve stable increases in penis size. The use of composite techniques provides better final results than the use of individual techniques performed alone due to the increase of the actual volume of the penis. An adequate informed consent is essential in all patients due to the unrealistic expectations expressed by the majority of them.

Key words:

Adipose tissue, fat grafting, lipofilling, penis augmentation

INTRODUCTION

One of the traditional benefits that aesthetic surgery offers to patients is the improvement in self-esteem. The appearance of the external genitalia, both male and female, can have similar degrees of influence on social relationships and may cause a concern similar to that generated by a lipodystrophy or a nose with inadequate proportions. Given the unrealistic expectations (sometimes fanciful) that these patients tend to assume about the anticipated results, it is essential to properly and thoroughly inform patients about treatment characteristics,

limitations, and what results they can expect. Although a large number of patients who are interested in genital aesthetic surgery request a consult for purely aesthetic motivation, as in other domains of aesthetic surgery, there are many in which a functional defect coexists with the aesthetic burden that can worsen patient experience in sexual or social relationships.

Generally speaking, aesthetic surgery of male genitalia is focused on increasing penis measures in both length and girth. There are, however, ancillary techniques that work to improve the "visual" size of the penis and scrotum. At the present time, there is only one technique capable of increasing girth in erection but none (at least known to the author) capable of increasing dynamically the length in erection. Therefore, currently, existing techniques are able to increase the girth in erection or flaccidity but not both. There are surgical techniques that increase the length in the flaccid state, but no reports known to the author that describe increasing the length of the penis in erection. For these reasons the enhancement of the penis size is better achieved by performing several surgical techniques

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.149374

simultaneously or in stages. If it is assumed that the penis is a cylindrical body, a more successful outcome should seek to increase the entire volume (diameter and length) than only one of the dimensions [Figure 1]. There is only one exception to this approach which is the treatment of a buried or partially buried penis. In this case, given the importance of adequate pubic skin redraping and marking the new peneopubic angle, the author recommends girth enhancement in a second staged step.

An important factor that is difficult to standardize is the measurement of penile length and girth in flaccidity and erection. Several ways to do this are postulated, with the main objective of obtaining an accurate estimate of the increase in these measures in postoperative follow-up for comparative purposes. As a general rule the established mean normal values of flaccid length are between 7.2 cm and 11.0 cm measured from the peneopubic angle to the tip of the glans, with an average of 9.5 cm. A normal girth will vary between 7.7 cm and 12.0 cm, with an average of 9.56 cm.^[1] It is extremely important that the surgeon standardize the method for taking these measurements to maintain consistency in daily practice.

The author presents his experience in a retrospective study of 275 augmentation phalloplasty procedures. The final analysis focuses on the main increase in penis measurements (girth and length) in the flaccid state and the stability of improvement over time.

METHODS

The author analyzed retrospectively the outcomes of 275 augmentation phalloplasty procedures performed in 259 patients. The main motivation for all patients was to achieve greater penis size without the development of any form of impotence or sexual dysfunction. Mean preoperative penis dimensions in the flaccid state were 8.9 cm in girth (range, 6.5-10.2 cm) and 9.2 cm in length (range, 7.4-12.2 cm). Of the 275 procedures, 127 underwent girth enhancements with fat grafting and 148 were undertaken for composite phalloplasties (girth enhancement with fat grafting and length improvement by suspensory ligament release). In 16 patients, these procedures were performed in two surgical stages, not < 6 months apart. All patients

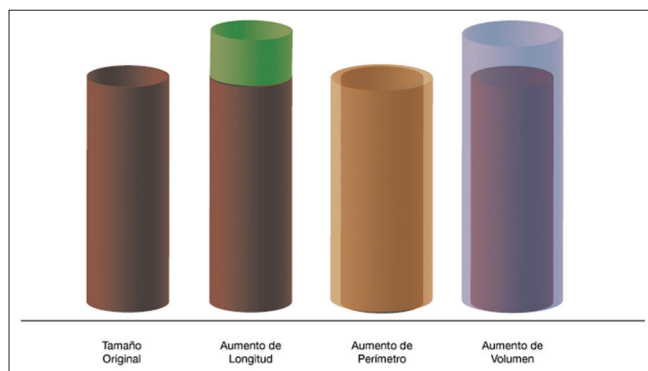


Figure 1: The penis can be approximated to a cylinder, and thus, enhancement of girth and length at the same time improves real volume. From left to right: original size, length improvement, girth improvement, both simultaneously

signed the corresponding informed consent. The age of patients ranged from 23 to 57 years with a mean age of 38 years. All cases of girth enhancement with fat grafts were performed under local anesthesia with sedation on an ambulatory basis; composite phalloplasty were performed under spinal anesthesia on an ambulatory basis as well. All pre and postoperative measures and pictures were taken in forced flaccidity (applying a light traction on the penis for about 3 s). Postoperative measurements were scheduled on the day after the operative procedure and again at 1, 4, 6, and 12 months postoperatively.

Girth enhancement with fat grafting

The technique of fat grafting used in this series has been published previously.^[2,3] Briefly, lipoaspirate is harvested with a 20-hole 3 mm cannula (Quirumat, Spain). The lipoaspirate is washed with Ringer's lactate, and layer separation is obtained by decanting for about 30 min. Once processed, the washed fat is injected under the dartos and Buck's fascia. The engrafting process must be performed with extreme caution, placing fat fragments of no > 3 mm in diameter to ensure a proper take and prevent necrosis and cyst formation. Whether girth enhancement is performed alone or in combination with suspensory ligament release, the infiltration cannula is advanced from the peneo-pubic angle towards the preputial skin or circumcision scar. The fat is injected in a retrograde fashion and distributed all around the girth; this is tailored to the needs of each patient, from the peneo-pubic angle to the coronal sulcus scar (if the patient is circumcised) or to the foreskin proper (if he is not circumcised). The distribution of fat is particularly important in the penis foreskin to prevent unaesthetic nodules or bulges or the presence of an offset devoid of fat when the patient removes the foreskin. This technique can be performed alone (127 + 16 cases in our series) or preferably at the same time as the suspensory ligament release (148 patients in our series).

The behavior of fat grafted to the penis is mostly the same as when performed in other body areas. Although postoperative swelling usually takes about 6 weeks to disappear, the volume loss in the grafts should stabilize by 3-4 months; at this timepoint the improvement in girth must be stable.

Composite augmentation phalloplasty

Figures 2 and 3 summarize the sequence of steps performed during suspensory ligament release as done in

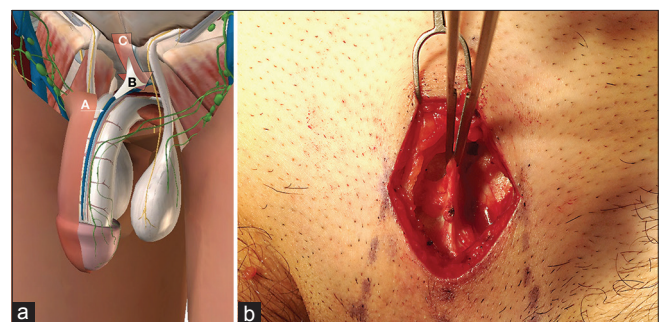


Figure 2: (a) Anatomy of the suspensory ligament: (A) deep neurovascular bundle; (B) suspensory ligament; (C) surgical approach. (b) Pick-ups are shown grasping the most caudal and superficial aspect of the ligament

the current series. Although composite phalloplasty can be performed under local anesthesia and sedation, the author prefers spinal anesthesia that adds little morbidity and enhances patient comfort. The procedure begins with a 3.5 cm incision located about 2.5-3.0 cm cranial to the peno-pubic angle. The first step is to perform the dissection and release of the fascial and fasciocutaneous attachments. The dissection then proceeds down to the front edge of the suspensory ligament. Thus, the release must be performed directly from the attachments to the symphyseal ligament to avoid accidental damage to deep penile neurovascular structures. The release is then carried further down, stopping at the start of the pelvic floor. The author usually does not release bone attachments except in cases of micropenis. After the ligament release is complete, corpora cavernosa will move easily forward and downward, creating a dead space between these structures and the pubic bone; This dead space must be filled with local tissues; the availability of these tissues can be extremely variable depending on the body mass index of the patient. In slim patients it is usually necessary to take the fat that surrounds the spermatic cords. When there is enough pubic fat, adipofascial flaps can be tailored and turned down as described by Hinderer and Espinosa.^[4] Available tissues are interposed inside the dead space created by the ligament release while simultaneously pulling on the penis and checking on the stability of the repair.

Upon completion of these steps, a skin gap can be observed and that is caused by penis advancement. Although a variety

of skin plasties can be planned in advance and performed at the beginning of the procedure, the author prefers to do this once the penis advancement has been completed, to modify for each situation. Treatment of the skin gap begins by closing the defect in a horizontal fashion [Figure 4]. This closure produces two dog ears that will provide the final measure of skin advancement. The distal dog ear is tailored to provide a Y or T advancement. The proximal dog ear is usually smaller and can be managed by defatting and direct closure; in about 2-3 months it will flat tenon on its own. Performed correctly, closure of the skin by an advancement plasty stabilizes and maintains the improvement in length [Figure 5]. It must be kept in mind that an overly ambitious cutaneous advancement usually results in the incorporation of hairy skin and some scrotalization of the penis shaft which worsens the aesthetic result. Before epidermal closure, the author inserts a vacuum drain and then proceeds to girth augmentation with fat grafting as previously described. All sutures used including epidermal closure can be performed with 4/0 absorbable monofilament.

As a rule composite augmentation phalloplasty can be performed on an outpatient basis. The drain is removed after 24 h and antibiotics are continued for 3 days. After

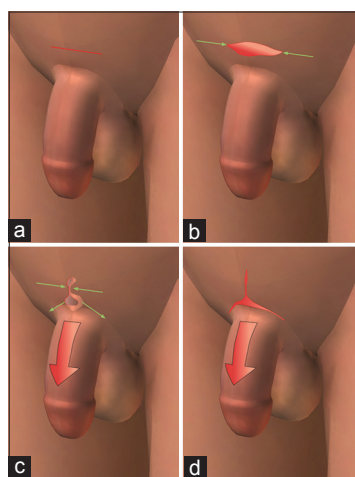


Figure 3: Sequence of suspensory ligament release as performed by the author. (a) Transverse incision; (b) symphysis approach and complete release; (c) transverse closure, advancement and dog ears; (d) dog ear treatment

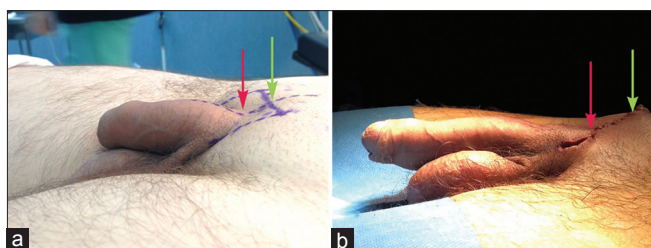


Figure 5: Intraoperative views (a) before and (b) after completion of composite augmentation phalloplasty. Green arrows depict initial incision location. Red arrows mark penopubic angle

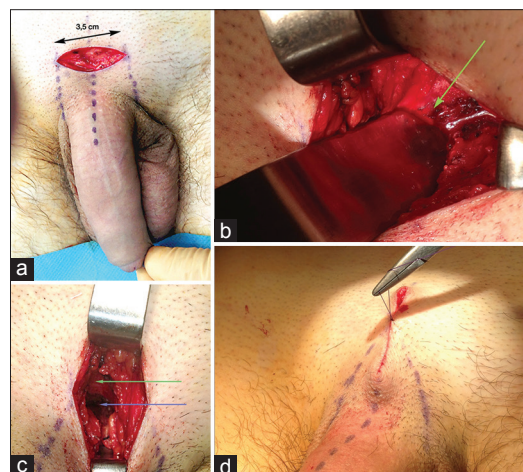


Figure 4: Sequence of suspensory ligament release as performed by the author. (a) Transverse incision; (b) symphysis approach; (c) complete release (green arrow: pubis, blue arrow: urogenital diaphragm); (d) transverse initial closure



Figure 6: Original model of traction system (JES extender). Today all brands look the same as the original

15 days, patients can start using the traction system if previously circumcised. In noncircumcised patients traction must be delayed until foreskin swelling has disappeared. The author recommends the use of an extender [Figure 6] because it ensures control over initial scar maturation and helps to prevent ligament reattachment. In addition, when used correctly, additional length is added to that offered by the surgical procedure. All patients are encouraged to maintain sexual abstinence during the 1st month postoperatively.

RESULTS

Of the 259 patients who underwent surgery, 160 provided a 6 months follow-up and 87 completed 12 months of follow-up. In 99 patients follow-up was < 6 months. The average increase in girth was 1.7 cm at 6 months and 1.6 cm at 12 months and the mean increase in length was 3.1 cm and 3.2 cm at 6 and 12 months, respectively. In 22 patients (8% of the series) the author detected minor complications that were treated without sequelae and without influencing the final result. No patient reported functional problems or difficulty in sexual activity after the second postoperative month. Postoperative length gain did not change during the first 6 months of follow-up. Patients who used the extender for at least 3 months after surgery achieved modest additional increases in length, which did not exceed 1.3 cm. The author was not able to properly analyze the increase in erection measurements due to lack of data. Figures 7-9 represent average results of composite augmentation phalloplasty. Figures 10 and 11 represent average results of penis girth enhancement with fat grafting.

Minor complications encountered after phalloplasty were combined infection: marginal wound dehiscence (3 cases, 2%), the development of small seromas that required aspiration (5 cases, 3.4%, especially when performing the suprapubic adipofascial flap), liponecrotic cysts that were resectable secondarily (4 cases, 2.7% in the first 4 years of experience). There were no incidents of keloid scar formation, however, in 5 cases the final scar was considered hypertrophic. The author currently recommends placement of silicone sheets or gels as part of the postoperative care. The use of a postoperative traction system is not mandatory but helps to minimize the chances of abnormal scarring and to gain extra length. Lack of compliance with the extender device or the presence of erosion caused by the pulling ring is a common cause for abandoning the use of postoperative traction. The author did not encounter any cases of postoperative paradoxical shortening.

Regarding girth enhancement performed as a stand-alone procedure, the complications were liponecrotic cysts in 7% of patients (9 cases in the first 5 years of experience), 1 case of postoperative infection that needed a complete antibiotic course (0.8%), and 1 case of fat overgrowth due to extreme weight gain (0.8%) [Figure 12]. Lack of abstinence, especially during the first 2 weeks, can certainly cause the loss of grafted fat to some degree, so the patient should be warned about this.

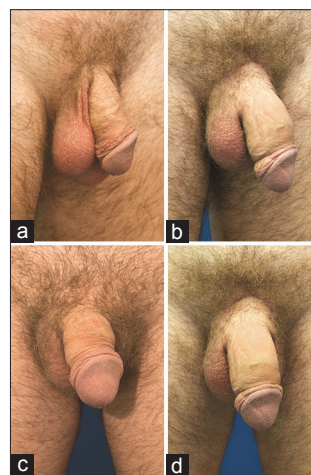


Figure 7: Case 1. preoperative and 11 months postoperative views of composite augmentation phalloplasty (40 mL of fat). (a and c) Preoperative; (b and d) 11 months postoperative



Figure 8: Case 2. preoperative and 16 months postoperative views of composite augmentation phalloplasty (55 mL of fat). (a and c) Preoperative; (b and d) 16 months postoperative



Figure 9: Case 3. preoperative and 12 months postoperative views of composite augmentation phalloplasty (65 mL of fat). (a and c) Preoperative; (b and d) 12 months postoperative

DISCUSSION

Standard measurement of the penis has been a controversial issue and a subject of discussion

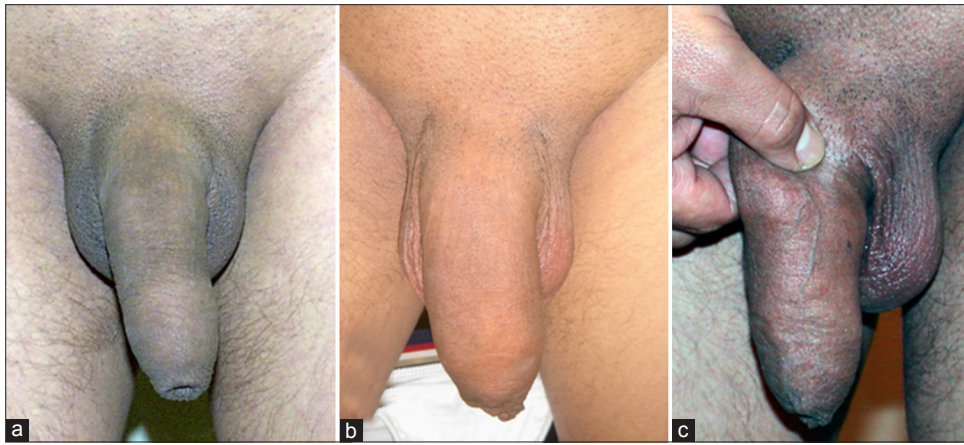


Figure 10: Case 4. preoperative and 3 years postoperative view of girth enhancement with fat grafting in two sessions (30 + 40 mL). (a) Preoperative; (b) 3 years postoperative; (c) pinch of implanted fat

for a long time. The racial controversy introduces more variables, which can influence decisions about justifying augmentation phalloplasty.^[5,6] The enhancement of penis size can be achieved using surgical or nonsurgical procedures. Unfortunately the uses of unproven techniques or synthetic fillers have made these treatments notorious for their sequelae or bad results.^[7] Nonsurgical techniques that use traction by weights have been employed by many cultures over the centuries and are based on cultural, religious or aesthetic purposes.^[8,9] The modern age of these treatments began at the end of the 1990's with the JES Extender device. These techniques exploit the ability of tissues to respond to physical stimuli as traction or expansion with hyperplasia and cell division, a well-known behavior used by plastic surgeons worldwide.

As in any medical or surgical procedure using expansion or distraction, while using a penis extender a pulling force of a certain intensity must be applied and must be as continuous as possible and for a minimum time period and hence that the biological phenomena responsible for tissue modification are started. The use of these devices often requires a great deal of diligences on the part of patients to get results that are minimally satisfactory. Erosions are sometimes produced by traction ring or by irregular use of the device and are some of the factors that negatively affect the results, which may be minimal. In any case, an adequate knowledge about the management of these devices must be present in the armamentarium of the surgeon performing phalloplasties, since it can be an extremely useful complement to the surgical procedure to secure, maintain and/or improve the outcome. The author always uses traction as an adjunct to surgical treatment and never as a stand-alone treatment.

As in the case of surgical lengthening, there is not a single surgical solution to increase the thickness or perimeter of the penis.^[10,11] Pericavernous techniques provide girth augmentation in flaccid penises but little or no improvement in erection. These techniques try to obtain an increase in girth by implanting some of the

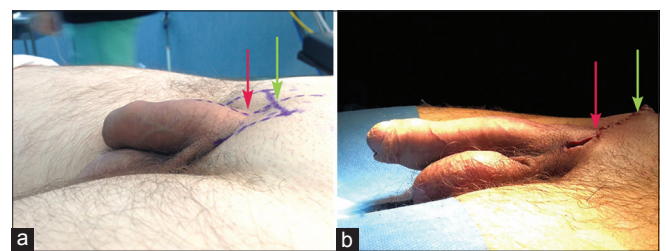


Figure 11: Case 5. preoperative and 9 months postoperative view of girth enhancement with fat grafting (35 mL of fat). (a) Preoperative; (b) 9 months postoperative

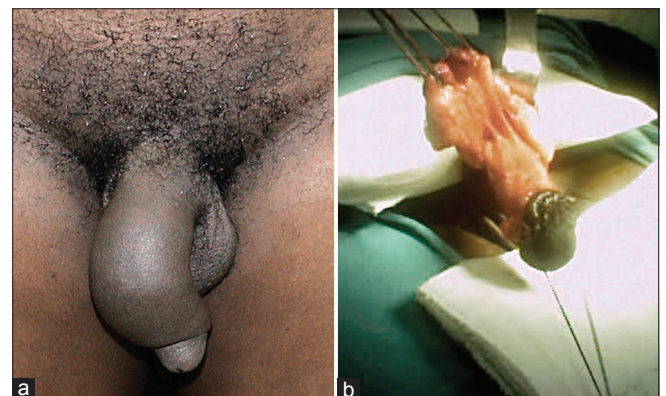


Figure 12: (a) Preoperative view of fat graft overgrowth due to 26 kg of weight gain 4 years after girth augmentation; (b) intraoperative view of complete lipectomy

available grafts (fat or dermofat grafts) or biological implants (acellular dermis) around the penis shaft outside the albuginea and under the dartos fascia. More advanced techniques using resorbable matrices together with autologous fibroblasts have also been described with good results.^[12,13] Albuginea techniques get good results in erection but none in flaccidity.^[14] The injection of synthetic fillers is probably one of the options that are frequently performed, but may cause many deformities and complications. All of these techniques are more invasive and thus can yield a greater number and severity of complications. Fat grafting is probably the least aggressive technique but requires fine control and technique to avoid complications and poor results. It was introduced as a technique for girth enhancement

in the mid-1980's and continues to be used due of its versatility.

Traction treatments are the only ones able to achieve effective length improvements of the penis, producing an increase in actual tissue mass and at the same time "softening" the corpora cavernosa fascial and osseous attachments. The combined use of both types of treatments (suspensory ligament release and extender use) can produce the best outcome by extending the "hidden" part of the penis with generation of additional tissue. All penis lengthening techniques are based on the release of natural physiologic anchors that bind the corpora cavernosa to the pubic symphysis, ischiopubic bone branches, and abdominal aponeurotic expansions. Although this lengthening can be performed through a simple transverse incision or even using an endoscope (not published), a number of ancillary skin advancements can be performed to ease ligament release and to procure advancement and stabilization, and thus prevent length loss due to scar contracture. In this regard several techniques have been published such as M-plasty (popularized in China and reported by Reed^[15]), VY advancement (Roos and Lissos^[16]), Z-plasty (Horton^[17]), double Z-plasty (Alter^[18,19]) and personal techniques of Abecassis^[20] and Panfilov.^[21] Although the author supports the use of local tissues to fill the advancement gap to additionally maintain advancement, some authors have published their experience inserting small testicular prostheses as spacers with no better results.^[22]

In our practice performing suspensory ligament release, skin flap advancement together with simultaneous girth enlargement using fat grafts is the most satisfactory approach to increase penis size. This composite technique generates real volume increase which results in a better perceptual outcome for the patient. Additionally, the increase in shaft convexity and downward position creates the illusion of a longer penis as well. The incidence of complications or side effects is relatively low and easy to solve without affecting final results. A thorough knowledge of regional anatomy helps to prevent serious or minor complications. There are two good safety rules: perform the ligament release as close to the bone as possible and do not perform any grafting that may exceed the capacity of the tissue. Although liponecrotic cyst occurrence can be solved easily, damage to the deep penile neurovascular structures usually has disastrous consequences. Patient satisfaction after augmentation phalloplasty is lower when compared with other popular aesthetic surgical procedures. In our series, only 32% perceived the result as very good and an additional 43% as good, in spite of being clearly informed about the limitations and outcomes for other patients and follow-up demonstration of improved average measurements. As with any other aesthetic surgery procedure, informing the patient is extremely important in achieving an adequate degree of satisfaction. Two relatively distinct patient groups exists: those who present with a real hypoplasia and those cases of body dysmorphic disorder. The former tend to show higher degrees of satisfaction and understand easily the

limitations of the techniques. Patients with unrealistic expectations that do not understand this information must be discouraged from the procedure because the level of disappointment will likely be very high. It is extremely important not to assure the patient that any type of result will be an improvement; patients should understand that it is possible to see no improvement, an event caused usually by an inadequate scar contraction.

Composite augmentation phalloplasty techniques are safe and reproducible and yield satisfactory results if properly performed. Although apparently easy to perform, a thorough knowledge of anatomy and grafting techniques is needed to get good results and avoid complications. Volumetric enhancement by ligament release and cutaneous advancement together with an increase in girth with fat grafting is probably a safer option, with better results and lower morbidity. The future of penis enlargement will be enhanced with techniques that provide dynamic improvements in size, possibly through the use of tissue engineering.

REFERENCES

1. Mondaini N, Ponchietti R, Gontero P, Muir GH, Natali A, Caldarera E, Di Loro F, Biscioni S, Rizzo M. Penile length is normal in most men seeking penile lengthening procedures. *Int J Impot Res* 2002;14:283-6.
2. Monreal J. Fat tissue as a permanent implant: new instruments and refinements. *Aesthet Surg J* 2003;23:213-6.
3. Monreal J. Male and female genital aesthetic surgery: basic techniques and concepts. *AECEP* 2006;1:8-17.
4. Hinderer UT, Espinosa JF. New enlargement technique with volume enhancement in penis hypoplasia and hypospadias. *Cir Plast Iberoamer* 1997;23:151-60.
5. Dillon BE, Chama NB, Honig SC. Penile size and penile enlargement surgery: a review. *Int J Impot Res* 2008;20:519-29.
6. Ghanem H, Gline S, Assalian P, Buvat J. Position paper: management of men complaining of a small penis despite an actually normal size. *J Sex Med* 2013;10:294-303.
7. Parodi PC, Dominici M, Moro U. Penis invalidating cicatricial outcomes in an enlargement phalloplasty case with polyacrylamide gel (Formacryl). *Int J Impot Res* 2006;18:318-21.
8. Oderda M, Gontero P. Non-invasive methods of penile lengthening: fact or fiction? *BJU Int* 2011;107:1278-82.
9. Colpi GM, Martini P, Scroppo FI, Macini M, Castiglioni F. Efficacy of daily penis-stretching technique to elongate the "small penis". *Int J Impot Res* 2002;14:155.
10. Shaeer O, Shaeer K. Penile girth augmentation using flaps "Shaeer's augmentation phalloplasty": a case report. *J Sex Med* 2006;3:164-9.
11. Alei G, Letizia P, Ricottilli F, Simone P, Alei L, Massoni F, Ricci S. Original technique for penile girth augmentation through porcine dermal acellular grafts: results in a 69-patient series. *J Sex Med* 2012;9:1945-53.
12. Jin Z, Wu YG, Yuan YM, Peng J, Gong YQ, Li GY, Song WD, Cui WS, He XY, Xin ZC. Tissue engineering penoplasty with biodegradable scaffold Maxpol-T cogenerated autologous fibroblasts for small penis syndrome. *J Androl* 2011;32:491-5.
13. Perovic SV, Byun JS, Scheplev P, Djordjevic ML, Kim JH, Bubanj T. New perspectives of penile enhancement surgery: tissue engineering with biodegradable scaffolds. *Eur Urol* 2006;49:139-47.
14. Austoni E, Guarneri A, Cazzaniga A. A new technique for augmentation phalloplasty: albuginea surgery with bilateral saphenous grafts -three years of experience. *Eur Urol* 2002;42:245-53.
15. Reed HM. Augmentation phalloplasty with girth enhancement employing autologous fat transplantation: a preliminary report. *Am J Cosmet Surg* 1994;11:85-9.
16. Roos H, Lissos I. Penis lengthening. *Int J Aesthetic Restorative Surg* 1994;2:89-96.
17. Horton CE, Vorstman B, Teasley D, Winslow B. Hidden penis release: adjunctive suprapubic lipectomy. *Ann Plast Surg* 1987;19:131-4.
18. Alter GJ, Salgado CJ, Chim H. Aesthetic surgery of the male genitalia. *Semin Plast Surg* 2011;25:189-95.

19. Alter GJ. Augmentation phalloplasty. *Urol Clin North Am* 1995;22:887-902.
20. Abecassis M, Berreby S, Boccara D. Penis enlargement surgery: lipopeneosculpture for length and girth enhancement. *Ann Chir Plast Esthet* 2010;55:135-42.
21. Panfilov DE. Augmentative phalloplasty. *Aesthetic Plast Surg* 2006;30:183-97.
22. Li CY, Kayes O, Kell PD, Christopher N, Minhas S, Ralph DJ. Penile suspensory ligament division for penile augmentation: indications and results. *Eur Urol* 2006;49:729-33.

How to cite this article: Monreal J. Composite augmentation phalloplasty: personal experience after 275 patients. *Plast Aesthet Res* 2015;2:27-33.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 19-09-2014; **Accepted:** 23-10-2014

Preliminary stages before nasal reconstruction using forehead flap: restoring perinasal subunits and nostril patency

Victor Diniz de Pochat¹, Fernando César Câmara de Oliveira¹, Felipe Simões da Rocha Mata¹, Marcelo Sacramento Cunha¹, Nivaldo Alonso², José Valber Lima Meneses¹

¹Division of Plastic Surgery, Federal University of Bahia, Salvador, Bahia 40110, Brazil.

²Division of Plastic Surgery, University of São Paulo, São Paulo 14040, Brazil.

Address for correspondence: Dr. Victor Diniz de Pochat, Division of Plastic Surgery, University Hospital Professor Edgard Santos, Federal University of Bahia, Salvador, Bahia 40110, Brazil. E-mail: victor.pochat@gmail.com

ABSTRACT

Due to the complex three-dimensional structure of the nose, the repair of the nasal defect requires reconstruction of three different layers: skin envelope, osteocartilaginous framework and nasal lining. Before nasal reconstruction can be accomplished, the nose must rest on a stable platform to avoid late nasal obstructions, and septal deviations resulting from scar contraction. We present three cases of nasal reconstruction using a forehead flap in which we performed a preliminary stage to increase reliability of outcomes.

Key words:

Forehead flap, nasal reconstruction, nostril stenosis, preliminary stages

INTRODUCTION

Reconstruction of the nose is complex, due to its three dimensionality, and its prominence in the central facial region.^[1,2] Full thickness nasal defects require repair of three different layers: skin envelope, osteocartilaginous framework and nasal lining. The latter one is considered the most challenging.^[3,4]

Often, nasal defects extend into adjacent regions of the face such as the lips and cheeks, increasing the complexity of wound reconstruction. One can choose to simply “fill the hole”; however, when planning nasal reconstruction, the surgeon should be aware that the defect may not reflect the actual tissue loss. Swelling, infiltration of anesthesia, the action of gravity on tissues and scar retraction may alter the dimensions of the defect; and

therefore, may not reflect the true defect at the time of presentation.^[5]

The nose rests on a platform consisting of the premaxilla and the piriform aperture surrounded by the adjacent soft tissues (upper lip and cheek) with a well-defined angle and location. Improper positioning of nasal structures, even for a few millimeters can generate significant distortions. If such a platform is unstable, it can displace the reconstructed alar region inferiorly or laterally over time. Preliminary procedures, such as the repair of the lip and cheek defects using local flaps and skin grafts flap are usually necessary to prevent distortions and scar contracture of the adjacent nose before nasal reconstruction.^[6,7]

There is limited information about preliminary stages before paramedian forehead flap discussed in the literature. The aim of this study is to demonstrate the experience of the Rhinology team of the Plastic Surgery Department (HUPES-UFBA) using a preliminary stage to stabilize the nasal platform before nasal reconstruction using the paramedian forehead flap.

Between May 2011 and May 2013, the department of Plastic Surgery, HUPES-UFBA, performed 12 nasal reconstruction surgeries that required paramedian

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.149377

forehead flaps. Of these, 3 patients required preliminary procedures to stabilize the nasal platform.

The selected cases were reported, highlighting the indication and the technique used in the reconstruction in the donor area of the flap as well as in the nasal and perinasal region. The patients involved in this article agreed to publish their facial pictures and signed the consent form.

CASE REPORT

Case 1

A 29-year-old man presented with a nasal deformity caused by paracoccidioidomycosis, which affected the right ala leading to the nostril stenosis. In a preliminary stage, the right nostril was opened with a Z-plasty and skin grafting was performed [Figure 1]. After 4 months, he underwent resection of the scarred area to construct the original defect using a three stage paramedian folded forehead flaps to resurface the lining and nasal subunits [Figure 2]. The cartilaginous support was achieved by a conchal cartilage graft performed in the second stage.



Figure 1: Case 1. Right ala destruction and nostril stenosis. (a) Frontal view, (b) oblique view, (c) preoperative landmark of aesthetic subunits, (d) immediate postoperative correction of the stenosis with Z-plasty and skin grafting

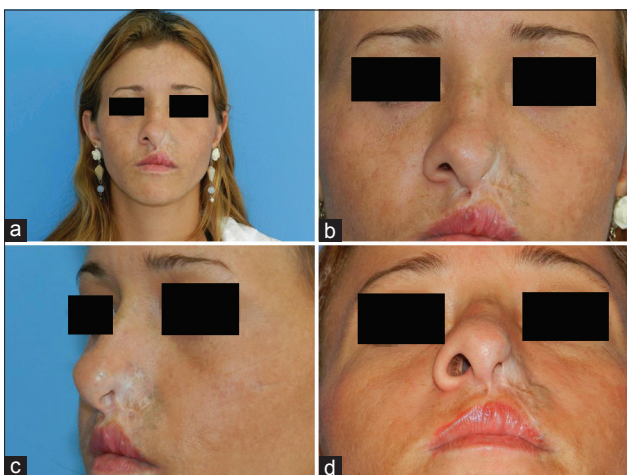


Figure 3: Case 2. Preoperative: (a) frontal view, (b) close up of frontal view showing upper lip retraction and deformity of left ala, (c) oblique view, (d) basal view

Case 2

A 26-year-old female, presented with a total loss of the left ala and upper lip retraction after a motorcycle accident 4 years prior [Figure 3]. A preliminary stage was indicated, and a Z-plasty with a full thickness skin graft was performed in order to fill the resulting gap. Furthermore, a nostril enlargement was performed using local flaps, and a tissue expander was placed in the forehead [Figure 4]. After 3 months, the expander was removed, and a paramedian forehead flap was transferred in two stages [Figure 5]. In addition, part of the left nostril scar was used as a hinge-over flap to resurface the missing nasal lining. The cartilaginous framework was rebuilt using a conchal graft.

Case 3

A 26-year-old man was referred to our department after an unsuccessful attempt at nasal reconstruction using a nasolabial flap. He sustained a gunshot trauma 8 years prior to presentation. In the preliminary stage, a costal cartilage graft was used for nasal dorsum augmentation. An advanced V-Y nasolabial flap was performed using the previous scar to fill the nasal base lining and a full thickness skin graft was placed to resurface nasal lining and unblock the left nostril. Three months later a three stage folded paramedian forehead flap was performed. In this case, a new forehead flap was required to allow better projection and support for the tip and resurfacing the columella [Figure 6].

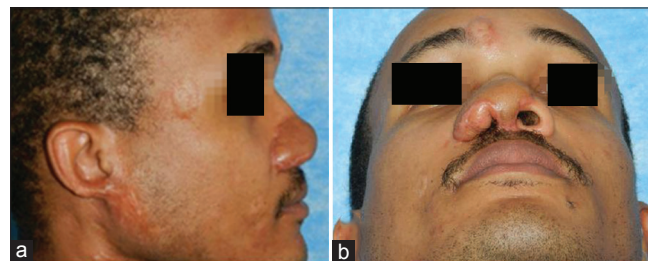


Figure 2: Case 1. One-month after the three-stage forehead flap. (a) Oblique view, (b) basal view



Figure 4: Case 2. Postoperative view after a preliminary stage including expansion of the forehead, correction of retraction of the upper lip and left nostril opening. (a) Frontal view, (b) lateral view, (c) oblique view, (d) frontal view with the landmarks



Figure 5: Case 2. Postoperative (4 months) after the expanded forehead flaps in two stages. (a) Frontal view, (b) oblique view, (c) lateral view, (d) base view

DISCUSSION

Scar contraction is a natural phenomenon in the healing process and is often not considered when planning surgical reconstruction. It is undesirable in nasal reconstruction, because minor flaws in preoperative plan can produce large distortions. The nose rests on a platform comprised of the premaxilla and the piriform aperture surrounded by the upper lip and cheek. This platform needs to be stable before planning a nasal reconstruction. In case 2, the lip position was corrected by releasing the retraction through a Z-plasty and skin grafting in the first stage. The forehead skin is the best donor site for nasal reconstruction because its color and texture are similar to the skin of the nose. It can be used for skin cover and lining repair.^[8-11] The donor site is only partially closed after the flap transfer, and it is allowed to heal by secondary intention.

In addition, after preliminary reconstruction of affected areas, tissue expanders can be used in the donor site before nasal reconstruction using forehead flap. Some authors suggested the use of expanders in the forehead to improve scarring in the donor area and to provide large surface area to cover large defects.^[9] In our department, scar improvement is not an indication for a saline expander. In patients with shortened vertical forehead height, the inclusion of scalp skin in the flap is not recommended due to the difference of texture and color of the nasal skin.^[10] In such cases, we consider the use of expanders as a primary indication prior to forehead flap. The expanded flap has the advantage of decreased thickness that allows accurate reconstruction in two stages. Thus, the three stages reconstruction is restricted to more complex cases that require lining repair.

The airway patency is restored by excising the scar tissue and releasing retraction. Remaining excess tissue can be used as a flap to increase the nasal lining or to open the airway instead of being discarded. The nose should be rebuilt in a late stage following the principle



Figure 6: Case 3. Preoperative. (a) Frontal view, (c) lateral view. Postoperative (8 months) after the last procedure (three-stage forehead flap). (b) frontal view, (d) lateral view

of the subunits when the adjacent soft tissue structures are stable. In preliminary stages, scar tissue should be thoroughly evaluated in order to recreate the defect and be used as local flaps for lining repair (hinge-over flaps or V-Y flaps) or to widen the nostril (Z-plasty and skin grafts) as performed in cases 1 and 2.

Restoration of nasal lining requires replacement of a well-vascularized, thin and supple tissue that supports cartilage grafts. It should provide an ideal shape while preventing nasal stenosis. Nasal lining can be reconstructed by advancing the residual lining, hinge-over lining flaps, and skin grafts. Lining can also be replaced by intranasal lining flaps, folded forehead flaps, nasolabial flaps, prefabricated forehead flaps and free flaps.

Any procedure performed on the nose produces the fibrosis that makes any subsequent manipulation difficult. In our study, the nostril expansion was performed in a preliminary because after a two or three stage forehead flap, one will find more fibrosis (mainly after muscle excision) that would render the thinning the alar margins more difficult and may decrease reliability of the vascularization of the small local flaps. Menick^[5] suggested using templates based on the contralateral normal ala. Thus, the adjacent nostril floor must be re-established and stabilized prior to nasal reconstruction.

In conclusion, correction of perinasal defects and the nostril stenosis should be performed as a preliminary stage to allow stabilization of the healing process. Any scar resection must be well-planned, since this tissue may be useful as hinge-over flaps for lining or as local flap for nasal stenosis correction.

REFERENCES

1. Taghinia AH, Pribaz JJ. Complex nasal reconstruction. *Plast Reconstr Surg* 2008;121:e15-27.
2. de Pochat VD, Alonso N, Figueredo A, Ribeiro EB, Mendes RR, Meneses JV. The role of septal cartilage in rhinoplasty: cadaveric analysis and assessment of graft selection. *Aesthet Surg J* 2011;31:891-6.
3. Murakami CS, Kriet JD, Ierokomos AP. Nasal reconstruction using the inferior turbinate mucosal flap. *Arch Facial Plast Surg* 1999;1:97-100.

4. Sedwick JD, Graham V, Tolan CJ, Sykes JM, Terkonda RP. The full-thickness forehead flap for complex nasal defects: a preliminary study. *Otolaryngol Head Neck Surg* 2005;132:381-6.
5. Menick FJ. Defects of the nose, lip, and cheek: rebuilding the composite defect. *Plast Reconstr Surg* 2007;120:887-98.
6. Menick FJ. Nasal reconstruction. *Plast Reconstr Surg* 2010;125:e138-50.
7. Menick FJ. Practical details of nasal reconstruction. *Plast Reconstr Surg* 2013;131:e613-30.
8. Alagöz MS, Isken T, Sen C, Onyedi M, Izmirli H, Yücel E. Three dimensional nasal reconstruction using a prefabricated forehead flap: case report. *Aesthetic Plast Surg* 2008;32:166-71.
9. Menick FJ. A 10-year experience in nasal reconstruction with the three-stage forehead flap. *Plast Reconstr Surg* 2002;109:1839-55.
10. Weng R, Li Q, Gu B, Liu K, Shen G, Xie F. Extended forehead skin expansion and single-stage nasal subunit plasty for nasal reconstruction. *Plast Reconstr Surg* 2010;125:1119-28.
11. Wang ZG, Chen XJ, Chen ZY. A modified bilobed flap design for nasal tip defects. *Plast Aesthetic Res* 2014;1:16-20.

How to cite this article: de Pochat VD, de Oliveira FCC, da Rocha Mata FS, Cunha MS, Alonso N, Meneses JVL. Preliminary stages before nasal reconstruction using forehead flap: restoring perinasal subunits and nostril patency. *Plast Aesthet Res* 2015;2:34-7.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 21-07-2014; **Accepted:** 08-10-2014

Primary repair of ear laceration with wedge resection

Bhupinder Singla, Inderjit Chawla, Prasant Gautam, Anupam Goyal, Jalaj Rath

Department of General Surgery, Rajindra Hospital, Patiala 147001, Punjab, India.

Address for correspondence: Dr. Bhupinder Singla, Department of General Surgery, Government Medical College, Samana Road, Patiala 147001, Punjab, India. E-mail: akash22singla@yahoo.com

ABSTRACT

Although major contributions have been made in the field of reconstructive surgery, reconstructive surgery of the auricle is a daunting prospect even for the most experienced surgeons. Here, we present a case who presented to us in the emergency surgical ward with a history of an accidental laceration of right ear. Primary repair of the ear laceration after wedge resection of the avulsed part was done. The cosmesis achieved by this technique is discussed.

Key words:

Ear laceration, primary repair, wedge resection

INTRODUCTION

Ear laceration is one of the common auricular injuries among traumatic injuries. The type of reconstruction selected for the lacerated ear depends on the size of the defect and the amount of cosmesis expected by the procedure. It ranges from the wedge resection and direct advancement to reconstruction with chondrocutaneous flaps. This report presents a case of auricular laceration in 18-year-old boy who was managed by primary repair of the ear after wedge resection. A good cosmetic result was achieved.

CASE REPORT

The 18-year-old boy presented in our emergency surgery department with a history of an accident. On examination, the boy was conscious with laceration of right ear involving the skin and cartilage with tissue loss [Figure 1]. The ear was washed thoroughly to remove any foreign body. The patient was taken to the emergency operation theatre for repair with local anesthesia with 1% lidocaine

with epinephrine 1:100,000. A wedge excision of the damaged part of the ear was done. The wound was then closed in a layered fashion re-approximating the cartilage with 30 catgut and re-approximating the epidermis with a running top suture of 5-0 prolene [Figure 2]. With regular dressings and antiseptic precautions, wound healed well with no residual necrosis [Figure 3].

DISCUSSION

Lacerations and abrasions are among the most common auricular injuries. The golden rule in such cases after adequate local anesthesia is to balance minimal debridement with maximal tissue preservation.^[1]

Reconstruction of composite (skin and cartilage) defects of the ear may be broadly classified into two groups: wedge resection and direct advancement, and reconstruction with chondrocutaneous flaps. Small helical defects (often up to 2 cm) involving the helix and antihelix can be repaired with a wedge excision.^[2] The apex of the wedge may extend into the conchal bowl. Wedge resections and helical advancements shorten vertical ear height but maintain the relative proportions.^[3]

For defects larger but < 25% of the auricle, a star excision, or anterior composite Burows triangle excision, can redistribute tension throughout the ear and avoid cupping.

Various chondrocutaneous reconstruction methods have been described for defects up to one-third of the auricle. Large composite defects require a new structural support followed by a vascularized skin flap.

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.149378



Figure 1: Ear laceration on helix extending anteriorly



Figure 2: Stitching with prolene 5-0. (a) During stitching, (b) after stitching



Figure 3: Postoperative follow-up. (a) At day 7, (b) lateral view, (c) posterior view

Primary repair of the ear after wedge resection is a standard procedure followed for auricle injuries. When the helical rim is affected, a vertical mattress suture should be placed initially at the rim to evert the wound edges and level the wound.^[4] It is also important to stress the important role of dressing and good wound care in order to obtain a better cosmetic outcome.^[1,5] For small composite defects of helix

and antihelix, a wedge or star-shaped excision technique is a preferable option.^[5] It consists of a full-thickness excision of skin and cartilage with the apex pointing to the anterior surface of the ear and extending to the conchal area. When designing the wedge, it is important to define an apex angle smaller than 30°.^[6] The resulting wound is then closed primarily in layers, with the cartilage secured by long lasting sutures.^[5] It is helpful, when possible, to use an offset skin closure around the rim. To decrease the risk of rim notching, the skin should not be approximated and secured over the cartilage space.^[7] Usually, the ear is shortened slightly while maintaining the premorbid contour.^[7] The advantages of wedge resection are: a one-stage operation, simple and fast dissection, and minimal resultant scar.

However, the limitation of this technique is that it can be applied only for small defects of the helical rim and neighboring structures. The wedge should be located in the superior or posterior third to avoid deformity of the ear. If the defect is larger or located near the anterior helix, wedge resection cannot be used without severe deformity of the ear.^[2]

Our technique is quite similar to the one described by Ferri^[8] and Schonauer *et al.*,^[9] in terms of excising a wedge triangle but lacks the second incision at the helical root level. Aesthetic results of the reconstructed ear are maximized by balancing forces on the frontal and sagittal planes. Furthermore, anatomical landmarks and relative proportions are preserved.

This report shows that good cosmetic results can be obtained by managing the ear avulsion with standard procedure of wedge resection followed by primary repair.

REFERENCES

1. Havlik RJ, Sadove AM. Repositioning the malpositioned ear. *Oper Tech Plast Reconstr Surg* 1997;4:141-5.
2. Elsayh NI. Reconstruction of the ear after skin and cartilage loss. *Clin Plast Surg* 2002;29:201-12, vi.
3. Reddy LV, Zide MF. Reconstruction of skin cancer defects of the auricle. *J Oral Maxillofac Surg* 2004;62:1457-71.
4. Elsayh NI. Acquired ear defects. *Clin Plast Surg* 2002;29:175-86, v-vi.
5. Park SS, Hood RJ. Auricular reconstruction. *Otolaryngol Clin North Am* 2001;34:713-38, v-vi.
6. Pham TV, Early SV, Park SS. Surgery of the auricle. *Facial Plast Surg* 2003;19:53-74.
7. Calhoun KH, Chase SP. Reconstruction of the auricle. *Facial Plast Surg Clin North Am* 2005;13:231-41, vi.
8. Ferri M. Treatment of partial losses of the helix. *Plast Reconstr Surg* 1998;101:2011-2.
9. Schonauer F, Campa D, Monaco A, Molea G. Staggered wedge technique for ear reconstruction. *Plast Reconstr Surg* 2010;125:e203-4.

How to cite this article: Singla B, Chawla I, Gautam P, Goyal A, Rathi J. Primary repair of ear laceration with wedge resection. *Plast Aesthet Res* 2015;2:38-9.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 21-05-2014; **Accepted:** 10-10-2014

Diode and Nd:YAG laser in a case of refractory acne keloidalis nuchae

Ravi Kumar Chittoria, Devi Prasad Mohapatra, Friji Meethale Thiruvoth, Dinesh Kumar, Arjun Asokan, Vijayaraghavan Nandhagopal

Department of Plastic Surgery, JIPMER, Gorimedu, Puducherry 605006, Tamil Nadu, India.

Address for correspondence: Dr. Arjun Asokan, Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Gorimedu, Puducherry 605006, Tamil Nadu, India. E-mail: arjunashokan@gmail.com

ABSTRACT

Acne keloidalis nuchae (AKN) is a disease of unclear etiology that mainly affects males. Medical treatment of AKN is difficult, with refractory cases often requiring ablation by laser or surgical resection. We report herein, a 23-year-old male with refractory AKN treated successfully with combined laser ablation, using an 810-nm diode laser and a 1064-nm Nd:YAG laser.

Key words:

Acne keloidalis nuchae, diode laser, Nd:YAG laser

INTRODUCTION

The term acne keloidalis nuchae (AKN) was coined in 1872 by Bazin.^[1] AKN is a condition characterized by follicular-based papules and pustules that form hypertrophic or keloid-like scars. The principal sites are the occipital scalp and posterior neck. The condition starts as mildly pruritic papules and pustules on the occipital scalp or nape of the neck. This may subsequently evolve to keloid-like plaques. Later, abscesses and multiple sinus tracts may develop. Patients may also present with cosmetic complaints with scarring alopecia in advanced cases. The condition has a male preponderance with a male:female ratio of approximately 20:1.^[2]

Treatment of AKN is difficult; numerous modalities have been used with varying degrees of success. There is no single definitive first-line therapy. Early, mild papular disease may respond to potent or superpotent topical steroids (e.g., Clobetasol). Intralesional triamcinolone acetonide injection can be helpful to reduce the size and firmness of papules and nodules. Refractory cases may respond to laser ablation.

CASE REPORT

A 23-year-old male presented with multiple papules in the occipital scalp of 3 years duration. His main complaints were cosmetic disfigurement and difficulty in combing the hair. He did not give a history of pruritus. On examination, multiple follicle-based papules were observed over the occipital scalp [Figure 1]. An incisional biopsy confirmed the diagnosis of AKN. Histological examination showed skin with orthokeratosis and with increased pigmentation and periadnexal lymphocytic inflammatory infiltrate [Figure 2].

He was initially treated by dermatologist with eight sittings of intralesional triamcinolone acetonide injections at three weekly intervals, subsequently followed by CO₂ laser delivery – 7 J/cm² (2 sittings), 5.5 J/cm² (1 sitting), and 9 J/cm² (1 sitting) – with no significant improvement in the symptoms. He was then referred to the Plastic Surgery Department for further management of the refractory lesions.

Since it was a case of refractory AKN, the patient was taken up for alternate laser treatment. Two modalities of lasers – the Nd:YAG (1064 nm) and the diode laser (810 nm) – were used as follows: the affected occipital scalp was divided arbitrarily at the midline into two halves and one modality was administered in each half with the intent to find out the modality that had a better response, which would be continued on both halves in subsequent treatments. The right side of the occipital scalp was treated with a diode laser (1 Hz/1 s/0.5 W) and the left side was treated with a Nd:YAG laser (30 J/cm²) with a spot

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.149380

size of 7 mm. A second treatment sitting with the above settings was repeated after 3 weeks, using the same laser applications on each side of the scalp as in the first treatment. Twelve days after the second sitting, there was complete resolution of the lesions with no residual scarring [Figure 3]. He was kept on observation for any



Figure 1: Acne keloidalis nuchae of the occipital scalp after failed CO₂ laser treatment and topical steroid and intralesional steroid injection

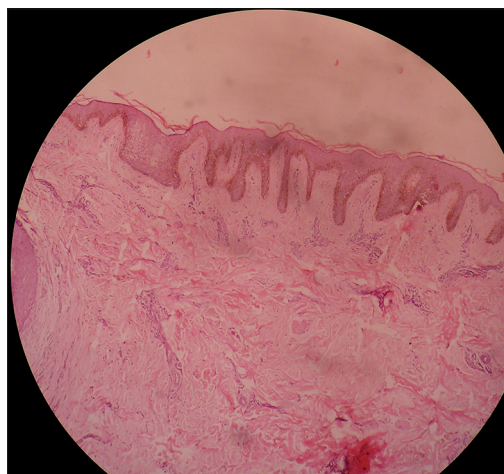


Figure 2: Histological examination showing the skin with orthokeratosis and with increased pigmentation and periannexal lymphocytic inflammatory infiltration



Figure 3: Post-Nd:YAG and -diode laser therapy; the lesion shows good resolution

recurrence. The patient was advised to avoid shaving the posterior part of the hairline close to the skin and to avoid wearing clothes that rub or irritate the posterior parts of the scalp and the neck. There was no recurrence of the lesion seen at 15 months follow-up.

DISCUSSION

AKN has an unclear etiology, with a predominant occurrence in males. The probable causes may be chronic irritation, chronic bacterial infections, or an autoimmune condition. Treatment of AKN is difficult. Early cases may be treated with topical potent steroids or intralesional steroids. Cryotherapy and intralesional 5-fluorouracil have also been tried. Refractory cases may respond to laser ablation (e.g., 10.6-μm carbon dioxide laser, 1064-nm Nd:YAG laser, or 810-nm diode laser). With long-pulsed Nd:YAG lasers at a wavelength of 1064 nm, there is a significant reduction in the papule count, probably due to the higher penetrance of the Nd:YAG laser into the dermis to disrupt the follicle, sparing the epidermis from heat absorption and thereby minimizing skin damage.^[3] A side effect of the Nd:YAG laser is hair fall-out, which grows back, but with thinner hair. The Nd:YAG laser is more suitable for applications in dark-skinned individuals (Fitzpatrick IV, V and VI types).^[3]

Diode lasers (using an 810 nm wavelength) act on the theory of selective thermolysis targeting the melanin in the hair follicles.^[4] There is coagulation necrosis of the follicle leading to temporary alopecia. The new hair that regrows, usually after 4-6 months, is much thinner causing less chance of recurrence. Both Nd:YAG and diode lasers act on the principle of selective thermolysis, leading to damage in the hair follicle and thereby causing relief of the disease process. This is in contrast to the earlier concept of using steroids which have mainly concentrated on the anti-inflammatory response, leading to a decrease in disease activity. Laser treatment is a relatively painless procedure with minimal complications. In refractory and advanced cases of AKN, both of these laser modalities may have a role in reducing the number of papules as well as improving the scar cosmetically.

Our patient presented with a refractory AKN, refractory to treatment with topical antibiotics, intralesional steroids, and carbon dioxide laser therapy. We successfully treated the AKN with both diode and Nd:YAG lasers. In this case, each laser was equally effective in ablation of the lesions, with complete resolution of the symptoms and good cosmetic outcome. However, the risk of hair loss in the treated area should be mentioned to the patient. Furthermore, the chance of the new hair that regrows being much thinner should be emphasized.

Further, large scale randomized control trials are needed for assessing the efficacy and advantage of one modality over the other.

REFERENCES

1. Gloster HM Jr. The surgical management of extensive cases of acne keloidalis nuchae. *Arch Dermatol* 2000;136:1376-9.
2. Kelly AP. Pseudofolliculitis barbae and acne keloidalis nuchae. *Dermatol Clin* 2003;21:645-53.
3. Attia A, Salah M, Sami N. Novel treatment of acne keloidalis using long pulsed Nd: YAG laser in dark skinned patients. *Egypt Dermatol Online J* 2009;5:1.
4. Shah GK. Efficacy of diode laser for treating acne keloidalis nuchae. *Indian J Dermatol Venereol Leprol* 2005;71:31-4.

How to cite this article: Chittoria RK, Mohapatra DP, Thiruvoth FM, Kumar D, Asokan A, Nandhagopal V. Diode and Nd:YAG laser in a case of refractory acne keloidalis nuchae. *Plast Aesthet Res* 2015;2:40-2.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 11-05-2014; **Accepted:** 15-09-2014

Temporary ectopic hand implantation

Xu Zhang, Hong-Wei Zhu

Department of Hand Surgery, The Second Hospital of Qinhuangdao, Changli, Qinhuangdao 066600, Hebei, China.

Address for correspondence: Dr. Xu Zhang, Department of Hand Surgery, The Second Hospital of Qinhuangdao, Changli, Qinhuangdao 066600, Hebei, China. E-mail: ahand@sina.com

ABSTRACT

Severe crushing injuries to the distal forearm can preclude immediate hand replantation, with temporary ectopic implantation as a practicable option under special circumstances. This report describes a case of temporary ectopic hand implantation for a crush injury extending from the wrist to the middle third of the forearm, using the left foot as the recipient site. The hand was replanted onto the left forearm 3 months after the ectopic implantation, with functional gains seen by 18 months. Satisfactory ambulation was retained, with no reported foot pain. Temporary ectopic implantation is a pragmatic alternative under select circumstances.

Key words:

Ectopic, hand, hand implantation, replantation, transplant

INTRODUCTION

Severe crushing injuries to the distal forearm are devastating and can preclude direct replantation for salvage of the hand. In such difficult situations, temporary ectopic implantation is a viable option under specific circumstances.^[1] The amputated part, when transferred to a healthy recipient site, allows the patient to recover from critical combined injuries, radical debridement, and related soft tissue repairs.^[2]

Previous temporary ectopic implantations have been reported in the literature. Wang *et al.*^[3] reported two cases of temporary ectopic implantation of complex amputated forearms, followed by successful replantation to their anatomic positions in a second stage, the contralateral upper extremity was an acceptable recipient site for temporary ectopic implantation. For subsequent replantation, a cross-arm flap was designed to carry the vascular pedicle from the ectopic implantation recipient to improve blood supply to the replanted part upon replantation to the original site and with when the blood supply was re-established. Li *et al.*^[4] temporarily implanted

thumbs ectopically onto the forearm and foot in two cases, the thumbs survived after second-stage replantation and the patients regained function 4 months after surgery. Tomlinson *et al.*^[5] implanted digits to the contralateral forearm, with subsequent reconstruction of the injured hand when combined with microvascular toe transfer. Their outcome was a functionally useful hand which could be incorporated into daily life and a cosmetic appearance preferable to that of amputation.

This report describes a case of temporary ectopic hand implantation. The left foot was used as the recipient site.

CASE REPORT

In May 14, 2010, a 35-year-old man sustained a machine injury to his left forearm [Figure 1]. The patient was consented for this technique. Physical examination revealed a severe crushing injury that extended from the wrist to the middle third of the forearm, with contamination and associated comminuted fractures. The remaining connecting tissues included the median and ulnar nerves, several flexor tendons, and a strip of skin with a severe contusion.

Proximal end management

Surgery was performed under axillary block and epidural anesthesia with pneumatic tourniquet control. Two surgical teams worked simultaneously. The limb was transected at the level of the radiocarpal joint [Figure 2a and b]. The proximal end of the forearm was debrided thoroughly, but was preserved as long as possible. The median and ulnar

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.149381

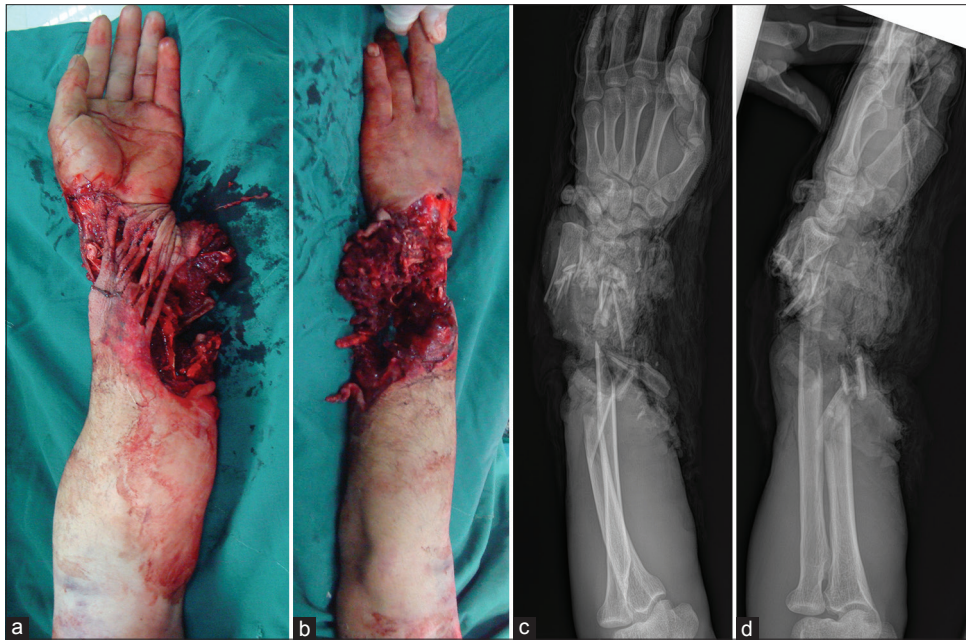


Figure 1: Extensive and complex crushing injury to the wrist and forearm. (a) Volar view; (b) dorsal view; (c) anteroposterior radiograph; (d) lateral view

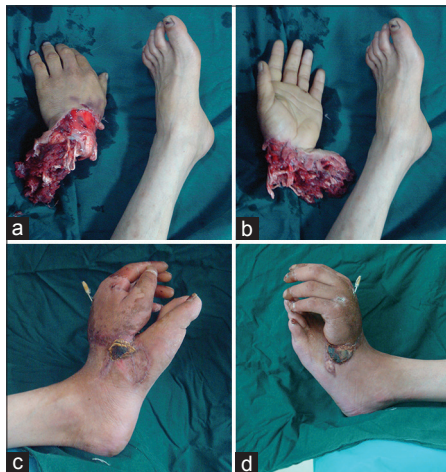


Figure 2: The hand is amputated. (a) Dorsal view; (b) palmar view. Ectopic implantation to the foot was completed. (c) Radial view; (d) ulnar view

nerves were transected at the distal-most level of the injury site and then turned proximally into the uninjured subcutaneous tissue. The severely crushed tendons were debrided. The proximal end of the forearm was sealed with vacuum drainage.

Hand-to-foot transfer

We selected the left foot as the ectopic recipient site because of vascular match. At the dorsum of the left foot, the dorsalis pedis artery was palpated and assessed using Doppler ultrasound. A dorsalis pedis fasciocutaneous flap, 7 cm × 8 cm in size, was raised on the dorsum of the foot as a base for the corresponding defect on the amputated part. The hand was stabilized to the tarsal bones with K-wires. Anastomoses were performed between the dorsalis pedis artery and the radial artery, between their venous counterparts, and between the greater saphenous vein and the cephalic vein. The skin defect was reconstructed with the dorsalis pedis fasciocutaneous flap and skin grafts [Figure 2c and d]. After surgery, the

patient was placed in a warm room. The implanted hand together with the recipient foot was elevated above the heart level. The patient was given 10 mL/kg dextran 40 twice a day for 7 days. A nurse monitored the color and capillary filling of the hand and the flap every 2 h. Three weeks after surgery, the patient was allowed to walk with the bank foot in a specially designed shoe.

Foot-to-forearm transfer

Three months after surgery, the ectopically implant hand was transferred back to the left forearm [Figure 3a]. The proximal end of the forearm was incised, and the end of the radius was debrided. The median and ulnar nerves were dissected, and the tendon ends were prepared. The hand together with the dorsalis pedis fasciocutaneous flap was incised as a single unit from the recipient foot [Figure 3b]. The dorsalis pedis artery, its accompanying veins and great saphenous vein were dissected proximally until suitable lengths were obtained. The hand was transferred to the left forearm [Figure 3c-e]. The radius and carpal bones were fused and stabilized with a plate and screw system. Anastomoses were performed between the dorsalis pedis artery and radial artery, between their accompanying veins, and between the greater saphenous vein and the cephalic vein. The median and ulnar nerves were repaired directly. We did not repair the radial nerve because there was a large nerve defect that precluded a direct repair. Moreover, the radial nerve is less important for hand function. We used the flexor digitorum superficialis tendons as grafts to repair the flexor digitorum profundus tendons, extensor and flexor pollicis longus, and extensor digitorum communis. The wound was then closed. The secondary defect on the left foot was resurfaced with skin grafts. Postoperative treatments were similar to the first operation. Four weeks after surgery, active range-of-motion exercises and physical therapy were started.

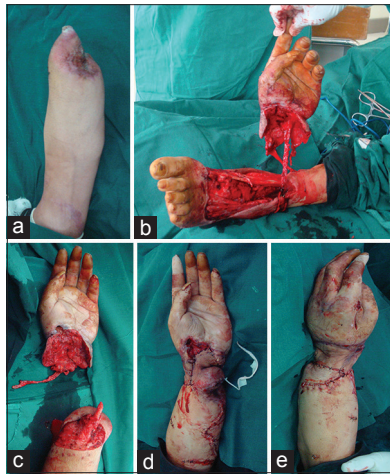


Figure 3: (a) The proximal end of the left forearm; (b) the implanted hand is dissected from the ectopic site; (c) the hand is amputated from the ectopic site; (d and e) replantation is completed, (d) palmar view; (e) dorsal view

Outcome evaluation

The hand survived with normal color and capillary refilling test, partial flap necrosis was noted, but healed with wound care. Bone healing was achieved 4 months after the second operation. Eighteen months after surgery [Figure 4], two-point discrimination on the pulps of the first through fifth digits was 4, 6, 7, 5, and 8 mm, respectively. Tenolysis was not performed because the patient refused. Range of motion arcs for the first to fifth metacarpophalangeal joints were 5°, 10°, 4°, 0°, and 3°, respectively; for the proximal interphalangeal joints, 2°, 5°, 2°, 3°, and 0°, respectively; and for the distal interphalangeal joints, 0°, 0°, 2°, 0°, and 0°, respectively. The patient reported no pain for the hand or forearm. The disability score for the arm, shoulder, and hand^[6] was 78. Based on a foot function assessment,^[7] the patient reported no foot pain and had no difficulty when he stood on tiptoe or walked in the house. The patient had no difficulty when he walked outside for four blocks, climbed or descended stairs, got up from a chair, climbed curbs, ran, or walked quickly.

DISCUSSION

Since the first replant almost 52-year-ago, thousands of severed hands have been reattached, preserving the quality of life for these patients through improved function and appearance that the void remaining after amputation cannot provide.^[8] Revascularization procedures are often easier than replantation, but incomplete amputations with an extensive crush-avulsion injury may be more difficult because debridement of nonviable tissue and bone shortening cannot retain healthy structures. In such cases, the percentage of viability is lower. Temporary ectopic implantation offers an approach to detach the distal part safely from the injured site, which improves subsequent viability.^[9]

Several recipient sites are available for temporary ectopic implantation, including the groin, lower leg, foot, and opposite arm and hand.^[4-7] Selection is generally based



Figure 4: Appearance 18 months after surgery. (a) Extension; (b) flexion

on matching the vessels between the recipient site and the implanted part. In our case, a venous network on the dorsum of the foot was presented, which can be included in the dorsalis pedis fasciocutaneous flap. In the second-stage foot-to-forearm transfer, the flap can be transferred to the forearm along with the hand, without the need for additional vascular anastomosis. In our case, the flap provided sufficient room for the underlying tendons and nerves. We believe a groin flap or superficial inferior epigastric artery flap may be needed in other cases for which a larger space may be needed to facilitate easier tendon and nerve reconstructions. In addition, physical therapy of the amputated parts before reattached to prevent joint stiffness and tendon adhesions, the special needs at the secondary replantation, such as flaps for the coverage soft tissue defects at the recipient site and patient acceptance should also be considered.

Indications for temporary ectopic hand implantation are severe injuries on the proximal end of the limb where salvation of the hand *in situ* is difficult, and the distal part is mildly injured. Contraindication is severe injured in the distal part where revascularization is impossible.

Function of the reattached parts can vary widely. As these are severe and complex injuries, satisfactory results may not be attained in many patients. In such case, the inconvenience during the banking period and inappropriateness of shoe wearing, especially in a cold area, should be considered. In addition, the cost is generally higher than that of direct replantation or revascularization. Therefore, the benefits and risks should be discussed carefully before undertaking these surgical reconstructions.

REFERENCES

1. Ni G, Wu X, Zhang D, Yang H, Ma X, Sun X. Temporary ectopic implantation of amputated fingers and dorsalis pedis flaps for thumb reconstruction and skin defect repair of hands. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2013;27:1094-7. (in Chinese)
2. Godina M, Bajec J, Baraga A. Salvage of the mutilated upper extremity with temporary ectopic implantation of the undamaged part. *Plast Reconstr Surg* 1986;78:295-9.

3. Wang JN, Tong ZH, Zhang TH, Wang SY, Zhang HQ, Zhao GQ, Zhang F. Salvage of amputated upper extremities with temporary ectopic implantation followed by replantation at a second stage. *J Reconstr Microsurg* 2006;22:15-20.
4. Li J, Ni GH, Guo Z, Fan HB, Cong R, Wang Z, Li MQ. Salvage of amputated thumbs by temporary ectopic implantation. *Microsurgery* 2008;28:559-64.
5. Tomlinson JE, Hassan MS, Kay SP. Temporary ectopic implantation of digits prior to reconstruction of a hand without metacarpals. *J Plast Reconstr Aesthet Surg* 2007;60:856-60.
6. Reichl H, Schütz T, Gabl M, Angermann P, Russe E, Wechselberger G. Hand replantation: differences in functional outcome considering patient age and sociomedical aspects. *Handchir Mikrochir Plast Chir* 2013;45:344-9.
7. Riskowski JL, Dufour AB, Hagedorn TJ, Hillstrom HJ, Casey VA, Hannan MT. Associations of foot posture and function to lower extremity pain: results from a population-based foot study. *Arthritis Care Res (Hoboken)* 2013;65:1804-12.
8. Hallock GG. Transient single-digit ectopic implantation. *J Reconstr Microsurg* 1992;8:309-11.
9. Zheng W, Zheng GQ. Should children who experience traumatic amputations be offered temporary ectopic implantation instead of a prosthesis? *MCN Am J Matern Child Nurs* 2014;39:6-7.

How to cite this article: Zhang X, Zhu HW. Temporary ectopic hand implantation. *Plast Aesthet Res* 2015;2:43-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 12-08-2014; **Accepted:** 27-09-2014

Surgical treatment of synovial-collagen disorders of the hand

H. Kirk Watson¹, Purnell Traverso¹, Lois Carlson¹, Daniel Mastella¹, Ronit Wollstein^{2,3}

¹Department of Orthopedic Surgery, Division of Hand and Upper Extremity Surgery, The Hand Center, Glastonbury, CT 06033, USA.

²Department of Orthopedic Surgery, The Technion School of Medicine, Haifa 31096, Israel.

³Department of Plastic Surgery, University of Pittsburgh Medical School, Pittsburgh, PA 15261, USA.

Address for correspondence: Prof. Ronit Wollstein, 3550 Terrace Street, Pittsburgh, PA 15261, USA. E-mail: ronitwollstein@gmail.com

ABSTRACT

Critical relationships between collagen and synovium exist and affect the function of the hand. Understanding these relationships enhances the ability to perform surgery including procedures addressing soft tissue and joint pathology. We present a series of surgical procedures based on this principle.

Key words:

Collagen, hand, plastic, surgery, synovium

INTRODUCTION

The practice of hand surgery requires an understanding of the anatomy, the intimate relationships between collagen and synovium, and the ultimate function of the hand. This is critical to the performance of surgery ranging from skin coverage following a crush injury to tendon or toe transfers in congenital hand cases. We present a series of surgical procedures based on this understanding.

Pathologic conditions resulting in synovial irritation or inflammation involve an array of molecular pathways, which can lead to the pathologic deposition of collagen in the hand and wrist. Chronically inflamed synovium will thicken adjacent collagen and create these phenomena (the “collasyn theory”). In the hand, collagen and synovial tissue are anatomically closely associated. The support structures, mostly made up of collagen (bones, tendons, ligaments), are lined with synovial tissue in areas where tissue motion requires a reduction in the coefficient of friction.

Surgical procedures must address the inflamed synovium, which, by virtue of its close anatomic proximity,

“communicates” with the adjacent collagen structures and may cause collagen thickening and multiple symptomatic changes. Surgery may be needed to: (1) remove inflamed synovium; (2) increase space around affected structures and (3) remove abnormal tissues (such as osteophytes) that occur secondary to the effects of the inflamed synovium on adjacent collagen structures. This surgical approach decreases symptoms and may enhance joint longevity.

SURGICAL SERIES

Rheumatoid arthritis

The deformities in the hand in rheumatoid arthritis often follow a predictable pattern. The formula is destructive synovitis plus load equals deformity. If viewed through the lens of the collasyn theory, synovitis will rupture tendons at the distal edge (load area) of the extensor retinaculum. Synovitis also stimulates protective over-activity of the intrinsic, creating abnormal loads in the fingers. These loads most often create pressure on the dorsoradial capsule and ligaments of the metacarpophalangeal (MP) joint resulting in volar and ulnar subluxation of the proximal phalanx. If there is insufficient synovitis in the MP joint, the MP joints will not subluxate. The intrinsic loads then are transmitted to the fingers, resulting in swan necks, boutonnières, dislocations or even interphalangeal fusion. Applying this concept allows prediction of expected deformity on clinical examination. Tight intrinsic (positive Bunnell test) should be released early, removing the load component of the destructive formula. The ulnar drift and deformities of the wrist are the result

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153192

of the “downslope” loads created by the anatomy of the articular surface of the distal radius.

Stenosing tenosynovitis or trigger finger

The effects of the interaction between synovium and collagen can be seen in trigger fingers. In stenosing tenosynovitis of the finger flexors, there is a thickened retinaculum or pulley that constricts the osseofibrous tunnel through which the tendon runs.^[1] Chronic synovial irritation affects collagen deposition in the A1 pulley and leads to a progressive thickening and sometimes metaplasia of the pulley^[1-3] [Figure 1]. During sleep, edema collects in the tendon proximal and distal to the pulley. The symptomatic sequelae include stiffness in the mornings as patients open and close their fingers to “milk” the fluid back into the natural shape of the tendons, or “locking” of the fingers if a nodule is too big to pass through the pulley. Conservative treatment may include steroid injections, splinting and activity modification. If this fails, surgery is indicated.^[4] A release of the A1 pulley increases space to allow normal tendon gliding. Surgery has been shown to be more successful in the absence of diabetes.^[5]

The collasyn theory explains why there is an increased incidence of stenosing tenosynovitis (trigger finger) in the thumb and little finger following carpal tunnel surgery. Infection can move from thumb to little finger through the common synovial lining between the thumb, the carpal tunnel and the fibro-osseous sheath of the little finger flexors. Surgery on the carpal tunnel produces inflammation of this communicating synovium, which then has its hypertrophic effect on the collagen of the A1 pulleys.

Fourth extensor compartment synovitis

Collasyn pathology is also seen in the extensor retinaculum. Patients with fourth extensor compartment stenosing tenosynovitis develop a thickened retinaculum. In performing ultrasound evaluation, Zhou *et al.*^[6] found that with increased extension of the wrist, the contact area between the extensor retinaculum and the extensor tendons decreased, causing increased friction. We have found that a release of the septa between the fourth and fifth extensor compartments without releasing the external retinaculum is all that is needed to provide sufficient room for the tendons.^[7]

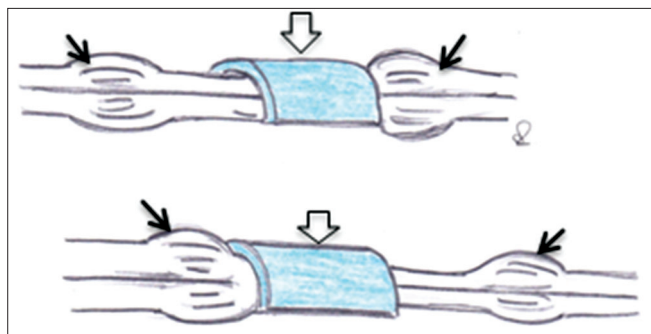


Figure 1: The A1 pulley thickens in response to synovitis and constricts the flexor tendons

Check reins

Treatment of proximal interphalangeal (PIP) joint contractures is often reported to be less than optimal.^[8] The volar plate at the PIP joint is a unique structure that prevents hyperextension at the PIP joint and absorbs enormous compression loads. The PIP volar plate is a thick, strong fibrocartilaginous structure, lined on the volar surface by peritendinous synovium of the fibro-osseous sheath and on the dorsal surface by joint synovium. These 2 layers of synovium lie on either side of the thin joint capsule at the lateral sides of the volar plate.^[9] Inflammation of these two different synovial surfaces influence each other and produce the unusual abnormal collagen hypertrophy termed the checkrein ligaments. These do not exist in the normal state but are produced under the influence of this “synovial sandwich.” When treating contractures of the PIP joints, one must release these pathological structures in order to increase the movement in the joint. Results of a study using this technique indicated full intraoperative extension in 110 of 115 joints, with 2 joints requiring a collateral ligament release. Three of the 115 digits required a second checkrein release after intraoperative gains were not maintained.^[9]

Peripheral arthritis

Peripheral arthritis is secondary to synovial traction and inflammation. Osteophytes and abnormal cartilage build up on the joint periphery. It is hypothesized that the areas of synovial attachment are responsible for the synovitic influence on collagen and bone formation. With chronic synovial inflammation, the mechanical traction at the synovial attachment point may play a part but the inflamed synovium communicates with the bone collagen resulting in osteophyte formation. Resecting these bone areas along with excision of involved synovium results in clearing of the patient's symptoms and significantly extending joint longevity. This occurs without having altered joint mechanics at the time of surgery.

Distal radioulnar joint

This approach has been used in the treatment of arthritis in the distal radioulnar joint (DRUJ). The treatment of DRUJ degenerative arthritis following failure of conservative treatment such as splinting and antiinflammatory medication includes complete elimination of the arthritic joint, as popularized by Darrach,^[10] a hemiresection-interposition technique,^[11] the matched distal ulna resection^[12] or the Sauvé-Kapandji procedure, as well as ulnar head or total joint replacement.^[13] A modified DRUJ arthritis technique based on the concept of proximal to distal progression of degenerative joint disease at the DRUJ has been described^[14] [Figure 2]. The proximal one-third to one-half of the articular surface is typically resected around the entire circumference of the joint. In one published study, all patients noted significant improvement in symptoms.^[14] One patient went on to have a matched ulna arthroplasty. In another report on results of 29 patients, 5 (17%) had additional surgery

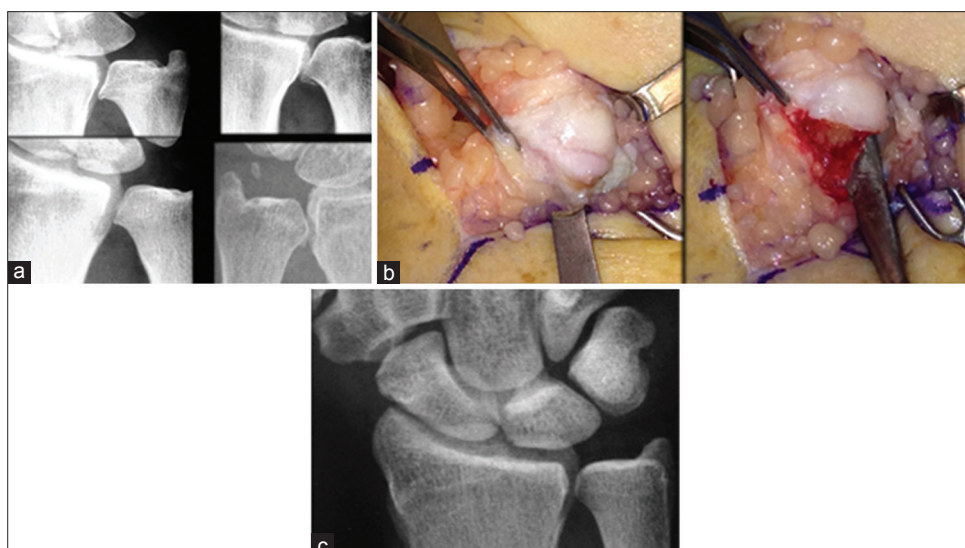


Figure 2: (a) Peripheral arthritis is an early stage of bone response to synovitis. In the DRUJ, it typically begins along the proximal joint where synovium attaches. It has the appearance of a "goatee" on the articular surface of the ulna as noted in these 4 symptomatic patients; (b) at surgery, the osteophyte is made up of soft reactive bone, which is easily removed circumferentially; (c) a 5-year postoperation follow-up shows no progression of DRUJ arthritis in this asymptomatic patient

after the DRUJ arthroplasty specific to the ulno-carpal/DRUJ complex (four patients matched ulna arthroplasty, one patient triquetral impingement ligament tear [TILT] and ulna styloidectomy).^[15]

Dorsal wrist syndrome

Another example of peripheral arthritis is the dorsal wrist syndrome (DWS). This common diagnosis of wrist pathology results from scaphoid instability after ligament tears, extreme loading of the wrist or a physiologically inadequate ligament system. The most common problem in the human wrist is the tendency for the proximal scaphoid pole to escape from beneath the capitate. Under load, this displacing scaphoid produces stretch and insult to the synovium. In its mildest form, acute wrist trauma produces scapholunate (SL) synovitis and ligamentous strain without a SL ligament tear. A more substantial ligament tear may result in a displacing scaphoid accompanied by chronic synovitis. These wrists are painful and will not tolerate loading. Conservative treatment consists of splinting and other types of activity modification.^[16]

Surgical management of DWS after 6 months of conservative care involves exploration of the SL joint with excision of the soft tissue synovial mass and any associated ganglia. Bony ridging and osteophytes form on the dorsum of the scaphoid and occasionally the lunate and are present in every case to some extent [Figure 3]. The dorsal ridging is believed to be the synovial attachment point responsible for molecular remodeling of collagen and bone due to the synovial inflammation. No change in scaphoid stability is accomplished. One hundred and fifty-one cases of surgically treated DWS were evaluated and <10% of these wrists required subsequent scaphoid stabilization (scaphoid-trapezium-trapezoid (STT) fusion). Wollstein *et al.*^[17] presented results on 80 patients surgically treated for DWS, with 25% requiring some form of further surgery, including 9 STT fusions and 2 proximal

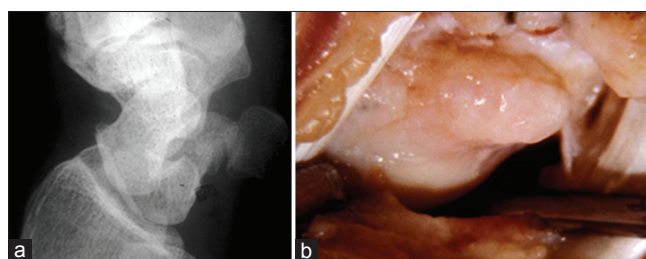


Figure 3: In dorsal wrist syndrome, the inflamed synovium produces peripheral osteophytes as noted on the dorsum of the scaphoid in this oblique X-ray (a) and at surgery (b)

row carpectomies. It is hypothesized that the resection of this synovitic attachment point is responsible for the relatively low rates of progression to arthritis despite continued abnormal scaphoid migration under load. A second group with a similar surgical procedure has been described with 86% of their patients having good to excellent results.^[18]

In conclusion, inflamed synovium influences adjacent collagen. This fundamental relationship is the basis for many of the pathologic conditions of the hand, from capsular and ligament collagen to bone collagen (the "collasyn theory"). Viewing pathology of the hand in this manner may enhance our understanding and consequent treatment of hand conditions. The synovial cells produce a multitude of molecules and mediators involved in normal joint function as well as inflammatory mediators such as cytokines in response to osteoarthritis.^[19,20] Lubricin and hyaluronic acid are two important lubricant molecules produced by synovium. Recent evidence has shown that these molecules are important in articular cartilage maintenance and loss of these substances can lead to osteoarthritic degeneration.^[21-23] A reactive synovium produces factors related to inflammation through participation in multiple pathways.^[24-27] Synovium includes mesenchymal stem cells capable of differentiating into

various tissue types including cartilage, muscle and bone.^[28-30] Thus, synovium plays a key role in the repair of injured connective tissue components, but may also create the environment in which further pathology occurs.^[19]

Further study in this area may allow us to understand and address this synovial influence before it exerts its effect on surrounding collagen.

REFERENCES

- Moutet F. Flexor tendon pulley system: anatomy, pathology, treatment. *Chir Main* 2003;22:1-12.
- Vuillemin V, Guerini H, Bard H, Morvan G. Stenosing tenosynovitis. *J Ultrasound* 2012;15:20-8.
- Tung WL, Kuo LC, Lai KY, Jou IM, Sun YN, Su FC. Quantitative evidence of kinematics and functional differences in different graded trigger fingers. *Clin Biomech (Bristol, Avon)* 2010;25:535-40.
- Huisstede BM, Hoogvliet P, Coert JH, Fridén J, European HANDGUIDE Group. Multidisciplinary consensus guideline for managing trigger finger: results from the European HANDGUIDE Study. *Phys Ther* 2014;94:1421-33.
- Mol MF, Neuhaus V, Becker SJ, Jupiter JB, Mudgal C, Ring D. Resolution and recurrence rates of idiopathic trigger finger after corticosteroid injection. *Hand (N Y)* 2013;8:183-90.
- Zhou CL, Wang XT, Chi ZY, Yan JL. Extensor tendon injury due to repetitive wrist dorsiflexion: morphological study of extensor retinaculum and extensor tendon. *Cell Biochem Biophys* 2014;70:1191-7.
- DiFelice A Jr, Seiler JG 3rd, Whitesides TE Jr. The compartments of the hand: an anatomic study. *J Hand Surg Am* 1998;23:682-6.
- Yang G, McGlinn EP, Chung KC. Management of the stiff finger: evidence and outcomes. *Clin Plast Surg* 2014;41:501-12.
- Watson HK, Light TR, Johnson TR. Checkrein resection for flexion contracture of the middle joint. *J Hand Surg Am* 1979;4:67-71.
- Berg E. The Darrach procedure in rheumatoid arthritis. *Clin Orthop Relat Res* 1979;138:310-1.
- Bowers WH. Distal radioulnar joint arthroplasty: the hemiresection-interposition technique. *J Hand Surg Am* 1985;10:169-78.
- Watson HK, Ryu JY, Burgess RC. Matched distal ulnar resection. *J Hand Surg Am* 1986;11:812-7.
- Friedman SL, Palmer AK. The ulnar impaction syndrome. *Hand Clin* 1991;7:295-310.
- Watson HK, Manzo RL. Modified arthroplasty of the distal radio-ulnar joint. *J Hand Surg Br* 2002;27:322-5.
- Wollstein R, Watson HK, Phillips J, Clavijo J, Patel V, Carlson L. Ulnar sided wrist pain and distal radioulnar joint osteoarthritis; is surgical arthroplasty enough? *Rheumatol Rep* 2012;4:6-8.
- Liao JC, Chong AK, Tan DM. Causes and assessment of subacute and chronic wrist pain. *Singapore Med J* 2013;54:592-7.
- Wollstein R, Watson HK, Wear-Maggitti K, Schmidt S, Carlson L. Surgical technique for the treatment of radial wrist pain. *Scand J Plast Reconstr Surg Hand Surg* 2008;42:149-52.
- Steinberg BD, Kleinman WB. Occult scapholunate ganglion: a cause of dorsal radial wrist pain. *J Hand Surg Am* 1999;24:225-31.
- Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone* 2012;51:249-57.
- Gara SK, Grumati P, Urciuolo A, Bonaldo P, Kobbe B, Koch M, Paulsson M, Wagener R. Three novel collagen VI chains with high homology to the alpha3 chain. *J Biol Chem* 2008;283:10658-70.
- Koyama E, Saunders C, Salhab I, Decker RS, Chen I, Um H, Pacifici M, Nah HD. Lubricin is required for the structural integrity and post-natal maintenance of TMJ. *J Dent Res* 2014;93:663-70.
- Hill A, Duran J, Purcell P. Lubricin protects the temporomandibular joint surfaces from degeneration. *PLoS One* 2014;9:e106497.
- Chang DP, Guilak F, Jay GD, Zauscher S. Interaction of lubricin with type II collagen surfaces: adsorption, friction, and normal forces. *J Biomech* 2014;47:659-66.
- Sakurada S, Kato T, Okamoto T. Induction of cytokines and ICAM-1 by proinflammatory cytokines in primary rheumatoid synovial fibroblasts and inhibition by N-acetyl-L-cysteine and aspirin. *Int Immunol* 1996;8:1483-93.
- Sakurai S, Hayashi T, Iwasaki S, Kohno T, Kohno M. Expression of wnt signaling molecules in the synovial membranes of rabbit ankle joints injected with *Enterococcus faecalis* cell fractions. *Mod Rheumatol* 2003;13:35-43.
- Miao CG, Yang YY, He X, Li XF, Huang C, Huang Y, Zhang L, Lv XW, Jin Y, Li J. Wnt signaling pathway in rheumatoid arthritis, with special emphasis on the different roles in synovial inflammation and bone remodeling. *Cell Signal* 2013;25:2069-78.
- Qin SS, Yu YX, Li QK, Yu ZW. Interaction of human synovial phospholipase A2 with mixed lipid bilayers: a coarse-grain and all-atom molecular dynamics simulation study. *Biochemistry* 2013;52:1477-89.
- Chen XM, Xia J, Zhou T, Yuan Q, Zhang WF, Hu CP, Li YJ, Jiang JL. Involvement of DDAH/ADMA pathway in the pathogenesis of rheumatoid arthritis in rats. *Int Immunopharmacol* 2013;16:322-31.
- Ozasa Y, Amadio PC, Thoreson AR, An KN, Zhao C. Repopulation of intrasynovial flexor tendon allograft with bone marrow stromal cells: an ex vivo model. *Tissue Eng Part A* 2014;20:566-74.
- Yang Z, Schmitt JF, Lee EH. Immunohistochemical analysis of human mesenchymal stem cells differentiating into chondrogenic, osteogenic, and adipogenic lineages. *Methods Mol Biol* 2011;698:353-66.

How to cite this article: Watson HK, Traverso P, Carlson L, Mastella D, Wollstein R. Surgical treatment of synovial-collagen disorders of the hand. *Plast Aesthet Res* 2015;2:47-50.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 16-10-2014; **Accepted:** 22-12-2014

A survey of analgesic and anti-inflammatory drug prescription for oral implant surgery

Rahul Datta¹, Yasmin Grewal², Jaspreet Singh Batth³, Amandeep Singh⁴

¹Department of Oral and Maxillofacial Surgery, Rayat Bahra Dental College and Hospital, Mohali 140104, Punjab, India.

²Department of Public Health Dentistry, Rayat Bahra Dental College and Hospital, Mohali 140104, Punjab, India.

³Department of Conservative Dentistry and Endodontics, BRS Dental College and Hospital, Panchkula 134109, Punjab, India.

⁴Department of Pharmacology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Patel Nagar, Dehradun 248001, Uttarakhand, India.

Address for correspondence: Dr. Rahul Datta, Department of Oral and Maxillofacial Surgery, Rayat Bahra Dental College and Hospital, Mohali 140104, Punjab, India. E-mail: docdatta@gmail.com

ABSTRACT

Aim: This study was conducted to determine the preferred analgesic and anti-inflammatory drugs prescribed by oral implantologists in India. **Methods:** A structured questionnaire was distributed to 332 dentists to gather information regarding their prescription habits for analgesics and anti-inflammatory drugs. Frequency distributions were computed by type of drug being prescribed and the protocol followed. **Results:** Analysis of data showed that majority of dentists (85.8%, $n = 285$) prescribed conventional non-steroidal anti-inflammatory drugs (NSAIDs) for implant surgery. The most common prescription was ibuprofen with paracetamol combination (32.2%, $n = 107$) followed by diclofenac (20.2%, $n = 67$). Most dentists reported prescribing different NSAIDs for the same procedure in different patients (64.7%, $n = 215$). Only, 35.5% ($n = 118$) followed the peri-operative protocol. Adjunctive prescription of steroids was done by only 33.7% ($n = 112$). **Conclusion:** Our study illustrates that the general trend of analgesic and anti-inflammatory drug prescription for dental implant surgery among Indian dentists is mostly in accordance with the guidelines for pain management worldwide. However, it is noteworthy that a few dentists do prescribe drugs not primarily indicated for dental pain management and use widely varying protocols for the same. Therefore, in order to avoid potential complications, it is essential to raise awareness of among the dental practitioners of the appropriate indications and dosage regimen of specific drugs.

Key words:

Dental implants, non-steroidal anti-inflammatory drugs prescription, steroid, protocol

INTRODUCTION

Pain management has always been an important part of dental care. With an estimated 30 million people benefited worldwide, non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs for managing surgical pain and inflammation. Consistently, NSAIDs are routinely prescribed for mild to moderate dental pain and will be supplemented/replaced by opioid analgesics in severe

pain. The role of steroids as adjunctive measures to reduce postoperative inflammation, swelling, and pain has also received importance in recent years.^[1-4]

Despite adherence to all surgical recommendations and precautions during dental implant surgery in a normal healthy patient, many patients experience mild to moderate pain and inflammation after the procedure.^[5,6] Though the role of NSAIDs and steroids in minimizing postoperative discomfort in dentoalveolar surgery has been reviewed extensively, specific recommendations regarding drugs, doses, and protocols with respect to dental implant surgery are not defined.^[7,8]

A comprehensive search of commonly used electronic databases such as PubMed and Google Scholar, using the key words “analgesics”, “anti-inflammatory” and “oral implants” was done. Published literature in this context related either to the use of analgesic or anti-inflammatory

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.153194

drugs by dental practitioners in routine clinical practice, with no specific relation to oral implant surgery.

Although the role of NSAIDs and steroids has been very beneficial in terms of pain relief, these drugs also have an associated risk of side effects and adverse drug reactions.^[5] Since safe usage of drugs in clinical practice entails maximizing the therapeutic efficacy and minimizing the adverse effects, it is important to gain knowledge of the pattern of use of these widely prescribed drugs by dentists in order to minimize the possible risks associated with these drugs.^[1-4] The aim of our study was therefore to assess the prescription pattern of analgesics and anti-inflammatory drugs during routine oral implant surgery in normal healthy patients among Indian dentists. To our knowledge, this is the first study of its kind to be conducted in the Indian subcontinent.

METHODS

A structured questionnaire was developed to elicit prescription preferences regarding analgesics and anti-inflammatory drugs prescribed for routine oral implant surgery in the normal healthy patients and the protocol(s) followed. Dental surgeons were personally

approached at various national events such as conferences and academic meetings and requested to provide the required information. Inclusion criteria for the study sample consisted of dental surgeons performing oral implant surgery and were willing to voluntarily complete the questionnaire. All data was manually transferred from the survey forms to an electronic spreadsheet for further analysis.

RESULTS

Out of a total of 332 dentists that responded to the survey, all study participants stated that they prescribed analgesic and anti-inflammatory drugs for implant surgery to their patients. Nine NSAIDs, acetaminophen (paracetamol) and two semi-synthetic opioid drugs were prescribed [Table 1]. Additionally, 33.7% ($n = 112$) participants prescribed steroids in conjunction with NSAIDs [Table 2].

The most preferred prescription was the combination of ibuprofen and paracetamol (32.2%, $n = 107$) [Figure 1]. The most commonly prescribed drugs were ibuprofen (44.3%, $n = 147$) and diclofenac (33.7%, $n = 112$). Paracetamol was prescribed by 54.2% ($n = 180$) of the dentists, however, all of these dentists prescribed paracetamol

Table 1: Profile of analgesic and anti-inflammatory drug prescription by dentists performing oral implant surgery

Drug name	n	Drug name used			Protocol			Route			Additional steroid prescription	Unrelated drugs prescribed
		Generic	Trade name	Both	Peri	Post	SOS	Oral	IM	IV		
Ibuprofen+PCM	107	34	66	7	37	70	23	107	0	0	19	29
Diclofenac	67	50	13	4	23	44	16	67	7	3	26	15
Diclofenac+PCM	45	26	13	6	23	22	9	45	0	0	7	24
Ibuprofen	40	31	8	1	18	22	9	40	0	0	13	9
NSAIDs (unspecified)	28	28	0	0	5	23	9	28	2	0	6	0
Ketorolac	22	1	21	0	4	18	4	22	1	0	7	8
Piroxicam	18	11	4	3	8	10	2	18	0	0	5	6
Tramadol	14	9	1	4	3	11	2	14	2	4	9	12
Aceclofenac+PCM	14	8	4	2	7	7	2	14	0	0	8	8
Nimesulide+PCM	12	3	9	0	6	6	6	12	0	0	2	4
Nimesulide	10	7	3	0	1	9	0	10	0	0	3	3
Aceclofenac	9	9	0	0	1	8	4	9	0	0	4	9
Dextropropoxyphene	5	0	5	0	2	3	2	5	0	0	0	0
Tramadol+PCM	2	1	1	0	2	0	0	2	0	0	2	0
Etoricoxib	2	2	0	0	2	0	0	2	0	0	0	2
Aspirin	2	2	0	0	0	2	0	2	0	0	0	0
Mefenamicacid+PCM	1	0	1	0	0	1	0	1	0	0	1	1
Total		222	144	27	18	140	253	86	393	12	7	112

PCM: Paracetamol, Peri: Peri-operative, Post: Post-operative route, PO: Per oral, IV: Intra venous, IM: Intra muscular, NSAIDs: Non-steroidal anti-inflammatory drugs, SOS: Stat on symptoms

Table 2: Profile of steroid drug prescription by dentists performing oral implant surgery

Drug name	n	Drug name used			Protocol			Route		
		Generic	Trade name	Both	Pre	Peri	Post	Oral	IM	IV
Prednisolone	33	28	5	0	3	7	23	107	0	0
Dexamethasone	57	42	15	0	19	2	36	67	7	3
Hydrocortisone	2	2	0	0	2	0	0	45	0	0
Betamethasone	20	9	11	0	10	3	7	40	0	0
Total	112	81	31	0	34	12	66	28	2	0

Pre: Pre-operative, Peri: Peri-operative, Post: Post-operative, Route: PO: Per oral, IV: Intra venous, IM: Intra muscular

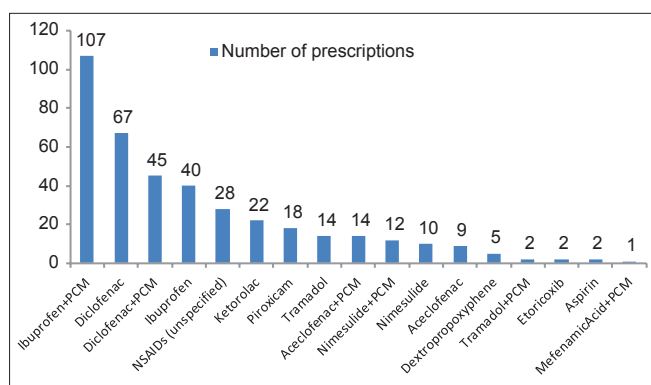


Figure 1: Prescription trend of analgesic/anti-inflammatory drugs for oral implant surgery. PCM: Paracetamol

as an additional drug in combination with some other analgesic, and in no case was paracetamol used as an analgesic-anti-inflammatory drug alone.

More than half of the dentists prescribed more than one drug (64.7%, $n = 215$), and of these 8.4% ($n = 28$) simply stated that they prescribed NSAIDs, without specifying any drug or trade name. Also, majority (56.9%, $n = 189$) used generic drugs names in their prescriptions, brand name was used by 37.3% ($n = 124$) and 5.7% mentioned both ($n = 19$). A single NSAID drug was prescribed by only 35.2% ($n = 117$) dentists. Unrelated drugs were mentioned by 27.4% ($n = 91$) dentists and 58.1% ($n = 193$) indicated the use of pre-formulated drug combinations.

The use of semi-synthetic opioids was noted by 9.0% ($n = 30$) dentists. Tramadol alone was prescribed by 3.3% ($n = 11$) dentists while 1.5% ($n = 5$) gave it in combination with paracetamol. Dextropropoxyphene was prescribed by 1.5% ($n = 5$) dentists only and it was part of a pre-formulated commercially available drug formulation.

Additional drugs were also prescribed along with analgesic-anti-inflammatory drugs. These included tissue enzymes such as serratiopeptidase (10.8%, $n = 36$), chymotrypsin (0.3%, $n = 1$) and chlorzoxazone (4.2%, $n = 14$). Caffeine was present in 1.5% ($n = 5$) of the prescriptions. All of these drugs were part of pre-formulated commercially available drug formulations.

Drug dose was mentioned by 5.4% ($n = 18$) dentists only. The peri-operative treatment protocol (pre-surgical dose followed by post surgical regimen) was preferred by 35.5% ($n = 118$) dentists while 64.7% ($n = 215$) gave the medication postoperatively only. The term 'Stat on Symptoms' was also mentioned by 21.6% ($n = 72$) dentists. Post-operative prescription duration ranged from 0 to 9 days, the most common being 5 days.

The oral route was recommended by all 332 dentists with an additional injection via intramuscular route (3.0%, $n = 10$) or intravenous route (1.5%, $n = 5$) along with this.

Regarding steroids, out of the 33.7% ($n = 112$) participants that prescribed steroids, dexamethasone (50.8%, $n = 57$) was the most preferred, followed by prednisolone (29.4%, $n = 33$). Also, majority used generic names in their

prescription (72.3%, $n = 81$) but only 19.6% ($n = 22$) mentioned the dose. It is notable that most dentists preferred injectable steroid therapy (58.9%, $n = 66$) [Table 2].

DISCUSSION

A review of our study results shows that most of the dentists prescribed traditional NSAIDs to patients undergoing routine dental implant surgery. Only a marginal section of the dentists prescribed the newer cyclo-oxygenase selective group of drugs on a regular basis. Similar prescription patterns for analgesics in the dental setting have also been observed in studies conducted in Istanbul,^[9] Bangladesh,^[10] Karnataka^[11] and Alabama.^[12] It is noteworthy that analogous results have also been reported in a study illustrating country comparisons in analgesic usage.^[13]

Evaluation of the prescription patterns revealed that there was a great deal of variability in the drugs prescribed and the protocols followed for their prescription. Regarding the analgesic drug prescribed, ibuprofen was the most prescribed, followed by diclofenac. The role of both these drugs in the management of dental and post-surgical inflammatory pain is recommended by many authors.^[14-17] Amongst recommendations regarding the use of NSAIDs in dentistry, it has been suggested that ibuprofen is an ideal prototype for consideration in pain of dental origin.^[2]

A noteworthy aspect of our study was the finding that the most common prescription pattern was the use of ibuprofen in combination with paracetamol, and diclofenac with paracetamol. No dentist prescribed paracetamol alone as an analgesic drug. Guidelines on sedation and management of dental pain^[16] state that it is irrational to combine two or more NSAIDs in therapy, however, paracetamol or opioid analgesics are suitable for combination with NSAIDs whenever a combination is required in severe pain only.^[18-21] A review of literature related to ibuprofen-paracetamol combination shows that the two drugs tend to provide efficacious pain control in the dental model when used together.^[22]

Additionally, our study participants have also prescribed a variety of other NSAIDs such as piroxicam and ketorolac. However, it may be noted that these drugs have not been recommended for pain control in the dental pain model and are known to have more severe side effects.^[2,4] Some dentists have also mentioned the use of unrelated NSAIDs in their prescriptions, indicating a subjective preference in prescribing different drugs to different patients.

Another matter for concern regarding the use of NSAIDs for analgesia is the incidence of side effects, specifically gastrointestinal (GI) bleeding.^[23] The safest drug in this regard has been noted as Ibuprofen.^[24] However, this has also been related to the frequency and duration of overall NSAID therapy. This may not be significant in normal healthy individuals taking short-term therapy for oral surgical related pain.^[2,4,25]

In relation to prescription patterns, there was some variability in the preference for perioperative regimens versus postoperative prescription only. The role of a preoperative or loading dose of analgesic medication before surgery has been recommended as a form of preemptive analgesia.^[19,26] In our study, only 35.5% ($n = 118$) of our participants who preferred the peri-operative regimen gave due consideration to this method of analgesic prescription.

The duration of prescription ranged from a self-medication preference or "stat-on-symptoms" approach to the medication being prescribed for 2 to 9 days post-surgically. Most authors recommend prescription duration of 4 to 6 days, and most of our study participants also fell into this range.^[16,27] All dentists in our study recommended the oral route of delivery, while only a few used an additional injection of NSAID drugs. Again, most authors recommend only oral NSAID therapy for dental and postoperative pain.^[16,27]

When considering the method of prescription, it was seen that fewer dentists wrote the brand names of the drugs prescribed. The majority preferred to use generic names of commercially available drugs, including pre-formulated drug combinations.

To manage NSAIDs associated adverse effects on the GI tract, a proton pump inhibitor or H2 receptor antagonist is usually recommended for patients that are at high risk of ulcers.^[10] Only five of our study participants mentioned these drugs in their prescriptions. Our study also illustrated that only a minority prescribed semi-synthetic opioid analgesics (tramadol and dextropropoxyphene) and this trend was also in accordance with indications for use of NSAIDs for dental and post-surgical pain.^[2,16]

The role of glucocorticoids as adjuncts for pain and edema has received interest in recent time.^[28] Literature has shown that the short-term use of corticosteroids is safe and provides analgesia in acute postoperative pain in healthy adults.^[29] However, the optimal dose, mode and timing of administration remain unclear.^[30] One meta-analysis has provided reliable evidence that dexamethasone is an ideal drug for ameliorating acute postoperative pain.^[5] Of the 30% of our study sample that did prescribe steroids, the majority did prescribe dexamethasone, but the duration, mode of delivery and protocol were variable. It is noteworthy that many of the dentists in our study prescribed injectable steroid therapy for up to seven days postoperatively.

It was interesting to note that pre-formulated commercially available drug combinations contained additional drugs such as serratiopeptidase and chlorzoxazone. The role of a muscle relaxant in dental implant surgery remains unclear.

Review of current literature reveals that almost all authors are in favour of the use of conventional NSAIDs, specifically ibuprofen, ibuprofen with paracetamol and diclofenac, for the management of dental and postoperative pain and inflammation. These drugs are also easily available

over the counter without prescription.^[9-11,13] The role of steroids, especially dexamethasone, as adjuncts in postoperative pain management has also been reviewed. NSAIDs are also associated with side effects such as GI bleeding and allergic reactions, and it is critical that these drugs be prescribed cautiously.^[19,24,25]

Our study illustrates that the current trend of prescription of analgesic and anti-inflammatory drugs for routine oral implant surgery among Indian dentists is in accordance with the guidelines for management of dental pain worldwide. However, evidence of prescription of drugs not primarily indicated for dental pain management and protocols not consistent with current recommendations, is noteworthy. It is essential that, to ensure safe delivery and avoidance of potential complications arising due to these drugs, dental practitioners should be more aware of the appropriate dose, dosage regimen and indications for specific analgesics. Additionally, further research is required to assess the outcomes, including adverse effects, related to the prescription of these drugs for oral implant surgery.

REFERENCES

1. Becker DE, Phero JC. Drug therapy in dental practice: nonopioid and opioid analgesics. *Anesth Prog* 2005;52:140-9.
2. Becker DE. Pain management: Part 1: managing acute and postoperative dental pain. *Anesth Prog* 2010;57:67-79.
3. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med* 1996;156:1530-6.
4. Ong KS, Seymour RA. Maximizing the safety of non-steroidal anti-inflammatory drug use for postoperative dental pain: an evidence-based approach. *Anesth Prog* 2003;50:62-74.
5. Turan A, Sessler DI. Steroids to ameliorate postoperative pain. *Anesthesiology* 2001;15:457-9.
6. Brodala N. Flapless surgery and its effect on dental implant outcomes. *Int J Oral Maxillofac Implants* 2009;24:118-25.
7. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. *J Clin Pharm Therap* 2001;26:257-64.
8. Datta R, Grewal Y, Batth JS, Singh A. Current trend of antimicrobial prescription for oral implant surgery among dentists in India. *J Maxillofac Oral Surg* 2013;DOI: 10.1007/s12663-013-0567-7.
9. Şermet S, Akgün MA, Atamer-Şimşek S. Analgesic prescription pattern in the management of dental pain among dentists in Istanbul. *Marmara Pharm J* 2012;16:41-7.
10. Mahadi HM, Jamiur RK, Binte WT, Sharmin CS. Study on the use pattern of NSAIDs in some general and specialized hospitals of Bangladesh. *Int Res J Pharm* 2012;3:152-5.
11. Jayanthi MK, Suresha RN. A study of prescribing patterns of NSAIDs in dental OPD of a tertiary care teaching hospital. *Asian J Med Clin Sci* 2013;2:27-9.
12. Barasch A, Safford MM, McNeal SF, Robinson M, Grant VS, Gilbert GH. Patterns of post-operative pain medication prescribing after invasive dental procedures. *Spec Care Dentist* 2011;31:53-7.
13. Abbott FV, Fraser MI. Use and abuse of over-the-counter analgesic agents. *J Psychiatry Neurosci* 1998;23:13-34.
14. Scottish dental clinical effectiveness programme. Drug prescribing for dentistry: a clinical guidance. 2nd ed. 2011. p. 51-63. Available from: <http://www.sdcep.org.uk/index.aspx?o=2334>. [Last accessed on 2015 Feb 02].
15. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on non-steroidal anti-inflammatory drugs. *Clin Med Res* 2007;5:19-34.
16. Pozzi A, Gallelli L. Pain management for dentists: the role of ibuprofen. *AnnStomatol* 2011;2:3-24.
17. Bhaskar H, Kapoor P, Ragini. Comparison of transdermal diclofenac patch with oral diclofenac as an analgesic modality following multiple premolar extractions in orthodontic patients: a cross over efficacy trial. *Contemp Clin Dent* 2010;1:158-63.

18. Ozkan BT, Durmus E, Kalayc A, Kurban S, Akca CN. The evaluation of safety and analgesic efficacy of paracetamol and ibuprofen followed by impacted third molar surgery. *Eur J Gen Med* 2010;7:310-6.
19. Haas DA. An update on analgesics for the management of acute postoperative dental pain. *J Can Dent Assoc* 2002;68:477-82.
20. Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, Davies E and Anderson BJ. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. *Br J Anaesth* 2010;104:80-8.
21. Gómez-Moreno G, Guardia J, Cutando A, Calvo-Guirado JL. Pharmacological interactions of anti-inflammatory-analgesics in odontology. *Med Oral Patol Oral Cir Bucal* 2009;14:81-9.
22. Rawal N, Macquaire V, Catalá E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial. *J Pain Res* 2011;4:104-10.
23. Mehlich DR. The efficacy of combination analgesic therapy in relieving dental pain. *J Am Dent Assoc* 2002;133:861-71.
24. Waring WS, Robinson OD, Stephen AF, Dow MA, Pettie JM. Does the patient history predict hepatotoxicity after acute paracetamol overdose? *QJM* 2008;101:121-5.
25. Jackson CH, MacDonald NC, and Cornett JW. Acetaminophen: a practical pharmacologic overview. *Can Med Assoc J* 1984;131:25-32.
26. Kissin I. Preemptive analgesia. *Anesthesiology* 2000;93:1138-43.
27. Hersh EV, Kane WT, O'Neil MG, Kenna GA, Katz NP, Golubic S, Moore PA. Prescribing recommendations for the treatment of acute pain in dentistry. *Compend Contin Educ Dent* 2011;32:22,24-30.
28. Bodnar J. Corticosteroids and oral surgery. *Anesth Prog* 2001;48:130-2.
29. Dahners LE, Mullis BH. Effects of non-steroidal anti-inflammatory drugs on bone formation and soft tissue healing. *J Am Acad Orthop Surg* 2004;12:139-43.
30. Salerno A, Hermann R. Efficacy and safety of steroid use for postoperative pain relief. *J Bone Joint Surg Am* 2006;88:1361-72.

How to cite this article: Datta R, Grewal Y, Batth JS, Singh A. A survey of analgesic and anti-inflammatory drug prescription for oral implant surgery. *Plast Aesthet Res* 2015;2:51-5.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 25-09-2014; **Accepted:** 18-12-2014

Heel pad avulsion injury: an approach with hyperbaric oxygen therapy

Pradeoth Korambayil Mukundan, Prashanth Varkey Ambookan

Department of Plastic Surgery and Burns, Jubilee Institute of Surgery for Hand, Aesthetic and Microsurgery, Jubilee Mission Medical College and Research Institute, Thrissur 680007, Kerala, India.

Address for correspondence: Dr. Pradeoth Korambayil Mukundan, Flat No. 102, Nandana, Haritha Gardens, Vadookara, Thrissur 680007, Kerala, India. E-mail: pradeoth@gmail.com

ABSTRACT

Aim: Crush injuries of the foot are often associated with partial or complete degloving of the heel pad. The purpose of this study is to present an algorithm for the management of various types of heel pad avulsion injuries, including hyperbaric oxygen (HBO) therapy in the treatment regimen. **Methods:** We present a prospective study of 27 patients with various types of heel pad avulsion managed in our institution from December 2012 to June 2013. Heel pad avulsion injuries were classified according to the angiosomal pattern. Partial or complete avulsions were classified and treated accordingly. HBO therapy was administered postoperatively. The postoperative period, hospital course, and follow-up were documented in patients with heel pad avulsion injuries. **Results:** Of 27 patients, 20 cases presented with partial avulsion and 7 cases were complete avulsion. Of 20 cases of partial avulsion, one of the flaps was anchored with K-wire. Nineteen cases of partial heel pad avulsion were managed by suturing. Eight patients out of 20 required skin grafting as a secondary procedure at a later date. Out of 7 cases of complete avulsion, one was managed by full-thickness skin grafting, one case by reverse sural artery flap coverage, and four cases were managed by free tissue transfer. No flap revisions were required, and no complications were experienced for the transferred flaps. **Conclusion:** HBO therapy may be a useful adjunct in the treatment of heel pad avulsion injuries.

Key words:

Angiosome, heel pad avulsion, hyperbaric oxygen therapy, soft tissue reconstruction

INTRODUCTION

Foot trauma is a significant cause of morbidity among the working age population. Crush injuries to the foot are often associated with avulsion injuries of the heel pad. Heel pad avulsion injuries are always a challenge for the plastic surgeons, as the reconstructed tissue, even though sensate, may not match the unique and complex nature of the native fat pad structure. Heel pad avulsion injuries may be partial or complete.^[1] When the avulsed heel pad tissue is avascular or clinically nonviable, avulsion is said

to be complete and may require removal of the avascular tissue and reconstruction with local or distant flaps. Providing sensate and glabrous skin may not be possible in patients with extensive injuries.^[2] There are clinical situations in which the avulsed heel pad structure may be viable, requiring debridement and anchoring of the heel pad flap in position. In cases of partial avulsion, the heel pad is, usually, debrided, reattached in position by sutures or K-wire fixation, and further surgical interventions are postponed until there has been a demarcation of the nonviable tissue.^[1] As the heel pad tissue is irreplaceable, there is a need for alternative methods of preserving the marginal tissue as well as preventing ischemia and hypoxic advancement of the injured tissue. In this prospective study, various treatment modalities including hyperbaric oxygen (HBO) therapy, primary closure, full thickness skin grafting/split thickness skin grafting (FTSG/STSG), and local or distant flap coverage were utilized to preserve and reconstruct the valuable heel pad tissue.

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153200

METHODS

Twenty-seven patients with heel pad avulsion (isolated/combined) were treated over a period of 7 months (December 2012 to June 2013). The avulsed heel pad flaps were classified on the basis of the angiosomal concept. Heel pad flaps based distally were classified as tissue receiving its vascular supply from the medial plantar and lateral plantar artery angiosomal territories. Flaps based distally and medially were considered to receive their vascular supply from the medial and lateral plantar arteries and the calcaneal branch of the posterior tibial artery. Flaps based distally and laterally were considered to have a vascular supply based on the medial and lateral plantar arteries and the calcaneal branch of the peroneal artery. Those flaps with proximal continuity were classified as having their blood supply from perforators of either the posterior tibial or peroneal vessels.

Following initial assessment and resuscitation of the patient according to the ATLS protocols, acutely presenting heel pad avulsion injuries were assessed for the extent of degloving, skeletal injury, associated soft tissue loss, vascularity to the heel pad flap, and flap avulsion patterns. Patients were informed about the line of management, possible treatment modalities, and the need for additional surgery procedures pertaining the pattern of injuries. Patients were started on empirical antibiotic therapy, including a third-generation cephalosporin and anaerobic coverage. Adequate analgesia was assured. Thorough wound debridement and fixation of the fractures was performed. In cases of partial avulsion requiring the anchorage, HBO therapy was initiated during the immediate postoperative period. Six sessions of HBO therapy, each session lasting 1 h and continued for 6 days, was administered to the patients postoperatively. In cases of complete avulsion, the nonviable tissues were debrided, and depending upon the patient's condition, soft tissue reconstruction was performed as early as possible. Postoperatively, 6 HBO therapy sessions were administered for all patients. Immobilization of the limb was done in all cases. Outcomes following each type of management and secondary procedures performed were noted.

The review board of Jubilee Mission Medical College and Research Institute approved this study.

RESULTS

The mode of injury for all patients was road traffic accident. Out of 27 patients, there were 5 female (18.1%) and 22 male patients (81.9%). Mean age was 34.18 years (range: 5-53 years). For 12 patients the avulsed flap was based distally, in 7 patients the flap was based distally and laterally, in 5 patients the flap was based distally and medially, in 2 patients the flap had proximal and distal connections with disruption in the medial and lateral aspects and in 1 patient the flap was continuous only in the lateral and medial aspects. Out of 20 cases of partial avulsion, one of the flaps was anchored with K-wires by the orthopedic department, and then referred to plastic surgery for soft tissue coverage. Nineteen cases of partial

heel pad avulsion were managed by primary closure. Eight patients out of 20 required skin grafting as a secondary procedure at a later date. Out of 7 cases of complete avulsion, one was managed by full-thickness skin grafting, one case by reverse sural artery flap coverage, and four cases were managed by free tissue transfer. Among the free tissue transfer, two were latissimus dorsi muscle flaps, one was a gracilis muscle flap, and one was an anterolateral thigh flap [Table 1]. There were no complications following flap transfer and graft take was adequate. The patients in our series did not experience the common side-effects of HBO therapy such as aural or pulmonary barotrauma or transient reversible myopia during the treatment sessions. No complications were noted during the follow-up period.

Case 1

A 43-year-old female was admitted with a crush injury to the right leg and foot region following a crush injury by a heavy vehicle [Figure 1a]. The patient presented with soft tissue loss over the anterior aspect of the leg and dorsum of the foot. The heel pad was avulsed from the calcaneum but was continuous to the proximal and the distal aspect by the skin and subcutaneous tissue [Figure 1b]. Stabilization of the ankle and heel pad was performed with an external fixator following wound debridement. Soft tissue coverage of the anterior aspect of the leg and dorsum of the foot was provided by a latissimus dorsi free flap and split-thickness skin grafting [Figure 1c and d]. The vessels of the latissimus dorsi flap were anastomosed end-to-side to the posterior tibial vessels as the anterior tibial vessels were avulsed up to the level of middle third of the leg. HBO therapy was administered in 6 sessions postoperatively. Following demarcation of the avascular tissue over the medial part of the leg and proximal heel pad, nonviable tissue was debrided. Because there was adequate soft tissue padding over the calcaneum, skin grafting was performed [Figure 1e-g]. Six sessions of HBO therapy were administered following skin grafting.

Case 2

An 18-year-old male was admitted with a crush injury of the right leg and foot with heel pad avulsion. Skin and subcutaneous tissue were connected in the proximal and distal aspects [Figure 2a]. The heel pad was anchored with K-wires by the orthopedic department, and the patient was then referred to plastic surgery for further management [Figure 2b]. HBO therapy was administered for six sessions. Following demarcation of the nonviable tissue, the avascular tissue was debrided [Figure 2c and d]. Most of the foot pad tissue was found to be preserved, and skin grafting was sufficient for coverage of the soft tissue defect following debridement [Figure 2e and f]. Six additional sessions of HBO therapy were administered following skin grafting.

Case 3

A 52-year-old male was admitted with heel pad avulsion based distally [Figure 3a]. Primary closure was performed following debridement [Figure 3b and c]. HBO therapy was

administered for 6 sessions. The wound healed without any additional intervention [Figure 3d].

DISCUSSION

Crush injuries to the foot are a significant cause of morbidity among the working age population and are

commonly associated with degloving of the heel pad.^[1] The heel pad flaps are typically elevated in a posterior to anterior direction. Crush injuries may disrupt the heel pad in various flap patterns, which are medially based, laterally based, medially and anteriorly based, or laterally and anteriorly based. In some cases, the soft tissues in the medial, posterior and lateral areas are disrupted, leaving

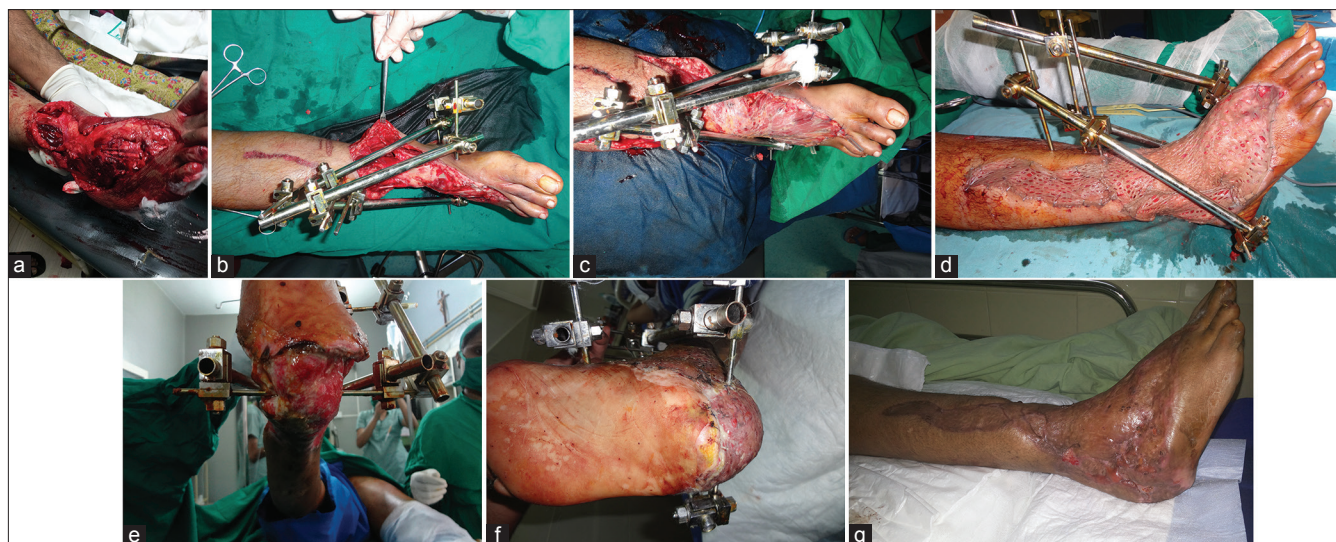


Figure 1: (a) Crush injury to the right leg and foot region; (b) soft tissue loss anterior aspect of leg and dorsum of foot with heel pad avulsed from the calcaneum with continuity to the proximal and the distal part; (c) soft tissue coverage of leg and dorsum of foot with latissimus dorsi free tissue transfer; (d) free muscle tissue covered with split thickness skin graft; (e) status of heel region following debridement and hyperbaric oxygen therapy after 3 weeks of injury; (f) postoperative picture following skin grafting over heel pad region; (g) late postoperative picture

Table 1: The patients treated for heel pad avulsion injury

No.	Age (years)/gender	Mode of injury	Base of vascularity	Primary management following debridement	Secondary procedure
1	32/male	RTA	Distal	Primary suturing	
2	23/male	RTA	Distal	Primary suturing	
3	24/female	RTA	Distal	Primary suturing	SSG
4	42/male	RTA	Distal	Primary suturing	SSG
5	53/male	RTA	Distal	Latissimodorsi flap	
6	34/female	RTA	Distal	Latissimus dorsi flap	
7	42/male	RTA	Distal and lateral	Primary suturing	
8	27/male	RTA	Distal and medial	Primary suturing	
9	34/male	RTA	Distal	Gracilis flap	
10	5/male	RTA	Distal	FTSG	
11	52/female	RTA	Distal	Primary suturing	
12	25/male	RTA	Distal and lateral	Primary suturing	SSG
13	27/male	RTA	Distal and lateral	Primary suturing	
14	21/male	RTA	Distal and lateral	Primary suturing	SSG
15	28/male	RTA	Distal and lateral	Primary suturing	
16	43/male	RTA	Distal and lateral	Primary suturing	
17	42/male	RTA	Lateral and medial	Primary suturing	SSG
18	37/male	RTA	Distal and lateral	Primary suturing	
19	43/female	RTA	Proximal and distal	Latissimus dorsi flap	SSG
20	35/male	RTA	Distal and medial	Primary suturing	
21	39/male	RTA	Distal and medial	Primary suturing	
22	42/male	RTA	Distal and medial	Primary suturing	
23	45/male	RTA	Distal and medial	Primary suturing	SSG
24	21/female	RTA	Distal	Primary suturing	SSG
25	18/male	RTA	Proximal and distal	Anchorage with K-wire	SSG
26	47/male	RTA	Distal	Reverse sural flap	
27	42/male	RTA	Distal	Anterolateral thigh flap	

RTA: Road traffic accident, FTSG: Full thickness skin grafting, SSG: Split thickness skin grafting

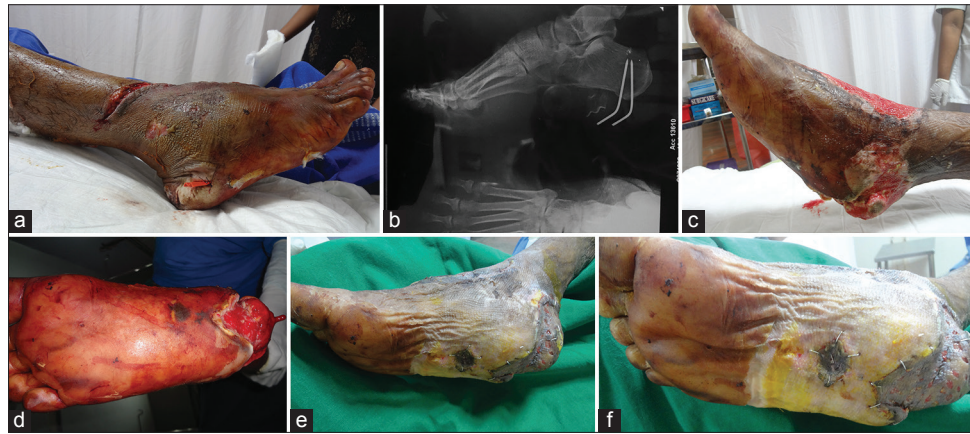


Figure 2: (a) Crush injury right leg and foot with heel pad avulsed skin and subcutaneous tissue connectivity in the proximal and distal part; (b) X-ray lateral view right foot showing K-wires used for stabilization of avulsed heel pad; (c) appearance of foot 3 weeks following debridement and hyperbaric oxygen treatment session; (d) plantar view of foot following 3 weeks; (e) medial view of the foot following skin grafting; (f) plantar view of the foot following skin grafting



Figure 3: (a) Heel pad avulsion based distally-medial view of left foot foot; (b) wound debridement and primary suturing after placing a suction drain; (c) picture presenting the wound status during immediate postoperative period; (d) late postoperative picture

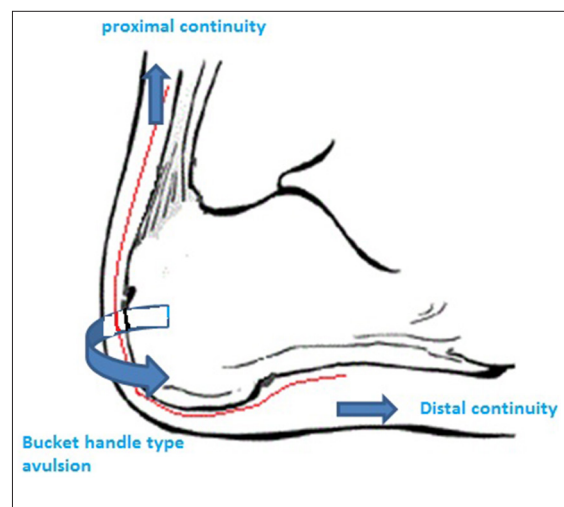


Figure 4: Diagram illustrating heel pad tissue degloved as a bucket handle type over the calcaneal bone with continuity proximally and distally with disruption of soft tissue medial and lateral aspect

only a soft tissue bridge anteriorly. In some instances, the heel pad tissue is degloved in a “bucket handle” configuration over the calcaneal bone, with continuity proximally and distally and disruption of the soft tissue in the medial and lateral aspects [Figure 4]. The heel pad tissue, with its unique architecture, demands preservation in cases of any possible vascular supply. Premature efforts to remove doubtful tissue may result in loss of valuable sensate heel pad tissue, which might have been preserved by delayed intervention. However, a delayed intervention may also result in decreased survival rates of local or distant tissue transfer secondary to tissue edema and an increase in inflammatory factors. Since the zone of soft tissue compromise may extend beyond the zone of injury of the foot, reconstruction of heel pad with local or distant soft tissue reconstruction can be challenging. In addition, efforts to replace the heel pad with vascularized or regional flaps may be limited by decreased fine sensation, bulky soft tissues, and alteration in gait function.^[3]

The vascular anatomy of the leg and foot by means of the angiosomal concept provides us with a better approach for

the management of such complicated injuries [Figure 5]. Out of 6 angiosomes of the foot and ankle, 3 angiosomes are supplied by the posterior tibial artery, 2 angiosomes are supplied by the peroneal artery, and 1 angiosome is supplied by the anterior tibial artery.^[4] The calcaneal branch of the posterior tibial artery supplies the medial aspect of the ankle and the plantar aspect of the heel pad region. The medial plantar branch of the posterior tibial artery feeds the medial aspect of the plantar instep. The lateral plantar branch of the posterior tibial artery feeds the lateral aspect of the forefoot, the plantar aspect of the midfoot, and the plantar aspect of the forefoot. The calcaneal branch of the peroneal artery supplies the lateral aspect of the heel pad region.^[5] Taylor *et al.*^[4] found that these angiosomes are interconnected by either reduced caliber choke vessels or by anastomotic arteries. The principle of utilizing HBO therapy for ulcers with vascular insufficiency and in radiation-induced wounds can be applied to the salvage of vital heel pad tissue. HBO therapy creates an increase in dissolved oxygen in the plasma where there is increased partial pressure of arterial oxygen. Oxygen delivery through

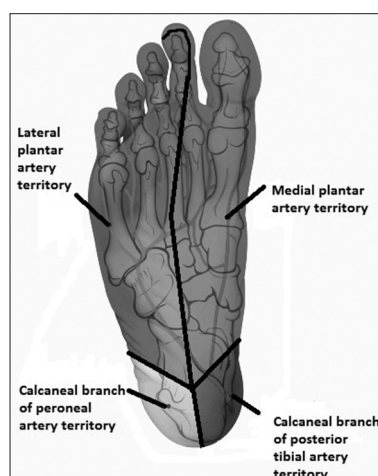


Figure 5: Angiosomal pattern of the heel pad and plantar foot region

the plasma is increased through hemoglobin-bound oxygen, facilitating oxygenation of the deprived tissue, stimulating angiogenesis, fibroblast proliferation, leukocyte oxidative killing, antibiotic synergy, toxin inhibition and vasoconstriction. Vasoconstriction significantly reduces tissue edema without hindering oxygenation. Decreasing edema is desirable in complicated plastic surgical wounds to relieve pressure on the surrounding vessels and structures. Oxygen delivery also leads to mature collagen formation and stimulates angiogenesis.^[6] Ulkür *et al.*^[7] illustrated the usefulness of HBO treatment during the delay period of the flap which can both decrease the time period needed for the delay procedure and increased the effect of the flap delay. The current study illustrates the utility of hyperbaric therapy in the treatment of heel pad avulsion injuries. Most heel pad avulsion injuries with partial continuity act similar to a delayed flap. Hence, considering the valuable heel pad tissue and the need for its preservation at any cost, management should include a modality which can potentially enhance vascularity and wound healing potential during the period of demarcation of necrotic tissue.

Hyperbaric oxygen therapy utilizes 100% oxygen at pressures greater than atmospheric pressure. In the current study, HBO was administered in a Monoplace chamber in which a single patient is placed in a chamber that is then pressurized with 100% oxygen. The pressure inside the chamber is adjusted, ranging from 2.0 ATA to 2.4 ATA for duration of 90 min. As an adjunct to surgery and antibiotics, HBO therapy can significantly decrease costs and complications.^[8] Vasoconstriction reduces edema and tissue swelling while ensuring adequate oxygen delivery and is thus useful in acute trauma wounds. Hyperoxygenation of the crush injury and compartment syndrome followed by flap salvage results in immune stimulation by restoring white blood cell function and enhancing phagocytic capabilities. Neo-vascularization in hypoxic areas is augmented by fibroblastic activity and capillary growth.^[8] Adequate shock management, direct surgical intervention with debridement, repair of soft tissues and any damaged vessels, and stabilization of bony elements are of paramount importance. Adjuvant HBO can be given early to prevent large regions of ischemic necrosis, minimize the frequency and extent of

tissue necrosis, reduce edema, control infection, support healing, and prevent reperfusion injury.^[9]

At the authors' institution, a strategy has been developed to overcome these difficulties and to successfully manage these patients with a combined approach that maximizes tissue perfusion and oxygenation, allowing for surgical correction of such injuries. The current treatment algorithm [Figure 6] begins with surgical debridement and initiation of HBO therapy in the immediate postoperative period. HBO provides supersaturation of the plasma with oxygen, allowing a several-fold increase in the oxygen diffusion gradient. Combination of the modalities allows preservation of marginal tissue, prevention of advancing ischemia and hypoxia and maximum preservation of heel pad tissue. This approach has been used in the current series of 27 patients, achieving maximal preservation of the heel pad with a return to ambulation.

Out of 27 patients, the avulsed flap was distally-based in 12 patients, distally and laterally based in 7 patients and distally and medially based in 5 patients. In 2 patients the flap had proximal and distal connections with disruption in the medial and lateral aspects, and in 1 patient the flap was continuous in only the lateral and medial aspects. In all cases, initial wound debridement was carried out and HBO therapy sessions were started. If flap coverage was required, surgery was scheduled as soon as the patient was stable. HBO therapy was withheld on the day of surgery and recommenced on postoperative day one. When skin grafting was performed at a later date, surgery was followed by six sessions of HBO therapy. Out of 20 cases of partial avulsion, one flap was anchored with a K-wire from the orthopedic department, and then referred to plastic surgery for soft tissue management. Nineteen cases of partial heel pad avulsion were closed primarily. Eight patients out of 20 required skin grafting as a secondary procedure at a later date. Split-thickness skin grafting was the method of choice when adequate soft tissue padding was present. In the authors' experience, the risk of calcaneal bone exposure was decreased in patients treated with HBO therapy. Split thickness grafting can suffice if adequate soft tissue padding is present.^[2] However, there is a need for a randomized controlled study of the preservation of heel fat pad tissue following HBO therapy. Out of 7 cases of complete avulsion, 1 patient was managed by full-thickness skin grafting. The benefit of HBO therapy is greatest in cases in which relatively large areas of tissue are grafted, as in full-thickness skin grafting.^[8] One patient with a heel pad defect was treated by reverse sural artery flap coverage, and four patients were managed by free tissue transfer. Among the free tissue transfer cases, 2 were latissimus dorsi muscle flaps, 1 was a gracilis muscle flap and one was an anterolateral thigh flap. There were no complications following any flap transfers. The patients in the current series did not experience the common side effects of HBO therapy, including aural or pulmonary barotrauma and transient reversible myopia during the treatment session. No recent literature is available on management of heel pad avulsion injuries using surgery and HBO therapy as a combined modality. Other advanced wound care

modalities including negative pressure wound therapy and limited-access dressings could well be utilized along with HBO therapy for the management of such challenging injuries. Complications and problems in wound healing are bound to occur in crush injuries of the foot involving heel pad region. HBO therapy is an adjunct in the management of marginal tissues, but cannot be utilized in an avascular

environment which requires surgical intervention. Measures that could improve the outcome with the adjunct use of HBO therapy should be considered [Figure 7].

In conclusion, the goal of management of heel pad avulsion injuries is to preserve as much viable heel pad tissue as possible and to provide sensate, stable coverage. Principles of wound management with wound evaluation,

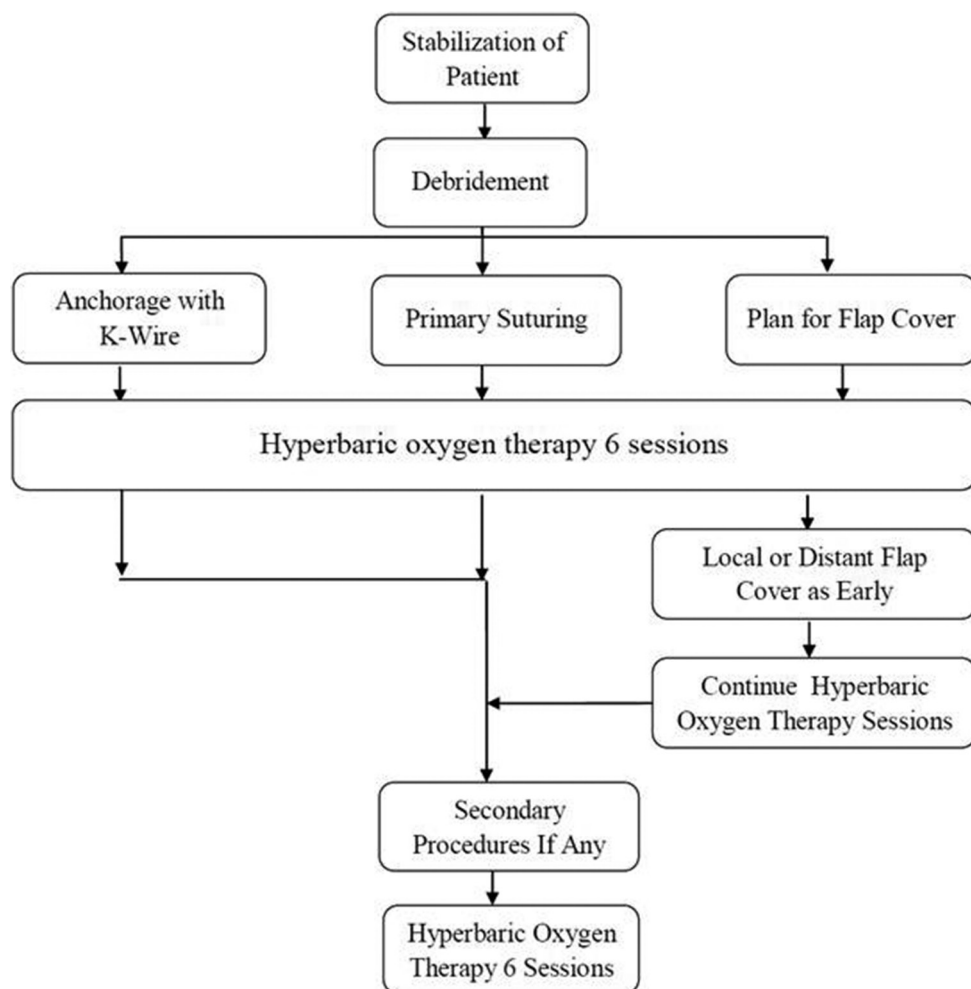


Figure 6: Algorithm for management for heel pad avulsion injuries in our institution

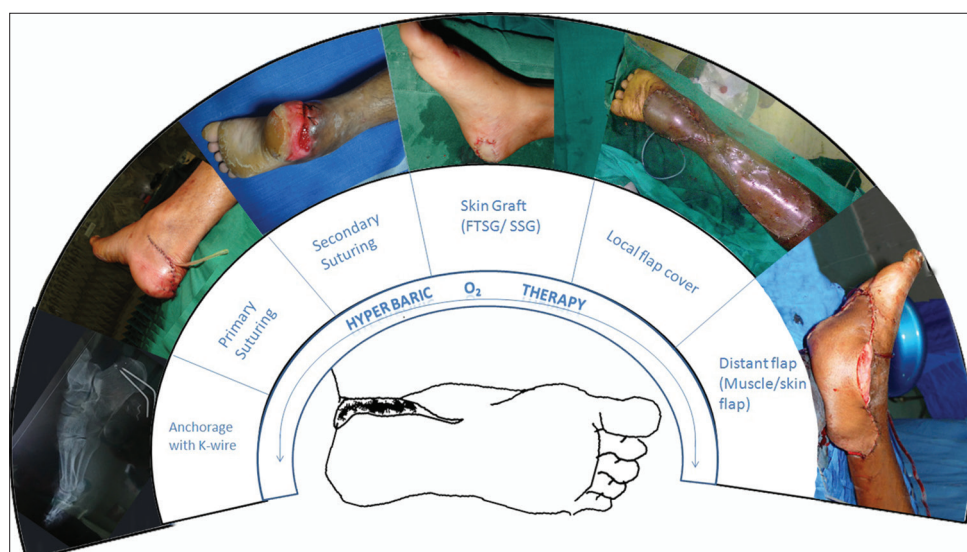


Figure 7: Hyperbaric oxygen therapy as an adjunct in the management of various patterns of heel pad avulsion injuries

debridement with preservation of viable tissue, fracture reduction, prevention of infection, and adequate soft tissue reconstruction are important in the management of heel pad avulsion injuries. The simplest and most appropriate technique is likely to produce the best outcome. This study presents a simple management algorithm for the management of various types of heel pad avulsion injuries. HBO therapy may be used as a useful adjunct in the treatment of such complicated injuries to offer speedy recovery as well as cost benefits.

REFERENCES

1. Mohammed R, Metikala S. Anchorage of partial avulsion of the heel pad with use of multiple kirschner wires. A report of four cases. *JBJS Case Connect* 2012;2:20.
2. Suri MP, Patel AG, Vora HJ, Raibagkar SC, Mehta DR, Vyas UH. Post-traumatic posterior heel soft tissue defect reconstruction. *Indian J Plast Surg* 2005;38:138-43.
3. Levin LS. Foot and ankle soft-tissue deficiencies: who needs a flap? *Am J Orthop (Belle Mead NJ)* 2006;35:11-9.
4. Acín F, Varela C, López de Maturana I, de Haro J, Bleda S, Rodriguez-Padilla J. Results of infrapopliteal endovascular procedures performed in diabetic patients with critical limb ischemia and tissue loss from the perspective of an angiosome-oriented revascularization strategy. *Int J Vasc Med* 2014;2014:270539.
5. Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. *Plast Reconstr Surg* 2006;117:5261-93.
6. Latham E, Hare MA, Neumeister M. Hyperbaric oxygen therapy. eMedicine. In: Schraga ED, Windle ML, Scudder L, editors. Medscape. Available from: <http://www.emedicine.com/plastic/topic526.htm>. [Last accessed on Aug 2014].
7. Ulkür E, Karagoz H, Ergun O, Celikoz B, Yildiz S, Yildirim S. The effect of hyperbaric oxygen therapy on the delay procedure. *Plast Reconstr Surg* 2007;119:86-94.
8. Bhutani S, Vishwanath G. Hyperbaric oxygen and wound healing. *Indian J Plast Surg* 2012;45:316-24.
9. Kemmer A. Crush injury and other traumatic ischemia. In: Mathieu D, editor. *Handbook on Hyperbaric Medicine*. Netherlands: Springer; 2006. p. 311-2.

How to cite this article: Mukundan PK, Ambookan PV. Heel pad avulsion injury: an approach with hyperbaric oxygen therapy. *Plast Aesthet Res* 2015;2:56-62.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 19-08-2014; **Accepted:** 28-09-2014

Simultaneous expander and deep inferior epigastric perforator reconstruction: indications and alloderm sling technique for protecting the anastomosis

Elizabeth Stirling Craig, Ajul Shah, Sarah Persing, Jeffrey Salomon, Stefano Fusi

Department of Surgery, Section of Plastic and Reconstructive Surgery, Yale University School of Medicine, New Haven, CT 06520, USA.

Address for correspondence: Dr. Ajul Shah, Department of Surgery, Section of Plastic and Reconstructive Surgery, Yale University School of Medicine, New Haven, CT 06520, USA. E-mail: ajul.shah@yale.edu

ABSTRACT

Aim: Autologous tissue is considered the “gold standard” for breast reconstruction today. However, little is known about deep inferior epigastric perforator (DIEP) flap reconstruction in combination with tissue expander (TE)/implant. The authors describe a series of combined DIEP flap/TE reconstruction, including its indications and technique to ensure protection of the pedicle during the expansion process. **Methods:** Between January 2009 and December 2012, patients undergoing immediate DIEP with TE reconstruction were retrospectively reviewed. Oncologic, comorbid conditions, intraoperative, postoperative expansion, complications, and technique data points were collected. Photographs were taken postoperatively and patient’s satisfaction surveys were obtained to assess overall satisfaction. **Results:** Five patients underwent immediate DIEP flap/TE reconstruction utilizing our alloderm sling technique. There were no complications to the pedicle, flap, expander, or mastectomy skin perioperatively or postoperatively. All patients describe being very satisfied, often with improved breast volume and projection as compared to their preoperative appearance. **Conclusion:** The results of this study suggest that DIEP flap/TE reconstruction is safe, in particular when utilizing the alloderm sling technique, and should be considered in patients who lack sufficient abdominal tissue, have existing breast asymmetries, or do not desire the scar deformity of latissimus dorsi.

Key words:

Alloderm, autologous, breast cancer, breast reconstruction, deep inferior epigastric perforator, tissue expander

INTRODUCTION

The overall goal of breast reconstruction is to recreate the most naturally appearing and feeling breasts for patients with breast cancer who are treated with mastectomies. Autologous reconstruction with either the transverse rectus abdominus myocutaneous (TRAM) flap, or more

recently the deep inferior epigastric perforator (DIEP) flap, is now considered the “gold standard” for breast reconstruction due to its ability to recreate natural and aesthetic results. However, not all women have sufficient abdominal tissue to make an aesthetically appearing breast. Often, in these cases, an alternative technique for breast reconstruction is the latissimus dorsi (LD) flap with an expander/implant. Miller *et al.*^[1] demonstrated that TRAM flap reconstruction can be simultaneously performed with placement of a tissue expander (TE) to provide improved volume and projection in safe manner for patients who have a thin body habitus with medium to large-sized breasts. Donor site and aesthetic outcomes proved to be statistically improved in patients who underwent TRAM/implant reconstruction when compared to LD/implant reconstruction.^[2] Figs *et al.*^[3] applied these

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153201

same principles to the recent advance in autologous reconstruction the development of the DIEP flap. In concordance with the TRAM/implant literature, Figus *et al.*^[3] demonstrated that placement of a sub-pectoral implant and DIEP flap can be safely performed and utilized in patients with insufficient abdominal tissue, in patients who need correction of breast asymmetries, and in patients that necessitate augmented volume and projection because they desire larger breasts. The main concern with the placement of the expander or implant simultaneously with a DIEP flap is potential injury to the pedicle. The authors describe a series of combined DIEP flap/expander reconstruction as well as the use of an alloderm sling to protect the pedicle from any immediate or delayed injury. The study was approved by review board of Yale University.

METHODS

Between January 2009 and December 2012, over 250 DIEP flaps were performed, and 91% were bilateral reconstructions. When clinical assessment demonstrated inadequate abdominal tissue to reconstruct the patient's desired breast size, discussions regarding the simultaneous use of an expander or implant were undertaken. Patients with a high probability of postoperative radiation were not offered the choice of a combined DIEP/expander procedure. However, history of preoperative radiation was not used as exclusion criteria. There were 5 patients who underwent simultaneous DIEP flap and expander/implant placement. These patient's charts were retrospectively reviewed, and data points were collected. These data points include patient demographics, co-morbid conditions, pre- or postoperative radiation, primary disease, operative details, the final volume of the expander postoperatively, length of follow-up, and complications. All patients had postoperative photos taken 4-12 months postoperatively. Patients were asked to assess their satisfaction with the reconstruction using a four-point scale, with the number 1 defined as dissatisfied and the number 4 as very satisfied.

Operative technique: alloderm sling

The borders of the breast are outlined preoperatively as is routinely done in expander-only reconstruction. Elevation of DIEP flaps occurs simultaneously while the general surgeons perform the mastectomy. Perforators are isolated, and the inferior epigastric pedicles are dissected and exposed. Once the mastectomies are complete [Figure 1], the subpectoral dissection is undertaken, and sizers are placed. Alloderm is routinely used infero-laterally to recreate the breast pocket and breast borders. The sizer is expanded to the desired final size, and the alloderm is secured in place [Figure 2]. The sizers are then deflated, and a window is created within the medial portion of the pectoralis, which allows access to the internal mammary artery and vein. At this time, dissection of the recipient vessels begins with the removal of the rib over the internal mammary vessels. Once the internal mammary vessels are dissected and exposed, the sizer is then replaced into the subpectoral pocket and re-inflated to the

desired breast volume. A piece of alloderm (approximately 4 cm × 5 cm) is shaped to fit the defect between the ribs and the lateral edge of the pectoralis window. The alloderm is first secured to the rib periosteum superiorly and inferiorly and is then draped along the lateral border of the pectoralis window [Figure 3]. The sizer is then exchanged with a smooth, round expander/implant, and a small pocket along the infero-lateral breast is dissected for placement of the external port. Saline is infused via the external port, and lateral digital pressure



Figure 1: Bilateral areola-sparing mastectomy defects

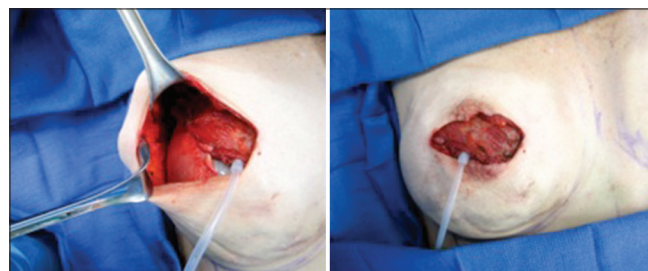


Figure 2: Standard technique of tissue expander reconstruction: placement of subpectoral sizer and securing alloderm inferiolaterally to the released pectoralis muscle edge. The sizer will be replaced with placement of a tissue expander with an external port

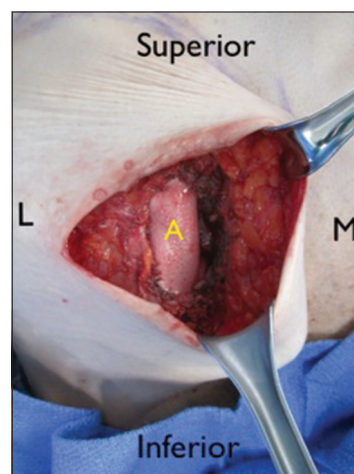


Figure 3: A small window within the pectoralis muscle is made medially and the internal mammary vessel is dissected and exposed. The alloderm sling is then sutured in place to form the lateral "wall" of the window within the pectoralis or the new medial boundary to the subpectoral expander

on the expander/implant confirms appropriate position and integrity of the alloderm sling [Figure 4]. The expander/implant is then deflated to allow room for the microvascular anastomosis of the internal mammary vessels to the deep inferior epigastric pedicle. The DIEP flap is then secured in place, the overlying mastectomy skin is approximated, and a subjective amount of saline is infused into the TE/implant. This is all done while ensuring that: (1) the alloderm sling is competent; (2) the DIEP flap appearance and Doppler signal do not change; and (3) the mastectomy skin appears well perfused. As in routine breast reconstruction, the patient is then placed in an upright position, and the appropriate placement of the DIEP flap and expander/implant with resolution of any volume asymmetries is confirmed. Two 10-flat Jackson Pratt drains are placed in each breast: one within the alloderm breast pocket and the other outside of the alloderm infero-laterally. Postoperatively, the patients are placed on DVT prophylaxis until day of discharge and antibiotics until the drains are discontinued. As historically described with TRAM/implant procedures, expansion was

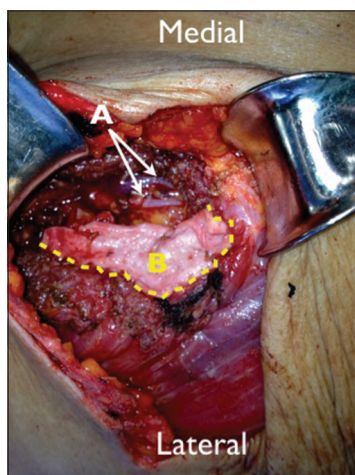


Figure 4: (A) Dissected and exposed recipient internal mammary artery and vein; (B) alloderm sling sutured in place to the rib periosteum superiorly and inferiorly as well as to the medial edge of the pectoralis. The subpectoral expander is therefore limited from migrating medially towards the internal mammary vessels by the alloderm sling

initiated 4-6 weeks postoperatively.^[4] Permanent smooth, round silicone gel implants were exchanged once the patient's desired breast volume was met.

RESULTS

Five patients underwent combined DIEP/TE reconstruction. The average age was 50 years, and all patients had early disease, few comorbidities, and were not smokers [Table 1]. Four patients had no prior reconstruction, one patient had prior bilateral TE placement with postoperative radiation and subsequent infections that led to significant deformities bilaterally and her desire for secondary reconstruction.

Of the 5 immediate DIEP flap/TE patients, four patients underwent bilateral reconstructions, and 1 patient had a stacked DIEP flap with implant placement for a unilateral defect [Figure 5]. There were no reoperations, episodes of venous congestion, hematomas, partial or total flap losses, seromas, infections, or expander/implant leaks [Table 2]. There were no instances of expander/implant extrusion, migration or palpability. The average final expander size was 325 mL \pm 132.5 mL (range: 200-400 mL). All patients have undergone an uneventful expander/implant exchange procedure, and none has necessitated a revision or fat grafting procedures to correct asymmetries. All patients describe being "very satisfied" with their reconstructive result (score 4) with subjective improvement in volume and projection of their breasts. Length of follow-up ranged from 6 to 18 months [Figure 6].

DISCUSSION

Plastic surgeons are constantly searching for ways to optimize techniques and perfect results. Koshima *et al.*^[1] was the first to improve upon the TRAM flap design by isolating the abdominal tissue on perforators and sparing the muscle. Not surprisingly, the DIEP flap has since gained widespread popularity and made inroads as the gold standard for autologous reconstruction, providing

Table 1: Cohort demographics, comorbid conditions and oncologic characteristics

Age (years)	Height (m)	Weight (kg)	BMI	Co-morbidities	Smoker	Preoperative radxn	Prior recon	Breast cancer stage	Bilat recon
41	1.54	68.03	28.3	None	No	No	No	I	Yes
50	1.70	58.51	20.4	None	No	No	No	0	No
55	1.60	58.51	23.4	None	No	Yes	Yes	II	Yes
49	1.70	71.66	25.1	None	No	No	No	I	Yes
50	1.65	57.15	20.7	HTN, DM	No	No	No	0	Yes

BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension

Table 2: Cohort operative details and complications

Patient	Expander size	Initial saline infused	Hematoma	Seroma	Injury to flap	Infection	Asymm	Satisfaction score (1-4)
1	350 mL	0 mL	No	No	No	No	No	4
2	250 mL	150 mL	No	No	No	No	No	4
3	250 mL	0 mL	No	No	No	No	No	4
4	250 mL	200 mL	No	No	No	No	No	4
5	275/400 mL	200/275 mL	No	No	No	No	No	4



Figure 5: Right stacked deep inferior epigastric perforator (DIEP) flap with immediate subpectoral 250 mL expander and nipple reconstruction. Left breast augmentation with subpectoral 250 mL gel implant. Three months postoperative

both a lasting result and breasts that appear and feel natural.

However, not all women who desire autologous reconstruction have sufficient abdominal tissue to recreate an aesthetic appearing breast. Alternative donor sites for autologous reconstruction include the gluteal region, posterior thigh, and medial thigh, however, these sites generally contribute even less tissue than the abdomen. Historically, the standard procedure for thin women desiring autologous reconstruction was a combined LD flap/implant breast reconstruction. Kronowitz *et al.*^[2] recently demonstrated that a superior alternative to the LD flap/implant procedure in this patient population is a combined TRAM/implant procedure. Eighteen TRAM/implant patients demonstrated a higher aesthetic score when compared to the LD/implant group by both the patients and a panel of blinded judges. The overall impression by the blinded judges was that the TRAM flap more accurately “recreated the breast with the implant contributing less to the overall shape” when compared with the LD/implant group. Serletti and Moran^[4] corroborated these findings by suggesting that the subcutaneous tissue of the TRAM flap more accurately resembles native breast tissue, and unlike the LD, will not atrophy over time. In fact, any fluctuations in weight will result in volume changes in the TRAM flaps.

In addition to superior aesthetic results, the TRAM/implant group experienced fewer donor site complications when analyzed against the LD/implant group.^[2] The scar from an LD flap tends to widen over time, and while it can be concealed behind a bra, the unilateral contour deformity of missing the LD muscle can be apparent.^[1] On the other hand, the TRAM or DIEP flap donor site scar does not tend to widen over time, has no contour deformity, and can be easily concealed with most under-garments.

While TRAM/implant procedures offer optimal aesthetic results when compared to standard techniques such as LD/implant, it is technically more challenging. Furthermore, concern lies in potentially injuring the TRAM flap when combined with implant placement. However, multiple authors have demonstrated that in experienced hands, TRAM flap reconstruction can be combined with implant placement without any occurrences of microvascular thrombosis or flap failure.^[5,6]

Figus *et al.*^[3] was the first to describe successfully combining DIEP flap reconstruction with immediate



Figure 6: One-year postoperative: bilateral deep inferior epigastric perforator (DIEP) with immediate expanders, subsequent expander/400 mL gel implant exchange. Delayed nipple and areola reconstruction

implant placement. Fourteen patients were selected as candidates for DIEP/implant reconstruction based on similar criteria to that previously reported in the literature; these patients were then prospectively followed. Ten patients had implants placed subpectorally at the time of the DIEP flap, and 4 patients had the implants placed in a delayed fashion directly under the DIEP flap. Their preferred vessel for anastomosis was the thoracodorsal artery and vein. They did not experience any total flap losses or episodes of microvascular thrombosis, however, they did experience an immediate postoperative infection and hematoma that led to partial flap loss and removal of the implant. In addition, they describe an accidental transection of the internal mammary vessels while placing a delayed implant directly beneath the flap. The aesthetic results were analyzed and revealed “very satisfied” and “excellent” outcomes.^[3]

Commentary in response to this data argued against placement of immediate implants or expanders with DIEP flaps for concerns that the implant would either directly or indirectly compromise the vascularity of the flap.^[7] This concern for injury to the pedicle, whether immediately or during the expansion, is the basis behind the development of our alloderm sling technique. We propose that this technique can prevent potential injury to the pedicle whether intraoperatively, in a reoperation or any delayed procedures. While total flap loss and microvascular thrombosis events have yet to be described in the literature with combined TRAM/implant procedures, we believe that the alloderm sling technique acts as a safety net to prevent the subpectoral implant/expander from injuring the pedicle. Clearly, this is less of a concern if the preferred recipient vessel is to the thoracodorsal artery and vein,^[3] but the alloderm technique may have prevented the reported transection of the inferior mesenteric artery/inferior mesenteric vein (IMA/IMV).

In our cohort, patients desired larger breasts than the overlying skin envelope could maintain and therefore we chose to place smooth, round subpectoral expanders with an external port (the external port was chosen

to limit potential injury to the flap during expansion). The subpectoral placement is the standard technique for expander reconstruction, leading to fewer capsular contractures and better concealing the outline of the expander.^[1,2,4,8] Initially, saline was not immediately infused into the expander for fear that it could indirectly injure the flap through pressure. However, in our subsequent cases various amounts of saline were infused into the expander and changes in the implantable Doppler, flap, and overlying mastectomy skin was directly visualized. If any of these variables were negatively affected by the expansion, the volume was decreased. In our cohort, there were no reoperations, partial or total flap losses, hematomas, infections, implant failures, or asymmetries. In contrast to previous reports, our cohort demonstrated no seromas in relation to the initial expansion of the expander at the time of surgery.^[3] We do, however, place drains within the expander pocket and continue them until the output is < 30 mL for 24 h. Furthermore, the cohort described is the initial experiences with the described technique, and thus is currently too small to make translatable conclusions.

Our data supports the proven safety of combined TRAM and DIEP/implant procedures as well as the excellent aesthetic results achieved with this procedure.^[1,2,4,8] Furthermore, there is evidence that combining an implant with autologous tissue appears to reduce implant related complications in previously irradiated breasts.^[6] If a patient has a unilateral defect, stacking two DIEP flaps on top of one another can often provide sufficient tissue to recreate a single breast. However, in cases where the patient desires larger breasts and the contralateral breast needs augmentation [Patient 4, Table 2 and Figure 4], combining a stacked DIEP flap with an expander/implant is an option. This technique achieves the volume and projection the patient desires by utilizing an implant, and gives a natural feel and appearance by utilizing an overlying DIEP flap. As suggested by Figus *et al.*,^[3] an implant/expander can be combined with a DIEP flap to address preoperative breast asymmetries. In our cohort, one patient demonstrated these asymmetries [Patient 5, Table 2], and a 275 mL expander was placed in one side and a 400 mL expander in the other to provide a more symmetric appearance. A noted alternative to simultaneous augmentation with DIEP flaps is to address any asymmetries is fat grafting. However, the advantage of using an implant is to correct the asymmetry immediately and eliminate the need for multiple revisional surgeries.

Additional reconstructive techniques being used in patients with inadequate abdominal tissue include the superior gluteal artery perforator (SGAP) flap, transverse upper gracilis (TUG) flap or the profunda femoris artery perforator (PAP) flap. These techniques, however, tend to be more complex and time intensive. The dissection of the muscle for the SGAP is technically difficult and possesses a relatively short vascular pedicle. There is also the possibility for contour deformity and asymmetry of the buttocks, particularly in the case of unilateral breast reconstruction.^[9] Although the TUG flap involves

a relatively easy dissection, it provides a rather small skin paddle and thin, fat pad, which limits its utility for reconstruction of small to medium-sized breasts. Furthermore, atrophy of the gracilis muscle may cause secondary volume and contour deformities, requiring additional corrections.^[10,11] The PAP flap has a relatively long vascular pedicle and the scar may be hidden in the lower buttock crease. However, there may be scar tenderness causing problems with sitting, visibility of the scar in swimwear or underwear, and asymmetrical donor site with unilateral breast reconstruction.^[12] Fat grafting is an option for increasing volume, but it requires multiple procedures and often does not allow for large volume augmentation in excess of 150 mL or more. Although this is certainly an option for revision and touch ups, the authors routinely do not use large volume fat grafting to augment the volume of DIEP flap reconstruction.

This cohort has the limitations inherent to any small cohort and retrospective review, which include the difficulties in making generalizations from a small sample size. Despite the potential benefits of combined DIEP/expander reconstruction in patients desiring larger breasts or with insufficient abdominal tissue, women who smoke or have significant co-morbidities may not be appropriate candidates for this technique.

In this retrospective review, we demonstrate that combined DIEP/expander reconstruction is safe and provides excellent long-term aesthetic results. We report our experience to further support the notion that combined DIEP/implant procedures can have superior aesthetic results when compared to many of the alternative procedures in this select group of patients.^[2,5,6] In addition, we describe a technique that may assist surgeons in preventing any inadvertent injury to the pedicle when performing simultaneous DIEP flap/expander reconstruction and using the IMA/IMV as the recipient vessels. The alloderm technique may provide plastic surgeons with the confidence to offer patients this technique as an alternative to traditional LD/implant techniques. This technique offers the ability to use an expander in women whose overall breast size is not yet finalized and who soft tissue envelope will not support a sizeable implant.

REFERENCES

1. Koshima I, Moriguchi T, Soeda S, Tanaka H, Umeda N. Free thin paraumbilical perforator-based flaps. *Ann Plast Surg* 1992;29:12-7.
2. Kronowitz SJ, Robb GL, Youssef A, Reece G, Chang SH, Koutz CA, Ng RL, Lipa JE, Miller MJ. Optimizing autologous breast reconstruction in thin patients. *Plast Reconstr Surg* 2003;112:1768-78.
3. Figus A, Canu V, Iwuagwu FC, Ramakrishnan V. DIEP flap with implant: a further option in optimising breast reconstruction. *J Plast Reconstr Aesthet Surg* 2009;62:1118-26.
4. Serletti JM, Moran SL. The combined use of the TRAM and expanders/implants in breast reconstruction. *Ann Plast Surg* 1998;40:510-4.
5. Tadiparthi S, Alrawi M, Collis N. Two-stage delayed breast reconstruction with an expander and free abdominal tissue transfer: outcomes of 65 consecutive cases by a single surgeon. *J Plast Reconstr Aesthet Surg* 2011;64:1608-12.
6. Roehl KR, Baumann DP, Chevray PM, Chang DV. Evaluation of outcomes in breast reconstructions combining lower abdominal free flaps and permanent implants. *Plast Reconstr Surg* 2010;126:349-57.
7. Chia HL, Breitenfeldt N, Canal AC, Malata CM. Implant augmentation

- after perforator flap breast reconstruction. *J Plast Reconstr Aesthet Surg* 2010;63:e172-3.
8. Fisher J, Hammond DC. The combination of expanders with autogenous tissue in breast reconstruction. *Clin Plast Surg* 1994;21:309-20.
 9. Tseng CY, Lipa JE. Perforator flaps in breast reconstruction. *Clin Plast Surg* 2010;37:641-54.
 10. Arnez ZM, Pogorelec D, Planinsek F, Ahcan U. Breast reconstruction by the free transverse gracilis (TUG) flap. *Br J Plast Surg* 2004;57:20-6.
 11. Wechselberger G, Schoeller T. The transverse myocutaneous gracilis free flap: a valuable tissue source in autologous breast reconstruction. *Plast Reconstr Surg* 2004;114:69-73.
 12. Saad A, Sadeghi A, Allen RJ. The anatomic basis of the profunda femoris

artery perforator flap: a new option for autologous breast reconstruction-a cadaveric and computer tomography angiogram study. *J Reconstr Microsurg* 2012;28:381-6.

How to cite this article: Craig ES, Shah A, Persing S, Salomon J, Fusi S. Simultaneous expander and deep inferior epigastric perforator reconstruction: indications and alloderm sling technique for protecting the anastomosis. *Plast Aesthet Res* 2015;2:63-8.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 27-08-2014; **Accepted:** 16-10-2014

Soft tissue defects of eyelid and malar region: an experience with the McGregor flap

Pradeoth Korambayil Mukundan¹, Prashanth Varkey Ambookan¹, Vinoth Kumar Dilliraj²

¹Jubilee Institute for Surgery of Hand, Aesthetic and Microsurgery, Jubilee Mission Medical College and Research Institute, Thrissur 680005, Kerala, India.

²Department of Plastic Surgery and Burns, Vijaya Hospital, Vadapalani, Chennai 600026, Tamil Nadu, India.

Address for correspondence: Dr. Pradeoth Korambayil Mukundan, Jubilee Mission Medical College and Research Institute, Bishop Alapatt Road, Thrissur 680005, Kerala, India. E-mail: pradeoth@gmail.com

ABSTRACT

Aim: Reconstruction of defects of the eyelids and malar region following trauma may result in considerable distortion of the adjacent tissue. A clinical study was undertaken to demonstrate the ability to utilize a modified McGregor flap for reliable soft tissue coverage. **Methods:** Nine patients with eyelids and malar soft tissue defects were treated over a period of 12 months from July 2013 to June 2014. In this prospective study, a McGregor flap was used for the closure of defects in 9 patients (7 men and 2 women), aged 20-36 years (mean age: 27 years). Three sessions of hyperbaric oxygen therapy were administered postoperatively, and patients received subsequent follow-up. **Results:** Six patients presented with malar and lower eyelid defects, 2 patients presented with malar defects, and one patient with upper eyelid, lower eyelid and malar defects following trauma. A McGregor flap was performed in all patients. The preexcision defects varied in size from 3 cm × 2 cm to 4 cm × 3 cm. No secondary procedures were required in any case. Sutures were removed between 7 and 9 days postoperatively. There were no cases of partial or total flap loss over the course of 10-14 months follow-up. **Conclusion:** The outcome following use of the McGregor flap procedure was functionally and aesthetically satisfactory in all cases. The McGregor flap is a useful option for the reconstruction of defects following trauma to the upper eyelid, lower eyelid, and malar regions.

Key words:

Eyelid defects, hyperbaric oxygen therapy, malar defects, McGregor flap

INTRODUCTION

Traumatic injuries of the malar region and lateral aspect of the upper and lower eyelids are common following a fall or abrasion. There is a need for a method of soft tissue coverage that can simultaneously address all three defects while preventing both a functional deficit and distortion of the adjacent tissue. When compared to the western

population, the potential for scar formation is profound in Asian patients secondary to their skin pigmentation. The McGregor flap provides satisfactory results when utilized for the reconstruction of such injuries.

METHODS

The study was conducted at the Jubilee Institute for Surgery of Hand, Aesthetics and Microsurgery, Jubilee Mission Hospital, Thrissur, India. The patients were enrolled in the Plastic and Reconstructive Surgery Department of Jubilee Mission Hospital. Nine patients with eyelids and malar soft tissue defects were treated with the McGregor flap during a period of 12 months from July 2013 to June 2014, followed by 3 sessions of hyperbaric oxygen therapy. The postoperative course and subsequent follow-up were noted. All involved patients agreed to have their facial pictures published and signed the consent form.

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153202

RESULTS

Six patients presented with malar and lower eyelid defects, 2 patients presented with malar defects, and 1 patient with upper and lower eyelid and malar defects following trauma. The patients' ages ranged from 20 to 36 years (with a mean age of 27 years). Among 9 patients, 7 were males and 2 were females. The defects varied in size from 2 cm × 3 cm to 3 cm × 4 cm. A McGregor flap was performed in all cases. No secondary procedures were required. Sutures were removed between 7 and 9 days postoperatively. There was no evidence of partial or total flap loss during the follow-up period [Table 1].

Patient with upper and lower eyelid and malar defects

A 26-year-old male patient presented with upper and lower eyelid and malar defects [Figure 1a]. Wound debridement was performed, and a modified McGregor flap was planned for reconstruction of the soft tissue defect [Figure 1b and c]. A modified McGregor flap was performed [Figure 1d and e], which provided coverage of the defect with the use of a Z-plasty at the lateral aspect of the flap for flap advancement. The patient underwent three sessions of hyperbaric oxygen therapy

postoperatively. Regular follow-up was performed, and the flap was noted to remain viable [Figure 1f and g].

Patient with lower eyelid and malar defect

A 36-year-old woman sustained an injury resulting in soft tissue deficits of the right malar and right lower eyelid [Figure 2a]. Wound debridement was carried out with use of the McGregor flap for coverage [Figure 2b]. The patient received three sessions of postoperative hyperbaric oxygen therapy and the flap healed well [Figure 2c].

Patient with malar defect

A 21-year-old man presented with a defect of the right malar region following a road traffic accident [Figure 3a]. Wound debridement with McGregor flap coverage was performed [Figure 3b]. Postoperatively, three sessions of hyperbaric oxygen therapy were administered. The flap healed well without complications [Figure 3c].

DISCUSSION

Soft tissue defects of the eyelids and malar regions following trauma may result in considerable disfiguration, functional derangement, and distortion of the adjacent

Table 1: The patients treated with use of the McGregor flap for soft tissue defects in the upper and lower eyelid and malar regions

Patients	Age (years)/gender	Trauma/etiology	Site	Defect area (cm ²)	Flap pattern
1	27/male	Road traffic accident	Right malar and lower eyelid regions	3 × 4	McGregor flap
2	23/male	Road traffic accident	Right malar region	3 × 3	McGregor flap
3	25/male	Road traffic accident	Right malar and lower eyelid regions	3 × 4	McGregor flap
4	36/female	Road traffic accident	Left malar and lower eyelid regions	3 × 4	McGregor flap
5	20/female	Road traffic accident	Right malar and lower eyelid regions	3 × 4	McGregor flap
6	34/male	Road traffic accident	Right malar and lower eyelid regions	4 × 4	McGregor flap
7	35/male	Road traffic accident	Right malar and lower eyelid regions	4 × 3	McGregor flap
8	21/male	Road traffic accident	Right malar region	3 × 3	McGregor flap
9	26/male	Road traffic accident	Right malar and lower and upper eyelid regions	3 × 3 in lower part, 3 × 2 in upper eyelid	Modified McGregor flap



Figure 1: (a) Posttraumatic soft tissue defect, right upper and lower eyelids and malar region; (b) soft tissue defect following surgical debridement; (c) planning of modified McGregor flap; (d) immediate postoperative picture following reconstruction; (e) immediate postoperative anterior view following reconstruction; (f) late postoperative anterior view following reconstruction; (g) late postoperative lateral view following reconstruction

tissue. Traumatic injuries of the malar region and lateral aspect of the upper and lower eyelids are common following a fall from the motorcycle, or in cases of severe facial abrasion following a fall and drag along a roadway [Figure 4]. There is a need for soft tissue



Figure 2: (a) Posttraumatic soft tissue defect, right lower eyelid and malar regions; (b) immediate postoperative picture following reconstruction; (c) late postoperative lateral view following reconstruction



Figure 3: (a) Soft tissue defect, malar region and planning of the McGregor flap; (b) immediate postoperative picture following reconstruction; (c) late postoperative lateral view following reconstruction



Figure 4: Schematic diagram representing soft tissue defect on the right side of the face following a road traffic accident

coverage which addresses all three defects simultaneously while preventing functional deficit and distortion of the adjacent tissue. The ideal reconstruction should avoid creating a “trap door” deformity, dog ear formation, ectropion, and sideburn displacement.^[1]

Various local flaps such as the rotation flap, transposition flap, advancement flaps, rhomboid flap, bilobed flaps, and “reading man” flaps can be employed for the reconstruction of such defects.^[2-6] Most of these flaps have been described for reconstruction of circular defects following tumor resection. Although rhomboid, bilobed and reading man flaps provide soft tissue coverage, they may result in scar formation secondary to the multiple incisions required for flap execution. The Tenzel flap is an advancement-rotation flap in which a semicircular skin-muscle flap is fashioned from the skin lateral to the lateral canthus, and which can be used for both upper and lower eyelids.^[7]

McGregor devised a flap that adds a Z-plasty to the Mustarde cheek advancement flap for moderate defects of the lower eyelid.^[7,8] An incision is made lateral to the eyelid, slanted upward gently, and carried into the temporal region. A backcut is then made at the temporal end of the incision and angled medially approximately 30°. A Z-plasty is created, which recruits the vertical laxity from the lateral periorbital region to correct horizontal defects of the lower eyelid. However, the same technique could well be utilized to cover moderate defects in the malar, as well as the upper eyelid region. Similarly by introducing certain modifications [Figure 1c] the same flap could be utilized to reconstruct defects of the eyelids and malar regions.

In our experience, the use of hyperbaric oxygen therapy may result in a favorable outcome in such injuries. Based on our clinical experience, a minimum of three sessions of hyperbaric oxygen therapy contributes to a reduction in edema, which increases the likelihood of flap survival. While steroids may contribute to the anti-edema effect, they may result in associated immunosuppression.^[9]

The modified McGregor flap is a useful option in the reconstruction of defects of the upper and lower eyelids and malar regions. Hyperbaric oxygen therapy, as an adjuvant to such traumatic facial injuries, will yield better outcomes.

REFERENCES

1. Mutaf M, Günel E, Temel M. Closure of defects of the malar region. *J Craniofac Surg* 2011;22:631-4.
2. Cecchi R, Fancelli L, Troiano M. The “reading man” flap in facial reconstruction: report of 12 cases. *Dermatol Online J* 2012;18:16.
3. Hayano SM, Whipple KM, Korn BS, Kikkawa DO. Principles of periocular reconstruction following excision of cutaneous malignancy. *J Skin Cancer* 2012;2012:438502.
4. Saito A, Saito N, Furukawa H, Hayashi T, Oyama A, Funayama E, Minakawa H, Yamamoto Y. Reconstruction of periorbital defects following malignant tumour excision: a report of 50 cases. *J Plast Reconstr Aesthet Surg* 2012;65:665-70.
5. Yenidunya MO, Demirseren ME, Ceran C. Bilobed flap reconstruction in infraorbital skin defects. *Plast Reconstr Surg* 2007;119:145-50.
6. Mutaf M, Günel E, Temel M. A new technique for closure of infraorbital

defects. *Ann Plast Surg* 2011;67:600-5.

7. Thornton JF, Kenkel JM. Eyelid Reconstruction. Vol. 10. Dallas: Selected Readings in Plastic Surgery, Inc.; 2005. p. 16.
8. Emsen IM. Functional lower lip reconstruction with a modification in McGregor flap technique. *Plast Reconstr Surg* 2007;119:2335-6.
9. Bhutani S, Vishwanath G. Hyperbaric oxygen and wound healing. *Indian J Plast Surg* 2012;45:316-24.

How to cite this article: Mukundan PK, Ambookan PV, Dilliraj VK. Soft tissue defects of eyelid and malar region: an experience with the McGregor flap. *Plast Aesthet Res* 2015;2:69-72.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 13-08-2014; **Accepted:** 04-01-2015

Aneurysmal bone cyst of the maxilla rare presentation with radiological and pathological correlation

Bharat Bhushan Sharma¹, Priya Ramchandran², Sandeep Sharma³, Shweta Sharma⁴

¹Department of Radio Diagnosis, PGIMER and Dr. RML Hospital, New Delhi 110001, India.

²Intensive Care Unit and Anesthesiology, Heartlands Hospital, B912AF, Brimingham, UK.

³Pain Management and Anesthesiology SGT Medical College, Gurgaon 122505, Haryana, India.

⁴ENT and Head and Neck Surgery, PGIMER and Dr. RML Hospital, New Delhi 110001, India.

Address for correspondence: Dr. Bharat Bhushan Sharma, Department of Radio Diagnosis, PGIMER and RML Hospital, B-32, Nivedita Kunj Sector 10 R.K. Puram, New Delhi 110001, India. E-mail: bbbhushan986@gmail.com

ABSTRACT

The incidence of aneurysmal bone cyst in the maxillofacial region is rare and may remain undiagnosed for a long period prior to becoming symptomatic. This may cause associated issues secondary to compression by extending to the surrounding vital anatomical areas. An aggressive course can lead to bony destruction with intracranial extension. We present a case of a 23-year-old man who presented with bilateral exorbitism with nasal obstruction.

Key words:

Aggressive course, aneurysmal bone cyst, bone destruction, intracranial extension

INTRODUCTION

Aneurysmal bone cysts (ABC) are typically found in long bones and the spine, but rarely can be seen in the craniofacial region. The incidence is 2% and 1.3% in the craniofacial region and maxillary region, respectively.^[1,2] These benign, expansile bony tumors of unknown etiology are often referred to as aneurysmal bone tumors rather than cysts because of their aggressive behavior.

CASE REPORT

A 23-year-old man presented with a history of anosmia, the sensation of a blocked nose with mild pain that had been increasing over 6 months, and a gradual increase in bilateral exorbitism. The patient denies any history of fever, trauma, epistaxis, or oral bleeding. His

physical examination was remarkable for a brownish bulge in the nasopharynx. The patient underwent computerized tomography (CT) and magnetic resonance imaging (MRI) examinations. Noncontrast computerized tomography (NCCT) of the nasopharynx region showed an expansile cystic lesion in the maxillary region bulging into the nasopharynx [Figure 1]. There was no cortical break [Figures 2 and 3]. Multiple fluid levels were seen within the lesion [Figures 4 and 5]. Cytology following fine-needle aspiration was performed, and a cytological diagnosis of ABC of the maxilla was given. The patient underwent enucleation of the mass. Histopathological examination further confirmed the diagnosis of a maxillary ABC, with cystic spaces filled with blood, and without an endothelial lining along with osteoclast giant cells [Figure 6a and b]. There were no surgical complications, and the patient was advised to follow-up in 3 months. His recovery has been uneventful.

DISCUSSION

The maxilla is a rare site of ABC. It is neither an aneurysm nor a cyst. The World Health Organization (WHO) defines an ABC as an "expanding osteolytic lesion consisting of blood-filled spaces of variable size separated by connective tissue septa containing trabeculae of osteoid tissue and

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.153203

our case. A patient will generally report to the hospital after becoming symptomatic. The underlying pathology of giant cell tumor is well-known in secondary types of ABC. It is always diagnosed when the patient undergoes three dimensional imaging modalities such as CT and MRI. Radiographically, ABC gives the impression of a “blown out” or “ballooned” appearance of the underlying bone. CT and MRI demonstrate classic fluid-level images, but histological examination remains the hallmark for the diagnosis. The solid component of the lesion can be visualized on CT and MRI, which further indicates a secondary nature. Multiple areas of high intensity surrounded by hypointense rings are observed on T1-weighted and T2-weighted images. These represent the different ages of blood in the lesion.^[4] There should be close collaboration between radiologist and pathologist when making the diagnosis, as a small specimen may miss the associated findings.

Surgical excision with enucleation remains the best treatment. The path to surgery depends upon the extent of involvement and its nature. Other potential options for treatment include percutaneous sclerotherapy, therapeutic embolization, curettage, block resection and reconstruction, radiotherapy and systemic calcitonin therapy.^[5] There have some cases of spontaneous healing.^[6]

In conclusion, ABC of hidden areas such as the maxilla as in our case poses a great diagnostic and management dilemma for the clinician. CT and MRI are quite helpful

modalities in guiding the management path. This further helps in ruling out intracranial extension. The radiological modalities further help the anesthesiologist in guiding intubation and determining the level of risk during surgery.

REFERENCES

1. Suzuki F, Fukuda S, Yagi K, Chida E, Inuyama Y. A rare aneurysmal bone cyst of the maxillary sinus: a case report. *Auris Nasus Larynx* 2001;28:S131-7.
2. Guzmán GP, Baeza OA, Araya OJ, Roa SJ, Brevis OL, Torres LP. Aneurysmal bone cyst of the maxilla. Report of one case. *Rev Med Chil* 2005;133:1355-60.
3. Bonakdarpour A, Levy WM, Aegerter E. Primary and secondary aneurysmal bone cyst: a radiological study of 75 cases. *Radiology* 1978;126:75-83.
4. Pahade J, Sekhar A, Shetty SK. Imaging of malignant skeletal tumors. In: Blake MA, Kalra MK, editors. *Imaging in Oncology*. New York: Springer-Verlag; 2008. p. 375.
5. Rai AT, Collins JJ. Percutaneous treatment of pediatric aneurysmal bone cyst at C1: a minimally invasive alternative: a case report. *AJNR Am J Neuroradiol* 2005;26:30-3.
6. Malghem J, Maldague B, Esselinckx W, Noel H, De Nayer P, Vincent A. Spontaneous healing of aneurysmal bone cysts. A report of three cases. *J Bone Joint Surg Br* 1989;71:645-50.

How to cite this article: Sharma BB, Ramchandran P, Sharma S, Sharma S. Aneurysmal bone cyst of the maxilla rare presentation with radiological and pathological correlation. *Plast Aesthet Res* 2015;2:73-5.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 21-09-2014; **Accepted:** 17-10-2014

A novel approach to achieve breast symmetry in a single-stage procedure

Benedetto Longo, Rosaria Laporta, Marco Pagnoni, Fabio Santanelli di Pompeo

Department of Plastic Surgery, Sant' Andrea Hospital, School of Medicine and Psychology, Sapienza University of Rome, 00189 Rome, Italy.

Address for correspondence: Prof. Fabio Santanelli di Pompeo, Via di Grottarossa 1035-1039, 00189 Rome, Italy.

E-mail: fabio.santanelli@uniroma1.it

ABSTRACT

Preservation of the skin envelope and the inframammary fold is the main factor in achieving breast symmetry in unilateral reconstruction. Skin sparing mastectomy (SSM) type-IV followed by immediate autologous reconstruction and contralateral symmetrization permits realizing this goal in large, ptotic breasted patients, and tumor superficially located in the inferior quadrants. If the tumor is superficially located in the superior or inferior quadrants with a previous lumpectomy or quadrantectomy scar in the superior quadrants, modified radical mastectomy and a staged procedure are recommended to avoid poor cosmetic results. Two patients who underwent immediate autologous reconstruction following SSM type-V with contralateral symmetrization in a one-stage procedure are presented.

Key words:

Autologous tissue reconstruction, breast symmetry, deep inferior epigastric perforator flap, single-stage breast reconstruction, wise-pattern mastectomy

INTRODUCTION

The re-creation of a natural-appearing breast mound while simultaneously achieving symmetry with the opposite breast represents a complex challenge during unilateral reconstruction.^[1,2]

Skin-sparing mastectomy type-IV (SSM-IV), followed by immediate autologous reconstruction, and a simultaneous contralateral procedure is an ideal technique for large, ptotic-breasted patients with tumor located in the inferior quadrants (IIQQ). However, if the tumor is located in the superior quadrants (SSQQ) or IIQQ with a prior lumpectomy or quadrantectomy scar in the SSQQ, SSM-IV is contraindicated. In these cases, tumor resection interferes with wise-pattern (WP) skin flaps, and a modified radical mastectomy is instead recommended. As a result, a contralateral procedure to achieve symmetry becomes a complex, multifactorial decision, and a staged procedure

may be preferred to avoid a poor cosmetic result. This report presents two patients who underwent simultaneous contralateral mastopexy during unilateral SSM-V, followed by immediate deep inferior epigastric perforator (DIEP) flap reconstruction, as a complete single-stage procedure for upper quadrant skin and tumor resection.

CASE REPORT

Case I

A 56-year-old non-smoking woman was diagnosed with phyllodes tumor located deeply to IIQQ of her right breast. Medical history included repeated excisions of lumps and a superior-lateral quadrantectomy of the right breast. She had large (C bra-cup), ptotic (second-degree) breasts with a mid-clavicular to nipple distance of 28 cm. She underwent a right SSM-V, axillary lymph-node dissection and immediate reconstruction with a 13 cm × 21 cm de-epithelialized DIEP flap. Her nipple areola-complex (NAC) was grafted, and a simultaneous contralateral mastopexy was performed. The postoperative course was uneventful, and no complications were observed at the DIEP flap, SSM-V skin flaps, contralateral mastopexy, or and to the abdominal donor site. Breast symmetry of shape and size was achieved [Figures 1 and 2]. Neither surgical revision nor secondary procedures were required at her 20 months follow-up.

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153204

Case 2

A 46-year-old non-smoking woman, with large (C bra-cup), ptotic (second-degree) breasts and mid-clavicular to nipple distance of 29 cm, underwent a right SSM-V with axillary lymph-node dissection for a ductal carcinoma located in the superior-lateral quadrant, followed by immediate reconstruction with a 12 cm × 18 cm de-epithelialized DIEP flap. Her NAC was grafted, and a contralateral mastopexy was performed in the same session. The postoperative course was uneventful. No complications were observed in the DIEP flap, SSM-V skin flaps, contralateral mastopexy or at the abdominal donor site. Breast symmetry of shape and size was achieved [Figures 3 and 4]. Neither surgical revision nor secondary procedures were required at follow-up of 16 months.

DISCUSSION

In unilateral breast cancer, the aesthetic quality of the reconstruction is also judged on the basis of symmetry of shape and size with the opposite breast. This often requires simple adjustments achieved by contralateral breast reduction, mastopexy or augmentation. Factors affecting the choice of surgical procedure for the contralateral side include the patient's anatomic breast characteristics, the surgeon's preferences, the patient's desires, mastectomy type and reconstructive procedure.

The ideal time to perform symmetrization remains controversial due to the increased operative time and risk of complications with immediate reconstruction. Some argue that it is easier to adjust the opposite breast once the reconstructed breast has reached a stable shape, volume,

and position and only after completion of any adjuvant therapy in order to avoid potential disadvantages.^[3,4] In contrast, Stevenson and Goldstein^[5] observed that the combination of transverse rectus abdominus myocutaneous flap reconstruction and immediate contralateral symmetrization neither increased morbidity nor decreased aesthetic satisfaction. Losken *et al.*^[6] also confirmed superior aesthetic results with a simultaneous approach because the corrected opposite breast becomes the model for breast reconstruction rather than the other way around. In this context, the preservation of the skin envelope and inframammary fold is the key element to achieving an optimal shape and size with the opposite side during the initial surgery. SSM-IV, immediate autologous reconstruction and contralateral symmetrization represents an excellent single-stage procedure for large, ptotic-breasted patients with tumor located in IIQQ. Success of this procedure depends on WP application to both breasts that will lead to the same shape, projection and degree of ptosis since the preserved skin envelope is comparable between the two breasts.^[7,8] Moreover, it saves the patient a second surgical procedure under general anesthesia with less psychological and emotional distress, while lowering operating room costs and time on waiting lists.

The aim of this report was to illustrate how the same goal can be achieved in patients with large, ptotic breasts, but with tumor lying superficially in the SSQQ or deep to the



Figure 1: Case 1. A 56-year-old non-smoking woman with phyllodes tumour (black dot) located in inferior-lateral quadrant of the right breast and a previous quadrantectomy scar in the upper right pole. (a) Preoperative markings; (b) pre- and (c) postoperative frontal view

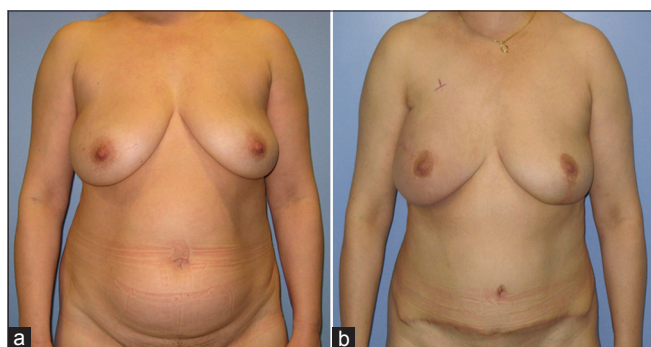


Figure 3: Case 2. A 46-year-old non-smoking woman with a ductal carcinoma located in superior-lateral quadrant of the right breast. (a) Pre- and (b) postoperative frontal view



Figure 2: Case 1. (a) Pre- and (b) postoperative oblique view

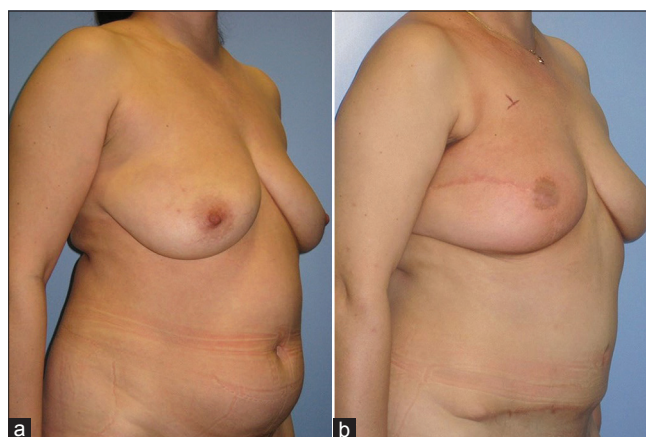


Figure 4: Case 2. (a) Pre- and (b) postoperative oblique view

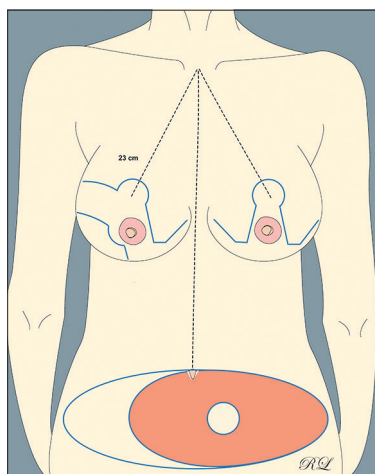


Figure 5: Modified wise-pattern for upper quadrant skin resection (skin-sparing mastectomy type-V) was applied on the affected breast. Standard wise-pattern was used to perform mastopexy/reduction on the opposite side. Deep inferior epigastric perforator flap markings with a round skin paddle and the de-epithelialized area (pink color) of the flap. The round skin paddle can replace the nipple areola-complex (NAC) if intraoperative frozen sections are positive

IIQQ with a prior lumpectomy or quadrantectomy scar in the upper quadrants.

The reported procedure entails a modified WP-SSM for upper quadrant skin resection, as described by Santanelli *et al.*,^[9,10] followed by immediate DIEP flap reconstruction and a contralateral symmetrization procedure. With the patient in standing position the median breast line was marked and the new nipple position was located at 23 cm from the sternal notch, then the WP was marked bilaterally. The general surgeon drew the skin area to be removed with breast parenchyma on the affected side and the plastic surgeon applied a modified WP to plan the SSM-V, while a “standard” WP was used to perform a mastopexy or breast reduction on the opposite side [Figure 5].

While the general surgeon performed the SSM-V with axillary lymph-node dissection, the plastic surgeons harvested the DIEP flap, tailoring it according to the final desired contralateral breast size. The flap was then transferred to the chest wall and revascularized by end-to-end anastomoses to the circumflex scapular vessels. The NAC was harvested and grafted if intraoperative frozen sections were negative [Figure 6].

There are many advantages to this novel approach. By preserving the skin envelope and infra-mammary fold on the affected side using a SSM-V, the WP can be applied to perform a simultaneous contralateral symmetrization, allowing both NACs to be placed at the same position. Furthermore, by preserving the skin envelope on the affected side a natural-appearing breast is achieved especially after autologous tissue reconstruction. Scarring is comparable to the SSM-IV with an additional equatorial scar located at the superior medial/lateral quadrant, which is less disfiguring when compared with a conventional mastectomy. Despite its surgical complexity, immediate DIEP flap reconstruction is the best chance for obtaining long-term symmetry because both breasts maintain natural ptosis and softness.^[11,12]

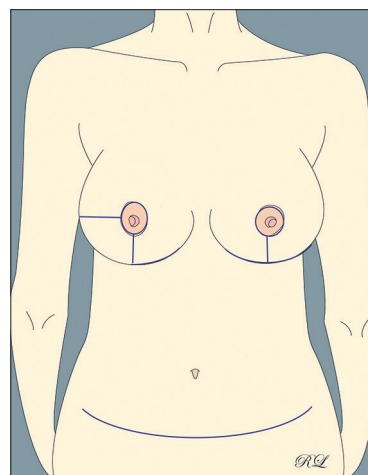


Figure 6: Scarring is comparable to the skin-sparing mastectomy type-IV with an additional equatorial scar located at the superior medial/lateral quadrant, which is less disfiguring when compared to a conventional mastectomy

REFERENCES

1. Kroll SS, Coffey JA Jr, Winn RJ, Schusterman MA. A comparison of factors affecting aesthetic outcomes of TRAM flap breast reconstructions. *Plast Reconstr Surg* 1995;96:860-4.
2. Blondeel PN, Hijawi J, Depypere H, Roche N, Van Landuyt K. Shaping the breast in aesthetic and reconstructive breast surgery: an easy three-step principle. *Plast Reconstr Surg* 2009;123:455-62.
3. Chang DW, Kroll SS, Dackiw A, Singletary SE, Robb GL. Reconstructive management of contralateral breast cancer in patients who previously underwent unilateral breast reconstruction. *Plast Reconstr Surg* 2001;108:352-8.
4. Labandter HP, Dowden RV. Surgical considerations in managing the remaining breast during postmastectomy breast reconstruction. *Clin Plast Surg* 1984;11:365-8.
5. Stevenson TR, Goldstein JA. TRAM flap breast reconstruction and contralateral reduction or mastopexy. *Plast Reconstr Surg* 1993;92:228-33.
6. Losken A, Carlson GW, Bostwick J 3rd, Jones GE, Culbertson JH, Schoemann M. Trends in unilateral breast reconstruction and management of the contralateral breast: the Emory experience. *Plast Reconstr Surg* 2002;110:89-97.
7. Jahlkola T, Asko-Seliavaara S, von Smitten K. Immediate breast reconstruction. *Scand J Surg* 2003;92:249-56.
8. Hudson DA, Skoll PJ. Single-stage, autologous breast restoration. *Plast Reconstr Surg* 2001;108:1163-71.
9. Santanelli F, Paolini G, Campanale A, Longo B, Amanti C. Modified wise-pattern reduction mammoplasty, a new tool for upper quadrantectomies: a preliminary report. *Ann Surg Oncol* 2009;16:1122-7.
10. Santanelli F, Paolini G, Campanale A, Longo B, Amanti C. The “Type V” skin-sparing mastectomy for upper quadrant skin resections. *Ann Plast Surg* 2010;65:135-9.
11. Granzow JW, Levine JL, Chiu ES, Allen RJ. Breast reconstruction with the deep inferior epigastric perforator flap: history and an update on current technique. *J Plast Reconstr Aesthet Surg* 2006;59:571-9.
12. Blondeel PN. One hundred free DIEP flap breast reconstructions: a personal experience. *Br J Plast Surg* 1999;52:104-11.

How to cite this article: Longo B, Laporta R, Pagnoni M, di Pompeo FS. A novel approach to achieve breast symmetry in a single-stage procedure. *Plast Aesthet Res* 2015;2:76-8.

Source of Support: Nil, **Conflict of Interest:** I myself Fabio Santanelli di Pompeo have submitted for publication on *Plastic and Aesthetic Research* a manuscript entitled: “A novel approach to achieve breast symmetry in a single-stage procedure”. I, hereby certify, that to the best of our knowledge no financial support or benefits have been received by me or any co-author, by any member of my (our) immediate family or any individual or entity with whom or with which I (we) have a significant relationship from any commercial source which is related directly or indirectly to the scientific work which is reported on in the article.

Received: 12-10-2014; **Accepted:** 03-11-2014

A rare case of bilateral absence of distal ulnar artery

Jung Ho Lee, Rock Kuen Ju, Young Joon Jun, Young Jin Kim

Department of Plastic and Reconstructive Surgery, College of Medicine, Catholic University of Korea, Seoul 110758, South Korea.

Address for correspondence: Dr. Jung Ho Lee, Department of Plastic and Reconstructive Surgery, Catholic University of Korea, 327 Sosa-ro, Wonmi-gu, Bucheon-si, Gyeonggi-do 420717, South Korea. E-mail: tfm0822@catholic.ac.kr

ABSTRACT

It is fairly common to find anatomic variations and anomalies in the arterial pattern of the upper extremities. However, a complete absence of the distal ulnar artery bilaterally is extremely rare. During preoperative assessment for a radial forearm free flap, we accidentally discovered bilateral distal ulnar artery agenesis. In this article, the clinical implications of this variation are discussed, along with a review of the literature.

Key words:

Forearm free flap, ulnar artery, variation

INTRODUCTION

The arterial patterns in the upper extremity have received attention in the field of clinical anatomy due to their high variability. McCormack *et al.*^[1] studied 750 upper limbs of cadavers and found anomalies of the brachial, radial, or ulnar artery in 112 cadavers. The radial artery was the most involved (81.3%), followed by the brachial artery (12.2%). Coleman and Anson^[2] showed direct continuity between the ulnar artery and superficial palmar arch and the dominance of the ulnar artery in the wrist. Keen^[3] noted that when the ulnar artery was larger than the radial artery at the elbow, the anatomical relationship was usually reversed at the wrist. Several other studies have also reported anatomical variances of the arteries in the forearm and hand.^[4,5] However, bilateral absence of the distal ulnar artery and superficial palmar arch is extremely rare.

We report a case of bilateral absence of the distal ulnar artery, which was accidentally discovered during preoperative evaluation for a radial forearm free flap.

CASE REPORT

A 58-year-old male was referred to the Department of Plastic and Reconstructive Surgery for management of squamous cell carcinoma of the tongue. Magnetic resonance imaging showed a 2.5 cm × 1.8 cm × 1 cm sized enhancing soft tissue mass in the tongue, and the patient was scheduled to undergo partial glossectomy.

We decided to reconstruct the patient's tongue using a radial forearm free flap. Preoperative Allen's test demonstrated dominance of radial artery bilaterally. An arteriography was performed to map the vasculature of the hand, and it showed a gradually narrowing ulnar artery in the right upper limb that vanished in the distal 2/3 of the forearm after branching off interosseous branches. In addition, the superficial palmar arch was absent, and the deep palmar arch was filled by radial artery alone [Figure 1]. The angiogram of left upper limb revealed symmetrical findings.

Due to the anatomical variation of ulnar artery in the forearm, the patient underwent reconstruction of the tongue using a free flap from anterolateral thigh and the patient was discharged home 2 weeks after the operation without any complications.

DISCUSSION

The ulnar artery is the main provider of blood supply to the hand via the superficial palmar arch.^[6] The superficial

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153205

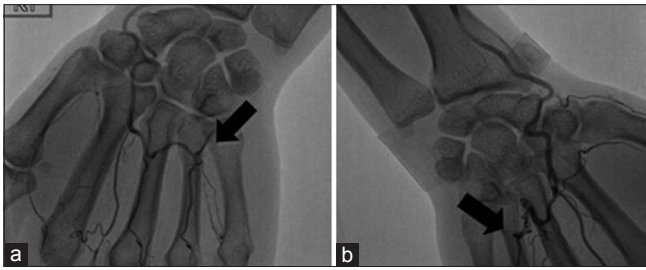


Figure 1: Arteriography of the hands showing the absence of the distal ulnar arteries and superficial palmar arches. Deep palmar arches are shown without any contribution from the ulnar artery (arrow) (a: right hand, b: left hand)

palmar arch has different types of anastomosis: (a) the “ulnar type” has minimal or absent flow from radial artery; (b) the “radio-ulnar type” is the arch is formed by the superficial palmar branch of radial artery and the larger ulnar artery; and (c) the “mediano-ulnar type” has predominant supply from median artery as it is able to reach the palm of the hand and forms the arch. It is reported that “ulnar type” is the most frequent (59%) and is followed by the “radio-ulnar type” (32%), and the “mediano-ulnar type” is the least common (9%).^[4] An arch is considered incomplete when there are no continuations among the ulnar, radial, and median arteries.^[7] This explains ischemic complications in the hand after harvesting of radial forearm flaps, because in patients with incomplete palmar arches, blood flow from the ulnar artery cannot reach the radial fingers.^[8]

The absence of the ulnar artery is an extremely rare anomaly. Coleman and Anson^[2] studied 650 cadaveric dissections and found no cases of a complete absence of the ulnar artery in the hand. Although several large-sample

studies have statistically analyzed the absence of the ulnar artery, the absence of the ulnar artery, its incidence may be considered $< 0.015\%$.^[5] Comparative anatomy studies suggest a theory of evolution underlying this anomaly.^[9,10] These studies state that complete or partial absence of the ulnar artery might be the transition form from its total absence which can be seen in some lower animals to its complete development in humans.

REFERENCES

1. McCormack LJ, Cauldwell EW, Anson BJ. Brachial and antebrachial arterial patterns: a study of 750 extremities. *Surg Gynecol Obstet* 1953;96:43-54.
2. Coleman SS, Anson BJ. Arterial patterns in the hand based upon a study of 650 specimens. *Surg Gynecol Obstet* 1961;113:409-24.
3. Keen JA. A study of the arterial variations in the limbs, with special reference to symmetry of vascular patterns. *Am J Anat* 1961;108:245-61.
4. Adachi B, Hasebe K, Daigaku K. The arterial system of the Japanese. Kyoto: Kaiserlich-Japanische Universität zu Kyoto; 1928. p. 365-8.
5. Rodríguez-Niedenführ M, Vázquez T, Nearn L, Ferreira B, Parkin I, Sañudo JR. Variations of the arterial pattern in the upper limb revisited: a morphological and statistical study, with a review of the literature. *J Anat* 2001;199:547-66.
6. Botte MJ, Doyle JR. *Surgical Anatomy of the Hand and Upper Extremity*. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 263.
7. Al-Turk M, Metcalf WK. A study of the superficial palmar arteries using the Doppler Ultrasonic Flowmeter. *J Anat* 1984;138:27-32.
8. Varley I, Carter LM, Wales CJ, Warnock N, Whitfield PH. Ischaemia of the hand after harvest of a radial forearm flap. *Br J Oral Maxillofac Surg* 2008;46:403-5.
9. Schwalbe E. Comparative anatomy of the forearm arteries, specially the Arcus volaris sublimis. *Gegenbaurs Morphol Jahrb* 1895;23:412-51.
10. Zuckerkandl E. The anatomy and evolution of the arteries of the forearm. *Anat Hefte* 1894;4:1-98.

How to cite this article: Lee JH, Ju RK, Jun YJ, Kim YJ. A rare case of bilateral absence of distal ulnar artery. *Plast Aesthet Res* 2015;2:79-80.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 15-08-2014; **Accepted:** 03-11-2014

Inferior dermoglandular flap for autologous breast remodeling following explantation of breast implants in ptotic breasts: a case report and literature search

Umar Daraz Khan

Reshape Clinic, West Malling, ME19 6QR, Kent, UK.

Address for correspondence: Mr. Umar Daraz Khan, Reshape Clinic, Reshape House, 2-4 High Street, West Malling, ME19 6QR, Kent, UK.
E-mail: mrumarkhan@aol.com

ABSTRACT

Explantation following aesthetic mammoplasty without implant replacement is quite uncommon and often leaves the patient worse off than prior to mammoplasty. A case is presented here in which patient's own tissue was used as an inferior dermoglandular flap for autologous breast remodeling. Inferior dermal flap has been described for breast reconstruction and simultaneous augmentation mammoplasty with mastopexy for prosthesis cover in the lower pole of the breast, but its use following explantation without implant replacement has not been described for breast remodeling and volume conservation.

Key words:

Autologous breast augmentation, bostwick flap, breast remodeling, explantation, revision augmentation mammoplasty

INTRODUCTION

Augmentation mammoplasty is a commonly performed procedure. The procedure helps to enhance breast cup size by filling out an empty breast skin envelope. Following implantation skin gets further stretched and thinned down due to the pressure exerted by implants in a tight space. Explantation alone following augmentation mammoplasty is not very common. Removal of prosthesis results in loose, empty and often a ptotic breast skin envelope leaving patient worse off than prior to the procedure. Ptosis and skin excess may necessitate mastopexy that may further reduce breast volume resulting in loss of female proportion and body silhouette. This anticipated loss of feminine curves and accompanied

loss of confidence is the reason that the explantation alone following aesthetic augmentation mammoplasty is not commonly performed. Breast remodeling in these patients is often challenging and extremely important and should be offered by a surgeon as an option, where possible. A case report is presented where autologous breast tissue is used in the form de-epithelialized inferior dermoglandular flap for volume conservation and breast remodeling along with simultaneous mastopexy using Wise pattern markings following bilateral explantation of breast implants.

CASE REPORT

A 42-year-old mother of 4 children and a care assistant presented with neck and back ache. She had augmentation mammoplasty 5 years ago using 450 mL Eurosilicone anatomical implants. She considered her breasts too large and was concerned with resultant neck and backache. She requested removal of implants without replacement. She requested reduction of her breast cup size down from E to C.

Examination showed a cup size of 34 E with jugular notch to nipple areola complex distance of 26 cm. Her nipple to

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153206

inframammary crease distance, was 11 cm bilaterally with a bilateral sliding ptosis of the skin envelope.

Preoperative discussion primarily centered on the size of her breast and breast esthetics following explantation alone. She was informed that her breasts were likely to look very saggy if explantation alone was performed and if a simultaneous mastopexy was carried out, especially using a Wise Pattern markings, resultant tissue excision would reduce her breast to a small B cup at the most. Autologous breast remodeling was discussed either using fat transfer as a secondary procedure or using de-epithelialized inferior dermoglandular flap as volume conservation and remodeling in the same setting. She showed her interest in the later procedure. The procedure was planned under general anesthetic and as a day case.

Markings and technique

Patient was marked in standing position. Neo nipple areolar complex (NAC) was marked at 21 cm using infra-mammary crease as a reference [Figure 1]. Wise pattern markings were used for skin reduction with a medially based flap. A transversely oriented skin area, to be de-zepithelialized, was marked and cross-hatched below 7 cm vertical limbs of the markings [Figure 2]. Procedure was done under

general anesthesia with the patient in supine position and arms abducted $< 90^\circ$. Patient received a single dose of Cephalosporin intraoperatively. Cross-hatched area and medially based flap was de-epithelialized leaving 4.5 cm Neo NAC. Intervening tissue between the markings and de-epithelialized area was excised (right 87 gm and left 119 gm) [Figure 3]. Both implants were removed, and both showed malorientation, fold flaw failures with a rupture on the right side [Figure 4]. De-epithelialized inferior dermoglandular flap was pulled up and stitched to pectoralis major, without tension and using 2-0 vicryl sutures [Figure 5]. Hemostasis was performed, and skin closure done using 3-0 vicryl and 4-0 monocryl and 4-0 monocryl was used suture to NAC. No drains were used, and patient was discharged on the same day. The patient was followed one and 3 weeks postoperatively, she had no neck or backache, her bra cup size was measured 34 C and was extremely pleased with the results [Figures 6-8].

DISCUSSION

Augmentation mammoplasty is one of the most

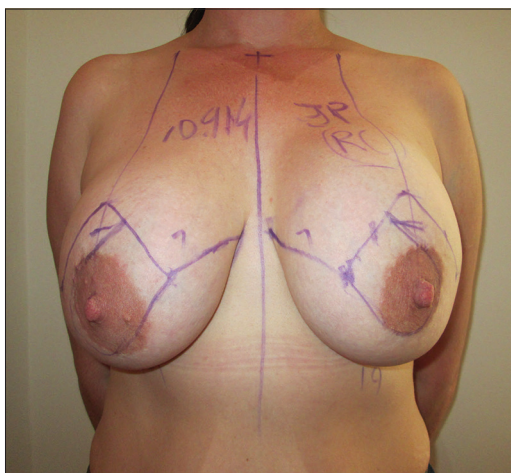


Figure 1: Patient showing preoperative wise pattern markings with medially based flap in standing position



Figure 2: Patient in supine position showing markings of left breast inferior dermoglandular flap as cross-hatched lines. Right breast showing an on table completed procedure



Figure 3: Left breast showing inferior dermoglandular flap and medially based nipple areolar complex flap de-epithelialized



Figure 4: Picture showing explanted form stable anatomical implants with fold flaw failure. Right implant showing rupture at its superior pole

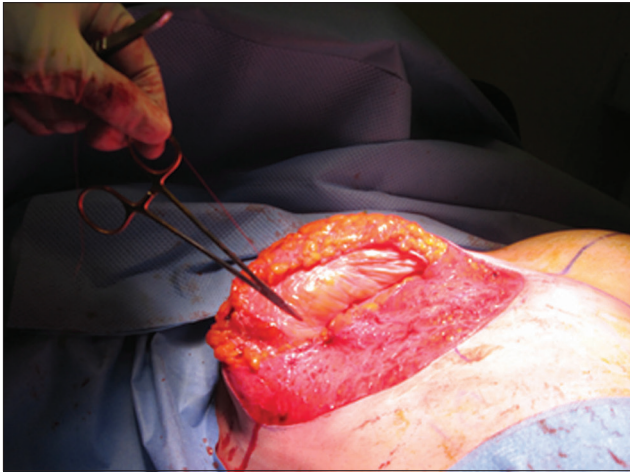


Figure 5: Picture showing right de-epithelialized inferior dermoglandular flap sutured to pectoralis major muscle

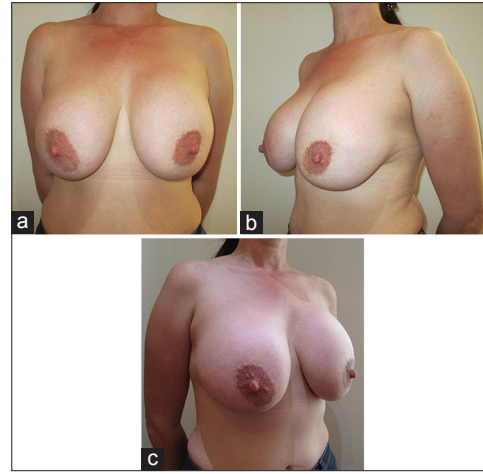


Figure 6: (a-c) Preoperative pictures of the patient before explantation



Figure 7: (a-c) Postoperative pictures showing results after 2 weeks following explantation and inferior dermoglandular de-epithelialized flap

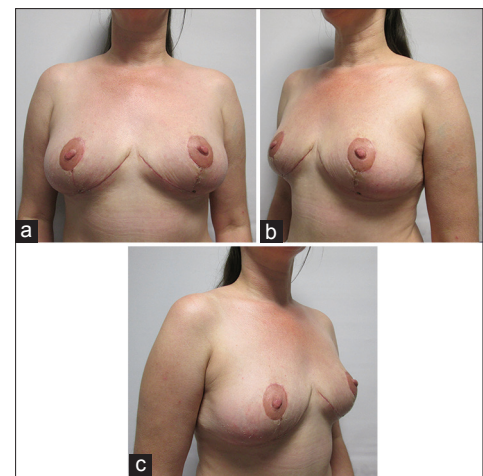


Figure 8: (a-c) Postoperative pictures showing results after 6 weeks following explantation and inferior dermoglandular de-epithelialized flap

commonly performed procedure by plastic and aesthetic surgeons today. Implant related mammoplasties for both primary and revision mammoplasties is considered a safe procedure with a high satisfaction rate and is due to the information available on the product, premarket surveys, enhanced implant safety and regular quality checks in place.^[1] It is not surprising that in 2012 alone 330,631 implant related mammoplasties were performed in USA.^[2] On the other hand, breast implant explantation without implant replacement following primary augmentation mammoplasty is very uncommon, the prevalence of the procedure or its incidence is lacking in the literature. In author's own experience, only three patients have requested explantation without breast implant replacement after performing over 4,000 implant related cosmetic mammoplasties. The rarity of the procedure makes it difficult to compile the effects on the patient or record the management of the loss of volume or resultant deformity. Explantation of breast prosthesis results in empty stretched and thinner skin envelope that is often accompanied with breast ptosis. The inferior de-epithelialized dermoglandular flap has been described for breast reconstruction with an aim to cover the prosthesis in the lower part of the breast.

The de-epithelialized flap maximizes implant coverage adding an extra layer of autologous tissue to minimize its extrusion.^[3-4] The inferior dermoglandular flap has also been described when simultaneous augmentation mammoplasty is performed with mastopexy.^[5] Volume enhancement using autologous fat transfer is safe and commonly performed today for cosmetic as well as reconstructive procedures since the publication of the article by Coleman.^[6] However, in cases following explantation of prosthesis, the patients are left with quite large empty space with a thin breast skin envelope that can make the autologous fat transfer not an easy option. Volume restoration and aesthetic appearance following explantation can be even more challenging if there is an associated ptosis. However, if a patient presents with a markedly ptotic breast, the use of the excess skin can be materialized. In these cases, wise pattern mastopexy can be performed with the use of an inferior dermoglandular flap. This de-epithelialize flap conserves breast volume and helps to remodel the breast in this group of selected cases. The procedure can also be staged where explantation can be performed initially followed by mastopexy at least 3 months later to adjust any recoil of the breast. Vertical scar mastopexy can be a possible option to conserve breast tissue, but

these markings for mastopexy may not be able to give adequate fullness or projection with a risk of bottoming down of the breast, especially when these patients presents with significant ptosis of breasts, excessive jugular notch to NAC or nipple to inframammary crease measurements.^[7] In recently described Four Flaps augmentation mastopexy, limited use of the width of the transverse inferior dermoglandular flap is recommended to avoid boxy appearance.^[5] In current case report, author has made use of the full transverse width for the de-epithelialized flap in order to maximize the autologous volume conservation as well as better breast projection and without any compromise to the aesthetic outcome. Ladizinsky *et al.*^[8] have modified the bostwick flap in their article suggesting full thickness incision in the medial and lateral inferior borders of the autoderm flap to optimize the implant coverage, limiting the medial and lateral transverse incisions and making vertical component short and narrow to minimize vascular compromise to breast envelope following subcutaneous mastectomy. No such measures are required in the use of inferior dermoglandular flap for autologous breast remodeling following explantation. The current case report is a useful technique that is aimed to conserve maximum possible autologous breast tissue and to minimize the physical and psychological morbidity associated following explantation in these patients.

In conclusion, wise pattern markings with a medially based NAC flap for mastopexy and its combination with inferior dermoglandular flap is a good option for breast

remodeling and autologous breast volume conservation in patients requesting for explantation and presenting with breast ptosis.

REFERENCES

1. Khan UD. Combining muscle splitting biplane with multilayer capsuloraphy for the correction of bottoming down following subglandular augmentation. *Eur J Plast Surg* 2010;33:259-69.
2. The American Society for Aesthetic Plastic Surgery. Cosmetic Surgery National Data Bank Statistics; 2012. Available from: <http://www.surgery.org/sites/default/files/2012stats.pdf>. [Last accessed on 2014 Sep 10].
3. Bostwick J. Prophylactic (risk-reducing) mastectomy and reconstruction. *Plastic and Reconstructive Breast Surgery*. Vol. II. St. Louis: Quality Medical Publishing; 1990. p. 1369-73.
4. King IC, Harvey JR, Bhaskar P. One-stage breast reconstruction using the inferior dermal flap, implant, and free nipple graft. *Aesthetic Plast Surg* 2014;38:358-64.
5. Forcada EM, Fernández MC, Aso JV, Iglesias IP. Augmentation mastopexy: maximal reduction and stable implant coverage using four flaps. *Aesthetic Plast Surg* 2014;38:711-7.
6. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2007;119:775-85.
7. Khan UD. Aesthetic surgery of the breast. In: Mugea TT, Shiffman MA, editor. Use of nipple-areolar to inframammary crease measurements to reduce bottoming out following augmentation mastopexy. Berlin: Springer; 2015. p. 649-56.
8. Ladizinsky DA, Sandholm PH, Jewett ST, Shahzad F, Khalil A. Breast reconstruction with Bostwick autoderm technique. *Plast Reconstr Surg* 2013;132:261-70.

How to cite this article: Khan UD. Inferior dermoglandular flap for autologous breast remodeling following explantation of breast implants in ptotic breasts: a case report and literature search. *Plast Aesthet Res* 2015;2:81-4.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 11-11-2014; **Accepted:** 22-12-2014

Isolated tibial nerve injury: a rare presentation

Rahul Krishnarao Patil¹, Prashant Verkey¹, Harshal Patil², Deepesh Manoharan¹

¹Jubilee Institute for the Surgery of Hand Aesthetic and Microvascular Surgery, Jubilee Mission Hospital, Thrissur 680005, Kerala, India.

²Department of General Surgery, Jubilee Mission Hospital, Thrissur 680005, Kerala, India.

Address for correspondence: Dr. Rahul Krishnarao Patil, Sparsh Hospital, Infantry Road, Opp. Commissioners Office, Bengaluru 560001, Karnataka, India. E-mail: doctrahul@yahoo.co.in

ABSTRACT

Tibial nerve injury is rare and is always associated with other injuries due to its close association with the other structures. We present a rare case of isolated injury to the tibial nerve where the nerve was avulsed from the middle third of the leg, but all other structures were intact. The nerve was reconstructed with sural nerve grafts. The patient recovered sensation of the sole twelve months following the reconstruction and was able to maintain a normal gait and is living normal life. The results of nerve repairs in lower limbs in general have been poor. The treatment options for such an interesting case are discussed along with the management and outcome of the presented patient.

Key words:

Nerve injuries in the lower limb, nerve reconstruction in lower extremity, tibial nerve injury

INTRODUCTION

The tibial nerve lies between the superficial and the deep muscles of the posterior compartment of the leg. It is well-protected from direct trauma due to this thick cover of muscles. In the lowermost part of the leg and ankle, the nerve is relatively superficial but is guarded anteriorly by the posterior surface of the medial malleolus, superficially by the flexor retinaculum and posteriorly by the Achilles's tendon. This protected location makes isolated injury to the tibial nerve is very uncommon. Even in cases of open fractures and associated vascular injuries of the lower extremity complete transaction of the tibial nerve is rare.^[1] Injuries to the sciatic and common peroneal nerves are more common due to their vulnerable position.^[2,3] Most of the available literature on peripheral nerve injuries in the lower extremity has documented the results and the treatment options for peroneal and sciatic nerve injuries.

Other common causes of lower limb neuropathy are diabetic neuropathy^[4] and compression neuropathies.^[5] Tibial nerve involvement is more common in these chronic

conditions. The common end result of the tibial nerve injury or neuropathy around the ankle is loss of sensations of the plantar foot, vasomotor changes due to lack of auto-regulation, subsequently leading to callosities and recurrent ulcerations and paralysis of the intrinsic muscles of foot leading to toe deformities.

We report a very unusual presentation of isolated posterior tibial nerve injury following a road traffic accident. Our search failed to reveal any similar case reported in the English literature.

CASE REPORT

A written consent was obtained from the patient and her attendants. A 15-year-old girl sustained injury to her left leg following road traffic accident. Though the exact mechanism of injury could not be elicited, she remembered falling down from her two-wheeler after it collided with a car. She sustained a small puncture wound over the lower posterior leg and was referred to our hospital after the first aid at a local hospital. On examination, she had a penetrating wound over the Achilles tendon with some soft tissue mass avulsed through the tear in the Achilles tendon [Figure 1]. The avulsed soft tissue was tender on touch. She had a lack of sensation over the plantar foot, and the foot was warm. The skin texture and turgor were found to be normal. With a provisional diagnosis of tibial nerve injury, the wound was explored. The soft tissue avulsed and protruding through the tendon was the tibial nerve [Figure 2a]. While the posterior tibial vessels and the flexor tendons were intact.

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153207

The leg was explored to find the proximal extent of injury. The nerve was found to be avulsed from the middle third as could be predicted from the length of avulsed segment [Figure 2b]. In view of the avulsion component and the force involved (site of rupture was around 8 cm from the site of a puncture wound), we decided to wait for 3 weeks before going in for definitive reconstruction. The nerve ends were tacked for future identification, and the wound was closed.

After 3 weeks, the wound was re-explored. The tibial nerve was traced proximally into unscarred tissues. After sectioning the nerve at this level, it was observed under microscope for healthy fascicles. The same procedure was followed in the distal leg to secure a healthy distal end of the nerve. The final defect of around 9.5 cm was reconstructed with 3 sural nerve cable grafts of 10 cm each [Figure 3] harvested from the contra-lateral lower extremity (the diameter of the tibial nerve at the proximal and distal end was suitable to accommodate 3 cables of a sural nerve graft). The patient was instructed regarding the care of the insensate foot, to avoid walking bare foot and perform regular inspection of the plantar foot.

She has completed 3 years of follow-up and the recovery so far is satisfactory. Except mild hallowing of the instep

area, there have been no deformities [Figure 4]. Patient has regained sensation over the heel and the instep area, and the progressive Hoffmann-Tinel signs had reached the forefoot area one and a half year after the surgery. Figure 5 shows an easy way to monitor the progressive Tinel signs in the patient's record. The patient has been using her limb during all her daily activities and was actively participating in sports. She has been following the instructions and did not have any pressure related complication over the plantar foot. For the past 3 years of follow-up, she has normal movements of the foot and the toes, no deformities and has recovered good protective plantar sensations.

DISCUSSION

Well recognized and documented examples of nerve injuries in the lower limb are the sciatic nerve injury at the hip during posterior fracture dislocations, iatrogenic injuries during injections and peroneal nerve injury following fracture of the neck of the fibula.^[2,3,6] Injury to the posterior tibial nerve is, fortunately, very rare.^[1,7,8]

Though the mechanism of injury is not exactly known in the presented case, some sharp object must have pierced the Achilles tendon to reach the nerve and due to change of the direction as the patient fell down it must have got entangled around the nerve, ultimately avulsing it.

The actual site of nerve injury was much higher than perceived site of injury, possibly a relatively fixed point like a muscular branch and is difficult to predict.^[9] This



Figure 1: Patient presenting with a small wound over the posterior aspect of the heel with soft tissue protruding through tendoachillis

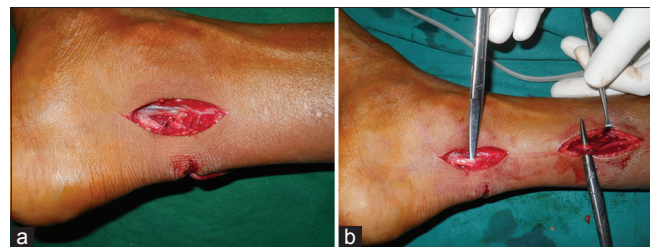


Figure 2: (a) On exploration, the soft tissue structure was found to be the posterior tibial nerve; (b) the nerve was explored in the leg and the nerve was found to have got avulsed from the middle third of the leg



Figure 3: Photograph taken during secondary reconstruction. The nerve being reconstructed with sural nerve cable grafts from the same leg



Figure 4: Picture taken after 3 weeks. The mark indicated the level of tunnels at that time. The wound has healed well

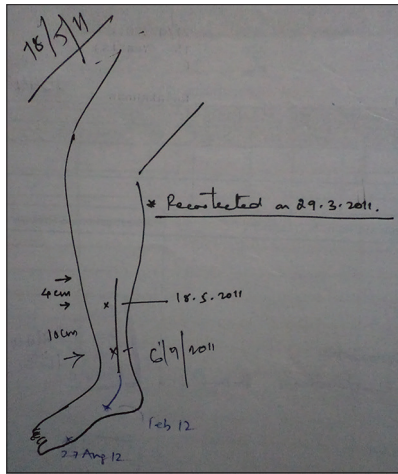


Figure 5: Picture from the progress note: showing an easy way of monitoring the recovery

can be considered analogues to brachial plexus injuries where the forces involved usually avulse the nerves from a relatively fixed point. This may also help in explaining the fact that the upper roots are either avulsed or ruptured (as they have few branches in the neck), but the lower roots are almost always avulsed in a global brachial plexus injury. Nerves are much tougher structures and considerable force is required to avulse a nerve completely. In the presented case the nerve was completely avulsed, indicating the force involved.

Nerve repair or reconstruction should be carried out as early as possible after the injury. Children have better potential for nerve recovery and primary repair should be attempted as and when possible. For grossly contaminated wounds, injuries with extensive crushing and cases where it is difficult to know the exact extent of injury, delayed primary repair is recommended.^[10] Radical debridement up to vital axons and nerve grafting was the only chance for recovery. In our case the avulsion of the nerve and the amount of damage observed on table warranted the waiting period of 3 weeks before definitive reconstruction.

After diagnosing the injury, there were two possible ways of reconstruction of the defect/loss. One option was a primary nerve transfer^[11,12] and the other was that of nerve reconstruction with nerve grafts.^[13] The number of axons in the donors locally available (superficial peroneal and sural) are limited, and also they have only sensory fibers. On the contrary, the tibial nerve has sensory and motor fibers for the intrinsic muscles of the foot. Nerve grafting in children has better success rate than in adults.^[14] We harvested nerve grafts from contra-lateral sural nerve to keep the option of nerve transfer open if required in the future. She recovered sensations completely in around one and half years after the reconstruction, and her age was the most important factor in her recovery.

Injury to the tibial nerve in the lower leg leads to the loss of sensation at the plantar foot. Though the function of

the leg muscles was preserved in this case, the insensate foot can be equally disabling due to loss of position sense and predisposition to injuries to the plantar foot. Atrophy and vasomotor changes complicate the injury. Furthermore, the paralysis of the intrinsic muscles of the foot leads to deformities over a period.

These patients need to protect their feet from injuries till they regain the protective sensations. Importance of the care of the insensate part has to be stressed during each follow-up visit. At the initial visit, the exploration of the wound for debridement and assessment of injury and the middle third of the leg for assessing the status of the proximal stump were necessary. We feel that these could have been possible through two separate incisions to decrease scarring. The nerve reconstruction also would have been possible at a later date through the same scars by tunneling the nerve grafts subcutaneously. In this case as the initial scar was present we went through the same scar for reconstruction.

In a selected and cooperative patient, nerve grafting in lower extremity can result in rewarding results.

REFERENCES

1. Waikukul S, Sakarnkosol S, Vanadurongwan V. Vascular injuries in compound fractures of the leg with initially adequate circulation. *J Bone Joint Surg Br* 1998;80:254-8.
2. Simon JP, Van Delm I, Fabry G. Sciatic nerve palsy following hip surgery. *Acta Orthop Belg* 1993;59:156-62.
3. Ferraresi S, Garozzo D, Buffatti P. Common peroneal nerve injuries: results with one-stage nerve repair and tendon transfer. *Neurosurg Rev* 2003;26:175-9.
4. Tudhope L. Treatment of diabetic neuropathy in the lower limb. *Diabet Neurop* 2010;28:186-9.
5. Beltran LS, Bencardino J, Ghazikhanian V, Beltran J. Entrapment neuropathies III: Lower limb. *Semin Musculoskelet Radiol* 2010;14:501-11.
6. Bigos SJ, Coleman SS. Foot deformities secondary to gluteal injection in infancy. *J Pediatr Orthop* 1984;4:560-3.
7. Brunner WG, Spencer RF. Posterior tibial nerve neurotmesis complicating a closed tibial fracture. A case report. *S Afr Med J* 1990;78:607-8.
8. Howard PV, Makin GS. Lower limb fractures with associated vascular injury. *J Bone Joint Surg Br* 1990;72:116-20.
9. Songcharoen P. Management of brachial plexus injury in adults. *Scand J Surg* 2008;97:317-23.
10. Songcharoen P. Neurotization in the treatment of brachial plexus injury. In: Omer GE, Spinner M, Van Beek AL, editors. *Management of Peripheral Nerve Problems*. Philadelphia: W.B. Saunders; 1998. p. 459-64.
11. Koshima I, Nanba Y, Tsutsui T, Takahashi Y. Deep peroneal nerve transfer for established plantar sensory loss. *J Reconstr Microsurg* 2003;19:451-4.
12. Gordon L, Buncke HJ. Restoration of sensation to the sole of the foot by nerve transfer. A case report. *J Bone Joint Surg Am* 1981;63:828-30.
13. Nunley JA, Gabel GT. Tibial nerve grafting for restoration of plantar sensation. *Foot Ankle* 1993;14:489-92.
14. Senes FM, Campus R, Becchetti F, Catena N. Lower limb nerve injuries in children. *Microsurgery* 2007;27:32-6.

How to cite this article: Patil RK, Verkey P, Patil H, Manoharan D. Isolated tibial nerve injury: a rare presentation. *Plast Aesthet Res* 2015;2:85-7.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 29-08-2014; **Accepted:** 13-10-2014

Pseudoangiomatous squamous cell carcinoma: a challenge for pathologists and plastic surgeons

Dimitrios Kanakopoulos¹, Evgenios Evgeniou², Panayiotis A. Dimitriadis³, Mahendra Kulkarni⁴

¹Department of Plastic Surgery, Southmead Hospital, Bristol, BS105NB, UK.

²Department of Plastic Surgery, Derriford Hospital, Plymouth, PL68DH, UK.

³Department of ENT, Lister Hospital, Stevenage, SG14AB, UK.

⁴Department of Plastic Surgery, Wexham Park Hospital, Slough, SL24HL, UK.

Address for correspondence: Mr. Evgenios Evgeniou, 43 Friars Place Lane, East Acton, London, W3 7AQ, UK.

E-mail: evgenios@doctors.org.uk

ABSTRACT

Pseudo-angiosarcomatous or pseudovascular squamous cell carcinoma (SCC) of the skin is an unusual variant form of acantholytic SCC that mimics the histopathological appearance of angiosarcoma. We describe a case of pseudovascular SCC in a 77-year-old lady to highlight the frequent recurrence and aggressiveness, as well as the clinicopathological features of this rare form of cutaneous SCC, and demonstrate the difficulties in establishing the correct diagnosis. Plastic surgeons involved in the care of patients with cutaneous malignancies should be aware of this variant of SCC and its aggressive nature in order to manage these patients appropriately.

Key words:

Carcinoma, pseudosarcoma, squamous, squamous cell carcinoma

INTRODUCTION

Squamous cell carcinoma (SCC) is a nonmelanoma skin cancer and the second most common type of skin cancer.^[1] These cases most commonly arise in sun-exposed skin areas in middle-aged or elderly patients.^[2] The classic presentation for a cutaneous SCC is a shallow ulcer with heaped-up edges, often covered by plaque, usually in a sun-exposed area. Typical surface changes may include a smooth or hyperkeratotic enlarged plaque, nodule, ulceration, crusting, or cutaneous horn.^[1] Histologically, there is a characteristic proliferation of atypical keratinocytes that invade the dermis, with areas of detachment from the overlying epidermis. These anastomosing growths of cords and nests are composed

of cells that have a glassy eosinophilic cytoplasm and enlarged nuclei. Mitotic figures, keratin pearls, and dyskeratotic keratinocytes are variably present.^[3] Pseudo-angiosarcomatous or pseudovascular SCC of the skin is an unusual and highly aggressive variant form of SCC.^[4]

CASE REPORT

A 77-year-old lady was referred to plastic surgery from dermatology with a biopsy that confirmed the presence of a poorly differentiated acantholytic SCC. On examination, she had an exophytic growth on the anterior aspect of the lower third of her left leg, with multiple satellite lesions and associated edema. There was no palpable lymphadenopathy or organomegaly present. An X-ray assessment of her left leg was performed, showing no bony involvement. A wide local excision of the lesion with a 1 cm peripheral margin down to the fascia was performed, and the wound was resurfaced with a split-thickness skin graft. Although histology confirmed that the tumor had been completely excised with an adequate margin and the wound had healed nicely within 3 weeks, the patient presented at 6 weeks with

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.153208

exophytic lesions at the edge of the skin grafted area [Figure 1]. The clinical appearance was consistent with an early recurrence. The patient underwent an urgent re-excision with 1 cm margins followed by split-thickness skin grafting. Histology confirmed a poorly differentiated SCC with marked acantholysis and pseudovascular spaces lined with atypical cells [Figures 2 and 3]. The differential diagnosis was that of a poorly differentiated pseudo-angiosarcomatous SCC or true angiosarcoma with prominent epithelioid cell morphology. Immunohistochemistry showed the tumor cells to be negative for the endothelial/vascular markers, erythroblast transformation specific related gene and cluster of differentiation 31, and for desmin and carcinoembryonic antigen. It was concluded that the tumor was a poorly differentiated acantholytic pseudo-angiosarcomatous SCC. Due to the narrow deep excision margin and the aggressiveness of the tumor, further excision was offered to the patient but this was refused. Less than 4 weeks from the second wide/local excision, the patient presented with a new erythematous lesion at the site of the original excision, which on histologic assessment indicated a further recurrence. Complete resection of the tumor was achieved. Several weeks postsurgery, the patient underwent radiotherapy to target any residual tumor cells and prevent further recurrence. A staging computed tomography evaluation did not reveal evidence of distant metastasis. After completion of the radiotherapy course and 6 months after her last operation she was evaluated by plastic surgery and found to be well with no local or regional recurrence and no lymphadenopathy.

DISCUSSION

Pseudo-angiosarcomatous or pseudovascular SCC of the skin is an unusual variant form of acantholytic (adenoid, pseudoglandular) SCC that mimics the histopathologic appearance of angiosarcoma.^[5] It is a relatively rare malignancy with only 19 cases described in the English literature.^[4] It is characterized by a pseudoglandular pattern in the histological study, and although the tumor has the clinical characteristics of SCC, histologically it may mimic an angiosarcoma.^[4,5] However, careful histological examination and immunohistochemical study can usually lead to the correct diagnosis. Acantholytic foci in these tumors may demonstrate changes in keratinocyte differentiation markers, and this may explain more aggressive biological behavior in the pseudovascular variant of SCC.^[6] Pseudovascular SCC share a poorer prognosis as they demonstrate a higher degree of recurrence and metastasis than other variants of SCC.^[7] Due to the possibility of early recurrence in these patients, plastic surgeons should consider evaluating patients with pseudovascular SCC more frequently than patients with other clinical subtypes of SCC.

Although there have not been specific studies regarding the role of adjuvant treatment in the management of



Figure 1: Recurrence of squamous cell carcinoma presenting as exophytic lesions (arrows) at the edge of the skin grafted area

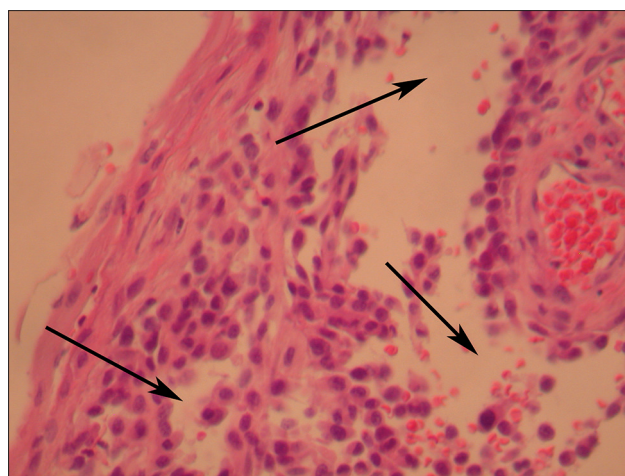


Figure 2: Histopathological specimen showing acantholysis with overlying epidermis (arrows)

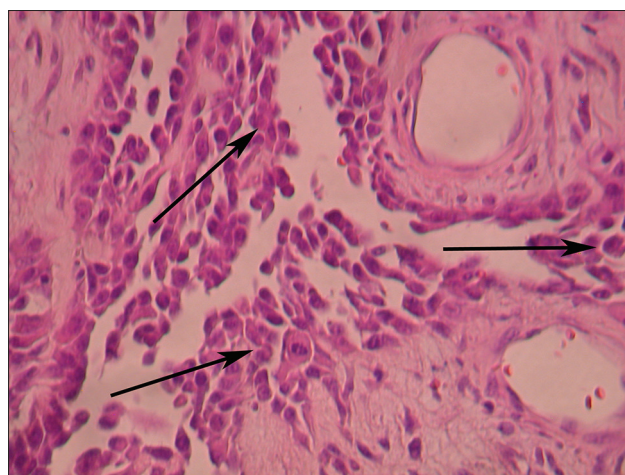


Figure 3: Histopathological specimen showing a pseudovascular space lined by tumor cells (arrows) and adjacent normal blood vessels

pseudovascular SCC, adjuvant radiotherapy has been recommended for cases of SCC with a high risk of recurrence, particularly perineurally invasive disease.^[8] The role of systemic chemotherapy and isolated limb perfusion in cutaneous SCC remains uncertain.^[9,10]

REFERENCES

1. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *BMJ* 2013;347:f6153.
2. Kivisaari A, Kähäri VM. Squamous cell carcinoma of the skin: emerging need for novel biomarkers. *World J Clin Oncol* 2013;4:85-90.
3. Edge S, Byrd D, Compton C. Cutaneous squamous cell carcinoma and other cutaneous carcinomas. In: *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2009. p. 301-9.
4. Koh SH, Oh SJ, Chun H, Kim SG. Pseudoangiosarcomatous squamous cell carcinoma developing on a burn scar: a case report and review of the literature. *Burns* 2014;40:e47-52.
5. Conde-Taboada A, Flórez A, De la Torre C, Feal C, García-Doval I, Cruces M. Pseudoangiosarcomatous squamous cell carcinoma of skin arising adjacent to decubitus ulcers. *Am J Dermatopathol* 2005;27:142-4.
6. Nappi O, Wick MR, Pettinato G, Ghiselli RV, Swanson PE. Pseudovascular adenoid squamous cell carcinoma of the skin. A neoplasm that may be mistaken for angiosarcoma. *Am J Surg Pathol* 1992;16:429-38.
7. Nagore E, Sánchez-Motilla JM, Pérez-Vallés A, Martínez-Lahuerta C, Alegre V, Aliaga A. Pseudovascular squamous cell carcinoma of the skin. *Clin Exp Dermatol* 2000;25:206-8.
8. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. *Dermatol Surg* 2009;35:574-85.
9. DeConti RC. Chemotherapy of squamous cell carcinoma of the skin. *Semin Oncol* 2012;39:145-9.
10. Turaga KK, Beasley GM, Kane JM 3rd, Delman KA, Grobmyer SR, Gonzalez RJ, Letson GD, Cheong D, Tyler DS, Zager JS. Limb preservation with isolated limb infusion for locally advanced nonmelanoma cutaneous and soft-tissue malignant neoplasms. *Arch Surg* 2011;146:870-5.

How to cite this article: Kanakopoulos D, Evgeniou E, Dimitriadis PA, Kulkarni M. Pseudoangiomatous squamous cell carcinoma: a challenge for pathologists and plastic surgeons. *Plast Aesthet Res* 2015;2:88-90.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 09-10-2014; **Accepted:** 13-11-2014

Reconstruction of palate with buccal fat pad secondary to resection of desmoplastic ameloblastoma

Bhimappa Mallappa Rudagi, Manjunatha Reddy Bandral, Reshma Hammannawar, Pritish Harish Padgavankar

Department of Oral and Maxillofacial Surgery, A.C.P.M. Dental College, Dhule 424001, Maharashtra, India.

Address for correspondence: Dr. Pritish Harish Padgavankar, Department of Oral and Maxillofacial Surgery, A.C.P.M. Dental College, Sakri Road, Dhule 424001, Maharashtra, India. E-mail: pritishharishchandra@gmail.com

ABSTRACT

Desmoplastic ameloblastoma (DA) is an unusual variant of ameloblastoma exhibiting important differences in the anatomical distribution, radiographic features and histologic appearance compared with the classic type of ameloblastoma. The purpose of this paper is to report a case of DA in the anterior left maxilla and to describe a simple method of reconstruction with the use of buccal fat pad (BFP). BFP is an excellent choice for reconstruction of small to medium sized defects. It should be manipulated gently and hemostasis should be achieved meticulously during this surgery. It should not be sutured under tension.

Key words:

Ameloblastoma, buccal fat pad, desmoplastic ameloblastoma, reconstruction, resection

INTRODUCTION

Ameloblastoma is a rare, benign, slowly growing and locally invasive neoplasm that accounts for about 1% of all cysts and tumors of the jaws and 18% of the various odontogenic neoplasms.^[1] In the recent histological classification of odontogenic tumors from the World Health Organization (WHO), ameloblastoma is defined as a benign, locally invasive epithelial odontogenic neoplasm of putative enamel organ origin.^[2] Various clinical types of ameloblastoma are solid-multicystic, unicystic, malignant and rare peripheral type. Histopathologically classified as follicular, acanthomatous, granular, basal, desmoplastic and plexiform ameloblastoma.^[3] Desmoplastic ameloblastoma (DA) was first described in detail by Eversole *et al.*^[4] In 1984 and in recent WHO classification of odontogenic tumors, it is defined as

“a variant of ameloblastoma with specific clinical, imaging and histological features”.^[5] Follicular and plexiform are the commonly encountered variants accounting for 32.5% and 28.2% respectively, followed by the acanthomatous subtype with 12.1% while desmoplastic is extremely uncommon with incidence rates ranging from 4-13% in various reports.^[5]

According to Shafer,^[6] the follicular type of ameloblastoma had the highest rate of recurrence (29.5%), plexiform subtype showed a 16.7% recurrence rate and acanthomatous type of ameloblastoma showed only 4.5% recurrence rate. DA requires special attention as it exhibits important differences in the anatomical distribution, radiographic and histomorphological compared with the classic type of ameloblastoma.^[2]

The purpose of this article is to present a case of DA in the anterior left maxilla and to describe a simple method of reconstruction with the use of buccal fat pad (BFP).

CASE REPORT

A 25-year-old male patient reported to the Department of Oral and Maxillofacial Surgery, A.C.P.M. Dental College, Dhule, Maharashtra, India with the complaint of swelling in the left anterior region of the upper jaw since 3 months.

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.153209

He revealed a history of insidious onset as a small nodule, gradually reaching the present size. The patient had no history of trauma to this region. Extraoral examination showed facial swelling with obliteration of left nasolabial fold. Swelling was oval, smooth, approximately 3 cm × 3 cm in size, extending antero-posteriorly from left ala of nose to canine fossa and superoinferiorly from left infraorbital foramen region to the left corner of upper lip. The skin over the swelling appeared normal without pain, pus discharge, or paresthesia. No lymphadenopathy was noted.

Intraorally, obliteration of upper buccal vestibule was seen on the left side [Figure 1]. The swelling extended from the upper left lateral incisor to the left second premolar buccally and palatally, superoinferiorly from the vestibular mucosa to the marginal gingiva of the teeth on buccal side and on the palatal side about 2 cm from the midline to marginal gingiva. The swelling was approximately 2.5 cm × 3 cm in size, well defined with intact mucosa causing bicortical expansion. On palpation, the swelling was nontender, bony hard, nonfluctuant, noncompressible, nonreducible and nonpulsatile, fixed to the underlying structure. No dental abnormality was seen in the region. An orthopantomogram of the region revealed a triangular radiolucency with ill-defined margins, causing mesial displacement of root of left lateral incisor and canine and proximity with distal displacement of root of the first and second premolar. Water's view showed haziness over the left maxillary sinus [Figure 2].

The overall clinical features were suggestive of an odontogenic tumor, probably an ameloblastoma, with differential diagnosis of a cyst, abscess, canine space infection, monostotic fibrous dysplasia, adenomatoid odontogenic tumor, central or peripheral giant cell granuloma, aneurysmal bone cyst. The radiographical differential diagnosis includes unilocular ameloblastoma, tumor of maxillary sinus, odontogenic keratocyst, radicular cyst, adenomatoid odontogenic tumor, ossifying fibroma, and odontogenic myxoma. To confirm the diagnosis, fine needle aspiration cytology was performed, but it was inconclusive, so incisional biopsy was performed, and histopathologic evaluation diagnosis of DA was established [Figure 3].

After confirmation of diagnosis as DA from the clinical, histological, and radiological examination, planning for surgical resection and reconstruction was done. Under general anesthesia and using a maxillary vestibular approach, incision was placed in the left buccal vestibule extending from the left central incisor to left second molar region, exposure of the lesion was done. Extraction of left upper central incisor and left second molar was done and osteotomy cut was performed on the buccal side from the extraction socket and connected to each other with a horizontal osteotomy cut just beneath the infraorbital foramen protecting infraorbital neurovascular bundle. On palatal side, incision was given from the socket of left upper central incisor to left second molar with an electrocautery, and a vertical osteotomy cut was performed. Partial maxillectomy with



Figure 1: Intraorally, swelling of 3 cm × 3 cm in size in the left anterior maxilla with intact mucosa causing bicortical expansion



Figure 2: Water's view showed haziness over the left maxillary sinus

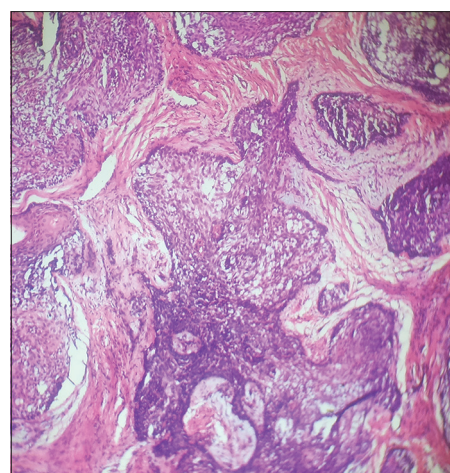


Figure 3: H and E stained section showed irregularly proliferating tumor island surrounded by dense fibrous stroma and extensive desmoplasia compressing the odontogenic epithelial island from the periphery

resection of the complete lesion (4 cm × 4 cm) was done [Figure 4]. After resection of the lesion, margins were examined, and immediate reconstruction with BFP was planned. BFP was harvested by exposing the left buccal mucosa and bluntly dissecting the area until BFP was visible and nontoothed forcep was used to grasp the BFP. It was gently teased and pulled to the wound.

The BFP was expanded and sutured with 4-0 vicryl to the underlying wound. A saframycin based oral pack was secured over the palate with 3-0 vicryl suture for primary protection for 1 week till the epithelization begins, and strict soft diet was followed [Figure 5]. The patient was kept on periodic recall every 2 months during the 1 year follow-up [Figure 6].



Figure 4: Partial maxillectomy was carried out and resection of the complete lesion was done

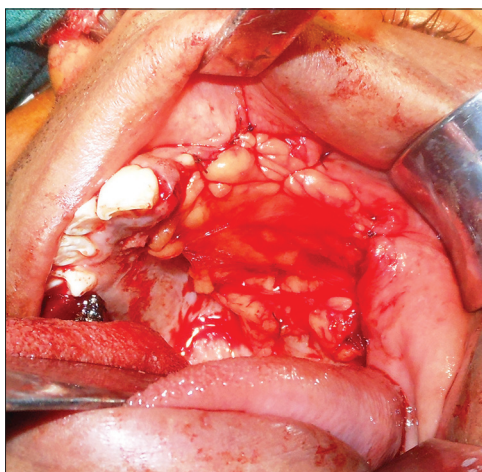


Figure 5: Reconstruction with buccal pad of fat. Immediate intra-operative picture



Figure 6: Postoperative picture after 1 year

DISCUSSION

The use of BFP as a grafting source was first described in 1977 by Egyedi.^[7] Anatomically BFP is a fatty mass in the buccal space of the cheek. It comprises 3 lobes: anterior, intermediate and posterior with 4 extensions, that is, buccal, pterygoid, pterygopalatine and temporal (superficial and profound). It is fixated by ligaments to the maxilla, posterior zygomatic bone, inner and outer rim of the orbital fissure, temporalis tendon and buccinators membrane.^[8] It is intimately associated with muscles of mastication, facial nerve and parotid duct. The use of the BFP as a grafting source in closure of intra-oral defects has gained popularity, because of the ease of harvesting, simplicity, versatility, rich blood supply, low complication rate and quick surgical techniques.^[5] Tideman *et al.*^[9] showed that the BFP is epithelialized within 3-4 weeks and therefore further skin graft are not required [Figure 5]. According to Alkan *et al.*,^[10] the success rate of the use of BFP is relatively high in all comparative studies.

In our case, we performed a partial maxillectomy procedure and complete resection of the lesion was done, after which a postsurgical defect was present in left anterior maxillary region. An immediate reconstruction with BFP was planned, and BFP was harvested from the left buccal mucosa. Intra-oral postsurgical defects reconstruction is always challenging one due to anatomical constraints and the specialized nature of intra oral tissues. The principal arterial supply to BFP is from buccal and deep branches of maxillary artery, from transverse facial branch of superficial temporal artery and from few branches of the facial artery.^[11] There should remain a reasonable size pedicle attached to the BFP to provide it with the crucial blood supply in the 1st week of its life. It is essential to stop bleeding from BFP during surgery with the help of electrocautery or small ligatures as a failure to do so leads to the formation of buccal haematoma and could compromise the viability of the flap. It is also important to be meticulous in dissecting out the flap, protecting the small branches of the facial nerve and parotid duct.

Buccal fat pad is morphologically different from subcutaneous fat but similar to orbital fat. The mean volume of BFP is about 10 mL and its mean thickness is 6 mm while the approximate weight is of 9.3 g. It can successfully be used for covering small to medium defects of about 4 cm in diameter.^[12] BFP has also been employed in the closure of surgical defects following tumor excision, excision of leukoplakia and submucous fibrosis, as well as closure of primary and secondary palatal clefts.^[13] Flap should be sutured gently to the borders of the defects and ideally there should not be any stretch within the tissue. Overstretching the tissue can lead to fragmentation of the flap and in the long term can lead to ischemic necrosis at the edges. Disadvantage with the use of the BFP flap is hematoma formation, partial necrosis, excessive scarring, infection or facial nerve injury. None of these changes was noted in our case. The use of BFP in patients with

prior local radiotherapy, malar hypoplasia, thin cheeks or Down's syndrome is contraindicated.^[14]

Approximately half of the desmoplastic lesions are located in the maxilla, and the vast majority of them occur in the anterior or premolar portion of the jaws. Maxillary lesions are more insidious than mandibular tumors owing to the proximity of vital structures and the maxillary sinus.^[15] Studies verify that DA shows a tendency to recur and the rate of recurrence is reported within the range of other histological subtypes.^[1,6] Since DA tends to infiltrate the surround bone trabeculae, curettage is considered an inappropriate treatment for DA. Therefore, block excision is the most widely accepted form of treatment for such lesions of the maxilla, particularly because recurrence is almost inevitable and difficult to treat.^[11,16] The majority of DA cases reported in the literature have been treated by resection, most likely due to ill-defined borders and an aggressive biological behavior.^[17]

Various surgical techniques have been suggested for the closure of oral defects such as primary closure, split-thickness skin graft, allogenic graft, with local flaps such as buccal advancement flap, palatal pedicled flap or double layered closure flaps using buccal and palatal tissues. However, the aforementioned procedures produce large denuded areas, result in decrease of vestibular sulcus and cannot be used to close large defects. Regional flaps including tongue flap, temporalis muscle or nasolabial flaps, etc., have also been successfully used for intra-oral reconstruction but generally preferred for defects of larger dimensions.^[14,18]

In conclusion, BFP is one of the reliable methods which can be used for the replacement and reconstruction of the oral mucosa due to postsurgical defect. BFP is an excellent choice for reconstruction of small to medium size defects. It should be manipulated gently and hemostasis should be achieved meticulously during this surgery. It should not be sutured under tension. Easy mobilization of the BFP and its excellent blood supply leading to rapid healing of wound and minimal donor site morbidity makes it a method of choice.

REFERENCES

- Reddy NV, Issrani R, Reddy S, Prabhu N, Nigam NK. Desmoplastic ameloblastoma-a case report with literature review. *J Res Adv Dent* 2013;2:95-100.
- Reichart PA, Philipson HP, Sonner S. Ameloblastoma: biological profile of 3677 cases. *Eur J Cancer B Oral Oncol* 1995;31B: 86-99.
- Rastogi V, Pandilwar PK, Maitra S. Ameloblastoma: an evidence based study. *J Maxillofac Oral Surg* 2010;9:173-7.
- Eversole LR, Leider AS, Hansen LS. Ameloblastomas with pronounced desmoplasia. *J Oral Maxillofac Surg* 1984;42:735-40.
- Angadi PV, Kale A, Hallikerimath S, Kotrashetti V, Mane D, Bhatt P, Shukla D. 'Hybrid' desmoplastic ameloblastoma: an unusual case report with immunohistochemical investigation for TGF- β and review of literature. *East J Med* 2011;16:9-17.
- Rajendran R. Cysts and tumors of odontogenic origin. In: Rajendran R, Sivapathasundharam B, editors. *Shafer's Textbook of Oral Pathology*. 5th ed. Noida: Reed-Elsevier India Private Limited; 2006. p. 357-432.
- Egyedi P. Utilization of the buccal fat pad for closure of oro-antral and/or oro-nasal communications. *J Maxillofac Surg* 1977;5:241-4.
- Durrani Z. Buccal fat pad flap in reconstruction of oral cavity defects: a case series of five patients. *JKCD* 2012;2:83-5.
- Tideman H, Bosanquet A, Scott J. Use of the buccal fat pad as a pedicled graft. *J Oral Maxillofac Surg* 1986;44:435-40.
- Alkan A, Dolanmaz D, Uzun E, Erdem E. The reconstruction of oral defects with buccal fat pad. *Swiss Med Wkly* 2003;133:465-70.
- Laxmana AR, Gogineni SB, Thomas PS, Shetty SR. Desmoplastic ameloblastoma-a report of two clinical cases. *Braz J Oral Sci* 2010;9:137-41.
- Chakrabarti J, Tekriwal R, Ganguli A, Ghosh S, Mishra PK. Pedicled buccal fat pad flap for intraoral malignant defects: a series of 29 cases. *Indian J Plast Surg* 2009;42:36-42.
- Ahmad SA, Khan S, Ahmad MS. Buccal fat pad reconstruction of oral mucosa in leukoplakia. *Ozean J Med Sci* 2010;1:13-8.
- Mohan MC, Manimaran K. Reconstruction of intra oral post surgical defects by buccal pad of fat-A clinical study. *J Indian Acad Dent Spec* 2010;1:1-4.
- Yazdi I, Seyedmajidi M, Foroughi R. Desmoplastic ameloblastoma (a hybrid variant): report of a case and review of the literature. *Arch Iran Med* 2009;12:304-8.
- dos Santos EP, Araújo FE, Valido DP, Lima SO, de Albuquerque RL Jr, Soares AF. Desmoplastic ameloblastoma mimicking a periapical lesion. *Rev Odontol Ciênc* 2010;25:306-9.
- Amaral MB, Freire-Maia B, Serpa MR, Mesquita RA. A case report of desmoplastic ameloblastoma. *J Clin Exp Dent* 2010;2:149-52.
- Grace S, Madhulaxmi. The use of buccal fat pad reconstruction in oral submucous fibrosis. *J Med Sci Clin Res* 2014;2:549-54.

How to cite this article: Rudagi BM, Bandral MR, Hammannawar R, Padgavankar PH. Reconstruction of palate with buccal fat pad secondary to resection of desmoplastic ameloblastoma. *Plast Aesthet Res* 2015;2:91-4.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 09-09-2014; **Accepted:** 14-10-2014

Straight line closure for correction of congenital isolated bilateral macrostomia

Narendra S. Mashalkar, Naren Shetty

Department of Plastic Surgery and Burns, St. John's Medical College, Koramangala, Bengaluru 560034, Karnataka, India.

Address for correspondence: Dr. Narendra S. Mashalkar, Department of Plastic Surgery and Burns, St. John's Medical College, Koramangala, Bengaluru 560034, Karnataka, India. E-mail: plasticnaren2005@yahoo.co.in

ABSTRACT

Congenital bilateral macrostomia is a very rare deformity of the mouth, and it is still rarer to see cases of isolated bilateral macrostomia. Although the creation of a symmetric neocommissure is imperative, this presents a technical challenge. A review of the literature for surgical solutions revealed various techniques, but no cases in which a bilateral straight line repair was described and adopted. This report presents the case of a 3-month-old boy with isolated bilateral macrostomia for whom straight line closure was performed on both sides. At 1 year follow-up, the oral commissures are symmetric with aesthetically pleasing scars and no lateral migration.

Key words:

Bilateral macrostomia, muscle repair, straight line closure

INTRODUCTION

Transverse facial cleft is a rare congenital anomaly with only 21 cases reported in the world literature.^[1-3] Many procedures have been developed for correction of this malformation,^[4] including the vermilion square flap technique described by Eguchi *et al.*,^[5] the Z-plasty technique described by Longacre *et al.*,^[6] the two triangular flaps method described by Ono and Tateshita,^[7] and another correction presented by Schwarz and Sharma *et al.*^[8] All techniques described highlight the importance and challenge of achieving a properly positioned symmetrical neocommissure. In this report, the straight line repair of isolated bilateral congenital macrostomia is presented for the first time. The father of the child involved in this article agreed to publish the child's pictures and signed the consent form.

CASE REPORT

A 3-month-old male child presented to us for definitive correction of congenital bilateral macrostomia [Figure 1].

The lateral extent of the cleft was located at the anterior border of the masseter muscle. After a thorough evaluation to rule out any associated anomalies, the child was scheduled for surgical correction.

Following nasal intubation, the neocommissure was determined by dropping a vertical line from the medial margin of both pupils and marking the well-defined change in color from the normal vermilion to cleft mucosa.

Both these reference points coincided [Figure 2]. The orbicularis oris was dissected and repaired after overlapping the muscle [Figures 3 and 4]. The postoperative period was uneventful [Figure 5]. At 12 months follow-up, there was no lateral migration and the aesthetic appearance was satisfactory with good oral competence [Figures 6 and 7].

DISCUSSION

The cleft of macrostomia includes a three layered defects of the skin, muscle and mucosa.^[9] Discontinuity in the muscle results in an incompetent oral sphincter.^[9] The goals of surgery for macrostomia include symmetric placement of the neocommissure, restoration of oral competence by repair of the orbicularis oris muscle, and closure of the buccal mucosa to achieve a normal contour and prevent lateral migration of the commissure.^[9] The point of the new commissure must be determined accurately to achieve the above goals. In the current

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.153210



Figure 1: Preoperative view



Figure 2: Markings intraoperative



Figure 3: Muscle repair 1

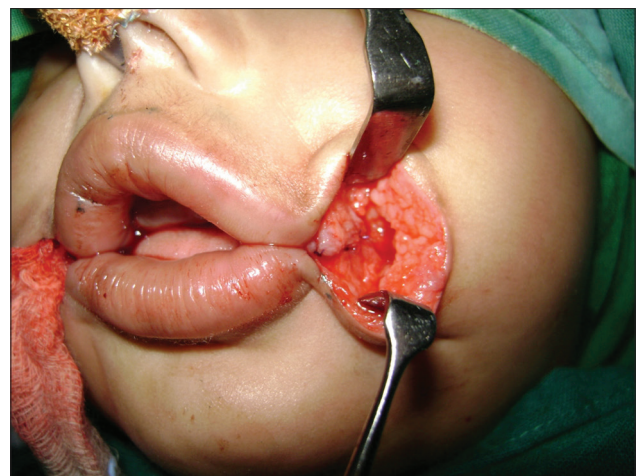


Figure 4: Muscle repair 2



Figure 5: Immediate intraoperative photo



Figure 6: Postoperative 6 months

case, a perpendicular line was dropped from the medial margin of the pupil, and the point at which the color of vermillion changes from normal vermillion to cleft vermillion was marked. Both the points coincided, and the entire surgical correction was centered on these points. The stump of the superior orbicularis oris was closed in a double-breasted fashion to the inferior orbicularis stump under adequate tension with reference to the overlying commissure. This maneuver is of vital

importance in creating competence, shape and contour at the commissure.^[9]

Vermilion square flap commissuroplasty is another technique, which has previously shown good results.^[8] The Z-plasty technique has fallen out of favor as the scar is more visible, particularly when smiling.^[3] Yoshimura *et al.*^[10] performed a study in which he compared five children with a Z-plasty repair and seven with a simple



Figure 7: Postoperative 1 year follow-up

line repair, and found that Z-plasty gives a less aesthetic result. Schwarz made a similar observation with regard to the Z-plasty repair.^[10] Younger patients are also at high risk of lateral migration of the commissure with advancing age with this technique.^[4]

In conclusion, simple line closure is a technically simple procedure and provides an esthetically pleasing scar without lateral migration or contraction in patients operated on at a young age.

REFERENCES

1. Makhija LK, Jha MK, Bhattacharya S, Rai A, Dey AB, Saha A. Transverse facial cleft: a series of 17 cases. *Indian J Plast Surg* 2011;44:439-43.
2. Gleizal A, Wan DC, Picard A, Lavis JF, Vazquez MP, Beziat JL. Bilateral macrostomia as an isolated pathology. *Cleft Palate Craniofac J* 2007;44:58-61.
3. Mahtar M, Benjelloun A, Chekkoury Idrissi A. Bilateral congenital macrostomia. *Rev Stomatol Chir Maxillofac* 2007;108:55-7.
4. Torkut A, Coskunfirat OK. Double reversing Z-plasty for correction of transverse facial cleft. *Plast Reconstr Surg* 1997;99:885-7.
5. Eguchi T, Asato PH, Takushima A, Takato T, Harii PK. Surgical repair for congenital macrostomia: vermilion square flap method. *Ann Plast Surg* 2001;47:629-35.
6. Longacre JJ, deStefano GA, Hommstrand KE. The surgical management of first and second brachial arch syndromes. *Plast Reconstr Surg* 1963;31:507-20.
7. Ono I, Tateshita T. New surgical technique for macrostomia repair with two triangular flaps. *Plast Reconstr Surg* 2000;105:688-94.
8. Schwarz R, Sharma D. Straight line closure of congenital macrostomia. *Indian J Plast Surg* 2004;37:121-3.
9. Chang HH, Tang YB, Hsu WM, Chen MT, Hsieh MH. Vermilion square flap for correction of bilateral macrostomia - A case report. *J Plast Surg Assoc ROC* 2008;17:399-404.
10. Yoshimura Y, Nakajima T, Nakanishi Y. Simple line closure for macrostomia repair. *Br J Plast Surg* 1992;45:604-5.

How to cite this article: Mashalkar NS, Shetty N. Straight line closure for correction of congenital isolated bilateral macrostomia. *Plast Aesthet Res* 2015;2:95-7.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 23-07-2014; **Accepted:** 17-12-2014

Hemifacial microsomia: management of the vertical ramus compartment

Maurice Yves Mommaerts

European Face Centre, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.

Address for correspondence: Prof. Maurice Yves Mommaerts, European Face Centre, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. E-mail: maurice.mommaerts@uzbrussel.be

ABSTRACT

Hemifacial microsomia and Goldenhar syndrome pose unique challenges to the craniofacial surgeon. The O.M.E.N.S. classification provides a description of the craniofacial features. For the “M” of O.M.E.N.S. (the mandible), the Pruzansky-Kaban classification provides therapeutic guidelines for joint and face reconstruction. A sequence of standard procedures, including temporomandibular joint reconstruction, facial rotation surgery, gluteal fat grafting, and patient-specific titanium implantation, each have their intricacies. The author provides his expert opinion, acquired over thirty years of experience, with an emphasis on descriptions of and solutions for ten problematic issues.

Key words:

Congenital abnormalities, goldenhar syndrome, mandibular reconstruction

INTRODUCTION

Hemifacial microsomia is the second most common facial birth disorder, with a prevalence of one in 3,500-6,000 live births.^[1] In 70% of individuals, the condition is unilateral [Figure 1]. The “O.M.E.N.S.” acronym is the most commonly used way to categorize hemifacial microsomia. This acronym stands for orbital, mandibular, ear, facial nerve, and soft tissue deficiencies, which are rated on a scale of 0-3, according to their severity.^[2] Most striking upon clinical examination are the external ear deformities [Figure 2] and the facial asymmetry. The latter is related to deficiencies in the vertical ramus compartment, originating from both skeletal tissues (mandible and skull base) and soft tissues (muscles of mastication and subcutaneous fat) [Figure 3]. The mandibular deformity, considered separately from the skull base (temporal bone and orbit) deformities, has been classified by Pruzansky and Kaban as Type I to III^[3,4] [Figures 4-7].

From the mid-1970s to the mid-1990s, treatment modalities for Type I and Iia Pruzansky-Kaban mandibular deformities included orthognathic treatment during adolescence or “functional” orthodontic appliances^[5] and early mandibular osteotomies to keep pace with the rate of vertical midfacial growth.^[6] For Type IIb and III deformities in growing children, joint reconstruction with costochondral grafting was indicated. In the mid-1990s, early distraction osteogenesis, before skeletal maturation and/or permanent dentition, was believed to induce the formation of not only bone, but also of soft tissue. However, a study published in 2002^[7] and a systematic review published in 2009^[8] concluded that there are no long-term benefits to early osteodistraction in the vertical ramus.

The aim of this article was to explain the author’s protocol for the reconstruction of the vertical ramus compartment in hemifacial microsomia, highlighting the key issues of the technique. All patients involved in this article agreed to publish their facial pictures and signed the consent form.

KEY ASPECTS OF SURGERY

To illustrate the author’s treatment strategy for a deficiency of the vertical ramus compartment, 10 salient points are presented with illustrative photographs from a series of patients. The general approach for the different Pruzansky-Kaban types is presented in Table 1. Orbito-zygomatic and jaw angle reconstructions are performed in all types of hemifacial microsomia

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.157097



Figure 1: An O0 M2a E2 N0 S2 case. (a) Frontal view; (b) left profile view; (c) frontal occlusion view

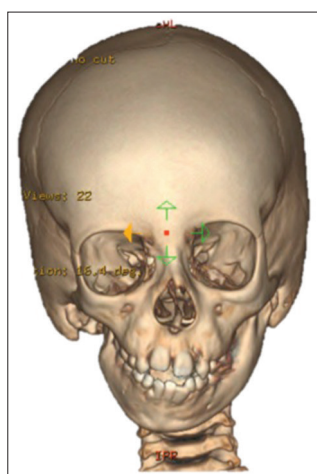


Figure 3: Three-dimensional (3D) reconstruction of a multi-slice computed tomography (CT) scan of the skull of an O1M2b, E1, N0, S1 case of hemifacial microsomia. The skeletal asymmetry in this case is due to the absence of the right-sided ascending ramus, with compensating downward growth of the skull base and orbit at the affected side

following the facial rotation procedure. Hard and soft tissue volume deficiencies can be addressed by free gluteal fat transplantation, three-dimensional (3D) printed patient-specific titanium implants or a combination of both.

Point 1: Skeletal symmetrization increases left/right soft tissue volume discrepancy

The facial rotation procedure,^[9] consisting of rotation of the maxillary, mandibular, and chin segments around a sagittal axis, while translating the midlines of all segments to the predetermined facial midline and advancing the lower face to the ideal facial profile in a sagittal plane,

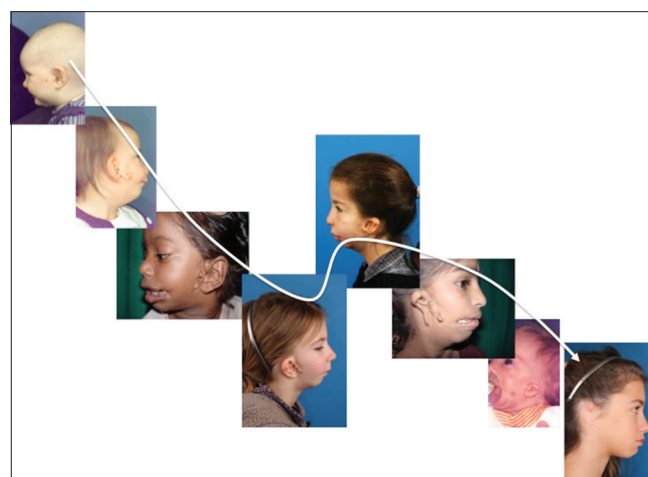


Figure 2: Ear deformities from 0 to 3 dysmorphic severity, as indicated by the white arrow

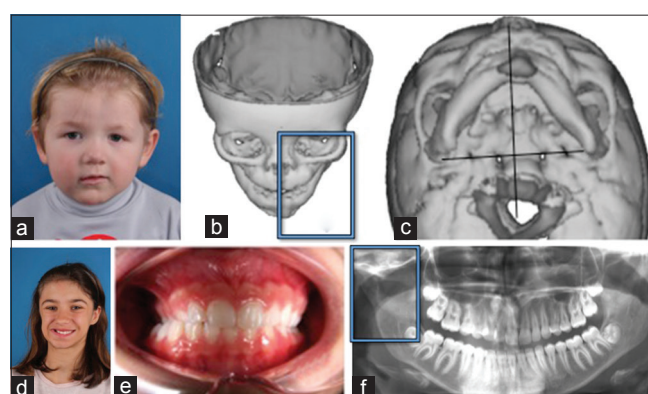


Figure 4: Pruzansky-Kaban Type I. All mandibular and temporomandibular joint components are present and normal in shape, but they are hypoplastic to a variable degree, compared to the contralateral side. (a) Frontal facial view of an affected girl during childhood; (b) three-dimensional (3D) reconstruction of a multi-slice computed tomography (CT) scan of the skull of a Type I deformity, with deviation of the mandibular midline to the left; (c) submento-vertical projection of the same 3D CT scan, demonstrating mandibular asymmetry; (d) frontal view of an affected girl during adolescence; (e) frontal view of the occlusion of the same girl in (d), demonstrating cross-bite on the right; (f) orthopantomogram of the girl in (d), showing the joint structures with a normal shape and location, but with a degree of hypoplasia. Note the downward growth of the skull base on the affected side

results in displacement of hard and soft tissues to the normal side [Figures 8-10]. This results in additional asymmetry when the left and right sides are mirrored, necessitating the next procedure: compensating for the volume deficit.

Point 2: Early osteodistraction of the horizontal ramus

Prior to orthodontic decompensation, at the age of 11-12, it is necessary to judge the retromolar bone stock. In view of the upcoming sagittal split osteotomy with the substantial advancement of the affected side, a decision must be made between removal of impacted second and/or third molars or osteodistraction of the horizontal ramus. Osteodistraction not only creates more bone to work with, but it can also partially correct the horizontal deficiency [Figure 11]. The fibrous tissues of the vertical ramus compartment can

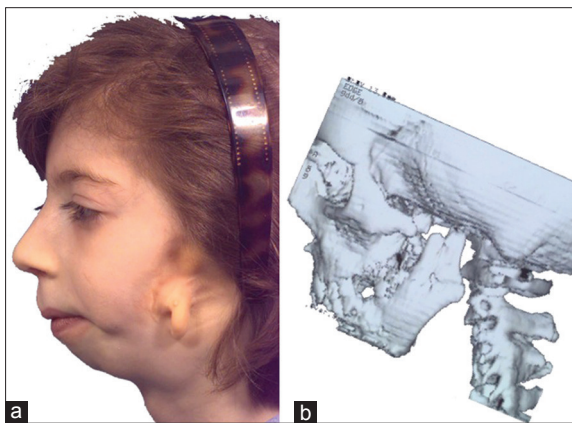


Figure 5: Pruzansky-Kaban Type IIa. The mandibular ramus, condyle, and temporomandibular joint are present but hypoplastic and abnormal in shape. The mouth can be symmetrically opened. (a) Profile view of the affected side in an adolescent girl; (b) three-dimensional (3D) reconstruction of a multi-slice computed tomography (CT) scan of the viscerocranium of the patient in a, demonstrating the abnormal shape and hypoplasia of the vertical ramus of the mandible

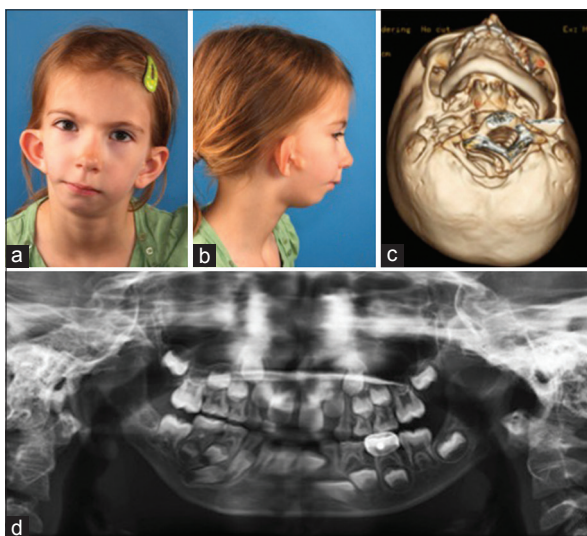


Figure 6: Pruzansky-Kaban Type IIb. The mandibular ramus is hypoplastic and markedly abnormal in form and location, being medial, anterior and inferior. There is no articulation with the temporal bone. (a) Frontal view of an affected adolescent; (b) profile view of the affected side of the girl in (a); (c) three-dimensional (3D) reconstruction of a multi-slice computed tomography (CT), submento-vertical view, demonstrating the abnormal location of the mandibular structures in abnormal location (the same patient as in (a) and (b)); (d) orthopantomogram of the girl in (a), (b), and (c), showing downward growth of the skull base on the affected side and no articulation

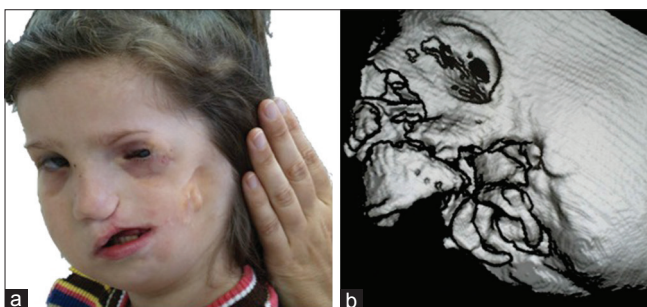


Figure 7: Pruzansky-Kaban Type III. The mandibular ramus, condyle, and temporomandibular joint are absent. The lateral pterygoid muscle and temporalis muscle, if present, are not attached to the mandibular remnant. (a) Three-fourths profile view of an affected girl; (b) three-dimensional (3D) reconstruction of a multi-slice computed tomography (CT) scan of the same girl as in a, showing the absence of the vertical ramus. The patient also had a unilateral cleft lip, alveolus, and palate

Table 1: General treatment strategies based on the Pruzansky-Kaban classification of mandibular abnormalities

Pruzansky-Kaban type	Treatment strategies
Type I	Orthognathic surgical correction "facial rotation" ^[9] after orthodontic alignment, coordination and decompensation. Standard le Fort I, bilateral sagittal split osteotomies, and sliding genioplasty techniques are used
Type IIa	Surgery is only performed early at the age of 4 and older, when there is a centric occlusion-centric relation shift of more than 5 mm. The surgery involves joint reconstruction with costochondral grafting Osteodistraction in the horizontal (not vertical) ramus is performed when there is insufficient bone stock to perform a sagittal split osteotomy after puberty Orthognathic surgical correction "facial rotation" after orthodontic alignment, coordination, and decompensation is performed at puberty and later
Type IIb and III	Joint and ramus reconstruction at the age of 4 and older. Orthognathic surgical correction "facial rotation" after orthodontic alignment, coordination and decompensation, at puberty and later

be stretched more easily when the process occurs gradually. After the latter procedure, vertical ramus lengthening is easier to perform, as more bony overlap allows for more stable osteosynthesis and improved healing.

Point 3: Choice of the pivot

Rotation of the maxilla around a sagittal axis determines the correction of the occlusal plane cant and helps to swing the mandible to the midline [Figure 12]. The dental midlines are translated toward the healthy side for alignment with the predetermined facial midline. Finally, the chin point is adjusted in a translational way to correct the skeletal mandibular midline. The chin point is often also rotated along a sagittal axis to deal with the symphyseal height difference.

Disimpacting the affected side necessitates a bone graft, obtained from the calvarium or iliac crest. Impacting the healthy side does not stretch the fibrous remains of the masticatory muscles on the other side and is possible only when a gummy smile exists on that side [Figure 13]. The decision for the pivot relates to aesthetic desiderata (normal tooth-to-incisor distance and limited gummy smile) and functional desiderata (anti-relapse biomechanics). Hence, the pivot can be located at one of three positions: at the zygomatic buttress of the healthy side, at the zygomatic buttress of the affected side, or at the nasal spine. Pivoting at the affected side (and hence impacting at the healthy side) provides the least risk of relapse.

Point 4: Skeletal suspension

Skeletal suspension is mandatory to control the correction of the occlusal plane cant and the dental midline during healing [Figure 14]. As most cases of

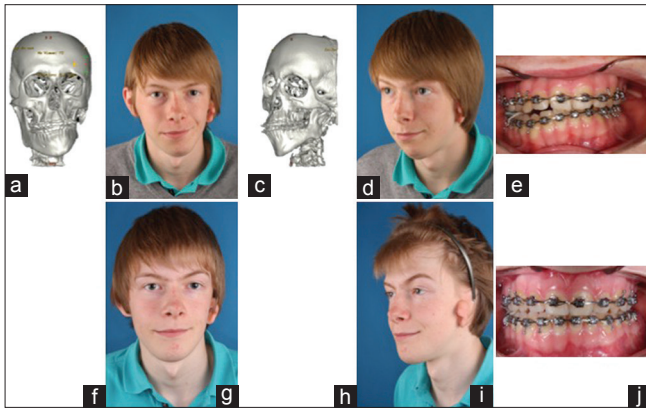


Figure 8: Pruzansky-Kaban Type IIa. (a-e) Situation prior to the facial rotation procedure; (f-j) situation after the primary skeletal and occlusal correction, demonstrating an increased left to right volume difference

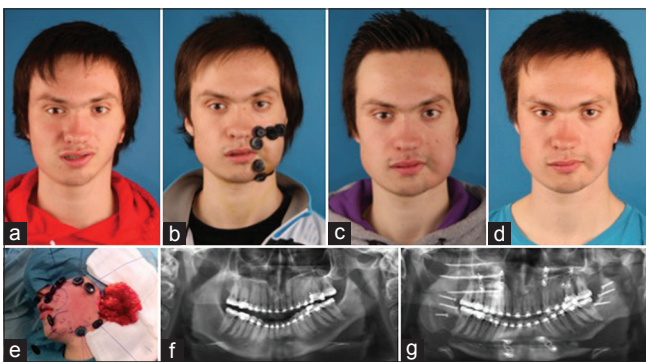


Figure 10: Pruzansky-Kaban Type IIa. (a) Frontal view after orthodontic preparation; (b) frontal view after facial rotation and free fat grafting; (c) frontal view six months after free fat grafting; (d) frontal view one year after free fat grafting; (e) gluteal fat tailored after facial requirements, ready to be inserted via a "short scar facelift" incision; (f) orthopantomogram after orthodontic preparation; (g) orthopantomogram immediately after the facial rotation procedure (note the massive chin osteotomy displacement)

hemifacial microsomia are unilateral, the rotational movement leads to different relapse vectors at both sides. Interarch elastics will safeguard the occlusal relationships, but not the skeletal relationships. The focus of interest is the occlusal plane and the lower dental midline. An orthodontic bone anchor or piriform aperture suspension wire(s) provide a means to suspend the rotated mandible with postoperative elastics to a stable osseous midface structure. Suspending the mandible to the repositioned maxilla is not sufficient, as it may give way and derotate.

Point 5: The reference plane

The oculo-auriculo-vertebral spectrum encompasses both hemifacial microsomia and Goldenhar syndrome. In addition to the aforementioned features of hemifacial microsomia, individuals with Goldenhar syndrome may exhibit ocular dermoid cysts, coloboma in the upper eyelids, delayed tooth eruption, speech and hearing disorders, and a cleft lip, alveolus, and palate. They may also have extracranial anomalies, including heart and kidney defects and fused or missing vertebrae (which occur in 30% of cases). The resulting scoliosis causes the cranium to be obliquely positioned on the thoracic

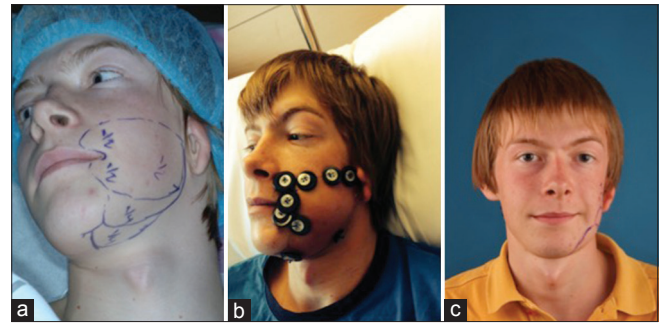


Figure 9: The same patient as in Figure 8 and one year after the facial rotation procedure. (a) Markings for free gluteal fat grafting, with access in front of the ear appendage; (b) immediate postoperative view, with buttons keeping the fat graft in position; (c) results one year after free fat grafting. Typically the fat graft has descended and requires tailoring via liposuction or lipofilling, which is marked on the skin

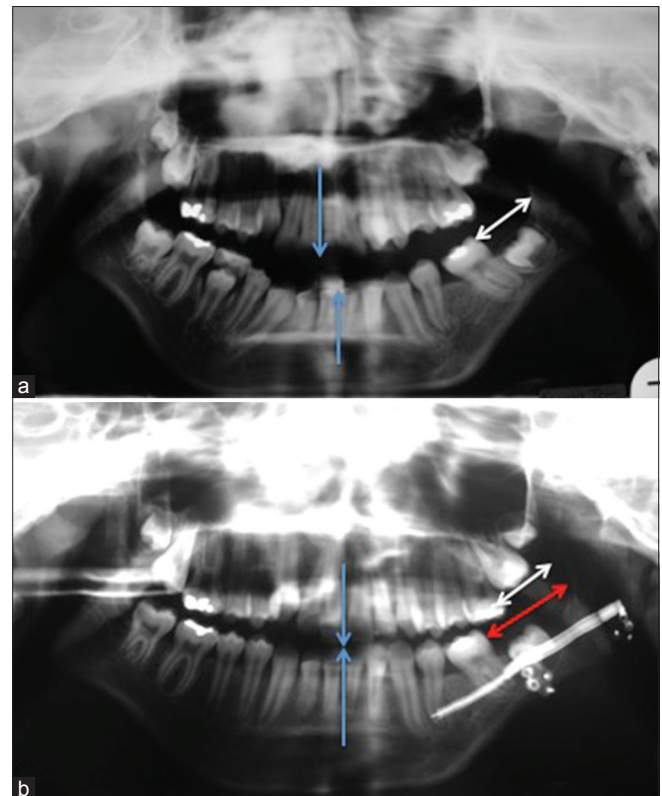


Figure 11: Pruzansky-Kaban Type IIa, illustrating the benefits of osteodistraction of the horizontal ramus. (a) Orthopantomogram prior to osteodistraction. Note the dental midlines are not aligned (blue arrows). The white arrow indicates the distance between the vertical ramus and the erupted last molar; (b) orthopantomogram immediately following osteodistraction. The dental midlines (blue arrows) are now aligned. The white arrow indicates the original and the red arrow represents the postdistraction distance (regenerate gain) between the ascending ramus and erupted last molar

spine [Figure 15]. In hemifacial microsomia, a missing, deformed, or dystopic orbit may already cause the normal reference frames (bipupillary plane, infraorbital plane, and brow plane) to be unreliable. When the patient is also scoliotic, the surgeon is challenged to find the best compromise for craniofacial symmetrization, as a completely symmetrical face may focus attention on an obliquely positioned head. In some instances, the orbital dystopia is striking and correctable with an orbital relocation osteotomy [Figure 16].

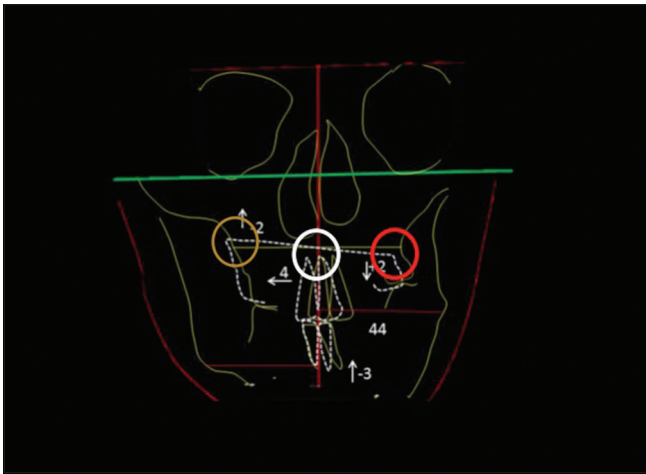


Figure 12: Choice of rotation pivot. The orange circle indicates impaction at the healthy side. The red circle indicates disimpaction at the affected side. The white circle indicates the pivot at the nasal spine

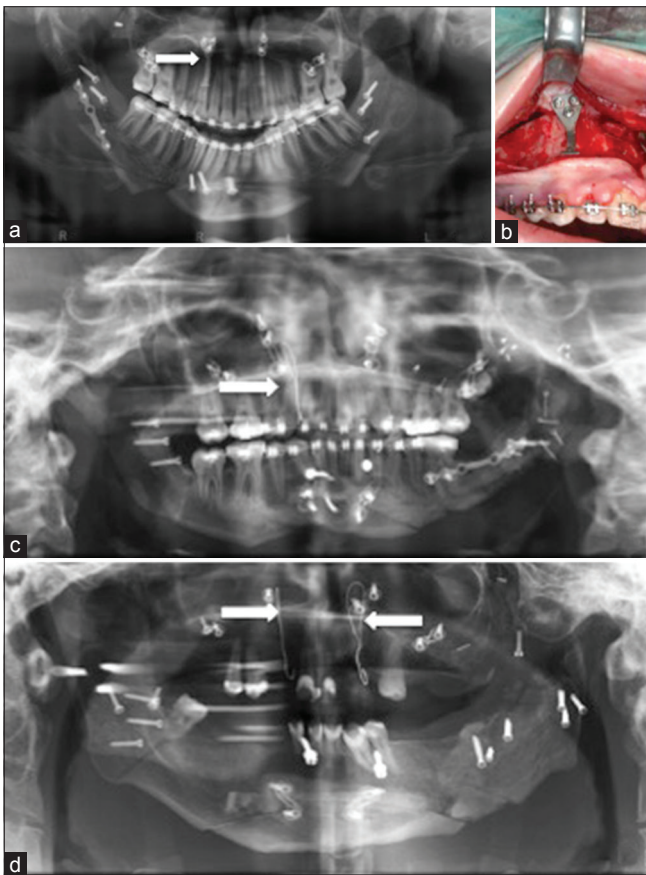


Figure 14: Skeletal suspension. (a) Orthodontic bone anchor (white arrow) placed at the affected side; (b) orthodontic bone anchor, which has to be removed via a mucoperiosteal flap dissection later on; (c) skeletal suspension by means of a piriform aperture skeletal wire (0.5 mm diameter stainless steel wire, white arrow). The advantage of this technique is that the wire can be easily removed using local anesthesia, without flap preparation (<http://www.scribd.com/doc/56442013/Inter-Maxillary-Fixation-Techniques-Manual>); (d) bilateral piriform suspension (white arrows) in a case of massive mandibular advancement

Point 6: Two costochondral grafts from ribs six and seven

Two pieces of rib are required: one fully cartilaginous piece to reconstruct the fossa and one osseo-cartilaginous piece to reconstruct the missing condyle/ramus [Figure 17]. The zygomatic arch is reconstructed or reinforced by a cranial

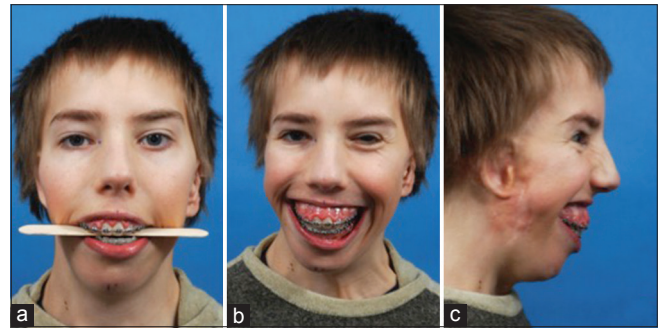


Figure 13: Pruzansky-Kaban Type IIb. This shows an ideal case with the horizontal occlusal plane in the maxilla and symmetrical gummy smile. A pivot was not chosen since overall impaction was required, with the translation of the dental midline to the left. (a) Frontal view, with the tongue spatula indicating a horizontal occlusal plane; (b) gummy smile in the frontal view; (c) gummy smile in the profile view



Figure 15: Pruzansky-Kaban Type IIb, after joint reconstruction with costochondral grafting. The patient has orbital facial nerve paresis, a small and displaced left orbit, cervical vertebral fusions and scoliosis, macrostomia and commissural symmetry, microtia, and hearing and speech problems (Goldenhar syndrome). Because of the vertebral column problems, her neck is in an oblique position, and her head is off-center in relation to her body. Her head is positioned somewhat less obliquely than her neck. Her bipupillary plane is not horizontal. There is no drooping of the brow on the affected side, despite the facial nerve paresis. It is difficult to know which reference plane to choose for positioning the occlusal plane and maxillary dental midline. (a) Frontal view, natural head position; (b) frontal view, with normal mouth opening

bone graft. The cartilaginous piece is inserted behind the arch onto the skull base and is retained by resorbable sutures placed around the *de novo* zygomatic arch. The condylar replacement is fixed onto the ramus, using the temporal approach alone or in combination with an intraoral approach for Pruzansky-Kaban Type III. The cartilaginous part of the condylar replacement may be 1 cm high, as growth is allowed.^[10] Swinging the mandible to the healthy side is permitted during joint reconstruction, but it should not cause strain. The main objective is to create a functioning joint, normal range of mouth opening, and abutment allowing for a stable facial rotation procedure at a later age. When obtaining the rib grafts, it is important to remember that rib cartilage may be required for ear reconstruction as well.

Point 7: Pruzansky-Kaban Type IIb reconstruction by a temporal approach

When only the upper part of the ascending ramus is absent, the craniofacial reconstruction (including calvarial

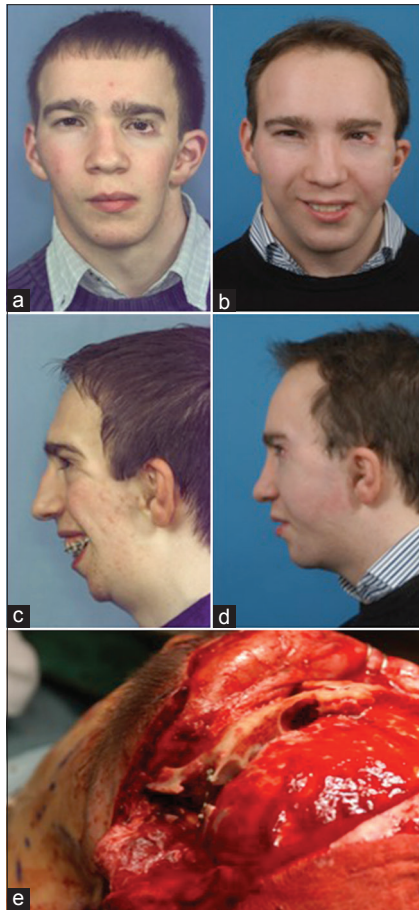


Figure 16: Goldenhar syndrome with scoliosis and orbital dystopia. The left orbit has been repositioned 1 cm higher. Free gluteal fat grafting, micro lipofilling, and a face-lift on the affected side were also performed after joint reconstruction and facial rotation. (a) Frontal view before the aforementioned procedures; (b) frontal view after the aforementioned procedures; (c) profile view before the aforementioned procedures; (d) profile view after the aforementioned procedures; (e) intraoperative view of the transcranial orbital repositioning (with the assistance of P. Staels, neurosurgeon)

bone harvesting, donor defect reconstruction, zygomatic arch and glenoid fossa reconstruction, and condylar reconstruction) can be performed via a single, wave line incision in the temporal region, extending to the lowest part of the auricular appendage [Figure 18]. Adding a retromandibular incision will jeopardize the facial nerve, as its location is abnormal. Adding an intraoral incision increases the risk of infection of the bone graft.

Point 8: Antero-medial reconstruction of the glenoid fossa versus postero-lateral relocation of the joint

The issue in Pruzansky-Kaban Type IIb and III deformities is the location for the reconstruction of the joint. Creating an abutting joint in a location that has been determined by the anomalous development is easier; however, it is doubtful whether medial reconstruction will allow symmetrization of the midface and lateral mandible at a later stage [Figure 19]. Relocation of the joint to a mirrored position is more difficult in terms of the healing of the reconstructed condyle being transplanted obliquely to the mandibular stump. The composition is mechanically unstable when it assumes a 30° angle in the frontal plane.

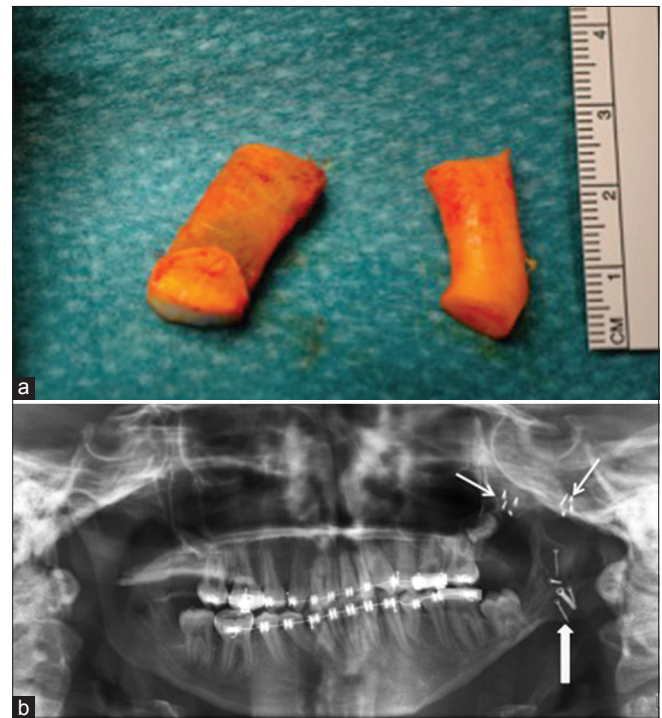


Figure 17: Pruzansky-Kaban Type IIb. Reconstruction of the temporomandibular joint. (a) Two harvested rib segments, one containing bony and cartilaginous components and the other containing only cartilage; (b) the zygomatic arch has been reconstructed using calvarial bone (two small arrows pointing at the micro osteosynthesis screws) and the fossa has been reconstructed using the cartilaginous segment (not visible). The condyle has been reconstructed using the costochondral segment, osteosynthesized via the temporal approach (big arrow pointing at oblique osteosynthesis screws)

Point 9: Respect the limits of lower facial advancement in favor of masticatory efficiency

In extreme cases of sagittal deficiency such as that found in Pruzansky-Kaban Type III it is not necessarily desirable to advance the mandible into a position that will allow the soft tissue profile of the chin to be the ideal, as determined by Facewizz software (Orthoface R and D, Sint-Martens-Latem, Belgium) (www.facewizz.com). Such advancement will be opposed by the sphenomandibular ligament and the geniohyoid muscles, thereby jeopardizing the maintenance of occlusal stability. Maxillary, mandibular, and chin advancements should be tailored to the encountered strain. In these instances, chin augmentation with calcium phosphate paste (Hydroset, Stryker, Kalamazoo, MI, USA) can be helpful in increasing chin projection [Figure 20].

Point 10: Reconstruction of the lateral and posterior ramus with added manufacturing technology

Several options exist for augmentation of the lateral aspect of the ramus, but few exist for augmentation of the posterior aspect. For lateral augmentation, sliced lyophilized cartilage grafting can be an option if this is still available. Bone grafting may lead to resorption, and alloplastic implants may lead to extrusion after infection, hydroxyapatite granules mixed with fibrin glue provide a better option.

Both lateral and posterior augmentation are possible using 3D printed titanium, designed according to the postoperative computed tomography scans. For this purpose, the authors use ProPlan CMF and 3-matic

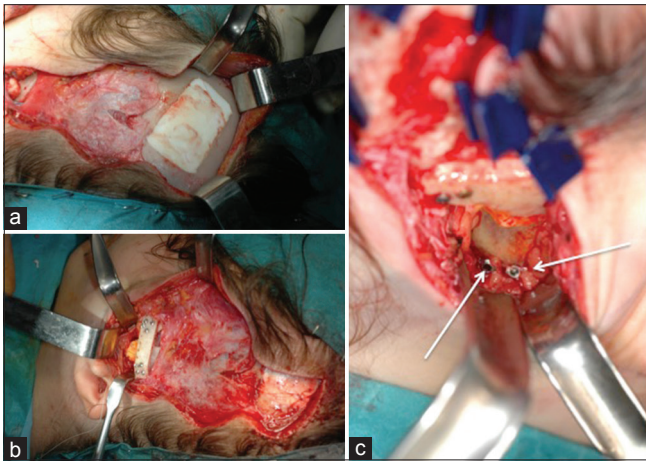


Figure 18: Pruzansky-Kaban Type IIb cases. A Temporal approach provides access to both the calvarial bone donor region and to the joint. Additional submandibular access is not required to osteosynthesize the costochondral graft to the ascending ramus. (a) The calvarial donor defect is reconstructed using calcium phosphate paste (Hydroset, Stryker); (b) the joint can be exposed and reconstructed in “open sky” mode; (c) two osteosynthesis screws have fixed the new condyle to the ascending ramus (arrows)

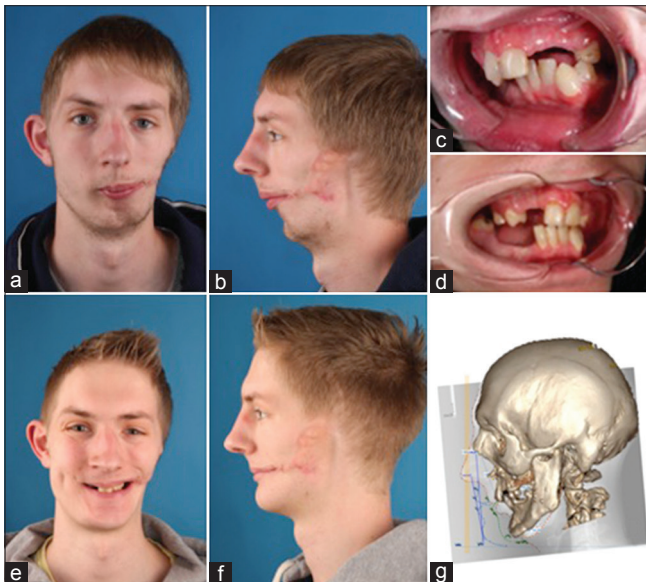


Figure 20: Pruzansky-Kaban Type III case undergoing a facial rotation procedure. The ideal profile line according to www.facewizz.com is coloured blue (g). The targeted profile is colored green. (a) Frontal view, relaxed, before facial rotation; (b) left profile view, relaxed, before facial rotation; (c) three-fourths profile view of the dental occlusion, before facial rotation; (d) three-fourths profile view of the dental occlusion, after facial rotation. Proper prosthetic rehabilitation can be undertaken secondary to occlusal stability; (e) frontal view, smiling, after facial rotation; (f) profile view, relaxed, after facial rotation; (g) planning of the advancement. A three-dimensional (3D) computed tomography (CT) reconstruction is layered over the profile cephalogram, which was used to predict the ideal advancement (blue profile line) and the targeted advancement (green profile line), based on the risk of postoperative relapse and the consequences related to dental occlusion

software of Materialise (Heverlee, Belgium). Layerwise 3D-Systems (Heverlee, Belgium) prints the implants with porous bone interfaces and sandblasted soft tissue interfaces [Figures 21 and 22]. Two important questions during the design process are: (1) is the “normal” jaw angle excessively prominent and in need of reduction, and (2) will the soft tissue (e.g. masseter muscle) deficiency already be compensated for by adding hardware?



Figure 19: Pruzansky-Kaban Type III cases with joint reconstruction. (a) This patient underwent early joint reconstruction at the age of 4 but did not comply with physiotherapy and was lost to follow-up during the next 16 years. He returned with temporomandibular joint ankylosis and severe tooth decay; (b) the ankylosis was removed and a new costochondral graft was directed to the original fossa location; (c) frontal view immediately postoperatively of a patient who underwent late joint reconstruction. She had undergone surgery for plagiocephaly at a younger age. The joint was relocated more posteriorly and laterally. As a consequence, the rib graft was inclined at a 30° angle to the ascending ramus. Healing and postoperative physiotherapy were uneventful. A mouth opening range of 37 mm was obtained with full graft union; (d) three-fourths right profile view of the case in (c)

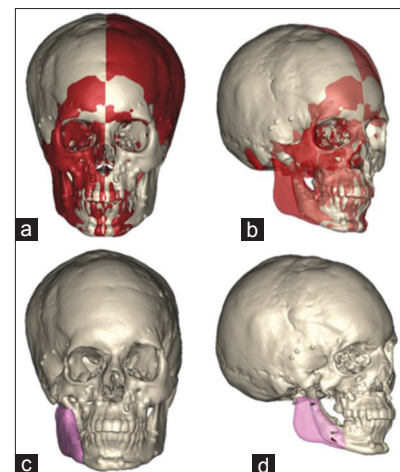


Figure 21: Pruzansky-Kaban Type III, following joint reconstruction and facial rotation. (a) Frontal view showing mirroring with ProPlan CMF. The red colored volumes are those with “normal” anatomy on the other side. Substantial vault asymmetry exists as this patient was also treated for plagiocephaly in the 1st year of life; (b) three-fourths right profile view. The transparency shows the underlying original. Nonetheless, it is hoped that the comprehensive treatment planning described in this report may be used to promote optimal patient care ascending ramus; (c) frontal view. Implant design in pink; (d) three-fourths profile view. Transparent implant design indicates the fixation screws

DISCUSSION

The vertical ramus compartment in hemifacial microsomia can exhibit variable degrees of hard or soft tissue deficiencies. Growth and development result in distorted proportions in both the transverse and sagittal dimensions. Surgical correction is challenging with respect to decision-making and execution, but is nonetheless highly rewarding. Older strategies have been tackled by newer technologies. The author has witnessed the rise in



Figure 22: The same patient as in Figure 20. (a and b) Before joint reconstruction; (c and d) after joint reconstruction; (e and f) before facial rotation, after orthodontic preparation; (g and h) after facial rotation; (i and j) after three-dimensional (3D) titanium print implantation of the right mandible

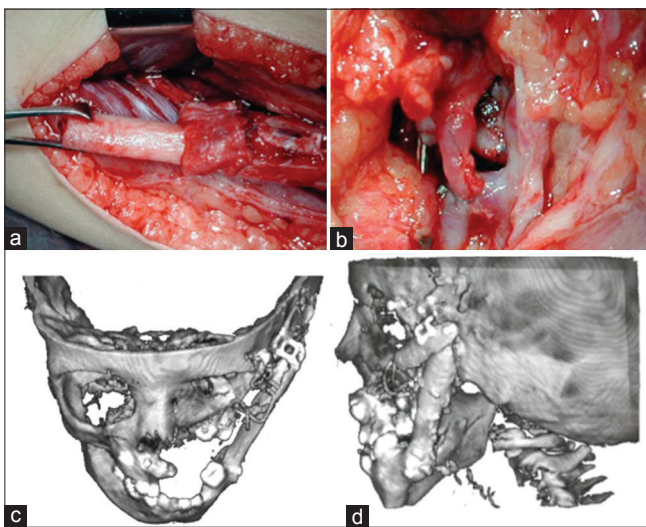


Figure 23: Pruzansky-Kaban Type III. Microvascular fibula transfer in a 10-year-old patient. (a) Harvesting of the fibula; (b) microvascular anastomosis; (c) three-dimensional (3D) computed tomography (CT) reconstruction after fibula transplantation to the left mandible; (d) 3D CT reconstruction, profile view

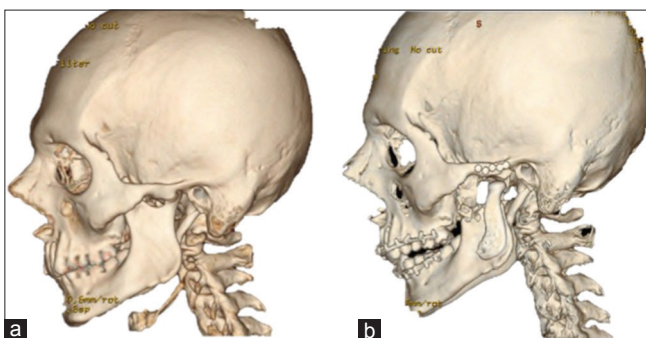


Figure 24: Bilateral three-dimensional printed temporomandibular joint (TMJ) prostheses. (a) TMJ ankylosis present; (b) fossa/condyle prosthesis in place

popularity of 3D early osteodistraction,^[11,12] and then its subsequent fall in use.^[13] Microvascular fibula transfer in a young patient^[14] [Figure 23] has been used, but the author has returned to nonvascularized rib transplantation.^[15] Microvascular parascapular dermofat transfer^[16] has been abandoned by the author in favor of nonvascularized gluteal fat transfer.^[17] The author has also used 3D

printed condyle/fossa reconstruction in adults with ankylosis^[18] [Figure 24] with consideration for integration in the facial rotation procedure for hemifacial microsomia following rib graft failure.

This article represents level 5 evidence, and therefore simply provides an expert opinion. The variability of pathology, lack of a gold standard, different surgical experiences, duration of the phased treatment, desiderata, compliance and economic situation of the patients, and use of new technologies prohibit valid sampling and prospective analyses. Nonetheless, it is hoped that the comprehensive treatment planning described in this report may be used to promote optimal patient care.

REFERENCES

1. Grabb WC. The first and second branchial arch syndrome. *Plast Reconstr Surg* 1965;36:485-508.
2. Vento AR, LaBrie RA, Mulliken JB. The O.M.E.N.S. classification of hemifacial microsomia. *Cleft Palate Craniofac J* 1991;28:68-76.
3. Pruzansky S. Not all dwarfed mandibles are alike. *Birth Defects* 1969;5:120-9.
4. Kaban LB, Moses MH, Mulliken JB. Surgical correction of hemifacial microsomia in the growing child. *Plast Reconstr Surg* 1988;82:9-19.
5. Harvold EP, Vargervik K, Chirici G. Treatment of Hemifacial Microsomia. New York: Alan R. Liss; 1983.
6. Kaban LB, Moses MH, Mulliken JB. Correction of hemifacial microsomia in the growing child: a follow-up study. *Cleft Palate J* 1986;23 Suppl 1:50-2.
7. Mommaerts MY, Nagy K. Is early osteodistraction a solution for the ascending ramus compartment in hemifacial microsomia? A literature study. *J Craniomaxillofac Surg* 2002;30:201-7.
8. Nagy K, Kuijpers-Jagtman AM, Mommaerts MY. No evidence for long-term effectiveness of early osteodistraction in hemifacial microsomia. *Plast Reconstr Surg* 2009;124:2061-71.
9. Obwegeser HL. Correction of the skeletal anomalies of oto-mandibular dysostosis. *J Maxillofac Surg* 1974;2:73-92.
10. Peltomäki T. Growth of the costochondral junction and its potential applicability for the reconstruction of the mandibular condyle. Turku: Turunlyopisto; 1993.
11. Molina F, Ortiz Monasterio F. Mandibular elongation and remodeling by distraction: a farewell to major osteotomies. *Plast Reconstr Surg* 1995;96:825-40.
12. Ortiz Monasterio F, Molina F, Andrade L, Rodriguez C, Sainz Arregui J. Simultaneous mandibular and maxillary distraction in hemifacial microsomia in adults: avoiding occlusal disasters. *Plast Reconstr Surg* 1997;100:852-61.
13. Kunz C, Brauchli L, Moehle T, Rahn B, Hammer B. Theoretical considerations for the surgical correction of mandibular deformity in hemifacial microsomia patients using multifocal distraction osteogenesis. *J Oral Maxillofac Surg* 2003;61:364-8.
14. Stelnicki EJ, Boyd JB, Nott RL, Barnavon Y, Uecker C, Henson T. Early treatment of severe mandibular hypoplasia with distraction mesenchymogenesis and bilateral free fibula flaps. *J Craniofac Surg* 2001;12:337-48.
15. Lee SJ, Lee HP, Tse KM, Cheong EC, Lim SP. Computer-aided design and rapid prototyping-assisted contouring of costal cartilage graft for facial reconstructive surgery. *Craniofac Trauma Reconstr* 2012;5:75-82.
16. Tanna N, Broer PN, Roostaeian J, Bradley JP, Levine JP, Saadeh PB. Soft tissue correction of craniofacial microsomia and progressive hemifacial atrophy. *J Craniofac Surg* 2012;23:2024-7.
17. Lim AA, Fan K, Allam KA, Wan D, Tabit C, Liao E, Kawamoto HK, Bradley JP. Autologous fat transplantation in the craniofacial patient: the UCLA experience. *J Craniofac Surg* 2012;23:1061-6.
18. Haq J, Patel N, Weimer K, Matthews NS. Single stage treatment of ankylosis of the temporomandibular joint using patient-specific total joint replacement and virtual surgical planning. *Br J Oral Maxillofac Surg* 2014;52:350-5.

How to cite this article: Mommaerts MY. Hemifacial microsomia: management of the vertical ramus compartment. *Plast Aesthet Res* 2015;2:99-106.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 01-02-2015; **Accepted:** 07-04-2015

Neurovascular plexus theory for “escape pain phenomenon” in lower third molar surgery

Gururaj Arakeri¹, Mandeep Gill Sagoo², Peter A. Brennan³

¹Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur 584101, Karnataka, India.

²Department of Anatomy and Human Sciences, King's College, London WC2R 2LS, UK.

³Department of Oral and Maxillofacial Surgery, Queen Alexandra Hospital, Portsmouth PO6 3LY, UK.

Address for correspondence: Dr. Gururaj Arakeri, Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur 584101, Karnataka, India. E-mail: gururaj.arakeri@gmail.com

ABSTRACT

Pain during extraction of impacted mandibular third molars which can occur despite adequate local anesthesia is termed as “escape pain phenomenon”. Recently, it was described during elevation of a mesioangular impacted mandibular third molar and also while curetting an extracted third molar socket. This phenomenon has been overlooked, as it was previously considered secondary to pressure effect on the inferior alveolar neurovascular bundle (IANB). However, it is unlikely that the pain impulses originate from direct pressure on the IANB, as the nerve is blocked more proximally at its entry into the mandible. The authors speculated that the occasional presence of a neurovascular plexus (NVP) independent of the IANB causes the escape of a pain impulse upon stimulation by root pressure or instrumentation. To validate the presence of such a plexus, a meticulous literature search and review were performed. The search revealed evidence of the occasional presence of a NVP consisting of auriculotemporal and/or retromolar neural filaments. The plexus may be present around the inferior alveolar artery or embedded within the IANB, and does not innervate the tooth. This plexus likely propagates pain impulses only upon stimulation by compression or instrumentation in the apical area of the tooth socket. This theory explains the absence of pain during tooth sectioning and bone guttering in the presence of a complete inferior alveolar nerve block.

Key words:

Inferior alveolar nerve, inferior dental plexus, escape pain phenomenon, third molar surgery

INTRODUCTION

The concept of the “escape pain phenomenon” (EPP) was described first by Carter and Keen^[1] in 4-5% of patients following an inferior alveolar nerve block. This phenomenon was observed during the entire course of the extraction procedure.^[1] Recently, a concern was raised regarding the incidence of pain upon the elevation of an impacted third molar.^[2,3] The pain typically manifested

during elevation of the tooth and even during curettage of the extraction socket at the apical region. This pain was thought to be an alert for the proximity of root apices to the inferior alveolar canal.^[2] However, the pain was absent during soft tissue retraction, bone guttering, and tooth section procedures.^[3]

The purpose of the present article was to postulate a theory which explains the EPP while elevation or curettage steps of third molar surgery based on a systematic literature search.

A literature search was conducted through the MEDLINE database using PubMed Central, Science Direct Search, Scopus, and Google. The keywords “neurovascular plexus” (NVP), “lower third molar”, “inferior dental artery”, “inferior alveolar nerve”, “variation”, “impaction and neurovascular complications” were used in all combinations. All papers are scrutinized for relevancy by a

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157098

panel involving three staffs from the Anatomy, Physiology and Oral and Maxillofacial Departments. Content from the relevant papers was tabulated for analysis.

A total of six relevant papers (cadaveric studies on third molar innervations) were selected, and findings from the papers were recorded. The relevant information from each of these cadaveric studies is summarized below.

Carter and Keen^[1] noted a fine network of neurovascular bundles in the area lateral to the roots of the mandibular molar teeth and extending up into the ramus. This network was traced backward to one or more foramina in the areas of insertion of the muscles of mastication. The most common connection occurred with bundles leaving the lateral pterygoid and temporal muscles. The neurovascular bundles leaving the temporalis muscle were traced to foramina in the retromolar fossa, where the lowest fibers of the temporalis gain their insertion. This part of the network ramified through the cancellous bone, and eventually established one or more obvious junctions with the main trunk of the inferior alveolar nerve, or with branches sent by the latter to the molar roots. Microscopically, several bundles of this posterior plexus and nerve fibers and blood vessels were consistently demonstrated. The largest of supplementary foramina (internal diameter 0-4 mm or greater) was most commonly seen in the retromolar fossa (one-third of the mandibles) and near the condyle (one-fifth of the mandibles). The foramina were commonly in or near the areas of insertion of the muscles of mastication, and probably transmitted the neurovascular bundles found on dissection.^[1] These "accessory" nerves formed a plexus in the cancellous bone of the ramus and the body of the mandible lateral to the molar roots and the inferior alveolar nerve. Branches of this plexus seemed to join either the inferior alveolar nerve or its molar branches.^[1] The links described are believed to offer an alternative escape route for pain impulses even after the effective blockade of inferior alveolar nerve at its entry into mandible.

Variations in the branching pattern or topographical relationships of the mandibular nerve often accounted for failure to obtain adequate local anesthesia for routine oral and dental procedures, and for unexpected injury to branches of the nerve during operation.^[4] In 2/20 dissections, Anil *et al.*^[4] noted the emergence of the auriculotemporal nerve from the posterior root of the mandibular nerve. They also observed a nerve originating from the auriculotemporal nerve and joining the inferior alveolar nerve on both sides just posterior to the maxillary artery. These two nerve branches and the mandibular nerve formed a loop reminiscent of the brachial plexus.^[4]

In a study by Zoud and Doran,^[5] the main trunk of the inferior alveolar nerve exhibited a branching structure reminiscent of the brachial plexus of the upper limb. This plexus-like structure was compounded by delicate interweaving of the inferior alveolar artery. There were numerous communications between the individual components, including fine filaments to the

auriculotemporal nerve both proximal and distal to its origin. In one of the specimens, a number of nerve fibers were observed entering the mandible via the retromolar fossa. A second "plexus" was located between the mandibular canal and the roots of the mandibular teeth, and was composed of small fine filaments which arose from the intramandibular plexus. These fine filaments appeared to enter the roots of the teeth on their lateral surfaces as well as at the apices. The relationship of the inferior alveolar artery to the nerve plexus was notable. Instead of the artery lying below the nerve in the main part of the bony canal, and then passing superior to the nerve in the distal part of the channel as is most often described, the nerve and artery formed an intertwined plexus throughout the canal. The NVP thus lay in a distinct bony canal which was observed as far as the mental foramen, but which disappeared distal to this point.^[5]

Blanton and Jeske^[6] found branches of the mandibular division of the inferior alveolar nerve originating high in the infratemporal fossa and travelling to the base of the coronoid process (high and anterior to the mandibular foramen) to enter the mandible. These branches carried sensory innervations to the second and third molars. Branches of the mandibular division or of its inferior alveolar or buccal branches also noted to enter the mandible in the retromolar fossa area and to carry sensory fibers to the first and third molars. The better-documented of the accessory nerves includes the mylohyoid nerve, as well as branches of the mandibular division (V3) of the trigeminal nerve, all of which arise high in the cranium and enter the mandible each according to its own route. The incidence of mylohyoid innervation to the mandibular teeth is approximately 60%. The mylohyoid nerve can arise from the inferior alveolar nerve anywhere from 5 mm to 23 mm proximal to the level of the mandibular foramen, and it enters the mandible at a point distal to the mandibular foramen. Therefore, deposition of local anesthetic in the vicinity of the mandibular foramen during the administration of an inferior nerve block often does not block the mylohyoid nerve. The authors^[6] recommended performing the mylohyoid nerve block in the vicinity of the retromental foramina.

Studies have reported the incidence of the retromolar foramen as 1.7%,^[7,8] 7.7%,^[9] and 19.5% in the general population,^[10] 23% in native populations of North America^[11] and 21.9% in the Indian population.^[12] However, Bilecenoglu and Tuncer^[12] found an incidence of 25% which is the second highest rate in the literature after Schejtman *et al.*^[13] study (72%). The histopathologic investigation found the contents of the neurovascular bundle to be striated muscle fibers, thin myelinated nerve fibers, numerous venules, and a muscular artery having a lumen of 120-130 μ m. This is similar to the results found in Schejtman's studies.^[13] Compared to the nutrient foramina and canals, the retromolar foramen and canal were found to have vascular and neural contents. The presence of this type of canal may explain anesthetic insufficiency and/or bleeding at this location during routine surgery.^[7] The distal end of the retromolar canal advanced to the

distal root of the third molar and retromolar area, and this distribution showed that the contents of this canal innervate and supplied the third molar and mucosa of the retromolar area.

Coleman and Smith^[14] speculated that aberrant nerve branches to the mandibular teeth and periodontium arising from major branches of the mandibular trunk high within the pterygomandibular space could also be bathed by anesthetic deposited at the mandibular neck. These branches would probably escape the drug when it is deposited at the mandibular foramen. The authors^[14] also cited Sutton's^[15] and Rood's^[16] papers which suggested that there may be accessory innervation of the mandibular teeth from branches of the lingual, buccal, facial, and upper cervical nerves from their clinical experience. With the exception of the buccal nerve, there is little anatomic evidence to support these opinions.

Neurovascular plexus theory

The above authors have demonstrated "accessory" nerves from the lateral pterygoid muscle, the temporal muscle, the auriculotemporal nerve, and the mylohyoid nerve. In most instances, these accessory nerves pass through foramina of the condylar neck, retromolar fossa, or within the infratemporal fossa to form a neural plexus which communicates with the inferior alveolar neurovascular bundle. However, all of the authors note that this accessory nerve or the plexus innervates the third molar. Conceptually, if this nerve plexus does, in fact, supply the third molar, then the pain would be expected from the commencement of tooth removal procedure, and not specifically during elevation of the tooth or socket curettage.

Based on the current literature search, the authors hypothesize that the EPP in lower third molar surgery can be attributed to the occasional presence of a NVP lying deep to the roots of the third molar which does not provide innervation. This plexus may be formed by various nerves including the auriculotemporal, mylohyoid, and retromolar plexus from the pterygoid and masseter

muscles. The pain impulses may be generated upon compression or stimulation of the plexus and be carried away causing pain escape in the presence of a complete nerve block [Figure 1].

DISCUSSION

Since the early 1970s, dentistry has experienced a resurgence of interest in the neuro-anatomical basis of local anesthesia, resulting in many scientific reports on the subject.^[6,17] Numerous studies have provided a detailed knowledge of the anatomy of the trigeminal nerve, which is important in obtaining profound local anesthesia.^[18-21] To explain the incidence of inadequate anesthesia in the mandibular region despite an efficient inferior alveolar nerve block, an EPP was first described by Carter and Keen.^[1] It was suggested to deposit local anesthetic solution in the vicinity of the retromandibular foramen to prevent the pain escape.^[6] However, the persistence of pain escape noted even after infiltrating the retromolar area with lidocaine solution in 5 of our cases. Recently, Ngeow^[2] noted the incidence of EPP while the elevation of an impacted tooth and assumed it as a result of compression of inferior alveolar nerve. It was postulated that the release of sodium and potassium ions from the compressed nerve may be responsible for propagating the pain impulses.^[2] This hypothesis was criticized because the pressure would result in paresthesia which sustains long even after the procedure.

The theory based on present literature validated the presence of a plexus at the apical region of the tooth which may be stimulated by inadvertent tooth elevation or postextraction curettage.

The incidence of pain escape seems to occur only during third molar surgery because of the inclination impacted tooth, as well as the curvature of the angle of the mandible. This brings the neurovascular bundle in proximity to the tooth root. It is not seen in the first and second molar regions as there is no possibility of compression of the neurovascular bundle.

There was also a significant incidence of bleeding following the EPP, which usually noted immediately following the elevation of the tooth fragment. This may be secondary to damage inferior alveolar vessels or vessels from the NVP.

A large-scale cadaveric study would confirm the presence of these independent NVP and their third molar innervations.

REFERENCES

1. Carter RB, Keen EN. The intramandibular course of the inferior alveolar nerve. *J Anat* 1971;108:433-40.
2. Ngeow WC. Tooth section technique for wisdom teeth. *Int J Oral Maxillofac Surg* 2009;38:908.
3. Arakeri G, Arali V. Tooth section technique and pain upon elevation in third molar removal. *Int J Oral Maxillofac Surg* 2010;39:98-9.
4. Anil A, Peker T, Turgut HB, Gülekon IN, Liman F. Variations in the anatomy of the inferior alveolar nerve. *Br J Oral Maxillofac Surg* 2003;41:236-9.

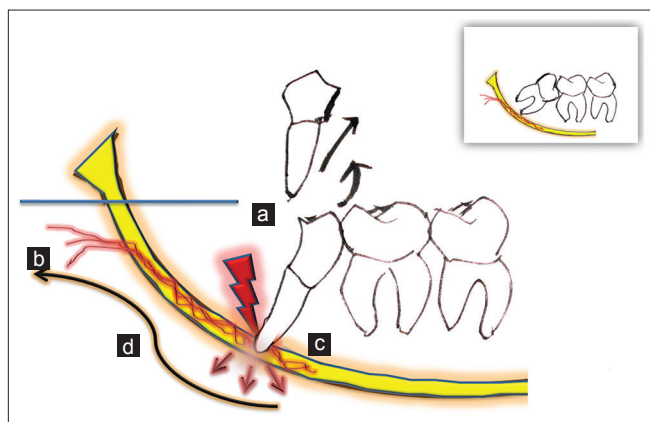


Figure 1: Diagrammatic illustration of escape pain phenomenon (EPP) and neurovascular plexus (NVP) theory during the two section technique of third molar removal (inner figure: mesioangular mandibular third molar impaction). (a) Conduction block; (b) neurovascular/nerve plexus entering into the bony canal; (c) compression of the neurovascular bundle; (d) escape of pain away from conduction blockade through neurovascular/nerve plexus

5. Zoud K, Doran GA. Microsurgical anatomy of the inferior alveolar neurovascular plexus. *Surg Radiol Anat* 1993;15:175-9.
6. Blanton PL, Jeske AH, ADA Council on Scientific Affairs, ADA Division of Science. The key to profound local anesthesia: neuroanatomy. *J Am Dent Assoc* 2003;134:753-60.
7. Ossenberg NS. Temporal crest canal: case report and statistics on a rare mandibular variant. *Oral Surg Oral Med Oral Pathol* 1986;62:10-2.
8. Ossenberg NS. Retromolar foramen of the human mandible. *Am J Phys Anthropol* 1987;73:119-28.
9. Sawyer DR, Kiely ML. Retromolar foramen: a mandibular variant important to dentistry. *Ann Dent* 1991;50:16-8.
10. Kadera H, Hashimoto I. A case of mandibular retromolar canal: elements of nerves and arteries in this canal. *Kaibogaku Zasshi* 1995;70:23-30.
11. Narayana K, Nayak UA, Ahmed WN, Bhat JG, Devaiah BA. The retromolar foramen and canal in South Indian dry mandibles. *Eur J Anat* 2002;6:141-6.
12. Bilecenoglu B, Tuncer N. Clinical and anatomical study of retromolar foramen and canal. *J Oral Maxillofac Surg* 2006;64:1493-7.
13. Schejtmann R, Devoto FC, Arias NH. The origin and distribution of the elements of the human mandibular retromolar canal. *Arch Oral Biol* 1967;12:1261-8.
14. Coleman RD, Smith RA. The anatomy of mandibular anesthesia: review and analysis. *Oral Surg Oral Med Oral Pathol* 1982;54:148-53.
15. Sutton RN. The practical significance of mandibular accessory foramina. *Aust Dent J* 1974;19:167-73.
16. Rood JP. The analgesia and innervation of mandibular teeth. *Br Dent J* 1976;140:237-9.
17. Zaytsev AY, Nazaryan DN, Kim SY, Dubrovin KV, Svetlov VA, Khovrin VV. Features of maxillary and mandibular nerves imaging during stem regional blockades. *Anesteziol Reanimatol* 2014;2:44-6.
18. Sinha P, Tamang BK, Sarda RK. Communication between Mylohyoid and Lingual Nerve: an anatomical variation. *J Clin Diagn Res* 2014;8:AD01-2.
19. Jing Q, Wan K, Wang XJ, Ma L. Effectiveness and safety of computer-controlled periodontal ligament injection system in endodontic access to the mandibular posterior teeth. *Chin Med Sci J* 2014;29:23-7.
20. Tan VL, Andrawos A, Ghabriel MN, Townsend GC. Applied anatomy of the lingual nerve: relevance to dental anaesthesia. *Arch Oral Biol* 2014;59:324-35.
21. Chiono J, Raux O, Bringuier S, Sola C, Bigorre M, Capdevila X, Dadure C. Bilateral suprazygomatic maxillary nerve block for cleft palate repair in children: a prospective, randomized, double-blind study versus placebo. *Anesthesiology* 2014;120:1362-9.

How to cite this article: Arakeri G, Sagoo MG, Brennan PA. Neurovascular plexus theory for "escape pain phenomenon" in lower third molar surgery. *Plast Aesthet Res* 2015;2:107-10.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 10-11-2014; **Accepted:** 10-04-2015

Role of topical heparin in the management of burns: experience in a district government hospital of Karnataka in South India

Ashish Gupta¹, Thangam J. Verghese², Priyanka Gupta³, Ashok K. Gupta⁴

¹Department of Plastic and Microvascular Surgery, SPS Apollo Hospitals, Ludhiana 141003, Punjab, India.

²Department of Surgery, Kasturba Medical College, Mangalore 575001, Karnataka, India.

³Department of Pediatric Hematology and Oncology, SPS Apollo Hospitals, Ludhiana 141003, Punjab, India.

⁴Department of Plastic Surgery and Burns, DMCH, Ludhiana 141001, Punjab, India.

Address for correspondence: Dr. Ashish Gupta, Department of Plastic and Microvascular Surgery, SPS Apollo Hospitals, Sherpur Chowk, GT Road, Ludhiana 141003, Punjab, India. E-mail: docashish2001@gmail.com

ABSTRACT

Aim: Heparin is a multifaceted compound with uses not only as an anticoagulant, but also as an anti-inflammatory, anti-allergenic, anti-histaminic, anti-serotonin, anti-proteolytic and neoangiogenic agent. The aim of the study was to study the effect of topical heparin in the management of second-degree burns. **Methods:** Between December 2005 and January 2007, 60 consecutive patients, aged 10-60 years, with first- and second-degree thermal injuries ranging from 10% to 60%, were randomly enrolled in the study divided into a control group (C) and a heparin group (H) of 30 patients each. **Results:** Patients treated with topical heparin experienced statistically significant improved pain relief, faster healing, fewer complications and shorter hospital stays. The majority of the patients admitted were in an economically productive age group and were predominantly female. The distribution between the two groups according to age, type of burns and extent of burns was not statistically different. **Conclusion:** The current study demonstrates the efficacy of topical heparin in the treatment of first- and second-degree burns.

Key words:

Benefits, burns, cost, epidemiology, heparin

INTRODUCTION

The earliest account of the treatment of burns dates back to the Egyptian period and the Ebers Papyrus. Rhazes (850-923 AD) prescribed rosewater cooled by snow for burn wounds, and Avicenna (980-1037 AD) described the importance of using cold water in the management of burn injuries.^[1]

Surgeons have advanced considerably from the use of oil-soaked cloth applications to the use of primary

tangential excisions and skin grafts with recombinant skin. With the advent of dedicated burn critical care units, there has been a concomitant improvement in the survival rates of critically injured burns patients and their return to society as economically productive members.

Heparin is a multifaceted compound with anti-inflammatory, anti-allergenic, anti-histaminic, anti-serotonin and anti-proteolytic enzyme properties. It has been used in both parenteral and topical forms in the management of thermal injuries to prevent burn extension, limit cutaneous tissue loss, promote faster healing with fewer contractures, relieve of pain, reduce tissue edema and weeping, prevent infection, and to promote revascularization, granulation and reepithelialization of deeply burned tissue. This study was conducted to study the role of topical heparin in the management of thermal burns and to validate its efficacy and safety in a District Government Hospital in South India.

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.157100

METHODS

A total of 326 patients with burns injuries were admitted to Government Wenlock Hospital, Mangalore, between December 2005 and January 2007. The first consecutive 60 patients with 10-60% second degree burns between the ages of 10 and 60 were enrolled in the study. Patients with liver disease, renal disorders, a blood-coagulating diathesis, an allergy to heparin, an active peptic ulcer, thrombocytopenia, active bleeding or potential bleeding from trauma were excluded. Patients who met the inclusion criteria were randomly assigned a control group (Group C) or heparin group (Group H). Thirty patients were started on topical heparin (Group H), while the other 30 patients in the control group (Group C) were treated with conventional dressings with silver sulfadiazine, intravenous antibiotics, analgesics and intravenous fluids.

The dose of heparin required for topical application was calculated to be 100,000 IU/15% burn surface area (BSA) per day in 3-4 divided doses. The medication was applied to the burnt surface drop by drop with a 50 mL syringe, until the pain was relieved, repeated for 2-4 times until blanching occurred. Beginning on the 2nd day, heparin was applied twice a day, using a diminishing quantity for 1 week.

Blisters were rinsed with heparin solution via hypodermic syringe and were not de-roofed. Blood was drawn to test for bleeding time, clotting time, and activated partial thromboplastin time, in addition to routine blood investigations.

Relief of pain as recorded by a visual analog scale, healing of wounds, dose of heparin, complications, mortality and duration of hospital stay were reported and analyzed. This was a single-blinded study that was approved by the Ethics Committee of the Institute. Written informed consent was obtained from the patients or guardians.

RESULTS

Among the 60 patients enrolled in the study, the age distribution between the two groups was not significantly different [Table 1]. The majority of the patients admitted were in the economically productive age group of 31-40 years old (19 patients, 31%).

There were equal numbers of male and female patients in Group H. The gender distribution among the two groups was not statistically significant [Table 2].

The study showed a statistically significant ($P = 0.017$) difference in the cause of burns between males and females. Accidental burns were seen in 33 patients as compared to 21 patients with homicidal intent, and 6 patients with suicidal aim. Males (18 patients) figured predominantly in the accidental group, whereas females were significantly more represented in the homicidal (17 patients) and suicidal (5 patients) subgroups [Table 3].

The distribution of the patients in the Group H and Group C cohorts as per the cause of burns was statistically not significant ($P = 0.176$) and is depicted in Figure 1.

The stratification of patients according to the extent of the thermal injury has been depicted in Table 4.

The division of burn patients in Groups H and C with respect to their duration of stay in the hospital revealed an earlier discharge from the hospital in Group H, except in cases of extensive burns of more than 50% BSA [Table 5]. The mean duration of hospital stay was significantly less in the Group H compared the Group C, in 10-20% burns (13 vs. 26 days), 20-30% burns (23 vs. 41 days), and 30-40% burns (26 vs. 67 days). A shorter hospital stay has many positive ramifications in an Indian family, in addition to the reduced economic burden of treatment.

Patients in Group C were prone to numerous complications as compared to Group H. The occurrence of these complications as depicted in Table 6 was highly statistically

Table 1: Age distribution of the patients under evaluation

Age group (years)	Number of patients	
	Group H	Group C
10-20	6	6
21-30	6	8
31-40	11	8
41-50	4	3
51-60	3	5
Total	30	30

Table 2: Distribution of patients according to gender

Gender	Number of patients	
	Group H	Group C
Male	15	8
Female	15	22

Table 3: Cause of burns

Cause of burns	Number of patients	
	Male	Female
Accidental	18	15
Homicidal	4	17
Suicidal	1	5
Total	23	37

Table 4: Number of patients according to extent of thermal injury

Percentage of burns (%)	Number of patients	
	Group H	Group C
10-20	8	10
21-30	10	5
31-40	9	7
41-50	0	4
51-60	3	4

significant ($P = 0.008$). The majority of Group C patients (24 patients) had wound contamination by the 5th postburn day, whereas in Group H only 4 patients developed wound infection, a highly statistically significant difference ($P < 0.001$) [Figure 2]. None of the patients in Group H had weeping wounds, as compared to Group C in which 76.7% of the patients developed weeping wounds ($P < 0.001$).

A reduction in infections was observed in nonweeping wounds in Group H as compared to Group C.

Fisher's exact test was used to calculate the significance of the lower analgesic requirement in Group H as compared to Group C [Table 7]. The lower requirement for opioids

in Group H had a positive effect on care, as patients were significantly more alert ($P < 0.001$).

There were fewer mortalities in Group H (1 patient) as compared to Group C (5 patients), but this difference was not statistically significant ($P = 0.197$). The decreased mortality rate could not statistically be attributed to the effect of heparin alone.

DISCUSSION

Sushruta, considered to be the father of Indian surgery, described the clinical symptoms of burnt patients in 800 BC. In 1607, Fabricus Hildnus^[1] of Switzerland provided the first printed extensive description of burns, their classification and treatment in his book "De Combustionibus."

Heparin has been shown to be very effective in the treatment of burns^[2] in a number of studies conducted in different centers across the globe.^[3] The use of heparin in burns has been shown to maintain blood circulation, inhibit blood clotting and infarctions, relieve pain, limit inflammation, revascularize ischemic tissue, enhance granulation, regulate collagen, and reduce scarring and contractures.^[4]

The addition of heparin affordably improved burn care in the current study. A majority of the burns were accidental (46.7% of Group C and 63.3% of Group H), while an appreciable number were homicidal in intent (36.7% of Group C and 33.3% of Group H).

The pain, erythema, and edema were reduced in patients who received treatment with heparin. The relief of pain with the use of heparin was remarkable as assessed on the visual analog scale as compared to the level of pain experienced in Group C. There was a direct relationship between the size of burns and the amount of heparin required to produce healing. The reduced use of pain medication and associated reduced side effects permitted Group H patients, who were more alert and cheerful, to ambulate sooner and participate in their burn treatment.^[2]

Irrigation of blisters in Group H removed the inflammatory exudates, and the skin functioned as an autologous biological dressing. Smooth new skin was evident beneath the dried thin blister when it usually flaked off in 10-14 days.

Table 5: Duration of hospitalization was significantly less than patients on conventional therapy

Percentage of burns (%)	Mean duration of hospitalization		P
	Group H	Group C	
10-20	13.6	26.2	0.018
21-30	23.2	41	0.003
31-40	26.4	67.9	0.001
41-50	0	45	
51-60	47.7	38	0.289

Table 6: Complications

Complications	Number of patients	
	Group H	Group C
Aspiration pneumonia	0	3
Atelectasis	0	1
Deep venous thrombosis	0	5
Pulmonary embolism	0	1
Septicemia	1	3
Urinary tract infection	3	6
No complications	26	11

Table 7: Use of opioid analgesic

Number of doses per day	Number of patients	
	Group H	Group C
1-2	6	2
3-4	0	28

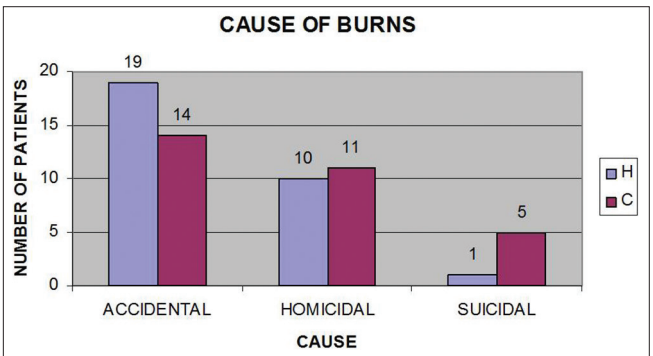


Figure 1: Distribution of patients according etiology among heparin and control groups

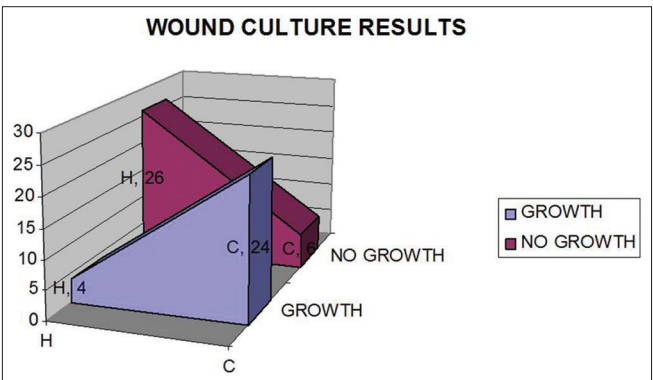


Figure 2: Wound culture and growths

The revascularization of ischemic tissue was the key feature preventing extension of burns and hence a better outcome in patients treated with heparin. These improvements were presumed to be a function of heparin's neoangiogenic effects.^[5-7]

Prior studies have suggested that orally administered antibiotics can reach burns secondary to an increase in blood flow mediated by the enhanced neoangiogenic-revascularization of the ischemic tissue.^[8-10] A reduction in intestinal bacterial translocation and sepsis found in another study may be another partial explanation for the reduction of infection seen in the current study.^[11]

The safety of large doses of topical heparin was demonstrated by laboratory determinations of blood clotting times, which were not altered. No bleeding problems or other serious complications occurred.^[12]

There were fewer skin grafting procedures required in Group H as compared to Group C, but this finding was not statistically significant. Mortality rates in Group H were lower than in Group C, with all of the deaths in the latter group occurring in 45-60% BSA injuries. Notably, there were more suicide patients in Group C (16.7%) as compared to Group H (3.3%), and suicide burns tend to be more severe. Early tangential excision and skin grafting are not practiced at our institute due to issues of nonavailability of blood products and lack of consent for surgery. Additional variables contributing to a prolonged hospital stay include the availability of free treatment in a government-aided hospital in conjunction with poor familial support.

In 1967, Dr. Saliba MJ Jr, originally published a report of the beneficial effects of intravenous heparin in large doses as a topical spray used to treat extensive burns in 28 patients.^[13] Another study conducted in 2007 showed the utility of the use of topical heparin in treating 100 patients with thermal injuries.^[14] Since that time, numerous studies have confirmed these results.^[15]

In conclusion, even as research for newer modalities in burn wound management continues, the authors find that some traditional modalities still have clinical relevance. Although there are numerous studies supporting the use of heparin in the treatment of burn wound management,

many of these are uncontrolled and inadequately define the appropriate treatment and outcomes. Further research is needed to assess the clinical utility of using heparin in the treatment of burn injuries.^[15]

REFERENCES

1. Teot L, Otman S, Brancati A, Mittermayr R. Burn scar treatment. In: Kamolz LP, Jescheke MG, Horsch RE, Küntscher M, Brychta P, editors. *Handbook of Burns*. Vienna: Springer; 2012. p. 55-67.
2. Masoud M, Wani AH, Darzi MA. Topical heparin versus conventional treatment in acute burns: a comparative study. *Indian J Burns* 2014;22:43-50.
3. Alrich EM. The effect of heparin on the circulating blood plasma and proteins in experimental burns. *Surgery* 1949;25:676-80.
4. Lu J, Xu T, Yang M, Xu XW, Wu B. Heparin for the treatment of burns (Protocol). *Cochrane Database Syst Rev* 2011;12:CD009483.
5. Reyes A, Astiazaran JA, Chavez CC, Jaramillo F, Saliba MJ. Burns treated with and without heparin: controlled use in a thermal disaster. *Ann Burns Fire Disasters* 2001;14:183-91.
6. Saliba MJ Jr, editor. *The Effects of Heparin in the Treatment of Burns*. Proceedings of International Meeting; 1994 Feb 24-27; San Diego, CA, USA.
7. Saliba MJ Jr. Heparin in the treatment of burns. *JAMA* 1967;200:650.
8. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clin Microbiol Rev* 2006;19:403-34.
9. Saliba MJ Jr. Heparin efficacy in burns. II. Human thermal burn treatment with large doses of topical and parenteral heparin. *Aerosp Med* 1970;41:1302-6.
10. Saliba MJ Jr, Dempsey WC, Kruggel JL. Large burns in humans. Treatment with heparin. *JAMA* 1973;225:261-9.
11. Ferreira Chacon JM, Mello de Andrea ML, Blanes L, Ferreira LM. Effects of topical application of 10,000 IU heparin on patients with perineal dermatitis and second-degree burns treated in a public pediatric hospital. *J Tissue Viability* 2010;19:150-8.
12. Elsayed E, Becker RC. The impact of heparin compounds on cellular inflammatory responses: a construct for future investigation and pharmaceutical development. *J Thromb Thrombolysis* 2003;15:111-8.
13. Saliba MJ Jr. The effects and uses of heparin in the care of burns that improves treatment and enhances the quality of life. *Acta Chir Plast* 1997;39:13-6.
14. Venakatachalapathy TS, Mohan Kumar S, Saliba MJ. A comparative study of burns treated with topical heparin and without heparin. *Ann Burns Fire Disasters* 2007;20:189-98.
15. Agbenorku P, Fugar S, Akpaloo J, Hoyte-Williams PE, Alhassan Z, Agyei F. Management of severe burn injuries with topical heparin: the first evidence-based study in Ghana. *Int J Burns Trauma* 2013;3:30-6.

How to cite this article: Gupta A, Verghese TJ, Gupta P, Gupta AK. Role of topical heparin in the management of burns: experience in a district government hospital of Karnataka in South India. *Plast Aesthet Res* 2015;2:111-4.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 13-07-2014; **Accepted:** 29-03-2015

Fat injection to correct contour deformities of the reconstructed breast: a single surgeon experience

Youssef Tahiri¹, Jonathan Kanevsky², Joshua Vorstenbosch³, James Lee², Karl Schwarz⁴

¹Department of Surgery, Division of Plastic and Reconstructive Surgery, Riley Hospital for Children, Indiana University, Indianapolis, IN 46202, USA.

²Department of Surgery, Division of Plastic and Reconstructive Surgery, McGill University Health Centre, Montreal, QC H3G 1B3, Canada.

³Department of Surgery, Section of Plastic Surgery, University of Manitoba, Winnipeg, MB R3T 2N2, Canada.

⁴Schwarz Plastic Surgery, Montreal, QC H3G 1B9, Canada.

Address for correspondence: Dr. Karl Schwarz, Schwarz Plastic Surgery, Montreal, QC H3G 1B9, Canada. E-mail: kaschwarz@gmail.com

ABSTRACT

Aim: Autologous fat grafting has gained acceptance as a technique to improve aesthetic outcomes in breast reconstruction. The purpose of this study was to share our clinical experience using autologous fat injection to correct contour deformities during breast reconstruction. **Methods:** A single surgeon, prospectively maintained database of patients who underwent autologous fat injection during breast reconstruction from January 2008 to November 2013 at McGill University Health Center was reviewed. Patient characteristics, breast history, type of breast reconstruction, volume of fat injected, and complications were analyzed. **Results:** One hundred and twenty-four patients benefited from autologous fat injection from January 2008 to November 2013, for a total of 187 treated breasts. The patients were on average 49.3 years old (± 8.9 years). Fat was harvested from the medial thighs (20.5%), flanks (39.1%), medial thighs and flanks (2.9%), trochanters (13.3%), medial knees (2.7%), and abdomen (21.9%). An average of 49.25 mL of fat was injected into each reconstructed breast. A total of 187 breasts in 124 patients were lipo-infiltrated during the second stage of breast reconstruction. Thirteen breasts (in 12 separate patients) were injected several years after having undergone lumpectomy and radiotherapy. Of the 187 treated breasts, 118 were reconstructed with expanders to implants, 45 with deep inferior epigastric perforator flaps, 9 with latissimus dorsi flaps with implants, 4 with transverse rectus abdominis myocutaneous flaps, and 13 had previously undergone lumpectomy and radiotherapy. Six complications were noted in the entire series, for a rate of 3.2%. All were in previously radiated breasts. Average follow-up time was 12 months (range: 2-36 months). **Conclusion:** Fat injection continues to grow in popularity as an adjunct to breast reconstruction. Our experience demonstrates a low complication rate as compared to most surgical interventions of the breast and further supports its safety in breast reconstruction. However, caution should be used when treating previously radiated breasts.

Key words:

Breast, contour deformities, fat injection

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157103

INTRODUCTION

Fat injection is a useful surgical modality to correct anatomic contour deformities.^[1-3] In 1987, the American Society of Plastic Surgeons published a report discouraging the use of autologous fat injections in the breast due to potential complications related to calcifications and detection of breast cancer.^[4] Improvements and technique

have since enhanced the clinical utility of fat grafting, and autologous fat injection is now commonly used to correct breast defects.^[5,6]

To date, retrospective studies have shown that complications associated with fat injection markedly decreased with the evolution of fat grafting protocols.^[7,8] Calcification and fat necrosis have been shown to correlate with the volume, as well as the technique of fat injection.^[9-11] There is also evidence that the volume injected correlates with survival of the grafted fat.^[12] The minimally invasive nature of the procedure allows patients to benefit from autologous tissue rather than foreign materials. As such, fat grafting has evolved into a safe procedure to correct contour deformities in the reconstructed breast.^[7]

Although some controversy remains with regards to the benefits and risks of autologous fat injections, it is widely used by reconstructive plastic surgeons to correct contour deformities in breast reconstruction.^[6] Our experience suggests this is a safe procedure that provides significant improvement to breast contour following reconstruction. This study describes a Karl Schwarz (KS) experience with fat injection to correct contour deformities during breast reconstruction.

METHODS

Patient population

The present study was approved by the McGill University Health Centre Ethics Board. A Karl Schwarz (KS), prospectively maintained database of patients who underwent autologous fat injection during breast reconstruction from January 2008 to November 2013 at McGill University Health Center was reviewed. Patient characteristics, breast history, type of breast reconstruction, volume of fat injected, and complications were analyzed retrospectively.

Technique

Autologous fat was harvested using previously described techniques.^[13] Donor sites included medial thighs, flanks, trochanters, arms, or abdominal subcutaneous fat. Under sterile conditions, fat was harvested using the Tulip liposuction system (Tulip Medical Products, San Diego, CA) with a 3 mm cannula. No donor site morbidity was observed in any of the patients enrolled in this study. The fat was then purified on large Telfa Pads (Covidien, Mansfield, MA) as previously described by Kanchwala *et al.*^[13] Once the fat reached a custard-like consistency, it was loaded into 10-mL syringes [Figure 1]. Based on preoperative topographic markings, fat was then injected into the breasts in 1 mL aliquots, distributing it evenly in multiple tissue planes, using multiple passes, to visibly correct the previously present contour deformity [Figure 2].

Review of the literature

As a measure of comparison with previously published studies, we conducted a literature search of the PubMed database using the keywords “fat graft breast” in PubMed. Our search yielded 149 articles, of which 12 met our inclusion criteria requiring that the studies enroll at least

10 patients, measure fat grafting in a clinical context, and include outcomes and complications [Table 1].

RESULTS

One hundred and twenty-four patients benefited from autologous fat injection from January 2008 to November 2013, for a total of 187 treated breasts. The patients were on average 49.3 years old (\pm 8.9 years). Fat was most often harvested from the medial thighs (20.5%), flanks (39.1%), medial thighs and flanks (2.9%), trochanters (13.3%), medial knees (2.7%), and abdomen (21.9%). An average of 49.25 mL (ranging from 8 to 210 mL) of fat was injected into each reconstructed breast [Table 2].

A total of 174 breasts in 112 patients were injected with autologous fat during the second stage of breast reconstruction. Thirteen breasts (in 12 separate patients) were injected after having undergone lumpectomy and radiotherapy. Eight breasts (in 5 separate patients) underwent a second round of fat injection 6 months after the initial lipoinjection. Of the 187 treated breasts, 118 were reconstructed with expanders to implants, 45 with deep inferior epigastric perforator (DIEP) flaps, 9 with latissimus dorsi flaps with implants, 4 with transverse rectus abdominis myocutaneous flaps [Table 3]. Thirteen of the breasts had previously undergone lumpectomy and radiotherapy. Representative images of patients treated with autologous fat grafting are shown in Figures 3 and 4.

Six complications in 3 separate patients were noted in the entire series, for a rate of 3.2%. All were in previously radiated breasts. One patient developed an isolated area of fat necrosis but also an occult pneumothorax treated conservatively. One patient developed a cellulitis treated successfully with antibiotics, and another patient developed an infection that was drained with a pig-tail catheter. Oil cysts were noted in 3 breasts.

DISCUSSION

Our experience suggests that autologous fat injection is a safe and effective procedure for correcting contour deformities following breast reconstruction. Of the 187 treated breasts in our study, we identified complications in only 6 patients for a complication rate of 3.2%. It should be noted that each of these complications occurred in previously irradiated breasts, which have been associated with impaired healing secondary due to radiation damage.^[5] Although our reported rates of fat necrosis and oil cysts are low in nonradiated breasts, it must be noted that they only represent those discovered on physical exam. It is likely that radiographic evaluation would yield higher rates.

Assessment of the literature and the data presented in this article suggest that fat injection can be a safe procedure. Although the studies reviewed demonstrate significant variability among complication rates, our 6 complications in 187 treated breasts lies on the lower end of the spectrum.

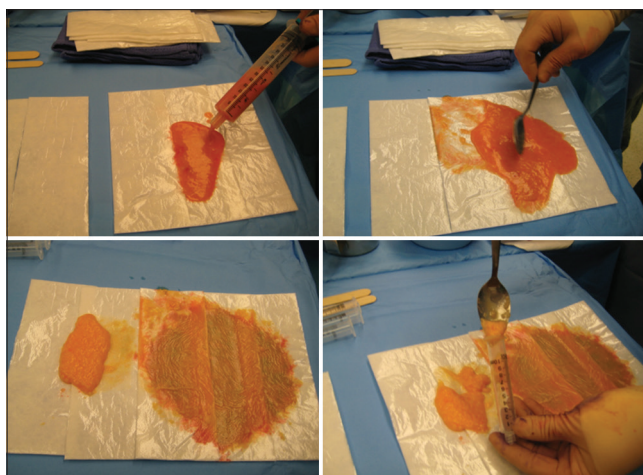


Figure 1: Fat is allowed to separate by gravity and then refined on a Teflon Pad until it reached a custard-like consistency. The refined fat was then transferred in 10-mL syringes



Figure 3: A 52-year-old female who had a left lumpectomy and radiation 3 years ago. She was treated with lipoinjection of the lateral contour deformity

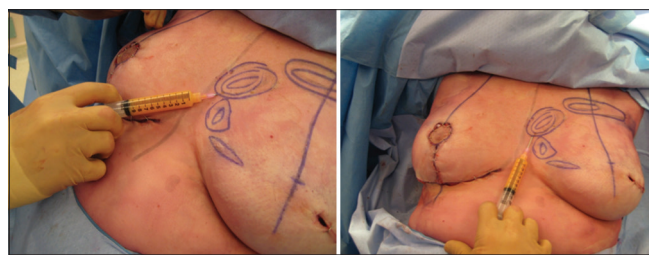


Figure 2: Relying on preoperative topographic markings, fat was injected on the breast in multiple tissue planes, through multiple passes



Figure 4: A 62-year-old female with a history of bilateral mastectomy and radiation therapy on the left breast; followed bilateral deep inferior epigastric perforator flap reconstruction. She benefited from 2 rounds of fat injection of the left upper breast contracture and serial excision of breast skin paddle

Table 1: Review of the literature

Authors	Year	Number of patients (n)	Average volume of fat injection (mL)	Complications
Pérez-Cano <i>et al.</i> ^[20]	2012	71	140	14.1% of patients developed cysts
Khoury <i>et al.</i> ^[21]	2012	81	277	16% of patients report fat necrosis after 1-year
Rubin <i>et al.</i> ^[22]	2012	27	526.5	25.5% of patients developed oil cysts 17.1% of patients developed fat necrosis
De Blacam <i>et al.</i> ^[23]	2011	49	67	3.6% of patients developed fat necrosis 1.8% of patients developed oil cysts 0.9% of patients developed infections
Kijima <i>et al.</i> ^[24]	2012	21	123	4.7% of patients developed fat necrosis 4.7% of patients developed infection
Kamakura and Ito ^[25]	2011	20	240	11% of patients developed oil cysts
Losken <i>et al.</i> ^[26]	2011	107	40	11% of patients reported fat necrosis, erythema, keloid scarring, and pain
Serra-Renom <i>et al.</i> ^[27]	2011	28	39.36	0% fat stable in all patients
Sinna <i>et al.</i> ^[28]	2010	244	176	2% of patients developed fat necrosis 1.2% of patients developed infection
Yoshimura <i>et al.</i> ^[29]	2010	15	264	0% no reported complications
Illouz and Sterodimas ^[30]	2009	820	145	9.2% of patients developed bruising 4.3% of patients developed striae 1.4% of patients developed hematomas 0.6% of patients developed infections
Panettiere <i>et al.</i> ^[31]	2009	61	24.5	0% no reported complications

Table 2: Source of fat for grafting

Site	Frequency (%)
Medial thighs	20.5
Flanks	39.1
Thighs + flanks	2.7
Abdomen	21.9
Trochanters	13.3
Medial knees	2.7

Table 3: Initial type of breast reconstruction

Type of surgery	Frequency (%)
Expander-implant	62.0
DIEP	24.1
Latissimus dorsi	4.8
Lumpectomy defect	7.0
TRAM	2.1

DIEP: Deep inferior epigastric perforator, TRAM: Transverse rectus abdominis myocutaneous

Despite having experienced few complications, all patients with a suspicious lesion or nodule were encouraged to follow-up with their breast surgeon and oncologist.^[8,11] Fortunately, radiographic evaluation can reliably distinguish calcifications, fat necrosis and oil cysts from malignant lesions.^[4]

The complications identified in our patients occurred only in radiated breasts. Despite the paucity of data regarding fat injection in radiated breasts, there is evidence demonstrating the success of fat injection into radiated tissue.^[14] While prior radiation may be a risk factor for fat necrosis, it appears that lipoinjection alleviates the damage associated with radiation.^[15,16] Clearly, further studies are needed to elucidate the advantages and pitfalls of fat injection in radiated breasts.

It is important to point out that familiarity with the technical aspects of fat injection affects the incidence of complications.^[7,8] While the incidence of fat necrosis and graft resorption is reduced when small aliquots are injected in multiple tissue planes, there is evidence that the long-term viability is increased with greater overall injection volumes.^[10,12,17]

A discussion on the safety of fat injection would not be complete without addressing the potential effects of lipoinjection on local breast cancer recurrence. The increase in vascularity promoted by injected adipose tissue may present a theoretical risk for recurrence.^[17] A study by Petit *et al.*^[18,19] describes early follow-up data suggesting that fat grafting does not present an increased risk for cancer recurrence, however, a follow-up cohort study by the same author suggests that the risk for recurrence could increase in women with high-grade intraepithelial neoplasia under the age of 50. An additional study funded by The Plastic Surgery Foundation is ongoing to further evaluate the oncologic safety of fat grafting in breast cancer patients.

In conclusion, contour irregularities are common problems associated with breast reconstruction and

can lead to suboptimal cosmetic results. Fat injection is a powerful tool that provides surgeons the ability to achieve esthetically superior results. Meticulous technique and proper planning, particularly assessing the recipient site and limiting injection volumes, allows surgeons to deliver results with low complication rates.

REFERENCES

1. Chajchir A, Benzaquen I. Liposuction fat grafts in face wrinkles and hemifacial atrophy. *Aesthetic Plast Surg* 1986;10:115-7.
2. Chajchir A, Benzaquen I. Fat-grafting injection for soft-tissue augmentation. *Plast Reconstr Surg* 1989;84:921-34.
3. Ellenbogen R. Free autogenous pearl fat grafts in the face: a preliminary report of a rediscovered technique. *Ann Plast Surg* 1986;16:179-94.
4. Report on autologous fat transplantation. ASPRS Ad-hoc Committee on New Procedures, September 30, 1987. *Plast Surg Nurs* 1987;7:140-1.
5. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2007;119:775-85.
6. Kling RE, Mehrara BJ, Pusic AL, Young VL, Hume KM, Crotty CA, Rubin JP. Trends in autologous fat grafting to the breast: a national survey of the American society of plastic surgeons. *Plast Reconstr Surg* 2013;132:35-46.
7. Delay E, Garson S, Tousson G, Sinna R. Fat injection to the breast: technique, results, and indications based on 880 procedures over 10 years. *Aesthet Surg J* 2009;29:360-76.
8. Gutowski KA, ASPS Fat Graft Task Force. Current applications and safety of autologous fat grafts: a report of the ASPS fat graft task force. *Plast Reconstr Surg* 2009;124:272-80.
9. Cotrufo S, Mandal A, Mithoff EM. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2008;121:701.
10. Mu DL, Luan J, Mu L, Xin MQ. Breast augmentation by autologous fat injection grafting: management and clinical analysis of complications. *Ann Plast Surg* 2009;63:124-7.
11. Walden JL. Complications after autologous fat injection to the breast. *Plast Reconstr Surg* 2009;124:326-7.
12. Choi M, Small K, Levovitz C, Lee C, Fadl A, Karp NS. The volumetric analysis of fat graft survival in breast reconstruction. *Plast Reconstr Surg* 2013;131:185-91.
13. Kanchwala SK, Glatt BS, Conant EF, Bucky LP. Autologous fat grafting to the reconstructed breast: the management of acquired contour deformities. *Plast Reconstr Surg* 2009;124:409-18.
14. Phulpin B, Gangloff P, Tran N, Bravetti P, Merlin JL, Dolivet G. Rehabilitation of irradiated head and neck tissues by autologous fat transplantation. *Plast Reconstr Surg* 2009;123:1187-97.
15. Sultan SM, Stern CS, Allen RJ Jr, Thanik VD, Chang CC, Nguyen PD, Canizares O, Szpalski C, Saadeh PB, Warren SM, Coleman SR, Hazen A. Human fat grafting alleviates radiation skin damage in a murine model. *Plast Reconstr Surg* 2011;128:363-72.
16. Salgarello M, Visconti G, Farallo E. Autologous fat graft in radiated tissue prior to alloplastic reconstruction of the breast: report of two cases. *Aesthetic Plast Surg* 2010;34:5-10.
17. Khonji N. Breast reconstruction using autologous fat. *Br J Surg* 2010;97:795-6.
18. Petit JY, Botteri E, Lohsiriwat V, Rietjens M, De Lorenzi F, Garusi C, Rossetto F, Martella S, Manconi A, Bertolini F, Curigliano G, Veronesi P, Santillo B, Rotmensz N. Locoregional recurrence risk after lipofilling in breast cancer patients. *Ann Oncol* 2012;23:582-8.
19. Petit JY, Rietjens M, Botteri E, Rotmensz N, Bertolini F, Curigliano G, Rey P, Garusi C, De Lorenzi F, Martella S, Manconi A, Barbieri B, Veronesi P, Intra M, Brambullo T, Gottardi A, Sommario M, Lomeo G, Iera M, Giovannazzo V, Lohsiriwat V. Evaluation of fat grafting safety in patients with intraepithelial neoplasia: a matched-cohort study. *Ann Oncol* 2013;24:1479-84.
20. Pérez-Cano R, Vranckx JJ, Lasso JM, Calabrese C, Merck B, Milstein AM, Sassoon E, Delay E, Weiler-Mithoff EM. Prospective trial of adipose-derived regenerative cell (ADRC)-enriched fat grafting for partial mastectomy defects: the RESTORE-2 trial. *Eur J Surg Oncol* 2012;38:382-9.
21. Khouri RK, Eisenmann-Klein M, Cardoso E, Cooley BC, Kacher D, Gombos E, Baker TJ. Brava and autologous fat transfer is a safe and effective breast augmentation alternative: results of a 6-year, 81-patient, prospective multicenter study. *Plast Reconstr Surg* 2012;129:1173-87.
22. Rubin JP, Coon D, Zuley M, Toy J, Asano Y, Kurita M, Aoi N, Harii K, Yoshimura K. Mammographic changes after fat transfer to the breast

- compared with changes after breast reduction: a blinded study. *Plast Reconstr Surg* 2012;129:1029-38.
23. De Blacam C, Momoh AO, Colakoglu S, Tobias AM, Lee BT. Evaluation of clinical outcomes and aesthetic results after autologous fat grafting for contour deformities of the reconstructed breast. *Plast Reconstr Surg* 2009;124:272-80.
 24. Kijima Y, Yoshinaka H, Hirata M, Umekita Y, Sohda M, Koriyama C, Mizoguchi T, Arima H, Nakajo A, Ishigami S, Ueno S, Natsugoe S. Clinical and pathologic evaluation of implanted free dermal fat grafts after breast cancer surgery: a retrospective analysis. *Surgery* 2012;151:444-55.
 25. Kamakura T, Ito K. Autologous cell-enriched fat grafting for breast augmentation. *Aesthetic Plast Surg* 2011;35:1022-30.
 26. Losken A, Pinell XA, Sikoro K, Yezhelyev MV, Anderson E, Carlson GW. Autologous fat grafting in secondary breast reconstruction. *Ann Plast Surg* 2011;66:518-22.
 27. Serra-Renom JM, Muñoz-Olmo J, Serra-Mestre JM. Treatment of grade 3 tuberous breasts with Puckett's technique (modified) and fat grafting to correct the constricting ring. *Aesthetic Plast Surg* 2011;35:773-81.
 28. Sinna R, Delay E, Garson S, Delaporte T, Toussoun G. Breast fat grafting (lipomodelling) after extended latissimus dorsi flap breast reconstruction: a preliminary report of 200 consecutive cases. *J Plast Reconstr Aesthet Surg* 2010;63:1769-77.
 29. Yoshimura K, Asano Y, Aoi N, Kurita M, Oshima Y, Sato K, Inoue K, Suga H, Eto H, Kato H, Harii K. Progenitor-enriched adipose tissue transplantation as rescue for breast implant complications. *Breast J* 2010;16:169-75.
 30. Illouz YG, Sterodimas A. Autologous fat transplantation to the breast: a personal technique with 25 years of experience. *Aesthetic Plast Surg* 2009;33:706-15.
 31. Panettiè P, Marchetti L, Accorsi D. The serial free fat transfer in irradiated prosthetic breast reconstructions. *Aesthetic Plast Surg* 2009;33:695-700.

How to cite this article: Tahiri Y, Kanevsky J, Vorstenbosch J, Lee J, Schwarz K. Fat injection to correct contour deformities of the reconstructed breast: a single surgeon experience. *Plast Aesthet Res* 2015;2:115-9.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 03-09-2014; **Accepted:** 27-02-2015

Use of the multiplane internal mastopexy for ptosis correction revision-augmentation mammoplasty

Umar Daraz Khan¹, Muhammad Riaz²

¹Department of Aesthetic Surgery, Reshape Clinic, West Malling, Kent, ME19 6QR, UK.

²Department of Plastic Surgery, Hull and East Yorkshire NHS Trust, Castle Hill Hospital, Cottingham, HU16 5JQ, UK.

Address for correspondence: Dr. Umar Daraz Khan, Department of Aesthetic Surgery, Reshape Clinic, West Malling, Kent, ME19 6QR, UK.
E-mail: Mrumarkhan@aol.com

ABSTRACT

Aim: Augmentation mammoplasty is a commonly performed procedure with a high satisfaction rate. Multiplane pocket was described for simultaneous internal mastopexy and augmentation using inframammary crease incision for selected primary and secondary mammoplasties. The use of the technique is presented with a larger experience for correction of ptosis in a patient presenting for revision surgery following subglandular augmentation mammoplasty. **Methods:** A retrospectively collected data were analyzed using the Excel Spread Sheet. A total of 25 patients had multiplane augmentation with the internal mastopexy following augmentation mammoplasty in subglandular pocket. Data of 25 patients who had their revision surgery in multiplane were analyzed. **Results:** The group included 25 patients with a mean age of 36.6 years (range: 25-54 years) with mean implant duration of 6.4 years (range: 1.5-13 years). Twenty-three of the patients were nonsmokers, 1 smoker and 1 patient's smoking status was not mentioned. Eighteen patients presented with grade I capsular contracture, 3 patients with grade II contracture and 4 patients had a combination of grade I and II capsular contracture. Pseudoptosis was present in 6, class B ptosis in 6, A/B ptosis in 3, water-down deformity in 5 and rippling in 5 patients. Average preoperative size of implant used initially was 334.4 mL (range: 250-340 mL) and the mean implant size selected for revision surgery was 416 mL (range: 260-525 mL). Mean follow-up time was 18 months (range: 6-48 months). Of 25 patients, 21 had a bilateral procedure whereas the technique was used unilaterally in 4 patients for the correction of asymmetry. All patients had a single dose of intravenous antibiotics and followed by an oral course for 5 days, there was no infection noted in the series. In the current series, no patient required revision surgery following the multiplane internal mastopexy. **Conclusion:** Multiplane internal mastopexy can be useful in selected cases of revisionary augmentation mammoplasty.

Key words:

Breast ptosis, internal mastopexy, mastopexy with augmentation, revision-augmentation mammoplasty

INTRODUCTION

Primary and revision-augmentation mammoplasty is a commonly performed procedure. The incidence of

implant related mammoplasties for both primary and revision mammoplasties is on the rise and is due to the information available on the product, premarket surveys, enhanced implant safety, and regular quality checks.^[1] It is not surprising that augmentation mammoplasty is one of the most commonly performed procedure and in 2012 alone 330,631 implant related mammoplasties were performed in USA.^[2] However, the data represent implant-related surgeries performed both for primary and secondary surgery making it difficult to obtain number of secondary or revision mammoplasties performed during the same period of time.^[3] Secondary procedures following mammoplasties can be divided into early or late. Early

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.157104

reasons for redo are uncommon and include infection and bleeding, but both may necessitate urgent attention or an emergency surgery.^[3] The late complications are more common and do not generally constitute emergency procedures.^[1] These late complications include capsular contracture, change for implant size and shape, implant rippling, asymmetry of shape, implant rupture or ptosis. Revision surgery for these complications is either performed alone or in combination, depending on the presentation. Revision surgery in these complications often requires a change of implant. These complications and their corrective surgery can often be challenging for a surgeon and requires a detailed history of previous surgery, thorough examination, patient's wishes for a desired results and a well thought, clear and meticulous plan. Patients presenting with these complications may have an associated ptosis that may require simultaneous mastopexy using either periareolar, vertical scar, wise pattern markings or their modifications.^[4] The pocket for implant replacement can be subglandular, partial submuscular, subfascial or muscle splitting.^[5] Multiplane internal mastopexy (MIM) or use of more than one pocket for augmentation and the internal mastopexy using an inframammary crease has been described and was used in selected patients. The technique allows avoidance of scar in the border line ptosis and especially suits those patients who are not interested in obvious scarring associated with conventional nipple mobilization. The technique was used for primary cases with a limited experience in revision mammoplasties.^[6] The current article describes a larger experience in selected patients who had their initial augmentation mammoplasty in subglandular pocket. The technique allows an addition to the armamentarium of surgeons for patients who present for revision surgery with minor to moderate ptosis following augmentation in subglandular pocket.

METHODS

A retrospectively collected data were analyzed in the Excel Spread Sheet (Microsoft). Between January 2008 and October 2013, 25 patients had MIM following their augmentation mammoplasty in subglandular pocket. Relevant data of 25 patients who had their revision surgery in multiplane pocket was further analyzed. Six months postoperatively, patients were asked whether they were very satisfied, satisfied or dissatisfied with the outcome of the surgery.

Examination

All patients are examined in standing and supine position. Supine position allows any excess pocket extension in lateral dimension. Breast ptosis with or without upper and medial quadrant rippling is an indication for the conversion technique. Lower and lower lateral skin envelope rippling is unlikely to be improved by muscle splitting conversion or any other submuscular technique. Degree of capsular contracture is noted, and information is gathered about the size and profile of the existing implants.

Technique

All procedures are performed under general anesthetic with full muscle relaxation and as a day case. Patients were placed in the supine position with arms abducted in less than 90°. Inframammary crease was used for the pocket access.

After explantation of the device, pocket was examined for its dimensions and extent and nature of the capsule. In grade 1 or 2 capsular contractures, only lower pole capsulotomies were performed. Breast presenting with advanced capsules, partial or complete capsulectomy was performed. The next step was to identify Pectoralis Major and marked by light scoring on the posterior layer of capsule, starting from the junction of the middle and lower third of sternum medially and going up and laterally to the anterior axillary fold. This line of the muscle split was transposed and marked anteriorly by scoring the anterior layer of the capsule, this scoring should ideally be at or just below the nipple level in the midline.

Pectoralis split was commenced medially at the junction of the middle and lower third of the sternum. Pectoralis muscle is pinched and lifted off the sternal margin using Gillis toothed forceps, and a small incision is made using cutting diathermy. The incision should be large enough to allow index finger, and once the finger is inserted, submuscular dissection was performed using index finger extending up to the 2nd intercostal space and to the anterior axillary line laterally. Once the submuscular dissection is completed, incision is usually large enough allowing the breast retractor to be inserted with its distal end pointing towards anterior axillary fold. Muscle split begins medially using cutting diathermy, and once the split gets closer to the anterior axillary fold, the dissection is slowed down. Here, coagulation of the muscle is performed before splitting or cutting it up further. The maneuver avoids inadvertent bleeding resulting from damage to thoracoacromial axis branches.

Once pectoralis split is completed, the lateral capsulotomy is extended upward to join the lateral extent of muscle split. The lower border of the upper split pectoralis is now stitched to the breast envelope below the marked and scored anterior capsule using 2-0 Vicryl interrupted stitches vicryl (Ethicon) [Figure 1a-c]. The level at which the anterior capsule is stitched to the lower border of upper split pectoralis depends on the degree of ptosis but should not be less than 2 cm [Figure 1a]. Hemostasis is achieved, and a preoperatively selected implant is placed in its new pocket. Before wound closure and once the new implant is in place, the flat of the hand is run over the skin envelope sliding the skin inferiorly over the mound of the implant. Creation of a crease or fold, due to an internal stitch placed too low inside the skin envelope, is an indication of replacing the stitch to a little higher position. The head end of the table can also be raised to confirm the fold, which depends from the anchoring suture inside and can also be felt by doing a bimanual digital examination using index

finger and thumb through inframammary incision. The incorrect positioning of the stitch is not visible without this maneuver when patient is lying in a supine position. More commonly, the sliding or tilting of the table may show minor puckering or dimpling of the skin envelope that can be left alone. Once suture incorrect position is established, implant is removed, and sutures are repositioned at a slightly higher level, using previously scored anterior capsule as a reference point and implant is replaced. The procedure can be repeated to assess the position of the newly position stitch.

Wound closure is done using continuous 2-0 Vicryl to deep fascial layer, subcutaneous 3-0 Vicryl interrupted and intradermal 4-0 continuous Monocryl stitch (Monocryl (Ethicon)). Once the wound closed and dressed, external support to breast envelope is provided using adhesive dressings. The external supportive dressings are applied starting from the lower pole and pulling, supporting, and stabilizing the breast envelope at a higher and desirable position. Support garments are applied, and patients are discharged on the same day.

Postoperatively, there is often some puckering of the skin envelope due to internal stitches. This puckering almost always disappears within 4-6 weeks after surgery [Figure 2a-d].

Patients are reviewed 2 and 4 weeks later to check for wound healing. Patients are generally allowed to drive and return to work 10 days following surgery. Patients involved in physically demanding work are advised to take 3 weeks off work.

RESULTS

The group included 25 patients with an average age 36.6 years (range: 25-54 years) with mean implant duration 6.4 years (range: 1.5-13 years), 23 of the

patients were nonsmokers, 1 smoker and 1 patient's smoking status was not mentioned. Eighteen patients presented with grade I capsular contracture, 3 patients with grade II ptosis and 4 patients had a combination of grade I and II capsular contracture. Pseudoptosis was present in 6, class B ptosis in 6, A/B ptosis in 3, sliding ptosis or water-down deformity in 5 and rippling in 5 patients. Average size implant from the initial surgery was 334.4 mL (range: 250-340 mL) and the mean implant size selected for revision surgery was 416 mL (range: 260-525 mL). Of 25 patients, 21 patients had a bilateral procedure whereas the technique was used unilaterally in 4 patients for the correction of asymmetry. Mean follow-up time was 18 months (range: 6-48 months). All patients had a single intravenous dose of predominantly Augmentin and followed by an oral course for 5 days, there was no infection noted in the series. In the current series, no patient required revision surgery following MIM. Patient satisfaction data were retrieved from the spreadsheet, 20 patients (80%) were very satisfied with the outcome and 5 patients were satisfied with the results, no patients showed dissatisfaction with the procedure.

DISCUSSION

Augmentation mammoplasty is primarily done either in front or behind the muscles.^[7,8] All modifications are the extensions of these 2 primary pockets. The existence of these 2 planes in each subject has the potential of these 2 pockets being used at the same time. Breast ptosis is the slackening and downward descent of the nipple areolar complex (NAC) and breast envelope in relation to the inframammary crease as defined by Regnault.^[9] The ptosis correction is commonly performed by using periareolar, vertical scar or wise pattern markings, depending on the presentation of the breast, wishes of the patient and the

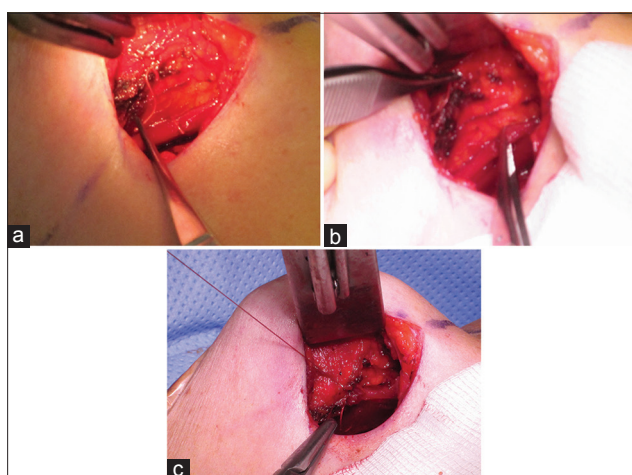


Figure 1: (a) Intraoperative picture showing scored anterior skin envelope marked with a Vicryl suture held at its loose end. Below and to the right in the picture, lower edge of the upper split muscle is also marked with Vicryl suture; (b) anterior capsule/wall of the pocket on the left and lower free edge of upper split muscle on the right, held separately in forceps before suturing; (c) tied suture knot between the marked anterior capsule/wall of envelope and lower edge of the upper split pectoralis major in place

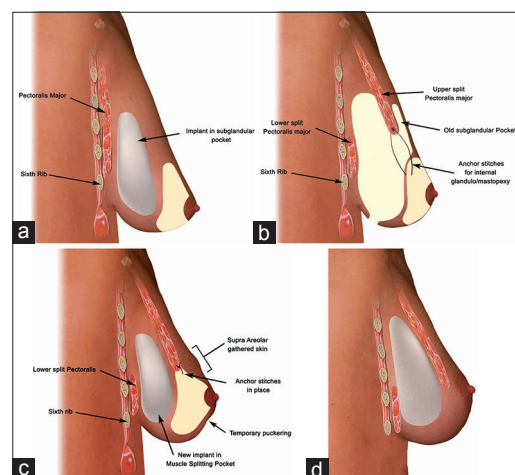


Figure 2: (a) Illustration showing side profile of an implant in subglandular pocket; (b) illustration showing dissected muscle splitting pocket with anchoring stitch placed between lower border of upper split muscle and breast envelope at a level just under the nipple areolar complex (NAC). Note the relative position of the sixth rib and the nipple areolar complex; (c) illustration showing the implant placed in muscle splitting pocket with a tied anchoring stitch between muscle and breast envelope. Note the puckering of the skin below NAC, gathered skin above NAC and relative position of the sixth rib; (d) implant in its new muscle splitting position with puckering and skin gathering settled

experience of the surgeon.^[4,10] Markings for mastopexy used are independent of the pocket, and choice of the pocket can be independent of markings.^[4,5] Even though breast lies in front of the muscle, most of the patients can have satisfactory breast volume restoration or further enhancement in partial submuscular pocket. Muscle splitting augmentation is a pocket that can be used primarily where an implant is placed behind the muscle in its upper part and front of the muscle in lower part of the breast pocket. The advantage of this technique is that the results have a more natural appearance with the advantage of muscle support in the ever-changing upper breast envelope.^[11-14] The use of muscle splitting pocket is also described for secondary procedures where partial submuscular and subglandular pockets are converted into muscle splitting pocket.^[15-18] Muscle splitting augmentation allows an immediate natural outcome, and the longevity of the results has been reported with a satisfactory outcome and reduced revision rate when compared with other commonly used techniques.^[19] The Multiplane technique is a procedure where muscle splitting procedure is used for submuscular implant placement and subglandular pocket is used for breast lift or mastopexy. In a previously published article, postoperative suprasternal notch to NACs distance was reported to be reduced when augmentation mammoplasty with multiplane technique distances was compared with its preoperative measurements.^[6] On the other hand, suprasternal notch to NAC distances was increased postoperatively following mammoplasty in subglandular and partial submuscular augmentation, with their respective preoperative measurements.^[6] The changes and distances are measured more following sub glandular than sub muscular mammoplasty and are primarily due to the support of an extra muscle layer added to the breast skin envelope when sub muscular pocket is used.^[20] In current series, average size of the implants used for the initial procedure was 334 mL as compared to 416 mL selected for the revision cases, a trend normally seen in revision mammoplasties.^[3,21] In revisionary aesthetic mammoplasty, patients almost always request for a larger implant size. The larger size of implant used in MIM acts as an internal splint and put an even pressure on the skin envelope that helps to stabilize the draped skin in this form of mastopexy. This internal splinting is supported by external supportive dressings while envelope is settling down in its relocated position. Since this form of mastopexy does not involve skin reduction, necessary tightening of the skin envelope is achieved when a larger implant is used. When subglandular to muscle splitting submuscular site change or pocket changed was performed for rippling alone without an internal mastopexy, and in a patient without ptosis or skin excess, moderate reduction in implant sizes did not show any untoward skin laxity or puckering, when skin envelope finally settled down. However, when a patient presents with breast ptosis and skin envelope excess and wishes to choose a smaller implant for replacement or go down in breast cup size, conventional skin reduction mastopexy with NAC mobilization is the recommended procedure of choice.

The multilane technique was initially described for primary cases with a limited experience for ptosis and rippling correction in patients following augmentation mammoplasty in subglandular pocket.^[6] The concept of the use of the two planes is not new and submuscular pocket for implant placement, and subglandular pocket dissection for breast envelope draping has been described in the past. However, the draping of mobilized breast envelope in Multiplane pocket is secured internally while the technique described by Hilton Becker relied on external support using dressings and adhesives bandages alone. Becker^[22] also used an expander prosthesis with an occasional combination of periareolar mastopexy in certain cases. Similarly, implant site change or pocket change from subglandular to submuscular, submuscular to neopectoral or subfascial is not new, and the idea has been frequently used and documented.^[17] Subglandular, dual plane and partial submuscular to muscle splitting biplane has also been reported for revisionary surgery with acceptable long-term results in various forms of aesthetic breast revisionary surgery.^[23-25] With the high number of aesthetic revisionary performed today, preexisting pockets conversion to muscle splitting biplane submuscular pocket, a combination of submuscular and subglandular pocket, remains a suitable option. The use of acellular dermal matrix (ADM) in revisionary aesthetic breast surgery has introduced another horizon to deal with various problems encountered in secondary aesthetic breast procedures.^[26] In small case series of three patients, the preemptive use of ADM in lower pole of poor quality breast tissue has been described for internal mastopexy in order to minimize the risk of ptosis in primary cases and in one patient ADM was used for internal mastopexy to correct an established ptosis following augmentation mammoplasty with mastopexy.^[27] The report is promising, however, a larger series with longer follow-up will be required to evaluate the efficacy of the technique. In a review article regarding the use of biological and synthetic meshes used in implants surgery, the use of these materials was predominantly limited to breast reconstruction following mastectomy. Even though the use of ADM has gained some popularity following the safety of skin or nipple sparing mastectomies, a high number of seroma, higher infection rate and the cost of the product has restricted its use in aesthetic secondary augmentation mammoplasties.^[28] The use of long-term synthetic mesh has shown more promising results in breast reconstructive and cosmetic surgery, however, the available data of its use in primary or secondary augmentation mammoplasties and augmentation mastopexies are limited.^[29] Breast implant capsule flaps are reported quite frequently, and various techniques have been described for its use in primary and secondary cosmetic and reconstructive surgeries with very good results.^[30] However, the use of these implants flaps, biological matrices and synthetic meshes is limited to support breast envelope, following mastectomies. These alternatives are also aimed to correct implant malposition, redefine or reconstruct inframammary crease both in cosmetic, as well as reconstructive surgery.^[28-30] The author also has described the use of existing capsules to recreate

new pockets for the correction of bottoming out, double bubble deformity and animation deformities.^[15-16] The use of these materials or techniques as supplementary breast supporting products are limited to reinforce or reconstruct breast dimensions, to support weak breast envelope or to prevent explant exposures but without the ability of reversing the NAC-inframammary crease (IMC) relationship seen following breast ptosis and as defined by Regnault.^[9] On the other hand, MIM has a unique ability to restore or improve the altered NAC-IMC relationship and without extra scarring in selected cases.

The augmentation mammoplasty with the internal mastopexy in prepectoral or subglandular pocket in revisionary cases has a marked advantage over simultaneous augmentation mammoplasty with the internal mastopexy in primary cases. In primary cases, especially those presenting with large size breasts, initial acceptable results may later show sliding ptosis of the NAC over the mound of the implant. However, when MIM is performed in secondary cases, initial mammoplasty in sub glandular pocket has generally compressed the breast tissue over a period of time. This comparatively thinner layer of the breast envelope is far easier to be elevated, anchored, and secured at a higher position on the muscle, in a predictable way and with longevity of results. The current series has a mean follow-up of 18 months (range: 6-48 months) with high satisfactory results. Despite the much desired scar-less MIM in selected cases, a longer follow-up will be desirable for a comparison with other conventional mastopexy techniques used today. The obvious disadvantage of MIM is the indirect measurements for a nipple areolar repositioning as compared to precise markings used in conventional skin reducing and nipple areolar mobilizing techniques. Minor asymmetry, if present, is well-tolerated and accepted by patients due to the normally occurring asymmetries in breast and NAC.^[31-33] The other disadvantage with MIM is that the technique

does not allow areolar reduction that may overshadow the true lift achieved in such cases presenting with large size NAC [Figure 3a and b]. In some cases, breast envelope puckering along the lower edge of the upper split muscle can be obvious in the early period of healing but resolves in time [Figure 4]. The added use of external supportive dressings stabilizes the mobilized skin envelope and conceals the temporary puckering that can be worrying for the patients in the early stage of healing. Removal of the dressings in 2 weeks' time almost always leaves behind a smoother skin envelope and muscle expansion and relaxation allows the implant to settle with more natural three-dimensional results [Figures 5 and 6].

Even though the study did not include a very large number of patients, the outcome showed a very high satisfaction

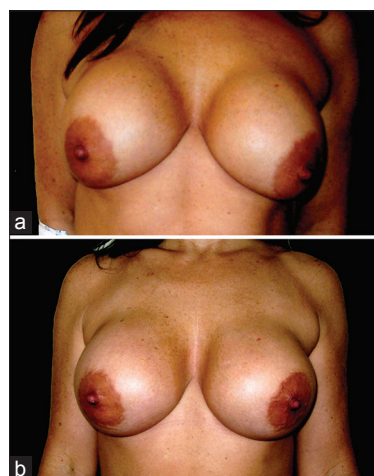


Figure 3: (a) Preoperative anterior view of a 39-year-old patient 9 years following her mammoplasty in subglandular pocket. Patient had 260 mL high profile Perouse Plastique (540T3) cohesive gel silicone implants with preoperative sternal notch to nipple areolar complex (NAC) of 24.5 cm; (b) three months following augmentation mammoplasty using multiplane technique. Patient had 380 g MHP CUI Allergan Prosthesis. The improvement of ptosis is masked by a large size NAC even after postoperative reduction in the sternal notch to NAC distance to 23.5 cm

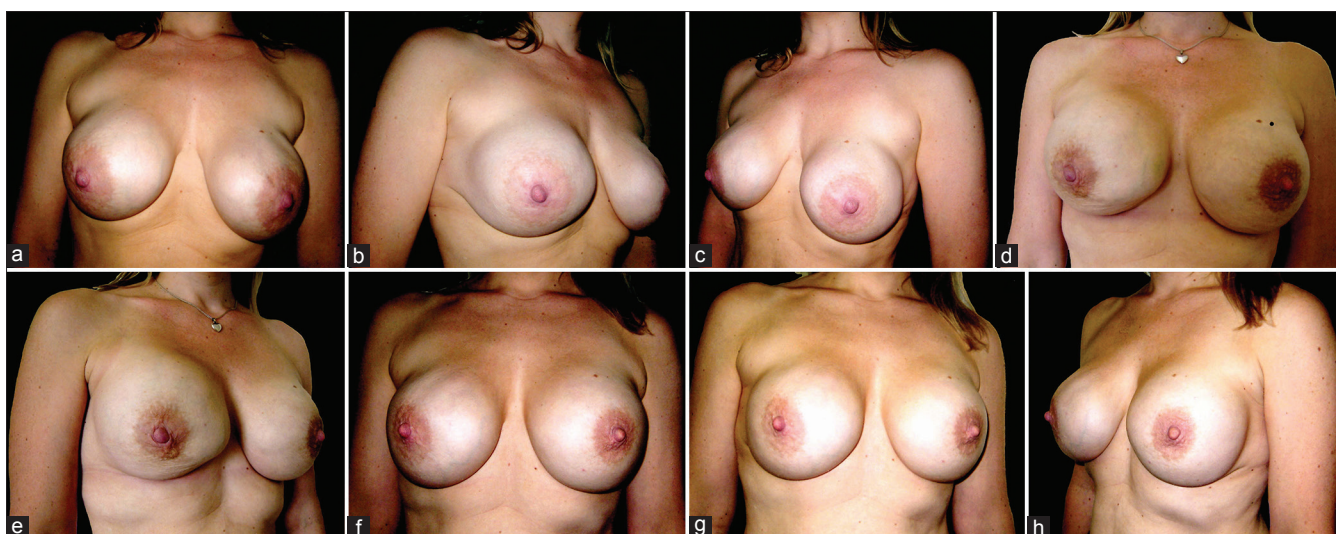


Figure 4: (a-c) Preoperative views of a 29-year-old patient who had 380 mL cohesive gel silicone implants placed in subglandular pocket with preoperative suprasternal notch to nipple areolar complex (NAC) distance of 23 cm right and 24 cm on left side. Patient presented with marked ptosis, rippling and asymmetry of breasts; (d-e) two months following the corrective surgery using 460 mL cohesive gel silicone. There is marked puckering of the right breast during early postoperative period; (f-h) postoperative pictures taken 5 months following surgery with good breast lift and symmetry. Her postoperative suprasternal notch to NAC distance was measured 20.5 cm both sides

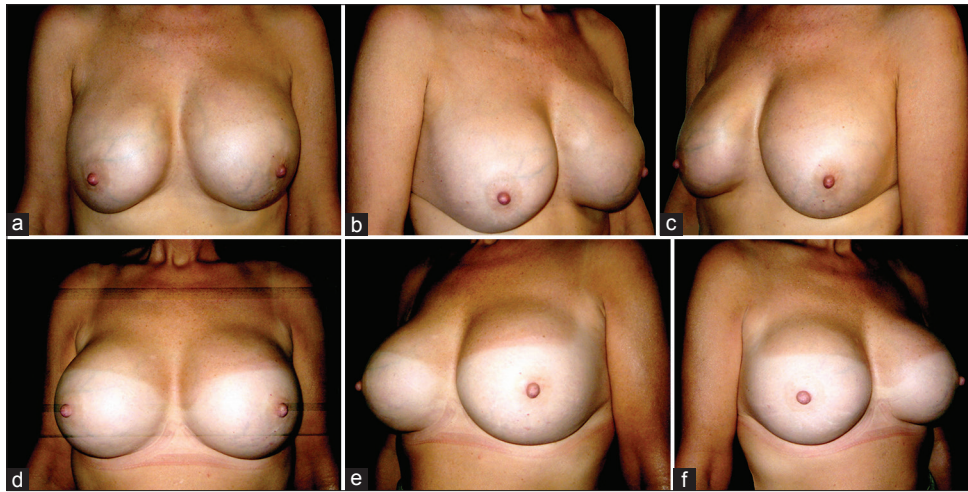


Figure 5: (a-c) A 43-year-old patient, following augmentation mammoplasty with 430 mL Poly Implant Prothese implants, in subglandular pocket. Patient presented with rippling, breast asymmetry associated with noticeably lowered nipple areolar complex (NAC) along with short NAC to the inframammary crease distance. Her preoperative suprasternal notch to NAC distance was 24.5 bilaterally; (d-f) ten months following the revision surgery with nice symmetry of the breasts and an adequate NAC to inframammary crease interrelationship. Her postoperative suprasternal notch to NAC distance was measured as 24 cm bilaterally

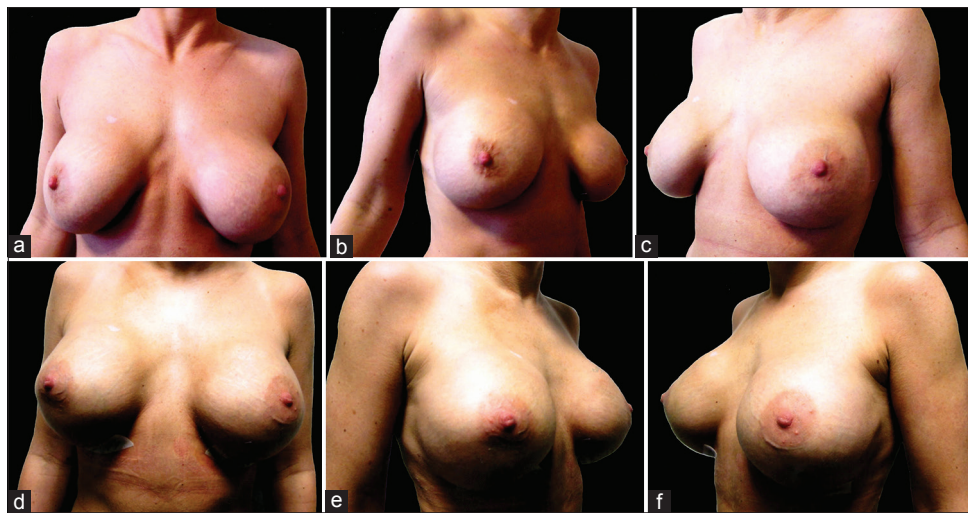


Figure 6: (a-c) Preoperative views of a 41-year-old patient following augmentation mammoplasty in sub glandular plane with 350 mL cohesive gel silicone implants. Patient presented with ptosis, rippling and absolute lack of the upper pole fullness; (d-f) postoperative views 6 weeks after revision surgery in multiplane internal mastopexy using 350 mL cohesive gel silicone implants. Patient showing upper pole fullness, lack of rippling along with rejuvenated breasts appearance

rate. A larger series with a longer follow-up, comparison of breast morphometrics with other conventional skin reducing and nipple mobilizing mastopexies will be desirable.

The technique allows avoidance of external scars in selected patients and can be a good choice especially in those who are not keen on conventional external scarring. With a mean follow-up of 18 months (range: 6-48 months) all patients had an acceptable results, and no further corrective surgery has been performed in the series analyzed.

REFERENCES

1. Khan UD. Combining muscle-splitting biplane with multilayer capsulorrhaphy for the correction of bottoming down following subglandular augmentation. *Eur J Plast Surg* 2010;33:259-69.
2. The American Society for Aesthetic Plastic Surgery Cosmetic Surgery National Data Bank Statistics; 2012. Available from: <http://www.cynosureaustralia.com/wp-content/blogs.dir/7/2013/05/ASAPS-2012-Stats.pdf>. [Last accessed on 2014 Sep 10].
3. Khan UD. Secondary augmentation mammoplasties and periprosthetic infection. A three year retrospective review of 92 secondary mammoplasties performed by a single surgeon. *Aesthet Surg J* 2012;32:465-73.
4. Khan UD. Vertical scar mastopexy with a cat's tail extension for prevention of skin redundancy: an experience with 17 consecutive cases after mastopexy and mastopexy with breast augmentation. *Aesthetic Plast Surg* 2012;36:303-7.
5. Khan UD. Augmentation mastopexy in muscle-splitting biplane: outcome of first 44 consecutive cases of mastopexies in a new pocket. *Aesthetic Plast Surg* 2010;34:313-21.
6. Khan UD. Multiplane technique for simultaneous submuscular breast augmentation and internal glandulopexy using inframammary crease incision in selected patients with early ptosis. *Eur J Plast Surg* 2011;34:337-43.
7. Cronin TD, Gerow FJ. Augmentation mammoplasty: new "natural feel" prosthesis. In: Thomas Ray Broadbent, American Association of Plastic Surgeons, American Society of Plastic and Reconstructive Surgeons, International Confederation for Plastic Surgery, Transactions of the International Society of Plastic Surgeons, editors. Transactions of the Third International Congress of Plastic Surgery. Amsterdam: Excerpta Medica; 1964. p. 41-9.
8. Regnault P. Partially submuscular breast augmentation. *Plast Reconstr Surg* 1977;59:72-6.
9. Regnault P. Breast ptosis. Definition and treatment. *Clin Plast Surg* 1976;3:193-203.

10. Khan UD. Vertical scar with the bipedicle technique: a modified procedure for breast reduction and mastopexy. *Aesthetic Plast Surg* 2007;31:337-42.
11. Khan UD. Muscle-splitting biplane breast augmentation. *Aesthetic Plast Surg* 2007;31:353-8.
12. Khan UD. Subglandular to muscle splitting biplane conversion for revision augmentation mammoplasty. In: Mugea TT, Schifmann MA, editors. *Aesthetic Surgery of the Breast*. 1st ed. New York: Springer-Verlag, Berlin Heidelberg; 2015. p. 535-41.
13. Khan UD. Selection of breast pocket using the pinch test in augmentation mammoplasty: can it be relied on in the long term? *Aesthetic Plast Surg* 2009;33:780-1.
14. Lang Stümpfle R, Figueras Pereira-Lima L, Alves Valiati A, da Silva Mazzini G. Transaxillary muscle-splitting breast augmentation: experience with 160 cases. *Aesthetic Plast Surg* 2012;36:343-8.
15. Khan UD. Dynamic breasts: a common complication following partial submuscular augmentation and its correction using muscle-splitting biplane technique. *Aesthetic Plast Surg* 2009;33:353-60.
16. Khan UD. High transverse capsuloplasty for the correction of malpositioned implants following augmentation mammoplasty in partial submuscular plane. *Aesthetic Plast Surg* 2012;36:590-9.
17. Baxter RA. Subfascial breast augmentation: theme and variations. *Aesthet Surg J* 2005;25:447-53.
18. Baxter RA. Update on the split-muscle technique for breast augmentation: prevention and correction of animation distortion and double bubble deformity. *Aesthetic Plast Surg* 2011;35:426-9.
19. Khan UD. Muscle-splitting, subglandular, and partial submuscular augmentation mammoplasties: a 12-year retrospective analysis of 2026 primary cases. *Aesthetic Plast Surg* 2013;37:290-302.
20. Khan UD. Breast expansion in augmentation mammoplasty: comparative data analysis in submuscular and subglandular planes. *J Muhammad Med Coll* 2012;3:8-10.
21. Khan UD. Poly Implant Prothèse (PIP) incidence of device failure and capsular contracture: a retrospective comparative analysis. *Aesthetic Plast Surg* 2013;37:906-13.
22. Becker H, van Leeuwen JB. The correction of breast ptosis with the expander mammary prosthesis. *Ann Plast Surg* 1990;24:489-97.
23. Khan UD. Correction of acquired synmastia with muscle-splitting biplane implant replacement. *Aesthetic Plast Surg* 2009;33:605-10.
24. Khan UD. Breast autoinflation with sterile pus as a marker of implant rupture: single-stage treatment and outcome for five consecutive cases. *Aesthetic Plast Surg* 2009;33:58-65.
25. Khan UD. Unilateral breast autoinflation and intraprostatic collection of sterile pus. An unusual operative finding of silicone gel bleed with silicone lymphadenitis. *Aesthetic Plast Surg* 2008;32:684-7.
26. Maxwell GP, Gabriel A. Acellular dermal matrix in aesthetic revisionary breast surgery. *Aesthet Surg J* 2011;31:S65-76.
27. Kornstein A. Porcine-derived acellular dermal matrix in primary augmentation mammoplasty to minimize implant-related complications and achieve an internal mastopexy: a case series. *J Med Case Rep* 2013;7:275.
28. Dieterich M, Faridi A. Biological matrices and synthetic meshes used in implant-based breast reconstruction - a review of products available in Germany. *Geburtshilfe Frauenheilkd* 2013;73:1100-6.
29. Becker H, Lind JG 2nd. The use of synthetic mesh in reconstructive, revision, and cosmetic breast surgery. *Aesthetic Plast Surg* 2013;37:914-21.
30. Persichetti P, Segreto F, Pendolino AL, Del Buono R, Marangi GF. Breast implant capsule flaps and grafts: a review of the literature. *Aesthetic Plast Surg* 2014;38:540-8.
31. Khan UD. Breast and chest asymmetries: classification and relative distribution of common asymmetries in patients requesting augmentation mammoplasty. *Eur J Plast Surg* 2011;34:375-85.
32. Rohrich RJ, Hartley W, Brown S. Incidence of breast and chest wall asymmetry in breast augmentation: a retrospective analysis of 100 patients. *Plast Reconstr Surg* 2006;118:S7-13.
33. Khan UD. Review of implant sizes in 146 consecutive asymmetrical augmentation mammoplasties. *Eur J Plast Surg* 2014;37:273-80.

How to cite this article: Khan UD, Riaz M. Use of the multiplane internal mastopexy for ptosis correction revision-augmentation mammoplasty. *Plast Aesthet Res* 2015;2:120-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 16-10-2014; **Accepted:** 05-02-2015

A guiding oblique osteotomy cut to prevent bad split in sagittal split ramus osteotomy: a technical note

Gururaj Arakeri¹, Peter A. Brennan²

¹Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur 584101, Karnataka, India.

²Department of Oral and Maxillofacial Surgery, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, UK.

Address for correspondence: Dr. Gururaj Arakeri, Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur 584101, Karnataka, India. E-mail: gururaj.arakeri@gmail.com

ABSTRACT

Aim: To present a simple technical modification of a medial osteotomy cut which prevents its misdirection and overcomes various anatomical variations as well as technical problems. **Methods:** The medial osteotomy cut is modified in the posterior half at an angle of 15°-20° following novel landmarks. **Results:** The proposed cut exclusively directs the splitting forces downwards to create a favorable lingual fracture, preventing the possibility of an upwards split which would cause a coronoid or condylar fracture. **Conclusion:** This modification has proven to be successful to date without encountering the complications of a bad split or nerve damage.

Key words:

Guiding oblique osteotomy cut, lingual bad splits, medial cut, sagittal split ramus osteotomy

INTRODUCTION

Sagittal split osteotomy of the ramus may be the procedure which defined the evolution of the art and science of oral surgery. Although the basic design of the sagittal split ramus procedure evolved very quickly, the elimination of complications has taken longer.^[1] The procedure has been modified many times since its introduction by Trauner and Obwegeser.^[2] One modification frequently used is a shortened medial horizontal osteotomy, which, instead of extending the cut to the posterior border, is carried only to the lingual fossa posterior to the lingula.^[3] In the majority of cases, this technique allows for adequate splitting of the mandible.^[3] However, this modification is not devoid of complications, as the medial cut can be misdirected due to anatomic variability of the ramus, or an improperly directed osteotomy cut, resulting in a bad lingual split.

Various studies have reported an incidence of bad splits ranging from 1.7% to 9.1%.^[4] Although the most common unfavorable splits involve a buccal plate fracture, these bad lingual splits may result in serious complications including fracture of the lingual cortical plate, condylar neck and coronoid process.^[4]

The purpose of this article is to suggest a modification of the medial osteotomy cut which will prevent misdirection while overcoming anatomical variations and technical problems.

METHODS

Surgical access for the sagittal split osteotomy is performed in the standard fashion. Following fine dissection over the anterior border of mandible, the insertion of the temporalis muscle is detached and elevated to the level of the sigmoid notch. The anterior ramus is then isolated with retraction of the soft tissues. The medial ramus is accessed by subperiosteal insertion of a malleable retractor above the foramen, and the inferior alveolar nerve is identified at the level of the lingula.

The medial osteotomy cut is directed parallel^[3] to the occlusal plane [Figure 1] at the level of superior aspect of lingula in the standard fashion, but ends at a point midway between the lingula and the ascending ramus.

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157105

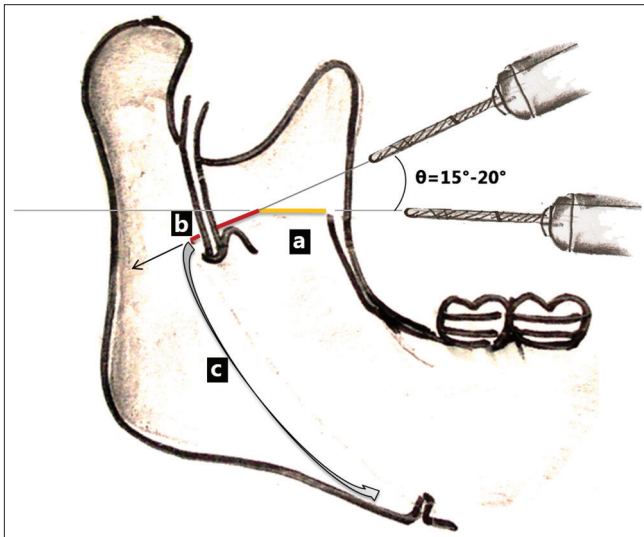


Figure 1: (a) Anterior half cut running parallel to occlusal plane (colored line); (b) posterior half cut (guiding oblique (GO) cut) with an angulation of “ θ ” running obliquely downwards and ending in lingual fossa; (c) favorable lingual split directed towards inferior body osteotomy by GO cut

This completes the anterior half of the traditional medial cut. The posterior half of the osteotomy cut is completed by directing the bur obliquely downwards at an angle of 15° - 20° to the anterior half of the osteotomy cut which is parallel to occlusal plane. Care is taken to avoid damage to the inferior alveolar neurovascular bundle.

After completing the guiding oblique (GO) osteotomy cut, rest of the procedure is continued following routine standard technique.^[3]

RESULTS

The GO cut extends downwards 3 mm posterior to the lingula from the point where the anterior half of the osteotomy cut was concluded. This creates an oblique angle between anterior and posterior osteotomy cuts and thus completes the modified medial ramus osteotomy. As the GO cut directs the splitting forces downwards, there is no possibility of the split propagating upwards to cause a coronoid or condylar fracture.

DISCUSSION

A major disadvantage of the traditional medial osteotomy cut is the effect that the anterior orientation of the bur has on the direction of the posterior cut. Another shortcoming of the cut is its abrupt termination at the posterior end. This produces a sharp angle at the junction of the buccal and lingual cortical plates of ramus of mandible. The forces applied in the sagittal split may concentrate at this angle, and the stress may be propagated in any direction to create bad splits. This is especially true in cases in which the posterior cut terminates in the monocortical area of the medial ramus rather in the bicortical region.

In contrast to the conventional medial cut, a simple modification which incorporates a GO cut in its posterior half minimizes the stress concentrated at this angle, and

directs the cut downward to give a favorable lingual split. The surgical design also provides flexibility in placing the anterior half of the cut downwards in favorable bicortical region in cases of anatomical variation this avoids the possibility of coronoid fracture.

Advantages of a GO osteotomy cut in specific situations to prevent bad splits are as follows: (1) in regular situations a GO cut provides flexibility in adjusting the direction of the posterior medial cut if the anterior cut has been placed in an unfavorable direction; (2) in cases in which the ramal occlusal plane angle^[3] is $< 70^{\circ}$, a parallel osteotomy would be directed superiorly, cutting the inferior portion of the neck of the condyloid process.^[1] To prevent this from occurring, it is advised to place the horizontal osteotomy cut at an altered angle of 10° - 15° inferiorly.^[3] As the suggested modification already includes a 15° bur angulation for the anterior cut, it is not necessary to adjust the osteotomy cut further; (3) in cases with a high lingula, there is an increased incidence of unfavorable fractures.^[3] A high lingula will place the medial osteotomy in a region of the mandibular ramus that has little or no cancellous bone.^[5] In this situation it is suggested that the medial osteotomy be angled from its typical location in the mid-ascending ramus up to the lingula of the medial ramus.^[5] If cancellous bone is not encountered, the medial cut is widened at the expense of cortex along the inferior aspect of the medial osteotomy until cancellous bone is seen.^[5] However, the widening creates an oblique medial cut directed upwards which increase the possibility of bad split. This complication is successfully avoided by the proposed modification which allows to place the anterior half of the cut in the favorable (bicortex) cancellous part of anterior ramus which is independent of the direction of posterior cut. A similar modification can be applied in cases of a thin mandible in which there is little cancellous bone; and (4) several investigators have demonstrated an increased risk of unfavorable fractures associated with the presence of third molars at the osteotomy site during sagittal split ramus osteotomy.^[5-8] The authors have observed a concentration of stress at the angle created by the buccal and lingual cortex of impacted third molar during the sagittal split which may result in a lingual plate fracture. For the same reason a lingual back cut^[5] posterior to the lingula is suggested. The addition of a lingual back cut helps direct the lingual fracture to a more favorable split at the inferior border of the osteotomy.^[5] The present GO cut acts as a back cut when directed 3-4 mm downwards with the same angulation which directs the lingual split laterally and inferiorly to the impacted molar providing a favorable split at the inferior border of the osteotomy.

In conclusion, splitting the straight medial cut into two components with angulation in the midpoint makes the anterior and posterior cuts independent of each other. Although there are many advantages and applications, a larger study is required to compare its versatility to that of the traditional medial cut. Nonetheless, the current modification has proven to be successful to date in the author's hands while avoiding the complications of a bad split or nerve damage.

REFERENCES

- Wyatt WM. Sagittal ramus split osteotomy: literature review and suggested modification of technique. *Br J Oral Maxillofac Surg* 1997;35:137-41.
- Trauner R, Obwegeser H. Operative oral surgery: the surgical correction of mandibular prognathism and retrognathia with consideration of genioplasty. *Oral Surg Oral Med Oral Pathol* 1957;10:677-89.
- Carleton AS, Schow SR, Peterson LJ. Prevention of the misdirected sagittal split. *J Oral Maxillofac Surg* 1986;44:81-2.
- Teltzrow T, Kramer FJ, Schulze A, Baethge C, Brachvogel P. Perioperative complications following sagittal split osteotomy of the mandible. *J Craniomaxillofac Surg* 2005;33:307-13.
- Cillo JE, Stella JP. Selection of sagittal split ramus osteotomy technique based on skeletal anatomy and planned distal segment movement: current therapy. *J Oral Maxillofac Surg* 2005;63:109-14.
- Mehra P, Castro V, Freitas RZ, Wolford LM. Complications of the mandibular sagittal split ramus osteotomy associated with the presence or absence of third molars. *J Oral Maxillofac Surg* 2001;59:854-8.
- Falter B, Schepers S, Vrielinck L, Lambrechts I, Thijs H, Politis C. Occurrence of bad splits during sagittal split osteotomy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:430-5.
- Doucet JC, Morrison AD, Davis BR, Robertson CG, Goodday R, Precious DS. Concomitant removal of mandibular third molars during sagittal split osteotomy minimizes neurosensory dysfunction. *J Oral Maxillofac Surg* 2012;70:2153-63.

How to cite this article: Arakeri G, Brennan PA. A guiding oblique osteotomy cut to prevent bad split in sagittal split ramus osteotomy: a technical note. *Plast Aesthet Res* 2015;2:127-9.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 10-11-2014; **Accepted:** 30-03-2015

Hyperbaric oxygen therapy and surgical delay improve flap survival of reverse pedicle flaps for lower third leg and foot reconstruction

Pradeoth Mukundan Korambayil, Prashanth Varkey Ambookan

Department of Plastic Surgery and Burns, Jubilee Institute of Surgery for Hand, Aesthetic and Microsurgery, Jubilee Mission Medical College and Research Institute, Thrissur 680005, Kerala, India.

Address for correspondence: Dr. Pradeoth Mukundan Korambayil, Department of Plastic Surgery and Burns, Jubilee Institute of Surgery for Hand, Aesthetic and Microsurgery, Jubilee Mission Medical College and Research Institute, Thrissur 680005, Kerala, India. E-mail: pradeoth@gmail.com

ABSTRACT

Aim: The purpose of the study is to present a management protocol for various types of soft tissue defects of the distal third region of leg and foot treated with pedicle flaps, by including hyperbaric oxygen (HBO) therapy in the treatment regimen with flap delay. **Methods:** We present a prospective study of 23 patients with various types of soft tissue defects of the foot, and lower third of leg managed in our institution from December 2012 to December 2013. All soft tissue defects were treated by a reverse pedicle flap. Twelve patients were managed with flap delay with HBO therapy and 11 patients with immediate flaps without HBO therapy. The postoperative period, hospital course, and follow-up were documented. **Results:** Of 12 patients with flap delay and HBO, 10 patients did not suffer any complications secondary to flap transfer. One patient had discoloration of the tip of the flap, which settled without the intervention, and 1 patient had recurrent abscess formation, which required debridement and closure. Of 11 patients with direct transfer, 6 patients presented with complications including flap congestion, partial flap loss, and tip necrosis, which required secondary intervention. **Conclusion:** HBO therapy is a useful adjunct in flap delay of the reverse pedicle flap for soft tissue reconstruction of the lower third of the leg and foot regions.

Key words:

Flap delay, hyperbaric oxygen therapy, reverse pedicle flap, soft tissue reconstruction

INTRODUCTION

Although numerous techniques ranging from skin grafting to free-tissue transfer have been utilized for reconstruction of soft tissue defects of the foot, and lower third of the leg regions, very few have yielded entirely satisfactory results. A safe, easy and reliable reconstructive option is required for reconstruction of

the lower third of the leg and foot regions. The lateral supramalleolar flap^[1,2] from the lateral aspect of the lower leg, and the flap supplied by a perforating branch of the dorsal peroneal artery are commonly used for coverage of the dorsum of the foot, the medial and lateral arches, and all regions of the heel. The reverse sural flap^[3,4] is raised from the posterior aspect of the calf and is commonly used for coverage of the hind foot, dorsum, and the lateral malleolus. Distally-based flaps based on the posterior tibial artery or the peroneal artery perforator plus flap^[5] also assist in the soft tissue coverage of defects of the distal third of the leg. In this prospective study, 23 patients were treated with distally-based pedicle flap coverage in which 12 patients underwent flap delay with hyperbaric oxygen (HBO) therapy, and 11 patients underwent immediate flap transfer without HBO therapy. The study was undertaken prospectively over a period of

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157107

13 months in a tertiary care unit. The purpose of this study was to present a management protocol for various types of soft tissue defects of the distal third of the leg and foot with pedicle flaps, by including HBO therapy in the treatment regimen with the flap delay. The study was approved by the review board of Jubilee Mission Medical College and Research Institute.

METHODS

A total of 23 patients with soft tissue defects of lower third of the leg and foot were treated over a period of 13 months (December 2012 to December 2013). On the basis of the defects, lateral supramalleolar, reverse sural and distally-based posterior tibial artery perforator plus flaps were utilized for soft tissue coverage. Of 23 patients, 12 patients were managed by flap delay with HBO therapy as an adjunct, and 11 patients were managed by direct flap transfer without HBO therapy. Outcomes following the different types of management and secondary procedures performed were noted. All involved patients gave their consent forms.

RESULTS

The mechanism of injury for 20 patients was a road traffic accident, 1 patient presented with an open wound secondary to a diabetic ulcer, 1 defect was due to osteomyelitis and 1 was due to a snake bite injury. Of 23 patients, there were 6 females (26.1%) and 17 males patients (73.9%). The mean age was 42 years (range: 13-68 years).

In 12 patients, the flap delay was performed, and HBO therapy was used as an adjunct. Of these 12 patients, 2 patients had sustained the defect due to an infectious source, and 10 cases occurred secondary to a road traffic accident. Among these 12 patients, 5 patients had diabetes mellitus, and 1 patient had soft tissue loss due to a snake bite injury. Two patients were scheduled for extended sural artery flap, and 1 patient had varicose veins as a comorbid condition. Five flaps were lateral supramalleolar flaps, 1 was a distally-based posterior tibial artery perforator flap, and 6 were reverse sural artery flaps. Among the 6 reverse sural flaps, 2 were extended reverse sural flaps. The severity of injury, time of referral, comorbid conditions, age of the patients, and the extent of the flap were considered to be qualifying conditions for flap delay with associated HBO therapy. One patient developed a recurrent abscess at the ankle joint, which required incision and drainage, and 1 patient had discoloration of the flap tip which resolved without intervention.

For 11 patients, direct transfer of the flap was performed. Of these 11 patients, 1 child had suffered soft tissue loss secondary to osteomyelitis, and the rest of the defects were due to road traffic accidents. Four flaps were lateral supramalleolar flaps and 7 were reverse sural artery flaps. Six patients developed postoperative complications. Five patients suffered tip necrosis, which required debridement and skin grafting, and 1 patient sustained partial loss of a reverse sural flap, which subsequently required skin grafting [Tables 1-3].

Case 1

A 34-year-old male with a crush injury to the right heel pad and ankle region was referred to our center 3 weeks following injury. The patient presented with necrosis of the heel pad with multiple lacerations over the ankle on both the medial and lateral aspects [Figure 1a-c]. The wound was debrided, and HBO therapy sessions were started. On postdebridement day 2, an extended reverse sural flap was elevated with flap delay [Figure 1d], continuing the hyperbaric sessions. On postdebridement day 4, flap inset was completed [Figure 1e]. The donor area was covered with a split-thickness skin graft. HBO therapy was administered for an additional 12 sessions. The postoperative period was uneventful [Figure 1f and g].

Case 2

A 68-year-old male developed an ulceration on the lateral malleolus with exposure of the ankle joint [Figure 2a]. HBO therapy sessions were started. The wound was debrided, and lateral supramalleolar flap coverage was planned [Figure 2b]. The lateral supramalleolar flap was elevated, and flap delay was performed, with continuation of the hyperbaric sessions [Figure 2c]. On postdebridement day 4, flap inset was completed, and the donor area was covered with a split-thickness skin graft [Figure 2d]. HBO therapy was administered for 12 additional sessions. The postoperative period was uneventful [Figure 2e].

Case 3

A 21-year-old male sustained injury to the lower third of the right leg with soft tissue loss and exposure of the tibial bone [Figure 3a]. Following debridement, a distally-based posterior tibial artery perforator plus flap was planned. A distally-based posterior tibial artery perforator plus flap was elevated, and flap delay was performed with continuation of the hyperbaric sessions [Figure 3b and c]. On postdebridement day 4, flap inset was completed, and the donor area was covered with a split-thickness skin graft [Figure 3d]. HBO therapy was administered for an additional 6 sessions. The postoperative period was uneventful [Figure 3e].

Case 4

A 39-year-old male sustained injury to the right foot secondary to a road traffic accident and presented with soft tissue loss over the medial malleolar and calcaneal regions [Figure 4a]. The wound was debrided, and a reverse sural artery flap was performed [Figure 4b and c]. The patient developed flap tip necrosis and required a skin graft for coverage [Figure 4d].

DISCUSSION

Soft tissue defects of the lower third of the leg and foot may be covered with skin grafts, local flaps, distally or proximally-based island flaps, and distant tissue transfer or cross leg flaps. In 1983, distally-based fasciocutaneous flaps were introduced, providing flaps with a reliable vascular supply regardless of their length to width ratio. The reverse sural artery flap, lateral supramalleolar flap, and inferiorly-based medial and lateral fasciocutaneous flaps

Table 1: Patients treated for soft tissue defects of the lower third of the leg and foot with reverse pedicle flaps with flap delay and HBO

No.	Age (years)/gender	Trauma/etiology	Co-morbidities	Site	Defect size (cm ²)	Flap size (cm ²)	Details	Type of flap, delay procedure, HBOT	Complications and secondary procedure
1	68/male	Diabetic ulcer	Diabetes mellitus	Lateral malleolar region with ankle joint exposure	5 × 4	6 × 4	Exposure of the lateral malleolus and ankle joint	Lateral supra malleolar fasciocutaneous flap	Recurrent infection of joint; debridement and suturing
2	40/female	Road traffic accident		Mid-distal junction of dorsum of foot	6 × 4	7 × 4	Exposure of extensor tendons of 2nd, 3rd, 4th, 5th toes	Lateral supra malleolar fasciocutaneous flap	Nil
3	43/male	Road traffic accident		Proximal foot dorso-medial aspect	6 × 4	7 × 4	Exposure of base of first metatarsal bone	Lateral supra malleolar fasciocutaneous flap	Tip discoloration
4	36/female	Road traffic accident		Achilles tendon	4 × 4	5 × 4	Exposure of distal Achilles tendon	Lateral supra malleolar fasciocutaneous flap	Nil
5	52/female	Road traffic accident	Diabetes mellitus	Lateral malleolus	5 × 4	6 × 4	Exposure of lateral malleolus and ankle joint	Lateral supra malleolar fasciocutaneous flap	Nil
6	21/male	Road traffic accident		Distal third of tibia	6 × 4	7 × 4	Exposure of distal third of tibia	Posterior tibial artery perforator plus flap	Nil
7	60/male	Road traffic accident	Diabetes mellitus	Achilles tendon	6 × 4	7 × 4	Exposure of distal Achilles tendon	Reverse sural artery fasciocutaneous flap	Nil
8	23/male	Road traffic accident	Varicose veins	Medial aspect of calcaneus	5 × 4	6 × 4	Exposure of medial calcaneus	Reverse sural artery fasciocutaneous flap	Nil
9	62/female	Road traffic accident	Diabetes mellitus	Achilles tendon	6 × 4	7 × 4	Exposure of distal Achilles tendon	Extended reverse sural artery fasciocutaneous flap	Nil
10	55/male	Infected snake bite injury	Cellulitis	Medial malleolus	6 × 4	7 × 4	Exposure of distal medial malleolus and ankle joint	Reverse sural artery fasciocutaneous flap	Nil
11	55/male	Road traffic accident	Diabetes mellitus	Lower third of tibia	5 × 4	6 × 4	Exposure of lower third of tibia and medial tendons	Reverse sural artery fasciocutaneous flap	Nil
12	34/male	Road traffic accident	Multiple wounds in ankle region	Heel pad, base of calcaneus and Achilles tendon	13 × 5	14 × 5	Exposure of plantar surface of calcaneus and heel pad	Extended reverse sural artery flap	Nil

HBO: Hyperbaric oxygen, HBOT: Hyperbaric oxygen therapy

Table 2: Patients treated for soft tissue defects of the lower third of the leg and foot with immediate reverse pedicle flaps without HBO

No.	Age (years)/gender	Trauma/etiology	Co-morbidities	Site	Defect size (cm ²)	Flap size (cm ²)	Details	Type of flap, delay procedure, HBO	Complications and secondary procedure
1	52/male	Road traffic accident	Nil	Lower third of tibia	5 × 4	6 × 4	Exposure of lower third of tibia	Lateral supra malleolar fasciocutaneous flap	Flap tip necrosis and skin grafting
2	48/male	Road traffic accident	Nil	Lower third of tibia	5 × 4	6 × 4	Exposure of lower third of tibia	Lateral supra malleolar fasciocutaneous flap	Nil
3	47/male	Road traffic accident	Nil	Midfoot dorsum	4 × 4	5 × 4	Exposure of second metatarsal bone shaft	Lateral supra malleolar fasciocutaneous flap	Flap tip necrosis and skin grafting
4	37/male	Road traffic accident	Nil	Midfoot dorsum	5 × 4	6 × 4	Exposure of second metatarsal bone shaft and extensor hallucis longus tendon	Lateral supra malleolar fasciocutaneous flap	Flap tip necrosis and skin grafting
5	48/male	Road traffic accident	Nil	Lower third of tibia	5 × 4	6 × 4	Exposure of lower third of tibia	Reverse sural artery fasciocutaneous flap	Nil
6	42/male	Road traffic accident	Nil	Achilles tendon	5 × 4	6 × 4	Exposure of distal Achilles tendon	Reverse sural artery fasciocutaneous flap	Nil
7	39/male	Road traffic accident	Nil	Medial malleolus	6 × 4	7 × 4	Exposure of distal part of medial malleolus and ankle joint	Reverse sural artery fasciocutaneous flap	Flap tip necrosis and skin grafting
8	24/male	Road traffic accident	Nil	Lateral malleolus and dorsum of foot	12 × 5	13 × 5	Exposure of lateral malleolus and dorsum of foot	Reverse sural artery fasciocutaneous flap	Nil
9	43/female	Road traffic accident	Nil	Calcaneus and Achilles tendon	5 × 4	6 × 4	Exposure of calcaneus and Achilles tendon	Reverse sural artery fasciocutaneous flap	Flap tip necrosis and skin grafting
10	13/female	Osteomyelitis	Nil	Medial malleolus	4 × 3	4 × 4	Exposure of medial malleolus	Reverse sural artery fasciocutaneous flap	Nil
11	23/male	Road traffic accident	Nil	Heel pad, calcaneus, Achilles tendon	13 × 5	14 × 5	Exposure of calcaneus and heel pad	Reverse sural artery fasciocutaneous flap	Partial flap loss and skin grafting

HBO: Hyperbaric oxygen, HBO: Hyperbaric oxygen therapy

Table 3: Table comparing HBO with flap delay and direct flap transfer without HBO

No.	Age (years)		Co-morbidity		Flaps		Complications	
	HBO with flap delay groups	Direct transfer without HBO group	HBO with flap delay groups	Direct transfer without HBO group	HBO with flap delay groups	Direct transfer without HBO group	HBO with flap delay groups	Direct transfer without HBO group
1	68	52	Diabetes mellitus	Nil	Lateral supra malleolar flap	Lateral supra malleolar flap	Recurrent infection to joint, debridement and suturing	Flap tip necrosis and skin grafting
2	40	48		Nil	Lateral supra malleolar flap	Lateral supra malleolar flap	Nil	Nil
3	43	47		Nil	Lateral supra malleolar flap	Lateral supra malleolar flap	Flap tip discoloration and no secondary intervention	Flap tip necrosis and skin grafting
4	36	37		Nil	Lateral supra malleolar flap	Lateral supra malleolar flap	Nil	Flap tip necrosis and skin grafting
5	52	48	Diabetes mellitus	Nil	Lateral supra malleolar flap	Reverse sural artery flap	Nil	Nil
6	21	42		Nil	Posterior tibial artery perforator plus flap	Reverse sural artery flap	Nil	Nil
7	60	39	Diabetes mellitus	Nil	Reverse sural artery flap	Reverse sural artery flap	Nil	Flap tip necrosis and skin grafting
8	23	24	Varicose veins	Nil	Reverse sural artery flap	Reverse sural artery flap cover	Nil	Nil
9	62	43	Diabetes mellitus	Nil	Extended reverse sural artery flap	Reverse sural artery flap	Nil	Flap tip necrosis and skin grafting
10	55	13	Cellulitis	Nil	Reverse sural artery flap	Reverse sural artery flap	Nil	Nil
11	55	23	Diabetes mellitus	Nil	Reverse sural artery flap	Reverse sural artery flap	Nil	Partial flap loss and skin grafting
12	34		Multiple wounds in ankle region		Extended reverse sural artery flap		Nil	
HBO: Hyperbaric oxygen								

HBO: Hyperbaric oxygen



Figure 1: (a) Crush injury to the right heel pad and ankle regions with multiple lacerations on the medial aspect of the foot; (b) crush injury to the right heel pad and ankle regions with multiple lacerations on the lateral aspect of the foot; (c) picture showing necrotic heel pad tissue; (d) extended reverse sural artery flap was elevated on day 2 following debridement; (e) extended reverse sural artery flap delay performed; (f) flap inset was completed on day 4 following debridement; (g) postoperative day 21 following surgery-posterior view



Figure 2: (a) Ulceration on the lateral malleolus with exposure of the ankle joint; (b) picture following wound debridement and planning of a lateral supramalleolar flap; (c) lateral supramalleolar flap was elevated on day 2 following debridement; (d) lateral supramalleolar flap delay performed; (e) flap inset was completed on day 4 following debridement



Figure 3: (a) Posttraumatic soft tissue defect exposing the lower third of the tibia; (b) distally-based posterior tibial artery perforator plus flap elevated; (c) distally-based posterior tibial artery perforator plus flap delay performed; (d) flap inset was completed on day 4 following debridement; (e) late postoperative picture of flap

based on the peroneal or posterior tibial artery perforators are frequently used for reconstruction of defects in this region.^[1-3] These flaps may be harvested as fasciocutaneous, island fasciocutaneous, adipofascial, or propeller flaps, or may be harvested as delayed extended flaps.

One common complication encountered during the utilization of distally-based flaps for such defects is

venous congestion, which may result in failure at the distal aspect of the flap, which may be covering a critical region of the defect. Causes for venous congestion include compression of the pedicle due to poor elasticity of the skin over the roof of the tunnel in island flaps, valvular incompetence, edema at the pedicle region, compartment syndrome, and compression of the pedicle by hematoma.



Figure 4: (a) Posttraumatic soft tissue defect with exposure of the medial malleolus and calcaneus; (b) picture following wound debridement; (c) reverse sural artery flap cover performed; (d) tip necrosis of the reverse sural flap covered with a skin graft

Almeida *et al.*^[3] experienced partial flap necrosis (22.1%), total flap necrosis (4.2%), infection (8.5%) and venous congestion (4.1%) in a total of 71 cases of transferred reverse sural flaps. Zayed *et al.*^[6] experienced venous congestion in five out of 25 cases of lateral supramalleolar flap coverage. Voche *et al.*^[2] reported venous congestion and partial flap necrosis (5-30%) in 41 cases of a lateral supramalleolar flap used for ankle and foot defects. Kneser *et al.*^[4] suggested a delayed neurofasciocutaneous sural flap, which is initially completely elevated and then fixed again at the donor site using running sutures for 7-15 days. After confirming the flap's survival, the flap is raised again and transposed into the soft tissue defect. This delay procedure could be an alternative to increase the reliability and viability of the distally-based fasciocutaneous flap. However, delay procedures are not feasible in every patient as they require a significant time delay for coverage of vital structures. Ulkür *et al.*^[7] demonstrated the usefulness of HBO treatment during the delay period of the flap which can lessen the time period required for delay, and which can also increase the effect of flap delay. This technique of reducing the delay period could well be utilized in the reduction of the duration of flap transfer in flap delay procedures. In addition, HBO therapy helps to prepare the recipient and donor areas, and the flap to be transferred during the delay period. There appears to be no harm in administering HBO therapy during the delay period, as it reduces the edema of the delayed tissue and provides an optimal outcome following transfer.

In our center, HBO is administered in a monoplace chamber in which a single patient is placed in a chamber, which is then pressurized with 100% oxygen. Vasoconstriction reduces edema and tissue swelling while ensuring adequate oxygen delivery and is thus useful in acute trauma wounds as well as in delayed flaps. Hyperoxygenation causes immune stimulation by restoring white blood cell function and enhancing their phagocytic capabilities and neo-vascularization in hypoxic areas by augmenting fibroblastic activity and capillary growth.^[8] Adequate shock management, debridement and repair of soft tissues, and stabilization of bony elements are of paramount importance. HBO therapy as an adjunct should be administered as early as possible to minimize the

frequency and extent of tissue necrosis, reduce edema, control infection, support healing and prevent reperfusion injury.^[9]

A recent retrospective analysis of 70 consecutive sural flaps reported a complication rate of 59% (41 of 70 flaps), with complete necrosis in 19% flaps and partial necrosis in 17%.^[10] In a series of lateral supramalleolar flaps by Ehab *et al.*,^[6] a total of 5 patients (20%) suffered complications out of 25 patients. Two cases were managed conservatively, 2 cases required revision with suturing, and 1 case required alternative flap coverage. Kang *et al.*^[11] experienced 4 patients with partial necrosis (30%) among 13 patients where distally-based sural artery and lateral supramalleolar flaps had been utilized for soft tissue defects of the leg and foot. We noted complete flap survival in patients who received HBO with flap delay in spite of their associated co-morbidities. In the transfer group without HBO treatments, 5 patients of 11 (45.4%) experienced flap tip necrosis, and 1 patient had partial flap loss.

At our institution, we have developed a strategy to successfully manage patients with defects of the lower third of the leg and foot using a combined approach that maximizes tissue perfusion and oxygenation, allowing for optimal surgical correction of such injuries. Our treatment algorithm begins with early surgical debridement and initiation of HBO therapy. Combination of the modalities allows preservation of marginal tissue, prevention of extension of ischemia, reduction of tissue edema and congestion, and maximum preservation of the transferred distally-based flap. In our series, no complications were noted in patients treated with this approach. However, several cases of the flap tip or partial necrosis were noted in patients who received direct flap transfer. In this series, flap delay procedures were scheduled based on various factors including severity of injury, time of referral, co-morbid conditions, patient age, reach of the flap, patient toleration of use of the chamber, and affordability of treatment. However, additional studies are required to determine any additional indications, as well as the optimal timing and dosage of HBO therapy for such procedures. The patients in the current series did not experience the common side effects of HBO therapy such as aural or pulmonary barotrauma or a transient reversible myopia. Optimal usage of HBO therapy may reduce the duration of flap delay and increase the effect of flap delay procedure, helping to an optimal outcome for the transferred tissue.

In conclusion, distally-based flaps provide effective coverage of variable sized soft tissue defects of the lower third of leg, ankle and foot following trauma. Adjunctive HBO therapy should be considered when possible for improved flap survival and optimal surgical outcomes.

REFERENCES

1. Demiri E, Foroglou P, Dionysiou D, Antoniou A, Kakas P, Pavlidis L, Lazaridis L. Our experience with the lateral supramalleolar island flap for reconstruction of the distal leg and foot: a review of 20 cases. *Scand J Plast Reconstr Surg Hand Surg* 2006;40:106-10.

2. Voche P, Merle M, Stussi JD. The lateral supramalleolar flap: experience with 41 flaps. *Ann Plast Surg* 2005;54:49-54.
3. Almeida MF, da Costa PR, Okawa RY. Reverse-flow island sural flap. *Plast Reconstr Surg* 2002;109:583-91.
4. Kneser U, Bach AD, Polykandriotis E, Kopp J, Horch RE. Delayed reverse sural flap for staged reconstruction of the foot and lower leg. *Plast Reconstr Surg* 2005;116:1910-7.
5. Mehrotra S. Perforator plus flaps: optimizing results while preserving function and esthesia. *Indian J Plast Surg* 2010;43:141-8.
6. Zayed EF. Lateral supramalleolar flap for reconstruction of the distal leg and foot, clinical experience with 25 cases. *Egypt J Plast Reconstr Surg* 2011;35:279-86.
7. Ulkür E, Karagoz H, Ergun O, Celikoz B, Yildiz S, Yildirim S. The effect of hyperbaric oxygen therapy on the delay procedure. *Plast Reconstr Surg* 2007;119:86-94.
8. Bhutani S, Vishwanath G. Hyperbaric oxygen and wound healing. *Indian J Plast Surg* 2012;45:316-24.
9. Kemmer A. Crush injury and other traumatic ischemia. In: Mathieu D, editor. *Handbook on Hyperbaric Medicine*. Netherlands: Springer; 2006. p. 311-2.
10. Baumeister SP, Spierer R, Erdmann D, Sweis R, Levin LS, Germann GK. A realistic complication analysis of 70 sural artery flaps in a multimorbid patient group. *Plast Reconstr Surg* 2003;112:129-40.
11. Kang HG, Kim JH, Cho HS, Han I, Oh JH, Kim HS. Soft tissue reconstruction of the foot using the distally based island pedicle flap after resection of malignant melanoma. *Clin Orthop Surg* 2010;2:244-9.

How to cite this article: Korambayil PM, Ambookan PV. Hyperbaric oxygen therapy and surgical delay improve flap survival of reverse pedicle flaps for lower third leg and foot reconstruction. *Plast Aesthet Res* 2015;2:130-7.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 07-12-2014; **Accepted:** 29-01-2015

Rupture of the flexor carpi radialis tendon secondary to trauma: case report and literature review

Jonathan Kanevsky¹, Dino Zammit², Jean-Paul Brutus³

¹Department of Plastic and Reconstructive Surgery, Montreal General Hospital, Montreal, QC H3G 1A4, Canada.

²Faculty of Medicine, McGill University, Montreal, QC H3G 1Y6, Canada.

³Centre Médical L'enjeu, Ville Mont-Royal, QC H3P 3E5, Canada.

Address for correspondence: Dr. Jonathan Kanevsky, Montreal General Hospital, 1650 Avenue Cedar, Montreal, QC H3G 1A4, Canada.
E-mail: jonkanevsky@gmail.com

ABSTRACT

The flexor carpi radialis (FCR) is one of the long flexors, which is important in flexing and abducting the hand at the wrist. It originates at the medial epicondyle of the humerus and attaches at the base of the second metacarpal. Closed rupture of the long flexors of the finger is well-described, especially in association with rheumatoid hands. However, rupture of the FCR is rare; only 11 cases reported in the literature, most of them associated with scaphotrapezial-trapezoidal osteoarthritis. We describe 1 case of complete FCR rupture secondary to trauma, showing that long-term disability following FCR rupture is minimal.

Key words:

Flexor carpi radialis, rupture, trauma

INTRODUCTION

Closed rupture of the long flexors of the finger is well described, especially in association with rheumatoid hands. However, rupture of the flexor carpi radialis (FCR) is rare with only 11 cases reported in the literature. Many of the described cases were associated with scaphotrapezial-trapezoidal (STT) osteoarthritis. We describe 1 case of complete FCR rupture secondary to trauma.

CASE REPORT

A 24-year-old right-hand dominant, professional male boxer suffered a traumatic blow to the left forearm during a sparring match. Four weeks after injury he presented to the clinic with a complaint of pain in his left wrist

and a notable swelling in the region of the left FCR. On examination, there was tenderness along the course of the FCR as well as a palpable mass at the FCR origin. There was minimal loss of function on range of motion. Ultrasound/X-ray examination confirmed complete rupture of the FCR at its distal insertion. The FCR tendon and muscle belly retracted to approximately the proximal third of the forearm. In addition to the tendinous injury, radiograph revealed an osseous fragment attached to the distal end of the torn tendon.

Conservative treatment was decided to be the best management of this patient given the 4-week delay from onset of injury to presentation in the clinic. Furthermore, given the patient's profession as an athlete and minimal functional impairment, the decision was made to avoid operative intervention and proceed to aggressive physiotherapy. He was followed at 3 months, 6 months, and 1 year, and was able to return to boxing 2 months after injury as deemed appropriate by the physical therapist, occupational therapist, and surgeon.

DISCUSSION

The FCR tendon runs through a synovial fibro-osseous tunnel in the forearm to its insertion at the base of the

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157108

second metacarpal. As the tendon traverses the carpal bones, it passes over the ulnar aspect of the scaphoid tubercle and along a groove in the medial surface of the trapezium. Two laminae (superficial and deep) of the transverse carpal ligament enclose the FCR tendon. The superficial lamina inserts on tubercle of the scaphoid and trapezium while the deep inserts on the medial lip of the groove of the trapezium.^[1] The tendon passes through the scaphotrapezial joint line to insert at the base of the second metacarpal. The course of the tendon over the scaphotrapezial joint is of importance because of the increased incidence of rupture associated with scaphotrapezial osteoarthritis.^[1]

In the English and French literature, 11 cases of closed spontaneous ruptures of the FCR tendon are described. Five cases of rupture were associated with a severe rheumatoid collapse.^[2] These cases were treated operatively with debridement and synovectomy, but no tendon repair. In 5 cases, STT osteoarthritis was the cause of the tendon rupture. In STT, osteoarthritis osteophytes extend from the joint and during extension can damage the FCR tendon sheath. In these cases, no tendon repair was done as there was minimal functional impairment.^[2] One case of FCR rupture secondary to fracture of the distal radius was described.^[3]

In the majority of cases, FCR rupture is a clinical diagnosis. Patients present with pain at the ruptured ends of the tendon. Palpation may reveal a gap along the course of the FCR.^[4] X-ray or computed tomography (CT) may be useful in determining the etiology of the rupture if bony spurs associated with osteoarthritis are suspected.

Complete rupture of the FCR tendon is generally conservative, as the deficit is relatively minor.^[2] Good functional results have been reported from simple splinting.^[5] Occupational therapy is considered the standard of treatment and consists of active and passive range of motion exercises after 3 weeks of splinting. Functional problems after tendon rupture are minimal, and retraction of the tendon stump often makes reattachment difficult.^[5] In fact, the FCR is a useful

donor for arthroplasty tendon can be safely used in the reconstruction.^[6]

In the case of partial ruptures, management with immobilization has been reported to successfully treat pain.^[7] Given the association of FCR rupture and osteoarthritis, severe and localized pain has been described to be worse than rupture of other tendons of the wrist.^[8]

Rupture of the tendon of the FCR is rare. Our case as well as the literature review demonstrates that long-term disability following FCR rupture is minimal. Although, commonly associated with scaphotrapezial osteoarthritis, our case demonstrates that rupture secondary to trauma is possible and should be considered in the differential diagnosis of pain and swelling on the flexor surface of the wrist and forearm.

REFERENCES

1. Chen PJ, Liu AL. Concurrent flexor carpi radialis tendon rupture and closed distal radius fracture. *BMJ Case Rep* 2014;10:2014.
2. Polatsch DB, Foster LG, Posner MA. An unusual rupture of the flexor carpi radialis tendon: a case report. *Am J Orthop (Belle Mead NJ)* 2006;35:141-3.
3. Allred DW, Rayan GM. Flexor carpi radialis tendon rupture following chronic wrist osteoarthritis: a case report. *J Okla State Med Assoc* 2003;96:211-2.
4. DiMatteo L, Wolf JM. Flexor carpi radialis tendon rupture as a complication of a closed distal radius fracture: a case report. *J Hand Surg Am* 2007;32:818-20.
5. Low TH, Hales PF. High incidence and treatment of flexor carpi radialis tendinitis after trapeziectomy and abductor pollicis longus suspensionplasty for basal joint arthritis. *J Hand Surg Eur Vol* 2014;39:838-44.
6. Tonkin MA, Stern HS. Spontaneous rupture of the flexor carpi radialis tendon. *J Hand Surg Br* 1991;16:72-4.
7. Bowe A, Doyle L, Millender LH. Bilateral partial ruptures of the flexor carpi radialis tendon secondary to trapezial arthritis. *J Hand Surg Am* 1984;9:738-9.
8. Ducharme G, Frick L, Schoofs M. Flexor carpi radialis tendon rupture following percutaneous osteosynthesis of the scaphoid: a case report. *Chir Main* 2009;28:50-2.

How to cite this article: Kanevsky J, Zammit D, Brutus JP. Rupture of the flexor carpi radialis tendon secondary to trauma: case report and literature review. *Plast Aesthet Res* 2015;2:138-9.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 11-11-2014; **Accepted:** 27-02-2015

Aesthetic rehabilitation of a patient with an anterior maxillectomy defect, using an innovative single-step, single unit, plastic-based hollow obturator

Vishwas Bhatia¹, Garima Bhatia²

¹Department of Prosthodontics, King Khalid University, Abha 61412, Saudi Arabia.

²Department of Oral Medicine and Radiology, PDM Dental College and Hospital, Bahadurgarh, Haryana 124507, India.

Address for correspondence: Dr. Vishwas Bhatia, Department of Prosthodontics, King Khalid University, Abha 61412, Saudi Arabia.
E-mail: vishwas211@yahoo.co.in

ABSTRACT

What could be better than improving the comfort and quality of life of a patient with a life-threatening disease? Maxillectomy, the partial or total removal of the maxilla in patients suffering from benign or malignant neoplasms, creates a challenging defect for the maxillofacial prosthodontist when attempting to provide an effective obturator. Although previous methods have been described for rehabilitation of such patients, our goal should be to devise one stage techniques that will allow the patient an improved quality of life as soon as possible. The present report describes the aesthetic rehabilitation of a maxillectomy patient by use of a hollow obturator. The obturator is fabricated through a processing technique which is a variation of other well-known techniques, consisting of the use of a single-step flasking procedure to fabricate a single-unit hollow obturator using the lost salt technique. As our aim is to aesthetically and functionally rehabilitate the patient as soon as possible, the present method of restoring the maxillectomy defect is cost-effective, time-saving and beneficial for the patient.

Key words:

Aesthetics, maxillectomy, palatal obturator, plastic-based, squamous cell carcinoma

INTRODUCTION

A conventional surgical excision is the most common method for treatment of a maxillary oral squamous cell carcinoma (SCC). The resulting surgical defect often includes part of the hard palate which results in oro-antral communication.^[1] Patients undergoing surgery alone without closure or obturation of the surgical defect face numerous problems in phonetics and mastication secondary to the passage of air, food and liquids into the nasal and maxillary sinus. In addition to the functional

deficit, there is a marked effect on aesthetics without the presence of an obturator.

An obturator is that component of a prosthesis, which fits into and closes a defect within the oral cavity or another body defect.^[2] In the past, various methods have been used to restore the maxillary defect using silicon bulb obturators, implant-supported obturators, and cast metal obturators. This clinical report describes a method for aesthetic rehabilitation of a patient with a partial maxillectomy defect, using a light-weight, single-unit, closed hollow obturator fabricated by an innovative single-step flasking technique using the lost salt method. The technique assists in fabrication of an obturator, which restores aesthetics, function, speech, and dental appearance.

CASE REPORT

A 47-year-old man, diagnosed with SCC of the palate extending into the maxillary sinus, underwent a partial

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157110

maxillectomy and was subsequently referred to the Department of Prosthodontics and Implantology, Eklavya Dental College and Hospital, Rajasthan, India. Immediate surgical reconstruction was not recommended given the need for further treatment with radiation therapy. External beam postoperative radiotherapy was administered over a period of 6 weeks. The patient tolerated the radiation well and was subsequently referred to possible prosthetic restoration of the oral defect after radiation therapy. Examination revealed a partial maxillectomy defect on the left side crossing the midline. The left side naso-maxillary region was depressed due to bone loss, and this was also evident in extra oral examination. The defect was a Class IV according to the Aramany Classification of Defects^[3] [Figure 1]. The patient agreed to have his pictures published and signed the consent form.

Aesthetic rehabilitation can be accomplished either surgically or prosthetically.^[4] The choice of rehabilitation depends on the site, size, severity, patient age, and patient preference. Contraindications to surgical reconstruction include advanced age, poor general medical condition, a history of radiation therapy, a complex anatomical defect and the patient's refusal to undergo further surgery.^[5]

Various modalities for prosthetic reconstruction were discussed with the patient, and he requested an economical solution. The treatment plan therefore was to provide a plastic-based, light-weight obturator to meet the aesthetic demands by replacing bone and teeth while assisting phonetics and mastication.

Procedure

An irreversible hydrocolloid was used to make an impression of the maxillary defect area after blocking all undercuts with wet gauge. The impression was poured, and the final cast was obtained, on which a custom tray was made using a self-curing autopolymerising resin.

Border molding for recording the soft tissue borders of the defect was carried out using a low-fusing impression compound. Additional silicone was used to make a wash impression, and the final master cast was poured. All undercuts on the cast were blocked out with plaster and wax [Figure 2]. The final denture base and occlusal wax rims were prepared to record maxillomandibular relations. After the maxillomandibular jaw relations had been obtained, the record was articulated, and teeth arrangement was performed. On completion, the wax prosthesis was verified at the trial insertion appointment. The wax prosthesis was invested, and the wax was eliminated [Figure 3]. A sheet of plastic based heat cure acrylic polymer in the dough stage was placed over the defect and the palatal area on the master cast. Pressure then applied to the base of the defect resulted in a cup-shaped depression of acrylic polymer over the defect [Figure 4]. Salt was then used to fill the depression [Figure 5]. Another thin sheet of acrylic polymer was placed, and packing was performed with conventional prosthodontic protocols. Finally, three to four holes were drilled on the palatal surface of the prosthesis covering the bulb [Figure 6]. Warm water was injected through the holes to dissolve and eliminate the



Figure 1: Intraoral view of the maxillectomy defect

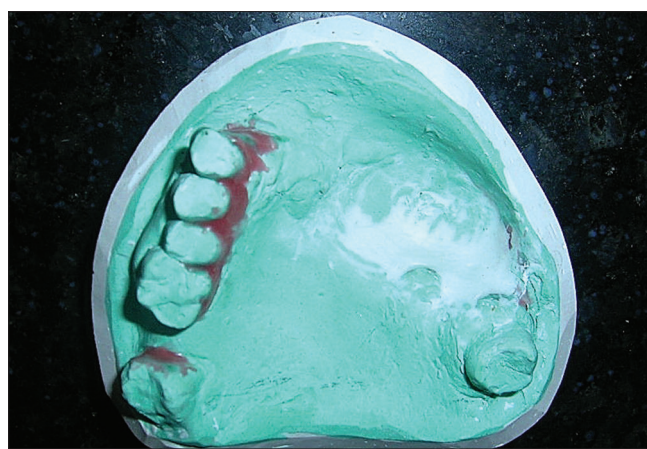


Figure 2: Blocking of undercuts on master cast by plaster and wax



Figure 3: Master cast after elimination of wax

salt present in the bulb [Figure 7], resulting in a hollow space inside the bulb. The holes were sealed with a layer of self-curing acrylic, and final finishing and polishing of the prosthesis was done [Figure 8].

The plastic-based hollow obturator was inserted into the defect, and the patient was instructed on home care and the prosthesis maintenance. To sanitize the wound, the patient was instructed to gently remove any exudates with a wet cotton tip soaked with a 5% Betadine solution and to clean the intaglio surface of the prosthesis once



Figure 4: Plastic based polymethylmethacrylate heat cure placed and pressed into the defect



Figure 5: Salt filled into the defect



Figure 6: Second layer of plastic-based acrylic placed over the defect



Figure 7: Elimination of salt through the holes



Figure 8: Finished and polished single unit hollow obturator closing the defect

a day. Post treatment photographs of the patient showed a marked improvement in aesthetics by replacement of missing teeth and restoration of the previously depressed nasomaxillary region [Figure 9a and b]. The patient was scheduled for his first adjustment 3 days following insertion. At the appointment, the surgical wound was examined to ensure health of the tissues and any part of prosthesis exerting pressure on the wound was smoothed. Hygiene and home care were emphasized, and the patient was advised to return in 3 months.



Figure 9: (a) Pretreatment photograph showing depressed left nasomaxillary region; (b) posttreatment photograph showing replaced missing teeth and marked improvement in aesthetics

DISCUSSION

Orofacial rehabilitation of patients with use of an obturator is an appropriate treatment modality for maxillofacial defects.^[6] Oromaxillary defects are associated with inflow and outflow of oral and nasal microflora, regurgitation of oral fluids, voice changes secondary to asynchrony in resonance, and difficulty in speech and swallowing. In addition, acquired maxillary defects have

a marked effect on facial aesthetics. Hence, effective treatment modalities for these defects are mandatory.^[7] Small defects can be managed by surgery, but large defects require prosthodontic rehabilitation by obturators. A multidisciplinary team consisting of an oncologist, an oral and maxillofacial surgeon, a maxillofacial prosthodontist, a specialist nurse, a dietitian and a speech therapist is ideal for care of head and neck cancer patients. A high level of cooperation between the prosthodontist and the surgeon prior to surgery is critical to achieving adequate rehabilitation for patients with maxillary defects.^[8]

This clinical report describes the rehabilitation of a Class IV maxillary defect with a plastic based light weight hollow obturator. Class IV defects represent the classic maxillary defect in which the hard palate, alveolar ridge, and dentition are removed beyond the midline.^[3] Advantages of hollow bulb obturators include decreased weight of the obturator, decreased pressure on surrounding tissues, and ease of deglutition. In addition, the light weight of the obturator minimizes excessive atrophy and physiological changes in muscle balance.^[9] The hollow bulb adds resonance, thus improving the clarity of speech.^[10]

Although prior techniques described in the literature fabricate obturators with the use of wax, sponge, polyurethane, foam and gas injection,^[11-13] the present technique uses a single-step flasking procedure, resulting in a comfortable, light-weight prosthesis with reduced fabrication time.

In conclusion, the goal of rehabilitation is creation of a prosthesis, which can restore aesthetics and function, while being easy to use, easy to clean to prevent recurrent infections, and which can be readily fabricated by simple time saving techniques. In order to achieve these goals, a single unit plastic based polymethylmethacrylate closed hollow obturator was fabricated by the lost salt method using single-step flasking. The prosthesis rehabilitated the patient aesthetically by replacing lost teeth and adding bulk to the depressed facial region, and functionally by providing better masticatory efficiency and phonetics. The present obturator is an additional alternative for plastic surgeons, oncologists and prosthodontists when planning treatment of such cases. In addition to being used following tissue healing, it can be used as an immediate surgical obturator by fabricating it on a presurgical model and trimming the affected area on the cast.

Educating and motivating the patient about the type of prosthesis and its limitations are the first steps in successful treatment.^[14] As this obturator is economical,

time-saving and light in weight, the surgeon can recommend it to patients who require an economical alternative or who are not willing or able to undergo surgical reconstruction of their defect.

The light-weight plastic-based hollow bulb obturator fabricated in the present case rehabilitated the patient aesthetically and functionally, providing him an opportunity to live his life as close to normal as possible.

REFERENCES

1. Cummings CW. Cummings Otolaryngology: Head and Neck Surgery. 4th ed. St. Louis: Elsevier; 2004. p. 1604-8.
2. GPT-8. The academy of prosthodontics. *J Prosthet Dent* 2005;94:56.
3. Aramany MA. Basic principles of obturator design for partially edentulous patients. Part I: classification. *J Prosthet Dent* 1978;40:554-7.
4. Fornelli RA, Fedok FG, Wilson EP, Rodman SM. Squamous cell carcinoma of the anterior nasal cavity: a dual institution review. *Otolaryngol Head Neck Surg* 2000;123:207-10.
5. Thawley SE, Batsakis JG, Lindberg RD, Panje WR, Donley S, editors. Comprehensive management of head and neck tumors. 2nd ed. St. Louis: Elsevier; 1998. p. 526-7.
6. Depprich R, Naujoks C, Lind D, Ommerborn M, Meyer U, Kübler NR, Handschel J. Evaluation of the quality of life of patients with maxillofacial defects after prosthodontic therapy with obturator prostheses. *Int J Oral Maxillofac Surg* 2011;40:71-9.
7. Mohamed Usman JA, Ayappan A, Ganapathy D, Nasir NN. Oromaxillary prosthetic rehabilitation of a maxillectomy patient using a magnet retained two-piece hollow bulb definitive obturator; a clinical report. *Case Rep Dent* 2013;2013:190180.
8. Tirelli G, Rizzo R, Biasotto M, Di Lenarda R, Argenti B, Gatto A, Bullo F. Obturator prostheses following palatal resection: clinical cases. *Acta Otorhinolaryngol Ital* 2010;30:33-9.
9. Curtis TA, Beumer J. Restoration of acquired hard palate defects: etiology, disability, and rehabilitation. In: Beumer J, Curtis TA, Firtell DN, editors. Maxillofacial Rehabilitation. Prosthodontic and Surgical Considerations. St. Louis: C.V. Mosby Co.; 1979. p. 183-243.
10. Rilo B, Dasilva JL, Ferros I, Mora MJ, Santana U. A hollow-bulb interim obturator for maxillary resection. A case report. *J Oral Rehabil* 2005;32:234-6.
11. Patil PG, Patil SP. Fabrication of a hollow obturator as a single unit for management of bilateral subtotal maxillectomy. *J Prosthodont* 2012;21:194-9.
12. Iramaneerat W, Seki F, Watanabe A, Mukohyama H, Iwasaki Y, Akiyoshi K, Taniguchi H. Innovative gas injection technique for closed-hollow obturator. *Int J Prosthodont* 2004;17:345-9.
13. Sridevi JR, Kalavathy N, Jayanthi N, Manjula N. Techniques for fabricating hollow obturator: two case reports. *SRM J Res Dent Sci* 2014;5:143-6.
14. Popli S, Parkash H, Bhargava A, Gupta S, Bablani D, Kar AK. A two-piece sectional interim obturator. A clinical report. *J Prosthodont* 2012;21:487-90.

How to cite this article: Bhatia V, Bhatia G. Aesthetic rehabilitation of a patient with an anterior maxillectomy defect, using an innovative single-step, single unit, plastic-based hollow obturator. *Plast Aesthet Res* 2015;2:140-3.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 15-11-2014; **Accepted:** 15-03-2015

Use of tensor fascia lata flap for reconstruction of the defect created following inguinal block dissection in a case of carcinoma penis: a case report and brief review of literature

Amitabh Jena¹, Banoth Manilal¹, Sriharsha Haranadh¹, Rashmi Patnayak²

¹Department of Surgical Oncology, Sri Venkateswara Institute of Medical Sciences, Tirupati 517507, Andhra Pradesh, India.

²Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati 517507, Andhra Pradesh, India.

Address for correspondence: Prof. Amitabh Jena, Department of Surgical Oncology, Sri Venkateswara Institute of Medical Sciences, Tirupati 517507, Andhra Pradesh, India. E-mail: dramitabh2004@yahoo.co.in

ABSTRACT

Tensor fascia lata (TFL) flap is a versatile myofasciocutaneous flap. It has varied usages as both free and pedicled flap. As a pedicled flap, it is a good option for reconstructing soft tissue defects after tumor ablation. The TFL perforator flap is a good alternative for anterolateral thigh (ALT) flap. The advantages of TFL flap are that dissection can be made through the same incision, without impairment of other donor sites. The reconstructive plan remains same as that of ALT flap. TFL flap offers a good volume of skin and can be made thin removing variable portions of muscle. The present case is a 63-year-old patient with a carcinoma penis who underwent left ilioinguinal block dissection resulting in a defect of 8 cm × 8 cm in the left inguinal region. TFL flap was raised with U-shaped incision and used for closure of the defect with good result.

Key words:

Groin reconstruction, myofasciocutaneous flap, tensor fascia lata flap

INTRODUCTION

Tensor fascia lata (TFL) flap is a myofasciocutaneous flap. In 1934, Wangenstein,^[1] first described it for abdominal wall reconstruction. It is a versatile flap with many uses in reconstructive plastic surgery like in management of pressure sores, facial reanimation and as a free flap in head and neck reconstruction.^[2] As a pedicled flap, its strong fascial layer has the advantage of reaching the lower abdomen and the groin. Thus, it is a good option for reconstructing soft tissue defects after tumor ablation.

The problem with TFL is distal necrosis in both pedicled and free form. The flap's safe dimensions and adequacy to minimize distal tip necrosis for a sound abdominal wall reconstruction remains controversial.^[2-5]

The aim of the present case report was to share our experience and clinical observations with TFL flap used in the reconstruction of a challenging defect following inguinal block dissection in a case of the carcinoma penis.

CASE REPORT

A 63-year-old male patient who was a diagnosed case of the carcinoma penis with bilateral inguinal lymphadenopathy underwent partial penectomy 6 months back. Left inguinal lymph node dissection was also planned after 2 weeks, and he was discharged on antibiotic cover. The patient defaulted for 3 months and presented with a fungating left inguinal lymph nodal mass. He was treated with external radiotherapy with 60 Gy in 30 fractions over 6 weeks.

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.157111

Later, the patient presented with a residual mass over left inguinal region. There was a hard swelling of 4 cm × 3 cm with restricted mobility in left inguinal region [Figure 1]. Also, multiple small lymph nodes were palpable on the right side, the largest measuring 1 cm × 1 cm.

Magnetic resonance image of the left inguinal region showed enlarged necrotic lymph node, anterior to femoral vessels in the subcutaneous plane. There was a loss of fat planes with left femoral vein. Left femoral artery and right inguinal region were normal. Fine needle aspiration cytology was done from bilateral inguinal lymph nodes. The left inguinal lymph node showed squamous cell carcinomatous deposit. The right inguinal lymph nodes were reactive in nature without any tumor deposit. Chest X-ray was reported as normal. Routine hematological and biochemical investigations like complete hemogram, serum urea and creatine were within normal limit. Viral markers like human retroviral antigen, hepatitis B and C were also negative.

He underwent left ilioinguinal block dissection. Perioperatively, there were necrotic lymph nodes of 4 cm × 4 cm in size, abutting the femoral vein. Multiple lymph nodes were present in iliac region, largest measuring 3 cm × 1 cm. The Cloquet lymph node was also present. Three cm skin margin was taken beyond the indurated area thereby creating a defect of 8 cm × 8 cm in the left inguinal region [Figure 2].

It was decided to cover the defect with TFL pedicle flap. We followed the same technique of harvesting of TFL as described by various authors.^[2,4] The donor flap outlining was done with U-shaped incision on the thigh. The elevation was carried out in a subfascial plane from distal to proximal. The lateral circumflex femoral artery was then easily identified high up as it passes between the rectus femoris and the vastus lateralis, where it gives the transverse branch, which pierces the TFL muscle accompanied by venae comitantes. Then dissection was performed to sufficiently mobilize the flap for proper defect coverage [Figure 3]. The medial end of the incision was joined to the lateral aspect of the inguinal defect. The free end of the flap was then rotated upward and medially [Figure 4] and sutured to the defect created by the inguinal dissection. Donor site could be approximated without any tension [Figure 5]. Drain was placed, and wound was closed in layers.

Postoperative period was uneventful. Flap was healthy on the seventh postoperative day, and the patient was discharged. He was advised to undergo regular follow-up. Suture and skin stapler was removed on the 14th day. There was no necrosis or dehiscence, and the cosmesis was acceptable.

Other options for alternative flaps in this case would have been perforator based anterolateral thigh (ALT)



Figure 1: Residual left inguinal lymph nodal mass (postradiotherapy)



Figure 2: Defect created after inguinal block dissection



Figure 3: Flap after dissecting all around



Figure 4: The free end of the flap was rotated upward and medially to the defect



Figure 5: Primary and donor site approximated without tension

flap. We preferred TFL particularly in this case. The dissection could be done through the incision joining inguinal block dissection. The defect created was closed without any tension and with acceptable cosmetic result. A simple upper and medial or rotation of the flap helped us to approximate the donor site and close it primarily [Figures 4 and 5].

DISCUSSION

The soft tissue tumors in the groin area need adequate resection to achieve optimal local treatment and to minimize recurrence. The resultant wounds are slow healing in nature and are frequently exposed to vital structures like femoral vessels, thereby increasing the complication rate.^[6-9]

Several flaps have been described to cover established groin defects, namely, inferiorly based rectus abdominis muscle or myocutaneous flap, rectus femoris, sartorius with abdominal skin flap, internal oblique muscle flap, and vastus lateralis flaps.^[2-5] These flaps have their advantages and disadvantages. Abdominal weakness, bulging or hernia, and knee weakness are some of the complications associated with these flaps.^[2]

ALT flap is considered as the gold standard in head and neck reconstructions as free flaps and as pedicle flaps in abdominal wall reconstruction.^[10,11] The advantage of this flap is that it offers a good volume of pliable tissues and a pedicle characterized by good caliber and adequate length. Its main disadvantage is its anatomical variability in number and location of perforator vessels. The absence of perforators is rare, but can occur. In these instances, TFL perforator flap can be a good alternative to ALT flap.^[10,11]

TFL flap is a myocutaneous flap that can either be used as a free flap or as a pedicle flap depending on the site. It can be used as a free flap in the head and neck reconstruction, and as a pedicle flap in abdominal wall reconstructions. The advantage of TFL flap is that it allows the usage of the same donor site thereby avoiding

another surgical incision. Its anatomy is more constant. Perforators are almost always present, and their pedicles are of sufficient length (average of 8 cm). As a perforator flap, a thinner and more pliable flap can be obtained, removing a variable portion of muscular tissue and leaving only a cuff around the pedicle. Therefore, it can be used for almost the same indications of ALT flap.^[2-5]

The published reports of TFL flap in groin reconstruction following inguinal node dissection have enumerated partial flap necrosis, distal tip necrosis, flap infection and lymphedema as various complications.^[2,3,5]

In our case, we found TFL perforator flap to be the best choice because it allowed maintaining the same reconstructive plan made with the ALT flap.

In conclusion, the TFL flap is a reliable flap for inguinal area defect reconstruction, without any donor site morbidity. Because we could close the defect primarily without skin graft, it was cosmetically very well accepted by the patient.

REFERENCES

1. Wangenstein OH. Repair of recurrent and difficult hernias and other large defects of the abdominal wall employing the iliotibial tract of fascia lata as a pedicled flap. *Surg Gynecol Obstet* 1934;59:766-80.
2. Murthy V, Gopinath KS. Reconstruction of groin defects following radical inguinal lymphadenectomy: an evidence based review. *Indian J Surg Oncol* 2012;3:130-8.
3. Agarwal AK, Gupta S, Bhattacharya N, Guha G, Agarwal A. Tensor fascia lata flap reconstruction in groin malignancy. *Singapore Med J* 2009;50:781-4.
4. Akhtar MS, Khurram MF, Khan AH. Versatility of pedicled tensor fascia lata flap: a useful and reliable technique for reconstruction of different anatomical districts. *Plast Surg Int* 2014;2014:846082.
5. Nirmal TJ, Gupta AK, Kumar S, Devasia A, Chacko N, Kekre NS. Tensor fascia lata flap reconstruction following groin dissection: is it worthwhile? *World J Urol* 2011;29:555-9.
6. Rifaat MA, Abdel Gawad VS. The use of tensor fascia lata pedicled flap in reconstructing full thickness abdominal wall defects and groin defects following tumor ablation. *J Egypt Natl Canc Inst* 2005;17:139-48.
7. Hubmer MG, Justich I, Haas FM, Koch H, Parvizi D, Feigl G, Prandl E. Clinical experience with a tensor fasciae latae perforator flap based on septocutaneous perforators. *J Plast Reconstr Aesthet Surg* 2011;64:782-9.
8. Mack LA, Temple WJ, DeHaas WG, Schachar N, Morris DG, Kurien E. Groin soft tissue tumors - a challenge for local control and reconstruction: a prospective cohort analysis. *J Surg Oncol* 2004;86:147-51.
9. Payne WG, Walusimbi MS, Blue ML, Mosiello G, Wright TE, Robson MC. Radiated groin wounds: pitfalls in reconstruction. *Am Surg* 2003;69:994-7.
10. Contedini F, Negosanti L, Pinto V, Tavaniello B, Fabbri E, Sgarzani R, Tassone D, Cipriani R. Tensor fascia latae perforator flap: an alternative reconstructive choice for anterolateral thigh flap when no sizable skin perforator is available. *Indian J Plast Surg* 2013;46:55-8.
11. Lannon DA, Ross GL, Addison PD, Novak CB, Lipa JE, Neligan PC. Versatility of the proximally pedicled anterolateral thigh flap and its use in complex abdominal and pelvic reconstruction. *Plast Reconstr Surg* 2011;127:677-88.

How to cite this article: Jena A, Manilal B, Haranadh S, Patnayak R. Use of tensor fascia lata flap for reconstruction of the defect created following inguinal block dissection in a case of carcinoma penis: a case report and brief review of literature. *Plast Aesthet Res* 2015;2:144-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 25-11-2014; **Accepted:** 13-02-2015

Preface to special issue on "Peripheral Nerve Repair and Regeneration"

Francesca Toia

Plastic and Reconstructive Surgery, Department of Surgical, Oncological and Oral Sciences, University of Palermo, 90127 Palermo, Italy.

Address for correspondence: Dr. Francesca Toia, Plastic and Reconstructive Surgery, Department of Surgical, Oncological and Oral Sciences, University of Palermo, 90127 Palermo, Italy. E-mail: francescatoia@gmail.com

Peripheral nerve surgery has achieved a great improvement in the last century. The introduction of microsurgery and the technical advances in reparative and reconstructive techniques has been instrumental in advancing nerve surgery techniques. Yet, in the last few decades, the scientific progress has slowed down significantly, and surgery is still far from reaching an optimal functional recovery in most cases.

New surgical approaches are increasingly used for various indications, but current research mainly focuses on the mechanisms of nerve damage and nerve regeneration. It is now clear that nerve regeneration not only relies on surgical reconstruction but also on understanding underlying biomolecular processes that could turn out to be the key for developing novel treatment strategies.

With the present special issue on “nerve regeneration and repair”, we wish to summarize the state of the art of translational and clinical research and present the current trends and future prospects in peripheral nerve surgery. For this purpose, most of the twelve papers in this issue are review papers.

This issue begins with an overview of the current neurophysiologic and imaging tests: preoperative diagnostic work-up and postoperative monitoring, to provide a clinical guide on the assessment of nerve injuries.

Then, we discuss nerve pain and dysfunction following surgery (e.g. in scar neuropathy or in recalcitrant compression neuropathy) and the treatment approaches. Using current literature, we summarize the analysis of reasons for treatment and the current clinical and surgical

recommendations. Three papers of this issue focus on different aspects of nerve pain, and suggest promising directions for research on the mechanism of nerve regeneration and nerve guidance (e.g. investigation of genetics and biochemical signaling) and novel therapeutic approaches (e.g. neurostimulation).

We also reviewed modern advances in surgical techniques for complex nerve injuries, such as vascularized nerve grafts, which are indicated for long nerve gaps and scarred beds, and nerve transfers, which are indicated for proximal nerve injuries.

Free vascularized nerve grafts were first described in the 1970s. After initial enthusiasm, their popularity decreased partly due to their technical difficulty, and only few surgeons used the technique. Yet, they perform better than nonvascularized nerve grafts and provide advantage in recovery in selected cases. Their potential could find a greater expression in the next future, as discussed in a review article.

Nerve transfers have opened new horizons in nerve repair strategies: first described in the 19th century, they have revolutionized the 21st century approach to nerve injuries, particularly proximal injuries. They are a valuable tool for otherwise unrepairable nerve lesions candidates to palliative treatment (e.g. tendon transfer) and are finding increasing indications for repair of both motor and sensory nerves. Current indications in the upper limb nerve injuries are reviewed. Also, two of the papers in this issue are focused on “sensory protection” and “babysitting procedures”: local nerves can be redirected to a distal target to prevent the muscle atrophy and the functional loss that follows prolonged denervation.

To complete the tableau of future prospects in nerve regeneration, two papers of this special issue are focused on two novel fields of research: tissue-engineered conduits and robotic-assisted microsurgery.

Ongoing research holds the potential of revolutionizing our approach to nerve repair and regeneration. Tissue-engineering investigates the potential of different biomimetic materials as peripheral nerve scaffold, and

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.160876

modifies and directs interactions between cells, growth factors and signaling molecules, and biomaterials, to guide nerve regeneration. Robotic-assisted microsurgery represents a great technological advance, which can be further developed for specific applications in peripheral nerve surgery. It allows a minimally invasive approach, reducing morbidity and perineural adhesences and favoring a better nerve regeneration.

Lastly, we looked at composite tissue allotransplantation, where nerve regeneration holds specific features, as the host interaction with allogenic tissues and the need for immunosuppression; the last paper of this issue discusses the role of cortical reorganization, drugs (such as tacrolimus) and adipose-derived stem cells for axonal regeneration and myelination.

I hope that the papers presented in this special issue will serve as a reference and inspiration for students, researchers, and clinicians who have interest in nerve surgery.

Thanks to all the authors and the reviewers for their contributions and to the editorial staff of *PAR*, for working on this special issue and for their precious and continuous support.

I hope you enjoy reading this special issue.

How to cite this article: Toia F. Preface to special issue on "Peripheral Nerve Repair and Regeneration". *Plast Aesthet Res* 2015;2:147-8.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 07-04-2015; **Accepted:** 20-05-2015

Clinical neurophysiology and imaging of nerve injuries: preoperative diagnostic work-up and postoperative monitoring

Andrea Gagliardo¹, Francesca Toia², Francesco Maggi², Alessio Vincenzo Mariolo², Michele Cillino², Francesco Moschella²

¹"Clinical Course" Neurophysiology Unit, NHS Accredited, 90146 Palermo, Italy.

²Plastic and Reconstructive Surgery, Department of Surgical, Oncological and Oral Sciences, University of Palermo, 90127 Palermo, Italy.

Address for correspondence: Dr. Francesca Toia, Plastic and Reconstructive Surgery, Department of Surgical, Oncological and Oral Sciences, University of Palermo, 90127 Palermo, Italy. E-mail: francescatoia@gmail.com

ABSTRACT

Peripheral nerve injuries are a heterogeneous group of lesions that may occur secondary to various causes. Several different classifications have been used to describe the pathophysiological mechanisms leading to the clinical deficit, from simple and reversible compression-induced demyelination, to complete transection of nerve axons. Neurophysiological data localize, quantify, and qualify (demyelination *vs.* axonal loss) the clinical and subclinical deficits. High-resolution ultrasound can demonstrate the morphological extent of nerve damage, fascicular echotexture (epineurium *vs.* perineurium, focal alteration of the cross-section of the nerve, any neuromas, *etc.*), and the surrounding tissues. High field magnetic resonance imaging provides high contrast neurography by fat suppression sequences and shows structural connectivity through the use of diffusion-weighted sequences. The aim of this review is to provide clinical guidelines for the diagnosis of nerve injuries, and the rationale for instrumental evaluation in the preoperative and postoperative periods. While history and clinical approach guide neurophysiological examination, nerve conduction and electromyography studies provide functional information on conduction slowing and denervation to assist in monitoring the onset of re-innervation. High-resolution nerve imaging complements neurophysiological data and allows direct visualization of the nerve injury while providing insight into its cause and facilitating surgical treatment planning. Indications and limits of each instrumental examination are discussed.

Key words:

Electromyography, imaging, injury, magnetic resonance imaging, nerve conduction studies, neurodiagnostic, peripheral nerve, ultrasound

INTRODUCTION

Every year more than 5% of patients admitted to a level one trauma center have a concurrent traumatic peripheral nerve injury.^[1] These patients are often young

adults at the peak of their employment productivity, and therefore, functional decline associated with nerve lesions is particularly significant.^[2] Thus, there is a great interest in optimizing both the diagnostic accuracy and early treatment of peripheral nerve injuries.

The purpose of this review is to discuss peripheral nerve injuries and their diagnostic management and outcomes evaluation with regard to clinical findings and neurodiagnostic studies and imaging.

The goal is to provide a practical guide for general management that is, applicable to all types of nerve injuries. The main classifications and basic principles of a correct clinical approach will be summarized. Next,

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.160877

the indications and correct timing for each instrumental examination will be reviewed, with a specific focus on innovative methods and future prospects.

CLASSIFICATION OF PERIPHERAL NERVE INJURIES

The most commonly used classification for peripheral nerve injuries is that by Seddon,^[3] and Sunderland.^[4] The Seddon classification places injuries into three basic types: neurapraxia, axonotmesis, and neurotmesis.

Neurapraxia (praxis: to do, to perform): the nerve axons are intact but cannot transmit impulses. This occurs secondary to ischemic damage with temporary myelin sheath damage. Without myelin, there is an alteration of “saltatory conduction” across the nodes of Ranvier with subsequent slowed or blocked nerve conduction. Neurapraxia is the mildest form of nerve injury; “Saturday night” radial palsy and entrapment neuropathies like carpal tunnel syndrome is good example for this condition.^[5,6] Nerve recovery occurs after remyelination and sensory-motor functions can usually completely restored within days to weeks.^[7]

Axonotmesis (tmesis: to cut): the axons are damaged or destroyed, but most of the connective scaffold (endoneurium, perineurium, and epineurium) remains intact. Axonotmesis is commonly seen in crush and stretch injuries.^[8] After injury, anterograde Wallerian degeneration of the distal axonal fibers is completed within a few days.

Neurotmesis: the nerve trunk is disrupted and loses anatomical continuity. Neurotmesis represents the most severe form of injury with disruption of the axons, myelin sheath, and connective tissues. It may occur following sharp injuries, massive trauma, or severe traction that partially or completely interrupts nerve continuity.^[9] In order to enhance the chances for reinnervation after neurotmesis, surgical nerve repair is mandatory.^[10] Without surgery, uncontrolled axonal re-growth will generate a neuroma.

The Sunderland classification includes five stages and identifies three types of neurotmesis: (1) stage I

corresponds to neuropraxia; (2) stage II corresponds to axonotmesis; and (3) stages III, IV, and V correspond to neurotmesis [Table 1], with impairment of the endoneurium, perineurium, and epineurium.

The distinction between the different types of injury is not always precise. Clinical evaluation benefits from instrumental approaches to discriminate severity at an earlier stage, thus allowing for appropriate and timely treatment.

CLINICAL APPROACH

Patient age, mechanism of injury and associated vascular and soft tissue injuries strongly influence the extent of recovery of the injured nerve. These elements are of great importance and are the primary details collected in the clinical history. A detailed examination includes evaluation of pain and muscular strength and sensory testing in the territory of the injured nerve. The homologous contralateral and other ipsilateral preserved nerves are used for comparison, particularly in polytrauma patients.^[11] Appropriate motor and sensory evaluation is mandatory to identify injuries to sensitive, motor, and mixed nerves; early and late signs of autonomic disorders should also be evaluated, including vasomotor disorders and trophic alteration of the skin, nails, and subcutaneous tissue.^[11,12] Both negative (e.g. hypoesthesia, muscle weakness, and atrophy) and positive symptoms (e.g. dysesthesia, pain, fasciculations) due to loss of nerve function or inappropriate spontaneous activity, respectively, should be noted.

The simplest standardized clinical evaluation of a cutaneous somatic sensitivity is the test of the pain pathway (the patient’s ability to perceive the touch of a sharp object).^[13] Clinicians and surgeons generally refer to cutaneous nociception because of less lower overlap of innervating territories when compared to tactile sensation.

Hypoesthesia generally involves all superficial and deep somatosensory systems (tactile, thermal, pain, and proprioception); anatomical charts and diagrams help to

Table 1: Classification of peripheral nerve injuries according to Seddon and Sunderland

Type of injury Seddon classification	Type of Injury Sunderland classification	Major structure involved	Prognosis	Neurodiagnostic findings	Requirement for surgical intervention
Neurapraxia	I	Myelin	Good	Slower conduction velocity or conduction block; EMG with no fibrillation, reduced recruitment and fast firing	None
Axonotmesis	II	Myelin, Axons	Fair (depending on how many fibers are involved)	Reduced CMAP and SNAP amplitudes; EMG with fibrillation, reduced recruitment and fast firing	Depends on extension of the lesion
Neurotmesis	III, IV, V	Myelin, Axons, Endoneurium Perineurium Epineurium	Poor (depending on how many fibers are involved)	Reduced or absent CMAP and SNAP; EMG with fibrillation and motor units loss	Often requires surgical repair

EMG: Electromyography, CMAP: Compound muscle action potential, SNAP: Sensory nerve action potential

identify areas that correspond to specific nerves or to dermatomes (useful for root or spinal level injuries).

Sensory disorders may also include positive (irritative) symptoms which that should be explored: (1) paresthesia (spontaneous feeling of needles, tingling, numbness, and electric shock); (2) dysesthesia and hyperalgesia (inaccurate interpretation of a sensory stimulus which is perceived as different and with an affective unpleasant sensation); and (3) neuropathic pain (spontaneous pain consequent to a lesion in the afferent somatosensory fibers coming from the cutaneous territory of a nerve).

Motor signs and symptoms as a consequence of a reduced number of functional motor units include: (1) hyposthenia: reduced muscle strength as described by the use of the British Medical Research Council scale that recognizes five grades of muscle strength: 0, neither contraction nor movement are visible; 1, minimal contraction visible or flickering (residual functioning motor units) without movement; 2, active movement possible only without gravity (i.e. in a horizontal plane); 3, active movement obtained against gravity; 4, active movement against mild resistance (4-), moderate resistance (4) or strong resistance (4+); and 5, normal strength;^[14] (2) muscular hypotrophy or atrophy: reduced volume of the muscle belly for both axonal damage and disuse; it will reach its maximum state in 3-4 months with a potential strength reduction of 80%. If denervation persists, a proliferation of fibroblasts characterizes the histological picture, as new collagen is deposited in both the endo- and perimysium, and atrophied muscle fibers are replaced by thickened connective tissue; (3) absence or reduction of osteotendinous (phasic) reflexes and of muscular tone (tonic reflex) due to involvement of both afferent sensory fibers from muscular spindles and efferent motor neuron axons of the somatic arc reflex; (4) hyposthenia, hypotrophy, and hypotonia configure the picture of partial or total flaccid paralysis of the group of muscles innervated by the affected nervous structures (roots, plexus, nerves); (5) positive symptoms (fasciculations and cramps) are rare in peripheral nerve injuries, but are often seen in radiculopathies; and (6) deformities: in chronic and severe cases, muscle paresis reduced joint movement in conjunction with healthy muscles may lead to deformities (cavus foot, claw-hand) and ankylosis.

No clinical evaluation can distinguish neurapraxia from axonotmesis, and no clinical or neurophysiological examination can distinguish axonotmesis from neurotmesis. To obtain the correct diagnosis and a plan appropriate to treatment, both neurophysiological and imaging studies and clinical re-evaluation over time are often required.

CLINICAL NEUROPHYSIOLOGICAL STUDIES

The neurophysiological or neurodiagnostic study represents an extension of the clinical examination; accordingly, neurodiagnostic tests should always be combined with a

directed neurologic examination, in order to identify the clinical abnormalities and establish a differential diagnosis. For this reason, the evaluation is commonly referred as the clinical neurophysiological examination.

Clinical neurophysiological examination is currently the gold standard for diagnosis and determination of prognosis in peripheral nerve injuries,^[15,16] in order to localize and quantify clinical and subclinical preoperative damage and postoperative recovery. As such, it yields key information on the type of involved fibers (sensory vs. motor), on the underlying pathophysiology (demyelination vs. axonal loss), on axonal loss quantification, and consequently on prognosis.

The core neurodiagnostic studies are nerve conduction studies and electromyography (EMG). These tools test the integrity and physiological function of peripheral sensory and motor fibers and the muscles.

In order to reveal axonal loss (presence of denervation potentials), the optimal timing of a neurodiagnostic study is 2-3 weeks after injury.^[17,18] Neurodiagnostic studies should be repeated 3 months or more following trauma or surgical repair to assess the ratio of denervation to reinnervation.^[19]

Nerve conduction studies

Nerve conduction studies are the first line studies in instrumental evaluation of nerve injuries. They are the most basic and easily performed types of neurodiagnostic studies, and also used for screening prior to any additional testing.^[20]

Nerves and muscles are excitable structures and their potentials can be induced and recorded by external electrodes. When the nerve is stimulated, a compound muscle action potential (CMAP) can be recorded from the muscle, and a nerve action potential (NAP) can be recorded from the nerve. Amplitude and latency of the evoked response and conduction velocity are analyzed.^[21]

The amplitude of the evoked response estimates the quantity of depolarized motor or sensory fibers, while conduction velocity measures the speed of the fastest (and large caliber) motor or sensory myelinated axons.

Sensory NAPs (SNAPs) are also helpful in differentiating between preganglionic (radiculopathies) and postganglionic lesions; postganglionic lesions produce abnormal SNAP due to Wallerian degeneration of the axons distal to the peripheral injury, whereas in preganglionic lesions axon degeneration occurs in the dorsal root and in the ascending central pathway, leaving peripheral fibers intact and SNAP unmodified, despite anesthesia in the examined cutaneous territory.^[21]

Caution should be paid to interpretation of pure or prevalent motor diseases. Although changes in the CMAP are frequently used to preliminarily diagnose peripheral nerve injuries, they are not specific and may reveal, spinal disease of the anterior horn cells (myelopathy, amyotrophic lateral sclerosis, etc.), myopathy (muscular

dystrophy, myositis, *etc.*), a myelin-related acquired or congenital disorders (chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-tooth disease)^[22] or presynaptic neuromuscular junction disorders (Eaton-Lambert syndrome, botulism).

In neurapraxia, nerve conduction is either slowed or blocked secondary to demyelination. With stimulation proximal to the lesion, the conduction velocity will be reduced (conduction slowing), or the evoked potential amplitude will drop with respect to the normal potential obtained by distal stimulation (conduction block). When nerve remyelination completes, these abnormalities progressively disappear, with eventual complete recovery.

In the case of axonotmesis and neurotmesis, after distal axonal degeneration (which completes in 3-5 days for motor fibers and in 6-10 days for sensory fibers), CMAP and SNAP are reduced in amplitude when stimulating distally to the injury; the ratio between CMAP/SNAP amplitudes on the injured side to the CMAP/SNAP of the normal side is a good estimate of the degree of axonal loss. The higher the axonal loss, the lower the odds of recovery.

For technical reasons, exploration of the proximal peripheral nervous system is more complex; late responses such as F waves and the H reflex can be obtained for further information and somatosensory or motor evoked potentials can be explored.^[23,24]

Electromyography

This examination requires the active participation of the patient. Needle EMG provides information on the function of the muscles function and their minimal functional units. It explores both the quantity and quality of motor unit action potentials (MUAP), their spatial-temporal recruitment in order to generate adequate movements, the presence of denervation, and the onset of re-innervation.^[18] In partial or gradual denervation, reinnervation occurs early through collateral sprouting by adjacent surviving axons. In nerve transection, the only mechanism available for re-innervation is axonal regrowth from the proximal stump of the injury site. This regrowth is slow (1 mm/day) and may take months to years to reach the target muscles, depends on the distance to be covered.

The first step in EMG of nerve injuries is the evaluation of pathological potentials at rest. Fibrillation potentials and positive sharp waves are the most common potentials and appear 10-21 days after injury, while complex repetitive discharges indicate chronic and ongoing denervation. Although all these potentials are a sign of muscle fiber denervation, they can also be found in myopathies and myositis, which also induce hyposthenia. Fasciculation potentials occur from the spontaneous activation of motor units (all muscle fibers innervated by one neuron), which can be visualized directly as minor muscle twitches. Cramps are a painful involuntary contraction of the muscle which tend to occur when a muscle is in the shortened position and contracting, and can be recorded as a firing of motor unit potentials at high frequency.

Many other spontaneous potential can be recorded from muscles, but their discussion is beyond the intent of this review.

The following step in the neurophysiological examination is the analysis of MUAP and their activation and recruitment patterns during voluntary contraction.

In acute axonal loss and pure demyelinating nerve injuries with conduction block, not all motor units can be recruited; the remaining MUAPs have normal morphology but fire with high frequency in order to obtain sufficient contraction, and the recruitment pattern results in incomplete interference. Note that denervation potentials will appear only in case of axonal damage.

In chronic axonal loss and denervation, early collateral sprouting from re-innervation of orphan muscle fibers by surviving axons is recorded on EMG as small satellite potentials of the MUAP's. Later, as the number of muscle fibers per motor unit increases with re-innervation, MUAP's become higher in amplitude, prolonged in duration, and polyphasic; these are the typical neurogenic MUAP's representing the pattern of denervation and reinnervation.

Incomplete nerve transection and in late stages of partial axonal loss, if regrowing axons from the site of injury eventually reach the target, very small low-voltage nascent MUAP potentials will be recorded. As reinnervation occurs, denervation potentials will gradually disappear.

NERVE IMAGING TECHNIQUES

Neurophysiological investigation offers information on the pathophysiology of the nerve deficit, the grade of severity, and prognosis. Although it is a fundamental tool in clinical evaluation, it does not provide precise information on the morphology, etiology or the extent of focal peripheral nerve injuries versus the focal involvement of only few fascicles.

In severe cases with unexcitable nerves and in postoperative patients who do not shows signs of improvement, EMG and conduction velocities cannot provide conclusive information on the presence of neurotmesis, nerve transection, the distance between nerve stumps, and the presence of multiple sites of injury.^[25] Imaging assessment, in particular high-resolution ultrasound (HRU) and magnetic resonance imaging (MRI), may overcome these problems by providing information on nerve morphology and its surrounding tissues; these are becoming popular instruments for planning nerve reconstruction and the surgical approach.

High-resolution ultrasound

Although MRI is still more commonly used, based on our experience and on a review of the recent literature, the authors believe that HRU currently represents the most easily available and practical imaging technique for investigation of peripheral nerve pathology [Figures 1 and 2]. These machines are widely available and, when associated with high frequency transducers (7-18 MHz), reach up



Figure 1: Axial scan of median nerve (arrow) at mid forearm; note the fascicular texture of the nerve and the homogeneous echogenicity of the surrounding muscles

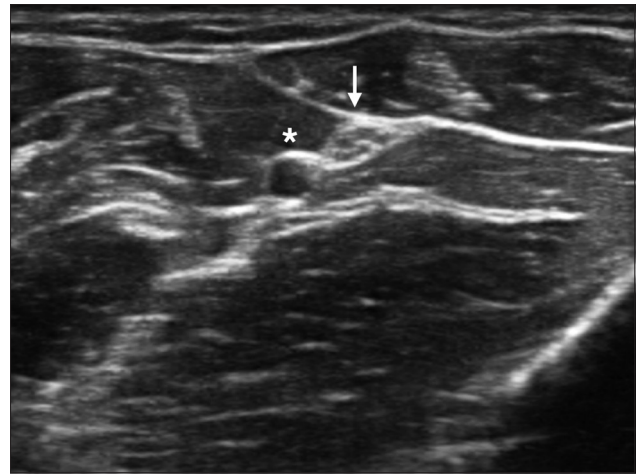


Figure 2: Axial scan of ulnar nerve (arrow) and ulnar artery (*) at forearm; in live scans pulsating arteries are a good landmark to be recognized

to 400 μm in axial resolution, which is higher than that achieved by a common MRI.^[26] There is increasing evidence in the literature on the helpfulness of HRU, in particular in cases with equivocal clinical and neurophysiological data;^[27] HRU may be diagnostic in a significant percentage of such patients.^[28] Its advantages include a bedside, painless study of the nerve along the entire limb, with color-Doppler analysis integration and dynamic scans. In addition, it can be utilized in the presence of metal implants and orthopedic screws, and therefore is preferable to a high-cost, single segment MRI study.

Sonographic criteria for nerve identification are based on fascicular echotexture detection.^[26] The cross-sectional area (CSA) of the nerve is one of the most studied parameters and is examined in each nerve along the length of the limb in an axial scan. CSA measurements are performed at the inner border of the thin hyperechoic rim of the nerve,^[29] across the site of entrapment or trauma to calculate the distal-proximal CSA ratio. The nerve CSA is significantly related to the neurodiagnostic data and, when performed side by side with a comprehensive neurodiagnostic exam, it increases its diagnostic sensitivity.^[30,31]

Echogenicity of the nerve should be reported; an increased CSA of the entire nerve or of a few fascicles, proximal to the site of entrapment or trauma, can be associated with fibrosis of the fascicles or epineurium. A few nerve pathologies, such as Schwannomas, will initially spare the nerve's conduction and sensory-motor functions, manifesting only with inconstant signs of irritation. Fiber sparing and dislocation can be recognized by an experienced HRU examiner.

Finally, nerve continuity can be assessed based on the analysis of the epi-perineurium and on the presence of a partial neuroma or transection.^[32]

Imaging will also uncover any predisposing anatomic abnormalities (i.e. bifid median nerve or persistent median artery) or other concurrent diseases in the surrounding tissues which may require a different therapeutic approach. Examples include space-occupying lesions, tumors, tenosynovitis, osteophytes, neurovascular

conflicts, abnormal muscles or muscle insertions, synovial cysts, nerve subluxation, postfracture fibrosis, and bone formation.

Neurophysiological and clinical parameters are good predictors of postsurgical recovery, but HRU has also demonstrated its usefulness when correlated with clinical neurophysiology in several nerve pathologies: (1) in patients with a history of trauma, it can reveal neuromas and neurotmesis; (2) in cases of postsurgical neuropathy of an iatrogenic origin, uncommon sites of injury can be localized; (3) in severe diseases with unequivocal nerve potentials on neurophysiological examination, the site of injury can be easily showed by ultrasound; (4) in patients with diffuse preexisting (and confounding) neurophysiological alterations and clinical signs of a new neuropathy, the nerve lesions can be delineated; (5) in entrapment neuropathies, for screening purposes (e.g. concomitant tenosynovitis is seen in 21.7% of carpal tunnel syndromes, and dynamic ulnar nerve subluxation is seen at the elbow in 28.5% of cubital grooves); (6) in all brachial plexus pathologies, to identify multiple sites of injury are common; (7) for early selection of surgical candidates;^[33,34] and (8) for detection of postsurgical improvement or complications.^[35]

HRU does have some limitations, high frequency probes provide optimal spatial resolution for superficial nerve imaging while the deeper nerve course may remain unexplored.^[36] The sciatic nerve trunk cannot be investigated over the horizontal gluteal fold, and the tibial and common peroneal nerves cannot be easily examined in the mid leg behind the calf. Both the deep nerve segments and nerve roots emerging from the spine should be explored by MRI. Expert HRU investigation can be used to visualize the cervical roots of the brachial plexus (the anterior branches of the spinal nerves as they emerge from the intervertebral foramen) as well as the trunks in the interscalene area and the cords in the supraclavicular and infraclavicular and axillary regions. A similar guide is helpful in interventional procedures to reach target nerves, such as in regional anesthesia or during steroid infiltrations, thus minimizing the risk of complications.

Ultrasound is already in use for a number of indications in the evaluation of nerves and is likely to find increasing indications in the future.^[37-39] However, further clinical and biomedical research is required to further validate its application in preoperative and postoperative monitoring.

Magnetic resonance imaging

MRI is appreciated mainly for its wide overview of the limb with the option of selective volume reconstruction. Direct nerve visualization by MRI has also been optimized;^[40,41] “MR neurography” combines fat suppression T2-weighted sequences and diffusion weighting in high magnetic field gradients (1.5T or higher). The nerve’s signal increases significantly following traumatic nerve injury, resulting in high contrast of the bright nerve (hyperintense) against the surrounding muscle or fat. The increased nerve signal due to axonal degeneration can be observed both at the site of the injury and distally, and is the single most searched MRI sign for localization of nerve injuries. However, it is not a specific sign, reflecting only endoneurial or perineural edema and slower axoplasmic transport secondary to axonal degeneration.

Diffusion-weighting imaging has the potential to detect structural anisotropy by determination of the main orientation of the axons within the nerves; this method is called diffusion tensor imaging (DTI). From DTI data, a three-dimensional reconstruction of major fascicles can be rendered and is referred to as “tractography”.^[42] Tractography provides structural information on the nerves, but has low spatial resolution and a low signal-to-noise ratio, adding no additional information to neurophysiological data.

Many techniques including MRI myelography, MR neurography, and DTI can be combined for additional data, for example in root avulsions in patients with brachial plexus injuries,^[43] but in order for the higher sequences to be carried out, greater acquisition times are required.

To overcome current limitations of MRI and enable investigation of nerves along a limb with faster image acquisition, widespread upgrade to 3T scanners combined with parallel imaging will be required.

Future application of new technologies for nerve imaging such as very high field magnetic fields (9.4T) MRI,^[44] or very high frequency ultrasound probes (55 MHz)^[45] will also increase spatial resolution up to a theoretical histological precision of 30 μm .

At this time, HRU provides the highest spatial resolution of direct nerve imaging along the limbs, while MRI provides a high contrast delineation of preselected single segments of the body. Both can assist in the resolution of pitfalls in injury localization, which may arise if only certain proximal nerve fascicles are injured, and others are spared, simulating a distal neuropathy.

CONCLUSION

Evaluation of peripheral nerve injuries remains a challenge for both clinicians and surgeons. A comprehensive clinical

and physical examination approach permits formulation of a differential diagnosis to guide the neurophysiological exam and estimate prognosis. Nerve imaging evaluation completes the work-up by visualizing fascicles and continuity of the nerve and its surrounding tissue.

Clinical and instrumental data should be integrated to plan adequate treatment and promote functional recovery. High-resolution nerve imaging, when correlated with neurophysiological data, provides the missing link to clinicians and surgeons, closing the gap between diagnostic and therapeutic approaches. To optimize prognosis, this comprehensive evaluation is mandatory not only during the preoperative stage, but also during follow-up in order to recognize late or non-recovery, thus preventing permanent neurological disability.

REFERENCES

1. Taylor CA, Braza D, Rice JB, Dillingham T. The incidence of peripheral nerve injury in extremity trauma. *Am J Phys Med Rehabil* 2008;87:381-5.
2. di Summa PG, Kalbermatten DF, Pralong E, Raffoul W, Kingham PJ, Terenghi G. Long-term *in vivo* regeneration of peripheral nerves through bioengineered nerve grafts. *Neuroscience* 2011;181:278-91.
3. Seddon HJ. A classification of nerve injuries. *Br Med J* 1942;2:237-9.
4. Sunderland S. The anatomy and physiology of nerve injury. *Muscle Nerve* 1990;13:771-84.
5. Gupta R, Rummel L, Steward O. Understanding the biology of compressive neuropathies. *Clin Orthop Relat Res* 2005;436:251-60.
6. Gupta R, Rowshan K, Chao T, Mozaffar T, Steward O. Chronic nerve compression induces local demyelination and remyelination in a rat model of carpal tunnel syndrome. *Exp Neurol* 2004;187:500-8.
7. Bernsen HJ, Koetsveld A, Frenken CW, van Norel GJ. Neuropraxia of the cervical spinal cord following cervical spinal cord trauma: a report of five patients. *Acta Neurol Belg* 2000;100:91-5.
8. Lee SK, Wolfe SW. Peripheral nerve injury and repair. *J Am Acad Orthop Surg* 2000;8:243-52.
9. Menorca RM, Fussell TS, Elfar JC. Nerve physiology: mechanisms of injury and recovery. *Hand Clin* 2013;29:317-30.
10. Koeppen AH. Wallerian degeneration: history and clinical significance. *J Neurol Sci* 2004;220:115-7.
11. Kleggetveit IP, Jørum E. Large and small fiber dysfunction in peripheral nerve injuries with or without spontaneous pain. *J Pain* 2010;11:1305-10.
12. Intiso D, Grimaldi G, Russo M, Maruzzi G, Basciani M, Fiore P, Zarrelli M, Di Rienzo F. Functional outcome and health status of injured patients with peripheral nerve lesions. *Injury* 2010;41:540-3.
13. Pinelli P, Poloni M. Neurology. Principles of Diagnosis and Therapy. 3rd ed. Rozzano: Casa Editrice Ambrosiana; 2003. p. 75-87.
14. Medical Research Council of the UK. Aids to the investigation of peripheral nerve injuries. Memorandum No. 45. London: Pendragon House; 1976. p. 6-7.
15. Aminoff MJ. Electrophysiologic testing for the diagnosis of peripheral nerve injuries. *Anesthesiology* 2004;100:1298-303.
16. Robinson LR. Traumatic injury to peripheral nerves. *Muscle Nerve* 2000;23:863-73.
17. Bergquist ER, Hammert WC. Timing and appropriate use of electrodiagnostic studies. *Hand Clin* 2013;29:363-70.
18. Kane NM, Oware A. Nerve conduction and electromyography studies. *J Neurol* 2012;259:1502-8.
19. Campbell VWW. Evaluation and management of peripheral nerve injury. *Clin Neurophysiol* 2008;119:1951-65.
20. Gutmann L, Pawar GV. An approach to electrodiagnosis of peripheral neuropathies. *Semin Neurol* 2005;25:160-7.
21. Fisher MA. Electrophysiology of radiculopathies. *Clin Neurophysiol* 2002;113:317-35.
22. Perry JD. Electrodiagnosis in musculo-skeletal disease. *Best Pract Res Clin Rheumatol* 2005;19:453-66.
23. Restuccia D, Valeriani M, Di Lazzaro V, Tonali P, Manguière F. Somatosensory evoked potentials after multisegmental upper limb stimulation in diagnosis of cervical spondylotic myelopathy. *J Neurol Neurosurg Psychiatry* 1994;57:301-8.

24. Le Pera D, Valeriani M, Tonali P, Restuccia D. Selective abnormality of the N13 spinal SEP to dermatomal stimulation in patients with cervical monoradiculopathy. *Neurophysiol Clin* 1998;28:221-9.
25. Gagliardo A, Avarino C, Giaimi G, Di Matteo D, Midiri M, Gagliardo C. Emerging Role of Ultrasound Imaging Associated to Clinical Neurophysiology as an Advanced Diagnostics of Peripheral Nerves Pathologies. A Sicilian Experience. *Neuroradiology*, 37th European Society of Neuroradiology Annual Meeting; 2013 September 28, October 1; Frankfurt, Germany. Berlin: Springer; 2013. p. S114.
26. Koenig RW, Schmidt TE, Heinen CP, Wirtz CR, Kretschmer T, Antoniadis G, Pedro MT. Intraoperative high-resolution ultrasound: a new technique in the management of peripheral nerve disorders. *J Neurosurg* 2011;114:514-21.
27. Beekman R, Visser LH. Sonography in the diagnosis of carpal tunnel syndrome: a critical review of the literature. *Muscle Nerve* 2003;27:26-33.
28. Padua L, Aprile I, Pazzaglia C, Frasca G, Caliendo P, Tonali P, Martinoli C. Contribution of ultrasound in a neurophysiological lab in diagnosing nerve impairment: a one-year systematic assessment. *Clin Neurophysiol* 2007;118:1410-6.
29. Cartwright MS, Passmore LV, Yoon JS, Brown ME, Caress JB, Walker FO. Cross-sectional area reference values for nerve ultrasonography. *Muscle Nerve* 2008;37:566-71.
30. Klauser AS, Halpern EJ, De Zordo T, Feuchtner GM, Arora R, Gruber J, Martinoli C, Löscher WN. Carpal tunnel syndrome assessment with US: value of additional cross-sectional area measurements of the median nerve in patients versus healthy volunteers. *Radiology* 2009;250:171-7.
31. Bayrak AO, Bayrak IK, Turker H, Elmali M, Nural MS. Ultrasonography in patients with ulnar neuropathy at the elbow: comparison of cross-sectional area and swelling ratio with electrophysiological severity. *Muscle Nerve* 2010;41:661-6.
32. Huang Y, Zhu J, Liu F. Ultrasound in diagnosis of retroperitoneal femoral nerve injury: a case report. *J Plast Reconstr Aesthet Surg* 2013;66:e50-2.
33. Gagliardo A, Avarino C, Giaimi G, Di Matteo D, Midiri M, Gagliardo C. Ultrasound combined with clinical neurophysiology in peripheral nerve pathologies: when it is worth? Preliminary data in 50 outpatients. *Clin Neurophysiol* 2013;124:e189.
34. Gagliardo A, Coraci D, Romano M, Fernandez Marquez EM, Tsukamoto H, de Franco P, Padua L. Clinical, neurophysiological and ultrasound assessment in post-surgical follow up of nerve injuries. A case report. *Clin Neurophysiol* 2013;124:e222.
35. Zhu J, Liu F, Li D, Shao J, Hu B. Preliminary study of the types of traumatic peripheral nerve injuries by ultrasound. *Eur Radiol* 2011;21:1097-101.
36. Torres C, Mailley K, Del Carpio O'Donovan R. MRI of the brachial plexus: modified imaging technique leading to a better characterization of its anatomy and pathology. *Neuroradiol J* 2013;26:699-719.
37. Wang Y, Zhao C, Passe SM, Filius A, Thoreson AR, An KN, Amadio PC. Transverse ultrasound assessment of median nerve deformation and displacement in the human carpal tunnel during wrist movements. *Ultrasound Med Biol* 2014;40:53-61.
38. Klauser AS, Tagliafico A, Allen GM, Boutry N, Campbell R, Court-Payen M, Grainger A, Guerini H, McNally E, O'Connor PJ, Ostlere S, Petroons P, Reijnierse M, Sconfienza LM, Silvestri E, Wilson DJ, Martinoli C. Clinical indications for musculoskeletal ultrasound: a Delphi-based consensus paper of the European Society of Musculoskeletal Radiology. *Eur Radiol* 2012;22:1140-8.
39. Kerasnoudis A. Which ultrasound method has the upper hand in the follow-up of the patients with recurrent carpal tunnel syndrome? *Ann Rheum Dis* 2013;72:e11.
40. Filler AG, Howe FA, Hayes CE, Kliot M, Winn HR, Bell BA, Griffiths JR, Tsuruda JS. Magnetic resonance neurography. *Lancet* 1993;341:659-61.
41. Howe FA, Filler AG, Bell BA, Griffiths JR. Magnetic resonance neurography. *Magn Reson Med* 1992;28:328-38.
42. Hiltunen J, Suortti T, Arvela S, Seppä M, Joensuu R, Hari R. Diffusion tensor imaging and tractography of distal peripheral nerves at 3 T. *Clin Neurophysiol* 2005;116:2315-23.
43. Gasparotti R, Lodoli G, Meoded A, Carletti F, Garozzo D, Ferraresi S. Feasibility of diffusion tensor tractography of brachial plexus injuries at 1.5 T. *Invest Radiol* 2013;48:104-12.
44. Bilgen M, Heddings A, Al-Hafez B, Hasan W, McIlff T, Toby B, Nudo R, Brooks WM. Microneurography of human median nerve. *J Magn Reson Imaging* 2005;21:826-30.
45. Kuffler DP. Ultrasound imaging of regenerating rat sciatic nerves *in situ*. *J Neurosci Methods* 2010;188:276-9.

How to cite this article: Gagliardo A, Toia F, Maggi F, Mariolo AV, Cillino M, Moschella F. Clinical neurophysiology and imaging of nerve injuries: preoperative diagnostic work-up and postoperative monitoring. *Plast Aesthet Res* 2015;2:149-55.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 10-04-2015; **Accepted:** 11-06-2015

Painful scar neuropathy: principles of diagnosis and treatment

Pierluigi Tos¹, Alessandro Crosio¹, Pierfrancesco Pugliese¹, Roberto Adani²,
Francesca Toia³, Stefano Artiaco¹

¹Department of Orthopedics, Reconstructive Microsurgery Unit, City of Health and Sciences of Turin, Trauma Hospital, 10100 Torino, Italy.

²Department of Hand Surgery and Microsurgery, University Hospital of Verona, 37126 Verona, Italy.

³Plastic and Reconstructive Surgery, Department of Surgical, Oncological and Oral Sciences, University of Palermo, 90127 Palermo, Italy.

Address for correspondence: Dr. Pierluigi Tos, Department of Orthopedics, Reconstructive Microsurgery Unit, City of Health and Sciences of Turin, Trauma Hospital, 10100 Torino, Italy. E-mail: pierluigi.tos@unito.it

ABSTRACT

Nerve-tissue interactions are critical. Peripheral nerve injuries may involve intraneural and extraneural scar formation and affect nerve gliding planes, sometimes leading to complex clinical presentations. All of these pathological entities involve pain as the main clinical symptom and can be subsumed under the term “painful scar neuropathy”. The authors review the literature on treatment approaches to peripheral nerve scar neuropathy and the outcomes of neurolysis-associated procedures and propose a simple classification and a therapeutic approach to scar neuropathy. The search retrieved twenty-one papers, twenty of which reported pain reduction or resolution with various techniques. There is no consensus on the best therapeutic approach to neuropathic pain due to scar tethering. Most authors report good or excellent results with different techniques, from nerve wrapping with anti-adhesion devices to nerve coverage or wrapping with vascularized tissue. The authors’ classification of and therapeutic approach to peripheral nerve scar lesions aims at promoting a logical approach based on the analysis of lesion type (perineural, or endoneural and perineural), pain type (due to traction or external trauma, pain at rest), and number of previous operations. Patients need to be informed that multiple procedures may be required, that outcomes may be partial, and that surgery can potentially worsen preoperative conditions. The review found no evidence for the best therapeutic approach to scar neuropathy, but there is consensus on a multidisciplinary approach.

Key words:

Complex regional pain syndrome type II, painful neuropathy, painful scar neuropathy, scar neuritis, traction neuropathy

INTRODUCTION

Peripheral nerves have the ability to adapt to different positions during limb and joint movements. Such flexibility is enabled by a gliding apparatus around the

nerve that provides for elongation during movement. Small nutritional vessels entering the epineurium from surrounding muscles are among the principal connections between nerves and soft tissue.

A peripheral nerve subjected to elongation stress can extend a few millimeters compared to its length at rest. Elongation is enabled by a conjunctiva-like structure^[1] constituting the outermost layer of the nerve trunk that Millesi *et al.*^[2] designated paraneurium. The inner nerve structure can also undergo elongation, and gliding planes have been detected between deep epineurium and perineurium^[3] as well as between individual fascicles. Joint excursion, therefore, involves complete epineurial and intraneural movement, where nerve elongation

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.160878

compensates for the tension generated by movement and requires an intact gliding surface between the nerve and its surrounding tissue.

Clearly, the movement also stretches perineural and intraneural vascular structures, inducing vessel strain and reducing blood flow. A healthy gliding system prevents excessive stress from being exerted on vessel walls and ensures a sufficient blood supply to axons and Schwann cells. Preclinical studies have demonstrated that an 8% increase in nerve tension induces a 50% reduction in intraneural blood flow, whereas tension exceeding 15% of the baseline value induces an 80% reduction.^[4] In a study of rat sciatic nerves subjected to crush lesions, Boyd *et al.*^[5] documented nerve tension exceeding the intraneural microvessel compression threshold due to physiological movements, and found that it resulted in perineural scar formation and reduced intraneural vascularization.

Similarly, in the clinical settings formation of a perineural scar for any reason increases the tension on the nerve and may lead to prolonged ischemia. Wilgis and Murphy^[6] described an association between reduced longitudinal gliding of the peripheral nerve and symptom recurrence following surgical decompression. In 1979, McLellan and Swash^[7] reported that impaired linear gliding can induce a nerve lesion at a distance from the compression area, thus introducing the notion of traction neuropathy. The term indicates a condition related to impaired nerve gliding, whereas in Hunter 1991 description,^[8] it designates neurological symptoms due predominantly to the movement of the affected nerve. However, traction neuropathy may be too narrow a definition, given that some patients with extensive perineural fibrotic reactions experience constant pain both at rest and in the absence of movement. The condition is likely due to a fibrotic response that is, initially perineural and eventually becomes intraneural due to compression secondary to chronic scarring. Perineural fibrosis can induce ischemic stress in the involved fascicles, followed by degeneration of distressed axons, the repair process may subsequently lead to formation of an in-continuity neuroma with residual nerve function whose symptoms also involve pain at rest.^[9] Pain at rest may also be related to a perineural scar associated with intraneural scarring due to a traumatic Grade III or IV injury or to a Grade V lesion (nerve transection) according to Sunderland's classification.^[10] A painful neuroma at the suture site has been described in nearly 5% of repaired nerves.^[11] We, therefore, agree with Elliot^[9] that "traction neuropathy" is a somewhat limited definition, whereas "scarring neuritis" or "scar neuropathy" encompass all the conditions related to formation of perineural and intraneural fibrotic tissue involving neurological symptoms and induced by a nerve injury (intraoperative lesion, cut injury, stretching, or extrinsic compression due to fracture or hematoma).^[12]

Based on our experience and the pathophysiology of nerve injuries, both fibrosis around a nerve (traction neuropathy) and inside/outside it (as in neuroma-in-continuity) can be classified as scarring neuritis/scar neuropathy, whose distinctive symptom is pain due to the pathological condition affecting the nerve.

End-neuromas, which are associated with similar symptoms, and neuromas-in-continuity without residual function, are not addressed in the present review, because their management is fairly well established: the former may benefit from relocation to deep, protected areas, whereas for the latter the initial treatment of choice is reconstruction with nerve grafts or conduits.

This review describes and discusses the main diagnostic and therapeutic approaches to neuropathic pain due to neuroma-in-continuity and peripheral nerve compression in scar tissue based on the literature and the authors' personal experience. The condition is complex and difficult to treat, and there is no consensus on the most appropriate surgical approach.

Different surgical procedures and products that limit scar formation and reduce pain are also reviewed, and a treatment algorithm based on the type of pain, lesion type, number of previous operations, and imaging data is proposed. Finally a review of the literature for treatment outcomes, with emphasis on the resolution of pain symptoms, is presented.

EPIDEMIOLOGY

Perineural scarring and consequently traction neuropathy have traditionally been considered to be complications of nerve decompression surgery. Nerve tethering in the surgical scar is still the main cause of symptoms related to perineural scarring. For instance, 7-20% of patients subjected to primary median nerve release report pain and symptom recurrence.^[13] The condition is difficult to manage, so much so that according to different reports compression symptoms persist after 40-90% of revision procedures,^[14] and 20% of patients actually require a third operation.^[14] Clinical failure rates of 25% have been reported after ulnar nerve release at the cubital tunnel,^[15] and a review of 50 studies found symptom recurrence in approximately 75% of treated patients.^[16] As noted above, 5% of nerve sutures have been estimated to induce a pain syndrome.^[11]

However, the problem is not confined to peripheral nerves. Indeed, one of the most common complications of microdiscectomy and laminectomy, found in 15-20% of patients, is failed back syndrome, which seems to be related to the formation of scars entrapping the released nerve roots.^[17] These patients often undergo additional procedures for the new symptoms.

Besides compression syndrome recurrence, neurogenic pain may be related to the formation of a neuroma-in-continuity associated with a partial lesion or severance of the peripheral nerve. This condition is found in 60-70% of traumatic injuries involving a peripheral nerve.^[18]

CLASSIFICATION OF SCARRING NEURITIS

Millesi *et al.*^[19] have extensively investigated peripheral nerve gliding and devoted considerable effort to describing

the role of the nerve-muscle tissue interface in normal nerve function.

Millesi *et al.*^[19] vast surgical experience with peripheral neurolysis led to the publication of a seminal paper describing a new anatomic-surgical classification of perineural and intraneural scar lesions. The classification is a useful approach to perineural and intraneural scar injury because it couples each subgroup of fibrotic lesions to specific types of surgical neurolysis based on scar severity. However, although intraneural lesions are described in excessive detail, the clinical outcomes do not seem to correlate with preoperative pain measurement.

Here we describe a simplification of Millesi *et al.*^[19] original classification and propose an approach that, by correlating the pathological findings to clinical and imaging data, has the potential to improve surgical treatment. The revised classification encompasses two injury types, extraneural and intraneural/extraneural scar lesions, based on the perineural tissue changes that impair nerve gliding and the intraneural problems that give rise to pain and hypersensitivity. Type I injuries are related to compression due to causes such as prior surgery, hematoma, and bone fragments, with involvement of the gliding surface (conjunctiva-nervorum) and formation of extensive scar tissue around the nerve, as depicted in Figure 1. These lesions are generally amenable to simple external neurolysis, with additional surgical procedures as required to avoid recurrence of perineural fibrosis (i.e. restoration of the gliding plane by anti-adhesion gel, vein conduit or other wrapping material). Pain is often related to joint movement and is less frequent at rest. On ultrasound (US) examination, the nerve has a normal fascicle structure. Type II injuries affect the entire nerve structure, from the epineurium to the endoneurium, and are usually secondary to significant nerve trauma such as a partial lesion or a transection of the nerve trunk treated by neurorrhaphy (neuroma-in-continuity). These injuries require procedures that may involve nerve fascicles and the epineurium, from epineurectomy and epineurotomy up to partial resection and grafting as described by Millesi *et al.*^[19] In type II lesions additional surgical procedures are directed not only at avoiding recurrence of perineural fibrosis, but also at protecting the nerve

against external mechanical insults. Outcomes are less predictable than in type I lesions. Pain at rest is common and is exacerbated by external trauma. US examination provides useful information on the intraneural pathology.

Type II lesions, with the exception of partial lesions due to a laceration or the sequelae of a nerve suture, correspond to Sunderland's third-degree lesions, which from the pathological standpoint include painful neuroma-in-continuity with residual function, one of the most challenging therapeutic problems. Fourth- and fifth-degree lesions are outside the scope of this review, as they lack residual nerve function and are managed by resection and reconstruction.

CLINICAL SYMPTOMS AND SIGNS

Patients typically report pain of four types, as described by Elliot^[9]: spontaneous pain, pressure pain, movement pain, and hypersensitivity or unpleasant skin sensation to light touch, including hyperesthesia, hyperpathia, and allodynia.

The causal association is most obvious for pressure pain and movement pain elicited by the motion of adjacent tendons and joints. At present, hypersensitivity usually involves the skin overlying the affected nerve portion. The most poorly understood and unpleasant of these pain types is spontaneous pain, which is found in the majority of patients; it is most often a continuous or basal pain with spikes of increased intensity, or spiking pain that is often severe, has a variable frequency, and may be associated with reflex motor activity, example, jerking of the entire upper limb.^[9]

These symptoms, presenting singly or combined, are compounded by complex regional pain syndrome type II (CRPS II) or causalgia,^[20,21] due to fiber disorganization within the neuroma-in-continuity. Typical CRPS II features are onset after a nerve injury and continuous pain or allodynia-hyperalgesia that is usually, but not invariably confined to the territory of the injured nerve. Edema, skin blood flow abnormalities, or abnormal sudomotor activity may be detected in the area affected by pain since the time of injury. Timely management appears to be critical.^[22]

DIAGNOSIS

History is crucial to establish the cause of symptoms, be it related to simple nerve decompression, reconstruction, direct trauma, or posttraumatic scarring.

Physical examination and pain type, at rest or elicited by movement or mechanical stimuli, may provide information on the lesion type. Pain at rest commonly entails that the scar involves the deep nerve structure. Perineural scarring usually induces nerve tethering, which is exacerbated by movement, that is, a loss of peripheral nerve gliding. Tinel's sign is invariably positive, and the patient often has hyperalgesia and/or allodynia in the territory of the involved nerve.^[9,23]



Figure 1: Median nerve entrapped in scar tissue

As regards diagnostic imaging, US provides reliable information on the actual extent of the nerve injury (due for instance to a previous procedure), the amount of scarring, and the state of the outer and inner connective tissue layers of the nerve trunk. It thus provides an indication for surgery by demonstrating, before the operation, the various degrees of scarring described by Millesi *et al.*^[19]

Moreover, according to a paper of the European Society of Musculoskeletal Radiology, musculoskeletal US seems to be the imaging technique of choice for peripheral nerve structure evaluation.^[24]

Most studies use US to investigate the intraneural structures and changes due to chronic compression or trauma.^[25] In these patients, US has proven to be even more effective than electrophysiological tests in depicting intraneural distress.^[25] Some studies compare US findings, including signs of edema, loss of echogenicity, and fascicular echostructure before and after tunnel syndrome surgery.^[26]

Padua *et al.*^[27] group has advanced an interesting proposal that agrees with our classification of scar lesions, highlighting that valuable US features include depiction of very small nerves and dynamic imaging, which can document how the nerve interacts with surrounding tissue. Indeed, key diagnostic features of scarring neuropathy are an assessment of the nerve's relationships with surrounding tissue and depiction of any gliding impairment.

A critical advantage of US is that it affords direct visualization of the nerve injury, thus providing information on its cause and enabling treatment selection.^[27] We thus feel that US scanning of the nerve and surrounding tissue entails a dual benefit for both patient and surgeon: it identifies the site of the nerve injury and depicts its relationships with scar tissue, documenting any obstacles to gliding. Combining anatomic-sonographic findings, electromyography data, and clinical information can help the surgeon select the most appropriate treatment approach.

Magnetic resonance imaging (MRI) enhances diagnosis and surgical planning; conventional MRI may depict indirect signs of nerve damage such as edema whereas high-resolution MRI provides direct visualization of injured and scar-tethered nerves, including the smaller peripheral branches.^[28,29]

In experienced hands, MRI and US can provide crucial information in preoperative planning of revision nerve release surgery by documenting residual or recurrent pathology or the sequelae of previous surgery.

Electromyography examination is also important because it documents the degree of peripheral nerve distress, and findings can be compared over time (preoperative, postoperative, follow-up examination).

However, it is still unclear why similar pathological conditions induce pain in some patients but are painless

in others, including patients with incontinuity neuromas and end-neuromas.

SURGICAL OPTIONS

Surgical exploration, neurolysis under magnification, and procedures aimed at preventing new scar formation such as flap coverage and application of anti-adhesion devices must be preceded by appropriate medical treatment and pharmacological and physical therapy with dedicated operators for at least six months. Although there is no consensus on surgery timing,^[30] surgery is generally indicated when medical and physical therapy have failed to bring benefit.

Some authors have achieved pain reduction in a large number of patients using pulsed radiofrequency before surgery or following a recurrence.^[31]

Surgical treatment of these conditions begins with neurolysis. External neurolysis is performed in cases with external compression, to free the nerve from the extrinsic compression. This may involve either accessing only the epineurium (epineurotomy) or removing part or all of it (partial or total epineurectomy) as shown in Figure 2a. Only in very selected cases is internal neurolysis performed, to treat an intraoperative iatrogenic injury or postoperative scar recurrence between fascicles. The procedure begins with identification of the normal proximal and distal nerve portions; the nerve is then mobilized above and below the injury site and its course toward the injury site is carefully dissected free of external scarring, points of tethering, or abnormalities.

The second step involves the relocation of the nerve tract involved by neurolysis to a "soft" vascularized bed enabling gliding.^[30] Other procedures use vascularized or nonvascularized autologous tissue or an anti-adhesion gel. However, anti-adhesion devices, flaps, or other autologous tissues are not unequivocally recommended.

Here we propose a management strategy of posttraumatic scar lesions based on two mainstays, including (1) lesion categorization into extraneural and intraneural as described above, and (2) clinical information in terms of pain symptoms.

A combination of history data and US findings, which document the intraneural injury in a very early phase, supplies critical work-up information and provides an indication for external neurolysis versus a more extensive

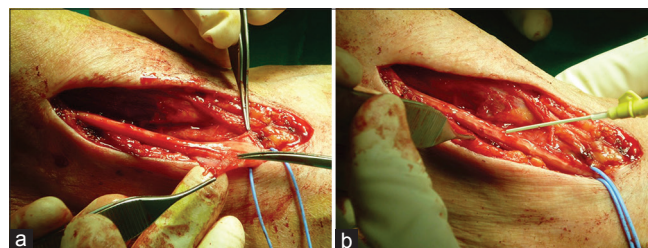


Figure 2: (a) External neurolysis and epineurectomy on median nerve at the elbow; (b) application of carboxy-methylcellulose/phosphatidylethanolamine gel on median nerve after neurolysis

neurolysis involving the epineurium and if necessary the perineurium.

Another key factor is the number of previous operations, simple external neurolysis is indicated after the first recurrence while a vascularized flap with a more extensive neurolysis is indicated following multiple failed surgical treatments.

Type I injuries, where scar tissue hampers gliding, should be managed by external neurolysis if the intraneural echostructure is normal, anti-adhesion gel, vein-wrapping, or thin flap coverage may be sufficient.

In type II lesions (neuromas-in-continuity), where US depicts a lack of structural homogeneity inside the nerve, more extensive neurolysis may be required, with epineurectomy and rarely, internal neurolysis under magnification. These patients also require deep nerve transposition, coverage with thick vascularized flaps, and restoration of a suitable gliding bed.

Patients with continuous pain due to an earlier traumatic injury to superficial nerves triggered by external stimuli, and those undergoing revision of a failed prior revision procedure, require deep nerve transposition and coverage with thick vascularized flaps providing both biological and mass effects.^[32]

Relevant clinical data, including pain type (due to external compression, continuous, or movement-related) and cause of the lesion, can indicate the most appropriate management strategy. Patients with pain due to direct trauma may benefit from the bulk effect of a flap or from nerve relocation to a deep, protected area, whereas simple neurolysis with application of anti-adhesion devices is preferable in simple traction neuropathy, where pain is more often secondary to external traction.

Early active movement after surgery is indicated to prevent adhesion recurrence.

The next section describes the main techniques used in the treatment of scarring neuropathy and painful neuroma-in-continuity with residual nerve function after neurolysis.

SURGICAL MANAGEMENT AFTER NEUROLYSIS

Commercial gels and anti-adhesion devices

These devices are used to restore the lost gliding surface. Since 1970, when intraperitoneal anti-adhesion devices were first introduced, a number of products characterized by different shapes and chemical compositions have been developed to limit perineural scar formation. Gels developed specifically for peripheral nerve-tissue began to be produced in 2000. Early anti-adhesion gels were based on collagen-dextran (ADCON-T/N) and were initially used in spinal surgery. Preclinical application to rat peripheral nerve achieved a satisfactory reduction of perineural scarring. These gels were, however, abandoned after reports of wound dehiscence and dural fistula formation.^[33]

Products based on hyaluronic acid (HA) have proved to be more effective. Initial preclinical studies have documented their anti-adhesion properties and safety.^[34] HA is marketed alone as Hyaloglide^(R)^[35] or associated to carboxy-methylcellulose (CMC, Seprafilm^(R)).^[36]

However, there is no consensus on the actual effect of anti-adhesion devices. According to some researchers they reduce collagen deposition by interfering with granulocyte diapedesis and blocking the synthesis of interleukin-1, which is crucial for fibroblast activation,^[37] whereas others deny an effect on cytokines and admit only to a physical barrier action.^[38]

CMC has subsequently been associated with other molecules, including phosphatidylethanolamine a nonionic molecule whose tensioactive properties provide tissue lubrication and a mechanical barrier to restore gliding.^[39] CMC-PE has also been shown to reduce perineural adhesions; it is already available on the market and has proven to be highly effective in preventing the formation of abdominal, spinal and tendon adhesions.^[40]

In 2005, another macromolecule, polyethylene glycol oxyde (PEO), was associated with CMC to enhance its anti-adhesion effect. Preclinical studies have documented its ability to reduce protein, hence collagen, deposition on tissue.^[40,41] However, there is no conclusive evidence for its effectiveness in the peripheral nervous system. A single paper has demonstrated its safety and effectiveness in an animal model (Tos *et al.*, paper submitted). A representative image of gel application after neurolysis is shown in Figure 2b.

Collagen-based products have recently been developed for wrapping around injured nerves.^[42,43] These products are theorized to form a microenvironment within the compressed nerve, which keeps nerve growth factors within the epineurium to enhance nerve gliding, and which are subsequently slowly absorbed.

A recent study of a small sample with a short follow-up describes a novel nerve-wrapping technique for the upper extremities using a type I collagen conduit wrap. Its effectiveness is similar to that of other anti-adhesion devices, but it entails a lower fewer risk of complications compared to wrapping the nerve in autologous tissue such as vein (Neura Wrap; Integra LifeSciences, Plainsboro, NJ, USA).^[43]

There are therefore several different types of anti-adhesion devices, but scant information as to which is the most effective at the clinical and preclinical level, even though all seem to limit perineural scarring formation without any particular side effects. A major advantage is their fast application and less invasive surgical dissection, without the need for further procedures (and possible attendant injury), which considerably reduces operating time compared to the surgical approaches described above.^[34] Notably, there are no clinical trials comparing the effectiveness of the two approaches. A recent case review has advanced the proposal to apply anti-adhesion devices in cases where the nerve, released from the scar, appears

healthy or only moderately injured, and to use local or free flaps for clearly distressed nerves in the presence of a strong inflammatory reaction.^[44]

Vein conduits

Masaer *et al.*^[45] was the first to describe nerve-wrapping in an “opened” vein segment, which provided satisfactory results both in terms of sensitivity improvement and of reduction of recurrences.^[46] Elliot^[9] reported poor outcomes in neuromas-in-continuity of the palm and the fingers, describing pain recurrence at the site of treatment due especially to repeated trauma, because the thin vein wall does not adequately protect the nerve against external insults.

Some authors suggest covering sutures with a vein, as earlier for collagen-gel, to prevent end-neuroma formation at direct suture sites.^[47]

Flaps

A variety of flaps, pedicled (local) or free, are used for coverage after neurolysis: synovial, fascial, adipofascial, muscle and skin with subcutaneous tissue flaps.

Compared to vein wraps, gels, and other anti-adhesion devices, flaps have a dual function: to envelop the injured nerve in a highly vascularized tissue to maximize nutrient supply, and to provide a bulk effect, for example, protection against external mechanical insults. This approach is often used in patients in whom revision surgery has had poor outcomes or when the quality of local tissue does not allow a simpler procedure.

Typical local flaps raised in patients with recurrences or sequelae of carpal tunnel syndrome (CTS) include the hypothenar fat pad flap first described by Cramer^[48] and improved by Strickland, and the palmaris brevis flap described by Rose *et al.*^[49] Their main advantage is that they provide a buffer of highly vascularized adipofascial or muscle tissue above the treated nerve. The synovial flap from the flexor tendons described by Wulle is still a very good option for recalcitrant CTS.^[50]

Thicker flaps can be raised from the volar forearm: the dorsal ulnar artery adipofascial flap described by Becker and Gilbert^[51] can be used as an adipofascial flap to wrap the nerve [Figure 3a and b] or as a fasciocutaneous flap to provide greater protection, the adipofascial radial artery perforator flap^[32] and the adipofascial variant of the posterior interosseous flap raised from the dorsal portion of the forearm^[52] can be employed in the same way; and the pronator quadratus muscle flap^[53] may be a useful solution when the injury is proximal to the wrist.

Numerous free vascularized flaps, described for coverage of freed nerves, are however, rarely used. The free omental flap,^[54] lateral arm flap, scapular flap, and groin flap^[44] seem to be more effective than local flaps, yet the approach is recommended only for use in patients with severe conditions who have already been treated and in those with hand and forearm lesions where a local flap would impair hand use. Yamamoto *et al.*^[20] have gone further, and they raised an anterolateral vascularized thigh flap that included the lateral cutaneous nerve of the thigh

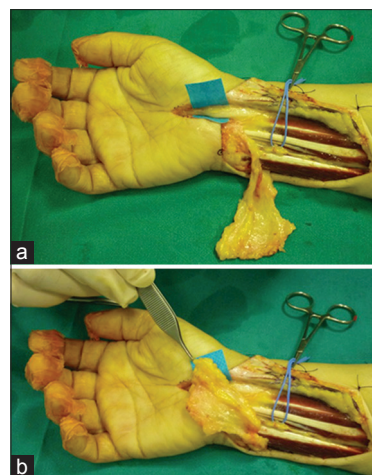


Figure 3: (a) Adipofascial dorsoulnar Becker flap covering and wrapping a median nerve; (b) the bulk effect of the flap protects the nerve from external trauma

to reconstruct the median nerve, and described early pain resolution and full recovery of wrist and hand mobility five months from the procedure. We recommend such complex procedures only in patients with severe nerve injury and failure of multiple surgical procedures, where another local flap could result in local tissue damage.

Pain neuromodulation

Multiple surgical failures may provide an indication for direct peripheral nerve stimulation, to relieve chronic pain through preferential activation of myelinated fibers, inducing long-term depression of synaptic efficacy.^[55,56]

Spinal cord stimulation, which is applied more often to treat CRPS I, may also be beneficial.^[57]

SCAR NEURITIS AND OUTCOMES: LITERATURE REVIEW

PubMed was reviewed for papers reporting treatment approaches and patient outcomes of scar neuritis and neuropathic pain, in particular studies of recurrent median and ulnar nerve compression, postsurgical fibrosis of lower and upper limb nerves, CRPS II, and application of HA acid and gels that also described pre- and post-operative pain assessment by the visual analogue scale (VAS) or numerical rating scale. Case reports and animal studies were excluded. Papers were sorted by the treatment approach to neurolysis.

Overall, 21 papers were retrieved; the majority described the treatment of median and ulnar nerve entrapment recurrence. The method most frequently associated with neurolysis was flap coverage (15 articles); the remaining papers described the use of anti-adhesion devices (3 articles) to reduce pain and prevent recurrences, and vein wraps (3 articles).

All approaches provided good outcomes, although most studies involved small samples, from 4 patients to 65 patients. All methods achieved a postoperative reduction of at least four VAS points. All but one study described complete or satisfactory pain reduction. These

data are summarized in Table 1. No alternative options are mentioned for patients reporting no improvement.

Despite published reports of highly satisfactory outcomes and success rates close to 100% with a range of techniques, clinical practice demonstrates that such conditions are difficult to treat and at times are only partially solved.

There is scant published evidence regarding the diagnostic work-up and treatment of scar neuropathy. Patients should be warned that their condition is not easy to address and that surgical treatment may have to be followed by a more aggressive approach if symptoms persist.

Patients with pain due to nerve entrapment in scar tissue require careful evaluation through history, assessment of pain type, and accurate US scanning, to establish the site of the scar tissue injury and whether the nerve contains internal damage. In patients for whom surgery will be straightforward local tissues provide a suitable bed, barrier devices may be applied first to attempt to treat the problem by a less invasive approach. Patients subjected to multiple procedures due to recurrences and those with a severely injured gliding bed require more extensive neurolysis and coverage with a local or free vascularized flap.

If symptoms are due exclusively to external trauma and the patient has pain at rest, wraps or thick adipofascial flaps are the treatment of choice to avoid external trauma and protect the nerve. If the lesion is external to the nerve and pain is due to scar tethering the prognosis is more favorable and the risk of recurrence lower, whereas pain due to intraneural injury is more difficult to treat because the outcome of internal neurolysis is unpredictable and may itself induce formation of even worse scarring.

Data on the timing of a recurrence varies widely, from twenty days to thirty days to months, the mechanism of recurrence is also unclear.

Helping patients with these conditions requires a multidisciplinary approach and close collaboration of the surgeon, pain clinician, physiotherapist, and psychologist, because for reasons that are still unclear the patient is often the very cause of the problem. The risk of persistent or even worsening pain symptoms should be clearly stated prior to surgery, as any intervention may induce symptom worsening in patients with complex pain syndromes.

If the pain is not alleviated following the initial procedure, subsequent operations are unlikely to be successful, and further attempts may involve diminishing returns.^[30,76]

Table 1: List of the 21 papers describing peripheral nerve neurolysis, associated procedures, and pain outcomes retrieved by the PubMed search, sorted by the technique used for neurolysis

Author	Surgical approach	Nerve	Pain alleviation. Number of patients and percentage (%) of pain reduction
Reisman and Dellon ^[58]	Abductor digiti minimi	Median	Pain reduction in 11/12 patients (91)
Strickland <i>et al.</i> ^[59]	Hypothenar fat pad flap	Median	Excellent results in alleviating recalcitrant idiopathic CTS (95 satisfaction in 62 patients)
Rose ^[60]	Palmaris brevis muscle flap	Median	Complete pain relief in all patients (13 hands) (100)
Jones ^[61]	Pedicled or free flaps	Median/ulnar	Pain reduction in 7/9 patients (78)
Giunta <i>et al.</i> ^[62]	Hypothenar fat pad flap	Median	Pain reduction in 8/9 patients (89)
Frank <i>et al.</i> ^[63]	Hypothenar fat pad flap	Median	Pain reduction in 8/9 patients (89)
Guillemot <i>et al.</i> ^[64]	Fat graft	Median	No pain reduction in 4 patients
Mathoulin <i>et al.</i> ^[65]	Hypothenar fat pad flap	Median	Pain resolution in 41/45 patients (98)
De Smet and Vandeputte ^[66]	Hypothenar/ulnar fat pad flap	Median	Pain reduction in 9/14 patients (64)
Dahlin <i>et al.</i> ^[67]	Pedicled ulnar, dorsal forearm flaps Free groin, scapular, lateral arm flaps	Median	Pain reduction in 10/14 patients (71)
Goitz and Steichen ^[54]	Free omental flaps	Median	Pain reduction in 7/11 patients (63)
Luchetti <i>et al.</i> ^[68]	Fascial and fasciocutaneous island flaps (hypothenar fat pad, forearm radial artery, forearm ulnar artery, ulnar fascial fat, and posterior interosseous)	Median	Four point VAS score reduction in 23/25 patients (92)
Craft <i>et al.</i> ^[69]	Hypothenar fat pad flap	Median	Pain resolution in 83% of 28 patients
Fusetti <i>et al.</i> ^[70]	Hypothenar fat pad flap	Median	Pain reduction in 18/20 patients (90)
Elliot <i>et al.</i> ^[71]	Vascularized forearm fascial flap	Median/ulnar	Pain resolution in 8/14 patients (57)
Soltani <i>et al.</i> ^[43]	Collagen: neurolysis + collagen wrap	Median/ulnar	Resolution/improvement in 4 patients (median) Resolution in 3/4 patients (cubital tunnel syndrome)
Espinoza <i>et al.</i> ^[72]	Microneurolysis alone versus ADCON/TN	Median/ulnar	Pain reduction in 80% of 54 patients
Atzei <i>et al.</i> ^[35]	Neurolysis or nerve repair with Hyaloglide ^(R)	Hand nerves	Pain reduction quicker with Hyaloglide ^(R) 14 patients treated with HA versus 16 treated without gel
Varitimidis <i>et al.</i> ^[73]	Autologous vein	Median	Pain reduction in 14/15 patients (93)
Masear ^[74]	Vein: autologous+allograft	Median and various peripheral nerves	Good/excellent results in 94/119 patients (79); no pain relief in 9/119 patients
Kokkalis <i>et al.</i> ^[75]	Vein wrap	Ulnar	Pain reduction in 100% of 17 patients

CTS: Carpal tunnel syndrome, VAS: Visual analogue scale

FUTURE DIRECTIONS

Overall, the diagnosis and treatment of scar neuritis and neuropathic pain still present significant problem areas. A clear lesion classification correlating injury with the clinical problem and convincing evidence of the effectiveness of one treatment above the others would improve both diagnosis and clinical outcomes.

Despite active clinical research, no gold standard treatment has been established, as no medical or surgical treatment has shown superiority over the others with regards to the rate and extent of clinical response. No treatment among the myriad that have been described assures an effective and/or reliable outcome, and the same treatment can lead to very different outcomes in different patients, from complete resolution to a worsening of symptoms. Currently, neither surgeons nor pain therapists are able to predict, which patient will respond to treatment and for what duration that response may last.

All these data suggest that the key for improving our approach to neuropathic pain lies in gaining better insight into its underlying mechanisms. A genetic predisposition is likely to exist, and individual differences in biochemical signals involved in nerve pain and their possible modulation for therapeutic purposes deserves further study.

Then, we foresee genetic and biomolecular research as promising fields of future investigation, which could ultimately lead to a better understanding and management of painful scar neuropathy.

REFERENCES

- Lang J. On connective tissue and blood vessels of the nerves. *Z Anat Entwicklungsgesch* 1962;123:61-79.
- Millesi H, Zoch G, Reihnsner R. Mechanical properties of peripheral nerves. *Clin Orthop Relat Res* 1995;314:76-83.
- Sunderland S, Bradley K. Stress-strain phenomena in denervated peripheral nerve trunks. *Brain* 1961;84:125-7.
- Clark WL, Trumble TE, Swiontkowski MF, Tencer AF. Nerve tension and blood flow in a rat model of immediate and delayed repairs. *J Hand Surg Am* 1992;17:677-87.
- Boyd BS, Puttlitz C, Gan J, Topp KS. Strain and excursion in the rat sciatic nerve during a modified straight leg raise are altered after traumatic nerve injury. *J Orthop Res* 2005;23:764-70.
- Wilgis EF, Murphy R. The significance of longitudinal excursion in peripheral nerves. *Hand Clin* 1986;2:761-6.
- McLellan DL, Swash M. Longitudinal sliding of the median nerve during movements of the upper limb. *J Neurol Neurosurg Psychiatry* 1976;39:566-70.
- Hunter JM. Recurrent carpal tunnel syndrome, epineural fibrous fixation, and traction neuropathy. *Hand Clin* 1991;7:491-504.
- Elliot D. Surgical management of painful peripheral nerves. *Clin Plast Surg* 2014;41:589-613.
- Sunderland S. Nerve Injuries and Their Repair: A Critical Appraisal. 3rd ed. London: Churchill Livingstone; 1991.
- Sunderland S. Nerves and Nerve Injury. 2nd ed. London: Churchill Livingstone; 1978.
- Ide C. Peripheral nerve regeneration. *Neurosci Res* 1996;25:101-21.
- Jones NF, Ahn HC, Eo S. Revision surgery for persistent and recurrent carpal tunnel syndrome and for failed carpal tunnel release. *Plast Reconstr Surg* 2012;129:683-92.
- Amadio PC. Interventions for recurrent/persistent carpal tunnel syndrome after carpal tunnel release. *J Hand Surg Am* 2009;34:1320-2.
- Lowe JB 3rd, Mackinnon SE. Management of secondary cubital tunnel syndrome. *Plast Reconstr Surg* 2004;113:E1-E6.
- Antoniadis G, Richter HP. Pain after surgery for ulnar neuropathy at the elbow: a continuing challenge. *Neurosurgery* 1997;41:585-9.
- Fransen P. Reduction of postoperative pain after lumbar microdiscectomy with DuraSeal Xact Adhesion Barrier and Sealant System. *Spine J* 2010;10:751-61.
- Mavrogenis AF, Pavlakakis K, Stamatakou A, Papagelopoulos PJ, Theoharis S, Zoubos AB, Zhang Z, Soucacos PN. Current treatment concepts for neuroma-in-continuity. *Injury* 2008;39 Suppl 3:S43-8.
- Millesi H, Rath TH, Reihnsner R, Zoch G. Microsurgical neurolysis: its anatomical and physiological basis and its classification. *Microsurgery* 1993;14:430-9.
- Yamamoto T, Narushima M, Yoshimatsu H, Yamamoto N, Mihara M, Koshima I. Free anterolateral thigh flap with vascularized lateral femoral cutaneous nerve for the treatment of neuroma-in-continuity and recurrent carpal tunnel syndrome after carpal tunnel release. *Microsurgery* 2014;34:145-8.
- Mackinnon SE. Evaluation and treatment of the painful neuroma. *Tech Hand Up Extrem Surg* 1997;1:195-212.
- Carroll I, Curtin CM. Management of chronic pain following nerve injuries/crps type II. *Hand Clin* 2013;29:401-8.
- Davis EN, Chung KC. The Tinel sign: a historical perspective. *Plast Reconstr Surg* 2004;114:494-9.
- Klauser AS, Tagliafico A, Allen GM, Boutry N, Campbell R, Court-Payen M, Grainger A, Guerini H, McNally E, O'Connor PJ, Ostlere S, Petroons P, Reijnierse M, Sconfienza LM, Silvestri E, Wilson DJ, Martinoli C. Clinical indications for musculoskeletal ultrasound: a Delphi-based consensus paper of the European Society of Musculoskeletal Radiology. *Eur Radiol* 2012;22:1140-8.
- Wang Y, Zhao C, Passe SM, Filius A, Thoreson AR, An KN, Amadio PC. Transverse ultrasound assessment of median nerve deformation and displacement in the human carpal tunnel during wrist movements. *Ultrasound Med Biol* 2014;40:53-61.
- Kerasnoudis A. Which ultrasound method has the upper hand in the follow-up of the patients with recurrent carpal tunnel syndrome? *Ann Rheum Dis* 2013;72:e11.
- Padua L, Di Pasquale A, Liotta G, Granata G, Pazzaglia C, Erra C, Briani C, Coraci D, De Franco P, Antonini G, Martinoli C. Ultrasound as a useful tool in the diagnosis and management of traumatic nerve lesions. *Clin Neurophysiol* 2013;124:1237-43.
- Andreisek G, Burg D, Studer A, Weishaupt D. Upper extremity peripheral neuropathies: role and impact of MR imaging on patient management. *Eur Radiol* 2008;18:1953-61.
- Thawait SK, Wang K, Subhawong TK, Williams EH, Hashemi SS, Machado AJ, Thawait GK, Soldatos T, Carrino JA, Chhabra A. Peripheral nerve surgery: the role of high-resolution MR neurography. *AJNR Am J Neuroradiol* 2012;33:203-10.
- Lipinski LJ, Spinner RJ. Neurolysis, neurectomy, and nerve repair/reconstruction for chronic pain. *Neurosurg Clin N Am* 2014;25:777-87.
- Haider N, Mekasha D, Chiravuri S, Wasserman R. Pulsed radiofrequency of the median nerve under ultrasound guidance. *Pain Physician* 2007;10:765-70.
- Adani R, Tos P, Tarallo L, Corain M. Treatment of painful median nerve neuromas with radial and ulnar artery perforator adipofascial flaps. *J Hand Surg Am* 2014;39:721-7.
- Hieb LD, Steves LD. Spontaneous postoperative cerebrospinal fluid leaks following application of anti-adhesion barrier gel: case report and review of the literature. *Spine* 2001;26:748-51.
- Burns JW, Skinner K, Colt MJ, Burgess L, Rose R, Diamond MP. A hyaluronate based gel for the prevention of postsurgical adhesions: evaluation in two animal species. *Fertil Steril* 1996;66:814-21.
- Atzei A, Calcagni M, Breda B, Fasolo G, Pajardi G, Cugola L. Clinical evaluation of a hyaluronan-based gel following microsurgical reconstruction of peripheral nerves of the hand. *Microsurgery* 2007;27:2-7.
- Gago LA, Saed GM, Chauhan S, Elhammady EF, Diamond MP. Septrafilm (modified hyaluronic acid and carboxy-methylcellulose) acts as a physical barrier. *Fertil Steril* 2003;80:612-6.
- Hiro D, Ito A, Matsuta K, Mori Y. Hyaluronic acid is an endogenous inducer of interleukin-1 production by human monocytes and rabbit macrophages. *Biochem Biophys Res Commun* 1986;140:715-22.
- Mensitieri M, Ambrosio L, Nicolais L, Bellini D, O'Regan M. Viscoelastic properties modulation of a novel autocrosslinked hyaluronic acid polymer. *J Mater Sci Mater Med* 1996;7:695-8.
- Sheldon HK, Gainsbury ML, Cassidy MR, Chu DI, Stucchi AF, Becker JM. A sprayable hyaluronate/carboxymethylcellulose adhesion barrier exhibits regional adhesion reduction efficacy and does not impair intestinal healing. *J Gastrointest Surg* 2012;16:325-33.

40. Arakawa T, Timasheff SN. Mechanism of poly (ethylene glycol) interaction with proteins. *Biochemistry* 1985;24:6756-62.
41. Liu LS, Berg RA. Adhesion barriers of carboxymethylcellulose and polyethylene oxide composite gels. *J Biomed Mater Res* 2002;63:326-32.
42. Thomsen L, Schlur C. Incidence of painful neuroma after end-to-end nerve suture wrapped into a collagen conduit. A prospective study of 185 cases. *Chir Main* 2013;32:335-40.
43. Soltani AM, Allan BJ, Best MJ, Mir HS, Panthaki ZJ. Revision decompression and collagen nerve wrap for recurrent and persistent compression neuropathies of the upper extremity. *Ann Plast Surg* 2014;72:572-8.
44. Abzug JM, Jacoby SM, Osterman AL. Surgical options for recalcitrant carpal tunnel syndrome with perineural fibrosis. *Hand (N Y)* 2012;7:23-9.
45. Masaer JR, Tullos JR, Mary ET, Meyer RD. Venous wrapping of nerve to prevent scarring. *J Hand Surg* 1990;15A: 817-8.
46. Sotereanos DG, Giannakopoulos PN, Mitsionis GI, Xu J, Herndon JH. Vein-graft wrapping for the treatment of recurrent compression of the median nerve. *Microsurgery* 1995;16:752-6.
47. Alligand-Perrin P, Rabarin F, Jeudy J, Cesari B, Saint-Cast Y, Fouque PA, Raimbeau G. Vein conduit associated with microsurgical suture for complete collateral digital nerve severance. *Orthop Traumatol Surg Res* 2011;97:S16-20.
48. Cramer LM. Local fat coverage for the median nerve. In: Lankford LL, editor. Correspondence Newsletter for Hand Surgery. Chicago, Ill: ASSH; 1985. p. 35.
49. Rose EH, Norris MS, Kowalski TA, Lucas A, Flegler EJ. Palmaris brevis turnover flap as an adjunct to internal neurolysis of the chronically scarred median nerve in recurrent carpal tunnel syndrome. *J Hand Surg Am* 1991;16:191-201.
50. Wulle C. The synovial flap as treatment of the recurrent carpal tunnel syndrome. *Hand Clin* 1996;12:379-88.
51. Becker C, Gilbert A. The cubital flap. *Ann Chir Main* 1988;7:136-42.
52. Vögelin E, Bignion D, Constantinescu M, Büchler U. Revision surgery after carpal tunnel release using a posterior interosseous artery Island flap. *Handchir Mikrochir Plast Chir* 2008;40:122-7.
53. Adani R, Tarallo L, Battiston B, Marcoccio I. Management of neuromas in continuity of the median nerve with the pronator quadratus muscle flap. *Ann Plast Surg* 2002;48:35-40.
54. Goitz RJ, Steichen JB. Microvascular omental transfer for the treatment of severe recurrent median neuritis of the wrist: a long-term follow-up. *Plast Reconstr Surg* 2005;115:163-71.
55. Huntoon MA, Burgher AH. Ultrasound-guided permanent implantation of peripheral nerve stimulation (PNS) system for neuropathic pain of the extremities: original cases and outcomes. *Pain Med* 2009;10:1369-77.
56. Deer TR, Levy RM, Rosenfeld EL. Prospective clinical study of a new implantable peripheral nerve stimulation device to treat chronic pain. *Clin J Pain* 2010;26:359-72.
57. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* 2009;13:1-154.
58. Reisman NR, Dellon AL. The abductor digiti minimi muscle flap: a salvage technique for palmar wrist pain. *Plast Reconstr Surg* 1983;72:859-65.
59. Strickland JW, Idler RS, Lourie GM, Plancher KD. The hypothenar fat pad flap for management of recalcitrant carpal tunnel syndrome. *J Hand Surg Am* 1996;21:840-8.
60. Rose EH. The use of the palmaris brevis flap in recurrent carpal tunnel syndrome. *Hand Clin* 1996;12:389-95.
61. Jones NF. Treatment of chronic pain by "wrapping" intact nerves with pedicle and free flaps. *Hand Clin* 1996;12:765-72.
62. Giunta R, Frank U, Lanz U. The hypothenar fat-pad flap for reconstructive repair after scarring of the median nerve at the wrist joint. *Chir Main* 1998;17:107-12.
63. Frank U, Giunta R, Krimmer H, Lanz U. Relocation of the median nerve after scarring along the carpal tunnel with hypothenar fatty tissue flap-plasty. *Handchir Mikrochir Plast Chir* 1999;31:317-22.
64. Guillemot E, Le Nen D, Colin D, Stindel E, Hu W, L'Heveder G. Perineural fibrosis of the median nerve at the wrist. Treatment by neurolysis and dermal-hypodermal graft. *Chir Main* 1999;18:279-89.
65. Mathoulin C, Bahm J, Roukoz S. Pedicled hypothenar fat flap for median nerve coverage in recalcitrant carpal tunnel syndrome. *Hand Surg* 2000;5:33-40.
66. De Smet L, Vandeputte G. Pedicled fat flap coverage of the median nerve after failed carpal tunnel decompression. *J Hand Surg Br* 2002;27:350-3.
67. Dahlin LB, Lekholm C, Kardum P, Holmberg J. Coverage of the median nerve with free and pedicled flaps for the treatment of recurrent severe carpal tunnel syndrome. *Scand J Plast Reconstr Surg Hand Surg* 2002;36:172-6.
68. Luchetti R, Riccio M, Papini Zorli I, Fairplay T. Protective coverage of the median nerve using fascial, fasciocutaneous or island flaps. *Handchir Mikrochir Plast Chir* 2006;38:317-30.
69. Craft RO, Duncan SF, Smith AA. Management of recurrent carpal tunnel syndrome with microneurolysis and the hypothenar fat pad flap. *Hand (N Y)* 2007;2:85-9.
70. Fusetti C, Garavaglia G, Mathoulin C, Petri JG, Lucchina S. A reliable and simple solution for recalcitrant carpal tunnel syndrome: the hypothenar fat pad flap. *Am J Orthop* 2009;38:181-6.
71. Elliot D, Lloyd M, Hazari A, Sauerland S, Anand P. Relief of the pain of neuromas-in-continuity and scarred median and ulnar nerves in the distal forearm and wrist by neurolysis, wrapping in vascularized forearm fascial flaps and adjunctive procedures. *J Hand Surg Eur Vol* 2010;35:575-82.
72. Espinoza DP, Kalbermatten DF, Egloff DV, Raffoul W. Neurolysis using a carbohydrate polymer gel for the treatment of postoperative neuropathic pain. *Scand J Plast Reconstr Surg Hand Surg* 2010;44:12-6.
73. Varitimidis SE, Riano F, Vardakas DG, Sotereanos DG. Recurrent compressive neuropathy of the median nerve at the wrist: treatment with autogenous saphenous veinwrapping. *J Hand Surg Br* 2000;25:271-5.
74. Masear VR. Nerve wrapping. *Foot Ankle Clin* 2011;16:327-37.
75. Kokkalis ZT, Jain S, Sotereanos DG. Vein wrapping at cubital tunnel for ulnar nerve problems. *J Shoulder Elbow Surg* 2010;19:91-7.
76. Vernadakis AJ, Koch H, Mackinnon SE. Management of neuromas. *Clin Plast Surg* 2003;30:247-68, vii.

How to cite this article: Tos P, Crosio A, Pugliese P, Adani R, Toia F, Artiaco S. Painful scar neuropathy: principles of diagnosis and treatment. *Plast Aesthet Res* 2015;2:156-64.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 09-12-2014; **Accepted:** 11-05-2015

The management of neuropathic pain from neuromas in the upper limb: surgical techniques and future directions

Tereze Laing^{1,2}, Aftab Siddiqui^{1,2}, Manu Sood^{1,2}

¹Department of Hand Surgery, St. Andrew's Centre for Plastic Surgery and Burns, Broomfield Hospital, Chelmsford, Essex CM4 9QZ, UK.

²Department of Plastic Surgery Research, St. Andrew's and Anglia Ruskin Research Unit, Bishop Hall Lane, Chelmsford, Essex CM1 1SQ, UK.

Address for correspondence: Ms. Tereze Laing, St. Andrew's Centre for Plastic Surgery and Burns, Broomfield Hospital, Chelmsford, Essex CM4 9QZ, UK. E-mail: terezelaing@yahoo.com

ABSTRACT

Neuropathic pain of the upper limb results from damage or disease of the upper limb somatosensory system caused by wide range of pathologies including peripheral neuromas. Treatment strategies depend on making an accurate diagnosis, recognizing co-existing pathologies, and formulating an individualized treatment plan that commonly involves multiple modalities. A long list of nonsurgical and surgical methods acting peripherally (neuromodulation, nerve blocks, surgical manipulation of the nerve) and centrally (medications, spinal cord, and deep brain stimulation) has been described and it is clear that no one treatment is wholly reliable. In this article, we briefly review the pathophysiology of pain caused by neuromas, the current treatment options and the latest research in therapeutic developments.

Key words:

Nerve, neuroma, neuromodulation, pain, relocation

INTRODUCTION

The international association for the study of pain defines neuropathic pain as pain resulting from a lesion or disease in the central or peripheral nervous system.^[1-3] This categorization is broad and includes a range of etiologies such as trauma, lesions of the central nervous system, diabetic peripheral neuropathy, multiple sclerosis, and herpetic nerve lesions. When the upper limb is involved, it also includes chronic nerve compression, neuritis and complex regional pain syndrome. A significant proportion of pain in the upper limb results from neuroma formation. Currently, our knowledge of the underlying mechanisms is limited for pain resulting from complex regional pain syndrome and diabetic peripheral neuropathy. However,

due to the wealth of research pain secondary to peripheral neuromas is reasonably well-understood.

PATHOPHYSIOLOGY OF THE PERIPHERAL NEUROMA

A neuroma is formed with when a nerve is transected and is not surgically repaired successfully. The word neuroma means "nerve tumor" and accurately describes the bulbous mass of regenerating axons that grow in an uncoordinated fashion from the proximal nerve end. This tissue consists of Schwann cells, fibroblasts, blood vessels, and regenerating axons. Neuromas may be further defined by the integrity of the nerve components. An end neuroma occurs following complete nerve transection or neurotmesis by Sunderland's classification. The term partial neuroma or neuroma-in-continuity (Sunderland grade 4-6 injury) is used to describe nerves that are partly intact.

Persisting pain arising from a terminal neuroma is relatively uncommon, estimated to occur in 3-5% of peripheral nerve injuries.^[4] In general, complete nerve transections do not result in major pain. Two main processes are believed to be responsible that of persistent abnormal peripheral nerve stimulation and central

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.160879

changes in cortical processing of pain. The first is that of persistent stimulation of free nerve endings at the site of injury with pain transmitted via the small diameter A delta and C fibers to the central somatosensory cortex.^[5] Following nerve injury, the proximal free nerve endings are unmyelinated, and these small diameter fibers have increased electrical activity and are stimulated at lower thresholds. Spontaneous, mechanical and chemical activity has also been demonstrated within the neuroma. This is accompanied by spontaneous activity in neurons of the dorsal root ganglion, dorsal horn and more proximally within the central nervous system. In addition, it is believed that changes in the central processing of the somatosensory cortex result in amplification of the pain response and perpetuation of the pain process even after the injury is treated successfully by surgery.^[6]

The most severe pain occurs after partial injuries to the nerve trunks or injury to the terminal branches of the smaller cutaneous nerves such as the superficial radial nerve, medial and lateral cutaneous nerves of the forearm, palmar branch of the median nerve and the sural and saphenous nerves of lower limbs. However, surgical removal of these nerves for use as grafts for nerve reconstruction rarely leads to neuropathic pain.

Presentation

The patient describes sensory symptoms in the distribution of the affected nerve. This is usually accompanied by a history of previous injury or surgery in the vicinity of the nerve. Other pathologies causing neuropathic pain such as nerve compression and complex regional pain syndrome must be ruled out as these conditions can co-exist with a neuroma.

Our unit previously described a simple assessment tool for grading pain from neuromas using characteristic symptoms: (1) baseline pain, (2) spontaneous spikes of pain, (3) pain exerted by pressure over the nerve, (4) pain on movement of the adjacent joints, and (5) cutaneous "hyperesthesia".

Other clinical terms used to describe the pain are: (1) dysesthesia: any abnormal unpleasant sensation; (2) allodynia: pain from a stimulus that is, not normally painful; (3) hyperpathia: exaggerated pain from a normally painful stimulus; (4) hyperesthesia-an abnormal increase in sensitivity to stimuli; and (5) paresthesia: an abnormal sensation typically tingling or prickling "pins and needles". Localization of the symptoms guides the clinician to identify the injured nerve. The range of symptoms varies from complete anesthesia distally (indicating nerve transection) to hyperesthesia or hyperpathia. Palpation of the neuroma bulb results in tenderness and light percussion over the nerve elicits paresthesias in the distribution of the nerve.

Neuropathic pain is intractable, severely debilitating, and disproportionately intense in relation to the initiating injury. Alongside sensory disturbances, there may be motor disturbance and abnormal sympathetic responses. In these cases, the distinction between neuroma pain and chronic regional pain syndrome or a severe compressive neuropathy may be difficult and

often there are overlapping features. In these situations, electrophysiologic studies and local anesthetic blocks are useful as diagnostic adjuncts. Electromyography and nerve conduction studies will usually establish if there is a compressive element. Neuroma pain is significantly reduced or diminished with infiltration of a small amount of local anesthetic around the nerve proximal to the suspected lesion.

Prevention

Given the challenges of treating neuroma pain, the importance of prevention must be stressed. Avoidance of nerve injury seems obvious yet cannot be emphasized enough given that iatrogenic injuries are cited as a major etiological source, especially with procedures such as ganglion resection, surgery for De Quervain's syndrome or procedures on ulnar head.^[7] It is imperative that once an injury is diagnosed an attempt at primary repair be undertaken as soon as possible. The precise microsurgical coaptation of the epineurium has been shown to reduce the incidence of neuroma formation.^[8] Providing the advancing axons are directed appropriately they may reestablish connections with their end-organs thereby restoring function in terms of muscle innervation and sensibility. If a nerve is found to be in continuity, it is advised to perform an external neurolysis and to initiate early mobilization after surgery.

TREATMENT STRATEGIES

Nonsurgical therapies

It is difficult to treat pain from neuroma, and a wide range of surgical and nonsurgical therapies have been described. Analgesia with or without supplementary neuropathic agents should be introduced early and prescribed to be taken regularly following any traumatic nerve injury. Early aggressive medical treatment and preemptive analgesia have both been shown to improve prognosis and reduce pain in upper limb pain conditions.^[9,10]

Medical management consists of four main classes of oral medication: (1) antidepressants with reuptake blocking effect, (2) anticonvulsants with sodium-blocking action, (3) anticonvulsants with calcium-modulating actions, and (4) opioids.

Topical treatments for patients experiencing cutaneous hyperalgesia and allodynia include capsaicin and local anesthetics administered as slow release patches. In many situations, an early combination of medications working at different levels of the pain pathway by different mechanisms is useful. Current randomized controlled trials provide general pain relief values for specific medications, which may explain the failure to obtain complete pain relief in neuropathic pain. A detailed review of medical therapies for upper limb neuropathic pain is beyond the scope of this article but we would refer readers to the articles in the references.^[11-14]

Neuromodulation

Our preferred next step in management is a trial of peripheral external electrical stimulation, also known as

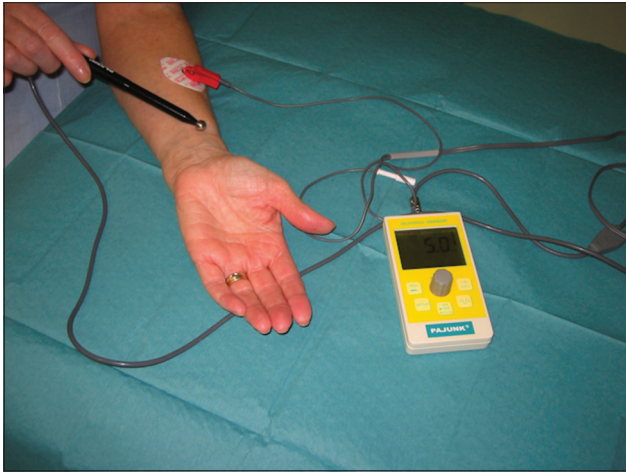


Figure 1: External neuromodulation requires minimal, inexpensive equipment which includes an external neuromodulator, electrocardiogram electrode and stimulating probe

neuromodulation [Figure 1]. This involves the application of an external stimulating probe to the affected nerve proximal to the site of the painful neuroma or over the nerve supplying the area of hypersensitivity for a period of 5-10 min. A low voltage current passes from the generator to the nerve through the skin. There is a paucity of literature relating to the use of neuromodulation in the upper limb. In our series of 102 patients with upper limb pain, greater than 30% patients experienced complete resolution of pain and 21.5% patients experienced pain relief lasting from days to weeks and elected for further treatment.^[15]

This still leaves a proportion of patients whose symptoms persist and who are considered candidates for surgery.

SURGERY FOR END-NEUROMAS

The surgical options described for management of the terminal neuroma can be broadly classified into the following categories: (a) neuroma resection and reconstruction, (b) simple neuroma resection, (c) containment of the neuroma, and (d) relocation of the nerve into different environments (denervated skin, muscle, bone).

Neuroma resection and reconstruction

When there is a delay in diagnosis of nerve transection by a few weeks or months, the nerve ends are often retracted, and primary repair of the nerve is not possible. The decision to reconstruct the nerve or not depends on two main factors: the functional importance of restoring some of the nerve's action and the likelihood of achieving a successful result. The former will be dictated by the nerve involved, the handedness and occupation of the patient; the latter by the patient's age, the time since the initial insult and the level of injury. The decision is made jointly with the patient. A vein, nerve, muscle or synthetic substance can be used for reconstruction. It is our preference to reconstruct small distal digital nerve gaps of less than 2 cm with posterior interosseous nerve grafts and any larger gaps with sural nerve grafts.

Simple neuroma resection

Resection of the neuroma alone is the least successful surgical method to treat neuromas of the hand and forearm.^[16] However, laboratory studies have revealed that the type of nerve transection can affect neuroma formation. Neuromas developed more often after electrocautery than simple scissors cut or suture ligation and division.^[17] Decreased neuroma formation and improved nerve regeneration have been noted with oblique transection in comparison with transverse sectioning for grafting.^[18,19] It is suggested that the longer fibers provide a growth pathway for the shorter ones with oblique transection.

Containment

A number of methods of containment have been described in the literature, but poor results have led this technique to be largely abandoned. The aim of this method is to contain regenerating fascicles within the nerve trunk thereby preventing the proliferation of axonal tissue into the surrounding structures. Although few studies report success with a technique of fascicle resection and ligation of the epineurial sleeve, there have been no studies published on the technique since 1989.^[8,20]

Other materials have been used in attempts to seal or cap the nerve following neuroma resection. Dahlin and Lundborg^[21] determined a potential role for the use of silicone tubes in peripheral nerve repair, observing in experimental studies a reduced tendency to neuroma formation. However, in the management of end neuromas other clinical studies showed no advantage of silicone capping over simple excisional neurectomy.^[8]

Other reported methods of containing end neuromas include the formation of end-to-side anastomoses or nerve loops. Experimental studies have demonstrated that by attaching the proximal nerve end-to-side to an adjacent nerve, the neuromas that form are smaller when compared to transection and epineurial ligation.^[22] However, only preliminary clinical studies using this technique have been reported with small patient numbers.^[23,24]

The "nerve-loop" procedure, also referred to as "centrocentral nerve union" consists of sequestration of regenerating axons and inhibition of regeneration by suturing one free nerve ending end to end to another. Although there are limited reports of success with this technique, we have no successful experience of its use.^[25]

Neuroma resection and nerve relocation

The method of nerve translocation into local muscle or bone was first introduced by Herndon *et al.*^[26] in 1967. Our unit and others have reported favorable results using this technique.^[27-30] Therefore, we recommend this procedure when the distal portion of the severed nerve is absent or irreparable. The neuroma and proximal nerve are carefully dissected free of the surrounding tissues for a distance that will allow relocation into a local muscle or bone without tension [Figure 2]. The neuroma is resected and the site for relocation determined in an area free of scar tissue or any potential compressive forces. A small

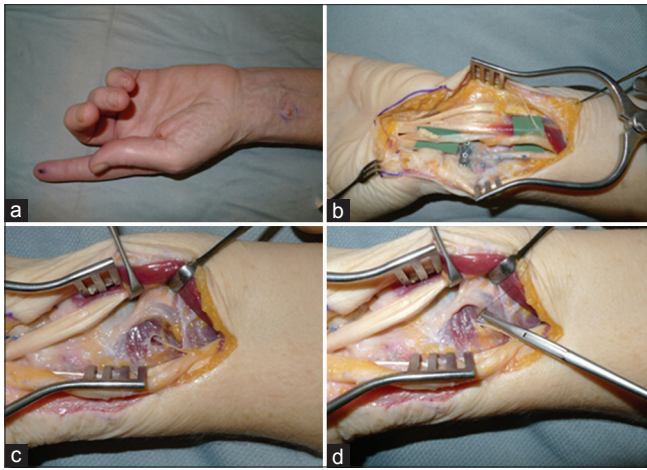


Figure 2: Technique of palmar cutaneous nerve relocation to pronator quadratus. (a) Preoperative skin marking shows neuroma of the palmar cutaneous branch of the median nerve; (b) dissection of palmar cutaneous nerve to origin from median nerve; (c) nerve relocated into muscle; (d) suture securing epineurium to epimysium

tunnel is dissected in the muscle, and the nerve is buried without tension. A single absorbable suture between the epineurium and epimysium holds the nerve in place. For placement into bone, a cortical hole is drilled obliquely to a size slightly larger than the nerve diameter. The nerve is relocated into this hole, and a single suture holds the epineurium to the adjacent periosteum [Figure 3]. It is important not to choose a site just distal to a joint where mobilization is likely to put strain on the nerve. It is also crucial to ensure there are no kinks or tension on the nerve and that it does not angle acutely on entering the bone. Our primary preferences for nerve relocation are as follows: (1) superficial radial nerve to the undersurface of brachioradialis or into radius; (2) palmar cutaneous branch of median nerve to pronator quadrates; (3) dorsal branch of ulnar nerve to pronator quadrates; (4) lateral cutaneous nerve of the forearm to pronator quadrates; (5) digital nerves at or distal to distal interphalangeal joint to the proximal phalanx; and (6) digital nerves proximal the distal interphalangeal joint to the metacarpal shaft.

SURGERY FOR NEUROMAS-IN-CONTINUITY

There is an even greater debate in the management of in-continuity neuromas. The treatment options fall into the following broad categories: (a) neurolysis alone, (b) nerve wrapping, (c) neuroma resection and reconstruction, and (d) neuroma resection and relocation.

Neurolysis alone

Preservation of functional sensitivity is vital for nerves such as the median and ulnar nerves. In these situations, neurolysis alone or nerve wrapping usually maintains the integrity of the intact axonal tissue. External neurolysis theoretically restores movement, thereby, preventing further scar adherence to the nerve, a suggested trigger for pain.^[31,32] A study of neurolysis alone in upper trunk brachial plexus neuroma-in-continuity revealed a functional improvement following neurolysis alone in cases where there was more

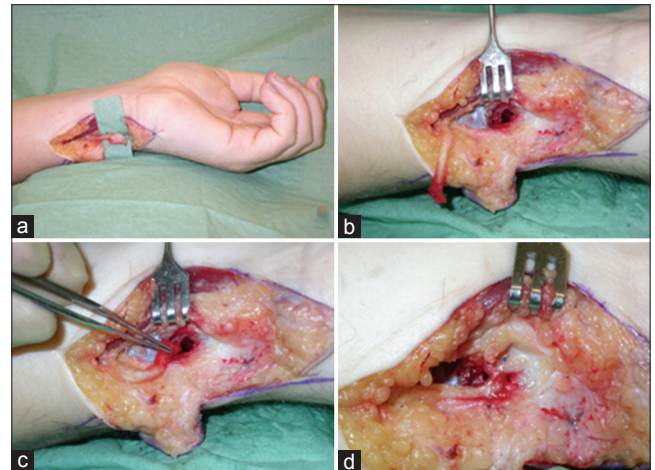


Figure 3: Technique of relocation of dorsal branch of ulnar nerve into ulna. (a) End neuroma of dorsal branch of ulnar nerve; (b) nerve dissected proximally; (c) nerve end can be placed in the ostium in distal ulna without tension; (d) epineurium is sutured to the periosteum to prevent displacement of nerve end

than 50% conduction demonstrated intraoperatively across the nerve.^[33] Opponents of neurolysis alone, however, warn of the risks of segmental revascularization and significant scar formation.^[34] This has led to the development of techniques designed to prevent recurrent scarring such as wrapping the nerve in a variety of protective substances.

Nerve wrapping

First described by Masear *et al.*,^[35] vein wrapping^[36] has been reported as a successful technique in the management of both refractory cubital and carpal tunnel syndromes. Initially, glutaraldehyde-preserved allograft was used but has since been shown to cause increased scarring and adherence compared to autograft vein.^[37] Our unit has not had success with either technique and our limited experience of re-exploration in these cases the nerve was found to be tethered at both the proximal and distal sites on entry and exit of the vein graft. In general, we prefer to use vascularized fascia to wrap nerves. The largest series of vein wrapping to date has been reported by Kokkalis *et al.*^[38] who performed the procedure on seventeen patients for recalcitrant ulnar nerve compression at the elbow. Although they reported a significant reduction in symptoms in most of the patients, pain was not abolished in any single case.

For neuromas involving the critical ulnar and median nerves at the wrist or forearm, it has been our practice to use local fascial flaps to wrap the nerve, occasionally incorporating overlying skin and fat. Our unit has previously presented results of the analysis of 14 cases of neurolysis and fascial wrapping for nerves-in-continuity of the distal forearm or wrist.^[39] There was a complete resolution of pain in 8 of the 14 patients, and 2 more patients had only mild pain at 6 month follow-up. This technique was also used for the branches of the median and ulnar nerves to the palm and digits in an effort to preserve distal sensation, using division and relocation as a secondary procedure in the case of failure. We have found that there is little functional loss with the relocation of these nerves and have had greater success in abolishing pain with this technique.

Neuroma resection and reconstruction

With a neuroma-in-continuity, there is an option to resect the neuroma and reconstruct the nerve. Again the same factors as mentioned previously will be considered (the functional importance of the nerve, the patient's desires, occupation, age). For noncritical nerves, we prefer to relocate the nerve as any loss of the remaining function is well-compensated for by relief of pain.

Neuroma resection and relocation

As discussed above, we now routinely relocate painful nerves as a primary procedure. Although yet to be published, our unit recently reviewed outcomes for relocation in this subset of patients who nerves were determined clinically or intraoperatively to be intact, that is, neuromas-in-continuity or tethered in surrounding scar tissue. Pain completely resolved in 21 of 23 patients. In the others pain reduced significantly in severity. Just 2 patients experienced mild pain at the site of relocation. The technique of relocation is the same as that for terminal neuromas as described previously.

FUTURE DIRECTIONS

Our treatment of choice in cases of neuromas involving the median and ulnar nerves refractory to nonsurgical means is neurolysis and wrapping the critical nerve in local vascularized fascia. It is usually easy to raise an adequate sized flap for this purpose based on the ulnar or radial arteries in the previously unscarred forearm. However, following multiple procedures the local tissue may be of substandard quality. Del Pinal *et al.*^[40] have reported the use of free vascularized adipofascial flaps in scarred beds in the forearm and hand to improve tendon gliding. The technique of free tissue transfer has been described previously to address scarred nerve beds of the brachial plexus.^[41,42] We are not aware of its application at more distal sites, and it is an avenue for future development.

Free fat grafting is one of the new ways to treat neuromas.^[43] This technique is minimally invasive and can be repeated. It has been shown to be valuable in treating Dupuytren's contracture and Raynaud's disease. Currently, we have no experience of this technique. We believe that there is a greater benefit from transferring vascularized fat attached to a fascial flap as it avoids the risk of fat necrosis seen with transferring aspirated fat.

Recently, there has been an introduction of biological and synthetic polymers to the field of nerve reconstruction. Excellent outcomes in terms of sensory recovery have been demonstrated using some of these materials as alternatives to autologous nerve grafts.^[44,45] The limitations include the length of the defect that can be treated (which is not longer than 2 cm). The importance of the alignment in nerve guide conduits has been recently revealed, and the designers of the conduits are taking this into account.^[46] Furthermore studies of Schwann cell-seeded biodegradable poly(d, l-lactic acid) conduits demonstrated additional trophic and physical support, improving recovery.^[47]

CONCLUSION

Pain following traumatic peripheral nerve injury falls into the category of neuropathic pain as defined by the international association for the study of pain yet these injuries are not frequently included in the neuropathic pain literature. Although there are several epidemiological and quality of life studies relating to neuropathic pain, very few of these studies include peripheral nerve injuries.^[48-51] This lack of knowledge was highlighted in a review by Novak and Katz.^[52] They concluded that there is very little information on incidence and severity of neuropathic pain, the associated disability, impact on quality of life or health status of patients with traumatic peripheral nerve injuries. Most studies report only on the physical impairment related to motor and/or sensory recovery. There are, however, a large number of reports detailing intervention outcomes that shows the enormity of the problem and the lack of a single reliable solution.

Determining the cause of postinjury pain is the key to success in treatment and can often be achieved by a thorough clinical evaluation alone. Injury of a sensory nerve may result in altered sensation or anesthesia in the distribution of the nerve. Unless accurate coaptation of the epineurium is achieved, neuroma formation is inevitable but is not in the majority of cases painful. The two main processes believed to be responsible for neuroma-mediated pain are local persistent mechanical or chemical stimulation of the nerve ending and central stimulation of dorsal ganglion, spinal cord and central nervous system pathways. This understanding has led to the development of techniques to wrap the nerve or move the nerve to a site where it is less irritated.

A multitude of surgical techniques has been described in cases that fail conservative measures. Indeed, such a wide array of treatments suggests that there is no single way of completely and effectively managing peripheral neuromas with surgery. There are some general principles, which guide the surgical choice. If the nerve injury is recent, we explore immediately with the aim to primarily repair the nerve if possible or resect the injury and reconstruct with autologous nerve grafts. In the case of established neuromas-in continuity, where the nerve provides a distal critical function such as in the case of the median or ulnar nerves, every effort is made to preserve the functional elements. Our procedure of choice is neurolysis and wrapping the nerve in a local vascularized fascial flap. When the smaller cutaneous nerves or digital nerves are involved, we generally opt for relocation to a site determined by the nerve injured and the level of injury. End-neuromas of these smaller cutaneous nerves are managed similarly with relocation to local muscle or bone.

REFERENCES

1. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, Serra J, Jensen TS. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* 2004;11:153-62.
2. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. *Pain* 2008;137:473-7.

3. Merskey H, Bogduk N. Classification of Chronic Pain: descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd ed. Seattle: IASP Press; 1994. p. 212.
4. Sunderland S. Nerve Injuries and Their Repair: a Critical Appraisal. Melbourne: Churchill Livingstone; 1991. p. 186-7.
5. Torebjörk E. Human microneurography and intraneural microstimulation in the study of neuropathic pain. *Muscle Nerve* 1993;16:1063-5.
6. Ochoa JL. The human sensory unit and pain: new concepts, syndromes and tests. *Muscle Nerve* 1993;16:1009-16.
7. Bonney G. Iatrogenic. In: Birch R, Bonney G, Parry CB editors. Surgical Disorders of the Peripheral Nerves. London: Churchill Livingstone; 1998. p. 293-333.
8. Tupper JW, Booth DM. Treatment of painful neuromas of sensory nerves in the hand: a comparison of traditional and newer methods. *J Hand Surg Am* 1976;1:144-51.
9. Sai S, Fujii K, Hiranuma K, Sato T, Nemoto T. Preoperative ampicillin reduces postoperative pain after hand surgery. *J Hand Surg Br* 2001;26:377-9.
10. Lee J, Nandi P. Early aggressive treatment improves prognosis in complex regional pain syndrome. *Practitioner* 2011;255:23-6,3.
11. Baron R. Neuropathic pain: a clinical perspective. *Handb Exp Pharmacol* 2009;(194):3-30.
12. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2014;4:CD007938.
13. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2014;4:CD005451.
14. Rowbotham MC. Pharmacologic management of complex regional pain syndrome. *Clin J Pain* 2006;22:425-9.
15. Siddiqui A, Laing T, Poel J, Want M, Sood M. Management of Nerve Pain in Upper Limb Using External Neuromodulator in an Outpatient Setting. Proceedings of the 12th Congress of ESPRAS; 2014 Jul 6-11; Edinburgh, UK. Bologna: Medimond Publishers; 2014.
16. Guse DM, Moran SL. Outcomes of the surgical treatment of peripheral neuromas of the hand and forearm: a 25-year comparative outcome study. *Ann Plast Surg* 2013;71:654-8.
17. Zeltser R, Beilin B, Zaslansky R, Seltzer Z. Comparison of autotomy behavior induced in rats by various clinically-used neurectomy methods. *Pain* 2000;89:19-24.
18. Kayıkçıoğlu A, Karamürsel S, Ağaoğlu G, Sargon MF, Keçik A. A new epineural nerve repair technique: oblique nerve coaptation. *Ann Plast Surg* 1999;43:506-12.
19. Marcol W, Kotulska K, Larysz-Brysz M, Bierzyńska-Macyszyn G, Wlasczuck P, Lewin-Kowalik J. Prevention of painful neuromas by oblique transection of peripheral nerves. *J Neurosurg* 2006;104:285-9.
20. Martini A, Fromm B. A new operation for the prevention and treatment of amputation neuromas. *J Bone Joint Surg Br* 1989;71:379-82.
21. Dahlin LB, Lundborg G. Use of tubes in peripheral nerve repair. *Neurosurg Clin N Am* 2001;12:341-52.
22. Low CK, Chew SH, Song IC, Ng TH, Low YP. End-to-side anastomosis of transected nerves to prevent neuroma formation. *Clin Orthop Relat Res* 1999;(369):327-32.
23. Al-Qattan MM. Prevention and treatment of painful neuromas of the superficial radial nerve by the end-to-side nerve repair concept: an experimental study and preliminary clinical experience. *Microsurgery* 2000;20:99-104.
24. Lagarrigue J, Chavoin JP, Belahouari L, Scavazza R. Treatment of painful neuroma by a nerve anastomosis, "neuronal trap" loop. *Neurochirurgie* 1982;28:91-2.
25. Kon M, Bloem JJ. The treatment of amputation neuromas in fingers with a centrocentral nerve union. *Ann Plast Surg* 1987;18:506-10.
26. Herndon JH, Eaton RG, Littler JW. Management of painful neuromas in the hand. *Bone Joint Surg Am* 1976;58:369-73.
27. Sood MK, Elliot D. Treatment of painful neuromas of the hand by relocation into the pronator quadratus muscle. *J Hand Surg Br* 1998;23:214-9.
28. Hazari A, Elliot D. Treatment of end-neuromas, neuromas-in-continuity and scarred nerves of the digits by proximal relocation. *J Hand Surg Br* 2004;29:338-50.
29. Dellon AL, Aszmann OC. Treatment of superficial and deep peroneal neuromas by resection and translocation of the nerves into the anterolateral compartment. *Foot Ankle Int* 1998;19:300-3.
30. Otfinowski J, Pawelec A, Kaluza J. Implantation of peripheral neural stump into muscle and its effect on the development of posttraumatic neuroma. *Pol J Pathol* 1994;45:195-202.
31. Millesi H, Zöch G, Rath T. The gliding apparatus of peripheral nerve and its clinical significance. *Ann Hand Surg* 1990;9:87-97.
32. Wilgis EF, Murphy R. The significance of longitudinal excursion in peripheral nerves. *Hand Clin* 1986;2:761-6.
33. Andrievic E, Taniguchi M, Partington MD, Agel J, Van Heest AE. Neurolysis alone as the treatment for neuroma-in-continuity with more than 50% conduction in infants with upper trunk brachial plexus birth palsy. *J Neurosurg Pediatr* 2014;13:229-37.
34. Jones NF, Shaw WW, Katz RG. Circumferential wrapping of a flap around a scarred peripheral nerve for salvage of end-stage traction neuritis. *J Hand Surg Am* 1997;22:527-35.
35. Masear VR, Colgin S. The treatment of epineural scarring with allograft vein wrapping. *Hand Clin* 1996;12:773-9.
36. Varitimidis SE, Riano F, Vardakas DG, Sotereanos DG. Recurrent compressive neuropathy of the median nerve at the wrist: treatment with autogenous saphenous vein wrapping. *J Hand Surg Br* 2000;25:271-5.
37. Ruch DS, Spinner RM, Koman LA, Challa VR, O'Farrell D, Levin S. The histologic effect of barrier vein wrapping of peripheral nerves. *J Reconstr Microsurg* 1996;12:291-5.
38. Kokkalis ZT, Jain S, Sotereanos DG. Vein wrapping at cubital tunnel for ulnar nerve problems. *J Shoulder Elbow Surg* 2010;19:91-7.
39. Elliot D, Lloyd M, Hazari A, Sauerland S, Anand P. Relief of the pain of neuromas in continuity and scarred median and ulnar nerves in the distal forearm and wrist by neurolysis, wrapping in vascularized forearm fascial flaps and adjunctive procedures. *J Hand Surg Eur Vol* 2010;35:575-82.
40. Del Pinal F, Moraleda E, de Piero GH, Ruas JS. Outcomes of free adipofascial flaps combined with tenolysis in scarred beds. *J Hand Surg Am* 2014;39:269-79.
41. Brunelli G. Neurolysis and freemicrovascular omentum transfer in the treatment of postactinic palsies of the brachial plexus. *Int Surg* 1980;65:515-9.
42. Brunelli GA, Brunelli F, Di Rosa F. Neurolyzed nerve padding in actinic lesions: omentum versus muscle use. An experimental study. *Microsurgery* 1988;9:177-80.
43. Vaienti L, Gazzola R, Villani F, Parodi PC. Perineural fat grafting in the treatment of painful neuromas. *Tech Hand Up Extrem Surg* 2012;16:52-5.
44. Lohmeyer JA, Kern Y, Schmauss D, Paprotzka F, Stang F, Siemers F, Mailaender P, Machens HG. Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature. *J Reconstr Microsurg* 2014;30:227-34.
45. Taras JS, Jacoby SM, Lincoski CJ. Reconstruction of digital nerves with collagen conduits. *J Hand Surg Am* 2011;36:1441-6.
46. Li J, McNally H, Shi R. Enhanced neurite alignment on micro-patterned poly-L-lactic acid films. *J Biomed Mater Res Part A* 2008;87:392-404.
47. Rutkowski GE, Miller CA, Jeftinija S, Mallapragada SK. Synergistic effects of micropatterned biodegradable conduits and Schwann cells on sciatic nerve regeneration. *J Neural Eng* 2004;1:151-7.
48. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology* 2007;68:1178-82.
49. Meyer-Rosberg K, Kvarnström A, Kinnman E, Gordh T, Nordfors LO, Kistofferson A. Peripheral neuropathic pain: a multidimensional burden for patients. *Eur J Pain* 2001;5:379-89.
50. Meyer-Rosberg K, Burckhardt CS, Huizar K, Kvarnstrom A, Nordfors LO, Kistofferson A. A comparison of the SF-36 and Nottingham Health Profile in patients with chronic neuropathic pain. *Eur J Pain* 2001;5:391-403.
51. Toth C, Lander J, Wiebe S. The prevalence and impact of chronic pain with neuropathic pain symptoms in the general population. *Pain Med* 2009;10:918-29.
52. Novak CB, Katz J. Neuropathic pain in patients with upper-extremity nerve injury. *Physiother Can* 2010;62:190-201.

How to cite this article: Laing T, Siddiqui A, Sood M. The management of neuropathic pain from neuromas in the upper limb: surgical techniques and future directions. *Plast Aesthet Res* 2015;2:165-70.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 10-02-2015; **Accepted:** 13-05-2015

Neuropathic pain after bilateral sagittal split osteotomy: management and prevention

Jimoh Olubanwo Agbaje^{1,2}, Ivo Lambrichts³, Reinhilde Jacobs¹, Constantinus Politis^{1,3}

¹Department of Imaging and Pathology, Faculty of Medicine, Catholic University of Leuven, 3000 Leuven, Belgium.

²Department of Oral and Maxillofacial Surgery, St. John's Hospital, 3600 Genk, Belgium.

³Faculty of Medicine, Morphology Research Group, Hasselt University, 3590 Diepenbeek, Belgium.

Address for correspondence: Prof. Constantinus Politis, Department of Imaging and Pathology, Faculty of Medicine, Catholic University of Leuven, 3000 Leuven, Belgium. E-mail: constantinus.politis@uzleuven.be

ABSTRACT

Neuropathic pain is characterized by spontaneous and provoked pain and other signs reflecting neural damage. Aberrant regeneration following peripheral nerve lesions leaves neurons unusually sensitive and prone to spontaneous pathological activity, abnormal excitability and heightened sensitivity to stimuli. This review covers the current understanding of neuropathic pain after bilateral sagittal split osteotomy (BSSO) of the lower jaw. The reported incidence of neuropathic pain after mandibular osteotomies is less than 1%, while the incidence in patients with iatrogenic inferior alveolar nerve (IAN) injuries during BSSO can be as high as 45%. The factors which modulate the healing process toward neuropathic pain during or after nerve damage have not yet been elucidated. Patients at highest risk for developing post-BSSO neuropathic pain are older than 45 years and have undergone procedures involving IAN compression, partial severance, or complete discontinuity of the lingual nerve with a proximal stump neuroma, patients with nerve injury repair delayed longer than 12 months and patients with chronic illnesses that compromise healing or increase risk for peripheral neuropathy. Although neuropathic pain tends to be long-lasting, some patients can recover completely. Preventive measures include risk assessment prior to surgery, prevention of nerve damage during surgery, and early repair of nerve injury.

Key words:

Bilateral sagittal split osteotomy, incidence, management, neuropathic pain, risk factor

INTRODUCTION

Neuropathic pain is a complex, chronic pain state caused by a lesion of the somatosensory nervous system.^[1] It usually results from tissue injury and excludes pain from a condition preceding surgery.^[2] Neuropathic pain can arise from damage to the nerve pathways at any point from the terminals of the peripheral nociceptors to the cortical neurons in the brain. In this type of pain, nerve fibers may be damaged, dysfunctional, or injured, resulting in a change in nerve function at both the site of injury and

adjacent tissue. These damaged nerve fibers in turn send incorrect signals to other pain centers.^[3]

Neuropathic pain is characterized by spontaneous and provoked pain mostly of a burning character, by positive symptoms such as paresthesias and dysesthesias, and by negative signs (sensory deficits) reflecting neural damage. Sensory disturbances in the area of surgery show a strikingly strong association with persistent postsurgical pain, suggesting nerve damage as a contributing factor in a significant portion of cases.^[2,3] Many investigations have confirmed the relevance of surgery as the initiating event for the development of persistent pain, even after a minor operation, such as tooth extraction.^[1]

Bilateral sagittal split osteotomy (BSSO) is a common procedure used to treat mandibular deformity. Because mandibular osteotomies are performed in close proximity to the neurovascular bundle in the mandibular canal, there is a high risk of injury to the inferior alveolar nerve (IAN).^[4-6] IAN injury during surgery largely results from manipulation

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.160880

of the nerve, its vascular supply, or structures surrounding the nerve during surgery.^[7-9] The placement of semi-rigid fixation plates and screws may also cause nerve damage either directly or via compression of the nerve between bony segments after screw fixation.

Inferior alveolar nerve-related neuropathic pain following iatrogenic damage to the nerve is a disabling condition that severely affects the quality of daily life.^[10-12] This review covers the current knowledge regarding neuropathic pain after BSSO and its incidence, pathophysiology, risk factors, management, and steps for prevention.

NEUROPATHIC PAIN AFTER BILATERAL SAGITTAL SPLIT OSTEOTOMY

Incidence

No single accurate value appears to be available for the overall prevalence of neuropathic pain. The development of chronic pain after surgery is fairly common, with estimates ranging from 10% to 50% after many common operations.^[13] The pain may be severe in 2-10% of these patients and is usually considered to be neuropathic.^[14,15]

Information about neuropathic pain following orthognathic surgery is sparse.^[16,17] Borstlap *et al.*^[18] prospectively followed 222 patients after BSSO surgery and reported no incidence of neuropathic pain. The reported incidence of neuropathic pain in the literature after mandibular osteotomies is less than 1% while the reported incidence in patients with iatrogenic IAN injuries during BSSO can be as high as 45%. Marchiori *et al.*^[19] reported seven cases of neuropathic pain among 1671 patients after BSSO, for an incidence of 0.42%, while Politis *et al.*^[20] reported 6 cases of neuropathic pain from 900 BSSOs with an incidence of 0.67%.

Other reports^[16,21] describe an incidence as high as 5% of neuropathic pain among patients who sustained peripheral trigeminal nerve injuries after sagittal split ramus osteotomy. Teerijoki-Oksa *et al.*^[22] prospectively followed 19 patients after BSSO surgery and found a 5% overall occurrence of neuropathic pain at 1-year follow-up, which is similar to the overall estimated incidence of neuropathic pain after traumatic and iatrogenic nerve injuries.^[23] Jääskeläinen *et al.*,^[21] on the other hand, found a 45% incidence of neuropathic pain in 58 patients with iatrogenic sensory deficits of the IAN and lingual nerve (LN).

Microsurgical repair of a damaged IAN after orthognathic surgery does not alleviate neuropathic pain if the latter was present before the repair. Furthermore, it does not cause neuropathic pain if the pain was not present beforehand.^[17]

Mechanism of nerve damage

The IAN is at significant risk in all stages of surgery [Table 1], and nerve manipulation during BSSO is a known risk factor for nerve injury.^[24] This nerve can be damaged at the following points: the spyx during the placement of a retractor posterior to or above the lingual,

Table 1: Location, cause, and type of nerve damage during BSSO

Location	Cause	Type of lesion
Spyx	Retractors	Compression
Osteotomy area	Chisels, compression bony surfaces, freeing nerve, screws, piezo, drill, saw	Compression, crushing, transection
Lower border	Partial or total transection	Drill, saw, piezo

BSSO: Bilateral sagittal split osteotomy

the ascending ramus during a horizontal osteotomy cut, the bone cut at the lower border of the mandible, the connecting bone cut between the lower border and the buccal osteotomy of the mandibular body, with chiseling during the sagittal split, between bone fragments after the bony movement, during placement of the osteosynthesis material and during insertion of an osteosynthesis screw.

Grades of nerve injury are categorized into neuropraxia, axonotmesis, or neurotmesis, depending on the extent of the damage.^[25] In clinical settings, various combinations of nerve damage can coexist, giving rise to a variety of sensory dysfunctions. After a peripheral nerve lesion, aberrant regeneration may occur.^[26] In some patients, neurons become unusually sensitive and develop a spontaneous pathological activity, abnormal excitability, and heightened sensitivity to chemical, thermal, and mechanical stimuli. Persistent pain or neuropathic pain such as allodynia, and pain and discomfort with occlusion^[27,28] can occur.

CLINICAL CHARACTERISTICS OF NEUROPATHIC PAIN

The main features of neuropathic pain include constant pain, which can be superficial or deep, sharp or aching, lancinating pain (i.e. sudden and sharp, severe bursts of pain), and allodynia (i.e. pain experienced after normally nonpainful stimuli, like light touch). The discomfort is usually of a chronic nature and may be described by the patient as a burning sensation, a sharp, stabbing, or shooting pain, or “like an electric shock”.^[20]

The complaints often seem to be out of proportion to the pain that would be expected to accompany the original injury.^[3,19] Neuropathic pain resulting from axonal nerve injury is often associated with crushing or stretching nerve injuries rather than total nerve transaction.^[20] Other characteristics of neuropathic pain include a lack of response to anti-inflammatory pain killers (nonsteroidal anti-inflammatories, paracetamol), improved symptoms in the mornings, minimal sleep disturbance, and worsening during the day or with stress, fatigue, and illness.

RISK FACTORS FOR NERVE DAMAGE AND NEUROPATHIC PAIN

The proximity of the mandibular canal to the lower border of the mandible is an important factor in self-reported hypoesthesia of the lower lip.^[27] The exposure and

dissection of the IAN from the mandibular canal during surgery has been shown to significantly increase the risk of neurosensory disturbance, while patients with a laceration of the IAN have higher chance of developing neuropathic pain.^[29]

Genioplasty and age at the time of surgery are significant predictors of hypoesthesia after BSSO, a 1-year increase in age may increase the odds of hypoesthesia of the lower lip by 5%, and the odds of hypoesthesia for patients with concurrent genioplasty are 4.5-fold greater than the odds for patients without concurrent genioplasty. Other factors include smoking and gender (women are at higher risk for hypoesthesia).^[27,29]

Patients most likely to develop neuropathic pain after BSSO are older than forty-five years and have undergone a procedure involving compression or partial severance of the IAN or complete discontinuity of the LN with a proximal stump neuroma. Others at risk include those with nerve injury repair delayed past twelve months, patients with chronic illnesses that compromise healing or enhance the risk for developing peripheral neuropathy (e.g. diabetes mellitus) and patients with preexisting chronic pain from any cause (e.g. lower back pain, postthoracotomy syndrome). Furthermore, potentially at risk are patients with certain psychological features such as depression, anger issues, posttraumatic stress disorder, and victims of abuse who have lost the ability to trust.^[19,26,30,31] Patients undergoing orthognathic surgery are usually young and healthy, which may explain the low incidence of neuropathic pain after BSSO surgery.

THE PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Chronic neuropathic pain represents a heterogeneous group of diseases in which pain is caused by nerve damage owing to various etiologies. Before pain is perceived in the central nervous system, different descending mechanisms must modulate the initial nociceptive stimulus. The imbalance between the amount of stimuli and the efficacy of modulation mechanisms is processed as the sensation of pain. High-magnitude or repetitive nociceptive impulses cause peripheral and central neuronal changes, leading to the maintenance and exacerbation of the pain sensation.^[26] These alterations are often irreversible and responsible for patient reports of long-term pain, even after many unsuccessful treatments. Most of the current ideas regarding the pathophysiology of neuropathic pain originated from experimental work in animal models. The underlying mechanisms are described below.^[26]

Peripheral sensitization

Pain sensations are normally elicited by activity in unmyelinated (C-) and thinly myelinated (A δ -) primary afferent neurons. These nociceptors are usually silent in the absence of stimulation and respond best to potentially noxious stimuli. Neurons become abnormally sensitive after damage to peripheral nerves and develop pathological spontaneous activity.^[32] These pathological

changes result from molecular and cellular changes at the level of the primary afferent nociceptor that are triggered by the nerve lesion. They are expressed as increased spontaneous firing, lowered activation threshold, and expanded receptive fields.^[33]

Central sensitization

Hyperactivity of the peripheral nociceptor results in secondary changes in the dorsal horn of the spinal cord with an associated increase in general excitability of multi-receptive spinal cord neurons. This hyper-excitability is manifested by increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields, and spread of spinal hyper-excitability to other segments. Central sensitization is initiated and maintained by activity in pathologically sensitized C-fibers. Importantly, the activation of both descending facilitatory and inhibitory supraspinal pain control systems requires intense noxious stimulation, resulting in activation of these brainstem centers to finally activate the descending arm of the spino-bulbo-spinal circuit.^[26] An imbalance between facilitatory and inhibitory systems, with higher activity in the former and lower in the latter, contributes to central neuronal sensitization and to the development and maintenance of pain.^[26]

Deafferentation: hyperactivity of central pain transmission neurons

Some patients experience a profound cutaneous deafferentation of the painful area without significant allodynia. In BSSO and orofacial neuropathic pain, the simultaneous occurrence of an exposed nerve or partial axonal IAN injury together with disruption of the bony environment of the IAN is a risk factor.^[34] The formation of a neuroma from a severed nerve ending has been associated with neuropathic pain, which is attributed to altered sensory processing in either the trigeminal ganglion or the central trigeminal nerve center.^[35] Politis *et al.*^[20] found no visible nerve damage on panoramic radiographs or magnetic resonance imaging (MRI) or computerized tomography (CT) scans in their case series of neuropathic pain after BSSO surgery, except in one patient in whom neuropathic pain started after loss of fixation and pathological movement of the bone segments due to pseudarthrosis. In this patient, the neuropathic pain disappeared after bone grafting and stabilization of the segments with adequate fixation.

Compression or crush lesions cannot be routinely visualized after orthognathic surgery by either CT or MRI secondary to artifacts from orthodontic appliances. Pathologic elongation of the nerve in BSSO surgery is certainly possible when the mandible has been surgically widened after a BSSO advancement with a midline split. Here too, cone beam CT, CT, and MRI cannot be used to directly visualize the nerve damage.

DIAGNOSIS

The diagnosis of neuropathic pain should be made only when the history and signs are indicative of neuropathy

in conjunction with a neuro-anatomically correlated pain distribution and sensory abnormalities within the area of pain. There should be partial or complete sensory loss in all or part of the painful area, and confirmation of a lesion or disease by quantitative sensory testing, surgical evidence, imaging, clinical neurophysiology, and/or biopsy.^[23]

Neuropathic pain should also be differentiated from other similar orofacial pain. The differential diagnosis of neuropathic pain includes inflammatory pain, traumatic trigeminal neuropathy, persistent idiopathic facial pain (atypical facial pain), atypical odontalgia, complex regional pain syndrome, and trigeminal neuralgia.^[23]

MANAGEMENT

Neuropathic pain tends to be long-lasting, although some patients recover completely, and others may find relief with pharmacotherapy and learn to cope with their symptoms. Neuropathic pain is treated mainly with anti-depressants and anti-epileptics, whereas simple analgesics are not efficacious. Management of pain should be tailored to the individual patient on the basis of pain type(s), the causative disease(s), and psychosocial aspects.

Psychological management

The assessment of neuropathic pain needs to include the measurement of multiple aspects of the quality of life. Mood, physical and social functioning, and pain-coping strategies such as catastrophizing and social support are all important domains. As with other chronically painful conditions, cognitive-behavioral interventions may improve the quality of life in neuropathic pain conditions.^[31] Reassurance and counseling of patients with neuropathic pain will go a long way toward alleviating their condition.

Medication

Neuropathic pain treatment remains unsatisfactory despite a substantial increase in the number of trials.^[36] The use of low-dose anti-depressants (amitriptyline, nortriptyline) is effective for symptomatic relief.^[37] carbamazepine, phenytoin, and valproic acid are effective in ameliorating diabetic neuropathy-related pain. Other anti-epileptic agents, including lamotrigine, oxcarbazepine, and topiramate, show some benefit for the treatment of neuropathic pain, although some studies have found them to be ineffective.^[37,38]

Topical 5% lidocaine patches offer a new therapeutic alternative for patients suffering from neuropathic pain. These patches have been shown to be useful in a subgroup of patients.^[39]

In BSSO patients, an accurate preoperative patient history, as well as early identification of the patient with severe or prolonged pain with the aim of initiating pain treatment as early as possible, is the key to success.^[29,34] Kuhlefeldt *et al.*^[29] suggest that patients with IAN damage after BSSO be put on neuropathic pain medication

immediately postoperatively before pain is well established. Psychological support and the volunteer of information by the surgeon are also important at this time.

Surgical management

Early repair of nerve injury has been deemed to be the most critical factor in the surgical management and prevention of neuropathic pain. For example, once the neuropathic pain has set in, late surgical trigeminal nerve repair will not improve the patient's symptoms.^[20] When an iatrogenic nerve injury is suspected, regular follow-up is advised. If there is no improvement during 10-12 weeks of follow-up or there are complaints of dysesthesia, surgical exploration, localization, and immediate repair or repair within days is advised. Repair should be carried out with a tension-free approximation.

PREVENTION

Patient profiling should be done and identification of risk factors for developing neuropathic pain made in all patients scheduled for orthognathic surgery. Proper localization of the IAN before BSSO is also an essential preventive step. The advent of cone beam CT has made IAN canal assessment in three-dimensions possible.

Furthermore, the development and modification of surgical techniques to reduce nerve injury during BSSO, such as safe surgical access to the mandibular nerve at the infratemporal fossa,^[40] and a modified technique to control the lower mandibular border cut,^[41] have been critical in reducing the incidence of damage to the IAN. Also useful is assessment of the IAN during BSSO, as by continuous monitoring of the status of the mandibular nerve through observation of changes in the sensory action potentials of the nerve during surgery.

Severe nerve injuries often result from drilling too deep past the bone into the nerve, or from placing the osteosynthesis screw on the nerve during fixation. The use of intraoperative CT during BSSO allows for the intraoperative evaluation of osteosynthesis screw penetration and depth. Intraoperative CT also allows for immediate assessment of treatment and provides the option to modify treatment if necessary. These preventive measures will help reduce the incidence of neuropathic pain and improve the quality of life of BSSO patients.

CURRENT TRENDS AND FUTURE PROSPECTS

Because neuropathic pain after BSSO involves an injured peripheral nerve which sends incorrect signals to neurons located in Meckel's cave, a temporary inhibition of such signals might be beneficial. Affordable long-acting liposomal local anesthetics, navigation guided procedures targeted at the exit of the mandibular nerve in the oval foramen, and miniaturized intra-oral neurostimulators applied proximal to the site of the nerve damage are possible treatment options that are currently under investigation.

CONCLUSION

Neuropathic pain after BSSO surgery is rare in spite of the frequent hypoesthesia that accompanies this surgical procedure. Contributing factors include patient factors (age, gender, patient profile), nerve-related factors (elongation, crushing, compression, transection), and local factors around the nerve (ischemia, bone infection). Once neuropathic pain has been established for more than three months, microsurgical nerve repair is unlikely to be successful in relieving the pain.

ACKNOWLEDGMENTS

Agbaje Jimoh Olubanwo is a postdoctoral researcher of the fund for Scientific Research (FWO-Vlaanderen).

REFERENCES

1. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013;154:95-102.
2. Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001;87:88-98.
3. Dobrogowski J, Przeklasa-Muszynska A, Wordliczek J. Persistent post-operative pain. *Folia Med Cracov* 2008;49:27-37.
4. Al-Bishri A, Rosenquist J, Sunzel B. On neurosensory disturbance after sagittal split osteotomy. *J Oral Maxillofac Surg* 2004;62:1472-6.
5. Boutault F, Diallo R, Marecaux C, Modiga O, Paoli JR, Lauwers F. Neurosensory disorders and functional impairment after bilateral sagittal split osteotomy: role of the anatomical situation of the alveolar pedicle in 76 patients. *Rev Stomatol Chir Maxillofac* 2007;108:175-82.
6. D'Agostino A, Trevisiol L, Gugole F, Bondi V, Nocini PF. Complications of orthognathic surgery: the inferior alveolar nerve. *J Craniofac Surg* 2010;21:1189-95.
7. Wijbenga JG, Verlinden CR, Jansma J, Becking AG, Stegenga B. Long-lasting neurosensory disturbance following advancement of the retrognathic mandible: distraction osteogenesis versus bilateral sagittal split osteotomy. *Int J Oral Maxillofac Surg* 2009;38:719-25.
8. Yoshioka I, Tanaka T, Khanal A, Habu M, Kito S, Kodama M, Oda M, Wakasugi-Sato N, Matsumoto-Takeda S, Fukai Y, Tokitsu T, Tomikawa M, Seta Y, Tominaga K, Morimoto Y. Relationship between inferior alveolar nerve canal position at mandibular second molar in patients with prognathism and possible occurrence of neurosensory disturbance after sagittal split ramus osteotomy. *J Oral Maxillofac Surg* 2010;68:3022-7.
9. Yamauchi K, Takahashi T, Kaneuji T, Nogami S, Yamamoto N, Miyamoto I, Yamashita Y. Risk factors for neurosensory disturbance after bilateral sagittal split osteotomy based on position of mandibular canal and morphology of mandibular angle. *J Oral Maxillofac Surg* 2012;70:401-6.
10. Colella G, Cannavale R, Viciodini A, Lanza A. Neurosensory disturbance of the inferior alveolar nerve after bilateral sagittal split osteotomy: a systematic review. *J Oral Maxillofac Surg* 2007;65:1707-15.
11. Lee EG, Ryan FS, Shute J, Cunningham SJ. The impact of altered sensation affecting the lower lip after orthognathic treatment. *J Oral Maxillofac Surg* 2011;69:e431-45.
12. Renton T, Yilmaz Z, Gaballah K. Evaluation of trigeminal nerve injuries in relation to third molar surgery in a prospective patient cohort. Recommendations for prevention. *Int J Oral Maxillofac Surg* 2012;41:1509-18.
13. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008;101:77-86.
14. Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study. *Pain* 2012;153:1390-6.
15. Schug SA. Persistent post-surgical pain: a view from the other side of the fence. *Pain* 2012;153:1344-5.
16. Bagheri SC, Meyer RA, Khan HA, Wallace J, Steed MB. Microsurgical repair of the peripheral trigeminal nerve after mandibular sagittal split ramus osteotomy. *J Oral Maxillofac Surg* 2010;68:2770-82.
17. Tay AB, Zuniga JR. Clinical characteristics of trigeminal nerve injury referrals to a university centre. *Int J Oral Maxillofac Surg* 2007;36:922-7.
18. Borstlap WA, Stoelinga PJ, Hoppenreijns TJ, van't Hof MA. Stabilisation of sagittal split advancement osteotomies with miniplates: a prospective, multicentre study with two-year follow-up. Part I. Clinical parameters. *Int J Oral Maxillofac Surg* 2004;33:433-41.
19. Marchiori EC, Barber JS, Williams WB, Bui PQ, O'Ryan FS. Neuropathic pain following sagittal split ramus osteotomy of the mandible: prevalence, risk factors, and clinical course. *J Oral Maxillofac Surg* 2013;71:2115-22.
20. Politis C, Lambrichts I, Agbaje JO. Neuropathic pain after orthognathic surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014;117:e102-7.
21. Jaaskelainen SK, Teerijoki-Oksa T, Forssell H. Neurophysiologic and quantitative sensory testing in the diagnosis of trigeminal neuropathy and neuropathic pain. *Pain* 2005;117:349-57.
22. Teerijoki-Oksa T, Jaaskelainen SK, Soukka T, Virtanen A, Forssell H. Subjective sensory symptoms associated with axonal and demyelinating nerve injuries after mandibular sagittal split osteotomy. *J Oral Maxillofac Surg* 2011;69:e208-13.
23. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618-25.
24. Westermarck A, Bystedt H, von Konow L. Inferior alveolar nerve function after sagittal split osteotomy of the mandible: correlation with degree of intraoperative nerve encounter and other variables in 496 operations. *Br J Oral Maxillofac Surg* 1998;36:429-33.
25. Seddon HJ. A classification of nerve injuries. *Br Med J* 1942;2:237-9.
26. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci* 2009;32:1-32.
27. Politis C, Sun Y, Lambrichts I, Agbaje JO. Self-reported hypoesthesia of the lower lip after sagittal split osteotomy. *Int J Oral Maxillofac Surg* 2013;42:823-9.
28. Agbaje JO, Salem AS, Lambrichts I, Jacobs R, Politis C. Systematic review of the incidence of inferior alveolar nerve injury in bilateral sagittal split osteotomy and the assessment of neurosensory disturbances. *Int J Oral Maxillofac Surg* 2014;10:440-8.
29. Kuhlefeldt M, Laine P, Suominen AL, Lindqvist C, Thoren H. Nerve manipulation during bilateral sagittal split osteotomy increases neurosensory disturbance and decreases patient satisfaction. *J Oral Maxillofac Surg* 2014;72:2052.e1-5.
30. Boogaard S, Heymans MW, Patijn J, de Vet HC, Faber CG, Peters ML, Loer SA, Zuurmond WW, Perez R. Predictors for persistent neuropathic pain: a Delphi survey. *Pain Physician* 2011;14:559-68.
31. Haythornthwaite JA, Benrud-Larson LM. Psychological assessment and treatment of patients with neuropathic pain. *Curr Pain Headache Rep* 2001;5:124-9.
32. Granovsky Y. Conditioned pain modulation: a predictor for development and treatment of neuropathic pain. *Curr Pain Headache Rep* 2013;17:361.
33. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol Dis* 1998;5:209-27.
34. Mensink G, Zweers A, Wolterbeek R, Dicker GG, Groot RH, van Merkesteyn RJ. Neurosensory disturbances one year after bilateral sagittal split osteotomy of the mandibula performed with separators: a multi-centre prospective study. *J Craniomaxillofac Surg* 2012;40:763-7.
35. Al-Sabbagh M, Okeson JP, Khalaf MW, Bhavsar I. Persistent pain and neurosensory disturbance after dental implant surgery: pathophysiology, etiology, and diagnosis. *Dent Clin North Am* 2015;59:131-42.
36. Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P, Force ET. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153-69.
37. Zin CS, Nissen LM, Smith MT, O'Callaghan JP, Moore BJ. An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. *CNS Drugs* 2008;22:417-42.
38. Jensen TS, Finnerup NB. Management of neuropathic pain. *Curr Opin Support Palliat Care* 2007;1:126-31.
39. Clere F, Delorme-Morin C, George B, Navez M, Rioult B, Tiberghien-Chatelain F, Ganry H. 5% lidocaine medicated plaster in elderly patients with postherpetic neuralgia: results of a compassionate use programme in France. *Drugs Aging* 2011;28:693-702.
40. Agbaje JO, Sun Y, Lambrichts I, Vrielinck L, Schepers S, Politis C. Safe surgical access to the mandibular nerve at the infratemporal fossae. *J Craniofac Surg* 2014;25:1454-7.
41. Politis C, Lambrichts I, Sun Y, Vrielinck L, Schepers S, Agbaje JO. Attachment rate of the inferior alveolar nerve to buccal plate during bilateral sagittal split osteotomy influences self-reported sensory impairment. *J Craniofac Surg* 2014;25:2121-6.

How to cite this article: Agbaje JO, Lambrichts I, Jacobs R, Politis C. Neuropathic pain after bilateral sagittal split osteotomy: management and prevention. *Plast Aesthet Res* 2015;2:171-5.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 03-11-2014; **Accepted:** 19-05-2015

Recalcitrant cubital tunnel syndrome

Adolfo Vigasio, Ignazio Marcoccio, Eleonora Morandini

Hand Surgery and Orthopaedic Microsurgery Unit, Istituto Clinico Città di Brescia-Gruppo San Donato, 25123 Brescia, Italy.

Address for correspondence: Dr. Ignazio Marcoccio, Hand Surgery and Orthopaedic Microsurgery Unit, Istituto Clinico Città di Brescia-Gruppo San Donato, 25123 Brescia, Italy. E-mail: info@ignaziomarcoccio.it

ABSTRACT

Ulnar nerve neuropathy at the elbow represents the second most frequent compression neuropathy of the upper extremity. Of the five different anatomical areas responsible for ulnar nerve compression at the elbow region, the epitrochlear-olecranon channel and Osborne's arcade are the most common. An additional cause of nerve damage is a dynamic process in which the ulnar nerve dislocates anteriorly at the epitrochlear-olecranon level during elbow flexion, partially or completely, causing nerve friction and constriction leading to chronic neuropathic pain. Failure after primary surgery is generally secondary to procedural errors or technical omissions, frequently represented by incomplete nerve decompression, failure to recognize nerve instability after nerve decompression, loosening of the nerve anchor after superficial nerve transposition with consequent spontaneous nerve relocation in the epitrochlear-olecranon channel, perineural fibrosis and neurodesis, which creates new nerve compression. In association with the clinical evaluation, electromyography studies, magnetic resonance imaging and ultrasound are useful tools that may aid in the decision-making process when considering revision surgery. Superficial anterior transposition is the most commonly employed technique but also has a high failure rate, as opposed to anterior deep transposition that is the method of choice for many surgeons despite being more technically demanding. The results of revision surgery following recalcitrant ulnar nerve compression at the elbow are inferior to those obtained after primary surgery. Nonetheless, the clinical advantages remain relevant provided that the revision surgery is performed by an expert surgeon. To avoid misinterpretation, the patient is completely informed of the quality of results.

Key words:

Cubital tunnel syndrome, failed nerve decompression, nerve transposition, recalcitrant nerve compression, ulnar nerve

INTRODUCTION

Ulnar nerve neuropathy at the elbow represents the second most frequent compression neuropathy of the upper extremity.^[1] The ulnar nerve may be compressed at the elbow region in the following five different anatomical areas,^[2] listed from proximal to distal: (1) arcade of Struthers, (2) the proximal epitrochlear region, (3) the epitrochlear-olecranon channel, (4) the fibrous arch between the humeral and ulnar portions of the flexor carpi ulnaris (FCU), better

known as Osborne's arcade, and (5) the vertical fibrous septum that originates from the ulna and separates the ulnar nerve and the ulnar part of the FCU from the pronator-flexor muscles innervated by the median nerve^[3] [Figure 1a and b]. The epitrochlear-olecranon channel and Osborne's arcade or ligament are the most frequent areas of compression. An additional cause of nerve damage at the epitrochlear-olecranon level is nerve instability. This is a dynamic process in which the ulnar nerve dislocates anteriorly during elbow flexion, reaching the epicondylar crest (subluxation) or passing over it completely (luxation). Ligamentous laxity or the absence of stabilization mechanisms^[4,5] causes a continuous snapping of the nerve over the epitrochlea, and in the case of complete anterior dislocation, the nerve kinks at the Osborne arcade, causing nerve friction and constriction leading to chronic neuropathic pain.^[6] Various surgical procedures have been described for the treatment of cubital tunnel syndrome, including *in situ*

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.160881

decompressions,^[7] medial epicondylectomy,^[8] subcutaneous transposition,^[9] intramuscular transposition,^[10] and submuscular transposition.^[11] However, as reported in the first description of this neuropathy by Panas^[12] in 1878, surgical treatment frequently yields poor results and may worsen the initial clinical condition. In a recent study conducted by the American Association of Hand Surgery,^[13] 61% of surgeons reported inferior results following surgical ulnar nerve decompression at the elbow compared with the results obtained following decompression after carpal tunnel release (44% satisfactory results vs. 88%, respectively).

According to the literature, no surgical technique may be defined as superior to the others.^[14-16] The persistence of preoperative symptoms after surgery is defined as failure, whereas the reappearance of symptoms after a period of relief is defined as recurrence, and surgical revision is indicated in both cases.^[15] Preoperative factors that may be associated with poor results after surgery depend on multiple elements, including an incorrect diagnosis,^[17] advanced neuropathy with a neurological lesion and muscular atrophy,^[18] coexisting pathologies such as double crush syndrome,^[16] cervical spine radiculopathies,^[19] thoracic outlet syndrome,^[20] ulnar compression syndromes at the wrist, endocrine disorders such as diabetes mellitus or thyroid disease, and polyneuropathies, particularly if they are associated with muscular atrophy or decreased sensation.^[13] Some of

these conditions may mimic ulnar nerve syndrome at the wrist, which, in addition to the different symptoms noted by patients, may render recognition of ulnar neuropathy at the elbow difficult.

CAUSES OF FAILURE AFTER PRIMARY SURGERY

Failure after surgery is mainly due to procedural errors or technical omissions, frequently represented by incomplete nerve decompression, failure to recognize nerve instability after the nerve has been decompressed, loosening of the nerve anchor after superficial nerve transposition with consequent spontaneous nerve relocation in the epitrochlear-olecranon channel, perineural fibrosis and neurodesis that creates a new site of nerve compression in areas different from those affected by the original compression, unintended injury to one or more sensory regional nerves or to the ulnar nerve itself, articular elbow instability due to unintended injury to the ulnar collateral ligament, or elbow stiffening in the flexed position.

It is widely accepted that when primary nerve decompression is performed, only one of the five possible sites of compression is generally found to actually be responsible for the nerve impingement,^[2] and these sites are usually the epitrochlear-olecranon channel or the Osborne fibrous arcade. The surgeon's experience will generally determine the decision to proceed with a wide nerve decompression or to perform a limited procedure.^[15]

The creation of a new nerve compression site may be realized when the anteriorly transposed nerve has not been widely released before the transposition. In fact, regardless of the method employed, when the nerve is anteriorly transposed, a new and nonanatomical path is created. It is therefore mandatory that the nerve lies in a soft and loose tissue bed such that no compression is endured by the nerve, which can occur when the medial intramuscular septum is not released or when the nerve kinks between the ulnar part of the FCU and the flexor and pronator muscle groups.^[13,14,16,21] To avoid such compression, when transposition is performed, it is advisable to widely release the nerve by opening the cubital channel and Osborne's arcade, removing the medial muscular septum, and opening both the arcade of Struthers and the septum between the ulnar stump of the FCU and the flexor-pronators.^[13] When *in situ* nerve decompression is completed, dynamic nerve instability during elbow flexion may occur (nerve subluxation or luxation), and the omission of nerve stability evaluation is considered to be a technical error. According to the literature,^[22] more than 50% of failures after simple decompression are due to the misdiagnosis of nerve instability. In cases of nerve instability, anterior nerve transposition, either deep or superficial, should be considered. Notably, nontraumatic nerve debridement and release, including that for a long tract (10-15 cm), does not damage the nerve or cause its devascularization, as was previously believed.^[13,15,23]

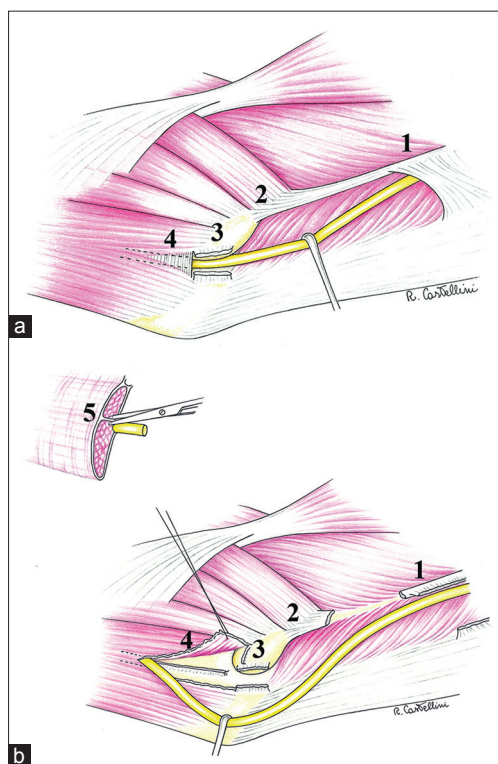


Figure 1: (a) There are five possible areas of ulnar nerve compression at the elbow level. (1): Arcade of Struthers; (2): proximal epitrochlear region; (3): epitrochlear-olecranon channel; and (4): fibrous arch between the humeral and ulnar parts of the flexor carpi ulnaris (FCU), better known as Osborne's arcade; (b) the figure shows the opening of Osborne's arcade (4) with the release of the septum between the ulnar part of the FCU and the flexor-pronator group (5). (1), (2) and (3) indicate the release of the other areas of decompression

Perineural fibrosis prevents the nerve from gliding during elbow excursion and may be related to patient predisposition or to improper intraoperative manipulation of the nerve.^[14] Fibrosis following simple decompression can cause adherence of the nerve to the epitrochlear-olecranon channel and can additionally cause the channel's closure due to the scarring at Osborne's ligament. Fibrosis after anterior transposition may occur independently of the technique employed and usually occurs at the site of a technical error or omission. Following superficial nerve transpositions, in particular, fibrosis preferentially localizes to the anterior soft tissue area and the epitrochlear region. According to the literature, superficial transposition presents the highest percentage of failure, suggesting that this technique has some intrinsic limitations represented by the position of the nerve under the skin, in a relatively hypovascular tissue susceptible to trauma.^[13,15] During anterior transposition, unintended injury to the subcutaneous antebrachial nerves may occur, leading to the formation of painful neuromas. During harvest of the ulnar nerve, in 61% of cases, 1 to 3 sensory nerves can be found proximal to the epicondyle (at a mean level of 1.8 cm from the epicondyle) or distally in 100% of cases (at a mean level of 3.1 cm from the epicondyle).^[24,13] An unintended nerve lesion may produce one or more painful neuromas, creating a hyperalgesic or hyperesthetic area in the medial part of the elbow, jeopardizing achieving satisfactory results from the decompression. Clinical studies have reported a nerve lesion rate of up to 90%, which is thought to occur secondary to the difficulty in locating and protecting these nerves during dissection.^[25,26] In contrast, lesions of the main trunk of the ulnar nerve are rare. To allow anterior nerve transposition, it is generally necessary to sacrifice the first motor fascicle to the FCU, which does not impair muscular function.^[27] Medial elbow instability is quite uncommon but may occur following damage to the collateral ulnar ligament, particularly during medial epicondylectomy, or as a consequence of an excessively aggressive anterior submuscular transposition.^[28] The ulnar collateral ligament is located just below the flexor-pronator group and originates, according to O'Driscoll *et al.*,^[28] from the medial epicondyle. Elbow stiffness presents as a flexion contracture due to prolonged immobilization, inappropriate postoperative rehabilitation, or excessive fibrosis formation in the soft tissues. The extension lag is generally from 5° to 30°.^[1,29,30] Stiffness occurs after deep transposition in 5-10% of cases^[14,15,31] and is generally due to prolonged immobilization. Following primary deep transposition, the authors permit the patient to remove the orthosis from the 3rd to 7th day postoperatively, for 1-2 h/day to perform active motion. The orthosis is definitively removed 20 days after surgery. In cases of persistent stiffness, adequate rehabilitation, and medical therapy are typically required.

CLINICAL EVALUATION

After obtaining a thorough clinical history, it is mandatory to verify the absence of neurological disorders originating from the upper extremities and cervical spine.

The evaluation may then proceed to the elbow with the evaluation of the position and extent of the surgical scar, as well as palpation of the ulnar nerve along its course, which may be inside the epitrochlear-olecranon channel or medial to the epicondyle if nerve transposition was performed. Areas of tenderness and nerve instability during elbow articular motion are carefully investigated. In cases of ulnar neuropathy at the elbow, palpation along the course of the nerve may trigger a Tinel's sign with the characteristic spread of paresthesias along the area innervated by the nerve up to the 4th and 5th fingers or, in the case of antebrachial sensory nerve neuropathies, to the medial part of the elbow and the medial proximal third of the forearm. An important provocative test is the "pressure-flexion test"^[32] in which pressure is exerted on the ulnar nerve for 1 min while the elbow is flexed. Sensitivity testing of the cutaneous territories of the ulnar and median nerves of the hand should be performed.^[14] The clinical evaluation is completed by motor testing. Advanced neuropathy is indicated by muscular hypotrophy or atrophy of the intrinsic muscles innervated by the ulnar nerve. Typically, atrophy initially involves the first dorsal interosseous muscle and then extends to the hypothenar muscles. Assessment for the griffe deformity at the 4th and 5th fingers (hyperextension of the metacarpophalangeal joint and flexion of the interphalangeal joint), the Froment and Wartenberg signs (abduction of the 5th finger) and the inability to cross the long fingers (crossed finger test) complete the motor testing. When present, muscle impairment represents a negative prognostic factor. In general, the neurological signs are less severe, with no alterations in muscle tone, and identification is based solely on the clinical evaluation of asthenia and/or diminished strength of the intrinsic muscles innervated by the ulnar nerve.

INSTRUMENTAL EVALUATION

Electromyography (EMG) is useful in the differential diagnosis to exclude radiculopathies, thoracic outlet syndrome, and median or ulnar nerve compression at the wrist. However, it fails to reveal neuropathies of the small sensory nerves in the elbow area. When preoperative EMG is performed, the results are particularly useful when assessing postoperative symptoms. In cases of recurrence, the neurological symptoms worsen, which correlates well with the conduction values, confirming the indication for surgical revision. Conversely, when worsening of the clinical condition is not confirmed by conduction studies, the indication for revision surgery should be dictated by the severity and persistence of symptoms. Notably, in cases of chronic axonal lesions, the conduction study results may be unchanged from the preoperative values while there is a slight improvement in the clinical condition.^[14] Therefore, when faced with worsening symptoms and unchanged conduction studies, it is difficult to determine whether it is more useful to base the treatment decision on the symptoms, which would suggest surgery, or on the conduction studies,

which would suggest a watchful waiting approach in the hopes of an eventual late recovery. Among 30 surgical revisions for the recalcitrant cubital tunnel, Gabel and Amadio^[15] performed surgery in 9 patients who had normal EMGs, concluding that normal conduction values were not sufficient to exclude surgical revision. Ultrasound (US) examination may also aid surgeons in the decision-making process. In fact, the dynamic and static evaluation of the ulnar nerve may reveal morphological alterations to the nerve trunk and to the surrounding soft tissues. In the authors' experience, magnetic resonance imaging (MRI) offers less information than a well-performed US. In association with the clinical evaluation, these 2 diagnostic tools may assist in the decision-making process. When surgery is postponed, and symptoms do not improve in a short period, revision surgery should be reconsidered. In conclusion, in some cases, particularly in those of primary nerve instability, the pre- and postoperative conduction studies may be negative even in the presence of severe neuropathic symptoms. In these cases, US examination and MRI may aid in identifying areas of mechanical nerve injury that may indicate the need for surgery.

Indications for revision surgery

The persistence or worsening of neuropathic pain, a decrease in cutaneous sensitivity with paresthesias along the territory of the ulnar nerve in the hand, and muscle deficits despite conservative medical treatment are indications for revision surgery,^[14,33] especially if they are associated with significant worsening of the conduction study results.

Techniques in revision surgery

The literature^[14-16] regarding surgical revision of failed ulnar nerve decompression at the elbow is limited to a few retrospective studies and case reports.^[26,29,34] According to these reports, superficial anterior transposition is the most commonly employed technique for primary surgery and presents a failure rate of 60-80%.^[35,36]

The goal of revision surgery is essentially to debride the nerve of its surrounding fibrosis that is causing the compression and kinking. Neurolysis has an important role in the revision of failed surgery of the ulnar nerve at the elbow. However, neurolysis cannot be used as an isolated technique because simple scar excision activates a fibrotic reaction that, within a brief time interval, will compress the nerve again, leading to failure.^[15] The removal of external perineural fibrosis is the primary indication for neurolysis.^[37-39] When the fibrosis extends within the nerve, among the fascicles, internal neurolysis should be considered. However, in such cases, damage to the vascular supply of the internal nerve may occur, and severe nerve scarring may develop, jeopardizing the attainment of a good result even in cases of anterior nerve transposition.^[15]

Medial epicondylectomy is not considered a satisfactory choice for revision surgery, as demonstrated by poor results in all of the cases treated by Goldberg *et al.*^[40] These results may be due to the fibrotic and hypovascular tissue in which the nerve remains following the procedure.^[19]

Anterior nerve transposition (subcutaneous, intramuscular, and submuscular) is the most commonly used revision technique after a failed nerve decompression,^[14,19] in cases of nerve instability (nerve subluxation or luxation), after medial epicondylectomy, and following a failed anterior transposition.

Among nerve transpositions, subcutaneous transposition yields unpredictable results when used in revision surgery, and, for this reason, it is rarely used by surgeons. If the nerve is moved from the cubital channel to reduce mechanical stress, it is transposed to a relatively hypovascular area^[13,15] where it is more exposed to direct trauma.^[19] Gabel and Amadio^[15] noted 12 poor results in 17 cases, whereas Caputo and Watson^[34] reported a 50% rate of poor results using this technique.

Intramuscular transposition is rarely used in revision surgery, with only two cases described in the literature, both of which yielded unsatisfactory results.^[15,18]

Submuscular transposition is widely used in revision surgery.^[41-43] With this technique, good results may be achieved following failed simple decompressions, medial epicondylectomy, and failed superficial transpositions.^[14-16] If performed using the proper technique, the results of anterior submuscular transposition are superior to those obtained with other techniques. In contrast, if this technique is employed for the treatment of failed submuscular transposition, the results are not satisfactory.^[15] In such cases, division of the epitrochlear muscular bridge and superficial transposition of the nerve with associated external neurolysis yields good results.^[34,44]

The following techniques are not effective and are rarely used: (1) the relocation of the nerve in the cubital tunnel has rarely been used by surgeons, as it is an ineffective method of treating recalcitrant ulnar nerve compression;^[14,22,33] (2) the results of nerve isolation with synthetic material, such as silicon or polymeric substances, are unsatisfactory;^[32,41] and (3) wrapping the ulnar nerve with autologous saphenous vein has been described with good results.^[45,46] Additional studies are needed prior to declaring this technique as an effective method for the treatment of failed ulnar nerve decompression.

The authors prefer nerve isolation by means of muscle flaps or fat tissue^[16,47] integrated with anterior submuscular transposition in cases of extensive perineural and soft tissue fibrotic reactions.

Technique preferred by the authors

Anterior deep transposition is the method of choice for many surgeons when revision ulnar nerve surgery is necessary. When approaching a revision surgery for recalcitrant ulnar nerve compression, it can be difficult to locate the area of nerve compromise. For this reason, a thorough exploration of all of the possible areas of compression is necessary, starting from the proximal arcade of Struthers to the deep septum between the FCU and the flexor-pronator group.^[3,14,15] The skin incision in revision

cases is generally longer than the initial incision, both in the proximal and distal directions. In the subcutaneous tissue, the identification of small regional sensory nerves may be difficult because they are frequently incorporated in the scar tissue from previous surgeries. It is not uncommon to find that one or more of these nerves have been severed. Possible neuromas must be removed,^[3,14,19] and proximal nerve stumps must be cauterized and positioned in good-quality soft tissue, such as the triceps muscle.^[3,14,19] In cases in which the ulnar nerve is entrapped in firm, fibrous scar tissue, it is advisable to begin the exploration proximal to the region of the previous incision to identify the nerve in a healthy area. Progressing distally, the nerve is then released from the scar. Depending on the technique used during the first surgery, the following three different situations may be encountered: (1) the nerve has been decompressed and is still in the epitrochlear-olecranon channel; (2) the nerve is outside of the epitrochlear-olecranon channel because dynamic nerve instability has occurred with recurrent anterior subluxation during elbow flexion, or because it has been transposed anteriorly in the subcutaneous tissue; or (3) the nerve is outside of the epitrochlear-olecranon channel because it has been transposed anteriorly under the flexor-pronator muscles. Regardless of where the nerve is located, the presence of scar tissue is a consistent pattern, which increases both the difficulty of the dissection and the risk of nerve damage. In these cases, identification of the nerve distal to the cubital channel at the FCU muscle entrance is recommended. From there, dissection proceeds in a distal to proximal direction. Once the nerve and potential compression areas have been released, the following different anatomical situations may be encountered: (1) the ulnar nerve was previously decompressed only and is still located in the epitrochlear-olecranon channel. Proceed with anterior submuscular transposition

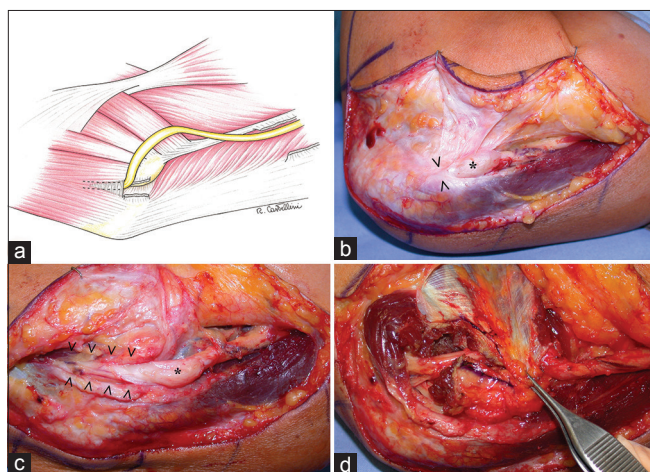


Figure 2: When decompression is insufficient, the nerve kinks at Osborne's arcade and is compressed by the intermuscular septum when transposed anteriorly. (a) The patient underwent two surgeries for simple nerve decompression. The nerve is dislocated anterior to the epitrochlear bone, presenting with a pseudoneuroma bulging (*) proximal to the compression area at Osborne's arcade level (>) which had not been previously released (<); (b) following decompression at zones 4 and 5 (refer to Figure 1) (<) and external neurolysis (*), nerve transposition may be performed; (c) anterior submuscular transposition using a muscle Z-lengthening procedure

with myotomy of the epitrochlear muscles using the Z-lengthening technique.^[16] It is of paramount importance that excision of the medial intermuscular septum and a complete opening of the distal septum between the FCU and the flexor-pronator muscle group are performed. If the transposition has been accomplished properly, the nerve will lie in its new location without areas of compression or kinking; (2) the ulnar nerve was previously transposed anteriorly and superficially, but there is currently severe fibrosis that renders nerve debridement difficult. If the intermuscular septum was not released during the previous surgery, the nerve passes over the septum, which dislocates the nerve from beneath, creating compression. In other cases, the nerve may be found atop the epitrochlear bone as a consequence of an erroneous transposition or of a failure of the soft tissue anchorage. This situation creates tension along the nerve, resulting in acute angulation and kinking of the nerve at Osborne's arcade or at the deep distal septum at the level of the FCU. External neurolysis and submuscular transposition are performed as described in section A [Figures 2-5]; and (3) the ulnar nerve was previously already transposed. Surgery then commences with identification of the nerve proximal and distal to the scarred area, isolation of the nerve from the point of fibrosis up to the entrance in the epitrochlear muscles, and decompression of the arcade of Struthers, the intermuscular septum proximally, and the deep flexor-pronator septum distally. Release of the nerve at the entrance, exits, and beneath the muscular channel is then performed. The nerve is generally found

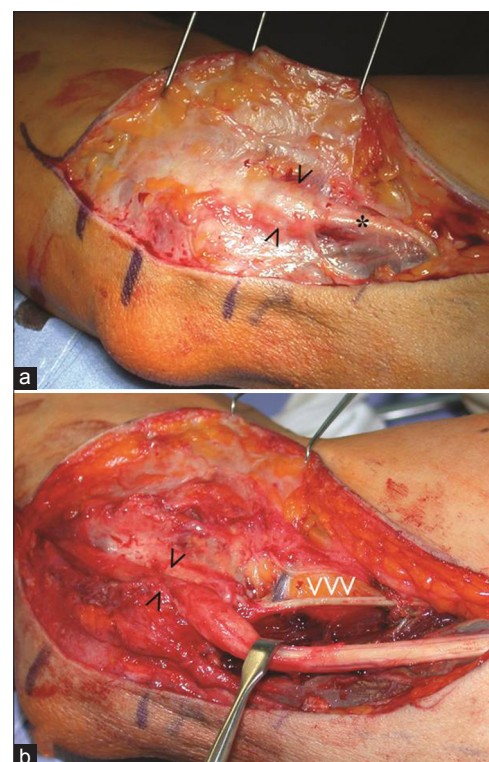


Figure 3: Failed nerve decompression treated with superficial anterior transposition. (a) The ulnar nerve (*) is fibrotic (<>), swollen, and hard to palpation; (b) the intermuscular septum (white arrows) and the distal deep septum in zone 5 (black arrows) were not released during the initial surgery

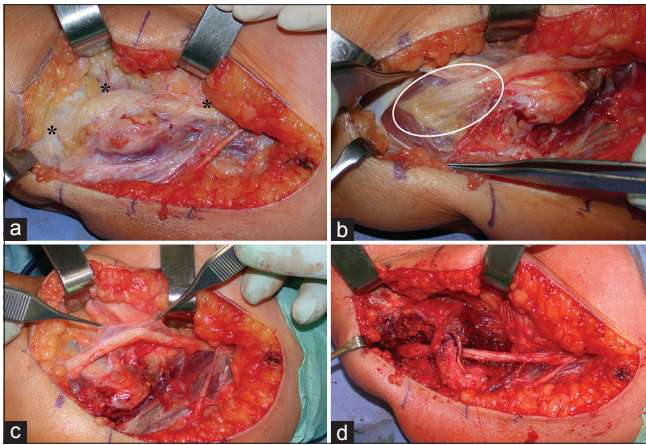


Figure 4: Failed superficial nerve transposition. (a) The nerve is taut over the epitrachlear bone (*) and kinks at the deep septum (zone 5) for an insufficient transposition; (b) nerve decompression by the release of the flexor carpi ulnaris and deep septum. The circled area shows the region of ischemic injury to the nerve secondary to compression; (c) after external neurolysis has been performed, the nerve is prepared for anterior submuscular transposition; (d) following transposition, the nerve lies in a soft and vascular tissue bed without tension

to be entrapped by fibrotic tissue^[44] in the new muscular channel and neurolysis is necessary. When neurolysis alone is insufficient for the release of the nerve or when the muscular channel has become fibrotic and does not provide adequate vascularization of the nerve, the muscular bridge is opened, and the nerve is transferred superficially.^[34]

POSTOPERATIVE TREATMENT

A brachial-metacarpal plaster cast is applied for 20 days, with the elbow at 100°-120° of extension. By the 3rd postoperative day, the patient is allowed to temporarily remove the plaster to perform careful active elbow flexion and extension movements. From the 7th day, the patient begins active careful supination with the elbow at 60°-90° of flexion. From the 15th day, supination with the elbow extended is permitted. The plaster is definitively removed 20 days postoperatively, and the patient is then placed under the care of a therapist.

FUTURE DIRECTIONS

Ulnar nerve anatomy at the elbow region and pathophysiology of the compression syndrome are well-recognized. Nonetheless, failure following nerve decompression alone or with associated anterior nerve transposition still occurs. The failure to recognize dynamic ulnar nerve instability, idiopathic or induced after *in situ* nerve decompression, represents the most frequent procedural error leading to surgical failure. A thorough understanding of the mechanisms causing ulnar nerve compression and injury would reduce the rate of recurrence.

CONCLUSION

The results of revision surgery following recalcitrant ulnar nerve compression at the elbow are inferior to those

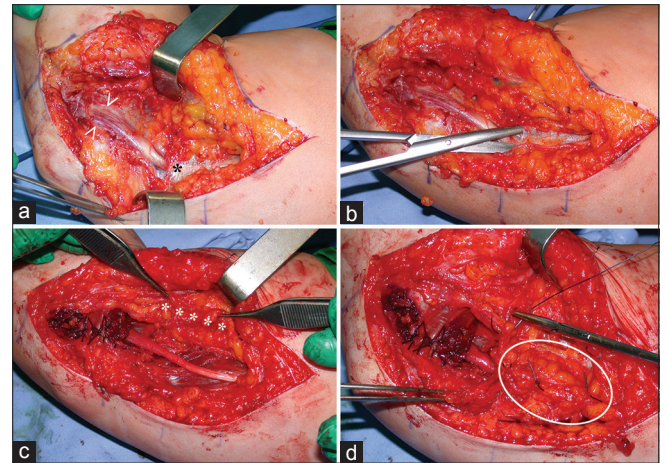


Figure 5: Failed superficial nerve transposition. (a and b) Arcade of Struthers (*) was not released during the first surgery, causing nerve kinking and compression. At the epitrachlear level, the nerve appears to lie within good tissue without tension (>); (c) following debridement, the nerve lies in a soft and vascular tissue bed without tension. An adipofascial flap is harvested (*); (d) anterior submuscular transposition with muscular Z-lengthening is performed. The adipofascial flap protects the nerve in the proximal epitrachlear region

obtained after primary surgery, particularly in patients over the age of 50 years, when conduction studies show muscle denervation, or when there is a history of multiple surgeries.^[15] To avoid the misinterpretation that the partial resolution of preoperative symptoms is a failure of treatment, it is mandatory that the patient be completely informed prior to surgery.^[16] Chronic axonal degeneration is frequently associated with marginal improvement of neuropathic pain, tenderness in the compression area, and hand dysesthesias,^[14,16] without a high rate of complete restoration of sensitivity and muscle strength. Nonetheless, the clinical advantages remain relevant provided that an expert surgeon performs the revision surgery.

REFERENCES

1. Dawson DM, Hallett M, Millender LH. Entrapment Neuropathies. 1st ed. Boston: Little Brown; 1983. p. 88.
2. Amadio PC. Anatomical basis for a technique of ulnar nerve transposition. *Surg Radiol Anat* 1986;8:155-61.
3. Mackinnon SE, Novak CB. Operative Findings in reoperation of patients with cubital tunnel syndrome. *Hand (N Y)* 2007;2:137-43.
4. Dellon AL. Musculotendinous variation about the median humeral epicondyle. *J Hand Surg Br* 1986;11:175-81.
5. O'Driscoll SW, Horii E, Carmichael SW, Morrey BF. The cubital tunnel and ulnar neuropathy. *J Bone Joint Surg Br* 1991;73B: 613-7.
6. Childress HM. Recurrent ulnar-nerve dislocation at the elbow. *Clin Orthop Relat Res* 1975;108:168-73.
7. Osborne GV. The surgical treatment of tardy ulnar neuropathy. *J Bone Joint Surg Br* 1957;39B:782.
8. King T, Morgan FP. Late results of removing the medial humeral epicondyle for traumatic neuritis. *J Bone Joint Surg Br* 1959;41B:51-5.
9. Curtiss BF. Traumatic ulnar neuritis: transposition of the nerve. *J Nerv Ment Dis* 1898;25:480-4.
10. Adson AW. The surgical treatment of progressive ulnar paralysis. *Minn Med* 1918;1:455-60.
11. Learmont JR. A technique for transplanting the ulnar nerve. *Surg Gynecol Obstetr* 1942;75:792-3.
12. Panas J. Upon a rare case of ulnar nerve palsy. *Arch Gen Med* 1878;2:5-22. (in French)
13. Novak BC, Mackinnon SE. Selection of operative procedures for cubital tunnel syndrome. *Hand (N Y)* 2009;4:50-4.

14. Ruchelsman DE, Lee SK, Posner MA. Failed surgery for ulnar nerve compression at the elbow. *Hand Clin* 2007;23:359-71.
15. Gabel GT, Amadio PC. Reoperation for failed decompression of the ulnar nerve in the region of the elbow. *J Bone Joint Surg Am* 1990;72A:213-9.
16. Vogel BR, Nossaman BC, Rayan GM. Revision anterior submuscular transposition of the ulnar nerve for failed subcutaneous transposition. *Br J Plast Surg* 2004;57:311-6.
17. Puckett BN, Gaston RG, Lourie GM. A novel technique for the treatment of recurrent cubital tunnel syndrome: ulnar nerve wrapping with a tissue engineered bio scaffold. *J Hand Surg Eur Vol* 2011;36:130-4.
18. Gay JR, Love JG. Diagnosis and treatment of tardy paralysis of the ulnar nerve: based on a study of 100 cases. *J Bone Joint Surg Am* 1947;29:1087-97.
19. Jackson LC, Hotchkiss RN. Cubital tunnel surgery, complications and treatment of failures. *Hand Clin* 1996;12:449-56.
20. Rayan GM. Thoracic outlet syndrome. *J Shoulder Elbow Surg* 1998;7:409-51.
21. Spinner M. Nerve decompression. In: Morrey BF, editor. *Master Techniques in Orthopaedic Surgery: The Elbow*. New York: Raven Press; 1994. p. 183-206.
22. Antoniadis G, Richter HP. Pain after surgery for ulnar neuropathy at the elbow: a continuing challenge. *Neurosurgery* 1997;41:585-9.
23. Heithoff SJ. Cubital tunnel syndrome does not require transposition of the ulnar nerve. *J Hand Surg Am* 1999;24A: 898-905.
24. Lowe JB 3rd, Maggi SP, Mackinnon SE. The position of crossing branches of the medial ante brachial cutaneous nerve during cubital tunnel surgery in humans. *Plast Reconstr Surg* 2004;114:692-6.
25. Mackinnon SE, Dellon AL, Hudson AR, Hunter DA. A primate model for chronic nerve compression. *J Reconstr Microsurg* 1985;1:185-95.
26. Rogers MR, Bergfield TG, Aulicino PL. The failed ulnar nerve transposition. Etiology and treatment. *Clin Orthop Relat Res* 1991;269:193-200.
27. Watchmaker GP, Lee G, Mackinnon SE. Intra-neural topography of the ulnar nerve in the cubital tunnel facilitates anterior transposition. *J Hand Surg Am* 1994;19:915-22.
28. O'Driscoll SW, Jalszynski R, Morrey BF, An KN. Origin of the medial ulnar collateral ligament. *J Hand Surg Am* 1992;17:164-8.
29. Broudy AS, Leffert RD, Smith RJ. Technical problems with ulnar nerve transposition at the elbow: findings and results of reoperation. *J Hand Surg Am* 1978;3:85-9.
30. Leffert RD. Anterior submuscular transposition of the ulnar nerves by Learmonth technique. *J Hand Surg Am* 1982;7:147-55.
31. Janes PC, Mann RJ, Farmworth TK. Submuscular transposition of the ulnar nerve. *Clin Orthop Relat Res* 1989;238:225-32.
32. Novak CB, Lee GW, Mackinnon SE, Lay L. Provocative testing for cubital tunnel syndrome. *J Hand Surg Am* 1994;19:817-20.
33. Filippi R, Charalampaki P, Reisch R, Koch D, Grunert P. Recurrent cubital tunnel syndrome. Etiology and treatment. *Minim Invasive Neurosurg* 2001;44:197-201.
34. Caputo AE, Watson HK. Subcutaneous anterior transposition of the ulnar nerve for failed decompression of cubital tunnel syndrome. *J Hand Surg Am* 2000;25:544-51.
35. Mowlavi A, Andrews K, Lille S, Verhulst S, Zook EG, Milner S. The management of cubital tunnel syndrome: a meta-analysis of clinical studies. *Plast Reconstr Surg* 2000;106:327-34.
36. Dellon AL. Review of treatment results for ulnar nerve entrapment at the elbow. *J Hand Surg Am* 1989;14A: 688-700.
37. Goth D. Animal experiment studies of neurolysis of peripheral nerves. *Handchir Mikrochir Plast Chir* 1987;19:212-6.
38. Graf P, Haewe W, Biemer E. Vascular supply of the ulnar nerve following neurolysis in the area of the elbow. *Handchir Mikrochir Plast Chir* 1986;18:204-6.
39. Rydevik B, Lundborg G, Nordborg C. Intra-neural tissue reactions induced by internal neurolysis. An experimental study on the blood-nerve barrier, connective tissues and nerve fibres of rabbit tibial nerve. *Scand J Plast Reconstr Surg* 1976;10:3-8.
40. Goldberg BJ, Light TR, Blair SJ. Ulnar neuropathy at the elbow: results of medial epicondilectomy. *J Hand Surg Am* 1989;14:182-8.
41. Posner MA. Compressive ulnar neuropathies at the elbow: II. Treatment. *J Am Acad Orthop Surg* 1998;6:289-97.
42. Siegel DB. Submuscular transposition of the ulnar nerve. *Hand Clin* 1996;12:445-8.
43. Kleinman WB. Revision ulnar neuroplasty. *Hand Clin* 1994;10:461-77.
44. Dagregorio G, Saint-Cast Y. Simple neurolysis for failed anterior submuscular transposition of the ulnar nerve at the elbow. *Int Orthop* 2004;28:342-6.
45. Vardakas DG, Varitimidis SE, Sotereanos DG. Findings of exploration of a vein-wrapped ulnar nerve; report of a Case. *J Hand Surg Am* 2001;26:60-3.
46. Varitimidis SE, Riano F, Sotereanos DG. Recalcitrant post-surgical neuropathy of the ulnar nerve at the elbow: treatment with autogenous saphenous vein wrapping. *J Reconstr Microsurg* 2000;16:273-7.
47. Godette GA, Rayan GM. Medial triceps flap coverage for an ulnar neuroma. *Orthop Rev* 1993;22:603-6.

How to cite this article: Vigasio A, Marcoccio I, Morandini E. Recalcitrant cubital tunnel syndrome. *Plast Aesthet Res* 2015;2:176-82.
Source of Support: Nil, **Conflict of Interest:** None declared.
Received: 02-02-2015; **Accepted:** 29-03-2015

Vascularized nerve “grafts”: just a graft or a worthwhile procedure?

Salvatore D’Arpa, Karel Etienne Yvonne Claes, Filip Stillaert, Britt Colebunders, Stan Monstrey, Phillip Blondeel

Department of Plastic and Reconstructive Surgery, University Hospital Ghent, 9000 Ghent, Belgium.

Address for correspondence: Dr. Salvatore D’Arpa, Department of Plastic and Reconstructive Surgery, University Hospital Ghent, 9000 Ghent, Belgium. E-mail: salvatore.darpa@uzgent.be

ABSTRACT

The aim of this review is to extrapolate evidence regarding the use of vascularized nerve grafts (VNGs) in peripheral nerve reconstruction and summarize available data on their indications, if any, and clinical applications. A review of the literature via the PubMed database was performed with analysis of ninety-five articles on the experimental and clinical studies of VNGs. Eight relevant questions were selected to be answered about VNGs. VNGs allow faster nerve regeneration and convey a functional advantage under certain clinical conditions such as large nerves, proximal lesions, and nonvascularized recipient beds. Several donor sites are available which have been being divided by body region in this manuscript. VNGs perform better than non-VNGs and provide an advantage in selected cases. However, limited availability and donor site morbidity still limit their application. We foresee a wider application of vascularized nerve allografts to overcome these problems.

Key words:

Nerve injury, nerve reconstruction, nonvascularized nerve graft, vascularized nerve graft

INTRODUCTION

The first nerve graft was performed by Phillipeaux and Vulpian in 1870.^[1] In 1939, Bunnell and Boyes^[2] reported their experience with thin autogenous nerve grafts, which were transplanted with encouraging results. Soon thereafter, the clinical outcomes of free autologous nerve grafting were improved by the application of cable grafts to improve graft revascularization and avoid the central necrosis observed in large grafts.^[3-5]

To overcome the problems caused by central necrosis due to insufficient vascularization observed with nonvascularized nerve grafts (NVNGs),^[5] VNGs were introduced as a solution to improve nerve graft outcomes.

The first VNG in the upper extremity was a pedicled nerve graft, described in 1945 by St. Clair Strange.^[6]

In 1976, Taylor and Ham^[7] reported the first free VNG: a 24 cm segment of the superficial radial nerve, based on the radial artery, was used to reconstruct a median nerve in a case of Volkmann’s ischemic contracture. Since then, several experimental and clinical studies have investigated the role and effectiveness of VNGs although conclusive findings have not been reported. The fact itself that VNGs are still named “grafts” instead of “flaps” testifies the doubts surrounding the benefits of a vascularized nerve repairing a nerve gap.

Although it is generally believed that VNGs perform better for longer gaps and larger nerves or in scarred beds, evidence is lacking. Whether a more complicated VNG procedure is justified or not, and when, is still unclear.

We have performed a review of the literature of both experimental and clinical studies on VNGs to find answers to the following questions:

- What is the theoretical advantage of a VNG?
- Do VNGs have an efficient vascularization?
- Is vascularization of a VNG superior to that of a NVNG?
- Regeneration in VNGs vs. NVNG
- What are the indications for a VNG?
- Comparison of donor sites in the upper and lower limbs
- How should we consider the nerve incorporated in a flap?

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.160882

WHAT IS THE THEORETICAL ADVANTAGE OF A VASCULARIZED NERVE GRAFT?

A VNG should be theoretically result in a more functional nerve for several reasons: (1) vascularization is maintained: revascularization of the nerve graft restores the extrinsic neural blood vessels; (2) reduction of intraneural fibrosis secondary to ischemia facilitates axonal regeneration; (3) faster reinnervation reduces denervation muscle atrophy; and (4) maintenance of vascularization promotes faster Wallerian degeneration and clearance of myelin debris, reducing obstruction to axonal growth into the graft with faster remyelination of regenerated axons.

Nerves have both an extrinsic and intrinsic blood supply. The extrinsic system consists of arteries and veins that accompany a nerve outside of its epineurium for a variable distance along its length. The intrinsic system consists of epineural, perineural and endoneural vessels running longitudinally within the nerve. The two systems freely interface through the vasa nervorum, which pass through the mesoneurium.

Conventionally, interpositional nerve grafting interrupts both the extrinsic and intrinsic systems, which can be restored only by peripheral neovascularization. Lind and Wood^[8] suggested that early ischemia of conventional nerve grafts may be associated with sufficient graft necrosis to hinder the stromal function of the graft as a conduit for advancing axons.

Revascularization of a nerve graft is carried out in two ways: vessels from the surrounding tissue bed grow into the graft tissue (centripetal revascularization) and vessels from the end of the graft sprout into the existing vascular tree (inosculation). Vascular ingrowth from the surrounding tissues is the most important.^[8,9] As donor nerve caliber increases, the ability for neovascularization to reach the center of the nerve decreases.^[2,5] Experimental and clinical evidence have confirmed that a critical diameter is reached beyond which central necrosis will result.^[10-12]

DO VNGs HAVE AN EFFICIENT VASCULARIZATION?

Several clinical and experimental studies have demonstrated that free and pedicled VNGs do have an efficient vascularization, that their extremities bleed well after isolation and transfer, that they are well-perfused and that their anastomoses stay patent.^[13]

It has been postulated that VNGs can be performed without the need for venous anastomosis because they drain through their cut ends. El-Barrany *et al.*^[14] have described five types of nerve vascularization patterns in relation to their feasibility for harvest as VNGs: (1) no dominant arterial pedicle; (2) one dominant arterial pedicle; (3) one dominant arterial pedicle that

divides into two branches which course along the nerve; (4) multiple dominant arterial pedicles; and (5) multiple dominant arterial pedicles which form a continuous artery accompanying the nerve.

According to the authors, the best nerves for use as VNGs are the superficial radial nerve and the deep peroneal nerve (type 2 grafts), the saphenous nerve (type 4 graft) and the ulnar nerve (type 5 graft).^[14]

Taylor and Ham^[7] also classified peripheral nerves according to their blood supply with special reference to their suitability for microvascular free transfer:

(1) Type A: considered to be the ideal nerve for free transfer, as the neurovascular bundle contains a long unbranched nerve that receives a segmental blood supply from a single parallel arteriovenous (AV) system. The superficial radial and ulnar neurovascular bundles, the posterior and anterior tibial neurovascular bundles and the median nerve with the brachial artery belong to this type; (2) Type B: similar to Type A, but the nerve branches early and must be reversed to avoid axonal loss, provided that the unidirectional flow of the veins is taken into account. The intercostal neurovascular bundle or the radial nerve with the profunda brachii artery belong to this type; (3) Type C: long unbranched nerve supplied by a single large nutrient vessel; the median nerve when supplied by a large median artery or the sciatic nerve when its arteria comitans is the dominant supply belong to this type; (4) Type D: long unbranched nerve which receives nutrient branches from different "parent" vessels of various diameters. The sciatic nerve in the thigh belongs to this type. Conversely, the sural nerve and the medial cutaneous nerve of the forearm are usually unsuitable, as the "parent" vessels which give rise to the nutrient branches are small and diverse; and (5) Type E: branching nerve with a fragmented blood supply; a most unsatisfactory situation for free transfer. The posterior cutaneous nerve of the forearm, the cutaneous nerves of the thigh, and the saphenous nerve in the calf belong to this type.

IS VASCULARIZATION OF A VNG SUPERIOR TO THAT OF A NVNG?

Yes, vascularization of a VNG is considered to be superior as it possesses an independent blood supply that avoids ischemia eliminating the need for revascularization from the surrounding wound bed. It is speculated that this avoids core necrosis and eventual scarring within the graft and maintains Schwann cells viability.^[7]

Although it has been shown that VNGs are efficiently vascularized, it can be postulated that revascularization of a NVNG can, under certain conditions, be as efficient as a well-vascularized bed. NVNG remain nonvascularized for 3 days in a well-vascularized bed^[15] and for up to 14 days in a nonvascularized bed.^[16] The flow across NVNG then catches up and is even superior to that of VNG.^[17] This difference can be explained by the flow

modifications observed in a pedicled flap^[18] such as sympathetic stimulation that reduces blood flow to 93% of normal through production of noradrenaline, vasoactive intestinal polypeptide, 5-hydroxytryptamine and substance P. Most experimental models assessed pedicled VNG affected by these factors, rather than free ones.^[19,20] Settergren and Wood.^[17] showed in their canine model a better blood flow after 4-6 days for NVNG compared to a VNG. A free VNG, not affected by sympathetic stimulation, would likely eliminate this difference.

While NVNGs, when placed in a well-vascularized bed, undergo a 72 h period of warm ischemia prior to neovascularization, VNGs do not.^[16,17] When placed in a nonvascularized bed, the ischemic period last up to 14 days for a short NVNG (30 mm nerve graft in rats),^[16] while VNGs have no ischemia time. Despite remaining avascular for 14 days, NVNGs eventually regained their vascularity and performed better than VNGs on nerve conduction velocity studies.^[16,17] Still it is unclear if this has any clinical relevance.

The above findings were observed in thin small animal nerves. It is likely that a larger nerve, such as a human mixed nerve of a limb, is not as efficiently revascularized from the surrounding bed as the small nerves investigated in animal models. Clinical experience has shown that small cable grafts are required to make a large caliber nerve that will be efficiently revascularized.^[10-12] Revascularization might not reach the core in a NVNG while a VNG stays well-perfused.

REGENERATION IN VASCULARIZED NERVE GRAFTS VERSUS NONVASCULARIZED NERVE GRAFT

Although the mechanism is not clear, VNGs appear to provide more effective regeneration than NVNGs. This difference becomes more evident and functionally relevant as length and caliber of the graft increase and as wound vascularization decreases. No comparison has been made in the clinical setting, but clinical reports generally agree that VNGs provide faster regeneration.

Studies of VNGs in animal models have reported conflicting results. For the purpose of clarity, we have divided the following discussion into studies performed on a vascularized bed and studies performed on a nonvascularized bed.

Normal (vascularized) bed

McCullough *et al.*^[21] found no difference between vascularized and nonvascularized grafts when studied by electrophysiological examination and the degree of axonal regeneration. In a similar rat sciatic nerve model, Seckel *et al.*^[22] found no differences in number of regenerated axonal fibers, amount of intraneural scarring, or thickness of regenerated myelin sheaths. Pho *et al.*^[23] performed histological studies in eighteen rat femoral nerves. Their experiment showed no

difference in the degree of vascularization, reticulin framework collapse, rate and extent of axonal regeneration and remyelination between non-vascularized and conventional nerve grafts.

In contrast, using a large sciatic nerve gap in the rabbit, Restepo *et al.*^[24] found that VNGs in all time periods studied (from 5 weeks to 15 weeks) did better in terms of remyelination and number of axonal fibers than did conventional nerve grafts. Shibata *et al.*^[25] reported results on 40 rabbits median nerve grafts (20 vascularized and 20 nonvascularized). Although there were no significant differences in nerve conduction, action potential, and axon diameters, there were statistically significant differences in muscle contraction force (20% greater in VNGs than NVNGs and comparable to the healthy control side) and axon counts. Kanaya *et al.*^[26] reported that the vascularized sciatic nerve graft group showed a better mean sciatic function index (SFI)^[27] ($n = 30$, $SFI = -64 \pm 11$) than the nonvascularized sciatic nerve graft group ($n = 27$, $SFI = 99 \pm 7$) ($P < 0.01$). A SFI of -100 represents a complete loss of function of the nerve. There was also a significantly higher nerve conduction velocity in the VNG group. This was the only study to evaluate the resulting function instead of morphologic parameters. In a normally vascularized bed, VNGs appear to perform better. Kärcher and Kleinert^[28] evaluated recovery following a 1.5 cm sciatic nerve defect in rats repaired with a pedicled femoral nerve graft with the creation of an AV fistula of the femoral vessels. He reported better and faster regeneration of a VNG that was complete at 5 months, but which was incomplete in the NVNG.

Scarred (nonvascularized) wound bed

Koshima and Harii^[29] tried to replicate a scarred wound bed using a rat burn wound model with nerves transplanted into silicone tubes. They demonstrated an increased size and density of myelinated axons and earlier regeneration of nerve fibers in VNGs as compared to conventional nerve grafting.

Mani *et al.*^[16] did not find any significant difference in nerve conduction velocity studies between vascularized and non-VNGs in avascular graft beds, even following a prolonged initial period of revascularization for non-VNGs.

Functional results

Prior studies have produced conflicting results secondary to a lack of homogeneity in evaluation methods. As previously noted, Kanaya *et al.*^[26] reported in their work that the vascularized sciatic nerve graft group showed a significantly better mean SFI^[27] than the nonvascularized sciatic nerve graft group.

Several authors had reported superior results when placing VNGs where previous conventional nerve grafts had already failed. Rose and Kowalski^[30] reported good results with the dorsalis pedis artery-peroneal nerve complex in five cases with a digital sensory nerve reconstruction in the setting of prior failed non-VNGs.

Other clinical studies have suggested that VNGs perform better in poorly vascularized,^[7,31] scarred beds.^[32-35]

WHAT ARE THE INDICATIONS FOR A VNG?

It is impossible to establish clear-cut indications for VNGs, as experimental settings fail to replicate actual clinical situations. Having established that VNGs perform better than NVNGs under specific conditions, the clinical papers available were reviewed. The currently available literature provides only case reports or case series where the indication is based on the surgeon's judgment and experience, rather than on experimental findings. However, the surgeon's judgment and experience are also worthy. The current indications for VNG are presented, divided into zone of injury.

Vascularized nerve grafts are not indicated in all nerve reconstruction procedures. When a NVNG works well, the additional complexity, and sometimes morbidity, of the procedure is not justified by superior results. A VNG must be considered in the following scenarios [Table 1]: (1) nerve gaps longer than 6 cm. This is an arbitrary and linear measure that does not take into the account the diameter of the nerve to be reconstructed. However, the diameter can be increased with cable grafting; (2) nonvascularized beds; (3) composite defects requiring a free flap. In these cases, the nerve can be included in the free flap with little complexity and no morbidity using the same donor site and the nerves directed to the flap; (4) proximal lesions (brachial plexus); (5) long denervation times. The faster reinnervation provided by a VNG might be an advantage in cases that have been referred late and in which muscle atrophy has ensued; (6) cases that have to undergo radiation therapy which could compromise or retard the rate of revascularization; and (7) presence of an available donor nerve in the same surgical field which can be harvested without additional morbidity, such as the pedicled great auricular nerve in facial nerve defects during parotidectomies.

Age is a controversial issue as regeneration is worse with aging, but a more complex procedure might also be less desirable in the elderly. Because recovery is slower with age, it might be a relative indication for a VNG. However, age alone is not a contraindication to a microsurgical procedure, and aged people in good general condition can be considered candidates for a VNG. This applies especially to motor nerves reconstruction and to late referrals.

In the following sections, clinical indications will be reviewed divided by anatomical region in order to provide a quick reference to those who approach VNG nerve reconstruction.

Facial nerve injuries

Since Balance and Due^[36] first introduced nerve grafting for the bridging of facial nerve defects, the sural nerve,

the ansa cervicalis, and the great auricular nerve have been the most commonly used NVNGs.^[37] In scarred, irradiated, or to be irradiated fields, functional recovery of the facial nerve can be less satisfactory and VNGs have been used for cases with these risk factors.^[38-41] Although these reports are anecdotal without comparison to NVNGs, there appears to be a consensus for this indication^[42] [Table 2].

The VNGs used are:

Vascularized great auricular nerve graft

Koshima *et al.*^[41] used a pedicled 4 cm vascularized ipsilateral great auricular nerve graft for the buccal branch and a nonvascularized sural nerve graft for the zygomatic branch to provide an inpatient control. They reported faster and better recovery for the VNG.

Vascularized lateral femoral cutaneous nerve graft

The lateral femoral cutaneous nerve (LFCN) can be harvested with an anterolateral thigh (ALT) flap, with a superficial circumflex iliac artery perforator (SCIP) flap or alone.^[40] Lida *et al.*^[43] reported the first successful use of a free vascularized LFCN graft combined with an ALT flap to repair the facial nerve and a soft tissue defect, and provided objective measurements of functional recovery at 14 months (House-Brackmann^[44] grade III/VI, 40-point grading system:^[45] 28/40). Kashiwa and colleagues described an inferolateral extension of the groin flap based on the vessels accompanying the LFCN^[46] for reconstruction of a facial skin and soft tissue defect including all branches of the facial nerve following tumor ablation with nerve gaps of up to 10 cm. The authors did not report any objective data but noted that facial animation began to return 6 months postoperatively, even in the setting of postoperative chemotherapy and radiotherapy. They observed that a relatively "comfortable" result was obtained, aside from some degree of synkinesis due to misdirection of the regenerated nerve.

Table 1: Indications for VNGs

Nerve gaps longer than 6 cm
Nonvascularized beds
Composite defects requiring a free flap
Proximal lesions (brachial plexus)
Long denervation times
Planned radiation therapy
Pedicled VNG available in the same field
Advanced age

VNG: Vascularized nerve graft

Table 2: Indications for a VNG in facial nerve injuries

Vascularized great auricular nerve
Vascularized LFCN
Vascularized deep peroneal nerve
Vascularized sural nerve
Vascularized motor nerve of the vastus lateralis muscle
Fascicular turnover method

VNG: Vascularized nerve grafts, LFCN: Lateral femoral cutaneous nerve

There are three shortcomings of this method. First, the location and direction of the nerve graft are restricted because the nerve graft is attached to the ALT flap. Therefore, a sufficient length of the nerve graft is required, theoretically increasing time to reinnervation. Second, the number of branches of the LFCN varies greatly among patients. In cases in which the number of branches is fewer than that required for facial nerve reconstruction, an additional free nerve graft is needed. Finally, if the recipient nerve is larger than the lateral femoral nerve branches and the nerve has to be cable grafted, vascularization will be interrupted, resulting in a mixed VNG/NVNG reconstruction.

Vascularized deep peroneal nerve graft

Koshima *et al.*^[39] reported a case in which a combined anteroposterior tibial perforator-based flap was used for the repair of a large facial defect involving the facial nerve (10 cm nerve gap). The deep peroneal nerve of the flap was interposed between the proximal stump and the transected zygomatic and buccal branches of the facial nerve. The authors reported the subjective judgment of a “considerable degree of facial animation” on the affected side eighteen months postoperatively. The disadvantages of this VNG are temporary postoperative edema, hypoesthesia of the donor foot and a poor donor site scar where skin has been harvested.

Deep peroneal, sural and vastus nerves

Kimata *et al.*^[38] reported 10 cases of facial nerve reconstruction in which several types of VNGs were used for reconstruction of multiple branches of the facial nerve. The nerves used were: (1) the free vascularized sural nerve graft, attached to a small peroneal monitoring flap and nourished by the peroneal vessels; (2) the free vascularized deep peroneal nerve graft attached to a small dorsalis pedis monitoring flap and nourished by anterior tibial vessels; (3) the free vascularized motor nerve of the vastus lateralis muscle nourished by the descending branch of the lateral circumflex femoral vessels; and (4) the free vascularized lateral femoral nerve of the thigh combined with an ALT flap.

In 4 patients, the functional recovery of the facial nerve could not be assessed because of local tumor recurrence soon after surgery. Results with the House-Brackmann system^[44] were grade II in 1 patient (vascularized sural nerve), grade III in 4 patients (three vascularized deep peroneal nerves and one vascularized motor nerve of the vastus lateralis), and grade IV in 1 patient (vascularized sural nerve). Results with the 40-point system^[45] ranged from 20 to 28 points (mean score, 23 points). No control was provided.

Fascicular turnover method

Koshima *et al.*^[47] described the “fascicular turnover method”, in which a vascularized fascicular flap was used for repairing nerve gaps. A 3 cm facial nerve gap was repaired with this technique with preservation of the zygomatic and marginal mandibular branches. The distal portion of the main buccal branch had three

fascicles. Therefore, a fascicular turnover flap from the distal buccal branch was elevated to reconnect the nerve gap without tension. The paralyzed major zygomatic muscle became active three months later. No control was provided.

When a single branch is compromised, the pedicled great auricular nerve is an option that causes no additional morbidity and which can be used with minimal additional effort.

The best method for repair of multiple branches of the facial nerve appears to be the LFCN graft without an ALT component that restricts motion. Should the skin or adipose tissue component of the ALT be needed together with the nerve to replace soft tissues, the best solution is harvest as a chimera, based on a different perforator than that nourishing the nerve, thus avoiding restrictions in nerve movement and allowing better inset. The branching of the nerve allows repair of up to three branches with adequate length and similar caliber. Using it with the ALT or SCIP requires an exceedingly long graft and limits motion. An alternative for the reconstruction of all five branches, which to our knowledge has not yet been utilized, is the long thoracic nerve.^[48]

Upper limb

Injuries to the ulnar nerve are the most frequent, occurring either in isolation or in association with the median nerve.^[49,50] These injuries, when compared to radial and median nerve injuries, are believed to have the least favorable outcome among nerve injuries in the upper extremity.^[51-54] Ulnar nerve injuries are the most common at the wrist, forearm, or elbow, secondary to trauma or entrapment.

Recovery of intrinsic muscles function is more important than sensory restoration.^[10] In their meta-analysis, Ruijs *et al.*^[52] reported that the chance of motor recovery in ulnar nerve injuries was 71% lower than in median nerve injuries. Multivariate logistic regression analysis showed that age, site (intermediate and high showed better results than low lesions), and delay between injury and repair were significant predictors of successful motor recovery. No significant difference was found between median and ulnar nerve injuries regarding sensory recovery. This is supported by other large studies.^[53,55] Age and delay between injury and repair were found to be significant predictors for sensory recovery.^[52]

Vascularized lateral femoral cutaneous nerve graft

Koshima *et al.*^[40] described a case of a 28-year-old woman with a wide massive tumor resection of the upper arm, which resulted in a soft tissue defect that included 12 cm long segments of the brachial artery and median nerve. A flow-through ALT flap and vascularized LFCN graft were harvested with separate vascular pedicles. Tinell's sign reached the wrist joint 6 months after surgery. Two and a half years postoperatively, moving 2-point discrimination (PD) on the fingers controlled by the

median nerve was 10 mm. No information is available about motor recovery.

Vascularized sural nerve graft

The sural nerve was reported initially as a vascularized graft by Gilbert and Fachinelli *et al.*^[56,57] although the dominant vascular pedicle was absent in a high percentage of cases.^[58] Fachinelli *et al.*^[57] reported that it receives its extrinsic vascular supply from two distinct sources. Proximally, the cutaneous nerve receives contributions from the superficial sural artery and distally from the musculocutaneous and fasciocutaneous perforators of the posterior tibial and peroneal (fibular) arteries. The medial sural nerve is a good donor for VNGs due to its long length, superficial accessibility, and minimal donor morbidity.

Vascularized sural nerve graft supplied by the superficial sural artery, Riordan *et al.*^[59] reported that the mean percentage of neural tissue within the sural nerve in the region where it is supplied by the superficial sural artery was 62% compared to 34% distally, where it was supplied by the posterior tibial and fibular (peroneal) arteries. They reported two clinical cases (right and left arm in the same patient) using the vascularized sural nerve with the superficial sural artery as folded cable grafts for repairing 20 cm and 12 cm median nerve defects, respectively. A subjectively evaluated good recovery was reported. No control was provided.

Vascularized sural nerve graft supplied by a muscular branch of the posterior tibial artery: in contrast to Riordan *et al.*^[59] Doi *et al.*^[31,32] stated that the superficial sural artery is unreliable as a nutrient vessel for the sural nerve. They used a vascularized sural nerve graft containing a muscular branch of the posterior tibial artery in 27 cases and compared them to 22 conventional sural nerves.

In 8 axillary nerve repairs (5 free vascularized sural nerve grafts and 3 conventional grafts), there was no statistically significant difference between the mean time to electromyographic reinnervation of the deltoid muscle or the strength of the deltoid muscle 24 months after surgery.

In 7 median nerve defects (4 vascularized sural nerve grafts and 3 conventional nerve grafts), there was a statistically significant difference between the vascularized and the nonvascularized sural nerve grafts in terms of mean speed of advancement of Tinel's sign (1.8 mm/day in the vascularized group vs. 0.5 mm/day in the conventional group, $P < 0.05$), mean time to S2 sensory reinnervation in the fingertip distal to the distal finger crease (16.8 weeks in the vascularized group vs. 30.7 weeks in the conventional group, $P < 0.05$) and time to electromyographic reinnervation of the abductor pollicis brevis muscle (6-8.5 months, mean: 7.4 months) in the vascularized group vs. 11-14 months (mean: 12.5 months) in the conventional group, $P < 0.05$).

In 7 lower ulnar nerve lesions (4 vascularized and 3 nonvascularized sural nerve grafts), the mean

advancement of Tinel's sign 2 months postoperatively (1.6 mm/day in the vascularized group vs. 0.6 mm/day in the conventional group, $P < 0.05$), the mean time to S2 sensory recovery in the tip of the small finger (4.3 months in the vascularized group vs. 6.7 months in the conventional group, $P < 0.05$), and mean time to electromyographic reinnervation of the abductor digiti minimi muscle (6.25 months in the vascularized group vs. 8.5 months in the conventional group, $P < 0.05$) were significantly shorter in the vascularized sural nerve graft group. Functional evaluation 2 years postoperatively was M3.3,^[60] S3 and M2, S2 for successful vascularized and conventional grafts, respectively. These differences in function were also statistically significant ($P < 0.05$).

Nine radial nerves (5 high and 4 low lesions) were repaired with 4 vascularized sural nerve grafts and 5 conventional sural nerve grafts. Two high radial nerve injuries were repaired with vascularized grafts, with significantly more rapid mean advancement of Tinel's sign 2 months postoperatively. The mean time to electromyographic reinnervation of the extensor digiti communis muscle in the vascularized group was also significantly faster. For low lesions, there was no significant difference in mean time to electromyographic reinnervation to the extensor digiti communis muscle and in final motor evaluation between VNG and NVNG groups.

Thirteen digital nerve defects in the palm were repaired with seven vascularized sural nerve grafts and six conventional sural nerve grafts. The mean advancement of Tinel's sign in the vascularized group was 1.7 mm/day, whereas the speed in the conventional graft group was 0.5 mm/day ($P < 0.05$). The final sensory recovery in the two groups was not statistically different.

Vascularized sural nerve graft supplied by the peroneal artery: although the peroneal artery does not directly supply the sural nerve, Hasegawa *et al.*^[42] used the fasciocutaneous perforators of the peroneal artery for sural nerve grafts. When a large nerve gap is accompanied by extensive scarring following severe trauma, soft tissue rich in blood vessels needs to be grafted along with the skin and nerve. Therefore, the authors conserved the blood flow to the sural nerve by harvesting the peroneal artery and vein as a vascular pedicle, along with the fascia and the subcutaneous fat tissue, which has a rich vascular plexus. They reported 6 patients who underwent vascularized sural nerve grafting (five to the median nerve and one to the ulnar nerve) with a monitoring skin flap, one of which failed.^[42] The length of the vascularized sural nerve grafts ranged from 20 to 30 cm, with a mean length of 23.3 cm. In the five successful cases, the mean static-2-PD at the corresponding fingertip was 14.2 mm (range: 10-20 mm). Semmes-Weinstein test findings were filament 6 in 2 patients and filament 10 in 3 patients. The authors concluded that vascularized sural nerve grafting should be considered as a clinical alternative for nerve reconstruction in patients with nerve defects longer than 20 cm. No controls were provided.

Vascularized sural nerve graft supplied by an arterialized saphenous vein: Townsend and Taylor^[33] presented five upper extremity cases in which a composite saphenous vein-sural nerve graft was used for median ($n = 3$) or ulnar nerve ($n = 2$) defect of 6-21 cm in length. The denervation time was 5 months to 2 years. Their results showed a Tinel's advancement comparable with a primary repair (1 mm/day in 2 cases). In 1 case with reconstruction of the median nerve with a 17 cm vascularized sural nerve graft, the advancement was 3 times faster.

Gu *et al.*^[61] presented the same model of a sural nerve graft based on an arterialized saphenous vein for the repair of median, ulnar, or radial nerves in 14 patients. As expected, the denervation time had a profound influence on final results: 2 patients (1 radial nerve injury of 13 cm and 1 ulnar nerve injury of 10 cm) with denervation time of less than 8 months had full restoration of motor function. In contrast, patients operated on after 18 months showed no motor recovery.

Vascularized nerve grafts with vascularized fascia

Terzis and Kostopoulos^[62] reported the results of twenty-one VNGs used for reconstruction of nerve injuries in the upper extremity. Vascularized fascia was used to improve the blood supply of the underlying bed by enveloping the nerve reconstruction. The authors reported satisfactory results although the study lacked a control group.

In case of a nerve injury of the upper limb associated with a soft tissue defect, the surgeon can use a flow-through ALT flap and a vascularized lateral femoral nerve graft. However, inset is difficult, and the nerve should be harvested as proximally as possible in order to obtain a larger caliber. To match the recipient nerve caliber, using cables from the donor as a NVNG may be necessary [Table 3].

When there is only a nerve injury for which a VNG is indicated, we advise using a vascularized sural nerve graft as there will be less caliber mismatch.

Brachial plexus injuries

Vascularized ulnar nerve graft

The vascularized ulnar nerve trunk graft can be used as a free microsurgical transfer or pedicled on the superior collateral ulnar artery.^[63]

Chuang *et al.*^[64] reported results of 167 patients who were treated for impaired elbow flexion caused by brachial plexus injury. Ruptured plexus injuries recovered better than root avulsions and infraclavicular plexus injuries performed better than supraclavicular injuries. Functional results revealed that nerve reconstruction produced results superior to muscle tendon transfers. The authors also found that vascularized ulnar nerve grafts were

superior to conventional long nerve grafts (12/15 patients or 80% success rate vs. 18/27 patients or 66% success rate). A pedicled VNG was more reliable than a free VNG for the reconstruction of elbow flexion; of the 9 patients who had a pedicled vascularized ulnar nerve graft, eight achieved a muscle grade greater than M3. However, of 6 patients with free vascularized ulnar nerve graft, only four achieved a grade greater than M3.

Terzis and Kostopoulos^[65] reported 151 reconstructions with ulnar nerves performed in 67 patients for brachial plexus injuries. Patients were divided into 4 groups: (1) pedicled vascularized ulnar nerve graft from ipsilateral donors, (2) free vascularized ulnar nerve graft from ipsilateral donors, (3) vascularized ulnar nerve graft from contralateral donors to the median nerve, and (4) vascularized ulnar nerve graft from contralateral donors to single motor targets (e.g. axillary, musculocutaneous and triceps) ($n = 25, 21, 13,$ and 8 respectively). Postoperative muscle strength for patients who were operated on late (denervation time > 12 months) was significantly decreased compared with the early group (< 6 months) ($P = 0.049$). The vascularized ulnar nerve grafts for median nerve neurotization also yielded protective sensation in the hand in 91.6% of the patients and produced better outcomes when compared to conventional nerve grafts (51% protective sensation).^[66] The authors concluded that, although VNGs can enhance the speed of regeneration, factors such as patient age (better results for younger patients), denervation time (poor results for late patient presentation), and graft length (better results for ipsilateral grafting) do influence the results.

Birch *et al.*^[67] reported 42 brachial plexus lesions that were reconstructed with a vascularized ulnar nerve graft (33 based on the ulnar vessel and 9 based on collateral vessels in the arm). Of the 42 patients, 33 patients regained functional elbow flexion after connecting the C5 root to the lateral cord or to the musculocutaneous nerve, using a free ulnar nerve graft shorter than 18 cm. Significant functional recovery of the hand occurred in only 1 patient. In 10 patients, recovery into the flexors of the wrist and/or the digits reached grade 3 power, but function was restricted to only a hook grasp. Sensory return sufficient for recognition of harmful stimuli and temperature change occurred in 10 patients. Delay from injury to operation had a significant bearing on the outcome: 4 patients with grafts performed more than 6 months following injury and 6 of 23 patients operated upon between 2 and 6 months did not achieve any functional recovery. These positive results match those of Oberlin *et al.*,^[68] who also used free vascularized ulnar nerve grafts. The grafts had a length between 8 and 25 cm (mean: 13.5 cm). In 83% of the 18 cases, there was a functional return of elbow flexion.

Bertelli and Ghizoni^[69] reported on results obtained with the reconstruction of elbow flexion. They used pedicled ulnar nerve grafts, averaging 30 cm of length, with which they connected the C5 root to the musculocutaneous nerve. None of the patients recovered useful function

Table 3: Indications for the upper limb nerve injury

Vascularized LFCN
Vascularized sural nerve
VNG with vascularized fascia

LFCN: Lateral femoral cutaneous nerve, VNG: Vascularized nerve grafts

mediated by the vascularized ulnar nerve, and none scored higher than M2 for either elbow flexion or wrist extension. These results may have been influenced by the delay to surgery, which occurred between 3 and 7 months after the injury.

Vascularized intercostal nerve transfers

Okinaga and Nagano^[70] compared nonvascularized ($n = 6$) with vascularized ($n = 5$) intercostal nerve transfers in patients with brachial plexus injuries. There were no statistically significant differences in (1) the time to appearance of a Tinel's sign, which radiated to the chest wall on the upper arm after surgery; (2) the rate of advancement of a Tinel's sign between the upper arm and the wrist; (3) the time interval between surgery and initiation of reinnervation as demonstrated by needle electromyography; (4) the strength of elbow flexion at the final examination according to the Medical Research Council's grading system; and (5) the strength of elbow flexion at the final examination as measured by a potentiometer held on the wrist at an angle of 100° of flexion. It is likely that statistical significance was not reached due to the small sample size.

Because most clinical evidence is in favor of the ipsilateral vascularized ulnar nerve trunk graft, we advise its use for reconstruction of a brachial plexus injury. We could not find evidence in favor of either the pedicled nerve graft or the free VNG [Table 4].

Hand

Vascularized deep peroneal nerve

Vascularized deep peroneal nerve supplied by a dorsalis pedis artery: Rose and Kowalski^[30] reported five cases with good results when reconstructing digital nerves in scarred tissue without a concomitant soft tissue defect by means of vascularized deep peroneal nerve segments. They concluded that the deep peroneal nerve-dorsalis pedis artery complex on the dorsum of the foot is an ideal donor site for segmental VNGs in digital sensory nerve reconstruction. Donor morbidity was negligible except for a neuroma in one case and slight superficial skin loss in another.

Koshima *et al.*^[71] reported one case of a deep peroneal VNG with skin from the first web space for reconstruction of a neurocutaneous defect in the finger. This technique has several drawbacks: the skin-grafted web can be a source of major morbidity,^[72,73] the skin flap does not adhere to the bone, and during grasping and gripping it will be unstable. Anatomic variations are quite common at the level of the first web space, and the nerve can travel far from the nutrient vessels,^[74,75] rendering the flap unusable.^[76]

Reversed venous arterialized deep peroneal nerve graft: influenced by the works of Townsend and Taylor^[33] and Gu *et al.*^[61] on reversed venous arterialized nerve grafts, Rose *et al.*^[34] investigated the deep peroneal nerve-dorsalis pedis venae comitantes system. Ten adult patients received a total of 14 VNGs. Mean moving 2-PD was 5.8 mm, and static 2-PD was 8.3 mm. The median of Semmes-Weinstein

monofilament measurements was 2.83 mm. In 3 digits, a vascularized and a nonvascularized nerve were used for adjacent digital nerve replacement in the same finger. The 3 "reversed venous" grafted nerves recovered with a mean moving 2-PD of 6.7 mm and a static 2-PD of 9.3 mm. By contrast, the conventional grafts returned moving 2-PD of 10.3 mm and static 2-PD of 14.3 mm.

Fascicular turnover method

Koshima *et al.*^[47] believe that, in cases with a digital nerve gap of less than 20 mm in length, a fascicular turnover flap from either the distal or proximal stump is the best option. However, in cases with nerve gaps measuring over 20 mm, fascicular turnover flaps from bilateral distal and proximal stumps are preferred to connect to the middle portion of the nerve gap, as excellent blood flow of bilateral short flaps can be expected rather than from an ipsilateral longer nerve flap.

Nerve reconstructions in the hand, when a VNG is indicated, appear to be better served by a deep peroneal nerve graft. However, a vascularized lateral femoral nerve graft may also be a useful tool, especially in multiple nerve injuries [Table 5].

Lower limb

Lower extremity nerve injuries are relatively less common than those of the upper extremities.^[10,77] The peroneal nerve is more susceptible to injury than the posterior tibial nerve given its superficial course over the neck of the fibula, where it is relatively fixed with less interfascicular connective tissue.^[78,79] Initial outcomes of peroneal nerve reconstruction were poor^[77] and the value of attempted repair of the peroneal nerve has been questioned.^[80] Although recent studies are more encouraging, the functional recovery of the peroneal nerve (muscle grade more than three) is still low, between 14% for grafts and 75% for neurolysis. Results are dependent upon the timing of surgical repair, the graft length, and the level of the injury.

Taylor's group reexamined the blood supply of each lower limb nerve and assessed the potential of each segment of each nerve for vascularized transfer.^[81] VNG and vascularized posterior calf fascia (VPCF) have been used to improve vascularization of the recipient bed and to minimize postoperative scar formation. When a VNG was required for reconstruction of a lower extremity nerve injury, the sural nerve was used, harvested as a pedicled nerve graft based on the superficial sural artery, or as an arterialized venous nerve graft based on the lesser saphenous vein. A concomitant VPCF can be used to improve vascularization.

Table 4: Indications for brachial plexus injuries

Vascularized ulnar nerve
Vascularized intercostal nerve

Table 5: Indications for a nerve injury in the hand

Vascularized deep peroneal nerve supplied by a dorsalis pedis artery
Reversed venous arterialized deep peroneal nerve graft
Fascicular turnover method

Terzis and Kostopoulos^[82] reported 14 lower extremity nerve injuries in 12 patients that had been reconstructed with VNGs. The common peroneal nerve (CPN) was injured in 12 patients and the posterior tibial nerve in 5 patients. The repair of CPN lesions was not recommended given the poor prognosis following nerve reconstruction.^[77,83] The vascularized sural nerve graft was used as a pedicled nerve graft based on the superficial sural artery or as an arterialized-venous nerve graft based on the lesser saphenous vein. Kim and Kline found that good functional recovery could not be expected with a graft length greater than 12 cm.^[84] It has been reported that in the lower extremity all patients with nerve grafts greater than 6 cm in length had fair or poor results.^[79] Grade 3 function was recovered in 38% of patients with grafts 6-12 cm and in only 16% of patients with graft lengths of 13-24 cm.^[85] In contrast, with VNGs of 13 cm or more, grade 3 function was recovered in 66.67% of patients. Terzis and Kostopoulos^[82] showed statistically significant differences ($P = 0.008$) for CPN injuries between patients who underwent surgery within 6 months from the time of injury and patients who presented later than 6 months. Preoperative and postoperative differences in dorsiflexor muscle strength were statistically significant ($P < 0.001$). A correlation between outcome and type of injury and between outcome and age was not found.

In lower extremity nerve injuries, when a VNG is indicated, the best choice is the sural nerve, either as a pedicled nerve graft based on the superficial sural artery and or as an arterialized venous nerve graft based on the lesser saphenous vein [Table 6].

Vascularized nerve allografting

The use of nerve autografts is limited by the availability of suitable donor sites. Allografting in reconstructive surgery has become more promising with advances in immunosuppression therapy.^[86] Mackinnon *et al.*^[87] have pioneered the technique of nerve allografting with encouraging results. Vascularized nerve allografts offer several theoretical advantages: (1) they allow *en bloc* reconstruction of nerve plexi; (2) they enhance the rate of nerve regeneration; and (3) they permit the use of larger "trunk" grafts without central necrosis.^[88]

Mackinnon *et al.*^[89,90] described 7 cases of traumatic extremity injuries with massive peripheral nerve deficits that could not be reconstructed by conventional means. Four upper extremities and 3 lower extremities were reconstructed. Nerve allografts were either used exclusively for the reconstruction (2/7) or in combination with autografts (5/7). Total allograft lengths varied from 72 cm in a 3-year-old patient to 350 cm for a three-nerve reconstruction in a 16-year-old patient. Initially, the allografts were harvested fresh and used immediately. In subsequent cases, the allografts were temporarily stored

in University of Wisconsin solution before engraftment. The immunosuppressive regimen in the first 3 patients consisted of triple therapy with cyclosporin A (CsA), Imuran, and prednisone. The subsequent 4 patients were treated with FK506, Imuran, and prednisone. Immunosuppression was withdrawn sequentially, beginning with prednisone. After the Tinel's sign had progressed into the distal segment of the reconstructed nerve, CsA or FK506 was withdrawn. No significant complications secondary to systemic immunosuppression have occurred. Six of the 7 allografts were clinically successful based on the recovery of sensory and/or motor function in the reconstructed distribution. One patient rejected his allograft.

Although some patients have recovered motor function, sensory recovery has been more consistently observed. Similarly, the predominance of superior sensory (temperature and pain) over motor (intrinsic) recovery has been described in hand transplant recipients. It is yet to be determined if this occurs secondary to differential sensory (particularly sympathetic) nerve regeneration, sensory-motor mismatch, or end organ (muscle) lack of receptivity to reinnervation.^[88]

COMPARISON OF DONOR SITES IN THE UPPER AND LOWER LIMBS

Ideally, donor nerves for free vascularized nerve transfer should exhibit a type A, B, or C pattern.^[7] Type A represents a nerve supplied segmentally by a long unbranching artery. Type B is similar to type A except that the nerve divides early. Type C is similar to type A, but the artery courses on the surface of the nerve instead of in parallel and gives several branches to the nerve that can subsequently be divided into multiple vascularized segments.

Upper limb

The study of Hong *et al.*^[91] examined all nerves of the upper limb. They identified the following nerves as suitable for microsurgical transfer, being of type A or C: (1) the ulnar nerve in the upper arm and in the forearm; (2) the median nerve in the upper arm and in the forearm; (3) the segment of the anterior interosseous nerve distal to the flexor pollicis longus branch; (4) the upper lateral brachial nerve; (5) the lower lateral brachial nerve; (6) the superficial radial nerve; (7) the terminal branch of the posterior interosseous nerve; and (8) a branch to the extensor indicis following the posterior interosseous artery (when present). In normal clinical situations, nerves 1 and 2 cannot be used because of their functional importance. Harvest of nerve 3 results in loss of function of the pronator quadratus, which may be acceptable. This leaves nerves 4 through 8 as donor nerves for vascularized nerve transfer, and potentially nerve 3 in normal situations, with the superficial radial nerve being the longest with the most acceptable morbidity.

Lower limb

The study of Suami *et al.*^[81] examined all nerves of the lower limb. They identified the following nerves: (1) the

Table 6: Indications for a lower limb nerve injury

Vascularized sural nerve based on a pedicled superficial sural artery
Vascularized sural nerve supplied by an arterialized lesser saphenous vein

terminal cutaneous portion of the saphenous nerve; (2) the vastus lateralis branch of the femoral nerve; (3) the deep peroneal nerve distal to the extensor hallucis longus branch; (4) the posterior cutaneous nerve of the thigh; (5) the pudendal nerve; (6) the tibial nerve; (7) the lateral plantar nerve; (8) the medial plantar nerve; and (9) the sciatic nerve, with one of the profunda artery perforators. However, nerves 5-9 are not suitable for VNGs because of their short length or functional importance, unless an amputated limb or limb stump becomes available for harvesting of donor nerves. Consequently, nerves 1-4 are regarded as possible donor nerves. The deep peroneal nerve is the longest available with the least morbidity together with the sural nerve. The other versatile donor is the LFCN.

Nonvascularized to vascularized wound bed

Experimental studies have shown that in a normally vascularized bed, VNGs and NVNGs are equivalent for the treatment of short gaps of thin nerves. As suggested by Breidenbach and Terzis,^[92] a poorly vascularized bed can be transformed into a well-vascularized bed by flap transfer and a NVNG placed into it with similar results. This is a practice that resembles well-established flap transfers in heavily scarred beds for tendon gliding^[93] or scar-tethered nerves.^[94] Many free or local options exist, and an NVNG can then be used to bridge the gap. This technique can replace a VNG only when its sole indication is a poorly vascularized bed.

HOW SHOULD WE CONSIDER THE NERVE INCORPORATED IN A FLAP?

Sensate or innervated flaps may provide a model for studying VNGs in the clinical setting. Innervated muscles show very efficient reinnervation even when radiated or placed in poorly vascularized beds.^[95] This is likely due to fact that a nerve included in a flap is in fact a VNG. Innervated flaps may be used to investigate the extent and speed of recovery of vascularized nerves transferred with flaps, either for reinnervation of the flap or to bridge composite defects that include nerves and soft tissues.

CONCLUSION

Whether it is worthwhile to perform a nerve graft and when remains controversial: VNGs do not have a real place in our reconstructive algorithm, resting in a limbo between 'grafts' and flaps. They are referred to as 'grafts' despite being vascularized, although by definition they possess a vascular pedicle and should be called 'flaps'.

Following this review, the authors conclude that VNGs do perform better than conventional nerve grafts by providing faster and better regeneration. However, this improvement in regeneration becomes relevant only in certain situation such as those shown in Table 1. The failure of several experimental studies to demonstrate an advantage may be due to lack of an appropriate model. No model to date has reproduced a long gap in a thick

nerve which would mimic those likely to benefit from a VNG in humans.

Although VNGs can potentially significantly improve results, the major limitation is the lack of donor sites. VNGs perform best in long proximal gaps of large nerves, but harvesting such a large donor nerve is associated with significant morbidity. Although this may be partially be solved by the use of cable grafting, the donor nerves available still may not be sufficient, require multiple donor sites, complex procedures, and high morbidity.

FUTURE DIRECTIONS

Vascularized nerve allografts, which are associated with immunosuppression, a well-known facilitator of nerve regeneration, will likely become a useful tool in nerve reconstruction with VNGs. Coupling VNGs with NVNGs which surround them may be an option for larger nerves. Prefabricated nerve grafts may also play a role, as the delay in reconstruction caused by prefabrication may be compensated by improved regeneration.

REFERENCES

1. Phillipeaux JM, Vulpian A. Note on the trial of a lingual nerve trunk graft between two stumps of the hypoglossal. *Arch Physiol Norm Pathol* 1870;3:618.
2. Bunnell S, Boyes JH. Nerve grafts. *Am J Surg* 1939;44:64-75.
3. Klar E. About experiences and successes in application of plastic bridging defects in peripheral nerves. *Z Neurol Psychiatr* 1943;176:533-55.
4. Seddon HJ. The use of autologous grafts for the repair of large gaps in peripheral nerves. *Br J Surg* 1947;35:151-67.
5. Tarlov IM, Epstein JA. Nerve grafts: the importance of an adequate blood supply. *J Neurosurg* 1945;2:49-71.
6. Strange FG. An operation for nerve pedicle grafting; preliminary communication. *Br J Surg* 1947;34:423-5.
7. Taylor GI, Ham FJ. The free vascularized nerve graft. *Plast Reconstr Surg* 1976;57:413-26.
8. Lind R, Wood MB. Comparison of pattern of early revascularisation of conventional versus vascularized nerve grafts in canine. *J Reconstr Microsurg* 1986;2:229-34.
9. Penkert G, Bini W, Samii M. Revascularization of nerve grafts: an experimental study. *J Reconstr Microsurg* 1988;4:319-25.
10. Sunderland S. Nerves and Nerve Injuries. 2nd ed. Edinburgh: Churchill Livingstone; 1978.
11. Brooks D. The place of nerve-grafting in orthopedic surgery. *J Bone Joint Surg Am* 1955;37:299-305.
12. Seddon HJ. Nerve grafting. *J Bone Joint Surg Br* 1963;45:447-61.
13. Best TJ, Mackinnon SE, Bain JR, Makino A, Evans PJ. Verification of a free vascularized nerve graft model in the rat with application to the peripheral nerve allograft. *Plast Reconstr Surg* 1993;92:516-25.
14. el-Barrany WG, Marei AG, Vallée B. Anatomic basis of vascularised nerve grafts: the blood supply of peripheral nerves. *Surg Radiol Anat* 1999;21:95-102.
15. Lux P, Breidenbach W, Firrell J. Determination of temporal changes in blood flow in vascularized and nonvascularized nerve grafts in the dog. *Plast Reconstr Surg* 1988;82:133-44.
16. Mani GV, Shurey C, Green CJ. Is early vascularization of nerve grafts necessary? *J Hand Surg Br* 1992;17:536-43.
17. Settergren CR, Wood MB. Comparison of blood flow in free vascularized versus nonvascularized nerve grafts. *J Reconstr Microsurg* 1984;1:95-101.
18. Appenzeller O, Dhital KK, Cowen T, Burnstock G. The nerves to blood vessels supplying blood to nerves: the innervations of vasa nervorum. *Brain Res* 1984;304:383-6.
19. Cowen T, MacCormick DE, Toff WD, Burnstock G, Lumley JS. The effect of surgical procedures on blood vessel innervations. A fluorescence histochemical study of degeneration and regrowth of perivascular adrenergic nerves. *Blood Vessels* 1982;19:65-78.

20. Selander D, Mansson LG, Karlsson L, Svanvik J. Adrenergic vasoconstriction in peripheral nerves of the rabbit. *Anesthesiology* 1985;62:6-10.
21. McCullough CJ, Grady O, Higgerson DW. Axon regeneration and vascularization of nerve grafts. An experimental study. *B J Hand Surg Br* 1984;9:323-7.
22. Seckel BR, Ryan SE, Simons JE, Gagne RG, Watkins E Jr. Vascularized versus nonvascularized nerve grafts: an experimental structural comparison. *Plast Reconstr Surg* 1986;78:211-20.
23. Pho RW, Lee YS, Rujiwetpongstorn V, Pang M. Histological studies of vascularised nerve graft and conventional nerve graft. *J Hand Surg Br* 1985;1:45-8.
24. Restepo Y, Merle M, Michon J, Folliguet B, Barrat E. Free vascularized nerve grafts: an experimental study in the rabbit. *Microsurgery* 1985;6:78-84.
25. Shibata M, Tsai TM, Firrel J, Breidenbach WC. Experimental comparison of vascularized and nonvascularized nerve grafting. *J Hand Surg Am* 1988;3:358-65.
26. Kanaya F, Firrel J, Tsai TM, Breidenbach WC. Functional results of vascularized versus nonvascularized nerve grafting. *Plast Reconstr Surg* 1992;5:924-30.
27. de Medinaceli L, Freed WJ, Wyatt RJ. An index of the functional condition of rat sciatic nerve based on measurements made from walking tracks. *Exp Neurol* 1982;77:634-43.
28. Kärcher H, Kleinert R. Regeneration in vascularized and free nerve grafts. A comparative morphological study in rats. *J Maxillofac Surg* 1986;14:341-3.
29. Koshima I, Harii K. Experimental study of vascularized nerve grafts: multifactorial analyses of axonal regeneration of nerves transplanted into an acute burn wound. *J Hand Surg Am* 1985;10:64-72.
30. Rose EH, Kowalski TA. Restoration of sensibility to anesthetic scarred digits with free vascularized nerve grafts from the dorsum of the foot. *J Hand Surg Am* 1985;4:514-21.
31. Doi K, Kuwata N, Kawakami F, Tamaru K, Kawai S. The free vascularized sural nerve graft. *Microsurgery* 1984;5:175-84.
32. Doi K, Kuwata N, Sakai K, Tamaru K, Kawai S. A reliable technique of free vascularized sural nerve grafting and preliminary results of clinical applications. *J Hand Surg Am* 1987;12:677-84.
33. Townsend PL, Taylor GI. Vascularised nerve grafts using composite arterialised neuro-venous systems. *Br J Plast Surg* 1984;37:1-17.
34. Rose EH, Kowalski TA, Norris MS. The reversed venous arterialized nerve graft in digital nerve reconstruction across scarred beds. *Plast Reconstr Surg* 1989;83:593-604.
35. Bonney G, Birch R, Jamieson AM, Eames RA. Experience with vascularized nerve grafts. *Clin Plast Surg* 1984;11:137-42.
36. Ballance C, Duel AB. The operative treatment of facial palsy by the introduction of nerve grafts into the fallopian canal and by other intratemporal methods. *Arch Otolaryngol* 1932;15:1-70.
37. Baker DC, Conley J. Facial nerve grafting: a thirty year retrospective review. *Clin Plast Surg* 1979;6:343-60.
38. Kimata Y, Sakuraba M, Hishinuma S, Ebihara S, Hayashi R, Asakage T. Free vascularized nerve grafting for immediate facial nerve reconstruction. *Laryngoscope* 2005;115:331-6.
39. Koshima I, Yamamoto H, Moriguchi T, Kawada S, Ono Y. Combined anteroposterior tibial perforator-based flap with a vascularized deep peroneal nerve for repair of facial defect. *Ann Plast Surg* 1994;33:421-5.
40. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Kawai A. Vascularized femoral nerve graft with anterolateral thigh true perforator flap for massive defects after cancer ablation in the upper arm. *J Reconstr Microsurg* 2003;19:299-302.
41. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S. New one-stage nerve pedicle grafting technique using the great auricular nerve for reconstruction of facial nerve defects. *J Reconstr Microsurg* 2004;20:357-61.
42. Hasegawa T, Nakamura S, Manabe T, Mikawa Y. Vascularized nerve grafts for the treatment of large nerve gap after severe trauma to an upper extremity. *Arch Orthop Trauma Surg* 2004;214:209-13.
43. Lida T, Nakagawa M, Asano T, Fukushima C, Tachi K. Free vascularized lateral femoral cutaneous nerve graft with anterolateral thigh flap for reconstruction of facial nerve defects. *J Reconstr Microsurg* 2006;22:343-8.
44. House JW. Facial nerve grading systems. *Laryngoscope* 1983;93:1056-69.
45. Yanagihara N. On standardised documentation of facial palsy. *Nihon Jibiinkoka Gakkai Kaiho* 1977;80:799-805.
46. Kashiwa K, Kobayashi S, Ogino K, Kashiwaya G, Higuchi H. Inferolateral extension of the groin flap based on the artery accompanying the lateral femoral cutaneous nerve. *J Reconstr Microsurg* 2009;25:181-9.
47. Koshima L, Narushita M, Mihara M, Ushida G, Nakagawa M. Fascicular turnover flap for nerve gaps. *J Plast Reconstr Aesthet Surg* 2010;63:1008-14.
48. Schultes G, Kärcher H, Gaggli A, Anderhuber F. Anatomic basis of vascularized nerve graft using the long thoracic nerve. *Surg Radiol Anat* 1999;21:91-4.
49. Kouyoumdjian JA. Peripheral nerve injuries: a retrospective survey of 456 cases. *Muscle Nerve* 2006;34:785-8.
50. Posch JL, dela Cruz-Saddul F. Nerve repair in trauma surgery: a ten-year study of 231 peripheral injuries. *Orthop Rev* 1980;9:35-45.
51. Bruyns CN, Jaquet JB, Schreuders TA, Kalmijn S, Kuypers PD, Hovius SE. Predictors for return to work in patients with median and ulnar nerve injuries. *J Hand Surg Am* 2003;28:28-34.
52. Ruijs AC, Jaquet JB, Kalmijn S, Giele H, Hovius SE. Median and ulnar nerve injuries: a meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. *Plast Reconstr Surg* 2005;116:484-94.
53. Vormdemvenne T, Langer M, Ochman S, Raschke M, Schult M. Long-term results after primary microsurgical repair of ulnar and median nerve injuries. A comparison of common score systems. *Clin Neurol Neurosurg* 2007;109:263-71.
54. Allan CH, Vanderhooft E. Functional outcomes after nerve grafting. *Atlas Hand Clin* 2005;10:93.
55. Jaquet JB, Luijsterburg AJ, Kalmijn S, Kuypers PD, Hofman A, Hovius SE. Median, ulnar, and combined median-ulnar nerve injuries: functional outcome and return to productivity. *J Trauma* 2001;51:687-92.
56. Gilbert A. Vascularized sural nerve graft. In: *Microreconstruction of Nerve Injuries*. Philadelphia: WB Saunders; 1987. p. 576-601.
57. Fachinelli A, Masquelet A, Restrepo J. The vascularized sural nerve. *Int J Microsurg* 1981;3:57-62.
58. Breidenbach W, Terzis JK. The anatomy of free vascularized nerve grafts. *Clin Plast Surg* 1984;11:65-71.
59. Riordan CL, Nanney LB, Upton J 3rd, Wolfort SF. Vascularized medial sural cutaneous nerve based on the superficial sural artery: a reliable nerve graft. *J Reconstr Microsurg* 2002;18:147-52.
60. Zachary RB. Results of nerve suture. *Spec Rep Ser Med Res Council* 1954;282:354-88.
61. Gu YD, Wu MM, Zheng YL, Li HR, Xu YN. Arterialized venous free sural nerve grafting. *Ann Plast Surg* 1985;15:332-9.
62. Terzis JK, Kostopoulos VK. Vascularized nerve grafts and vascularized fascia for upper extremity nerve reconstruction. *Hand (N Y)* 2010;5:19-30.
63. Lebreton E, Bourgeon Y, Lascombes P, Merle M, Foucher G. Systemization of the vascularization of the ulnar nerve in its upper arm. *Ann Chir Main* 1983;2:211-8.
64. Chuang DC, Epstein MD, Yeh MC, Wei FC. Functional restoration of elbow flexion in brachial plexus injuries: results in 167 patients (excluding obstetric brachial plexus injury). *J Hand Surg Am* 1993;18:285-91.
65. Terzis JK, Kostopoulos VK. Vascularized ulnar nerve graft. 151 reconstructions for posttraumatic brachial plexus palsy. *Plast Reconstr Surg* 2009;123:1276-91.
66. Terzis JK, Vekris MD, Soucacos PN. Outcomes of brachial plexus reconstruction in 204 patients with devastating paralysis. *Plast Reconstr Surg* 1999;19:1221-40.
67. Birch R, Dunkerton M, Bonney G, Jamieson AM. Experience with the free vascularized ulnar nerve graft in repair of supraclavicular lesions of the brachial plexus. *Clin Orthop Relat Res* 1988;237:96-104.
68. Oberlin C, Alnot JY, Comtet JJ. Vascularized nerve trunk grafts. Technique and results of 27 cases. *Ann Chir Main* 1989;8:316-23.
69. Bertelli JA, Ghizoni MF. Results of C5 root grafting to the musculocutaneous nerve using pedicled, vascularized ulnar nerve grafts. *J Hand Surg Am* 2009;6:1821-6.
70. Okinaga S, Nagano A. Can vascularization improve the surgical outcome of the intercostal nerve transfer for traumatic brachial plexus palsy? A clinical comparison of vascularized and non-vascularized methods. *Microsurgery* 1999;19:176-180.
71. Koshima L, Murashita T, Soeda S. Free vascularized deep peroneal neurocutaneous flap for repair of digital nerve defect involving severe finger damage. *J Hand Surg Am* 1991;16:227-9.
72. Willemart G, Kane A, Morrison WA. Island dorsalis pedis skin flap in combination with toe or toe segment transfer based on the same vascular pedicle. *Plast Reconstr Surg* 1999;104:1424-9.
73. Samson MC, Morris SF, Tweed AE. Dorsalis pedis flap donor site: acceptable or not? *Plast Reconstr Surg* 1998;102:1549-54.
74. Gilbert A. Composite tissue transfer from the foot: anatomic basis and surgical technique. In: Daniller AI, Strauch B, editors. *Symposium on Microsurgery*. St. Louis: CV Mosby; 1976. p. 230-42.
75. May JW Jr, Chait LA, Cohen BE, O'Brien BM. Free neurovascular flap from the first web of the foot in hand reconstruction. *J Hand Surg Am* 1977;2:387-93.
76. del Pinal F, Garcia-Bernal FJ, Regalado J, Studer A, Cagigal A, Ayala A. The tibial second toe vascularized neurocutaneous free flap for major digital nerve defects. *J Hand Surg Am* 2007;32:209-17.

77. Seddon HJ. Surgical Disorders of the Peripheral Nerves. Edinburgh: Churchill Livingstone; 1972.
78. Berry H, Richardson PM. Common peroneal nerve palsy: a clinical and electrophysiological review. *J Neurol Neurosurg Psychiatry* 1976;39:1162-71.
79. Wood MB. Peroneal nerve repair. Surgical results. *Clin Orthop Relat Res* 1991;267:206-10.
80. Demuynck M, Zuker RM. The peroneal nerve: is repair worthwhile? *J Reconstr Microsurg* 1987;3:193-7.
81. Suami H, Taylor GI, Pan WR. Angiosome territories of the nerves of the lower limbs. *Plast Reconstr Surg* 2003;112:1790-8.
82. Terzis JK, Kostopoulos VK. Vascularized nerve grafts for lower extremity nerve reconstruction. *Ann Plast Surg* 2010;64:169-76.
83. Platt H, Lond MS. The classic. Traction lesions of the external popliteal nerve. By Harry Platt. 1940. *Clin Orthop Relat Res* 1986;210:5-8.
84. Kim DH, Kline DG. Management and results of peroneal nerve lesions. *Neurosurgery* 1996;39:312-9.
85. Kim DH, Murovic JA, Tiel RL, Kline DG. Management and outcomes in 318 operative common peroneal nerve lesions at the Louisiana State University Health Sciences Center. *Neurosurgery* 2004;54:1421-8.
86. Petit F, Minns AB, Dubernard JM, Hettieratchy S, Lee WP. Composite tissue allotransplantation and reconstructive surgery: first clinical applications. *Ann Surg* 2003;237:19-25.
87. Mackinnon SE, Doolabh VB, Novak CB, Trulock EP. Clinical outcome following nerve allograft transplantation. *Plast Reconstr Surg* 2001;107:1419-29.
88. Bain JR. Peripheral nerve and neuromuscular allotransplantation: current status. *Microsurgery* 2000;20:384-8.
89. Mackinnon SE, Hudson AR. Clinical application of peripheral nerve transplantation. *Plast Reconstr Surg* 1992;90:695-9.
90. Mackinnon SE. Nerve allotransplantation following severe tibial nerve injury. Case report. *J Neurosurg* 1996;84:671-6.
91. Hong MK, Hong MK, Taylor GI. Angiosome territories of the nerves of the upper limbs. *Plast Reconstr Surg* 2006;118:148-60.
92. Breidenbach WC, Terzis JK. Vascularized nerve grafts: an experimental and clinical review. *Ann Plast Surg* 1987;18:137-46.
93. del Pinal F, Moraleta E, de Piero GH, Ruas JS. Outcomes of free adipofascial flaps combined with tenolysis in scarred beds. *J Hand Surg Am* 2014;39:269-79.
94. Elliot D. Surgical management of painful peripheral nerves. *Clin Plast Surg* 2014;41:589-613.
95. Cordova A, D'Arpa S, Moschella F. Gracilis free muscle transfer for morpho-functional reconstruction of the lower lip. *Head Neck* 2008;30:684-9.

How to cite this article: D'Arpa S, Claes KE, Stillaert F, Colebunders B, Monstrey S, Blondeel P. Vascularized nerve "grafts": just a graft or a worthwhile procedure?. *Plast Aesthet Res* 2015;2:183-94.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 03-02-2015; **Accepted:** 20-05-2015

Nerve transfers of the forearm and hand: a review of current indications

Paolo Sassu, Katleen Libberecht, Anders Nilsson

Department of Hand Surgery, Sahlgrenska University Hospital, SE41345 Gothenburg, Sweden.

Address for correspondence: Dr. Paolo Sassu, Department of Hand Surgery, Sahlgrenska University Hospital, SE41345 Gothenburg, Sweden. E-mail: sassupaolo@gmail.com

ABSTRACT

Nerve transfer surgery, also referred to neurotization, developed in the mid 1800s with the use of animal models, and was later applied in the treatment of brachial plexus injuries. Neurotization is based on the concept that following a proximal nerve lesion with a poor prognosis, expendable motor or sensory nerves can be re-directed in proximity of a specific target, whether a muscle or skin territory, in order to obtain faster re-innervation. Thanks to the contribution of several authors including Oberlin, MacKinnon and many others, the field of nerve transfer surgery has expanded in treatment of not only the brachial plexus, but also the arm, forearm and hand. This article reviews the recent literature regarding current concepts in nerve transfer surgery, including similarities to and differences from tendon transfer surgery. Moreover, indications and surgical techniques are illustrated for different types of nerve injury affecting the extrinsic and intrinsic musculature of the hand as well as sensory function.

Key words:

Brachial plexus, nerve transfer, peripheral nerve

INTRODUCTION

The concept of nerve transfer developed almost two hundred years ago when Flourens^[1] reported his first experiments with the brachial plexus of a rooster. He demonstrated that proximal nerve stumps could be coupled to different target nerves, obtaining not only re-innervation, but also a function that was dependent on the new motor nerve.^[2] This report stimulated a number of animal studies under the label of “nerve crossing”,^[3] followed by a series of clinical cases in the early twentieth century showing the feasibility of suturing a proximal nerve stump to a distal one with a different target organ.^[4-7]

Using this concept, several options have been developed over the years, in which expendable donor nerves or their fascicles are re-directed to recipient nerves in close

proximity to their target muscle or skin territory. The technique was initially used in brachial plexus injuries and has slowly become a routine procedure for peripheral nerve lesions where poor functional results are expected due to the distance between the site of injury and the innervated muscles.

GENERAL CONCEPTS IN NERVE TRANSFERS

Brachial plexus injuries and peripheral nerve lesions at or proximal to the elbow result in denervation and loss of sensation and may not recover due to the long distance between the lesion and the target organ. Even when treated early, the axon regeneration process does not always have the capacity to reach the proper muscle before irreversible changes have taken place. The primary aim of nerve transfers is to promote re-innervation in proximity to a certain target organ (whether a muscle or a skin territory) following a proximal nerve injury.^[8-11]

Axonal regeneration progresses at a rate of 1-2 mm/day.^[12] Because muscle fibers undergo irreversible changes after 12-18 months of denervation,^[13] it is imperative that treatment be undertaken promptly for functional recovery.^[14] Very proximal lesions in the arm or brachial plexus, even

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.160887

when treated within 3 months following injury, carry a high risk of incurring irreversible muscle atrophy before the regenerating axons can reach the motor end plates. Transferring a motor nerve that is close to the motor end plate shortens the distance for axon regeneration and consequently the time for muscle re-innervation. In this respect, nerve transfer promotes a functional rather than an anatomical reconstruction.^[15] This is the main concept in nerve transfer surgery. Other equally important concepts include the use of tension-free sutures directly between the donor and recipient nerves without the use of nerve grafts to ensure that the maximal number of regenerating axons is directed toward the end organ. By working at a location distal to the zone of injury, a pristine, vascular field can be used, which will not interfere with nerve regeneration.^[9-11]

Although sensory receptors have a wider margin for recovery even many months after the injury, earlier repairs clearly lead to better outcomes.^[14,16]

Postoperative rehabilitation is facilitated when a nerve with synergistic function is chosen for re-innervation.^[8,17-19] To ensure a tension-free transfer, it is essential to dissect the donor nerve as distal as possible and the recipient as proximal as possible. When antagonistic nerves have been used, the learning process is more difficult and the patient may require additional time to understand how to activate the injured muscles.^[20] The process of re-adaptation is still unclear, but a certain grade of brain plasticity is involved in learning how to utilize a muscle that is now supplied by a different motor nerve.^[21-24]

INDICATIONS

Nerve transfer surgery has evolved greatly over the last two decades due to a better knowledge of intraneural anatomy and a better understanding of functional re-innervation rather than anatomical reconstruction. As a result, in select cases with high-level nerve lesions, it is advisable to address the injury in terms of functional recovery rather than pure anatomic restoration.

In the absence of a proximal nerve stump, nerve transfer provides an alternative for re-innervation of the target muscle. This is often the case in brachial plexus injuries with root avulsion. Another indication is a very proximal nerve lesion or delayed presentation, where muscle atrophy most likely will have occurred prior to functional re-innervation. In cases in which surgical exploration is difficult secondary to a previous extensive injury, distal nerve transfer, will shorten the time to re-innervation and avoid nerve repair in a highly fibrotic bed.^[9,15,8,25]

The presence of a nerve defect itself represents a good indication for nerve transfer, first because there is no need to harvest a nerve graft from another site, and second because comparable if not better results with nerve transfer rather than long nerve grafts have been reported.^[14,26-28]

As a general rule, instead of focusing on anatomic reconstitution of the damaged nerve(s), the goal becomes functional reconstruction with re-innervation of specific

muscle(s) and skin territory. A specific movement will still be performed by the original muscle, without the need to re-route different tendons or muscles, which might in turn lose some of their original power.

RADIAL NERVE DEFICITS

Indications

The radial nerve can suffer from a multitude of injuries, with humeral fracture being the most common.^[29-31] Other causes include brachial plexus injuries, neuritis, direct trauma and compression. Radial nerve paralysis has been commonly treated by either neurolysis, nerve graft or tendon transfers with successful results.^[32] Nevertheless, some authors have reported the potential impairment of pronation following the transfer of the pronator teres (PT), and unnatural coordination after tendon transfer, especially while performing a full hand grip.^[33,34] In 2002, Lowe *et al.*^[34] described the possibility of transferring branches of the median nerve to recover wrist and finger extension in radial nerve palsy, alone or in conjunction with tendon transfers. Since then several reports have elucidated the technical feasibility and the possible advantages.^[35-38]

Nerve transfers

Motor

Currently, priority is given to re-innervation of the extensor carpi radialis brevis (ECRB) for wrist extension and the posterior interosseous nerve (PIN) for finger and thumb extension. The branch to the flexor digitorum superficialis (FDS) muscle (median nerve) is rotated to the ECRB and branches to the palmaris longus (PL) and flexor carpi radialis (FCR) (median nerve) are coaptated to the PIN [Figure 1].

Schematic description

A lazy “S” incision is made on the volar surface from the cubital fossa down to the mid-forearm. The lacertus

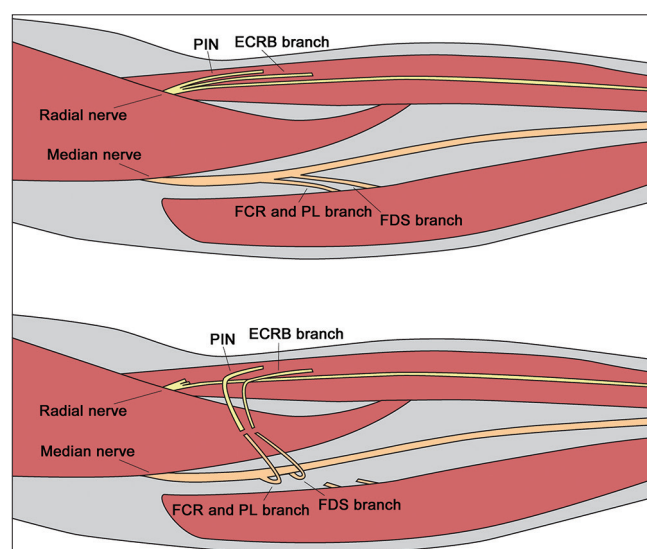


Figure 1: Radial nerve deficit. Transfer of the motor branch to flexor digitorum superficialis muscle to the extensor carpi radialis brevis, and the motor branches to flexor carpi radialis muscle and palmaris longus muscle, to the PIN. PIN: Posterior interosseous nerve, ECRB: Extensor carpi radialis brevis, FCR: Flexor carpi radialis, FDS: Flexor digitorum superficialis, PL: Palmaris longus

fibrosus is divided, and the radial vascular bundle, and the median nerve are identified. Distally, step lengthening of the superficial part of the PT allows better medial retraction of the muscle so as to visualize the branches of the median nerve to the FDS and FCR. Lateral retraction of the brachioradialis exposes the superficial radial nerve, the PIN, and the ECRB branches. Once both the donor branches to the FDS and FCR and the recipient branches are identified, they are isolated as needed in order to divide them following the rule of “donor distal/recipient proximal” described by Brown and Mackinnon,^[15] without tension on the nerve coaptation.

Sensory

The lateral antebrachial cutaneous nerve (LACN) runs close to the sensory radial branch in the distal forearm and matches it very well in size. It is expendable, and its use does not create any significant morbidity along its territory.

MEDIAN NERVE DEFICITS

Indications

In high-level injuries of the median nerve both extrinsic and intrinsic muscles of the forearm and hand, as well as the sensation on the volar-radial part of the hand, are affected and need restoration. In low-level injuries thumb, opposition and sensation in the 1st, 2nd, 3rd, and radial half of the 4th fingers are addressed for reconstruction. The most common donor is the radial nerve and its branches to the supinator and ECRB. In case of isolated injuries to the anterior interosseous nerve (AIN), intra-median nerve transfers have been described using intact branches of the median nerve which are redirected.

Motor nerve transfers

Thumb opposition

When available the AIN (branch to the pronator quadratus) is isolated and transferred to the motor branch of the thenar muscles [Figure 2]. The donor and recipient match well in size, but transfer requires a nerve graft which leads to the inevitable loss of some of the regenerating axons. In high-level injuries, ulnar nerve to median (third lumbrical motor branch)^[39] or radial nerve to median (motor branch

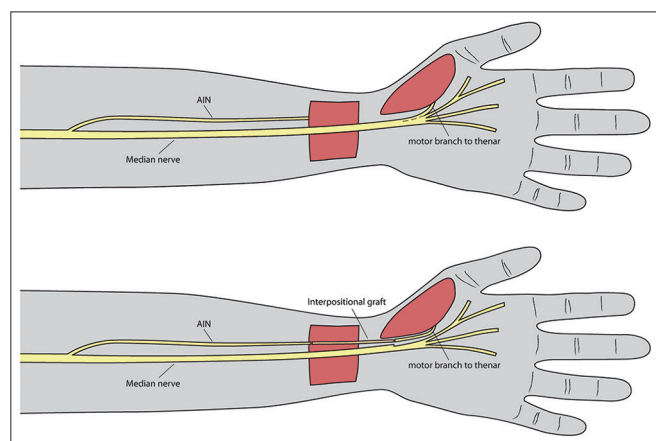


Figure 2: Distal median nerve deficit. Transfer of the terminal branch of the anterior interosseous nerve to the motor branch to the thenar muscles, using an interpositional graft. AIN: Anterior interosseous nerve

to the extensor digiti minimi and extensor carpi ulnaris) via interposition graft have been described, but results are uncertain and thus common tendon transfers might be considered instead.^[15]

Schematic description

A carpal tunnel incision is made to expose the median nerve and its motor branch at the level of the wrist. The latter is gently isolated proximally as far as its fibers can be distinguished. The AIN and its branch to the pronator quadratus are then isolated with intramuscular dissection in order to obtain the maximal possible length. A nerve graft is usually necessary for a tension-free closure. Although the number of axons matches well, the need for a nerve graft downgrades the level of outgrowth and, therefore, the actual potential for re-innervation.

Pronator function

The pronator teres function can be impaired in high median nerve injuries or secondary to an isolated deficit.^[40] In the first case the radial nerve, and specifically the motor branch to the ECRB is isolated and re-oriented to the branch, which innervates the PT.^[41] The surgical approach is similar to that described for radial nerve palsy when the opposite transfer is planned. In case of isolated PT deficiency, an intra-median nerve transfer is planned using one of the branches to the FDS^[40] sutured to the PT motor branch.

Extrinsic muscle function

In high-level median nerve injury several extrinsic muscles such as PT, FCR, FDS, flexor pollicis longus, the radial component of the FDP, and PQ are denervated. Two main problems are faced: first, the lack of flexion in the thumb, index and the long fingers, and second, the loss of pronation.^[15] The first option is to re-direct the motor branch to the ECRB towards the AIN, in a similar fashion described above for radial nerve palsy, but in a reverse direction [Figure 3]. If there is a significant discrepancy in size, the branch to the supinator can also be included.

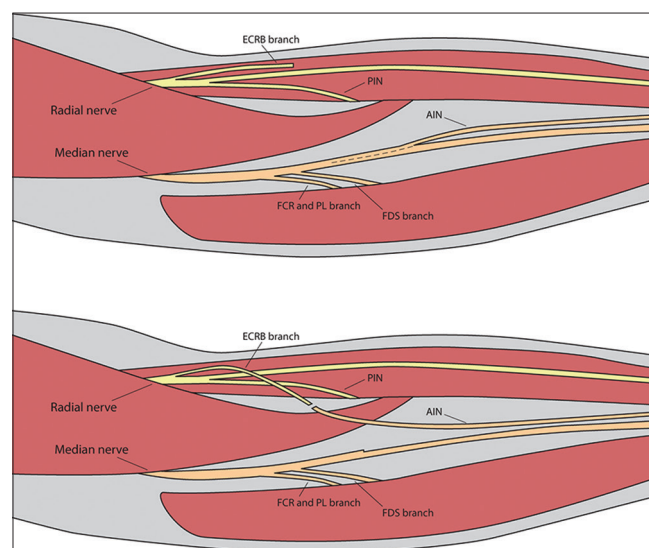


Figure 3: High median nerve deficit. Transfer of the motor branch to extensor carpi radialis brevis to the anterior interosseous nerve. ECRB: Extensor carpi radialis brevis, PIN: Posterior interosseous nerve, AIN: Anterior interosseous nerve, FCR: Flexor carpi radialis, FDS: Flexor digitorum superficialis, PL: Palmaris longus

In this case the AIN needs to be traced proximally in order to reach comfortably the motor branch to the supinator.^[15,41,42]

Schematic description: the AIN is identified in the forearm. A lazy-S incision is made over the volar aspect of the mid-forearm, and the lacertus fibrosus is divided. The tendon of the superficial part of the PT is lengthened to allow the muscle to be retracted, and the median nerve exposed. The AIN lies on the radial side of the median nerve and does not always course as a distinct fascicle. A longitudinal vessel often demarcates it from the rest of the median nerve. Once isolated, it should be traced proximally to obtain enough length for a tension-free suture. The motor branch to the ECRB is then identified under the brachioradialis muscle, coursing close to the sensory branch of the radial nerve. This is followed as distal as possible and then rotated toward the AIN. In case of a size mismatch, the radial nerve is isolated proximally in order to include the motor branch to the supinator, which in turn will reach the AIN if appropriate proximal dissection is completed.

In the event of isolated AIN palsy, an intra-median nerve transfer can be considered with redirection of branches to the FDS or PL/FCR to the AIN.

In lower brachial plexus injuries where both the median and ulnar nerve have been compromised, the AIN can be reinnervated by using the branch to brachialis muscle^[43] or the branch to the brachioradialis muscle,^[44] after both the donor and recipient are isolated for the necessary length at the elbow or a slightly proximal level.

Sensory nerve transfers

Priority is given to the ulnar side of the thumb and the radial side of the index finger in order to re-establish functional pinch and grip. Several donors can be considered depending upon their availability. The first choice includes the digital nerves to the fourth web space, innervated by the ulnar nerve^[15] [Figure 4]. An alternative is the dorsal sensory branch from the radial nerve to the thumb.^[45,46] Finally, as illustrated by Ross *et al.*^[47] in upper plexus lesions, the sensory components to the third web space come from a distinct fascicle, which can be isolated proximally in the median nerve and utilized as a donor to the thumb and index finger.

Schematic description

A carpal tunnel incision is made and prolonged distally in a zig-zag fashion toward both the first and the fourth interdigital spaces. Deep to the superficial arterial arch and the digital arteries, the common digital nerves to the ulnar side of the ring finger and the radial side of the little finger are isolated, traced proximally, and divided as distally as possible. The digital nerves to the first web space are then identified and isolated proximally in order to obtain enough length to be sutured to the donor nerves. The remainder of the sensory median nerve can then be divided proximally and coupled in an end-to-side fashion to the ulnar digital nerve of the 5th finger in order to restore protective sensation.

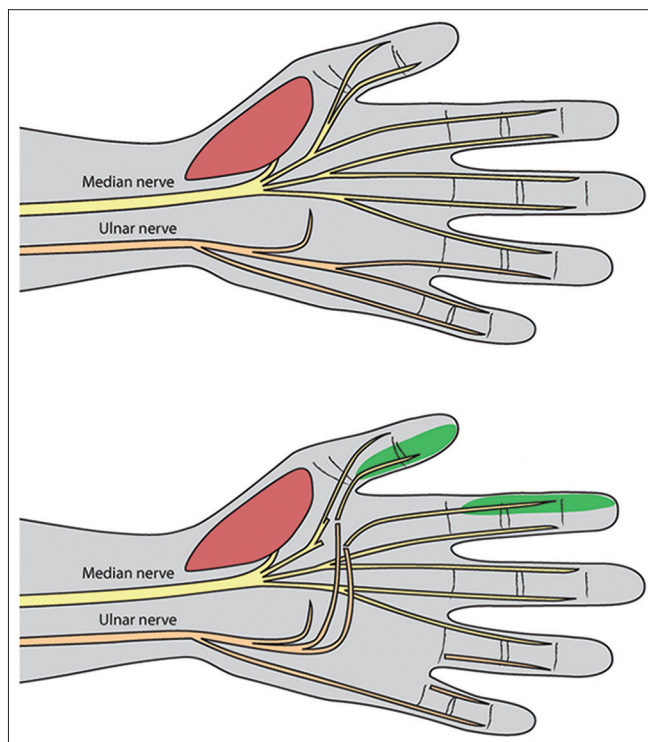


Figure 4: Sensory median nerve deficit. Transfer of the sensory branches from the ulnar nerve to the fourth web space to the sensory branches of the first web space

ULNAR NERVE DEFICITS

Indications

High-level nerve injuries lead to the loss of both grip and pinch strength in the hand, and sensation in the little finger and the ulnar side of the ring finger. Even following an early repair it is difficult to obtain a functional re-innervation of the intrinsic musculature, a fact which caused some authors to question the utility of surgical intervention at the site of lesion.^[48-51] Tendon transfers can avoid chronic deformities, but do not always allow fluid motion and adequate strength. Alternatively, the median nerve can provide motor and sensory branches in the forearm and hand that compensate for the ulnar nerve deficiency.^[52-55] In the event of a combined ulnar and median nerve injury, motor branches from the radial nerve are selected as donor axons.

Motor

If the median nerve is intact, the distal part of the AIN can re-innervate the distal motor component of the ulnar nerve [Figures 5-7]. Brown *et al.*^[56] performed the first case in 1991 and since then several authors have described successful results. Recently, Sukegawa *et al.*^[57] provided technical clarification regarding identification and separation of the motor branch of the ulnar nerve, the number of fascicles in the AIN and the motor ulnar nerve, and the shortest path required for the AIN to reach its recipient target. The motor component of the ulnar nerve can be reached through a Taleisnik incision^[58] which extends from the interthenar region proximal to the distal forearm. First, the ulnar nerve is isolated at the Guyon's canal and the motor branch is identified during its course toward

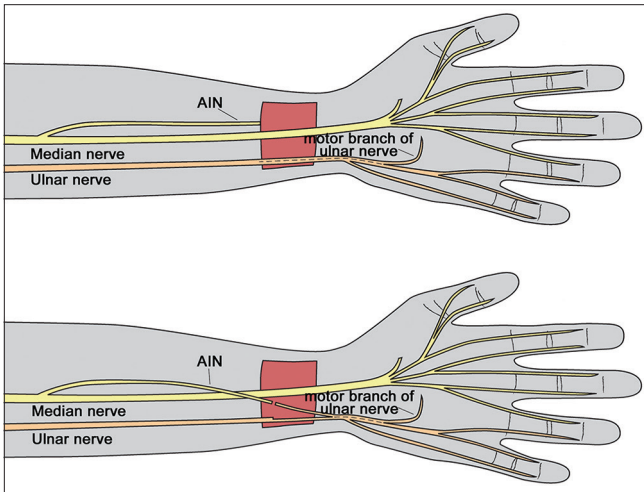


Figure 5: Ulnar nerve deficit. Transfer of the terminal branch of the anterior interosseous nerve to the motor branch of the ulnar nerve. AIN: anterior interosseous nerve

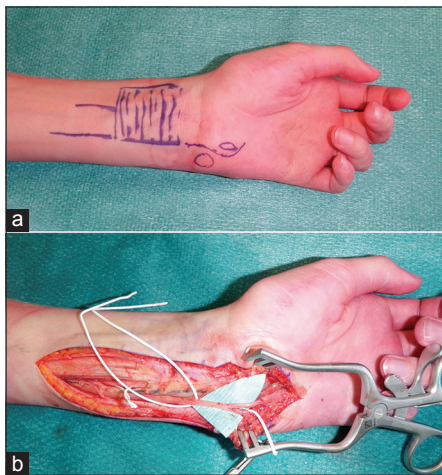


Figure 6: Ulnar nerve deficit. (a) Preoperative drawing showing the course of the motor branch of the ulnar nerve, and the terminal branch of the anterior interosseous nerve into the pronator quadrates; (b) the ulnar nerve and its motor branch after extensive neurolysis

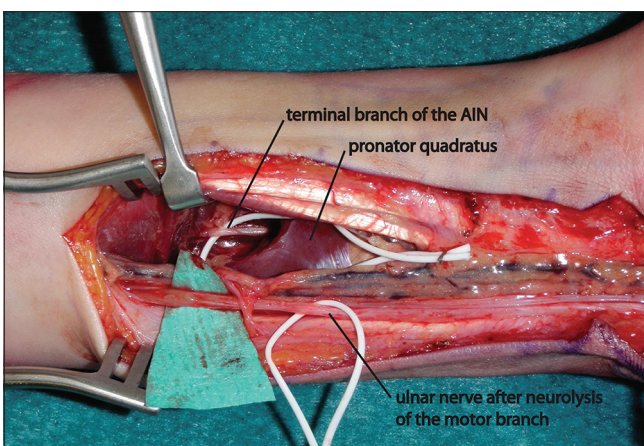


Figure 7: Terminal branch of the anterior interosseous nerve in the pronator quadratus muscle

the hook of the hamate. Once the point of divergence is identified, the motor nerve is followed proximally by blunt dissection. As reported by Sukegawa *et al.*,^[57] this is usually possible for about 33 mm. Sharp dissection is then required for an average of 19 mm. A longitudinal vascular

bundle usually separates the motor from the sensory part of the ulnar nerve. Through the forearm incision, the AIN is identified while entering the pronator quadratus. The dissection is carried as distal as possible into the muscle, and the AIN is then passed dorsal to the FDP in order to reach the motor branch of the ulnar nerve.^[56] The AIN has at this level approximately 506 axons, whereas the ulnar motor nerve 1523 axons.^[56] The transfer is not synergistic and recovery is generally suboptimal, but it is sufficient to prevent clawing of the ulnar digits.

In combined ulnar and median nerve injuries, motor branches from the radial nerve to the extensor digiti minimi and extensor carpi ulnaris originating from the PIN can be used to re-innervate the motor ulnar nerve. Coaptation is achieved by the use of an interpositional nerve graft from the mid-proximal forearm to the wrist. Although intrinsic muscle recover is not complete, it may be sufficient to prevent claw deformity of the fingers.^[59] As an alternative, branches to abductor pollicis longus, extensor pollicis brevis, and extensor indicis proprius can be re-oriented without the need for an interpositional nerve graft.^[60]

Sensory

In cases of ulnar nerve palsy, the functioning median nerve has been used by several authors with various methods to provide sensation to the ulnar nerve territory. Battiston and Lanzetta^[53] described the use of the palmar sensory branch of the median nerve to the sensory component of the ulnar nerve. Brown *et al.*^[56] used the sensory component to the third web space as a donor to the fourth web space, coupled in an end-to-end fashion, while the dorsal sensory branch of the ulnar nerve was sutured to the sensory part of the median nerve in an end-to-side manner after performing an epineural window.

In 2011, Flores^[61] described a similar technique but instead of an end-to-end anastomosis, he sutured the sensory component of the ulnar nerve in an end-to-side manner to the sensory nerve of the third web space without an epineural window. The author noted that at this level the epineural layer is thin and that the microsurgical sutures represent a sufficient trauma to stimulate the necessary sprouting into the donor's nerve. Oberlin *et al.*^[62] used the LACN as a donor in the forearm, coapted to the dorsal branch of the ulnar nerve by an interpositional nerve graft harvested from the sural nerve. In his two cases, he was able to avoid donor site morbidity when using donor sensory nerves from the median nerve territory in the hand. Ruchelsman *et al.*^[63] revised this technique by use of a longer dissection of the LACN in the forearm and suturing it without an interpositional graft in an end-to-side fashion to the ulnar nerve before the take-off of the sensory branch.

CONCLUSION

The numerous advantages offered by transposing a functional nerve stump in proximity to a target muscle or skin territory have created new and exciting alternatives for the management of nerve injuries, particularly those occurring far proximal in the arm or the brachial plexus. Some of these options have been described only

recently, and some only as case reports. In order to have a better understanding and use of such promising field, blinded randomized studies comparing traditional tendon transfers to nerve transfers are required.

REFERENCES

- Flourens P. Experiences on the repair and healing of the spinal cord and peripheral nerve injuries. *Ann Sci Naturelles* 1828;13:113-22.
- Meals RA, Nelissen RG. The origin and meaning of "neurotization". *J Hand Surg Am* 1995;20:144-6.
- Cunningham RH. The restoration of coordinated, volitional movement after nerve "crossing". *Am J Physiol* 1898;1:239-54.
- Ballance CA, Ballance HA, Stewart P. Remarks on the operative treatment of chronic facial palsy of peripheral origin. *Br Med J* 1903;1:1009-13.
- Körte W. A case of engrafting of the facial nerve into the hypoglossal nerve. *Dtsch Med Wochenschr* 1903;29:293-5.
- Harris W, Low VW. On the importance of accurate muscular analysis in lesions of the brachial plexus; and the treatment of Erb's palsy and infantile paralysis of the upper extremity by cross-union of the nerve roots. *Br Med J* 1903;24:1035-8.
- Harris RI. The treatment of irreparable nerve injuries. *Can Med Assoc J* 1921;11:833-41.
- Boyd KU, Nimigan AS, Mackinnon SE. Nerve reconstruction in the hand and upper extremity. *Clin Plast Surg* 2011;38:643-60.
- Lee SK, Wolfe SW. Nerve transfers for the upper extremity: new horizons in nerve reconstruction. *J Am Acad Orthop Surg* 2012;20:506-17.
- Mackinnon SE, Colbert SH. Nerve transfers in the hand and upper extremity surgery. *Tech Hand Up Extrem Surg* 2008;12:20-33.
- Garg R, Merrell GA, Hillstrom HJ, Wolfe SW. Comparison of nerve transfers and nerve grafting for traumatic upper plexus palsy: a systematic review and analysis. *J Bone Joint Surg Am* 2011;93:819-29.
- Pfister BJ, Gordon T, Loverde JR, Kocher AS, Mackinnon SE, Cullen DK. Mackinnon SE, Cullen DK. Biomedical engineering strategies for peripheral nerve repair: surgical applications, state of the art, and future challenges. *Crit Rev Biomed Eng* 2011;39:81-124.
- Seddon H. Surgical Disorders of the Peripheral Nerves. 2nd ed. New York: Churchill Livingstone; 1973. p. 164.
- Samii A, Carvalho GA, Samii M. Brachial plexus injury: factors affecting functional outcome in spinal accessory nerve transfer for the restoration of elbow flexion. *J Neurosurg* 2003;98:307-12.
- Brown JM, Mackinnon SE. Nerve transfers in the forearm and hand. *Hand Clin* 2008;24:319-40.
- Lee SK, Wolfe SW. Peripheral nerve injury and repair. *J Am Acad Orthop Surg* 2000;8:243-52.
- Dvali L, Mackinnon S. Nerve repair, grafting, and nerve transfers. *Clin Plast Surg* 2003;30:203-21.
- Mackinnon SE, Novak CB, Mykатыn TM, Tung TH. Results of reinnervation of the biceps and brachialis muscles with a double fascicular transfer for elbow flexion. *J Hand Surg Am* 2005;30:978-85.
- Mackinnon SE, Novak CB. Nerve transfers. New options for reconstruction following nerve injury. *Hand Clin* 1999;15:643-66.
- Pet MA, Ray WZ, Yee A, Mackinnon SE. Nerve transfer to the triceps after brachial plexus injury: report of four cases. *J Hand Surg Am* 2011;36:398-405.
- Anastakis DJ, Malessy MJ, Chen R, Davis KD, Mikulis D. Cortical plasticity following nerve transfer in the upper extremity. *Hand Clin* 2008;24:425-44.
- Anastakis DJ, Chen R, Davis KD, Mikulis D. Cortical plasticity following upper extremity injury and reconstruction. *Clin Plast Surg* 2005;32:617-34.
- Davis KD, Taylor KS, Anastakis DJ. Nerve injury triggers changes in the brain. *Neuroscientist* 2011;17:407-22.
- Taylor KS, Anastakis DJ, Davis KD. Cutting your nerve changes your brain. *Brain* 2009;132:122-33.
- Tung TH, Mackinnon SE. Nerve transfers: indications, techniques, and outcomes. *J Hand Surg Am* 2010;35:332-41.
- Chuang DC, Epstein MD, Yeh MC, Wei FC. Functional restoration of elbow flexion in brachial plexus injuries: results in 167 patients (excluding obstetric brachial plexus injury). *J Hand Surg Am* 1993;18:285-91.
- Socolovsky M, Di Masi G, Battaglia D. Use of long autologous nerve grafts in brachial plexus reconstruction: factors that affect the outcome. *Acta Neurochir (Wien)* 2011;153:2231-40.
- Wolfe SW, Johnsen PH, Lee SK, Feinberg JH. Long-nerve grafts and nerve transfers demonstrate comparable outcomes for axillary nerve injuries. *J Hand Surg Am* 2014;39:1351-7.
- Foster RJ, Swiontkowski MF, Bach AW, Sack JT. Radial nerve palsy caused by open humeral shaft fractures. *J Hand Surg Am* 1993;18:121-4.
- Bumbasirevic M, Lesic A, Bumbasirevic V, Cobeljic G, Milosevic I, Atkinson HD. The management of humeral shaft fractures with associated radial nerve palsy: a review of 117 cases. *Arch Orthop Trauma Surg* 2010;130:519-22.
- Bishop J, Ring D. Management of radial nerve palsy associated with humeral shaft fracture: a decision analysis model. *J Hand Surg Am* 2009;34:991-6.
- Green DP. Radial nerve palsy. In: Green DP, Hotchkiss RN, Pederson WC, Wolfe SW, editors. *Green's Operative Hand Surgery*. Philadelphia: Elsevier; 2005. p. 1113-29.
- Bowden RE, Napier EJ. The assessment of hand function after peripheral nerve injury. *J Bone Joint Surg Br* 1961;43:481-92.
- Lowe JB 3rd, Sen SK, Mackinnon SE. Current approach to radial nerve paralysis. *Plast Reconstr Surg* 2002;110:1099-113.
- Humphreys DB, Mackinnon SE. Nerve transfers. *Oper Tech Plast Reconstr Surg* 2002;9:89-99.
- Lowe JB 3rd, Tung TR, Mackinnon SE. New surgical option for radial nerve paralysis. *Plast Reconstr Surg* 2002;110:836-43.
- Mackinnon SE, Roque B, Tung TH. Median to radial nerve transfer for treatment of radial nerve palsy. Case report. *J Neurosurg* 2007;107:666-71.
- Tung TH, Weber RV, Mackinnon SE. Nerve transfers for the upper and lower extremities. *Oper Tech Orthop* 2004;14:213-22.
- Schultz RJ, Aiache A. An operation to restore opposition of the thumb by nerve transfer. *Arch Surg* 1972;105:777-9.
- Tung TH, Mackinnon SE. Flexor digitorum superficialis nerve transfer to restore pronation: two case reports and anatomic study. *J Hand Surg Am* 2001;26:1065-72.
- Hsiao EC, Fox IK, Tung TH, MacKinnon SE. Motor nerve transfer to restore extrinsic median nerve function: case report. *Hand (N Y)* 2009;4:92-7.
- Murphy RK, Ray WZ, Mackinnon SE. Repair of a median nerve transection injury using multiple nerve transfers, with long-term functional recovery. *J Neurosurg* 2012;117:886-9.
- Gu Y, Wang H, Zhang L, Zhang G, Zhao X, Chen L. Transfer of brachialis branch of musculocutaneous nerve for finger flexion: anatomic study and case report. *Microsurgery* 2004;24:358-62.
- García-López A, Sebastian P, Martinez F, Perea D. Transfer of the nerve to the brachioradialis muscle to the anterior interosseous nerve for treatment for lower brachial plexus lesions: case report. *J Hand Surg Am* 2011;36:394-7.
- Rapp E, Lallemand S, Ehrler S, Buch N, Foucher G. Restoration of sensation over the contact surfaces of the thumb-index pinch grip using the terminal branches of the superficial branch of the radial nerve. *Chir Main* 1999;18:179-83.
- Bertelli JA, Ghizoni MF. Very distal sensory nerve transfers in high median nerve lesions. *J Hand Surg Am* 2011;36:387-93.
- Ross D, Mackinnon SE, Chang YL. Intraneural anatomy of the median nerve provides "third web space" donor nerve graft. *J Reconstr Microsurg* 1992;8:225-32.
- Pfaeffle HJ, Waitayawinyu T, Trumble TE. Ulnar nerve laceration and repair. *Hand Clin* 2007;23:291-9.
- Vastamäki M, Kallio PK, Solonen KA. The results of secondary microsurgical repair of ulnar nerve injury. *J Hand Surg Br* 1993;18:323-6.
- Sammer DM, Chung KC. Tendon transfers: part II. Transfers for ulnar nerve palsy and median nerve palsy. *Plast Reconstr Surg* 2009;124:e212-21.
- Gaul JS Jr. Intrinsic motor recovery: a long term study of ulnar repairs. *J Hand Surg Am* 1982;7:502-8.
- Wang Y, Zhu S. Transfer of a branch of the anterior interosseous nerve to the motor branch of the median nerve and ulnar nerve. *Chin Med J (Engl)* 1997;110:216-9.
- Battiston B, Lanzetta M. Reconstruction of high ulnar nerve lesions by distal double median to ulnar nerve transfer. *J Hand Surg Am* 1999;24:1185-91.
- Haase SC, Chung KC. Anterior interosseous nerve transfer to the motor branch of the ulnar nerve for high ulnar nerve injuries. *Ann Plast Surg* 2002;49:285-90.
- Novak CB, Mackinnon SE. Distal anterior interosseous nerve transfer to the deep motor branch of the ulnar nerve for reconstruction of high ulnar nerve injuries. *J Reconstr Microsurg* 2002;18:459-64.
- Brown JM, Yee A, Mackinnon SE. Distal median to ulnar nerve transfers to restore ulnar motor and sensory function within the hand: technical nuances. *Neurosurgery* 2009;65:966-78.
- Sukegawa K, Kuniyoshi K, Suzuki T, Ogawa Y, Okamoto S, Shibayama M, Kobayashi T, Takahashi K. An anatomical study of transfer of the anterior

- interosseous nerve for the treatment of proximal ulnar nerve injuries. *Bone Joint J* 2014;96:789-94.
58. Taleisnik J. The palmar cutaneous branch of the median nerve and the approach to the carpal tunnel. An anatomical study. *J Bone Joint Surg Am* 1973;55:1212-7.
 59. Tung TH, Barbour JR, Gontre G, Daliwal G, Mackinnon SE. Transfer of the extensor digiti minimi and extensor carpi ulnaris branches of the posterior interosseous nerve to restore intrinsic hand function: case report and anatomic study. *J Hand Surg Am* 2012;38:98-103.
 60. Phillips BZ, Franco MJ, Yee A, Tung TH, Mackinnon SE, Fox IK. Direct radial to ulnar nerve transfer to restore intrinsic muscle function in combined proximal median and ulnar nerve injury: case report and surgical technique. *J Hand Surg Am* 2014;39:1358-62.
 61. Flores LP. Distal anterior interosseous nerve transfer to the deep ulnar nerve and end-to-side suture of the superficial ulnar nerve to the third common palmar digital nerve for treatment of high ulnar nerve injuries: experience in five cases. *Arq Neuropsiquiatr* 2011;69:519-24.
 62. Oberlin C, Teboul F, Severin S, Beaulieu JY. Transfer of the lateral cutaneous nerve of the forearm to the dorsal branch of the ulnar nerve, for providing sensation on the ulnar aspect of the hand. *Plast Reconstr Surg* 2003;112:1498-500.
 63. Ruchelsman DE, Price AE, Valencia H, Ramos LE, Grossman JA. Sensory restoration by lateral antebrachial cutaneous to ulnar nerve transfer in children with global brachial plexus injuries. *Hand (N Y)* 2010;5:370-3.

How to cite this article: Sassu P, Libberecht K, Nilsson A. Nerve transfers of the forearm and hand: a review of current indications. *Plast Aesthet Res* 2015;2:195-201.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 13-02-2015; **Accepted:** 27-05-2015

Sensory protection to enhance functional recovery following proximal nerve injuries: current trends

Boa Tram Nghiem, Ian C. Sando, Yaxi Hu, Melanie G. Urbanchek, Paul S. Cederna

Department of Surgery, Section of Plastic and Reconstructive Surgery, University of Michigan Health System, Ann Arbor, MI 48109, USA.

Address for correspondence: Dr. Paul S. Cederna, Department of Surgery, Section of Plastic and Reconstructive Surgery, University of Michigan Health System, Ann Arbor, MI 48109, USA. E-mail: cederna@med.umich.edu

ABSTRACT

Proximal nerve injury can lead to devastating functional impairment. Because axonal regeneration is slow, timely reinnervation of denervated muscle does not occur. These denervated muscles atrophy and lose function. Sensory protection is a surgical technique thought to prevent denervated muscle impairment using local sensory nerves to provide trophic support to the muscle until motor nerves can regenerate, and neuromuscular junctions are reestablished. We performed a comprehensive literature search using multiple databases to find primary articles reporting on the outcomes and treatment of sensory protection. This paper reviews the three main approaches to sensory protection: (1) end-to-end neurorrhaphy, (2) end-to-side neurorrhaphy, and (3) direct muscle neurotization. It discusses the evidence supporting each technique and outlines goals for future investigations.

Key words:

Denervation, muscle, nerve, neurorrhaphy, protection, regeneration, sensory

INTRODUCTION

Approximately, 65% of peripheral nerve injuries occur in the upper extremity. Healthy males between the ages of 18 and 35 are most commonly affected and the majority of peripheral nerve injuries are caused by trauma or malignant disease.^[1] Axonal regeneration is slow, and there is a critical window for muscle reinnervation before the denervated muscle becomes permanently impaired.^[2] Two months after injury, the denervated muscle exhibits reduced motor units but does not demonstrate changes in muscle fiber.^[3,4] After 6 months, however, the muscle experiences irreversible muscle atrophy and weakness.^[4,5] If primary repair cannot reestablish motor endplate connections within this critical

window, one should consider alternative approaches to protect the muscle before irreversible structural or functional impairments occur.

When nerve transection is not amenable to primary tensionless neurorrhaphy, the gold standard for repair is early nerve reconstruction using autologous nerve grafting.^[6] This method is not always feasible, however, due to delays in operative management, limitations of the donor nerve, including insufficient graft length or diameter, or morbidity to the donor site. Alternative approaches to early autologous nerve repair include use of decellular xenografts, synthetic grafts, or sensory protection.

Sensory protection is used to prevent denervated muscle from atrophy and subsequent functional loss. Temporarily protecting denervated muscle or “babysitting” it with a nearby branch of a motor nerve successfully maintains the muscle viability.^[7] At a second surgery, the babysitter nerve is replaced with a nerve with the needed control once that residual end has elongated, and neurorrhaphy can be performed.^[2,8] Similar babysitting with a sensory nerve is also a way to maintain muscle viability.^[9] A sensory nerve is coapted to the motor nerve stump in close proximity

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.156982

to the muscle for maintenance of muscle health while the proximal motor nerve is regenerating.^[9-11] A donor sensory nerve is thought to provide trophic support to the denervated muscle until the native motor axon is able to regenerate and reinnervate its target.^[12] In essence, sensory protection provides an interim protective effect on the denervated muscle prior to surgical nerve reconstruction.

We performed an extensive literature search using PubMed, Ovid, and Embase databases using keywords “sensory”, “nerve”, “protection”, “regeneration”, and “denervation” to find primary articles reporting on the treatment and outcomes of the sensory protection either in humans or animal models. This paper discusses the three main approaches to sensory protection and reviews the literature for each. We set the framework for future studies and advocate for further investigation of sensory protection in the upper extremities.

MUSCLE DENERVATION AND REINNERVATION

Nerve injury and muscle denervation

The peripheral nervous system has a remarkable capacity for regeneration following nerve injury. When a peripheral nerve is severed, it undergoes Wallerian degeneration and triggers a cascade of biochemical changes allowing future regrowth. Muscle fibers maintain viability immediately following denervation, however, atrophic changes such as reabsorption of myofibrils, shrinkage of muscle cells, and expansion of the extracellular matrix with collagen rapidly commence following denervation.^[13] Proteases play a role by promoting axonal degeneration, macrophage infiltration, and myelin degradation in damaged nerves.^[14]

Without prompt reinnervation, myofibril disorganization, and later mosaic disappearance marks imminent muscle fiber cell death.^[15] Prolonged denervation leads to muscle fiber necrosis, connective tissue hyperplasia, decreased vascularity, and depletion of satellite cells needed for regeneration.^[4,9,16] Further, denervated muscles become less receptive to regenerating motor axons due to the loss of neurotransmitters, neurotrophic factors, and viable muscle cells.^[2,17] These structural changes significantly impact the muscle's contractile properties. The decrease in cross-sectional area of muscle fibers translates to a reduction in maximum tension generated by tetanic muscle contractions. Later on, myofibril disorganization and collagenization diminishes specific force capacity (force per physiological cross sectional unit of muscle). From a functional perspective, maximum tension, specific force, and power all progressively decrease with time.^[13]

Nerve regeneration and muscle recovery

Regenerative processes occur synchronously with degradative mechanisms to ensure maximal recovery. Axonal regeneration occurs at a rate of 1 mm/day and is affected by age, nerve type, and grade of injury.^[18] Recovery involves axonal growth, synapse formation, and restoration of contractile properties. Schwann cells play an essential role in regrowth by increasing regenerative

proteins, including growth factors and adhesion molecules, to create a growth-rich milieu.^[19] In addition, native endoneurial conduits guide the reestablishment of neuromuscular connections. Research shows that preservation of the original motor endplates is essential for precise contact, synaptic differentiation, and maintenance of reestablished neural connections.^[20,21] This growth-supportive environment is significantly diminished if reinnervation does not occur in a timely manner.^[2] Although the exact timeframe is debatable, Sulaiman and Gordon^[22] proposed a 4-week window for nerve repair, after which the motor neuron has diminished ability to regenerate axons into the distal nerve stump.

Both time and distance limit spontaneous reinnervation of muscles. When immediate nerve reconstruction is not possible, sensory protection is the most effective means of providing temporary trophic support to prevent muscle degeneration. The three surgical techniques for sensory protection include: (1) end-to-end neurorrhaphy, (2) end-to-side neurorrhaphy, and (3) direct muscle neurotization. Nerve transfers with end-to-end neurorrhaphy or end-to-side neurorrhaphy are the most commonly used approaches for sensory protection. End-to-end neurorrhaphy joins the ends of a transected motor nerve and sensory nerve while end-to-side neurorrhaphy connects the end of a transected donor sensory nerve to the side of the injured motor nerve stump. Neurotization, the third and least favored approach, is the direct implantation of a divided sensory nerve into the belly of a denervated muscle. Figure 1 illustrates each technique.

SENSORY PROTECTION - THREE APPROACHES

End-to-end neurorrhaphy

End-to-end neurorrhaphy is the classic approach for sensory protection. Bain *et al.*^[9] demonstrated the positive effects of sensory protection on the architecture and

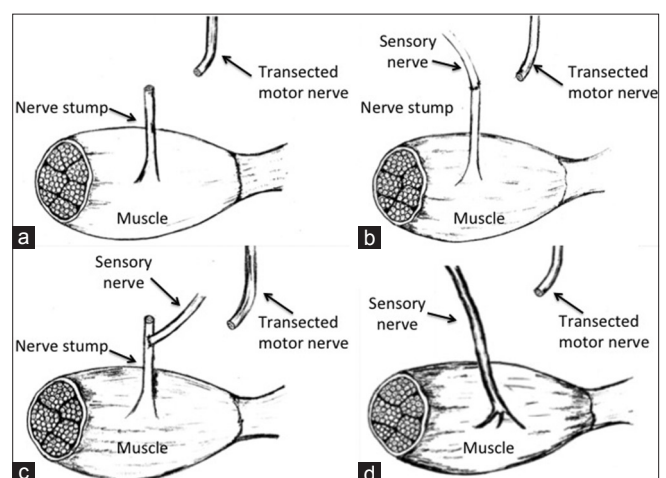


Figure 1: Schematic representation of surgical methods for sensory protection. (a) Transected nerve, denervated muscle without sensory protection; (b) sensory protection by end-to-end neurorrhaphy; (c) sensory protection by end-to-side neurorrhaphy; (d) sensory protection by direct muscle neurotization

function of the gastrocnemius and soleus muscles following denervation. The sensory-protected group underwent saphenous-to-tibial nerve transfer using end-to-end repair. Compared to the unprotected group, gross and histological examination showed the sensory-protected group had higher muscle weight and greater preservation of muscle structure, including less fiber atrophy and connective tissue hyperplasia. More importantly, the sensory-protected rats demonstrated larger maximum compound action potentials and relative preservation of isometric force overtime.^[9] Follow-up studies showed sensory protection also prevented muscle spindle deterioration.^[23] Nonetheless, rats that underwent immediate nerve repair had the best structural and functional outcomes.

The benefits of sensory protection have been substantiated by other groups.^[24-26] Common outcomes of end-to-end sensory nerve grafting in the lower limbs include preservation of fiber distribution, maintenance of motor endplates, and less muscle atrophy, fibrosis, collagenization, and fat deposition.^[16,25] Consistent with lower extremity studies, Beck-Broichsitter *et al.*^[11] found that sensory-protection in the upper extremity resulted in higher muscle weight, larger axon diameter, and larger nerve fiber surface area. However, there was no definitive difference in grasping strength between the sensory-protected and unprotected groups.^[11]

The protective effect by a purely sensory nerve can be explained by a number of factors. First, the trophic effect of the sensory nerve provides a supportive milieu for the maintenance of skeletal muscles. More specifically, sensory protection modulates the expression of both glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), thereby optimizing the environment for muscle preservation and reinnervation.^[12,27] Second, the sensory nerve helps maintain the architecture of the residual nerve stump and basal lamina of endoneurial tubes, thus facilitating later access by regenerating motor axons.^[4,28] Third, Schwann cells of the distal stump switch from a myelinating phenotype to a growth-supporting phenotype by upregulating specific genes associated with regeneration.^[19] These trophic effects help maintain a growth-supportive environment, which would otherwise deteriorate with time.

Although the research overwhelmingly supports the benefits of sensory protection, it is important to recognize points of contention. Sulaiman *et al.*^[29] proposed that the presence of sensory nerves instead create an unfavorable environment that reduces motor axonal regeneration and myelination of regenerated axons. The authors advocated that sensory nerves actively inhibit motor axonal regeneration by not only physically occupying the endoneurial pathways, but by altering Schwann cells in the distal nerve stump. Specifically, sensory nerves shift Schwann cells toward a phenotype that is less receptive to regenerating motor axons, in part by down-regulating the expression of L2/HNK-1 required for interaction between Schwann cells and motor axons.^[29,30] Furthermore, the investigators argue that the functional outcome of chronic denervation is primarily

determined by its effect on the injured nerve stump and secondarily by its effect on the muscle.^[29] Other studies have not largely substantiated these claims.

End-to-side neurorrhaphy

End-to-side neurorrhaphy provides trophic support from the donor nerve and enables the regenerated motor axons to reach their target, thus bypassing the need for a second operation to replace the motor nerve supply. In contrast, end-to-end neurorrhaphy requires cutting the donor sensory nerve and suturing it to its native stump once the motor nerve has regenerated, essentially denervating the muscle twice. Studies have shown that two cycles of denervation and reinnervation lead to suboptimal functional recovery, as demonstrated by reduced muscle power and force.^[31]

End-to-side coaptation is a compelling alternative when conventional end-to-end coaptation is not practical. Such cases occur when the transected end of the motor nerve stump is far from its muscle target or when there are multiple denervated muscles. Zijldendorp *et al.*^[32] recently investigated the efficacy of sensory protection using end-to-side neurorrhaphy. The investigators sutured the divided end of the sural nerve to the lateral aspect of the tibial nerve stump and examined the gastrocnemius muscle at 5 weeks and 10 weeks postoperatively. Compared to primary end-to-end neurorrhaphy, the sensory-protected group demonstrated a statistically significant increase in muscle weight and decrease in muscle atrophy compared to the unprotected group.^[32] Despite the ongoing debate over the efficacy, end-to-side neurorrhaphy remains a viable approach that requires further investigation.

Researchers have also used the end-to-side neurorrhaphy model to study the protective effects of mixed nerve containing both motor and sensory axons. The use of mixed nerve is supported by a recent study by Li *et al.*^[33] who compared muscle protection following denervation using the peroneal nerve (mixed protection) or sural nerve (sensory protection). They showed that both the mixed- and sensory-protected groups demonstrated preservation of muscle architecture and better functional recovery following reinnervation compared to the unprotected group. Further, the investigators showed that mixed protection was superior to sensory protection in terms of axon structure (more regenerated myelinated axons, larger axonal diameter, thicker myelin sheath) and function (greater contraction force).^[33] They controlled for stump reinnervation by the motor component of the mixed nerve by performing end-to-side coaptation and capping the end of the transected motor nerve. In contrast, another study by Michalski *et al.*^[27] reported no difference between mixed- and sensory-protected groups in terms of number of regenerating axons, axon diameter, and myelin cross-sectional area in the distal stump. However, there was a difference in the expression of denervation-induced GDNF, and BDNF expression between the two groups, which suggests that the main benefit of mixed protection is more rapid normalization of trophic factors.

More researches are needed to elucidate the exact mechanism of sensory protection and compare its functional outcomes with mixed protection. Goals for future studies include comparing differences in Schwann cell phenotype and neurotrophic expression between sensory protection and mixed protection. While mixed protection appears more advantageous compared to sensory protection, the need to sacrifice innervation to a donor muscle to harvest mixed nerve may preclude its use clinically.

Side-to-side neurorrhaphy

As an extension of end-to-side neurorrhaphy, researchers have also examined the efficacy of performing side-to-side neurorrhaphy. The technique involves joining the side of an intact donor nerve with the side of an injured nerve using a nerve “bridge” composed of either synthetic conduit or autologous graft. The few basic science and clinical studies investigating this technique have yielded mixed results. Experimentally, Shea *et al.*^[34] demonstrated the benefits of side-to-side neurorrhaphy using a synthetic collagen bridge to connect a healthy peroneal nerve with a transected tibial nerve in a rodent model. The investigators noted superior muscle preservation (higher muscle weight and less histologic evidence of muscle damage) and improved functional outcome (gait assessment) in their side-to-side nerve bridge group compared to denervated controls. However, no rats in the experimental group showed axonal regeneration along the length of the entire conduit. Clinically, Magdi Sherif and Amr^[35] showed the potential effectiveness of using autologous nerve graft bridges between median and ulnar nerve fascicles at the wrist in patients with high median or ulnar nerve injuries. However, this was a small case series without rigorous outcome measures making it difficult to definitively state that this technique is clinically efficacious.

Although the process of axonal repopulation and end-organ reinnervation is similar between end-to-side and side-to-side neurorrhaphy, the efficacy of side-to-side neurorrhaphy is less. Without donor axon, disruption and injury to the recipient nerve, the neurotrophic signals stimulating Schwann cell proliferation and axonal sprouting through nerve bridges are substantially diminished.^[33,36,37] As a result, few axons are available downstream for reinnervation or to provide trophic factors. Thus, compared to other techniques, side-to-side neurorrhaphy is a relatively inefficient technique for nerve reconstruction, and it does not result in clinically significant functional recovery or offer sufficient “protection” from muscle atrophy.

Direct muscle neurotization

Neurotization showed limited success in early human studies.^[38,39] Poor outcomes are in part due to the failure to form new neuromuscular junctions.^[40] Specifically, directly implanting a sensory nerve into muscle forces axonal regeneration to occur outside of native endoneurial conduits. The endoneurial conduit is important in regeneration because Schwann cells and basal lamina of

the endoneurial sheath produce key components that promote growth (e.g. collagen, fibronectins, and laminin) and provide a substrate for reinnervation.^[16,41-43] Impaired reinnervation translates into reduced capacity to generate force.^[44]

Recent neurotization experiments using animal models have been more promising. Wang *et al.*^[24] demonstrated that implantation of either a sensory nerve or preganglionically avulsed sensory nerve could slow muscle atrophy. Compared to unprotected controls, the implantation groups demonstrated higher fibrillation potential, muscle weight, cross sectional area, and protein content at one and three months after neurotization. In parallel experiments, Ochi *et al.*^[45,46] showed that joining the isografted dorsal root ganglia to the common peroneal nerve stump also mitigated muscle atrophy. Microscopy demonstrated sensory neuron survival and growth of fine axonal branches into the muscle. Although the sensory axons did not reinnervate motor endplates, the neurotized group showed functional advantages over unprotected controls with higher twitch tension and tetanic contraction. Similar to other techniques, the protective effect of neurotization is attributed to trophic factors derived from or stimulated by the sensory nerve. Compared to neurorrhaphy, however, the structural and functional results of direct muscle neurotization remain inferior.

Clinically, neurotization has limited applicability for patients with multiple denervated muscles, including those with proximal median or ulnar nerve injuries. For example, with proximal median nerve transection, over ten muscles in the arm may be affected. Each denervated muscle would require implantation with a separate sensory nerve, rendering this approach impractical. Thus, direct muscle neurotization is only appropriate for a selective group of patients.

FUTURE DIRECTIONS

To date, the outcomes of peripheral nerve manipulations such as end-to-end and end-to-side neurorrhaphy have primarily been assessed using histomorphometric analysis. Inferences about functional recovery have been made using anatomic measurements such as axonal density and myelin thickness. However, anatomic proxies for nerve regeneration offer little information about functional recovery.^[47] For years, muscle contractile properties, such as twitch force, tetanic force, peak-to-peak tension, and contractile velocity have been used to evaluate the degree to which motor axons reestablish their functional connections with muscle. Further studies measuring contractile properties as they relate to sensory protection would provide a more direct measure of muscle integrity and nerve regeneration. In addition, when compared with supra-physiological measures like tetanic force, functional outcomes such as grip strength, ambulation biomechanics, and upper extremity performance tests provide clinically relevant information about the extent and quality of muscle reinnervation.

Bain *et al.*^[10] set the stage for future clinical trials when they reported the first significant clinical application of sensory protection in a patient with complete sciatic nerve palsy and profound distal denervation following a total hip arthroplasty. The patient underwent end-to-side grafting of fascicles of the saphenous nerve to the motor nerve to the gastrocnemius and the deep branch of the peroneal nerve, thereby protecting the gastrocnemius and tibialis anterior muscles, respectively. One year after surgery, the patient demonstrated notable functional recovery of the gastrocnemius and anterior tibialis muscles based on electrophysiological testing and showed improved performance with activities of daily living. In comparison, none of the unprotected muscles below the knee showed electrophysiological or clinical improvement. Given the degree of sciatic nerve injury, the timing and extent of his improvements could not have been attributed to spontaneous recovery alone. Thus, this sentinel case offers a convincing argument for further clinical trials.

CONCLUSION

Based on its consistently favorable results in animal models, we advocate for the clinical application of sensory protection in upper limb injuries. Although end-to-end neurorrhaphy has produced the most favorable results, end-to-side coaptation may circumvent the need for a second neurorrhaphy procedure and it avoids multiple episodes of denervation. This effect becomes especially important in proximal injuries with diffuse muscle denervation. Neurotization can be a salvage technique in select patients when the proximal nerve stump is completely avulsed, and nerve transfer is not feasible. Together, these techniques offer hope for patients with peripheral nerve injuries in whom primary repair cannot reestablish motor endplate connections in sufficient time, thus bypassing the need for a second operation.

REFERENCES

1. Kreiger N, Kelsey JL, Harris C, Pastides H. Injuries to the upper extremity: patterns of occurrence. *Clin Plast Surg* 1981;8:13-9.
2. Aydin MA, Mackinnon SE, Gu XM, Kobayashi J, Kuzon WM Jr. Force deficits in skeletal muscle after delayed reinnervation. *Plast Reconstr Surg* 2004;113:1712-8.
3. Finkelstein DI, Dooley PC, Luff AR. Recovery of muscle after different periods of denervation and treatments. *Muscle Nerve* 1993;16:769-77.
4. Fu SY, Gordon T. Contributing factors to poor functional recovery after delayed nerve repair: prolonged denervation. *J Neurosci* 1995;15 (5 Pt 2):3886-95.
5. Gutmann E, Young JZ. The re-innervation of muscle after various periods of atrophy. *J Anat* 1944;78(Pt 1-2):15-43.
6. Evans GR. Peripheral nerve injury: a review and approach to tissue engineered constructs. *Anat Rec* 2001;263:396-404.
7. Mersa B, Tiangco DA, Terzis JK. Efficacy of the "baby-sitter" procedure after prolonged denervation. *J Reconstr Microsurg* 2000;16:27-35.
8. Terzis JK, Tzafetta K. The "babysitter" procedure: minihypoglossal to facial nerve transfer and cross-facial nerve grafting. *Plast Reconstr Surg* 2009;123:865-76.
9. Bain JR, Veltri KL, Chamberlain D, Fahnstock M. Improved functional recovery of denervated skeletal muscle after temporary sensory nerve innervation. *Neuroscience* 2001;103:503-10.
10. Bain JR, Hason Y, Veltri K, Fahnstock M, Quartly C. Clinical application of sensory protection of denervated muscle. *J Neurosurg* 2008;109:955-61.

11. Beck-Broichsitter BE, Becker ST, Lamia A, Fregnan F, Geuna S, Sinis N. Sensoric protection after median nerve injury: babysitter-procedure prevents muscular atrophy and improves neuronal recovery. *Biomed Res Int* 2014;2014:724197.
12. Zhao C, Veltri K, Li S, Bain JR, Fahnstock M. NGF, BDNF, NT-3, and GDNF mRNA expression in rat skeletal muscle following denervation and sensory protection. *J Neurotrauma* 2004;21:1468-78.
13. Lien SC, Cederna PS, Kuzon WM Jr. Optimizing skeletal muscle reinnervation with nerve transfer. *Hand Clin* 2008;24:445-54, vii.
14. Liu H, Kim Y, Chattopadhyay S, Shubayev I, Dolkas J, Shubayev VI. Matrix metalloproteinase inhibition enhances the rate of nerve regeneration *in vivo* by promoting dedifferentiation and mitosis of supporting schwann cells. *J Neuropathol Exp Neurol* 2010;69:386-95.
15. Borisov AB, Carlson BM. Cell death in denervated skeletal muscle is distinct from classical apoptosis. *Anat Rec* 2000 1;258:305-18.
16. Veltri K, Kwiecien JM, Minet W, Fahnstock M, Bain JR. Contribution of the distal nerve sheath to nerve and muscle preservation following denervation and sensory protection. *J Reconstr Microsurg* 2005;21:57-70.
17. Irintchev A, Draguhn A, Wernig A. Reinnervation and recovery of mouse soleus muscle after long-term denervation. *Neuroscience* 1990;39:231-43.
18. Fex S, Thesleff S. The time required for innervation of denervated muscles by nerve implants. *Life Sci* 1967;6:635-9.
19. Mirsky R, Jessen KR. The neurobiology of Schwann cells. *Brain Pathol* 1999;9:293-311.
20. Bader D. Reinnervation of motor endplate-containing and motor endplate-less muscle grafts. *Dev Biol* 1980;77:315-27.
21. Sanes JR, Marshall LM, McMahan UJ. Reinnervation of muscle fiber basal lamina after removal of myofibers. Differentiation of regenerating axons at original synaptic sites. *J Cell Biol* 1978;78:176-98.
22. Sulaiman OA, Gordon T. Effects of short- and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. *Glia* 2000;32:234-46.
23. Elsohemy A, Butler R, Bain JR, Fahnstock M. Sensory protection of rat muscle spindles following peripheral nerve injury and reinnervation. *Plast Reconstr Surg* 2009;124:1860-8.
24. Wang H, Gu Y, Xu J, Shen L, Li J. Comparative study of different surgical procedures using sensory nerves or neurons for delaying atrophy of denervated skeletal muscle. *J Hand Surg Am* 2001;26:326-31.
25. Hynes NM, Bain JR, Thoma A, Veltri K, Maguire JA. Preservation of denervated muscle by sensory protection in rats. *J Reconstr Microsurg* 1997;13:337-43.
26. Papakonstantinou KC, Kamin E, Terzis JK. Muscle preservation by prolonged sensory protection. *J Reconstr Microsurg* 2002;18:173-82.
27. Michalski B, Bain JR, Fahnstock M. Long-term changes in neurotrophic factor expression in distal nerve stump following denervation and reinnervation with motor or sensory nerve. *J Neurochem* 2008;105:1244-52.
28. Sunderland S, Bradley KC. Denervation atrophy of the distal stump of a severed nerve. *J Comp Neurol* 1950;93:401-9.
29. Sulaiman OA, Midha R, Munro CA, Matsuyama T, Al-Majed A, Gordon T. Chronic Schwann cell denervation and the presence of a sensory nerve reduce motor axonal regeneration. *Exp Neurol* 2002;176:342-54.
30. Martini R, Schachner M, Brushart TM. The L2/HNK-1 carbohydrate is preferentially expressed by previously motor axon-associated Schwann cells in reinnervated peripheral nerves. *J Neurosci* 1994;14 (11 Pt 2):7180-91.
31. Yoshimura K, Asato H, Jejurikar SS, Cederna PS, Urbanchek MG, Kuzon WM Jr. The effect of two episodes of denervation and reinnervation on skeletal muscle contractile function. *Plast Reconstr Surg* 2002;109:212-9.
32. Zuidendorp HM, Tra WM, van Neck JW, Mollis L, Coert JH. Delay of denervation atrophy by sensory protection in an end-to-side neurorrhaphy model: a pilot study. *J Plast Reconstr Aesthet Surg* 2010;63:1949-52.
33. Li QT, Zhang PX, Yin XF, Han N, Kou YH, Deng JX, Jiang BG. Functional recovery of denervated skeletal muscle with sensory or mixed nerve protection: a pilot study. *PLoS One* 2013;8:e79746.
34. Shea JE, Garlick JW, Salama ME, Mendenhall SD, Moran LA, Agarwal JP. Side-to-side nerve bridges reduce muscle atrophy after peripheral nerve injury in a rodent model. *J Surg Res* 2014;187:350-8.
35. Magdi Sherif M, Amr AH. Intrinsic hand muscle reinnervation by median-ulnar end-to-side bridge nerve graft: case report. *J Hand Surg Am* 2010;35:446-50.
36. Hayashi A, Pannucci C, Moradzadeh A, Kawamura D, Magill C, Hunter DA, Tong AY, Parsadani A, Mackinnon SE, Myckatyn TM. Axotomy or compression is required for axonal sprouting following end-to-side neurorrhaphy. *Exp Neurol* 2008;211:539-50.
37. Brenner MJ, Dvali L, Hunter DA, Myckatyn TM, Mackinnon SE. Motor

- neuron regeneration through end-to-side repairs is a function of donor nerve axotomy. *Plast Reconstr Surg* 2007;120:215-23.
38. Mackinnon SE, McLean JA, Hunter GA. Direct muscle neurotization recovers gastrocnemius muscle function. *J Reconstr Microsurg* 1993;9:77-80.
 39. Brunelli GA, Brunelli GR. Direct muscle neurotization. *J Reconstr Microsurg* 1993;9:81-90.
 40. Swanson AN, Wolfe SW, Khazzam M, Feinberg J, Ehteshami J, Doty S. Comparison of neurotization versus nerve repair in an animal model of chronically denervated muscle. *J Hand Surg Am* 2008;33:1093-9.
 41. Cornbrooks CJ, Carey DJ, McDonald JA, Timpl R, Bunge RP. *In vivo* and *in vitro* observations on laminin production by Schwann cells. *Proc Natl Acad Sci U S A* 1983;80:3850-4.
 42. McGarvey ML, Baron-Van Evercooren A, Kleinman HK, Dubois-Dalcq M. Synthesis and effects of basement membrane components in cultured rat Schwann cells. *Dev Biol* 1984;105:18-28.
 43. Muir D. The potentiation of peripheral nerve sheaths in regeneration and repair. *Exp Neurol* 2010;223:102-11.
 44. Cederna PS, Youssef MK, Asato H, Urbanchek MG, Kuzon WM Jr. Skeletal muscle reinnervation by reduced axonal numbers results in whole muscle force deficits. *Plast Reconstr Surg* 2000;105:2003-9.
 45. Ochi M, Kwong WH, Kimori K, Takemoto S, Chow SP, Ikuta Y. Delay of the denervation process in skeletal muscle by sensory ganglion graft and its clinical application. *Plast Reconstr Surg* 1996;97:577-86.
 46. Ochi M, Kwong WH, Kimori K, Chow SP, Ikuta Y. Reinnervation of denervated skeletal muscles by grafted dorsal root ganglion. *Exp Neurol* 1992;118:291-301.
 47. Cederna PS. Discussion: patterns of target tissue reinnervation and trophic factor expression after nerve grafting. *Plast Reconstr Surg* 2013;131:1001-3.

How to cite this article: Nghiem BT, Sando IC, Hu Y, Urbanchek MG, Cederna PS. Sensory protection to enhance functional recovery following proximal nerve injuries: current trends. *Plast Aesthet Res* 2015;2:202-7.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 01-02-2015; **Accepted:** 11-03-2015

“Babysitting” procedures in proximal nerve trunk injuries: two case reports and a review

Michele R. Colonna¹, Antonio Russo², Mariarosaria Galeano³, Gabriele Delia¹, Giorgio E. Pajardi⁴, Francesco Stagno d’Alcontres¹

¹Department of Experimental Specialistic Medical and Surgical Sciences and Odontostomatology, University of Messina, 98121 Messina, Italy.

²Department Hand Surgery, Multimedica Hospital, 20122 Milan, Italy.

³Department of Surgical Specialties, University Hospital of Messina, 98125 Messina, Italy.

⁴Department of Clinical and Community Sciences, University of Milan, 20122 Milan, Italy.

Address for correspondence: Prof. Michele R. Colonna, Department of Experimental Specialistic Medical and Surgical Sciences and Odontostomatology, University of Messina, 98121 Messina, Italy. E-mail: mrcolonna1@gmail.com

ABSTRACT

One of the most important goals in treating proximal nerve injuries is to maintain the function of distal effectors during axonal regeneration. “Babysitting”, that is, connecting the injured nerve to a healthy trunk provides a bypass for distal neural regeneration or reactivation. It avoids degeneration of sensory and motor terminations, with minimal donor nerve damage. We present a technique where a nerve graft is used between ulnar and median nerve through two end-to-side sutures in the distal third of the forearm, in two different cases of proximal ulnar nerve injury. Both patients were young manual workers, the former suffered a total nerve disruption proximal to the elbow following a car accident and the latter suffered a perineurial scar from a high voltage injury at the proximal third of the forearm. The proximal injury was grafted with a sural nerve in the former and treated by neurolysis in the latter. Results were graded by the Highet-Zachary scale for both sensory and motor recovery. The outcomes of our series were compared to six other case reports in the literature (including median nerves) treated with this technique. Both clinical and experimental data show that babysitting effectively protects distal effectors.

Key words:

Denervation, end-to-side neural repair, Martin Gruber anastomosis, nerve graft, sensory recovery

INTRODUCTION

Proximal nerve injuries are well-known to produce atrophy of the distal effectors. This is evident in injuries of major nerve trunks in the upper limb. The ulnar nerve has shown to have the lowest regenerative rate.^[1,2] Distal neurotization through end-to-side coaptation has been

employed^[3] to bring new axons into distal effectors in case of proximal nerve trunk injury to avoid distal effector degeneration. End-to-side nerve repair is a microsurgical technique in which nerve fibers are transferred from an intact donor nerve to a denervated recipient nerve directly or through a bridge graft.^[4-7] Although the value of end-to-side coaptation is debated in the literature, good functional results can be achieved when this technique is applied with special care to the donor nerve.^[6]

The “babysitter” procedure combines^[5] cross-facial nerve grafting with the segmental transfer of the hypoglossal nerve to the affected facial nerve. This technique has shown satisfactory to excellent results. In long-lasting paralysis, nonetheless, the babysitter procedure may need to be combined with muscle(s) flap(s) for enhanced outcomes.^[5,8]

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.160888

The authors report two cases of ulnar nerve injury proximal to the elbow: a double end-to-side coaptation through a nerve graft allowed axons from the donor median nerve to rehabilitate the recipient ulnar nerve (a surgically induced Martin Gruber anastomosis). This model was recently proposed by Kayikcioglu *et al.*^[9] and Magdi Sherif and Amr.^[10] In our cases, proximal ulnar nerve repair was performed through a long traditional nerve graft by end-to-end coaptation in the former, and by neurolysis in the latter. In both cases, a Zancolli lasso procedure was added distally. Our results are compared to six cases that were previously published and the effects of injury type, time from the initial trauma, surgical techniques, and future perspectives are discussed.

CASE REPORT

Case 1

A 22-year-old man, a hand worker, presented with proximal left ulnar nerve injury. He was found to have head trauma and an open contaminated wound of the left elbow with more than 12 cm of missing ulnar nerve. The wound was found to be contaminated with *Actinobacter baumannii*. Extensive debridement of the wound was carried out, and a cable graft from the sural nerve was performed 1 month after. A small remnant of the cutaneous medialis antebrachii nerve was found during scar removal, and it was used for the babysitting procedure.

At the distal third of the volar aspect of the forearm, 5 cm proximal to the distal palmar wrist crease, almost 4 cm of both the median and the ulnar nerve were exposed [Figure 1]. On both trunks, an epiperineural window was created on both the sides containing motor fascicles, the palmar ulnar side of the median nerve and the palmar radial side of the ulnar nerve, respectively (no stimulation was used). The 2 windows were connected through the graft obtained from the cutaneous antebrachii, which was sutured to the main trunks with 2 11-0 nylon sutures on each side [Figure 2]. Furthermore, the “lasso” procedure described by Zancolli

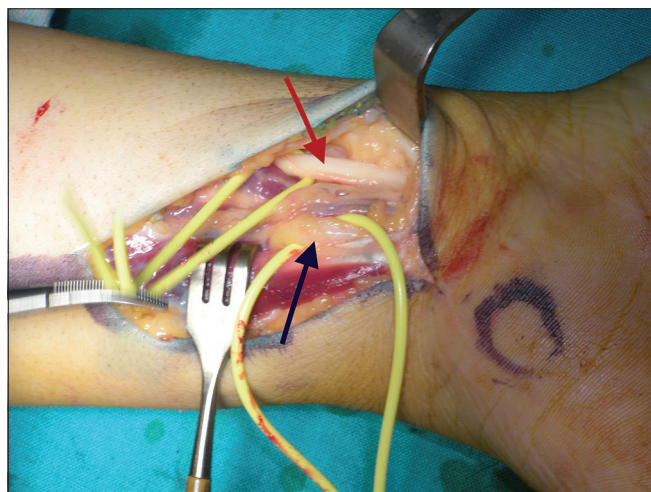


Figure 1: Planning of the procedure: at the distal third of the volar aspect of the forearm, 5 cm proximal to the distal palmar wrist crease, almost 4 cm of both the median (red arrow) and the ulnar (black arrow) nerve are exposed (label median and ulnar nerve)

was performed on the 4th and 5th digits. The hand was casted for immobilization, and the elbow was maintained in semi-extended position for 20 days, followed by progressive elbow mobilization.

The Highet-Zachary scheme was applied for motor evaluation, and a modification of Mackinnon *et al.*^[11] Sensory recovery scale was used with static and moving 2-point discrimination test. Early (20 days) protective sensation recovery was registered, but the 36-month and 6-year follow-up showed poor outcomes both for sensation (S1) and motion (M0).

Case 2

A 46-year-old man presented with proximal ulnar nerve injuries following a high voltage injury to the upper third of his left forearm. Three months after trauma, an electrophysiological study was performed which showed the absent motor and sensory potentials. An extensive surgical exposure and external neurolysis were performed together with distal babysitting technique. The terminal branch of the cutaneous medialis antebrachii was taken during ulnar exposure, and it was used as bridge graft without nerve stimulation; a Zancolli lasso procedure was also performed on the fourth and fifth digits. After two weeks, sensory and motor rehabilitation began following the same protocol applied to the first patient.

Outcome evaluation was performed as in case 1. Also in this case, early protective sensation recovery (24 days) was registered at 12-month follow-up. This high-voltage injury showed good results (S5 and M4) at 12-month follow-up.

DISCUSSION AND REVIEW

Denervation after nerve injury is known to cause important structural and functional changes within skeletal muscle, and long-term denervation with improper axonal recruitment has shown to produce atrophy of the end

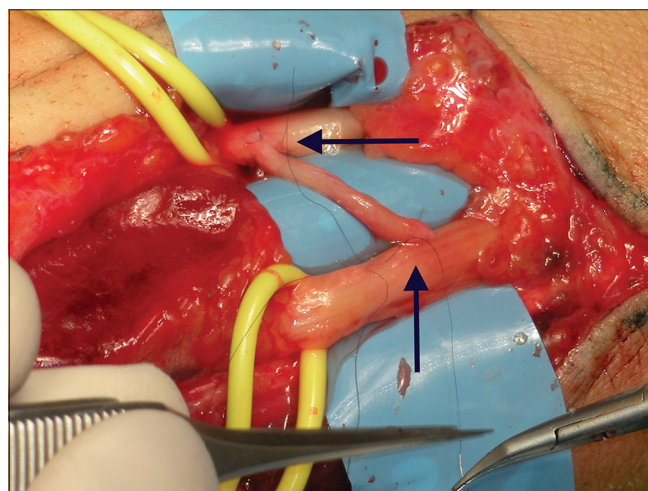


Figure 2: On both trunks, an epiperineural window has been opened, on both the sides containing motor fascicles, the palmar ulnar side of the median nerve and the palmar radial side of the ulnar nerve, respectively. The two windows have been connected through a cross graft of the cutaneous antebrachii, which was sutured (arrows) to the main trunks with two 11-0 nylon sutures on each side (label)

organs (both motor and sensory).^[1,2] Nerve babysitting^[3-5] provides distal effector organs (muscle, skin) reinnervation through end-to-side and side-to-side neurotization coming from healthy donor nerves when a proximal nerve trunk repair has been done. The rationale of using this technique are: (a) distal sensory corpuscles (Pacinian and Meissner) as well as motor plates undergo atrophy after denervation;^[1] (b) creating a connection distal to the injury, in a safe territory with the least damage to the donor nerve is a desirable goal when repairing a proximal nerve injury.^[3-5,8] However, experimental studies reported that mixing sensory and motor axons allows gain of sensation but fails in motor reinnervation.^[11] Moreover, Wallerian degeneration with time produces a poorer turnover and attraction of Schwann cells as well as a lower production of specific neurite growth factors;^[12-14] and (c) both clinical and experimental evidences have showed that donor axons can be induced into a recipient trunk through an opening of the epiperineurial connective tissue,^[3,6] and the capability of axonal attraction through a nerve graft used as a bridge through two different nerve trunks has also been demonstrated.^[4] This could also be achieved

using epineurial windows bridged with autologous vein as shown in a previous study.^[15]

Six cases have been published in the literature. First, Kayikcioglu *et al.*^[9] reported 2 cases of neural graft bridging the median and ulnar nerve (creating a Martin Gruber connection distal to the injury) just proximal to the wrist in a case of a median nerve cut at the elbow and of ulnar injury 5 cm proximal to the medial epicondyle. They reported poor motor and sensate results. Afterward Magdi Sherif and Amr^[10] reported 4 patients with ulnar or median nerve proximal lesions, which were treated with a modified Kayikcioglu's technique for comparison of main features of injuries and repair [Table 1]. In this paper, we report our experience with the application of a modified Kayikcioglu's technique to 2 patients. To date, a total of 8 proximal nerve injuries have been treated by this method (includes two cases from this report): 5 ulnar and 3 median nerves.

Magdi Sherif and Amr^[10] reported their best results in median nerve effector protection; dealing with ulnar nerve, they report a good result in a proximal (arm)

Table 1: Comparing main features of nerve injuries in the published series

Study	Patient number	Gender/ age (years)	Nerve	Level of injury	Trauma	Repair and time from trauma	Protection	Follow-up (months)	Outcome M and S
Kayikcioglu <i>et al.</i> ^[9]	1	Male/35	Median	Mid left arm	Window pane laceration during a seizure	Sural graft 6 cm two cables; 16 months after	Cross nerve graft above the wrist; donor of axons: ulnar	18	S and M poor
	2	Male/58	Ulnar	Mid right arm	Aggression	Direct immediate exploration and repair	Cross nerve graft above the wrist (four cables from sural); donor of axons: median	21	S and M poor
Magdi Sherif and Amr ^[10]	1	Male/34	Median	Left forearm elbow	Tangential trauma disruption	Sural graft four cables; third intervention after trauma	Cross nerve graft in palm between motor branches (one cable); donor of axons: ulnar	12	Complete S and M recovery
	2	Male/23	Ulnar	Mid left forearm	Broken glass	Sural graft three cables; 6 months after	Cross nerve graft above the wrist (one cable); donor of axons: median	9	M3 S3
	3	Female/49	Ulnar	Medial aspect arm	Broken glass	No mention (direct?); 2 months after	Cross nerve graft above the wrist (one cable); donor of axons: median	9	M4; no mention of S
	4	Female/8	Median	Left cubital fossa	Broken glass	Direct; immediate exploration and repair	Cross nerve graft above the wrist (one cable); donor of axons: ulnar	4	M3; no mention of S
Colonna <i>et al.</i> (in this series)	1	Male/26	Ulnar	Left lower third arm	Tangential trauma nerve disruption	Sural graft six cables; 1-month after trauma	Cross nerve graft above the wrist (one cable from medial cutaneous antebrachii); donor of axons: median	18	M and S poor
	2	Male/47	Ulnar	Left middle forearm	High-voltage injury	Neurolysis; 3 months after	Cross nerve graft above the wrist (one cable from cutaneous medialis antebrachii); donor of axons: median	18	Complete recovery

M: Motor, S: Sensate

injury as well as an incomplete outcome (partial sensate recovery, up to hypothenar region, and M3 only for finger abduction-adduction) in a lower (forearm) ulnar nerve injury.

The patients were 6 adult men (4 ulnar nerve and 2 median nerve injuries), one woman (ulnar) and an 8-year-old girl (median). With the exception of the child (patient number 4), they all underwent surgical repair 1 month after initial trauma. Optimal results were achieved in median nerves and in the pediatric patient. Interestingly, among the five ulnar nerves treated: (1) two showed good results (the former, unexpected, from the Magdi Sherif and Amr.^[10] series, a more proximal injury at arm level, and the latter our case of high voltage injury, but it was more distal and required only a neurolysis); (2) another produced a mediocre recovery (even if the injury was located more distally at forearm level); and (3) the remaining 2 achieving poor results.

Time may also be affecting against both proximal repair and distal babysitting; experimental evidences claim the role of decreasing the recruitment of Schwann cells together with lower production of growth factors when Wallerian degeneration is in process.^[12-14] Patient number three has the best outcome for the most proximal injury as an earlier combined treatment possibly led to better results than the same treatment in a more distal injury repaired later.

From a clinical point of view, it can be said that proximal ulnar injuries maintain their black legend of poor recovery prognosis while median nerve injuries have a better chance. This occurs especially in case of old (more than two months) injuries.

Cross nerve grafts above the wrist have proven ineffective in bringing axons distally to protect effectors in both Kayikcioglu's *et al.*^[9] and one case from our series. In Magdi Sherif and Amr.^[10] series, three cases treated by nerve bridging above the wrist showed good results in one median nerve (a child, see below for further considerations) and an ulnar nerve (M4), as well as mediocre results in another ulnar nerve. This could be explained by worse prognosis dealing with a ulnar nerve; time from injury could also have had a negative influence, whereas the good result (M4) in the other case remains surprising.

These considerations could also apply to our series: two ulnar nerves, the former showing poor outcome, the latter a complete recovery. Some other recommendations must be taken into consideration, too, such as selecting pure motor donor fibers through electrostimulation following Jabaley's *et al.*^[16] topographical anatomy.

However, another consideration is that there is no consensus about the negative influence of sensate fibers. Some authors^[17,18] experience agrees with this last opinion, but several other and more recent experimental experiences^[19-22] do not. In these studies, sensate fibers produce end-to-side regeneration and reinnervation of distal muscle.^[23,24] Thus, we believe that sensate fibers'

negative role should be reconsidered. In pediatric patients, special regenerative and brain adaptive properties should be considered. The pediatric patient in Magdi Sherif and Amr.^[10] stimulates further comments. Even ulnar nerve lesions that have the worst outcome in adults, seem to produce better outcomes in children. In their series, Magdi Sherif and Amr.^[10] showed electrical conduction in both grafts due to child's regenerative capability. They also reported "minimal intrinsic muscle wasting" as an effect of possible damage to the donor nerve produced by end-to-side surgical coaptation (the so-called "escape effect"). Interestingly, this is the only clinical report of this fearful complication of axonal escape from the donor ulnar in that series. Finally, the last technical concern could be risen regarding the number of bridge grafts ("cables") needed to produce the best result; even, in this case, Magdi Sherif and Amr.^[10] make the correct comment: the treated cases suggest that higher quantity should not be a valid concern to attract more axons and one cable is enough.

Cross nerve grafts in the palm, such as in patient number one by Magdi Sherif and Amr.,^[10] as connecting pure motor branches, produce better results. We agree that this could be due to a pure motor axonal component as well as due to decreased distance for regenerating fibers from the donor nerve. We add that the higher number of axons in the motor branch of the ulnar nerve could also be claimed as a cause. However, the authors^[10] noted a difficult dissection of the deep ulnar motor branch, owing to the presence of closer important anatomical structures. Moreover, there is a lack of description of the surgical technique: the authors do not explain where the cable between the median thenar and ulnar motor branch is positioned whether subcutaneous or deep.

We believe that Magdi Sherif and Amr.^[10] have refined the original technique, and their recommendations should be followed when applying this technique of babysitting. We recommend one cable grafting, use of stimulator, and most distal grafting to avoid fiber escape and muscle wasting in the territory of the donor nerve. Another negative factor to be struggled is time, which produces a decrease in neurite growth factors and Schwann cells migration. This could be achieved through a microsurgical approach coupled with basic sciences applications, such as gene therapy and tissue engineering with scaffolds and regenerating cells.^[25] Moreover, early exploration of nerve injuries could also help in struggle against time and Wallerian degeneration,^[26] its rationale is based on both experimental evidences of early neuronal death as far as in motor ventral horn and in dorsal root ganglia^[27] and more recent clinical data from early brachial plexus exploration and repair.^[28] Regardless of final outcomes, coupling of (a) both neurons (neuroprotection)^[27] and effectors (babysitting in wrist or palm)^[9,10] is preferred to (b) traditional repair through grafts^[2] or distal neurotization^[29-31] could be regarded as the future in management of proximal nerve injuries.

REFERENCES

- MacKinnon SE, Dellon AD. Anatomy and physiology of the peripheral nerve. Sensory receptors. *Surgery of the Peripheral Nerve*. New York: Thieme; 1988. p. 26-31.
- Millesi H. Nerve graft indication techniques and prognosis. In: Omer GE, Spinner M, van Beek AL editors. *Management of Peripheral Nerve Problems*. Philadelphia: WB Saunders; 1998. p. 280-90.
- Viterbo F, Trindade JC, Hoshino K, Mazzoni Neto A. End-to side neurorrhaphy with removal of the epineural sheath. *Plast Reconstr Surg* 1994;94:1038-47.
- Viterbo F, Trindade JC, Hoshino K, Mazzoni A. Two end-to-side neurorrhaphies and nerve grafts with removal of epineurial sheath: experimental study in rats. *Br J Plast Surg* 1994;47:75-80.
- Terzis JK, Tzafetta K. "Babysitter" procedure with concomitant muscle transfer in facial paralysis. *Plast Reconstr Surg* 2009;124:1142-56.
- Lundborg G, Zhao Q, Kanje M, Danielsen N, Kerns JM. Can Sensory and motor collateral sprouting be induced from intact peripheral nerve by end-to-side anastomosis? *J Hand Surg Br* 1994;19:227-82.
- Kostakoğlu N. Motor and sensory reinnervation in the hand after an end-to-side median to ulnar nerve coaptation in the forearm. *Br J Plast Surg* 1999;52:404-7.
- Cederna PS, Kallainen LK, Urbanchek MG, Rovak JM, Kuxzon WM Jr. "Donor" muscle structure and function after end-to-side neurorrhaphy. *Plast Reconstr Surg* 2001;107:789-96.
- Kayikcioglu A, Karamursel S, Agaoglu G, Kecick A, Celiker R, Cetin A. End-to-side neurorrhaphy of the ulnar and median nerves at the wrist: report of two cases without sensory or motor improvement. *Ann Plast Surg* 2000;45:641-3.
- Magdi Sherif M, Amr AH. Intrinsic hand muscle reinnervation by median-ulnar end-to-side bridge nerve graft: case report. *J Hand Surg Am* 2010;35:446-50.
- Sulaiman OA, Midha R, Munro CA, Matsuyama T, Al-Mayed A, Gordon T. Chronic Schwann cell denervation and the presence of sensory nerve reduce motor axonal regeneration. *Exp Neurol* 2002;176:342-54.
- Sulaiman OA, Gordon T. Effects of short-and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. *Glia* 2000;32:232-46.
- Borisov AB, Dedkov EI, Carlson BM. Interrelations of myogenic response, progressive atrophy of muscle fibers, and cell death in denervated skeletal muscle. *Anat Rec* 2001;264:203-18.
- Kawabuchi M, Zhou CJ, Wang S, Nakamura K, Liu WT, Hirata K. The spatiotemporal relationship among Schwann cells, axons and postsynaptic acetylcholine receptor regions during muscle reinnervation in aged rats. *Anat Rec* 2001;264:183-202.
- Manasseri B, Raimondo S, Geuna S, Risitano G, D'Alcontres FS. Ulnar nerve repair by end-to-side neurorrhaphy on the median nerve with interposition of a vein: an experimental study. *Microsurgery* 2007;27:27-31.
- Jabaley ME, Wallace WH, Heckler FR. Internal topography of major nerves of the forearm and hand: a current view. *J Hand Surg Am* 1980;5:1-18.
- Nichols CM, Brenner MJ, Fox IK, Tung TH, Hunter DA, Rickman SR, Mackinnon SE. Effects of motor versus sensory nerve grafts on peripheral nerve regeneration. *Exp Neurol* 2004;190:347-55.
- Ray WZ, Mackinnon SE. Management of nerve gaps: autografts, allografts, nerve transfers, and end-to-side neurorrhaphy. *Exp Neurol* 2010;223:77-85.
- Zuijdendorp HM, Tra WM, van Neck JW, Mollis L, Coert JH. Delay of denervation atrophy by sensory protection in an end-to-side neurorrhaphy model: a pilot study. *J Plast Reconstr Aesthet Surg* 2010;63:1949-5.
- Ladak A, Schembri P, Olson J, Udina E, Tyreman N, Gordon T. Double end-to-side nerve grafts sustain chronically denervated peripheral nerve pathways during axon regeneration and result in improved functional reinnervation. *Neurosurgery* 2011;68:1654-65.
- Li QT, Zhang PX, Yin XF, Han N, Kou YH, Deng JX, Jiang BG. Functional recovery of denervated skeletal muscle with sensory or mixed nerve protection: a pilot study. *PLoS One* 2013;7:e79746.
- Li QT, Zhang P, Yin X, Han N, Kou Y, Jiang B. Early sensory protection in reverse end-to-side neurorrhaphy to improve the functional recovery of chronically denervated muscle in rat: a pilot study. *J Neurosurg* 2014;121:415-22.
- Fujiwara T, Matsuda K, Kubo T, Tomita K, Hattori R, Masuoka T, Yano K, Hosokawa K. Axonal supercharging technique using reverse end-to-side neurorrhaphy in peripheral nerve repair: an experimental study in the rat model. *J Neurosurg* 2007;107:821-9.
- Beck-Broichsitter BE, Becker ST, Lamia A, Fregnan F, Geuna S, Sinis N. Sensoric protection after median nerve injury: babysitter-procedure prevents muscular atrophy and improves neuronal recovery. *Biomed Res Int* 2014;2014:724197.
- Manasseri B, Cuccia G, Moimas S, D'Alcontres FS, Polito F, Bitto A, Altavilla D, Squadrito F, Geuna S, Pattarini L, Zentilin L, Collesi C, Puligadda U, Giacca M, Colonna MR. Microsurgical arteriovenous loops and biological templates: a novel *in vivo* chamber for tissue engineering. *Microsurgery* 2007;27:623-9.
- Kay SJP, Wiberg M, and Thornton DJ. Nerves are living structures whose injury requires urgent repair. *J Plast Reconstr Aesthet Surg* 2010;63:1939-40.
- Hart AM, Terenghi G, Wiberg M. Neuronal death after peripheral nerve injury and experimental strategies for neuroprotection. *Neural Res* 2008;30:999-1011.
- Jivan S, Kumar N, Wiberg M, Kay S. The influence of pre-surgical delay on functional outcome after reconstruction of brachial plexus injuries. *J Plast Reconstr Aesthet Surg* 2009;62:472-9.
- Schmidhammer R, Redl H, Hopf R, van der Nest DG, Millesi H. Synergistic terminal motor end-to-side nerve graft repair: investigation in a non-human primate model. *Acta Neurochir Suppl* 2007;100:97-101.
- Schmidhammer R, Nográdi A, Szabó A, Redl H, Hausner T, van der Nest DG, Millesi H. Synergistic motor nerve fiber transfer between different nerves through the use of end-to-side coaptation. *Exp Neurol* 2009;217:388-94.
- Brown JM, Yee A, Mackinnon SE. Distal median to ulnar nerve transfers to restore ulnar motor and sensory function within the hand: technical nuances. *Neurosurgery* 2009;65:966-77.

How to cite this article: Colonna MR, Russo A, Galeano M, Delia G, Pajardi GE, d'Alcontres FS. "Babysitting" procedures in proximal nerve trunk injuries: two case reports and a review. *Plast Aesthet Res* 2015;2:208-12.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 02-02-2015; **Accepted:** 05-06-2015

Tissue-engineered constructs for peripheral nerve repair: current research concepts and future perspectives

Alba C. de Luca¹, Wassim Raffoul², Francesco Giacalone³, Maddalena Bertolini³, Pietro G. di Summa^{2,3}

¹EPFL, Centre for Neuroprosthetics, Laboratory for Soft Bioelectronic Interfaces, 1015 Lausanne, Switzerland.

²Department of Plastic, Reconstructive and Hand Surgery, University Hospital of Lausanne (Centre Hospitalier Universitaire Vaudois), 1011 Lausanne, Switzerland.

³Department of Hand Surgery and Microsurgery, CTO-Maria Adelaide Trauma Center, 10126 Torino, Italy.

Address for correspondence: Dr. Pietro G. di Summa, Department of Plastic, Reconstructive and Hand Surgery, University Hospital of Lausanne (Centre Hospitalier Universitaire Vaudois), 1011 Lausanne, Switzerland. E-mail: pietro.di-summa@chuv.ch

ABSTRACT

Traumatic injuries resulting in peripheral nerve lesions lead to important morbidity with devastating social and economic consequences. When the lesioned nerve cannot be sutured directly, a nerve graft is generally required to bridge the gap. Although autologous nerve grafting is still the first choice for reconstruction, it has the severe disadvantage of the sacrifice of a functional nerve. Research in tissue engineering and nerve regeneration may have a dramatic impact on clinical and surgical treatment of such nerve lesions. The authors review the latest concepts in tissue engineering for nerve repair, including scaffold engineering of neural guides, biomaterial modification, cell therapy, growth factors delivery, and electrical stimulation. Recent literature is reviewed in detail, pointing out the most interesting present achievements and perspectives for future clinical translation. Electronic search of the literature was performed using MEDLINE, Embase, and the Cochrane Library to identify research studies on peripheral nerve regeneration through tissue-engineered conduits. The following medical subject headings were used to carry out a systematic search of the literature: “nerve regeneration”, “stem cells”, “biomaterial”, “extracellular matrix”, “functional regeneration”, “growth factors” and “microchannels”. Included literature was published between 1991 and 2014. The reference lists from the retrieved articles were also reviewed for additional articles. In total, 76 articles were included in this study.

Key words:

Cell transplantation, extracellular matrix, growth factors, nerve guidance conduit, peripheral nerve repair, surface modification

INTRODUCTION

The success of repair after peripheral nerve injury depends on the type and the extension of the trauma. In the event of nerve compression or sheath loss, the structural elements in the nerve tissue are preserved,

and injury recovery can occur without surgery. However, severe trauma can cause the complete disruption of the nerve (neurotmesis), resulting in the complete loss of continuity and function.^[1]

The two segments generated after nerve transection retract, and edema occurs at the distal stump. The latter starts to swell and degenerates within hours in a process known as “Wallerian degeneration”.^[2] The regeneration process takes place at the proximal stump, where the axon soma is still included, forming the growth cone that expands toward the distal stump to bridge the gap.

When nerves are severed, and denervation occurs, the longer the lag time reinnervation, the worse the functional recovery.^[3] Long denervation time, as clinically seen in

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.160889

brachial plexus injuries, causes complete atrophy of target tissues, followed by fibrosis and fragmentation of motor fibers.

The current “gold standard” in peripheral nerve surgeries is an autograft, which is defined as the interposition of autologous nerve segments (typically from the leg or the forearm). Despite the ideal core structure provided by the autologous tissue transferred, autografts allow only partial functional recovery, involve double surgery and cause donor tissue morbidity, calling for tissue engineered solutions to overcome these inconveniences.

A nerve guidance conduit (NGC) is a valid alternative to autograft, providing a confined environment for the entire regenerative process. NGC can be made of both natural and artificial materials. Its chemical and physical properties can be optimized to achieve the best performance in terms of tissue regeneration and inflammatory response, as illustrated by several reviews.^[4-6] However, despite the number of proposed engineered materials, the functional recovery after conduit repair of peripheral nerve injuries still fails where long (> 3 cm) gaps are created.

In the last decade, researchers have focused on different approaches to control and guide the regeneration of the injured tissue. The most promising options will be discussed below, including modification of the inner lumen architecture, transplantation of glial/stem cells (SCs), inclusion of extracellular matrix (ECM) components and neurotrophic factors [Figure 1].

INTRALUMINAL ARCHITECTURE

The importance of designing new NGC has been raised in the last decade. Topography of the inner lumen can dramatically affect the ability of both the nerve to regenerate across the gap and the endogenous cells to migrate and proliferate along the structure to modulate production and release of neurotrophic factors. Using

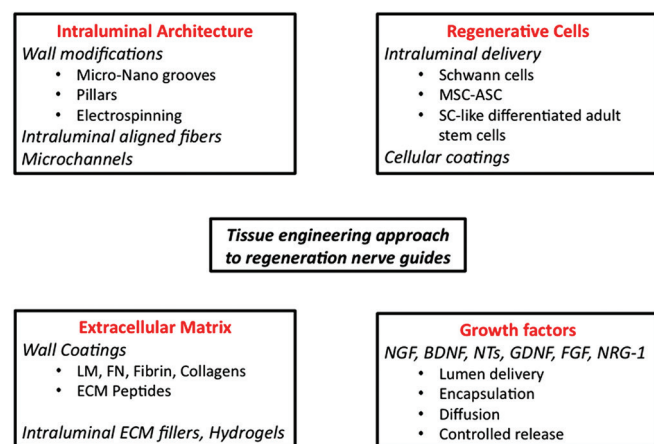


Figure 1: Different tissue engineering approaches to improve nerve conduits for peripheral nerve regeneration. MSC: Mesenchymal adult stem cells, ASC: Adipose-derived adult stem cells, LM: Laminin, FN: Fibronectin, ECM: Extra cellular matrix, NGF: Nerve growth factor, BDNF: Brain-derived neurotrophic factor, NTs: Neurotrophins, GDNF: Glial-derived neurotrophic factor, FGF: Fibroblast growth factor, NRG-1: Neuregulin 1

features from micro- to nanoscale, several surface modifications have been performed in order to simulate the organized native structure of the neuronal tissue, including micro- or nanogrooves to direct SC and neurite alignments in a mechanism also known as “conduct guidance”, micro-pits and pillars.^[7,8] Microgrooves triggered SC alignment and migration along the pattern direction,^[9-11] simulating the organized structure of the glial cells when forming the bands of Büngner. Another technique commonly used to recreate longitudinal patterns in the conduit lumen is electrospinning, which allows the fabrication of micro- or nanofibrous conduits. Nerve conduits fabricated with electrospun aligned fibers influence cell migration and nerve fiber alignment after regeneration.^[7] Aligned micro-^[12] and submicro-^[13] electrospun fibers were compared to a random fiber configuration in an *in vivo* study, with the oriented topography stimulating axon outgrowth and glial cell migration along the direction of the fibers. Moreover, variations in fiber diameter and distribution have been shown to affect both the permeability and the porosity of the neural tube, finally influencing cell response.^[4]

A different approach to alter the architecture of nerve conduit guidance is to fill the empty tube with oriented intraluminal frameworks or filaments, characterized by a larger total surface area compared to a bare conduit. However, these fillers may hinder the regenerative process, and it is necessary to accurately control their “packing density” and distribution, which may have a large impact on the final ability of the nerve to regenerate.

Thin films of polyacrylonitrile-co-methyl acrylate composed of aligned fibers were inserted into the lumen of polysulfone conduits and compared to randomly aligned fibers and smooth films in a short-term *in vivo* study using a rat model.^[14] Nerve regeneration was accelerated in conduits containing the aligned fibrous film, resulting in higher levels of myelination and muscle reinnervation when compared to the other groups. This could be due to a high directionality and alignment of endogenous SC, which are involved in the formation of the new tissue and the myelination of the regenerated axons.

Microchannel elongating across the length of the tube is an alternative lumen modification to guide axonal growth in a confined environment. Agarose multi-channel conduits were shown to allow axonal growth after injury, and vascularization occurred after 10 weeks *in vivo*.^[15] In a recent study, a silicon-based conduit containing 24 micro-fabricated parallel channels with a diameter of 130 μm allowed the regeneration of the nerve across the injury gap in a rat model, resulting in 85% axon myelination.^[16] It was demonstrated that innervation was unsuccessful at the external ring of the concentric microchannels while all the remaining channels were filled with neuronal tissue and blood vessels. When cells were preloaded in microchannel conduits, the internal guides also helped the seeding and increased the availability of the cells, with enhanced outcomes.^[17] Interestingly, when similar multichannel structures were created with fibrin,

no differences in terms of regeneration between numbers and diameters of the channels were observed.^[18]

In addition to providing a physical path for the regenerative process, microchannels also act as “axonal signal amplifiers” when applied in nerve stimulating-recording devices. The electrical resistance of the intracellular medium is increased by the constricted environment, and the recorded signal of the extracellular potential is therefore amplified when specific electrodes are embedded in the structure, according to Fitzgerald *et al.*,^[19] Microelectrodes arrays are in fact commonly used to record neural activity during the regeneration process at the injury site. New technological frontiers have allowed researchers to fabricate stretchable electrodes to better conform and deform along the tubular nerve conduit, responding more anatomically to the physical stress which conduits undergo *in vivo* and reducing the inflammatory response.^[16,20]

INFLUENCE OF EXTRACELLULAR MATRIX MOLECULES AND FILLERS

Peripheral nerves have the potential to regenerate after injury, as opposed to the central nervous system. This is mainly attributed to the presence of SC basement membranes rich in ECM components, such as laminin (LM) and fibronectin (FN), which promote axonal regeneration in the peripheral nervous system. The ECM milieu of the regenerating nerve is not simply a passive scaffold for regrowth, as its molecules can synergistically signal with growth factors and growth cone molecules to influence regrowth.^[21] LM, fibrin, FN and collagen are the main ECM proteins used as coatings for peripheral nerve repair. ECM molecules such as LM,^[22] FN^[23,24] and collagen^[25] have been shown to enhance axonal regeneration when incorporated into nerve guidance channels.^[26]

Alternatively, FN- and LM-derived peptide moieties, such as RGD (Arg-Gly-Asp),^[27,28] IKVAV (Ile-Lys-Val-Ala-Val),^[29,30] and YIGSR (Tyr-Ile-Gly-Ser-Arg),^[31] have been recognized to trigger specific interactions between neural cells and the accordingly modified substrate.

Different from coatings, ECM proteins have been used for the formation of gels or matrices as intraluminal fillers of NGCs, such as fibrin gels, shown interesting results in terms of regeneration.^[32] However, this ECM protein maintains SC in a nonmyelinating state^[33] and therefore, the degradation time of the gel should be optimized in order to trigger axon myelination in due time during regeneration.

Another composite hydrogel containing collagen and hyaluronan, with or without growth factors, was used in combination with poly(L-lactide-co-caprolactone).^[34] Both the compound muscle action potential and the muscle recovery were improved when compared to the empty control, while no differences were observed in presence or absence of nerve growth factor (NGF).

For a detailed review on the effect of ECM components on peripheral nerve regeneration, readers are advised to consult a recent publication.^[35]

CELL TRANSPLANTATION

Cell-based therapy is considered a valid approach to stimulate and enhance the regeneration of the injured nerve, overcoming the delayed recruitment and response of endogenous SC at the injury site, and therefore reducing their progressive atrophy *in vivo*. SC have been either injected at the injury site or preseeded in the nerve conduit,^[36,37] with high rates of successful axon regeneration and myelination. In addition, various growth factors expression in SC can be induced as needed for the specific purpose. Prior studies have presented successful transfections of SC with either fibroblast growth factor (FGF)^[38] or NGF,^[39] both stimulating nerve repair in an injury rat model. Recently, SCs were transplanted *ex vivo* before implantation in order to investigate the impact of brain-derived nerve factor (BDNF), ciliary neurotrophic factor (CNTF), and neurotrophin 3 (NT-3) on nerve regeneration and recovery. The result was a significant improvement of axon outgrowth and myelination,^[40] with cells remaining viable for up to 8 weeks *in vivo*. However, the harvest of autologous SC involves a significantly debilitating biopsy from the patient. In addition, SC adhesion and proliferation are considerably slower when compared to cells cultured *in vitro* (requiring for instance the precoating of each culture substrate), resulting in long culture time in order to achieve a suitable number for therapeutic uses.

Stem cells have become very attractive in tissue engineering and regenerative medicine due to their ability to self-renew and differentiate into most cell phenotypes.^[41] Mesenchymal SCs (MSCs) are derived from bone marrow stromal progenitors and have been demonstrated to be able to trans-differentiate into several cell lineages, including osteoblasts, chondrocytes, endothelial cells, myocytes, neurons, and glial cells. In particular, when MSC are differentiated into SC-like cells, they are able to express the characteristic glial markers and enhance peripheral nerve regeneration *in vivo* by improving myelination of axons and increasing regeneration distances.^[42]

Undifferentiated MSC was preseeded in a chitosan conduit in an *in vivo* study for 6 weeks using a rat model, with successful regeneration similar to autografting.^[17] In addition, these cells were used in a monkey model to repair a 50-mm median nerve defect in a long-term *in vivo* experiment.^[43] Cells were injected directly after implantation at the proximal stump to overcome the deficit of local SC, resulting in enhanced regenerative properties compared to the nonseeded conduits. Similar outcomes comparable to autografts were then assessed in a dog model, bridging a 50-mm sciatic nerve gap with successful muscle reinnervation.^[44] Signs of local transdifferentiation into an SC-like phenotype were observed after 8 weeks postimplantation by Oliveira *et al.*,^[45] resulting in higher formation of myelinated and unmyelinated axons, as well as blood vessels, when compared to empty conduits.

Alternatively, SCs can be isolated from white adipose tissue using liposuction to avoid invasive procedures.^[46,47] Like MSC, adipose-derived SCs (ASCs) are able to differentiate into a SC phenotype, and their characteristic elongated spindle-shaped morphology has been confirmed through microscopy.^[47-49] Their ability to express specific glial-markers, that is, S-100, p75 and glial fibrillary acidic protein,^[50,51] as well as the protein P0 responsible for the myelin formation,^[51] has also been demonstrated. Finally, differentiated ASC (dASC) are able to express the neuronal-associated protein nestin,^[48,50,51] as well as the neuron-specific enolase and the neuron-specific protein.^[48]

When undifferentiated ASC were preloaded in polycaprolactone conduits to investigate their effect on axonal outgrowth, it was observed that they were able to prevent neuron apoptosis by up-regulating the expression of anti-apoptotic BCL-2 and down-regulating the expression of caspase and BAX.^[52] These results were comparable to N-acetylcysteine treatments, which guarantee the preservation of cell signaling and survival as previously demonstrated.^[53-55] Both ASC and dASC have been frequently used for transplantation in NGC to repair injury gaps, although different and sometimes conflicting results have been observed due to the various experimental conditions.^[56-59] Signs of *in vivo* transdifferentiation of undifferentiated SCs into an SC-like phenotype have been also observed, further stimulating interest in using ASC for peripheral nerve repair.^[59] However, depending on the scaffold used, the viability of the preloaded cells can be strongly affected, reducing the initial beneficial effect of the cell therapy.^[56] All of these results suggest the potential use of ASC (or dASC) in peripheral nerve repair, substituting SC.

The ultimate strategy in cell therapy is the formation of tissue engineered nerve grafts with the application of an intraluminal "cellular coating" composed of co-cultured SC and dorsal root ganglia, which are able to release and up-regulate the production of neurotrophic factors in the lumen over time. Long-term results of up to 12 weeks have shown a significant ability to regenerate the nerve comparable to nerve grafts.^[60] An even more advanced development would be the fabrication of scaffoldless neural conduits providing a confined environment without using polymeric structures, as proposed by Adams *et al.*,^[61] In their study, their group attempted to construct a nerve guide using a monolayer of ASC differentiated into fibroblasts co-cultured with neurospheres. This system supported the *in vivo* expression of growth factors, such as FGF, ascorbic acid, epidermal growth factor, and transforming growth factor (TGF)- β 1, which induced the transdifferentiation of the SCs into SC-like cells.^[61]

GROWTH FACTORS AND THEIR RELEASE IN NERVE GUIDANCE CONDUIT

Neurotrophic factors belong to the family of growth factors, and they are produced by SCs during Wallerian degeneration after injury.^[62] Acting through their receptors, neurotrophic factors are involved in the

neuronal activity, promoting nerve regeneration.^[63,64] In addition, their expression is strictly dependent on time after axotomy, which biases the regenerative capacity of axons, as well as the supporting activity of SCs.^[3]

Neurotrophins constitute one of the most important family of factors, including NGF, BDNF, NT-3, and NT-4/5.^[65] After release, a density gradient of factors is formed around regenerating axons.^[62] NGF is the one of the most important NTs involved in nerve regeneration and is up-regulated rapidly in the distal stump after injury.^[66] It is able to promote the survival and outgrowth of sensory neurons, although NGFs are not involved in the motor neuron response.^[65] BDNF is up-regulated in denervated SCs in order to allow myelination and nerve regeneration.^[66] It is involved in the outgrowth of both sensory and motor neurons.^[62,65] Finally, NT-3 and NT-4/5 promote survival of both motor and sensory neurons.

Besides NTs, other neurotrophic factors are involved in the regenerative process of nerves. CNTF is a neurokine protein down-regulated after injury,^[65] implicated in motor neuron survival,^[63] outgrowth and sprouting.^[65] Moreover, glial cell line-derived neurotrophic factor (GDNF),^[64,66] FGF,^[62,65] neuregulin-1,^[64,66] and leukemia inhibitory factor^[63,64] also play an important role in peripheral nerve regeneration. Finally, TGF- β is necessary for the nonmyelinating status of SCs during the proliferation process.^[64] Nevertheless, all neurotrophic factors described above co-operate in order to enable neuron survival and axonal outgrowth.^[63]

Following injury, axotomy conditions and chronic denervation cause a reduced availability of neurotrophic factors and their supplement at the injury site is needed to stimulate and support regeneration.^[3,67] As reviewed by Pfister *et al.*,^[68] growth factors can be released into the lumen through different mechanisms of drug delivery from an empty conduit (i.e. dissolution in a solution, encapsulation in the conduit wall, diffusion through microspheres) or by use of an intraluminal filler (i.e. microfiber impregnation, binding and release in a matrix). However, results reported in the literature are sometimes contradictory, and optimization of their concentration and the release mechanism is, therefore, necessary. In addition, due to their low stability in solution, growth factors need to be protected when encapsulated or bond to a substrate in order to prevent their degradation and prolong their activity *in situ*. In fact, some ECM molecules can form specific bonds with growth factors, preserving their functionality. For example, it was found that binding to heparin or heparin sulfate can specifically stabilize FGF, GDNF, and NGF, which are then gradually released in the delivery system.^[68] Furthermore, polymer coatings of the surface of the loaded biomaterial or microsphere with polylactide-co-glycolide^[12,69-71] can protect and gradually control the neurotrophic factor delivery over time.

Gordon's group has extensively investigated the role of neurotrophic factors in nerve regeneration, particularly focusing on the effect of BDNF and GDNF in the system.

Neurotrophic factors were supplemented at the injury site using a mini-osmotic pump and no effect was observed at low doses.^[3] Conversely, very high concentrations of BDNF inhibited the axonal regeneration, with a mechanism that seemed to be dose-dependent. In addition, a combination of BDNF and GDNF resulted in better nerve repair.^[3] Madduri *et al.*^[70,71] tested instead the efficiency of cross-linked NGF and GDNF as single growth factors or in combination to repair peripheral nerve injuries, resulting in enhanced early regeneration after two weeks postimplantation and higher SC migration. Since neurotrophic factors are gradually released in the regenerative environment by cells as a response to the natural events occurring during Wallerian degeneration and axon regeneration and myelination, it may be beneficial to recreate a molecular gradient along the inner surface of the NGC, guaranteeing the necessary supply of factors to support the regeneration process. An *in vitro* study demonstrated that a patterned gradient of immobilized NGF on chitosan substrates would increase axon sprouting and branching in the direction of the gradient itself.^[13] Tang *et al.*^[72] were also able to control the gradient distribution of NGF along a poly(ϵ -caprolactone)-block-poly(L-lactic acid-co- ϵ -caprolactone) conduit and observed a higher sciatic function index (SFI) when compared to uniform distribution of the neurotrophic factor.

The ECM-matrix inclusion of growth factors that are gradually released in the inner lumen of the NGCs have also been considered to be a valuable alternative for the optimization of the bioengineered construct. A successful study was presented by Cao *et al.*^[73] during which collagen scaffolds were loaded with an LM filler containing CNTF, promoting high levels of myelination after twelve weeks postimplantation and enhancing both SFI and nerve conduction velocity.

Cell transduction can also be thought of as an alternative approach to release specific growth factors at the site of regeneration. Godinho *et al.*^[40] implanted peripheral nerve grafts containing SC expressing BDNF, CNTF, and NT-3, respectively, resulting in different outcomes as a function of the growth factor. Following accurate locomotor investigation by using the gait analysis system Catwalk®,^[74-76] they showed a significant improvement of functional recovery under CNTF and NT-3 conditions while NT-3 stimulated a higher degree of myelination.^[40]

CONCLUSION AND FUTURE DIRECTIONS

Despite advancements in microsurgical techniques, nerve repair clinically provides suboptimal results, and autologous nerve grafts are the primary choice for nerve reconstruction, especially over long gaps. This opens the field for research and the development of tissue engineered nerve guides [Figure 1]. The transplant of regenerative cells into biodegradable conduits could be a clinical tool translating into improved regeneration. In our experience,^[47,49,58] ASCs contribute to axonal regeneration and myelination with the improvement of

functional outcomes in long-term experiments. Given their abundance and plasticity, we personally consider these cells to be one of the main options in future nerve repair studies. In this review, we have attempted to present a complete tableau of the different components which we believe are relevant for successful regeneration. To perform at their best, transplanted cells need a favorable environment, with proper attachment to biomaterials and directionality driven through conduits. If present, the external delivery of growth factors should be controlled to avoid inhibitory effects on regeneration. This would support both transplanted and native Schwann cell performance, improving nerve regeneration. The stronger mechanical stability shown by cells seeded on an ECM such as FN and LM may be essential for cell migration and control of local signaling environment.^[36] The influence of cell behavior on material coatings is an interesting question, as this effect is not dependent upon an external delivery source (as in the case of growth factors). Similarly, interactions between cells and biomaterials may influence cell performance and directionality, making it an interesting field for future research.

ACKNOWLEDGMENTS

The authors are grateful to the Swiss National Found for supporting their current research. P.G. di Summa is thankful to the SICPA foundation and the University Hospital of Lausanne (CHUV) for supporting his hand surgery training and research in peripheral nerve injury and regeneration.

REFERENCES

1. Burnett MG, Zager EL. Pathophysiology of peripheral nerve injury: a brief review. *Neurosurg Focus* 2004;16:E1.
2. Geuna S, Raimondo S, Ronchi G, Di Scipio F, Tos P, Czaja K, Fornaro M. Chapter 3: histology of the peripheral nerve and changes occurring during nerve regeneration. *Int Rev Neurobiol* 2009;87:27-46.
3. Gordon T. The role of neurotrophic factors in nerve regeneration. *Neurosurg Focus* 2009;26:E3.
4. Daly W, Yao L, Zeugolis D, Windebank A, Pandit A. A biomaterials approach to peripheral nerve regeneration: bridging the peripheral nerve gap and enhancing functional recovery. *J R Soc Interface* 2012;9:202-21.
5. Geuna S, Tos P, Titolo P, Ciclamini D, Benigno T, Battiston B. Update on nerve repair by biological tubulization. *J Brachial Plex Peripher Nerve Inj* 2014;9:1-6.
6. Nectow AR, Marra KG, Kaplan DL. Biomaterials for the development of peripheral nerve guidance conduits. *Tissue Eng Part B Rev* 2012;18:40-50.
7. Hoffman-Kim D, Mitchel JA, Bellamkonda RV. Topography, cell response, and nerve regeneration. *Annu Rev Biomed Eng* 2010;12:203-31.
8. Cunha C, Panzeri S, Antonini S. Emerging nanotechnology approaches in tissue engineering for peripheral nerve regeneration. *Nanomedicine* 2011;7:50-9.
9. Sun M, McGowan M, Kingham PJ, Terenghi G, Downes S. Novel thin-walled nerve conduit with microgrooved surface patterns for enhanced peripheral nerve repair. *J Mater Sci Mater Med* 2010;21:2765-74.
10. Mitchel JA, Hoffman-Kim D. Cellular scale anisotropic topography guides Schwann cell motility. *Plos One* 2011;6:e24316.
11. Mobasser SA, Terenghi G, Downes S. Micro-structural geometry of thin films intended for the inner lumen of nerve conduits affects nerve repair. *J Mater Sci Mater Med* 2013;24:1639-47.
12. Madduri S, Papaliozou M, Gander B. Topographically and topographically functionalized silk fibroin nerve conduits for guided peripheral nerve regeneration. *Biomaterials* 2010;31:2323-34.
13. Yu LM, Miller FD, Shoichet MS. The use of immobilized neurotrophins to support neuron survival and guide nerve fiber growth in compartmentalized chambers. *Biomaterials* 2010;31:6987-99.
14. Mukhatyar V, Pai B, Clements I, Srinivasan A, Huber R, Mehta A,

- Mukhopadaya S, Rudra S, Patel G, Karumbaiah L, Bellamkonda R. Molecular sequelae of topographically guided peripheral nerve repair. *Ann Biomed Eng* 2014;42:1436-55.
15. Tansey KE, Seifert JL, Botterman B, Delgado MR, Romero MI. Peripheral nerve repair through multi-luminal biosynthetic implants. *Ann Biomed Eng* 2011;39:1815-28.
16. FitzGerald JJ, Lago N, Benmerah S, Serra J, Watling CP, Cameron RE, Tarte E, Lacour SP, McMahon SB, Fawcett JW. A regenerative microchannel neural interface for recording from and stimulating peripheral axons *in vivo*. *J Neural Eng* 2012;9:016010.
17. Zheng L, Cui HF. Enhancement of nerve regeneration along a chitosan conduit combined with bone marrow mesenchymal stem cells. *J Mater Sci Mater Med* 2012;23:2291-302.
18. Scott JB, Afshari M, Kotek R, Saul JM. The promotion of axon extension *in vitro* using polymer-templated fibrin scaffolds. *Biomaterials* 2011;32:4830-9.
19. FitzGerald JJ, Lacour SP, McMahon SB, Fawcett JW. Microchannels as axonal amplifiers. *IEEE Trans Biomed Eng* 2008;55:1136-46.
20. Lacour SP, Benmerah S, Tarte E, FitzGerald J, Serra J, McMahon S, Fawcett J, Graudejus O, Yu Z, Morrison B 3rd. Flexible and stretchable micro-electrodes for *in vitro* and *in vivo* neural interfaces. *Med Biol Eng Comput* 2010;48:945-54.
21. Yanagida H, Tanaka J, Maruo S. Immunocytochemical localization of a cell adhesion molecule, integrin alpha5beta1, in nerve growth cones. *J Orthop Sci* 1999;4:353-60.
22. Buettner HM, Pittman RN. Quantitative effects of laminin concentration on neurite outgrowth *in vitro*. *Dev Biol* 1991;145:266-76.
23. Whitworth IH, Brown RA, Dore C, Green CJ, Terenghi G. Orientated mats of fibronectin as a conduit material for use in peripheral nerve repair. *J Hand Surg Br* 1995;20:429-36.
24. Tom VJ, Doller CM, Malouf AT, Silver J. Astrocyte-associated fibronectin is critical for axonal regeneration in adult white matter. *J Neurosci* 2004;24:9282-90.
25. Woolford TJ, Toriumi DM. The enhancement of nerve regeneration using growth factors: a brief review. *J Long Term Eff Med Implants* 1995;5:19-26.
26. Labrador RO, Buti M, Navarro X. Influence of collagen and laminin gels concentration on nerve regeneration after resection and tube repair. *Exp Neurol* 1998;149:243-52.
27. de Luca AC, Faroni A, Downes S, Terenghi G. Differentiated adipose-derived stem cells act synergistically with RGD-modified surfaces to improve neurite outgrowth in a co-culture model. *J Tissue Eng Regen Med* 2013;DOI: 10.1002/term.1804.
28. de Luca AC, Stevens JS, Schroeder SL, Guilbaud JB, Saiani A, Downes S, Terenghi G. Immobilization of cell-binding peptides on poly-epsilon-caprolactone film surface to biomimic the peripheral nervous system. *J Biomed Mater Res A* 2013;101:491-501.
29. Wei YT, Tian WM, Yu X, Cui FZ, Hou SP, Xu QY. Hyaluronic acid hydrogels with IKVAV peptides for tissue repair and axonal regeneration in an injured rat brain. *Biomed Mater* 2007;2:S142-6.
30. Hosseinkhani H, Hiraoka Y, Li CH, Chen YR, Yu DS, Hong PD, Ou KL. Engineering three-dimensional collagen-IKVAV matrix to mimic neural microenvironment. *ACS Chem Neurosci* 2013;4:1229-35.
31. Maseali E, Wieringa PA, Morshed M, Nasr-Esfahani MH, Sadri S, van Blitterswijk CA, Moroni L. Peptide functionalized polyhydroxyalkanoate nanofibrous scaffolds enhance Schwann cells activity. *Nanomedicine* 2014;10:1559-69.
32. Kalbermatten DF, Kingham PJ, Mahay D, Mantovani C, Pettersson J, Raffoul W, Balcin H, Pierer G, Terenghi G. Fibrin matrix for suspension of regenerative cells in an artificial nerve conduit. *J Plast Reconstr Aesthet Surg* 2008;61:669-75.
33. Akassoglou K, Yu WM, Akpınar P, Strickland S. Fibrin inhibits peripheral nerve remyelination by regulating Schwann cell differentiation. *Neuron* 2002;33:861-75.
34. Jin J, Limburg S, Joshi SK, Landman R, Park M, Zhang Q, Kim HT, Kuo AC. Peripheral nerve repair in rats using composite hydrogel-filled aligned nanofiber conduits with incorporated nerve growth factor. *Tissue Eng Part A* 2013;19:2138-46.
35. de Luca AC, Lacour SP, Raffoul W, di Summa PG. Extracellular matrix components in peripheral nerve repair: how to affect neural cellular response and nerve regeneration? *Neural Regen Res* 2014;9:1943-8.
36. di Summa PG, Kalbermatten DF, Raffoul W, Terenghi G, Kingham PJ. Extracellular matrix molecules enhance the neurotrophic effect of Schwann cell-like differentiated adipose-derived stem cells and increase cell survival under stress conditions. *Tissue Eng Part A* 2013;19:368-79.
37. Berrocal YA, Almeida VW, Gupta R, Levi AD. Transplantation of Schwann cells in a collagen tube for the repair of large, segmental peripheral nerve defects in rats. *J Neurosurg* 2013;119:720-32.
38. Haastert K, Lipokatic E, Fischer M, Timmer M, Grothe C. Differentially promoted peripheral nerve regeneration by grafted Schwann cells over-expressing different FGF-2 isoforms. *Neurobiol Dis* 2006;21:138-53.
39. Tannemaat MR, Verhaagen J, Malessy M. The application of viral vectors to enhance regeneration after peripheral nerve repair. *Neurol Res* 2008;30:1039-46.
40. Godinho MJ, Lip T, Pollett MA, Goodman D, Hodgetts SI, Sweetman I, Walters M, Verhaagen J, Plant GW, Harvey AR. Immunohistochemical, ultrastructural and functional analysis of axonal regeneration through peripheral nerve grafts containing Schwann cells expressing BDNF, CNTF or NT3. *Plos One* 2013;8:e69987.
41. Tohill M, Terenghi G. Stem-cell plasticity and therapy for injuries of the peripheral nervous system. *Biotechnol Appl Biochem* 2004;40:17-24.
42. Keilhoff G, Gohl A, Stang F, Wolf G, Fansa H. Peripheral nerve tissue engineering: autologous Schwann cells vs. transdifferentiated mesenchymal stem cells. *Tissue Eng Part A* 2006;12:1451-65.
43. Hu N, Wu H, Xue C, Gong Y, Wu J, Xiao Z, Yang Y, Ding F, Gu X. Long-term outcome of the repair of 50 mm long median nerve defects in rhesus monkeys with marrow mesenchymal stem cells-containing, chitosan-based tissue engineered nerve grafts. *Biomaterials* 2013;34:100-11.
44. Ding F, Wu J, Yang Y, Hu W, Zhu Q, Tang X, Liu J, Gu X. Use of tissue-engineered nerve grafts consisting of a chitosan/poly(lactic-co-glycolic acid)-based scaffold included with bone marrow mesenchymal cells for bridging 50-mm dog sciatic nerve gaps. *Tissue Eng Part A* 2010;16:3779-90.
45. Oliveira JT, Almeida FM, Biancalana A, Baptista AF, Tomaz MA, Melo PA, Martinez AM. Mesenchymal stem cells in a polycaprolactone conduit enhance median-nerve regeneration, prevent decrease of creatine phosphokinase levels in muscle, and improve functional recovery in mice. *Neuroscience* 2010;170:1295-303.
46. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng Part A* 2001;7:211-28.
47. Kingham PJ, Kalbermatten DF, Mahay D, Armstrong SJ, Wiberg M, Terenghi G. Adipose-derived stem cells differentiate into a Schwann cell phenotype and promote neurite outgrowth *in vitro*. *Exp Neurol* 2007;207:267-74.
48. Strem BM, Hickok KC, Zhu M, Wulur I, Alfonso Z, Schreiber RE, Fraser JK, Hedrick MH. Multipotential differentiation of adipose tissue-derived stem cells. *Keio J Med* 2005;54:132-41.
49. di Summa PG, Kingham PJ, Raffoul W, Wiberg M, Terenghi G, Kalbermatten DF. Adipose-derived stem cells enhance peripheral nerve regeneration. *J Plast Reconstr Aesthet Surg* 2010;63:1544-52.
50. Gimble J, Guilak F. Adipose-derived adult stem cells: isolation, characterization, and differentiation potential. *Cytotherapy* 2003;5:362-9.
51. Xu Y, Liu L, Li Y, Zhou C, Xiong F, Liu Z, Gu R, Hou X, Zhang C. Myelin-forming ability of Schwann cell-like cells induced from rat adipose-derived stem cells *in vitro*. *Brain Res* 2008;1239:49-55.
52. Reid AJ, Sun M, Wiberg M, Downes S, Terenghi G, Kingham PJ. Nerve repair with adipose-derived stem cells protects dorsal root ganglia neurons from apoptosis. *Neuroscience* 2011;199:515-22.
53. Hart AM, Terenghi G, Kellerth JO, Wiberg M. Sensory neuroprotection, mitochondrial preservation, and therapeutic potential of N-acetyl-cysteine after nerve injury. *Neuroscience* 2004;125:91-101.
54. Welin D, Novikova LN, Wiberg M, Kellerth JO, Novikov LN. Effects of N-acetyl-cysteine on the survival and regeneration of sural sensory neurons in adult rats. *Brain Res* 2009;1287:58-66.
55. Reid AJ, Shawcross SG, Hamilton AE, Wiberg M, Terenghi G. N-acetylcysteine alters apoptotic gene expression in axotomized primary sensory afferent subpopulations. *Neurosci Res* 2009;65:148-55.
56. Erba P, Mantovani C, Kalbermatten DF, Pierer G, Terenghi G, Kingham PJ. Regeneration potential and survival of transplanted undifferentiated adipose tissue-derived stem cells in peripheral nerve conduits. *J Plast Reconstr Aesthet Surg* 2010;63:e811-7.
57. Shen CC, Yang YC, Liu BS. Peripheral nerve repair of transplanted undifferentiated adipose tissue-derived stem cells in a biodegradable reinforced nerve conduit. *J Biomed Mater Res A* 2012;100:48-63.
58. di Summa PG, Kalbermatten DF, Pralong E, Raffoul W, Kingham PJ, Terenghi G. Long-term *in vivo* regeneration of peripheral nerves through bioengineered nerve grafts. *Neuroscience* 2011;181:278-91.
59. Orbay H, Uysal AC, Hyakusoku H, Mizuno H. Differentiated and undifferentiated adipose-derived stem cells improve function in rats with peripheral nerve gaps. *J Plast Reconstr Aesthet Surg* 2012;65:657-64.
60. Tang X, Xue C, Wang Y, Ding F, Yang Y, Gu X. Bridging peripheral nerve defects with a tissue engineered nerve graft composed of an *in vitro* cultured nerve equivalent and a silk fibroin-based scaffold. *Biomaterials* 2012;33:3860-7.

61. Adams AM, Arruda EM, Larkin LM. Use of adipose-derived stem cells to fabricate scaffoldless tissue-engineered neural conduits *in vitro*. *Neuroscience* 2012;201:349-56.
62. Ide C. Peripheral nerve regeneration. *Neurosci Res* 1996;25:101-21.
63. Terenghi G. Peripheral nerve regeneration and neurotrophic factors. *J Anat* 1999;194:1-14.
64. Chen ZL, Yu WM, Strickland S. Peripheral regeneration. *Annu Rev Neurosci* 2007;30:209-33.
65. Schmidt CE, Leach JB. Neural tissue engineering: strategies for repair and regeneration. *Annu Rev Biomed Eng* 2003;5:293-347.
66. Kingham PJ, Terenghi G. Bioengineered nerve regeneration and muscle reinnervation. *J Anat* 2006;209:511-26.
67. Gordon T, Tyreman N, Raji MA. The basis for diminished functional recovery after delayed peripheral nerve repair. *J Neurosci* 2011;31:5325-34.
68. Pfister LA, Papaloizos M, Merkle HP, Gander B. Nerve conduits and growth factor delivery in peripheral nerve repair. *J Peripher Nerv Syst* 2007;12:65-82.
69. Yang Y, De Laporte L, Rives CB, Jang JH, Lin WC, Shull KR, Shea LD. Neurotrophin releasing single and multiple lumen nerve conduits. *J Control Release* 2005;104:433-46.
70. Madduri S, di Summa P, Papaloizos M, Kalbermatten D, Gander B. Effect of controlled co-delivery of synergistic neurotrophic factors on early nerve regeneration in rats. *Biomaterials* 2010;31:8402-9.
71. Madduri S, Feldman K, Tervoort T, Papaloizos M, Gander B. Collagen nerve conduits releasing the neurotrophic factors GDNF and NGF. *J Control Release* 2010;143:168-74.
72. Tang S, Zhu J, Xu Y, Xiang AP, Jiang MH, Quan D. The effects of gradients of nerve growth factor immobilized PCLA scaffolds on neurite outgrowth *in vitro* and peripheral nerve regeneration in rats. *Biomaterials* 2013;34:7086-96.
73. Cao J, Sun C, Zhao H, Xiao Z, Chen B, Gao J, Zheng T, Wu W, Wu S, Wang J, Dai J. The use of laminin modified linear ordered collagen scaffolds loaded with laminin-binding ciliary neurotrophic factor for sciatic nerve regeneration in rats. *Biomaterials* 2011;32:3939-48.
74. Hamers PT, Lankhorst AJ, Van Laar TJ, Veldhuis WB, Gispen WH. Automated quantitative gait analysis during overground locomotion in the rat: its application to spinal cord contusion and transection injuries. *J Neurotrauma* 2001;18:187-201.
75. Bozkurt A, Deumens R, Scheffel J, O'Dey DM, Weis J, Joosten EA, Fuhrmann T, Brook GA, Pallua N. CatWalk gait analysis in assessment of functional recovery after sciatic nerve injury. *J Neurosci Methods* 2008;173:91-8.
76. Deumens R, Jaken RJ, Marcus MA, Joosten EA. The CatWalk gait analysis in assessment of both dynamic and static gait changes after adult rat sciatic nerve resection. *J Neurosci Methods* 2007;164:120-30.

How to cite this article: de Luca AC, Raffoul W, Giacalone F, Bertolini M, di Summa PG. Tissue-engineered constructs for peripheral nerve repair: current research concepts and future perspectives. *Plast Aesthet Res* 2015;2:213-9.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 01-02-2015; **Accepted:** 17-04-2015

Endoscopic telemicrosurgery or minimally invasive robotically-assisted microsurgery for peripheral nerve repair

Satoshi Ichihara^{1,2}, Sybille Facca¹, Frédéric Bodin³, Sarah Hendriks¹, André Gay⁴, Philippe Liverneux¹

¹Department of Hand Surgery, Strasbourg University Hospital, FMTS, University of Strasbourg, 67403 Illkirch, France.

²Department of Orthopaedic Surgery, Juntendo University, Tokyo 1138421, Japan.

³Department of Plastic Surgery, Strasbourg University Hospital, FMTS, University of Strasbourg, 67000 Strasbourg, France.

⁴Department of Hand Surgery, La Timone Teaching Hospital, Aix Marseille Université, 13000 Marseille, France.

Address for correspondence: Dr. Philippe Liverneux, Department of Hand Surgery, Strasbourg University Hospital, FMTS, University of Strasbourg, 67403 Illkirch, France. E-mail: philippe.liverneux@chru-strasbourg.fr

ABSTRACT

Microsurgery comprises a variety of surgical procedures such as neurovascular anastomoses, performed under optical magnification and with fine instrumentation. While refinements have been made since its advent in the 1960s, robotics offers the potential for major technological advancement. Endoscopic telemicrosurgery is minimally invasive, robotically-assisted microsurgery. This technique removes some limitations of conventional microsurgery and enhances visual and manual dexterity. Vision is enhanced through greater magnification, three-dimensionality, and functionalization, all through an endoscopic view. Manual dexterity is improved by suppression of physiological tremor and tremor filtration, while permitting useful enhancement of movement amplitudes and tactile feedback forces. Furthermore, better endoscopic ergonomics, new hand tools and the ability for multi-manual and remote work, confer a distinct advantage. Endoscopic telemicrosurgery is already in clinical use. Some of the advantages above are incorporated into the DaVinci[®] robot, that is, used in brachial plexus surgery. Conventional brachial plexus surgery requires large incisions for exploration and neurotization, with its attending risks of unsightly scars, prolonged hospital stay, sepsis, and perineural adhesions that interfere with nerve regrowth. Endoscopic telemicrosurgery limits the incisions and these risks, with minimal compromise. Endoscopic telemicrosurgery, through the amplification of human capabilities may pave the way for a major advancement in the microsurgical field.

Key words:

DaVinci, endoscopy, microsurgery, robot

INTRODUCTION

Microsurgery is the surgical technique that uses both optical magnification and fine instruments in order to perform inframillimetric vascular and nerve anastomoses. The

optical magnification allows a better visualization of tissue structures than with the naked eye. The term “microsurgery”, is sometimes abused because the optical magnification of surgical microscopes and surgical magnifying glasses does not exceed forty times, at best fifty times better with some supermicrosurgical microscopes. A surgical microscope must therefore be considered as binocular magnifying glass, that can visualize structures invisible to the naked eye and is not, strictly speaking, a microscope.

Microsurgical instruments provide a better repair of tissue damage than conventional instruments. Their design comes from the craft of watchmaking, whose forceps are identical. Microsurgery approaches watchmaking in which one uses a monocular magnifying glass placed over

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.158860

one eye and a fine forceps held in one hand. It differs by the use of binocular loupes and fine instruments held in both hands. The three-dimensional (3D) vision is made possible by the treatment of a shifted image for each eye, which is essential in microsurgery where the smallness of the depth of the operating field requires very precise movements.

FROM MICROSURGERY TO ENDOSCOPIC TELEMICROSURGERY

Since its inception in the 1960s, microsurgery has experienced a paradoxical development. Countless surgical techniques have been described starting from digit replantation to hand transplant, through nerve repair by direct and indirect nerve grafts and neurotizations, free, and pedicled flaps, and finally to the recent applications of perforator flaps and the use of supermicrosurgery applied to less than 0.5 mm diameter vessels. Meanwhile, the technology itself (i.e. microscopes and instruments) has not changed in over fifty years. Microscopes have indeed evolved toward voice control screens with 3D glasses, digital image recording, and intraoperative videos, but the optical magnification has not evolved since the beginning of microsurgery. Microsurgical instruments are now made in titanium, but have remained exactly the same since their conception. Any technology experiences a revolution every half a century: it is an invariable law of industry. Hence, why has microsurgery not registered a technological leap since the 1960s? Is this due to its compartmentalization, its ignorance on the progress of other surgical disciplines? In other words, what is the future of microsurgery?

Surgery has undergone two major technological advances since the second half of the twentieth century: endoscopic surgery in the 1980s and telesurgery in the 2000s. Endoscopic surgery is the surgical technique that uses both a miniature two-dimensional (2D) camera and appropriate instruments to perform procedures by mini-invasive approaches. The operator instinctively gets an impression of 3D vision thanks to the micro motion of the cameras, which allows the surgeon to scan the operative field, but it is not a true 3D vision. Telesurgery is a surgical technique that uses a robotic remote manipulator to perform procedures without direct contact between the operator and the patient. The term robotic is an abuse of language, since the movements of the remote manipulator are performed under the direct control of the operator. Telesurgery, which suppresses the physiological tremor of the operator can combine the advantages of conventional open microsurgery with a 10 times optical magnification (up to 25 times with a digital zoom) and a 3D vision to those of endoscopic surgery thanks to instrumental and optical arms whose length allows to penetrate the surgical field by minimally invasive incisions. Telesurgery, which has many other properties, is most likely the next technological leap for the advancement of microsurgery, thanks to a new concept: telemicrosurgery.

Endoscopic telemicrosurgery and minimally invasive robotically-assisted microsurgery, which is still in its infancy, could experience a significant development in the 2020s, when a specialized robot will have been devised. The market potential is huge, especially if we think of the replacement of all conventional surgical microscopes with robotically-assisted microscopes.

PROPERTIES OF ENDOSCOPIC TELEMICROSURGERY

Only robots will cross the limits of human capabilities. Some surgical robots have already disappeared from the market (Aesope®, Zeus®), and others are under development (Amadeus®, Newton®, Gumby®, *etc.*) including some prototypes specific to microsurgery (MSR, RAMS®). In fact, only the DaVinci® robot is currently available on the market.

The prospect of microsurgery is to develop systems in order to enhance human capabilities of vision and to enhance manipulation of tissue repair. Ultimately, conventional microsurgery only increases two human capabilities: the 3D optical magnification thanks to binocular magnification glasses, and the manipulation of inframillimetric tissue structures by fine instruments. Endoscopic telemicrosurgery enhances other visual and manual abilities that cannot be done by conventional microsurgery [Figures 1 and 2].

Magnified vision

Optical magnification, a constitutive property of microsurgery, is possible in both conventional microsurgery and telemicrosurgery. Conventional surgery allows magnification of vision in general up to 25 times. Some supermicro surgical microscopes allow magnification up to 50 times, but the handling of tissues with ultra-fine instruments and nylon up to 14/0, at the extreme limit of human capabilities, represent a barrier to the common use of supermicrosurgery. The DaVinci® robot is the only surgical robot currently available, and



Figure 1: Installation of an endoscopic telemicrosurgical intervention in pigs. In the foreground, the operator manipulates the instruments remotely from the surgical field using the surgical console of the DaVinci® robot

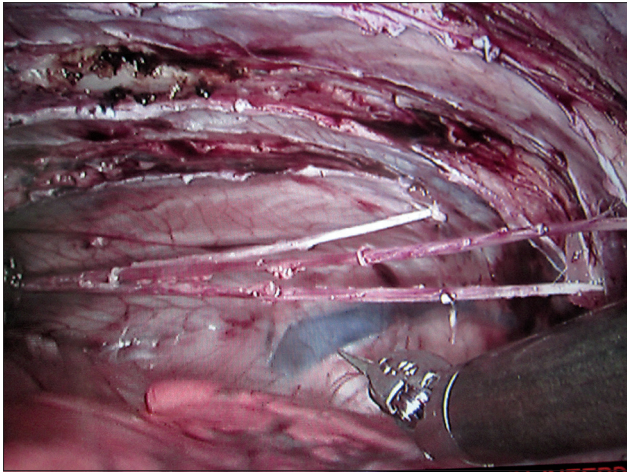


Figure 2: Intrathoracic view of three intercostal nerves in a pig harvested with the DaVinci® robot during a telemicrosurgical intervention

it allows magnification of vision up to 25 times thanks to a digital zoom. Although the current magnification of the DaVinci® robot is lower than that of conventional microscopes, it is not a limiting factor to its use in conventional microsurgery, but it is not feasible in supermicrosurgery. Considering the prospects, a specific robot to telemicrosurgery shall improve its optical magnification capacity.

Three-dimensional vision

3D vision is required in microsurgery because the depth of the operating field is less than 1 cm. 2D vision does not allow to assess acutely the position of anatomical structures and instruments into space, and can lead to tissue damage. Conventional microsurgery and telemicrosurgery allow 3D vision, a shifted image arriving to each eye in both cases, by an optical lens or CCD camera. Considering perspectives, one can mention the extreme miniaturization of cameras and obtaining a 3D vision with a single camera with methods of real-time image processing.

Functionalized vision

Vision through a conventional microscope is an external magnified vision. Various tools make it possible to see beyond the mere external appearance, revealing functional properties.^[1] Some systems enable to form an additional image that reveals microcirculation and therefore make it easier to distinguish cancerous tissue from healthy tissue by the injection of a small amount of indocyanine green, a dye tracer visualized by an infrared system. This noninvasive technique also verifies the effectiveness of a vascular anastomosis. The micro-Doppler allows to study the permeability of a vascular suture by transforming visual information of arterial or venous flow into an audible sound to the naked ear. Considering the prospects, some micro-ultrasound systems could allow to study microvascularization, but also the internal structure of peripheral nerves. This could be very useful to determine precisely the exact level of nerve transaction before performing a nerve graft of the brachial plexus for example, with respect to the method currently used (simple manual palpation of the nerve in order to perceive an internal loss of substance).

Endoscopic vision

Endoscopic surgery consists in using an endoscope within a natural or artificial body cavity. Conventional microsurgery, which uses an exoscope, does not allow endoscopic vision. The 3D camera of the DaVinci® robot can be used either as an exoscope or as an endoscope in order to practice open or endoscopic telemicrosurgery.

Augmented vision

Augmented reality consists in representing virtual data on a real image. Since the invention of this concept by Thomas Caudell in the early 1990s, augmented reality has been applied to many areas. In medicine, it naturally found technical applications using an optical devices and/or a camera: laparoscopy,^[2] arthroscopy, endoscopy, and microsurgery. Among all fields of use, the purpose of augmented reality is to simplify and to accelerate access to complex data by combining the elements of the operating field of the surgeon. Augmented reality can be applied to conventional microsurgery, but indications remain limited due to the impossibility to use endoscopy because a conventional microscope remains an exoscope and does not allow internal vision. Considering the prospects, endoscopic telemicrosurgery of the brachial plexus could evolve. From an internal view of a cavity, the anatomical structures of the brachial plexus and their relationship with other structures including vascular tissues can be difficult to identify. The registration in real time by magnetic resonance angiography images with direct intraoperative vision could act as a true anatomical global positioning system.

Manual tremor filtration

Physiological tremor in microsurgery is detrimental and unfavorable in supermicrosurgery. Telemicrosurgery makes it vanish through an interface filter, which not only improves the comfort of the surgeon, but it can also be suggestive of facilitating supermicrosurgery.

Magnification of the manual movement

The scaling of hand movement is a fundamental property in microsurgery because it increases the precision of the operator's movement. It will become indispensable in supermicrosurgery, as for example in lymphatic vessels. In the old S version of DaVinci® robot, the scale reached 1/5. On the newer SI versions of the DaVinci® robot, the scale is reduced to 1/3. The reason is that the current market is focused on telesurgery and urological laparoscopic surgery, which do not require a greater scaling. Considering the prospects, the development of a specific robot to telemicrosurgery should increase the scale of the movement up to 1/10 or even more for supermicrosurgery.

Magnification of manual movement amplitudes

Movements of the upper extremity and hand have limited average amplitudes due to their anatomy. For example, the normal range of motion of supination averages 180°. It is therefore not possible in microsurgery to make a movement of more than 180° without dropping the instrument. The DaVinci® robot allows pronosupination up

to 540°, repeating several times the position of the hands in the handles of the surgeon's console. The recovery of the hand position could be avoided by magnifying pronosupination in the way of a power steering system in cars. Assuming a magnification of 1/3, an operator performing a pronosupination of 180°, could perform a pronosupination of 540° in 1 time. Considering the prospects, the completion time of a vascular anastomosis could be easily decreased by performing one unique movement with the needle going from one vessel wall to the other without having to repeat the movement, especially in deep surgical fields or hard to access as in the repair of the collateral ulnar artery during thumb replantation.

Magnification of the manual force feedback sensation

The absence of force feedback or haptic sensation is often criticized in robotic surgery practiced with the DaVinci® robot. In reality, the force feedback does not exist in conventional microsurgery. Some authors have shown that the tightening sensation of a node with a 10/0 nylon is perceived by a minority of individuals.^[3] In practice, the haptic sensation in conventional microsurgery is obtained indirectly by visualization of the deformity of the soft tissues in which it has acquired experience in conventional procedures where the operator directly manipulates the instruments. Unlike the DaVinci® robot, the Amadeus® robot is equipped with a device for haptic sensation, but its marketing is still confidential. The Mimic® simulator solely dedicated to training in robotic surgery is also equipped with a device for haptic sensation. Considering the prospects, if the force feedback is not currently used in conventional microsurgery and telemicrosurgery, it is not inconceivable that its magnification becomes a capital property, especially in supermicrosurgery in order to perform vascular, lymphatic, and nerve anastomoses that are currently inaccessible because of their small size.

Multi-manual work

A surgeon uses both hands to work, but an organist also uses his feet. If the DaVinci® robot has 3 instrumental arms, the same operator can only handle 2 simultaneously, even in the latest versions of the robot. The third arm is like the hand of an assistant, the operator places for example to place a retractor. In microsurgery, certain delicate gestures are performed. The advantage of the DaVinci® robot is that the third arm, unlike that of an assistant, does not tremble nor changes position. Considering the prospects, the theoretical possibility to use more than 2 instrumental arms simultaneously and by the same operator is not to be immediately eliminated on the pretext that surgeons have only used 2 of their hands till now. In fact, unconsciously, surgeons are already using their feet to activate an electrocoagulation pedal, an arthroscopic shaver or a fluoroscope. Admittedly the foot is only to activate an instrument used by hand, but it is not impossible to imagine that the order of 1 or 2 instrumental arms could be confided independently to one or two feet of a same operator. The acquisition of the independence of feet will require an equivalent learning

curve to that of an organist. The assistant operational function remains to be defined.

Endoscopic manual work

Endoscopic microsurgery requires not only the introduction of a camera into a natural or artificial biological cavity, but also requires the introduction of appropriate instruments to repair damaged tissue. Conventional microsurgical instruments are not suitable for endoscopy. However, the instrumental arms of the DaVinci® robot, having a length of 50 cm, are equipped at their termination with a miniature wrist or EndoWrist® that allows the introduction of instruments by a minimally invasive approach and which goes straight to the surgical target, as if a miniaturized operator's wrist could directly penetrate inside the body. The disadvantage remains of having performed four converging approaches. Considering the prospects, the "single port" with a miniaturized 3D endoscope equipped with instruments passing through the same flexible tube, seems to be an interesting research pathway.

Augmented ergonomics

Microsurgery is time-consuming. Interventions are long and the fatigue of the surgeon is a deleterious factor. Any factor that can improve the comfort of the surgeon can improve the quality of the intervention. In conventional microsurgery, the gaze direction of the operator does not follow a direct line between the surgeon's eye and his target. The image undergoes deflections. The consequence is that the hand-eye-head coordination is disrupted. The position of the head corresponds to a target distant to the actual target. To maintain this position, the contraction of the muscles of the neck does not match that of the actual target and can cause eyestrain and muscle fatigue. In telemicrosurgery, the gaze direction of the operator follows a direct line to his hands and the target. Paradoxically, although the surgical console is not in contact with the patient, the position of the operator's head and hand is more ergonomic than in conventional microsurgical where the operator's hands are in direct contact with the patient. In conventional microsurgery, the operative field is cluttered by the hands of the operator and his assistant. This can increase fatigue as the surgeon may have to operate in uncomfortable positions. In contrast, the operating field in telemicrosurgery is cleared, thanks to the instrumental arm length, the fineness of the EndoWrist®, and especially the absence of the operator's hands.

Remote working

Conventional microsurgery requires direct contact between the patient and the surgeon. This proximity seems logical, but it is not always possible, especially when a highly specialized technical gesture is required, and no specialist surgeon is available. It is clear that at present the use of a remote expert is not current practice, but considering the prospects, in the future in the middle of a procedure requiring a very specific gesture, it may be interesting to call on a remote expert who could take control of the robot and perform a very specific task.

CLINICAL APPLICATIONS

All properties mentioned above are not available with the DaVinci® robot. However, some of them already allow telemicrosurgical clinical applications. Among the many clinical applications, we describe its use in peripheral nerve surgery.

What has been done until now?

Our first experimental study using telemicrosurgery technique assessed the feasibility of peripheral nerve repair.^[2] Regardless of the different type of anatomical materials used (rat, pig, and human cadaver), the telemanipulator removed the physiological tremor factor during anatomical epiperineural repairs. From this experimental result, we moved to our first clinical trial to test the feasibility of the restoration of elbow flexion by Oberlin procedure using the DaVinci robot.^[4] All patients recovered elbow flexion and good functional results despite a slight difficulty in visualizing the operative field by an endoscopic approach. The development of specific retractors and instruments will probably ease these challenges. In a second clinical trial, we presented a new approach to brachial plexus surgery using mini-invasive robot-assisted surgery to perform a biopsy of an intraneural perineurioma in a 12-year-old girl.^[5] Tigan *et al.*^[6] also studied the surgical dissection of chronic peripheral nerve tumors using the telemicrosurgical technique to improve their results. Most recently, robot-assisted neurotization of deltoid muscle using the nerve to the long head of the triceps was described as a feasible application for the restoration of shoulder abduction after brachial plexus or axillary nerve injury.^[7] These results demonstrate that telemicrosurgery allows very safe and precise peripheral nerve repairs by counteracting physiological tremor and by improving the view of the surgical field.

What are the clinical indications?

From an anatomic positional point of view, brachial plexus injuries are the most ideal indications for telemicrosurgery. Brachial plexus injuries are caused by stretching and excessive traction on the shoulder, usually during motorcycle accidents or childbirth. We can distinguish total paralysis of the brachial plexus (most frequent lesions), paralysis of the upper C5-C6 and C5-C6-C7 roots, and paralysis of the lower C8-T1 roots, which are rarer than total paralysis of the brachial plexus. Telemicrosurgery can also be helpful to distinguish supraclavicular and infraclavicular plexus lesions. Regardless on the type of plexus lesion, large incisions are needed either to explore the plexus or to perform neurotizations from a healthy nerve in order to reinnervate a paralyzed nerve. Apart from the unsightly appearance of these large incisions, and the lengthening of hospitalization time, these large incisions involve risks of infection and perineural adherence that interfere with the quality of nerve regrowth. Endoscopic telemicrosurgery allows interventions on peripheral nerves with minimally invasive incisions.^[8] Mantovani *et al.*^[9,10] developed an effective minimally invasive approach to brachial plexus

injury and showed the feasibility of using telerobotic manipulation to perform microsurgical root-to-root nerve repair of the brachial plexus with an endoscopic approach. In a cadaveric and experimental study, we already accomplished neurotization of the spinal accessory nerve to the motor branch of the musculocutaneous nerve, neurotization of the long portion of the triceps to the anterior branch of the axillary nerve,^[11] neurotization of the motor nerve fascicle of the ulnar nerve on the musculocutaneous nerve,^[4] neurolysis of the long thoracic nerve, and neurolysis of the intercostal nerve.^[12] A series of eight clinical cases of nerve damage around the shoulder girdle were operated on using the DaVinci® robot. Successful microneural repair was confirmed in all clinical studies. However, an open incision was still required. Robotic-assisted surgery of the shoulder girdle and brachial plexus is still in its early stages.^[13]

What are the future fields of application in nerve surgery?

In a recent experimental study, we reported on the feasibility of robotic phrenic nerve harvest in a pig model.^[11] The advantages of using an endoscopic technique to harvest the phrenic nerve include a magnified, clear, and illuminated visualization, a better remote access incision site and an atraumatic technique. Robot-assisted neurolysis may be clinically useful for harvesting the phrenic nerve for brachial plexus reconstruction by the thoracoscopic approach.

CONCLUSION

Microsurgical techniques, magnification, and micro-instruments, have not evolved since their first use in the 1960s. Endoscopic telemicrosurgery, through the amplification of human capabilities, may be the expected technological leap to introduce microsurgery in the 21st century.

REFERENCES

1. Brahmabhatt JV, Gudelloglu A, Liverneaux P, Parekattil SJ. Robotic microsurgery optimization. *Arch Plast Surg* 2014;41:225-30.
2. Nectoux E, Taleb C, Liverneaux P. Nerve repair in telemicrosurgery: an experimental study. *J Reconstr Microsurg* 2009;25:261-5.
3. Panchulidze I, Berner S, Mantovani G, Liverneaux P. Is haptic feedback necessary to microsurgical suturing? Comparative study of 9/0 and 10/0 knot tying operated by 24 surgeons. *Hand Surg* 2011;16:1-3.
4. Naito K, Facca S, Lequint T, Liverneaux PA. The Oberlin procedure for restoration of elbow flexion with the da Vinci robot: four cases. *Plast Reconstr Surg* 2012;129:707-11.
5. Lequint T, Naito K, Chaigne D, Facca S, Liverneaux P. Mini-invasive robot-assisted surgery of the brachial plexus: a case of intraneural perineurioma. *J Reconstr Microsurg* 2012;28:473-6.
6. Tigan L, Miyamoto H, Hendriks S, Facca S, Liverneaux P. Interest of telemicrosurgery in peripheral nerve tumors: about a series of seven cases. *Chir Main* 2014;33:13-6.
7. Miyamoto H, Leechavengvongs S, Atik T, Facca S, Liverneaux P. Nerve transfer to the deltoid muscle using the nerve to the long head of the triceps with the da Vinci robot: six cases. *J Reconstr Microsurg* 2014;30:375-80.
8. Finley D, Sherman JH, Avila E, Bilsky M. Thoracoscopic resection of an apical paraspinal schwannoma using the da Vinci surgical system. *J Neurol Surg A Cent Eur Neurosurg* 2014;75:58-63.

9. Mantovani G, Liverneaux P, Garcia JC Jr, Berner SH, Bednar MS, Mohr CJ. Endoscopic exploration and repair of brachial plexus with telerobotic manipulation: a cadaver trial. *J Neurosurg* 2011;115:659-64.
10. Garcia JC Jr, Mantovani G, Liverneaux PA. Brachial plexus endoscopy: feasibility study on cadavers. *Chir Main* 2012;31:7-12.
11. Porto de Melo P, Miyamoto H, Serradori T, Ruggiero Mantovani G, Selber J, Facca S, Xu VVD, Santelmo N, Liverneaux P. Robotic phrenic nerve harvest: a feasibility study in a pig model. *Chir Main* 2014;33:356-60.
12. Latif MJ, Afthinos JN, Connery CP, Perin N, Bhora FY, Chwajol M, Todd GJ, Belsley SJ. Robotic intercostal nerve graft for reversal of thoracic sympathectomy: a large animal feasibility model. *Int J Med Robot* 2008;4:258-62.
13. Facca S, Hendriks S, Mantovani G, Selber JC, Liverneaux P. Robot-assisted surgery of the shoulder girdle and brachial plexus. *Semin Plast Surg* 2014;28:39-44.

How to cite this article: Ichihara S, Facca S, Bodin F, Hendriks S, Gay A, Liverneaux P. Endoscopic telemicrosurgery or minimally invasive robotically-assisted microsurgery for peripheral nerve repair. *Plast Aesthet Res* 2015;2:220-5.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 18-11-2014; **Accepted:** 27-04-2015

Nerve regeneration in vascularized composite allotransplantation: current strategies and future directions

Anirudh Arun, Nicholas B. Abt, Sami Tuffaha, Gerald Brandacher, Angelo A. Leto Barone

Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.

Address for correspondence: Dr. Angelo A. Leto Barone, Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA. E-mail: aletobarone@jhmi.edu

ABSTRACT

Vascularized composite allotransplantation (VCA) has emerged as a viable treatment option for limb and face reconstruction of severe tissue defects. Functional recovery after VCA requires not only effective immunosuppression, but also consideration of peripheral nerve regeneration to facilitate motor and sensory reinnervation of donor tissue. At the time of transplantation, the donor and recipient nerves are typically coapted in an end-to-end fashion. Following transplantation, there are no therapies available to enhance nerve regeneration and graft reinnervation, and functional outcomes are dependent on the recipients' innate regenerative capacities. Functional outcomes to date have been promising, but there is still much room for improvement, studies have demonstrated reliable return of protective sensation (pain, thermal, gross tactile), while discriminative sensation and motor function show more inconsistent results. In order to maximize the benefit afforded to the by VCA, we must develop consistent and reliable procedures and therapies to ensure effective nerve regeneration and functional outcomes. New technologies, such as nerve guidance conduits and fibrin glues, and the use of stem cells to facilitate nerve regeneration remain untested in VCA but are proving worthwhile in the context of peripheral nerve repair. VCA presents a unique set of challenges with regards to surgical techniques, postoperative regimen, and health of donor tissue. In this review, we discuss current challenges underlying achievement of nerve regeneration in VCA and discuss novel technologies and approaches to translate nerve regeneration into functional restoration.

Key words:

Adipose-derived stem cells, allograft, fibrin glue, nerve regeneration, tacrolimus, vascularized composite allotransplantation

INTRODUCTION

The field of vascularized composite allotransplantation (VCA) has rapidly developed over the past few decades, propelled by major advancements in surgical technique and posttransplant immunosuppression. VCA differs from solid organ transplantation (SOT) in the composition of

the transplanted tissue, whereas SOT generally involves one or a few organs and associated cell types, VCA tissues are composed of skin, vascular structures, nerves, muscles, bone, and connective tissue.^[1] The enhanced immunogenicity of such composite tissues proved to be a major roadblock in the success of these transplants in the long-term, but the development and use of multiple immunosuppressive drugs, such as tacrolimus (FK506), have significantly reduced incidence of rejection.^[2] VCA can currently be performed in various body regions, including, but not limited to, the hand, the proximal upper extremity, and the face.^[1]

A major challenge of VCA over SOT is that reperfusion of tissues is not sufficient to restore function, instead, functional recovery in VCA is dependent on the recipient's

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.158853

axons regenerating into the graft and reinnervating the transplanted muscle and skin, so as to establish motor control and receive sensory input.^[1] Nerve damage is inevitable in the process of transplantation, from peripheral axonal degeneration occurring from the time of organ harvest to surgical reconnection of the donor tissue to the host. Host cortical reorganization plays a paramount role in the restoration of function, as the lack of sensory input from the injured or missing body region results in aberrant cortical response to restoration of sensory input from, and motor output to, the newly innervated tissue following prolonged periods of denervation.^[3] Peripheral nerve regeneration is a slow process, occurring at 1-3 mm/day, partly depending on the microenvironment surrounding axonal sprouts and the caliber of the nerve.^[4]

Thus, there exists a need for more effective and consistent strategies for nerve regeneration in VCA. This area is a popular field of study in the context of peripheral neuropathy repair, but the VCA context provides unique challenges in the necessity for immunosuppression and the circumstances in which the transplantation is performed.

PATHOPHYSIOLOGY OF NERVE DAMAGE AND REGENERATION

Following transplantation, axons within the graft undergo Wallerian degeneration. Originally thought to be mediated by impaired transport of nutrients to distal axonal segments and subsequent death, Wallerian degeneration is now considered a product of a self-destruct program distinct from that of apoptosis.^[5]

Although Wallerian degeneration ultimately claims axons distal to the site of organ harvest, the reorganization of Schwann cells and macrophages around the dying axons fosters an environment that favors axonal regeneration. However, in the context of VCA, this process is affected by the presence of widespread axonal damage and by the need for a balance between immunosuppression and tissue rejection.

Due to the transplantation process, all cellular nerve components distal to the transection point are derived from donor populations. Regeneration of host peripheral nerves requires host-derived Schwann cells to populate the distal stump, which in turn requires proliferative and migration signals. Induction of these signals seems to require partial rejection of the VCA to eliminate donor Schwann cells. Thus, immunosuppression regimens should be carefully determined to provide optimal nerve regeneration through optimal host Schwann cell proliferation and migration while avoiding greater tissue injury during the controlled rejection process. The complete lack of a rejection period may potentially block host Schwann cell migration, leading to impaired peripheral nerve growth. If rejection leads to rapid donor Schwann cell death, unsupported endoneurium may degenerate, blocking further regeneration.^[6]

CURRENT SURGICAL STRATEGIES FOR NERVE REPAIR AND REGENERATION

Surgical coaptation (tension-free repair)

Because additional nerve length can usually be harvested from the donor, tension-free direct end-to-end neurotaphy of recipient and donor nerve stumps can typically be achieved. Nerve coaptations have been and are still widely used for various procedures in reconstruction, peripheral nerve injury repair, and in VCA. Opening of the donor nerve perineurium and induction of deliberate nerve injury during end-to-side coaptation has been shown to increase the regeneration of axons from the host into donor axons.^[7] In the context of facial transplants, tension-free nerve coaptations have been shown to have the most predictable and reliable results in nerve reconstruction.^[8] Performing the neurotomy in the epineurial vs. perineurial layer has not yielded a definitive determination of which procedure yields the best postoperative functional results.^[9]

Nerve transfers are another method by which healthy axons that traditionally serve one area can be rerouted and coapted to provide sensory and motor function to another. However, the clinical applicability of this procedure is untested in VCAs, in the context of the cortical somatosensory reorganization of these redirected sensory and motor domains.^[10]

Nerve autograft

Nerve autografting is a surgical procedure that allows for repair of relatively long lesion gaps with the patient's own tissues when nerve coaptation cannot be performed without excess tension on the nerve stumps. Although the graft can provide the scaffold for regrowth with Schwann cells and neurotrophic factors, there is obvious secondary morbidity associated with graft harvest. Nerve autografting has primarily been used in a variety of clinical scenarios requiring nerve repair.^[11] Since allografts from donor nerve tissue can be supplemented to the existing composite transplantation without any additional immunosuppressive burden, nerve autografts have limited use in the context of VCA. In addition, challenges in large-caliber nerve revascularization and limited capacity for diffusion-mediated perfusion of such nerves must be taken into consideration.^[12]

Nerve allograft

While autografts are considered ideal in the case of peripheral nerve damage since these grafts do not face any immunological mismatch, such is not the case in nerve allografts. However, the primary benefit of this latter method is that the secondary morbidity associated with autograft harvesting, such as sensory loss and scarring, is avoided.^[13] When performed in the context of VCA, where immunosuppression is already used to avoid rejection of the primary tissue, use of additional nerve allografts from the cadaveric source of the VCA tissue to ensure tension-free nerve coaptation does not add new immunological consequences. Furthermore,

immunosuppression following allografts may be discontinued after a period of treatment after nerve regeneration becomes present.^[14] Allografts can also be processed in such a way as to reduce their antigenicity by means of decellularization, although nerve growth can suffer from lack of extracellular signaling cues.^[12]

It has been shown that the cessation of immunosuppression is necessary for replacement of donor Schwann cells in the allograft with those of the host. In a mouse model of sciatic nerve allografts, a continuous postgrafting treatment with cyclosporin A maintained allograft association with donor Schwann cells until a “chronic rejection process” prevailed. This led to clearance of donor Schwann cells and subsequent replacement by host Schwann cells. However, to most efficiently facilitate replacement of donor Schwann cells with those of the host, a temporary immunosuppressive regimen to gradually allow for rejection, is recommended.^[15] This controlled rejection process allows for a gradual replacement of Schwann cells such that the growing axons maintain associations with endoneurial Schwann cells. If the replacement does not occur and an acute rejection process suddenly destroys donor Schwann cells supporting host axonal growth, then the entire regenerative process may be compromised.

Outcomes following repair of mid-level brachial plexus injuries with cadaveric/living-related donor nerve allografts in eight patients revealed no complications during or immediately after the operation. Postprocedure immunosuppression included basiliximab, tacrolimus, azathioprine, and co-trimoxazole. Seven of these patients displayed return of motor and sensory function. The eighth was noncompliant with the posttransplant immunosuppressive regimen, leading to impaired motor and sensory regeneration.^[16]

Tacrolimus (FK506)

Tacrolimus represents the current backbone of conventional immunosuppressive regimen in SOT. Surprisingly, its use was also shown to have an enhanced effect on nerve regeneration in a dose-dependent, calcineurin-independent mechanism.^[17] This combination of effects makes this drug very appealing in the context of VCA. Tacrolimus sustains this effect with both systemic and local administrations.^[18]

Specific to applications in VCA, administration of tacrolimus in a swine model of ulnar nerve grafting demonstrated doubling of nerve growth parameters (nerve density, mean fiber count) postautograft. In allografts, tacrolimus was necessary for posttransplant neuroregeneration, as the absence of the drug abolished regeneration altogether.^[19] Early studies of reinnervation of hemifacial VCAs in rats revealed that immunosuppression provided by tacrolimus coupled with nerve repair in the form of epineurial neurotaphies was successful in developing and maintaining sensory reinnervation of the graft tissues.^[20] Tacrolimus used in an orthotopic rat hind limb transplant model was shown to enhance neural regeneration, further enhanced when a bone marrow-derived stem cell (BMSC) suspension was injected into the distal end of the injured nerve.^[21] Low dose tacrolimus (0.1 mg/kg/day) in peripheral nerve

regeneration in rat sciatic nerve transplantation model demonstrated significant re-myelination and regeneration of the transected and transplanted nerve.^[22] Tacrolimus was also shown to enhance nerve repair following nerve crush injury in sciatic nerves in rats as compared to cyclosporin A, which had no effect on the rate of axonal regeneration.^[23]

With respect to Schwann cell migration, tacrolimus administration after sciatic nerve allografts in mice demonstrated rapid host cell migration followed by a slow replacement phase after 15 weeks (replacement of donor Schwann cells by those of the host). Controlled withdrawal of tacrolimus in this period can accelerate the replacement process.^[24] Temporally controlling the onset of an acute rejection process either early (5 days posttransplant) or late (8 weeks posttransplant) in the regenerative timeframe demonstrated differing degrees of repair. The group undergoing early rejection had a significantly better functional recovery in innervated muscles than those undergoing late rejection. Interestingly, immunohistochemical staining for Schwann cells revealed no difference in staining intensity between late and early rejection groups, although neural fiber width was decreased in late rejection rats, potentially due to impaired myelination production from damaged Schwann cells.^[25]

The use of tacrolimus in posttransplant immunosuppressive regimens can enhance nerve regeneration and growth of axon sprouts into donor tissue. Further work remains to be done regarding elucidation of the exact mechanism by which tacrolimus affects nerve regeneration, but outcomes data, so far, has been promising. A 3-year follow-up examination of motor recovery after hand transplant in a 47-year-old patient revealed a “remarkable speed” of regeneration. The investigators attribute this to the neurotrophic effects of tacrolimus and note that regeneration is possible even after the patient’s median and ulnar nerves had been severed for 14 years prior to the operation and immunosuppressive regimen.^[26] However, studies comparing tacrolimus to other immunosuppressive modalities and their resulting effects on nerve regeneration have not been conducted. Promising results from animal models, applications in crushed nerve injury models, Schwann cell studies, and preliminary data from VCA point to tacrolimus being a key neurotrophic candidate along with its well-characterized immunosuppressive capacity.

A summary of recent and pertinent publications can be found in Table 1.

Outcomes studies

Due to the limited number of hand and face transplants, and the diversity of such patients, large sample size analyses of sensory and motor regeneration are challenging, and few have been performed (requiring the establishment of a patient database for longitudinal and cross-sectional outcomes monitoring). Many outcomes studies look into specific or small sets of patients. For example, patient JM, who underwent a partial face transplant at Brigham and Women’s Hospital in Boston

Table 1: Summary of recent publications pertaining to tacrolimus in nerve regeneration

Authors	Year	Title	Summary
Liu <i>et al.</i> ^[27]	2014	Rapamycin promotes Schwann cell migration and nerve growth factor secretion	With a similar mechanism of action as tacrolimus, rapamycin was demonstrated to enhance nerve regeneration at lower concentrations than tacrolimus, although Schwann cell proliferation was not affected
Mekaj <i>et al.</i> ^[28]	2014	Application of topical pharmacological agents at the site of peripheral nerve injury and methods used for evaluating the success of the regenerative process	While topical administration of tacrolimus over the site of peripheral nerve injury enhances nerve regeneration and functional recovery, the repair process remains sub-optimal
Yan <i>et al.</i> ^[25]	2013	Nerve regeneration in rat limb allografts: evaluation of acute rejection rescue	In limb transplant, early rejection led to prompt rescue of the regenerating axons, while late rejection affected motor function the most
Song <i>et al.</i> ^[21]	2012	Use of FK506 and bone marrow mesenchymal stem cells for rat hind limb allografts	In hindlimb allograft, treatment with tacrolimus and local BMSC injection enhanced sciatic nerve regrowth with increased presence of Schwann cells
Que <i>et al.</i> ^[29]	2012	Tacrolimus reduces scar formation and promotes sciatic nerve regeneration	Treatment of sciatic nerve transection with tacrolimus gavage in rats demonstrated enhanced regeneration with thicker and myelinated fibers and reduced collagen fiber content and scar area in the area of nerve anastomosis
Azizi <i>et al.</i> ^[30]	2012	Effects of topically administered FK506 on sciatic nerve regeneration and reinnervation after vein graft repair of short nerve gaps	Loading of an inside-out-vein graft with tacrolimus demonstrated an increase in the number and diameter of myelinated regenerating fibers in the repair of a rat sciatic nerve injury model
Yan <i>et al.</i> ^[31]	2012	Efficacy of short-term FK506 administration on accelerating nerve regeneration	Short-term administration of tacrolimus in a posttransection injury model yielded significant benefits in functional motor recovery
Toll <i>et al.</i> ^[18]	2011	The role of immunophilin ligands in nerve regeneration	Systemic tacrolimus administration, as well as other nonimmunosuppressive immunophilins, enhances nerve regeneration
Whitlock <i>et al.</i> ^[24]	2010	Dynamic quantification of host Schwann cell migration into peripheral nerve allografts	GFP-tagged host Schwann cells followed after nerve allograft procedure and tacrolimus administration revealed definitive migration patterns into the donor tissue
Li <i>et al.</i> ^[32]	2010	ImmunophilinFK506 loaded in chitosan guide promotes peripheral nerve regeneration	Repair of rat sciatic nerve injury model with a chitosan guide loaded with tacrolimus demonstrated enhanced electrophysiology following nerve repair as well as increased maturity of myelinated axons
Rustemeyer <i>et al.</i> ^[33]	2010	Administration of low-dose FK506 accelerates histomorphometric regeneration and functional outcomes after allograft nerve repair in a rat model	Repair of rat sciatic nerve injury model with isograft transplant and tacrolimus demonstrated enhanced functional recovery in walking-track analysis at low doses of drug
Rustemeyer <i>et al.</i> ^[22]	2009	Histomorphological and functional impacts of postoperative motor training in rats after allograft sciatic nerve transplantation under low-dose FK506	Tacrolimus was shown to demonstrate significant effects on regeneration following allograft transplantation, although benefits of motor training in addition to tacrolimus were not observed
Landin <i>et al.</i> ^[20]	2008	Functional outcome after facial allograft transplantation in rats	In hemifacial transplant, direct nerve repair of facial and trigeminal nerves yielded the best clinical and neurophysiological recovery of the graft
Jensen <i>et al.</i> ^[19]	2005	Effect of FK506 on peripheral nerve regeneration through long grafts in inbred swine	Treatment with systemic tacrolimus demonstrated enhanced axonal regeneration in nerve autografts and allografts in swine
Owen <i>et al.</i> ^[26]	2001	Peripheral nerve regeneration in human hand transplantation	Inclusion of tacrolimus in the postoperative immunosuppression of a 1998 hand transplantation in France was hypothesized to contribute significantly to peripheral nerve regeneration, as well as surgical technique/skill and neurotrophic factors secreted by the patient's own nerves
Wang <i>et al.</i> ^[23]	1997	Comparative dose-dependence study of FK506 and cyclosporin A on the rate of axonal regeneration in the rat sciatic nerve	Tacrolimus administered at 5 mg/kg to rats in a sciatic nerve crush injury model demonstrated significant increase in the rate of nerve regeneration as compared to that with cyclosporin A administration

BMSC: Bone marrow-derived stem cell, FK506: Tacrolimus, GFP: Green fluorescent protein

with coaptation of “all identifiable motor and sensory nerves as distally as recipient anatomy allows” achieved, after three years posttransplant, return of pressure sensation to 92% of the allograft surface with poorer pressure threshold over the nose. Return of discriminatory sensation and muscle strength was more variable.^[34]

To aggregate data on functional outcomes following hand transplantation, the International Registry on Hand and Composite Tissue Transplantation was developed. A 2004 publication following 18 male patients who underwent upper extremity transplantations between 1998 and 2004 at various levels reported 100% patient and graft survival

and universal return of protective sensation (pain, thermal, and gross tactile sensation) in all grafted hands. Results in discriminative sensation and motor recovery were more variable across these patients.^[35] A 2010 publication following 49 hands transplanted between 1998 and 2010 across 33 patients revealed universal recovery of protective sensation and more variable recovery of discriminatory sensation and motor function in grafts at least 1 year posttransplant.^[36] While these results look promising, it appears that success can be further optimized in the realm of motor regeneration.

Pomahac *et al.*^[37] reported 1 year postoperative functional outcomes of a partial face transplant of a 59-year-old male following an electrical burn injury. “Meticulous neuroorrhaphy” was used to bring together the buccal, infraorbital, and branches of facial nerves. Protective and discriminatory sensations returned to the entire graft by 6 months, and symmetrical smiling was achieved by 1 year.

A 2009 study compared functional recovery in a patient who received a dominant mid-forearm transplantation to that of four patients who underwent mid-forearm replantations following traumatic amputation. The two procedures vary in certain regards, including longer ischemic times in transplantation as compared to replantation, excess allograft tissue requirements for transplants, and the unique need for cortical somatosensory reorganization following a transplant. While the transplant demonstrated increased innervation of intrinsic hand muscles (hypothesized to be due to the effects of tacrolimus), grip strength remained greater in replantations, potentially due to muscle fibrosis and atrophy in the recipient’s proximal forearm stump.^[38]

Post-VCA cortical reorganization has been studied closely, since recovery of motor and sensory function requires not only peripheral nerve regeneration, but the reestablishment of cortical areas representing those regions. Since VCAs are often performed many years after the loss of the limb, underlying cortical plasticity leads to loss of that limb’s representation in primary motor (M1) cortex and primary somatosensory (S1) cortex. Relatively acute reestablishment of afferent and efferent pathways in VCA has been shown to result in significant cortical reorganization.^[39,40] A functional magnetic resonance imaging (fMRI) study of hand and elbow representations in M1 in the months following abilateral hand transplantation revealed a reversal of the cortical reorganization induced by that amputation in a patient who underwent traumatic bilateral amputation 4 years in advance.^[41] Similar results were demonstrated with transcranial magnetic stimulation in a patient who underwent bilateral hand transplantation 3 years following traumatic amputation.^[42] fMRI evaluation of S1 reorganization in a unilateral hand transplant patient 35 years following traumatic amputation demonstrated the significant return of cortical activity despite such a prolonged absence of a limb.^[43]

A study comparing cortical reorganization in 2 patients, one of whom underwent bilateral hand transplantation 6 years following traumatic amputation, and another

who underwent hand replantation 2 h after traumatic amputation, revealed several observations in the reorganization process. The authors observe that supplementary motor area activation is resistant to reorganizing effects in long-term amputation, and this is more prominently seen in M1. Activation patterns in M1 increased over 2 years following the bilateral transplantation. In the patient undergoing hand replantation, structural differences in cortical representation were not observed, suggesting a functional cortical reorganization instead.^[44] Magnetoencephalographic study of cortical representation in 13 patients following limb replantation found a negative correlation between the extent of reorganization and patient-reported pain following replantation.^[45]

Ultimately, forming comparisons between patients, grafts, and outcomes studies are complicated by varying degrees of existing transplant-area injury in recipients, differences in the circumstances under which donor VCA tissue is procured, and surgical protocols and challenges unique to each procedure. However, aggregation of outcomes is necessary to determine overarching trends since the number of patients undergoing VCA transplantation remains relatively low.

A summary of recent and pertinent publications regarding functional outcomes in VCA can be found in Table 2, and regarding cortical reorganization in VCA in Table 3.

FUTURE DIRECTIONS

Nerve guidance conduits

The use of nerve guidance conduits (NGCs) to appose nerve stumps protects against scar infiltration and the development of neuromas, thereby enhancing the fidelity of regeneration.^[48] A NGC is a doubly open-ended tube that requires separated nerve ends to be attached to either end of the structure, and the internal composition provides a protected environment for nerve sprouts to extend longitudinally towards the opposing end.^[49] Early versions of NGCs only demonstrated the limited extent of repair over a few centimeters.^[50]

With respect to VCA, however, the benefit of NGCs has not been studied in humans, as the gold standard remains surgical coaptation with or without the use of nerve allografts. This technology has primarily been used in the repair of peripheral nerve damage, and a review of studies published through 2006 evaluating close to three hundred patients reported “satisfactory” results in some patients experiencing suboptimal results. At this point, NGCs are primarily limited to the repair of short lesion gaps, but advances in this technology seek to increase the feasibility and consistent success of its use.^[51] Currently, the theoretical benefits of using NGC over nerve allograft in VCA are limited since donor allografts can be utilized to fill large gaps without additional immunosuppression or without concerns for donor-site morbidity in the cadaveric donor.

Chondroitinase

Chondroitin sulfate proteoglycans (CSPGs) are found in the extracellular matrix and are known to inhibit axonal

Table 2: Summary of recent publications pertaining to functional outcomes in VCA

Authors	Year	Title	Summary
Diaz-Siso <i>et al.</i> ^[34]	2013	Facial allotransplantation: a 3-year follow-up report	Face transplant of a 2009 patient demonstrated near-normal sensation after 3-year, along with improving motor function
Unadkat <i>et al.</i> ^[46]	2013	Functional outcomes following multiple acute rejections in experimental VCA	Multiple acute rejection episodes in rat orthotopic hindlimb transplants led to decreased motor function due to muscle atrophy and fibrosis, although axon density and electrophysiology remained intact
Pomahac <i>et al.</i> ^[37]	2011	Restoration of facial form and function after severe disfigurement from burn injury by a composite facial allograft	1-year follow-up of a 59-year-old patient with face transplant demonstrated recovery of sensation and basic motor function in emotional display, speech, and feeding
Petruzzo <i>et al.</i> ^[36]	2010	The IRHCTT. Transplantation	Analysis of 49 transplanted hands revealed universal recovery of protective sensation and return of tactile and discriminative sensation in most grafts
Jablecki <i>et al.</i> ^[38]	2009	A detailed comparison of the functional outcome after mid-forearm replantations versus midforearm transplantation	Comparison of forearm transplant to replantation in human patients revealed greater grip strength in replantation but better recovery of sensation in transplantation
Breidenbach <i>et al.</i> ^[47]	2008	Outcomes of the first two American hand transplants at 8 and 6 years posttransplant	Long-term posthand transplant follow-up of 2 patients revealed improvements in motor strength comparable to postreplant results with significant increases in patient quality of life
Lanzetta <i>et al.</i> ^[35]	2005	The IRHCTT. Transplantation	Analysis of 18 hand/forearm/thumb transplants revealed universal graft survival, achievement of protective sensation, and recovery of enough motor activity for most daily activities

VCA: Vascularized composite allotransplantation, IRHCTT: International Registry on Hand and Composite Tissue Transplantation

Table 3: Summary of recent publications pertaining to cortical reorganization in VCA

Authors	Year	Title	Summary
Blume <i>et al.</i> ^[45]	2014	Cortical reorganization after macroreplantation at the upper extremity: a magnetoencephalographic study	Patient-reported pain was found to be negatively correlated with extent of cortical reorganization following limb transplantation in a study of 13 patients
Vargas <i>et al.</i> ^[42]	2008	Re-emergence of hand-muscle representations in human motor cortex after hand allograft	TMS of patient LB, who underwent bilateral hand transplantation 3-year after traumatic amputation demonstrated M1 representation reestablished to the newly attached muscles within 10 months posttransplant
Frey <i>et al.</i> ^[43]	2008	Chronically deafferented sensory cortex recovers a grossly typical organization after allogenic hand transplantation	Hand transplant of a patient 35 years postamputation revealed S1 reorganization within 4 months, re-establishing gross hand cortical representation
Brenneis <i>et al.</i> ^[44]	2005	Cortical motor activation patterns following hand transplantation and replantation	M1 reorganization was most pronounced in hand transplantation and compared to replantation, while SMA was resistant to reorganization in long-term amputation
Giraux <i>et al.</i> ^[41]	2001	Cortical reorganization in motor cortex after graft of both hands	Reversal of M1 reorganization following a traumatic bilateral amputation was reported in the months after a bilateral hand transplantation

VCA: Vascularized composite allotransplantation, TMS: Transcranial magnetic stimulation, SMA: Supplementary motor area

regeneration. Treatment with chondroitinase, to cleave glycosaminoglycans from and inactivate CSPGs, has been shown to improve nerve regeneration following nerve injury and repair.^[52,53] Chondroitinase treatment is part of the processing used in an off-the-shelf decellularized nerve allograft that has been gaining popularity for nerve repair.^[54,55] Our group performed a translational study assessing the use of chondroitinase in VCA and found that a single intraneural injection at the time of transplantation resulted in significantly improved axonal regeneration.^[56] As such, this may represent a promising therapeutic option to enhance functional outcomes in clinical VCA.

Fibrin glue

Traditional nerve coaptation requires the suturing of nerves, which leads to traumatic damage to the stumps. Thus, a more optimal ligation technique is needed to avoid this procedurally-induced impairment. Fibrin glue was demonstrated to quickly and efficiently reattach transected ends of nerves. However, Original

studies comparing the effectiveness of fibrin glue and suture-based repair demonstrated differing observations on the preservation of electrophysiology across the transected region.^[57,58] Decreased regenerative capacity of the glued stumps may be, in part, due to the enhancement of nerve regeneration following traumatic injury to distal nerve segments, as explained earlier.

Recent histological studies of fibrin glue ligations have demonstrated decreased inflammatory response and fibrosis as compared to sutured reattachments. The use of Quixil, a human fibrin glue sealant, also led to better axonal regeneration and alignment of nerve fibers in a rat model of median nerve transection. Additional of nerve growth factor to the fibrin glue led to enhanced nerve regeneration.^[59] Incorporation of microspheres that slowly release glial cell-derived neurotrophic factor into fibrin gels encasing the site of transection was also shown to facilitate regeneration.^[60] Although research has demonstrated the benefits of fibrin glue, microsutures remains the mainstay procedure for nerve segment

Table 4: Summary of recent publications pertaining to ASCs in peripheral nerve gap repair

Authors	Year	Title	Summary
Kuo <i>et al.</i> ^[62]	2014	Proteomic analysis in serum of rat hind-limb allograft tolerance induced by immunosuppressive therapy with ASCs	Analysis of serum proteome revealed significant differences after inclusion of ASC in the immunosuppressive regimen with increased levels of markers for tolerance
Cheng <i>et al.</i> ^[75]	2014	Syngeneic ASCs with short-term immunosuppression induce VCA tolerance in rats	Addition of ASCs to post-VCA immunosuppressive regimen results in enhanced tolerance of the VCA graft with elevated levels of circulating regulatory T cells
Wu <i>et al.</i> ^[76]	2014	Donor age negatively affects the immunoregulatory properties of both adipose and bone marrow derived mesenchymal stem cells	As the age of the stem cell donor increases, the quality of collected bone marrow and ASCs decreases
Hsueh <i>et al.</i> ^[67]	2014	Functional recoveries of sciatic nerve regeneration by combining chitosan-coated conduit and neurosphere cells induced from ASCs	Seeding of a chitosan-coated conduit with neurosphere cells differentiated from ASCs leads to "substantial improvements in nerve regeneration" in a 10 mm sciatic nerve lesion in rats
Watanabe <i>et al.</i> ^[68]	2014	Undifferentiated and differentiated ASCs improve nerve regeneration in a rat model of facial nerve defect	Seeding of silicone conduits with ASCs (both differentiated and undifferentiated) or Schwann cells to repair a 7 mm facial nerve lesion in rats demonstrated similar therapeutic results in nerve regeneration across cell types
Hundepool <i>et al.</i> ^[73]	2014	The effect of stem cells in bridging peripheral nerve defects: a meta-analysis	Meta analysis of in vivo experimentation of nerve conduits stem cell seeding for nerve gap repair revealed systematically that use of stem cells results in the most beneficial effects for reconstruction
Qureshi <i>et al.</i> ^[77]	2014	Human adipose-derived stromal/stem cell isolation, culture, and osteogenic differentiation	Provides methods for the lipoaspiration of ASCs, culture and preservation of that cell population, synthesis of scaffolds, and techniques for loading those scaffolds with isolated cells
Leto Barone <i>et al.</i> ^[63]	2013	Immunomodulatory effects of ASCs: fact or fiction	ASCs demonstrate beneficial tolerogenic qualities in preliminary studies, but further clinical work must be done to understand this effect
Ying <i>et al.</i> ^[78]	2013	Effects of intracavernous injection of ASCs on cavernous nerve regeneration in a rat model	In a model of cavernous nerve crush injury, injection of ASCs to the site of injury demonstrated enhanced nerve regeneration and restoration of erectile function
Mohammadi <i>et al.</i> ^[69]	2013	Effects of undifferentiated cultured omental ASCs on peripheral nerve regeneration	Repair of a 10 mm sciatic nerve lesion with a silicone conduit seeded with uASCs demonstrated increased numbers and sizes of regenerating fibers
Zaminy <i>et al.</i> ^[79]	2013	Transplantation of schwann cells differentiated from adipose stem cells improves functional recovery in rat spinal cord injury	Collagen scaffolds loaded with Schwann cells differentiated from ASCs effectively support axon regeneration and functional recovery in 3 mm spinal cord lesions in rats
Marconi <i>et al.</i> ^[70]	2012	Human adipose-derived mesenchymal stem cells systemically injected promote peripheral nerve regeneration in the mouse model of sciatic crush	Intravenous administration of ASCs after sciatic nerve crush injury in mice demonstrated 'clear therapeutic potential' by secreting neuroprotective factors
Shen <i>et al.</i> ^[80]	2012	Peripheral nerve repair of transplanted undifferentiated adipose tissue-derived stem cells in a biodegradable reinforced nerve conduit	Repair of 10 mm sciatic nerve gap with a genipin-gelatin-tricalcium phosphate conduit seeded with ASCs demonstrated similar results in regeneration to autologous nerve grafts
Orbay <i>et al.</i> ^[72]	2012	Differentiated and uASCs improve function in rats with peripheral nerve gaps	In a model of 10 mm sciatic nerve gap, repair with various modalities, including nerve grafts, conduits, and ASC-seeded conduits, the seeding of the conduit with stem cells yielded best outcomes in regeneration and nerve conduction velocity
Faroni <i>et al.</i> ^[64]	2011	Schwann-like adult stem cells derived from bone marrow and adipose tissue express GABA type B receptors	Schwann cells derived from bone marrow and ASCs express functional GABA-B receptors, which can modulate cellular function
Mohammadi <i>et al.</i> ^[65]	2011	Comparison of beneficial effects of undifferentiated cultured bone marrow stromal cells and omental adipose-derived nucleated cell fractions on sciatic nerve regeneration	In the repair of a 10 mm sciatic nerve lesion with a vein graft infused with stem cells, ASCs demonstrated enhanced regenerative effects as compared to those from bone marrow

VCA: Vascularized composite allotransplantation, ASC: Adipose-derived stem cells, GABA: Gamma-aminobutyric acid, uASC: Undifferentiated adipose-derived stem cell

ligation and further development of technologies must be performed.^[61] To date, due to the high inflammatory response and fibrosis ensuing during their use, fibrin glues offer limited applicability in VCA, particularly given the enhanced regeneration observed following trauma when nerve segments are re-anastomosed with microsurgical techniques. The future development of bioactive fibrin glues that may artificially provide the neurotrophic factors normally present following nerve trauma, may offer a

more efficient and consistent alternative for end-to-end ligation of nerve stumps.

Adipose-derived stem cells

In addition to demonstrating tolerogenic effects in transplanted tissues,^[62,63] both BMSCs and adipose-derived stem cells (ASCs) have also been shown to exert positive effects on peripheral nerve regeneration.^[64] The relative ease of isolating ASCs and developing Schwann cell populations from this cell type makes them more

efficient to use than BMSCs. These characteristics, coupled with the observation that there is no significant difference between ASCs and BMSCs in facilitating nerve regeneration, points to ASCs as being a more efficient option in stem cell-based enhancement of nerve regeneration.^[65]

While the transplantation of Schwann cells into nerve conduits has demonstrated increased regenerative potential,^[66] ASCs have also been demonstrated to have a pro-regenerative effect on growing axons.^[67-70] The mechanism for this effect is in the differentiation of ASCs into Schwann cell-like phenotypes in the context of nerve injury and regeneration. Interestingly, undifferentiated ASCs (uASCs) can also promote nerve growth.^[71] *In vitro* differentiation of uASCs into Schwann cells prior to seeding demonstrated no significant difference as compared to uASCs in the graft-guided regeneration of a ten millimeter injury of rat sciatic nerve.^[72] Similar findings were demonstrated in facial nerve repair with uASC/differentiated ASC seeding of the graft.^[68] A large meta-analysis published in July 2014 examining data from forty-four animal studies revealed that the use of ASCs in nerve grafts offers significant benefits toward nerve regeneration in sciatic, median, ulnar, and radial nerve lesion models in rats, dogs, monkeys, and mice.^[73]

The regenerative benefits of ASCs require their seeding along the path of the growing axon sprouts, as well as being in an environment that maintains the population for the weeks to months required for axonal regrowth. Existing Food and Drug Administration-approved nerve conduits with specialized matrices for ASC maintenance adequately meets these requirements, thereby creating a microenvironment in which such stem cells can readily affect pro-regenerative signals on growing axons in a spatially constrained path. ASCs are capable of secreting nerve growth factors, vascular endothelial growth factor, and brain-derived neurotrophic factor, among a wider set of cytokines and other cell signaling molecules.^[71] The strength of a cellular graft over one that merely elutes neurotrophic factors is that the molecular microenvironment can be regulated by ASCs in response to the penetrating sprouts.^[74]

ASCs prove to be a promising area of research for the facilitation of nerve regeneration in VCA. Early *in vivo* research demonstrating seeding of these cells into artificial conduits and grafts has provided promising results. However, these remain restricted to animal models of the peripheral nerve lesion. The combined promise of beneficial immunomodulatory effects and enhanced nerve regeneration makes these cells a tantalizing therapeutic supplementation in VCA. The extent of these benefits as a clinical application in VCA remains to be studied.

A summary of recent and pertinent publications regarding ASCs in VCA/nerve regeneration can be found in Table 4.

CONCLUSION

Sensory and motor regeneration are major hurdles that must be addressed to realize the fullest potential of VCA. Advances continue to be made in peripheral nerve repair, and these results must be explored in the context of transplant surgery. Results in post-VCA functional outcomes continue to improve, and soon, we can expect more consistent, reliable, and faster recovery of sensation and motor control to donor tissues. Exciting advancements in the area of ASC-enhanced nerve regeneration may offer a promising frontier towards addressing this challenging question.

REFERENCES

1. Chim H, Amer H, Mardini S, Moran SL. Vascularized composite allotransplant in the realm of regenerative plastic surgery. *Mayo Clin Proc* 2014;89:1009-20.
2. Fischer S, Lian CG, Kueckelhaus M, Strom TB, Edelman ER, Clark RA, Murphy GF, Chandraker AK, Riella LV, Tullius SG, Pomahac B. Acute rejection in vascularized composite allotransplantation. *Curr Opin Organ Transplant* 2014;19:531-44.
3. Oliveira JT, Bittencourt-Navarrete RE, de Almeida FM, Tonda-Turo C, Martinez AM, Franca JG. Enhancement of median nerve regeneration by mesenchymal stem cells engraftment in an absorbable conduit: improvement of peripheral nerve morphology with enlargement of somatosensory cortical representation. *Front Neuroanat* 2014;8:111.
4. Scheib J, Höke A. Advances in peripheral nerve regeneration. *Nat Rev Neurol* 2013;9:668-76.
5. Raff MC, Whitmore AV, Finn JT. Axonal self-destruction and neurodegeneration. *Science* 2002;296:868-71.
6. Glaus SW, Johnson PJ, Mackinnon SE. Clinical strategies to enhance nerve regeneration in composite tissue allotransplantation. *Hand Clin* 2011;27:495-509, ix.
7. Oyamatsu H, Koga D, Igarashi M, Shibata M, Ushiki T. Morphological assessment of early axonal regeneration in end-to-side nerve coaptation models. *J Plast Surg Hand Surg* 2012;46:299-307.
8. Pomahac B, Pribaz J. Facial composite tissue allograft. *J Craniofac Surg* 2012;23:265-7.
9. Lykissas MG. Current concepts in end-to-side neuroorrhaphy. *World J Orthop* 2011;2:102-6.
10. Audolfsson T, Rodríguez-Lorenzo A, Wong C, Cheng A, Kildal M, Nowinski D, Rozen S. Nerve transfers for facial transplantation: a cadaveric study for motor and sensory restoration. *Plast Reconstr Surg* 2013;131:1231-40.
11. Rinker B, Vyas KS. Clinical applications of autografts, conduits, and allografts in repair of nerve defects in the hand: current guidelines. *Clin Plast Surg* 2014;41:533-50.
12. Rivlin M, Sheikh E, Isaac R, Beredjikian PK. The role of nerve allografts and conduits for nerve injuries. *Hand Clin* 2010;26:435-46, viii.
13. Moore AM, Kasukurthi R, Magill CK, Farhadi HF, Borschel GH, Mackinnon SE. Limitations of conduits in peripheral nerve repairs. *Hand (N Y)* 2009;4:180-6.
14. Mackinnon SE, Doolabh VB, Novak CB, Trulock EP. Clinical outcome following nerve allograft transplantation. *Plast Reconstr Surg* 2001;107:1419-29.
15. Midha R, Mackinnon SE, Becker LE. The fate of Schwann cells in peripheral nerve allografts. *J Neuropathol Exp Neurol* 1994;53:316-22.
16. Elkwood AI, Holland NR, Arbes SM, Rose MI, Kaufman MR, Ashinoff RL, Parikh MA, Patel TR. Nerve allograft transplantation for functional restoration of the upper extremity: case series. *J Spinal Cord Med* 2011;34:241-7.
17. Gold BG. FK506 and the role of immunophilins in nerve regeneration. *Mol Neurobiol* 1997;15:285-306.
18. Toll EC, Seifalian AM, Birchall MA. The role of immunophilin ligands in nerve regeneration. *Regen Med* 2011;6:635-52.
19. Jensen JN, Brenner MJ, Tung TH, Hunter DA, Mackinnon SE. Effect of FK506 on peripheral nerve regeneration through long grafts in inbred swine. *Ann Plast Surg* 2005;54:420-7.
20. Landin L, Cavadas PC, Gonzalez E, Rodriguez JC, Caballero A. Functional outcome after facial allograft transplantation in rats. *J Plast Reconstr Aesthet Surg* 2008;61:1034-43.
21. Song Y, Wang Z, Wang Z, Zhang H, Li X, Chen B. Use of FK506 and bone marrow mesenchymal stem cells for rat hind limb allografts. *Neural Regen Res* 2012;7:2681-8.

22. Rustemeyer J, Krajacic A, Dicke U. Histomorphological and functional impacts of postoperative motor training in rats after allograft sciatic nerve transplantation under low-dose FK 506. *Muscle Nerve* 2009;39:480-8.
23. Wang MS, Zeleny-Pooley M, Gold BG. Comparative dose-dependence study of FK506 and cyclosporin A on the rate of axonal regeneration in the rat sciatic nerve. *J Pharmacol Exp Ther* 1997;282:1084-93.
24. Whitlock EL, Myckatyn TM, Tong AY, Yee A, Yan Y, Magill CK, Johnson PJ, Mackinnon SE. Dynamic quantification of host Schwann cell migration into peripheral nerve allografts. *Exp Neurol* 2010;225:310-9.
25. Yan Y, MacEwan MR, Hunter DA, Farber S, Newton P, Tung TH, Mackinnon SE, Johnson PJ. Nerve regeneration in rat limb allografts: evaluation of acute rejection rescue. *Plast Reconstr Surg* 2013;131:e499-511.
26. Owen ER, Dubernard JM, Lanzetta M, Kapila H, Martin X, Dawahra M, Hakim NS. Peripheral nerve regeneration in human hand transplantation. *Transplant Proc* 2001;33:1720-1.
27. Liu F, Zhang H, Zhang K, Wang X, Li S, Yin Y. Rapamycin promotes Schwann cell migration and nerve growth factor secretion. *Neural Regen Res* 2014;9:602-9.
28. Mekaj AY, Morina AA, Bytyqi CI, Mekaj YH, Duci SB. Application of topical pharmacological agents at the site of peripheral nerve injury and methods used for evaluating the success of the regenerative process. *J Orthop Surg Res* 2014;9:94.
29. Que J, Cao Q, Sui T, Du S, Zhang A, Kong D, Cao X. Tacrolimus reduces scar formation and promotes sciatic nerve regeneration. *Neural Regen Res* 2012;7:2500-6.
30. Azizi S, Mohammadi R, Amini K, Fallah R. Effects of topically administered FK506 on sciatic nerve regeneration and reinnervation after vein graft repair of short nerve gaps. *Neurosurg Focus* 2012;32:E5.
31. Yan Y, Sun HH, Hunter DA, Mackinnon SE, Johnson PJ. Efficacy of short-term FK506 administration on accelerating nerve regeneration. *Neurorehabil Neural Repair* 2012;26:570-80.
32. Li X, Wang W, Wei G, Wang G, Zhang W, Ma X. Immunophilin FK506 loaded in chitosan guide promotes peripheral nerve regeneration. *Biotechnol Lett* 2010;32:1333-7.
33. Rustemeyer J, van de Wal R, Keipert C, Dicke U. Administration of low-dose FK 506 accelerates histomorphometric regeneration and functional outcomes after allograft nerve repair in a rat model. *J Craniomaxillofac Surg* 2010;38:134-40.
34. Diaz-Siso JR, Parker M, Bueno EM, Sisk GC, Pribaz JJ, Eriksson E, Annino D, Tullius SG, Pomahac B. Facial allotransplantation: a 3-year follow-up report. *J Plast Reconstr Aesthet Surg* 2013;66:1458-63.
35. Lanzetta M, Petruzzo P, Margreiter R, Dubernard JM, Schuind F, Breidenbach W, Lucchina S, Schneeberger S, van Holder C, Granger D, Pei G, Zhao J, Zhang X. The international registry on hand and composite tissue transplantation. *Transplantation* 2005;79:1210-4.
36. Petruzzo P, Lanzetta M, Dubernard JM, Landin L, Cavadas P, Margreiter R, Schneeberger S, Breidenbach W, Kaufman C, Jablęcki J, Schuind F, Dumontier C. The international registry on hand and composite tissue transplantation. *Transplantation* 2010;90:1590-4.
37. Pomahac B, Pribaz JJ, Eriksson E, Annino D, Caterson S, Sampson C, Chun Y, Orgill D, Nowinski D, Tullius SG. Restoration of facial form and function after severe disfigurement from burn injury by a composite facial allograft. *Am J Transplant* 2011;11:386-93.
38. Jablęcki J, Kaczmarzyk L, Patrzalek D, Domanasiewicz A, Chelmonski A. A detailed comparison of the functional outcome after midforearm replantations versus midforearm transplantation. *Transplant Proc* 2009;41:513-6.
39. Dubernard JM, Sirigu A, Seulin C, Morelon E, Petruzzo P. Fifteen years later: main lessons from composite tissue allografts. *Clin Transpl* 2013;113-9.
40. Siemionow M, Mendiola A. Methods of assessment of cortical plasticity in patients following amputation, replantation, and composite tissue allograft transplantation. *Ann Plast Surg* 2010;66:344-8.
41. Giraux P, Sirigu A, Schneider F, Dubernard JM. Cortical reorganization in motor cortex after graft of both hands. *Nat Neurosci* 2001;4:691-2.
42. Vargas CD, Aballéa A, Rodrigues EC, Reilly KT, Mercier C, Petruzzo P, Petruzzo P, Dubernard JM, Sirigu A. Re-emergence of hand-muscle representations in human motor cortex after hand allograft. *Proc Natl Acad Sci U S A* 2009;106:7197-202.
43. Frey SH, Bogdanov S, Smith JC, Watrous S, Breidenbach WC. Chronically deafferented sensory cortex recovers a grossly typical organization after allogenic hand transplantation. *Curr Biol* 2008;18:1530-4.
44. Brenneis C, Löscher WN, Egger KE, Benke T, Schocke M, Gabl MF, Wechselberger G, Felber S, Pechlaner S, Margreiter R, Piza-Katzer H, Poewe W. Cortical motor activation patterns following hand transplantation and replantation. *J Hand Surg Br* 2005;30:530-3.
45. Blume KR, Dietrich C, Huonker R, Götz T, Sens E, Friedel R, Hofmann GO, Miltner WH, Weiss T. Cortical reorganization after macroreplantation at the upper extremity: a magnetoencephalographic study. *Brain* 2014;137:757-69.
46. Unadkat JV, Bourbeau D, Afrooz PN, Solari MG, Washington KM, Pulikkottil BJ, Weber DJ, Lee WP. Functional outcomes following multiple acute rejections in experimental vascularized composite allotransplantation. *Plast Reconstr Surg* 2013;131:e720-30.
47. Breidenbach WC, Gonzales NR, Kaufman CL, Klapheke M, Tobin GR, Gorantla VS. Outcomes of the first 2 American hand transplants at 8 and 6 years posttransplant. *J Hand Surg Am* 2008;33:1039-47.
48. Félix SP, Pereira Lopes FR, Marques SA, Martinez AM. Comparison between suture and fibrin glue on repair by direct coaptation or tubulization of injured mouse sciatic nerve. *Microsurgery* 2013;33:468-77.
49. Isaacs J, Browne T. Overcoming short gaps in peripheral nerve repair: conduits and human acellular nerve allograft. *Hand (N Y)* 2014;9:131-7.
50. Jiang X, Lim SH, Mao HQ, Chew SY. Current applications and future perspectives of artificial nerve conduits. *Exp Neurol* 2010;223:86-101.
51. Schlosshauer B, Dreesmann L, Schaller HE, Sinis N. Synthetic nerve guide implants in humans: a comprehensive survey. *Neurosurgery* 2006;59:740-7.
52. Muir D, Engvall E, Varon S, Manthorpe M. Schwannoma cell-derived inhibitor of the neurite-promoting activity of laminin. *J Cell Biol* 1989;109:2353-62.
53. Neubauer D, Graham JB, Muir D. Chondroitinase treatment increases the effective length of acellular nerve grafts. *Exp Neurol* 2007;207:163-70.
54. Whitlock EL, Tuffaha SH, Luciano JP, Yan Y, Hunter DA, Magill CK, Moore AM, Tong AY, Mackinnon SE, Borschel GH. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. *Muscle Nerve* 2009;39:787-99.
55. Brooks DN, Weber RV, Chao JD, Rinker BD, Zoldos J, Robichaux MR, Ruggeri SB, Anderson KA, Bonatz EE, Wisotsky SM, Cho MS, Wilson C, Cooper EO, Ingari JV, Safa B, Parrett BM, Buncke GM. Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. *Microsurgery* 2012;32:1-14.
56. Tuffaha S, Quigley M, Ng T, Gorantla VS, Shores JT, Pulikkottil B, Shestak C, Brandacher G, Lee WP. The effect of chondroitinase on nerve regeneration following composite tissue allotransplantation. *J Hand Surg Am* 2011;36:1447-52.
57. Smahel J, Meyer VE, Bachem U. Glueing of peripheral nerves with fibrin: experimental studies. *J Reconstr Microsurg* 1987;3:211-20.
58. Moy OJ, Peimer CA, Koniuch MP, Howard C, Zielezny M, Katikaneni PR. Fibrin seal adhesive versus nonabsorbable microsuture in peripheral nerve repair. *J Hand Surg Am* 1988;13:273-8.
59. Ma S, Peng C, Wu S, Wu D, Gao C. Sciatic nerve regeneration using a nerve growth factor-containing fibrin glue membrane. *Neural Regen Res* 2013;8:3416-22.
60. Wood MD, Gordon T, Kim H, Szyrak M, Phua P, Lafontaine C, Kemp SW, Shoichet MS, Borschel GH. Fibrin gels containing GDNF microspheres increase axonal regeneration after delayed peripheral nerve repair. *Regen Med* 2013;8:27-37.
61. Owusu A, Mayeda B, Isaacs J. Surgeon perspectives on alternative nerve repair techniques. *Hand (N Y)* 2014;9:29-35.
62. Kuo YR, Chen CC, Goto S, Huang YT, Tsai CC, Yang MY. Proteomic analysis in serum of rat hind-limb allograft tolerance induced by immunosuppressive therapy with adipose-derived stem cells. *Plast Reconstr Surg* 2014;134:1213-23.
63. Leto Barone AA, Khalifian S, Lee WP, Brandacher G. Immunomodulatory effects of adipose-derived stem cells: fact or fiction? *Biomed Res Int* 2013;2013:383685.
64. Faroni A, Mantovani C, Shawcross SG, Motta M, Terenghi G, Magnaghi V. Schwann-like adult stem cells derived from bone marrow and adipose tissue express gamma-aminobutyric acid type B receptors. *J Neurosci Res* 2011;89:1351-62.
65. Mohammadi R, Azizi S, Delirez N, Hobbenaghi R, Amini K. Comparison of beneficial effects of undifferentiated cultured bone marrow stromal cells and omental adipose-derived nucleated cell fractions on sciatic nerve regeneration. *Muscle Nerve* 2011;43:157-63.
66. Rodríguez FJ, Verdú E, Ceballos D, Navarro X. Nerve guides seeded with autologous schwann cells improve nerve regeneration. *Exp Neurol* 2000;161:571-84.
67. Hsueh YY, Chang YJ, Huang TC, Fan SC, Wang DH, Chen JJ, Wu CC, Lin SC. Functional recoveries of sciatic nerve regeneration by combining chitosan-coated conduit and neurosphere cells induced from adipose-derived stem cells. *Biomaterials* 2014;35:2234-44.
68. Watanabe Y, Sasaki R, Matsumine H, Yamato M, Okano T. Undifferentiated and differentiated adipose-derived stem cells improve nerve regeneration in a

- rat model of facial nerve defect. *J Tissue Eng Regen Med* 2014;DOI: 10.1002/term.1919.
69. Mohammadi R, Azizi S, Amini K. Effects of undifferentiated cultured omental adipose-derived stem cells on peripheral nerve regeneration. *J Surg Res* 2013;180:e91-7.
 70. Marconi S, Castiglione G, Turano E, Bissolotti G, Angiari S, Farinazzo A, Constantin G, Bedogni G, Bedogni A, Bonetti B. Human adipose-derived mesenchymal stem cells systemically injected promote peripheral nerve regeneration in the mouse model of sciatic crush. *Tissue Eng Part A* 2012;18:1264-72.
 71. Faroni A, Terenghi G, Reid AJ. Adipose-derived stem cells and nerve regeneration: promises and pitfalls. *Int Rev Neurobiol* 2013;108:121-36.
 72. Orbay H, Uysal AC, Hyakusoku H, Mizuno H. Differentiated and undifferentiated adipose-derived stem cells improve function in rats with peripheral nerve gaps. *J Plast Reconstr Aesthet Surg* 2012;65:657-64.
 73. Hundepool CA, Nijhuis TH, Mohseny B, Selles RW, Hovius SE. The effect of stem cells in bridging peripheral nerve defects: a meta-analysis. *J Neurosurg* 2014;121:195-209.
 74. Widgerow AD, Salibian AA, Kohan E, Sartini Ferreira T, Afzel H, Tham T, Evans GR. "Strategic sequences" in adipose-derived stem cell nerve regeneration. *Microsurgery* 2014;34:324-30.
 75. Cheng HY, Ghetu N, Huang WC, Wang YL, Wallace CG, Wen CJ, Chen HC, Shih LY, Lin CF, Hwang SM, Liao SK, Wei FC. Syngeneic adipose-derived stem cells with short-term immunosuppression induce vascularized composite allotransplantation tolerance in rats. *Cytotherapy* 2014;16:369-80.
 76. Wu LW, Wang YL, Christensen JM, Khalifian S, Schneeberger S, Raimondi G, Cooney DS, Lee WP, Brandacher G. Donor age negatively affects the immunoregulatory properties of both adipose and bone marrow derived mesenchymal stem cells. *Transpl Immunol* 2014;30:122-7.
 77. Qureshi AT, Chen C, Shah F, Thomas-Porch C, Gimble JM, Hayes DJ. Human adipose-derived stromal/stem cell isolation, culture, and osteogenic differentiation. *Methods Enzymol* 2014;538:67-88.
 78. Ying C, Yang M, Zheng X, Hu W, Wang X. Effects of intracavernous injection of adipose-derived stem cells on cavernous nerve regeneration in a rat model. *Cell Mol Neurobiol* 2013;33:233-40.
 79. Zaminy A, Shokrgozar MA, Sadeghi Y, Norouzi M, Heidari MH, Piryaei A. Transplantation of schwann cells differentiated from adipose stem cells improves functional recovery in rat spinal cord injury. *Arch Iran Med* 2013;16:533-41.
 80. Shen CC, Yang YC, Liu BS. Peripheral nerve repair of transplanted undifferentiated adipose tissue-derived stem cells in a biodegradable reinforced nerve conduit. *J Biomed Mater Res A* 2012;100:48-63.

How to cite this article: Arun A, Abt NB, Tuffaha S, Brandacher G, Leto Barone AA. Nerve regeneration in vascularized composite allotransplantation: current strategies and future directions. *Plast Aesthet Res* 2015;2:226-35.

Source of Support: Nil, **Conflict of Interest:** None declared.

Received: 19-02-2015; **Accepted:** 13-04-2015

Limited access dressing and wound infection

Pramod Kumar

Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

Address for correspondence: Dr. Pramod Kumar, Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia. E-mail: pkumar86@hotmail.com

Acute and chronic wound infection poses a major problem to wound care physicians (also known as woundologists). Emergence of multidrug-resistant (MDR) bacteria and biofilm is a real challenge to physicians. Failure to use antimicrobials judiciously leads to toxic damage to host cells with a wide spectrum of problems and super infections. Newer methods of dissolving biofilms and interrupting cell-to-cell communication are yet to be established and included into routine practice.

Intermittent negative pressure regimen of limited access dressing (LAD)^[1] could be effectively used for most issues related to wound infection and its spread (wound to environment and vice versa) in the following manner:

Wound isolation and safe disposal of drainage: occlusive dressing in LAD isolates the wound from the environment and the safe disposal of wound drainage in a closed system with prefilled disinfectants (for viruses, spores and resistant strains) may prove vital in reducing cross infections and hospital-acquired infections.

Prevention of wound invasion: invasive bacteria actively induce their own uptake by phagocytosis of normally non-phagocytic cells, and then either establish a protected niche within which they survive and replicate or disseminate from cell-to-cell by means of an actin-based motility process.^[2] Alternatively, intermittent negative pressure channel effectively to divert bacteria to the drainage system, which mechanically prevents wound invasion^[1] and hence prevents them from establishing a protected niche required for dissemination.

Mechanical disruption of quorum sensing by negative pressure: bacteria communicate with one another using chemical signal molecules. Chemical communication in bacteria involves producing, releasing, detecting and responding to small hormone-like molecules, termed

autoinducers. This process, termed “quorum sensing”, allows bacteria to monitor the environment for other bacteria and to alter the behavior on a population-wide scale in response to changes in the number and/or species of bacteria present in a community (wound environment).^[3] Quorum sensing signals are the essential components of the communication system. These signals regulate virulence gene expression in a variety of plant and animal (including human) bacterial pathogens.^[4] The detection of a minimum stimulatory concentration threshold of an autoinducer leads to an alteration in gene expression. In general, Gram-negative bacteria use acylated homoserine lactones as autoinducers and Gram-positive bacteria use processed oligopeptides for communication. Recent advances in the field indicate that cell-to-cell communication via autoinducers occurs both within and between bacterial species.^[5] Community cooperation probably enhances the effectiveness of processes like virulence factor expression (invasion) and biofilm development (resistance to treatment).^[6] Various chemicals are identified for chemical quenching of quorum sensing (quorum quenching).^[4,7] LAD may be used to mechanically remove the chemical signal molecules intermittently by negative pressure before it reaches a concentration level to produce effective quorum sensing for virulence factor expression, thereby preventing the invasion of host tissues.

Mechanical disruption of biofilm: in general, bacteria have two life forms during growth and proliferation. In one form, bacteria exist as single, independent cells (planktonic) assumed to produce acute infections. In the other form, bacteria are organized into sessile aggregates, commonly referred to as biofilm growth phenotype. In cases, where bacteria form a biofilm within the human host, the infection becomes chronic with extreme resistance to antibiotics and conventional antimicrobial

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.158856

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kumar P. Limited access dressing and wound infection. *Plast Aesthet Res* 2015;2:237-8.

Received: 17-10-2014; **Accepted:** 20-04-2015

agents, and an extreme capacity for evading the host's defenses.^[8] An established biofilm structure comprises microbial cells and an extracellular polymeric substance matrix; it has a defined architecture and it provides an optimal environment for the exchange of genetic material between cells. Cells may also communicate via quorum sensing.^[9] The extracellular digestion of biofilms by multiple bacteriolytic and proteolytic enzymes is being exploited for biofilm control.^[10] LAD may be used to mechanically disrupt the biofilm by intermittent negative pressure.^[1]

Furthermore, wound infection by MDR organisms can be effectively treated by applying negative pressure as they are resistant to drugs but not to the negative pressure.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kumar P. Exploiting potency of negative pressure in wound dressing using limited access dressing and suction-assisted dressing. *Indian J Plast Surg* 2012;45:302-15.
2. Cossart P, Sansonetti PJ. Bacterial invasion: the paradigms of enteroinvasive pathogens. *Science* 2004;304:242-8.
3. Waters CM, Bassler BL. Quorum sensing: cell-to-cell communication in bacteria. *Annu Rev Cell Dev Biol* 2005;21:319-46.
4. Dong YH, Wang LH, Xu JL, Zhang HB, Zhang XF, Zhang LH. Quenching quorum-sensing-dependent bacterial infection by an N-acyl homoserine lactonase. *Nature* 2001;411:813-7.
5. Miller MB, Bassler BL. Quorum sensing in bacteria. *Annu Rev Microbiol* 2001;55:165-99.
6. Chen X, Schauder S, Potier N, Van Dorsselaer A, Pelczar I, Bassler BL, Hughson FM. Structural identification of a bacterial quorum-sensing signal containing boron. *Nature* 2002;415:545-9.
7. Kalia VC. Quorum sensing inhibitors: an overview. *Biotechnol Adv* 2013;31:224-45.
8. Bjarnsholt T. The role of bacterial biofilms in chronic infections. *APMIS Suppl* 2013;136:1-51.
9. Donlan RM. Biofilms: microbial life on surfaces. *Emerg Infect Dis* 2002;8:881-90.
10. Gökçen A, Vilcinskis A, Wiesner J. Biofilm-degrading enzymes from *Lysobacter gummosus*. *Virulence* 2014;5:378-87.

Assessment of the histological state of the healing wound

Akriti Gupta¹, Pramod Kumar²

¹Department of Pathology, Seth GS Medical College and KEM Hospital, Mumbai 400012, Maharashtra, India.

²Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

Address for correspondence: Dr. Akriti Gupta, Department of Pathology, Seth GS Medical College and KEM Hospital, Mumbai 400012, Maharashtra, India. E-mail: dr.akriti@gmail.com

ABSTRACT

The dynamic process of wound healing has various phases, and the knowledge of which is essential for identification of the pathology involved in a chronic intractable wound. Various instruments for the assessment of wound healing have been described, primarily for clinical assessment of the wound. However, very few instruments are currently available for histological grading of the wound. The aim of this article is to review all available literature from 1993 to 2014 on the objective histological scoring of the state of wound healing. This review article emphasizes the importance of histological grading of wounds based on the different parameters from each phase of wound healing and the need for an ideal grading system in order to help assessment of wound status. The parameter chosen in an experimental model should be defined by the scientific question, the underlying hypothesis and the pathogenesis of the disease.

Key words:

Experimental wound assessment, grading of wound, histopathologic grading, wound assessment, wound grading, wound healing, wound histology

INTRODUCTION

The dynamics of wound healing are complex. A thorough understanding of the normal healing process is a prerequisite for unveiling the pathology. Wound healing begins with homeostasis at the site of injury, progresses to an inflammatory phase followed by proliferation of the epithelial and matrix components, and ends with the formation of scar tissue marked by laying down of a highly organized collagen matrix.^[1] Various factors, extrinsic and intrinsic to the injured tissue, affect the healing process.^[2] These are broadly categorized into local and systemic factors. Factors directly influencing the immediate wound environment are considered to be local factors, while the overall health of the individual affecting his ability to heal constitutes the systemic factors^[3] [Table 1].

Impaired wound healing is not an uncommon occurrence in clinical practice. Both local and systemic factors are responsible for impaired healing and weak scar tissue formation.^[2] Acute wounds heal following the normal sequence of the healing process. Acute wounds that fail to progress in a timely and orderly fashion through the normal stages of healing are described as chronic wounds.^[1] Because of associated early and late complications, chronic wounds remain an intractable clinical problem and a frequent cause of morbidity and mortality.^[1]

Various interventions are available for amelioration of impaired healing. Hence, it is important to evaluate wound healing in order to compare the efficacy of

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.158862

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Gupta A, Kumar P. Assessment of the histological state of the healing wound. *Plast Aesthet Res* 2015;2:239-42.

Received: 29-12-2014; **Accepted:** 18-03-2015

Table 1: Factors influencing the wound healing

Local factors	Systemic factors
Oxygenation	Age, gender
Foreign body	Disease: diabetes, keloids, fibrosis, jaundice, uremia
Blood supply	Medications: NSAIDs, glucocorticoids, chemotherapy
	Stress, nutrition, alcoholism
	Immunocompromised status, AIDS, cancer, radiation
NSAIDs: Nonsteroidal anti-inflammatory medications, AIDS: Acquired immune deficiency syndrome	

different interventions. Wound healing is evaluated by both clinical features and biochemical and histological parameters. Nuclear medicine can assist in assessing the vascularity of healing tissue, and hence plays a role in recording inflammation. However, study of the histological features appears to be more reliable as the findings can be recorded photographically for evaluation by different experts.

A literature search was performed on histological scoring of wound from 1993 to 2014. A total of 30 available relevant literatures on wound healing and histological scoring based on various parameters from different stages of wound healing were selected for review.

NORMAL PROCESS OF WOUND HEALING

The sequence of events in normal wound healing has been widely studied and described in literature.^[4] Wound healing is a complex biological process that takes place in all tissues in all organs of the body. Various cell types, including keratinocytes, neutrophils, macrophages, lymphocytes, fibroblasts and endothelial cells, are involved in this process.^[3] The necrotic tissue is either removed by scavenger cells or separated from living tissue by the process of phagocytosis.

The wound healing process consists of four phases: hemostasis, inflammation, proliferation and remodeling.^[1]

Coagulation and hemostasis

The initial step assists in the protection of the vascular system to maintain the functionality of the organ. The clot formed as a result of coagulation provides a matrix for the cells involved in subsequent steps of hemostasis and inflammation.^[1] Various pro-inflammatory cytokines and growth factors are released by the clot and wound tissue. Inflammatory cells then migrate to the wound site by the process of chemotaxis and promote the inflammatory phase.^[4-6]

Inflammation

The goal of the inflammatory phase is to fight potential bacterial contamination of the wound and to activate cytokine secretion.^[1,7] Uncontrolled inflammation can destroy the early migratory effect, leading to an arrest of the healing process.^[8]

Proliferation

The proliferation phase overlaps with the preceding inflammatory phase. It represents a proliferation of

both epithelial and dermal elements which results in reepithelialization of the wound and laying down of the primary extracellular matrix.^[3] Epidermal stem cells and bone marrow derived stem cells also play a role during this phase. Angiogenesis occurs secondary to endothelial progenitor cells, a derivative of hematopoietic stem cells.^[9,10]

Wound remodeling leading to scar formation

This phase marks the final step in tissue remodeling and differentiation leading to recovery of the skin and its aesthetic restoration.^[8,11] Reconstruction of the dermis occurs by reorganization of the matrix collagen.^[7] Fibroblasts differentiation into myofibroblasts, leading to wound contraction and closure.^[12]

ASSESSMENT OF THE WOUND

Impaired wound healing occurs secondary to disordered collagen formation^[13] and underlying predisposing conditions.^[14] In order to effectively manage chronic wounds, periodic assessment of the healing process is necessary.^[15] The insights gained from this type of assessment are expected to facilitate the development of novel therapies by stratifying their specific contributions to the wound healing process in time and stage-specific manner.^[7] Hence, a standardized and reproducible model is required to obtain information about the wound healing process as well as to better understand the pathology and improve medical technologies.^[16] Instruments to assess wound healing can help to enhance communication among clinicians by defining a common language and standardizing assessment of wound characteristics.^[15]

Because healing is a dynamic process, it is difficult to evaluate and requires consistent measurements.^[17] A complete assessment of the wound must include the size, associated attributes, host factors and environmental factors, all of which impact optimal wound management.^[17] In addition, demographics and quality of care also provided aid in assessing the repair process.^[17]

Various tools for assessing wound healing clinically have been described, including the Pressure Ulcer Score for Healing (PUSH), the Sussman Wound Healing Tool (SWHT), the Wound Healing Scale, the Leg Ulcer Measurement Tool (LUMT) and the granulometer.^[18] However, these instruments can only measure changes in wound healing and do not predict healing or measure wound characteristics.^[18] Additional tools to assess the status of the healing wound include Laser-Doppler Flowmetry (LDF) to evaluate cutaneous blood flow and planimetry.^[19]

The assessment of the histological state of the healing wound is important in clinical practice for postoperative patient management.^[20] Histological evaluation should include the basic components of the healing process including angiogenesis, inflammation, fibroplasia and restoration of the connective tissue matrix, wound contraction and remodeling, epithelialization and differentiation.^[17]

Comparison of histologic patterns with the known physiologic variation in tissue morphology assists in

qualitative derivation of the diagnosis. The degree of changes observed when scored on an ordinal scale, namely, low, medium or high grade, provides a semi-quantitative score. On the other hand, the exact quantitative measurement in terms of the absolute number of cells and areas of tissue gives a quantitative score.^[21] A quantitative scoring system, while being highly specific and standardized, is difficult to score because in most cases it is difficult to objectify the exact interval between two values.^[21] Hence, semi-quantitative scoring systems remain in wide use in the world of the biomedical research.

Various studies have been conducted, and wound healing models have been proposed to understand the normal healing process and to standardize the semi-quantitative and quantitative evaluation of selected parameters of wound healing. In a study assessing wound healing in the maxillofacial region, Sultana *et al.*^[20] utilized scoring of 6 histological parameters to give a healing score [Table 2]. The total healing score in each case was calculated by adding the scores of individual criteria, with lower scores indicating poorer wound healing. Healing status was graded as good (16-19), fair (12-15) and poor (8-11). Using this healing score, Sultana *et al.*^[20] concluded that risk factors in the study group were correlated with delayed wound healing in comparison to the control group.

While studying the overall process of wound healing, Braiman-Wiksman *et al.*^[7] evaluated the role of multiple processes involving the skin components including the epidermis, dermis, hypodermic, blood vessel and connective tissue [Table 3]. They stressed an objective assessment and quantification of wound healing. Using a quantitative assessment method, the authors provide insight into the specific defects found at various stages, which involve a variety of cells and pathways in the process of wound healing.

In their experimental model of open-skin wound healing in corticosteroid-treated and diabetic rats, Gal *et al.*^[22] used both semi-quantitative and quantitative methods in a time- and stage-bound assessment of wound healing [Table 4]. Consistent with previous studies,^[22,23] they concluded that there is only a quantitative difference between primary and secondary wound healing. In contrast to the quantitative method, the semi-quantitative scoring system can evaluate keratinization, suggesting that keratinocyte differentiation is important in wound healing. Hence, a quantitative assessment alone is not sufficient to demonstrate significant differences in skin wound healing.

Lemo *et al.*^[21] provided a mathematical model for healing and a remodeling index in experimental skin wounds. The mathematical model involves measurement of five specific parameters [Table 5], based on which three indices can be determined: the superficial contraction index (SCI), the deep contraction index (DCI) and the wound contraction index (WCI). These indices, however, measure only the contraction of the wound, which represents the initial stage of healing. To assess the mid- and long-term healing process, Lemo *et al.*^[21] provide the global healing index (GHI), given

Table 2: Parameters assessed to calculate healing score

Number	Histological Parameter
1	Amount of granulation tissue (profound-1, moderate-2, scanty-3, absent-4)
2	Inflammatory infiltrate (plenty-1, moderate-2, a few-3)
3	Collagen fiber orientation (vertical-1, mixed-2, horizontal-3)
4	Pattern of collagen (reticular-1, mixed-2, fascicle-3)
5	Amount of early collagen (profound-1, moderate-2, minimal-3, absent-4)
6	Amount of mature collagen (profound-1, moderate-2, minimal-3)

Number 1-4: H and E, Number 5-6: Masson's trichrome stain, old collagen fibers take deep blue color and the new collagen fibers stain light blue

Table 3: Histological skin cell parameters for the assessment of wound healing

Healing parameter	Assessment parameter
Epidermal closure	Basal layer of the epidermis to assess the newly formed epidermis
Epidermal differentiation	Spinous epidermal differentiation (early) Granular epidermal differentiation (late)
Epidermal migration	Migrating cells
Granulation tissue formation and Epidermal hyperplasia	Proliferating cells
Granulation tissue and matrix formation	Collagen fiber deposition
Inflammation dermal closure	White blood cells abscesses matrix remodeling
Late stage of matrix remodeling	Elastin fiber deposition

Table 4: Parameters of histologic assessment of wound

Semi-quantitative method	Quantitative method
Wound reepithelialization: migration of keratinocytes, bridging of cells, keratinization	Polymorphonuclear leucocytes/ tissue macrophages ratio
Inflammatory cells: absence/ presence (mild/moderate/marked)	Percentage of reepithelialization
Fibroblasts: absence/presence (mild/moderate/marked)	Area of the granulation tissue
New vessels: absence/presence (mild/moderate/marked)	-
Collagen: absence/presence (mild/moderate/marked)	-

Table 5: Parameters measured in the mathematical model

Length of the reepithelialization zone (L)
Distance between the borders of the wound (S)
Depth of the wound (D)
Thickness of the connective tissue (T)
Thickness of the natural dermis on both sides of the wound (N)

by the formula $GHI = SCI + DCI - WCI$. This index allows scoring of the healing process and follow-up of its progress.

Tascilar *et al.*^[24] used Abramov's histologic scoring system to demonstrate the effectiveness of N-acetyl cysteine administration in alleviation of the negative effects of radiotherapy on incisional wound healing. Abramov's histologic scoring system encompasses a semi-quantitative

scoring of acute and chronic inflammation, the amount of granulation tissue, the level of fibroblast maturation, the amount of collagen deposition and the level of reepithelialization and neovascularization.^[25]

Ancillary techniques such as special stains and immunohistochemistry in addition to light microscopic examination can help in the accurate assessment of the components of a healing wound. For instance, Masson's trichrome staining is used to demonstrate the presence of collagen in the healing wound.^[26,27] In addition, various immunohistochemical markers have been used to demonstrate the components of the healing wound, such as antiloricrin for epithelial differentiation,^[26] CD31 for angiogenesis^[28] and antibodies against cytokine ligands and receptors.^[29] Some authors have studied apoptosis using Annexin V-FITC binding assay^[30] and TUNEL Assay.^[26]

Histopathology has always been the gold standard in diagnosing certain infectious, degenerative or neoplastic diseases in humans and animals.^[21] The number of studies performed to provide a standardized system for histological evaluation of the wound demonstrates the importance of histopathology. Careful assessment of chronic wounds can shed light on the exact pathology and assist in developing a strategy for further management. It can also be a powerful tool in the evaluation of the effect of novel drugs on wound healing.^[19] Histopathology also provides information on the usefulness of combination therapy and determining effective drug dosage in order to minimize adverse effects.

There are numerous scoring systems provided by various pioneers in the field. However, the need for uniformity persists. Although the selection of parameters in most scoring systems is generally based on a basic knowledge of the wound healing, the parameters chosen in an experimental model should be defined by the scientific question, the underlying hypothesis and the pathogenesis of the disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Int Med Res* 2009;37:1528-42.
- Kumar V, Abbas AK, Fausto N, Aster JC. Inflammation and repair. Robbins and Cotran Pathologic Basis of Disease. 9th ed. Philadelphia: Elsevier Saunders; 2014. p. 69-110.
- Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res* 2010;89:219-29.
- Gosain A, DiPietro LA. Aging and wound healing. *World J Surg* 2004;28:321-6.
- Broughton G 2nd, Janis JE, Attinger CE. The basic science of wound healing. *Plast Reconstr Surg* 2006;117:S12-34.
- Campos AC, Groth AK, Branco AB. Assessment and nutritional aspects of wound healing. *Curr Opin Clin Nutr Metab Care* 2008;11:281-8.
- Braiman-Wiksmann L, Solomonik I, Spira R, Tennenbaum T. Novel insights into wound healing sequence of events. *Toxicol Pathol* 2007;35:767-79.
- Diegelmann RF, Evans MC. Wound healing: an overview of acute, fibrotic and delayed healing. *Front Biosci* 2004;9:283-9.
- Wu Y, Wang J, Scott PG, Tredget EE. Bone marrow-derived stem cells in wound healing: a review. *Wound Repair Regen* 2007;15 Suppl 1:S18-26.
- Rea S, Giles NL, Webb S, Adcroft KF, Evill LM, Strickland DH, Wood FM, Fear MW. Bone marrow-derived cells in the healing burn wound-more than just inflammation. *Burns* 2009;35:356-64.
- Hackam DJ, Ford HR. Cellular, biochemical, and clinical aspects of wound healing. *Surg Infect (Larchmt)* 2002;3 Suppl 1:S23-35.
- Gabbiani G. The myofibroblast in wound healing and fibrocontractive diseases. *J Pathol* 2003;200:500-3.
- Baum CL, Arpey CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. *Dermatol Surg* 2005;31:674-86.
- Gohel MS, Taylor M, Earnshaw JJ, Heather BP, Poskitt KR, Whyman MR. Risk factors for delayed healing and recurrence of chronic venous leg ulcers-an analysis of 1324 legs. *Eur J Vasc Endovasc Surg* 2005;29:74-7.
- Mullins M, Thomason SS, Legro M. Monitoring pressure ulcer healing in persons with disabilities. *Rehabil Nurs* 2005;30:92-9.
- Motlik J, Klíma J, Dvoránková B, Smetana K Jr. Porcine epidermal stem cells as a biomedical model for wound healing and normal/malignant epithelial cell propagation. *Theriogenology* 2007;67:105-11.
- Lazarus GS, Cooper DM, Knighton DR, Percoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. *Wound Repair Regen* 1994;2:165-70.
- Pillen H, Miller M, Thomas J, Puckridge P, Sandison S, Spark JL. Assessment of wound healing: validity, reliability and sensitivity of available instruments. *Wound Pract Res* 2009;17:208-17.
- Karayannopoulou M, Tsioli V, Loukopoulou P, Anagnostou TL, Giannakas N, Savvas I, Papazoglou LG, Kaldrymidou E. Evaluation of the effectiveness of an ointment based on Alkannins/Shikonins on second intention wound healing in the dog. *Can J Vet Res* 2011;75:42-8.
- Sultana J, Molla MR, Kamal M, Shahidullah M, Begum F, Bashar MA. Histological differences in wound healing in maxillofacial region in patients with or without risk factors. *Bangladesh J Pathol* 2009;24:3-8.
- Lemo N, Marignac G, Reyes-Gomez E, Lilin T, Crosas O, Ehrenfest DM. Cutaneous reepithelialization and wound contraction after skin biopsies in rabbits: a mathematical model for healing and remodelling index. *Vet Arh* 2010;80:637-52.
- Gal P, Kilik R, Mokry M, Vidinsky B, Vasilenko T, Mozes S, Lenhardt L. Simple method of open skin wound healing model in corticosteroid-treated and diabetic rats: standardization of semi-quantitative and quantitative histological assessments. *Vet Med* 2008;53:652-9.
- Barbul A, Regan MC. Biology of wound healing. In: Fischer JA, editor. Surgical Basic Science. St. Louis: Mosby Year-Book; 1993. p. 68-88.
- Tascilar O, Cakmak G, Emre A, Bakkal H, Kandemir N, Turkcu U, Demir E. N-acetylcysteine attenuates the deleterious effects of radiation therapy on incisional wound healing in rats. *Hippokratia* 2014;18:17-23.
- Abramov Y, Golden B, Sullivan M, Botros SM, Miller JJ, Alshahrour A, Goldberg RP, Sand PK. Histologic characterization of vaginal vs. abdominal surgical wound healing in a rabbit model. *Wound Repair Regen* 2007;15:80-6.
- Lee YH, Chang JJ, Chien CT, Yang MC, Chien HF. Antioxidant sol-gel improves cutaneous wound healing in streptozotocin-induced diabetic rats. *Exp Diabetes Res* 2012;2012:504693.
- Piskin A, Altunkaynak BZ, Tümentemur G, Kaplan S, Yazici OB, Hökelek M. The beneficial effects of *Momordica charantia* (bitter melon) on wound healing of rabbit skin. *J Dermatolog Treat* 2014;25:350-7.
- Huang SP, Huang CH, Shyu JF, Lee HS, Chen SG, Chan JY, Huang SM. Promotion of wound healing using adipose-derived stem cells in radiation ulcer of a rat model. *J Biomed Sci* 2013;20:51.
- Zheng Z, Lee KS, Zhang X, Nguyen C, Hsu C, Wang JZ, Rackohn TM, Enjamuri DR, Murphy M, Ting K, Soo C. Fibromodulin-deficiency alters temporospatial expression patterns of transforming growth factor- β ligands and receptors during adult mouse skin wound healing. *PLoS One* 2014;9:e90817.
- Kim SV, Zhang HZ, Guo L, Kim JM, Kim MH. Amniotic mesenchymal stem cells enhance wound healing in diabetic NOD/SCID mice through high angiogenic and engraftment capabilities. *PLoS One* 2012;7:e41105.

Role of angiogenesis and angiogenic factors in acute and chronic wound healing

Thittamaranahalli Muguregowda Honnegowda¹, Pramod Kumar^{1,2},
Echallasara Govindarama Padmanabha Udupa³, Sudesh Kumar⁴, Udaya Kumar⁴, Pragna Rao³

¹Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India.

²Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

³Department of Biochemistry, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁴Department of Surgery, District Government Hospital, Udupi 576108, Karnataka, India.

Address for correspondence: Dr. Pramod Kumar, Department of Plastic Surgery and Burns, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia. E-mail: pkumar86@hotmail.com

ABSTRACT

Angiogenesis plays a crucial role in wound healing by forming new blood vessels from preexisting vessels by invading the wound clot and organizing into a microvascular network throughout the granulation tissue. This dynamic process is highly regulated by signals from both serum and the surrounding extracellular matrix environment. Vascular endothelial growth factor, angiopoietin, fibroblast growth factor and transforming growth factor-beta are among the potent angiogenic cytokines in wound angiogenesis. Specific endothelial cell ECM receptors are critical for morphogenetic changes in blood vessels during wound repair. In particular integrin ($\alpha v \beta 3$) receptors for fibrin and fibronectin, appear to be required for wound angiogenesis: $\alpha v \beta 3$ is focally expressed at the tips of angiogenic capillary sprouts invading the wound clot, and any functional inhibitors of $\alpha v \beta 3$ such as monoclonal antibodies, cyclic RGD peptide antagonists, and peptidomimetics rapidly inhibit granulation tissue formation. In spite of clear knowledge about influence of many angiogenic factors on wound healing, little progress has been made in defining the source of these factors, the regulatory events involved in wound angiogenesis and in the clinical use of angiogenic stimulants to promote repair.

Key words:

Angiogenic factors, endothelium, extracellular matrix protein, granulation tissue, wound healing

INTRODUCTION

Neovascularization or angiogenesis is important for wound healing as it involves the growth of new capillaries to form granulation tissue.^[1-4] Three to five days after tissue injury, new capillaries become visible in the wound bed as granulation tissue, which acts as a matrix for proliferating blood vessels, migrating fibroblasts and new collagen.^[5] Impaired granulation is a hallmark of chronic wounds encountered with diabetes and venous or arterial insufficiency.

In 1960s, research began in the field of angiogenesis to determine how new blood vessels enhance solid tumor growth.^[6] Physiologists later discovered that neovascularization occurs during tissue regeneration.^[7] Proliferating capillaries bring oxygen and micronutrients to growing tissues and remove catabolic waste products. These vessels are present in the endothelium that secretes paracrine factors to promote survival of adjacent cells by preventing apoptosis or programmed cell death.^[8] Because

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Honnegowda TM, Kumar P, Udupa EG, Kumar S, Kumar U, Rao P. Role of angiogenesis and angiogenic factors in acute and chronic wound healing. *Plast Aesthet Res* 2015;2:243-9.

Received: 20-10-2014; **Accepted:** 28-01-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165438

angiogenesis is required for wound healing, its induction is beneficial in many clinical situations for achieving wound closure.^[9]

PHYSIOLOGICAL CONTROL OF ANGIOGENESIS

Angiogenesis plays a critical role in wound healing. By developing capillary sprouts, which digest endothelial cells and invade the extracellular matrix (ECM) stroma after penetrating through the underlying vascular basement membrane (VBM), and form tube-like structures that continue to extend, branch, and form networks. During angiogenesis capillary advancement in ECM occurs by endothelial cell proliferation and direction of growth is guided by chemotaxis from the target region. The interaction among endothelial cells, angiogenesis factors and surrounding ECM proteins is temporally and spatially synchronized.^[9,10]

Angiogenesis can be induced in response to injury via pro- and anti-angiogenic factors present throughout the body. Pro-angiogenic factors consist of thrombin, fibrinogen fragments, thymosin- β 4 and growth factors. Angiogenic growth factors are stored in platelets and inflammatory cells that circulate in the bloodstream, and are sequestered within the ECM. The production of these factors is regulated by genes expressed in response to hypoxia and inflammation, such as hypoxia-inducible factors (HIF) and cyclooxygenase-2 (COX-2).^[11-13] In contrast, angiogenesis inhibitor factors suppress blood vessel growth.^[14,15] Some inhibitors circulate in the blood stream at low physiological levels while others are stored in the ECM surrounding blood vessels. Vascular growth is suppressed when there is a physiological balance between angiogenesis stimulators and inhibitors.^[15] Immediately following injury, however, angiogenic stimuli are released into the wound bed, and a shift occurs in regulators favoring vascular growth [Figure 1].

THE ANGIOGENESIS CASCADE

Angiogenesis occurs as an orderly cascade of molecular and cellular events in the wound bed:

1. Endothelial cell surface has receptors to which angiogenic growth factors bind in preexisting venules (parent vessels);
2. Growth factor-receptor binding activates signaling pathways within endothelial cells;

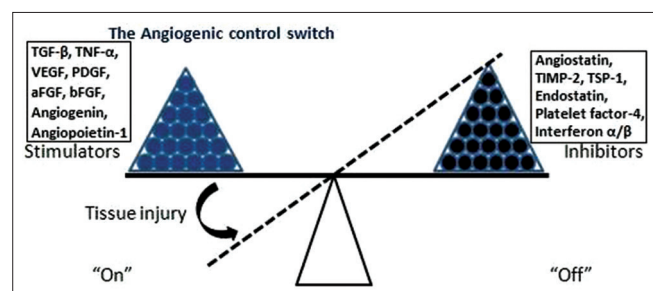


Figure 1: Angiogenesis is a balance between stimulators (growth factors) and inhibitors as shown in this model

3. Proteolytic enzymes released by activated endothelial cells dissolve the basement membrane of surrounding parent vessels;
4. Endothelial cells proliferate and sprout outward through the basement membrane;
5. Endothelial cells migrate into the wound bed using integrins ($\alpha\beta$ 3, $\alpha\beta$ 5 and $\alpha\beta$ 1) which are cell surface adhesion molecules;
6. Matrix metalloproteinases (MMPs) dissolve the surrounding tissue matrix in the path of sprouting vessels;
7. Vascular sprouts form tubular channels that connect to form vascular loops;
8. Vascular loops differentiate into afferent (arterial) and efferent (venous) limbs;
9. New blood vessels mature by recruiting mural cells (smooth muscle cells and pericytes) to stabilize the vascular architecture;
10. Blood flow begins in the mature stable vessel.

These complex growth factor-receptor, cell-cell and cell-matrix interactions characterize the angiogenesis process, regardless of the stimuli or its location in the body.

THE ANGIOGENESIS MODEL OF WOUND HEALING

Wound healing occurs in four major overlapping stages: (1) hemostatic, (2) inflammatory stage, (3) proliferative stage, and (4) remodeling stage. Although granulation is assigned to the proliferative stage, angiogenesis is initiated immediately after tissue injury and is mediated throughout the wound healing process.

Step 1: Angiogenesis initiation

Basic fibroblast growth factor (bFGF) stored within intact cells and the ECM is released from damaged tissue.^[16] Bleeding and hemostasis in a wound also initiate angiogenesis. Cellular receptors for vascular endothelial growth factor (VEGF) are upregulated by thrombin in the wound.^[17] Endothelial cells exposed to thrombin also release gelatinase A (MMP-2), which promotes the local dissolution of basement membrane, a necessary early step of angiogenesis.^[18] Platelets release multiple growth factors, including platelet-derived growth factor (PDGF), VEGF, transforming growth factor (TGF- α , TGF- β), bFGF, platelet-derived endothelial cell growth factor and angiopoietin-1 (Ang-1). These factors stimulate endothelial proliferation, migration and tube formation.^[19-22]

Step 2: Angiogenesis amplification

Macrophages and monocytes release numerous angiogenic factors, including PDGF, VEGF, Ang-1, TGF- α , bFGF, interleukin-8 (IL-8) and tumor necrosis factor alpha into the wound bed during the inflammatory phase amplifying angiogenesis further.^[23,24] Several growth factors (PDGF, VEGF and bFGF) synergize in their ability to vascularize tissues.^[25] Proteases that break down damaged tissue matrix further release matrix-bound angiogenic stimulators. Enzymatic cleavage of fibrin yields fibrin fragment E, which stimulates angiogenesis directly and also enhances the

effects of VEGF and bFGF.^[26] Expression of the inducible COX-2 enzyme during the inflammatory stage of healing also leads to VEGF production and other promoters of angiogenesis.^[27]

Step 3: Vascular proliferation

Hypoxia is an important driving force for wound angiogenesis. Expression of gene HIF-1 α , due to hypoxic gradient between injured and healthy tissue triggers VEGF production.^[24,28] VEGF is present in both wound tissue and exudate.^[28,29] VEGF is also known as vascular permeability factor since it increases permeability of capillaries.^[30] Hypoxia also leads to endothelial cell production of nitric oxide (NO). NO promotes vasodilation and angiogenesis to improve local blood flow.^[31]

Step 4: Vascular stabilization

Vascular stabilization is governed by Ang-1, tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (Tie-2), smooth muscle cells and pericytes. Production of PDGF and recruitment of smooth muscle cells and pericytes to the newly forming vasculature are regulated by binding of Ang-1 to its receptor Tie-2 on activated endothelial cells.^[32-34] A PDGF deficiency leads to poorly-formed immature blood vessels.^[35]

Step 5: Angiogenesis suppression

Angiogenesis is suppressed at the terminal stages of healing.^[36] As tissue hypoxia is restored, and inflammation subsides, the level of growth factors decline in the wound. Pericytes which stabilize endothelial cells secrete an inhibitory form of activated TGF- β that impedes vascular proliferation.^[34,37,38] A cleavage product of collagen XVIII, endostatin, is present surrounding the VBM, and it inhibits wound vascularity.^[39,40]

WOUND ANGIOGENIC STIMULATORS AND INHIBITORS

A number of angiogenic stimulators have been identified in wound and others are likely to exist that play an important role in the repair [Table 1]. The stimulators in wound fluids are growth factors known to increase endothelial cell migration and proliferation *in vitro*.^[41]

The FGF comprises of 23 homologous structures that are small polypeptides with a central core containing

140 amino acids. Acidic FGF and bFGF are the first few to be discovered and are now designated as FGF-1 and FGF-2, respectively.^[42] Both are preferentially involved in the process of angiogenesis.^[43,44] These compounds are polypeptides of about 18 kDa, single chained and nonglycosylated. They transmit their signals through FGF receptor-4 (FGFR-4) high-affinity, protein family of transmembrane tyrosine kinases (FGFR-1 to FGFR-4), that bind to different FGFs with different affinities. The strong interactions of FGF-1 and FGF-2 with glycosaminoglycans, such as heparin sulfate present in the ECM,^[45] makes the FGFs stable against thermal, proteolytic denaturation and limits its diffusibility. Thus, the ECM acts as a reservoir for pro-angiogenic factors. Most members of the FGF family act as a broad spectrum mitogen that stimulates the proliferation of mesenchymal cells of mesodermal origin, as well as ectodermal and endodermal cells.

FGF-1 and FGF-2 are synthesized by a variety of cell types including inflammatory cells and dermal fibroblasts that are involved in angiogenesis and wound healing. When liberated from ECM, they act on the endothelial cells in a paracrine manner, or when released by endothelial cell they act in an autocrine manner promoting cell proliferation and differentiation. During the formation of granulation tissue, FGF-2 promotes cell migration through surface receptors for integrins, which mediate the binding of endothelial cells to ECM.^[44]

Vascular endothelial growth factor increase vaso-permeability by increasing the fenestration and hydraulic conductivity. This allows leakage of fibrinogen and fibronectin, which are essential for the formation of the provisional ECM.^[46-48] The ECM is produced in large quantities by the epidermis during wound healing.^[49] Low oxygen tension that occurs in tissue hypoxia is a major inducer of VEGF^[50] and its receptors.^[51] Thus, cell disruption and hypoxia appear to be strong initial inducers of potent angiogenesis factors at the wound site. VEGF family currently includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor.^[52] VEGF-A is a homodimer glycoprotein whose subunits are linked by 2 disulfide bonds. VEGF-A is synthesized from internal rearrangements (“alternative splicing”) of mRNA. Thus, there is the production of 7 isoforms with 121 to 206 amino acids.^[53-55] Among these, the VEGF121, VEGF165, VEGF189 and VEGF206 are the predominant isoforms.^[56] These isoforms show similar biological activities, but differ in their binding properties to heparin and ECM.^[57]

Vascular endothelial growth factor is a potent vascular endothelial cell-specific mitogen that stimulates endothelial cell proliferation, microvascular permeability and regulates of several endothelial integrin receptors during sprouting of new blood vessels.^[58] Furthermore, VEGF also acts as a survival factor for endothelial cells by inducing the expression of an anti-apoptotic protein B-cell lymphoma 2.^[59]

TGF- β stimulates the formation of granulation tissue by acting as a chemoattractant for neutrophils, macrophages and fibroblasts. Hence, TGF- β is an important modulator of angiogenesis during wound healing by regulating cell

Table 1: Angiogenic stimulators and inhibitors

Stimulators	Inhibitors
aFGF (FGF-1)	Thrombospondin-1
bFGF (FGF-2)	Tissue inhibitors of matrix metalloproteinases
TGF- α	Interferon alpha/beta/gamma
TGF- β	Angiostatin
PGE2	Endostatin
TNF- α	
VEGF	
EGF	

FGF: Fibroblast growth factor, aFGF: Acidic fibroblast growth factor, bFGF: Basic fibroblast growth factor, TGF- α : Transforming growth factor-alpha, TGF- β : Transforming growth factor-beta, VEGF: Vascular endothelial growth factor, EGF: Endothelial growth factor, PGE2: Prostaglandin E2

proliferation, migration, capillary tube formation and deposition of ECM.^[60,61]

The angiopoietins are members of the VEGF family, which is largely specific for vascular endothelium. They include a naturally occurring agonist, Ang-1, and antagonist, Ang-2, both of which act by means of the Tie-2 receptor. Two new angiopoietins, Ang-3 in mice and Ang-4 in humans, have been identified, but their function in angiogenesis is unknown.^[62]

Mast cell tryptase, stored in granules of activated mast cells, is an additional angiogenesis factor that directly degrades the ECM components or release matrix-bound growth factors by its proteolytic activity,^[63,64] and acts indirectly by activating latent matrix metalloproteases. The addition of tryptase to microvascular endothelial cells cultured on a basement membrane matrix (matrigel) caused a marked increase in capillary growth. Furthermore, tryptase can induce endothelial cell proliferation in a dose-dependent manner, whereas specific tryptase inhibitors suppress the capillary growth.^[65]

IMPAIRED ANGIOGENESIS IN CHRONIC WOUNDS

Angiogenesis is impaired in all chronic wounds leading to further tissue damage results from chronic hypoxia and impaired micronutrient delivery. Specific defects have been identified in diabetic ulcers, venous insufficiency ulcers and ischemic ulcers.

Diabetic ulcers

Patients with diabetes show abnormal angiogenesis in various organs. Vasculopathies associated with diabetes include abnormal blood vessel formation (e.g. retinopathy, nephropathy) and accelerated atherosclerosis leading to coronary artery disease, peripheral vascular disease, and cerebrovascular disease.^[65] However, in diabetics, angiogenesis is decreased^[66] resulting in poor formation of new blood vessels and thus decreased entry of inflammatory cells and their growth factors. Growth factors such as FGF-2 and PDGF, essential for wound healing have been found to be reduced in experimental diabetic wounds models.^[67-70] Furthermore, in rat models, topical administration of high glucose to wounds was shown to inhibit the normal angiogenic process,^[71] suggesting a direct role for high glucose levels in diminished angiogenesis.

Vascular endothelial growth factor plays an important role in vascular growth and has been shown to be deficient in diabetic wounds in experimental and clinical models.^[72] Studies have shown that modulation of oxidative damage^[73] or inhibition of the receptors for advanced glycation end products^[74] improve wound healing and were associated with the up-regulation of endogenous VEGF. Moreover, VEGF administration improves wound healing in nondiabetic ischemic wounds^[75] and blocking VEGF with neutralizing antibodies impedes tissue repair.^[76] These studies support the notion that VEGF is critical for repair in impaired healing states and that the addition of VEGF could have a potential clinical use.^[77] In fact,

Galiano *et al.*^[78] found that topical VEGF accelerates wound healing in a diabetic mouse model.

Weinheimer-Haus *et al.*^[79] found that low intensity vibration (LIV) applied vertically at 45 Hz with peak acceleration of 0.4 g for 30 min a day for 5 days a week starting on the day of injury in diabetic mice increases expression of pro-healing growth factors and chemokines (insulin-like growth factor-1, VEGF and monocyte chemotactic protein-1) in wound environment. Though there was no evidence of a change in the phenotype of CD11b+ macrophages, however, LIV resulted in trend toward a less inflammatory phenotype in the CD11b2 cells which comprised of fibroblasts, endothelial cells and/or keratinocytes. These findings indicate that LIV may exert beneficial effects on wound healing by enhancing angiogenesis and granulation tissue formation, and these changes are associated with an increase in pro-angiogenic growth factors.^[79]

Venous insufficiency ulcers

Venous insufficiency ulcers or venous stasis ulcers result from incompetent valves in lower extremity veins, leading to venous stasis and hypertension that makes the skin susceptible to ulceration. Pathological findings associated with venous stasis ulcers include microangiopathy, fibrin “cuffing” and trapping of leukocytes within the microvasculature.^[80,81]

Chronic venous stasis ulcer patients have elevated levels of VEGF in their circulation.^[82] This may explain the vascular permeability and increased transudation of serum fluid in their wounds. Biopsies of these ulcers reveal microvessels that are surrounded by fibrin cuffs composed of fibrin and plasma proteins, such as α -macroglobulin, thought to compromise gas exchange.^[83-85] Clinical studies have shown that transcutaneous oxygen tension may be up to 85% lower in venous stasis ulcers compared with normal skin regions.^[86] VEGF expression is up-regulated by hypoxia, which further exacerbates vascular permeability, formation of pericapillary fibrin cuffs and compromised gas exchange, which ultimately reduces growth factor availability in the wound.^[87,88] VEGF promotes the formation tortuous, aberrant glomeruloid-like vascular structures found in granulation tissue.^[89] Laboratory animals treated with VEGF form these glomeruloid vascular structures within 3 days and are characterized by poor perfusion.^[90] In venous ulcers, the persistence of glomeruloid vessels may interfere with oxygen delivery and delay healing. In chronic venous stasis ulcers, high levels of proteases such as neutrophil elastase, MMPs and urokinase-type plasminogen activator are present.^[91] Concomitantly, there are decreased levels of protease inhibitors, such as plasminogen activator inhibitor-2. Excessive protease activity may degrade the growth factors and destroy granulation tissue.

Ischemic ulcers

Peripheral arterial disease (PAD) may result in severe ischemia.^[92] Reduce tissue perfusion due to ischemia results in progressive tissue hypoxia, ischemia, necrosis and skin breakdown. In theory, tissue hypoxia should

initiate angiogenesis via inducing an HIF-1 α and angiogenic growth factors. In patients with PAD, serum levels of hepatocyte growth factor are elevated than in normal subjects.^[93] The tissue compromise caused by severe macrovascular disease, however, may over dominate the angiogenic response. Inter-individual differences in the ability to mount angiogenesis under hypoxic conditions also exist among patients with atherosclerosis. Such variations may explain that patients with PAD are unable to generate adequate collateral circulation and unable to heal arterial ulcers despite surgical bypass. Therapeutic growth factors or other methods designed to stimulate angiogenesis might benefit patients with a defective angiogenic capacity. VEGF gene transfer^[94] or autologous transplantation of bone marrow-derived endothelial progenitor stem cells^[95] improved healing of arterial ulcers in patients.

ANGIOMODULATORY STRATEGIES

Wound angiogenesis represents a realistic model to study molecular mechanisms involved in the formation and remodeling of vascular structures. In particular, the repair of skin defect offers an ideal model to analyze angiogenesis as it is easy to control and manipulate this process.^[96] Vessel growth is controlled by the local actions of chemical mediators, the ECM, metabolic gradients and physical forces. Manipulation of some of these factors is being tried to improve healing in experimental wounds.^[97] Scientists are working on mathematical models which describe the role of angiogenesis as observed during (soft tissue) wound healing. Through this model manipulation of the capillary tip, macrophage-derived chemical attractant profile, extracellular matrix and fibroblast diffusion coefficient may be analyzed to enhance wound healing.^[98]

CONCLUSION

Angiogenesis is a physiological process that is vital for normal wound healing. A number of factors regulate wound angiogenesis, including hypoxia, inflammation and growth factors. The molecular and cellular events in angiogenesis have been elucidated, and defects in this process are present in chronic wounds. Based on this knowledge, new wound healing strategies are emerging to deliver growth factors to the wound bed. Surgeons and other wound-care specialists can use this knowledge to identify defects and select interventions that may promote improved wound granulation and healing.

Financial support and sponsorship
Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Li WW, Li VW, Tsakayannis D. Angiogenesis therapies. Concepts, clinical trials, and considerations for new drug development. In: Fan TPD, Kohn EC, editors. *The New Angiotherapy*. Totowa: Humana Press; 2002. p. 547-71.
- Folkman J. Seminars in medicine of the Beth Israel hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med* 1995;333:1757-63.
- Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 2007;39:44-84.
- Rees M, Hague S, Oehler MK, Bicknell R. Regulation of endometrial angiogenesis. *Climacteric* 1999;2:52-8.
- Tonnesen MG, Feng X, Clark RA. Angiogenesis in wound healing. *J Invest Dermatol Symp Proc* 2000;5:40-6.
- Shah F, Balan P, Weinberg M, Reddy V, Neems R, Feinstein M, Dainauskas J, Meyer P, Goldin M, Feinstein SB. Contrast-enhanced ultrasound imaging of atherosclerotic carotid plaque neovascularization: a new surrogate marker of atherosclerosis? *Vasc Med* 2007;12:291-7.
- Folkman J. Angiogenesis. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson LJ, editors. *Harrison's Textbook of Internal Medicine*. 15th ed. New York: McGraw-Hill; 2001. p. 517-30.
- O'Connor DS, Schechner JS, Adida C, Mesri M, Rothermel AL, Li F, Nath AK, Pober JS, Altieri DC. Control of apoptosis during angiogenesis by survivin expression in endothelial cells. *Am J Pathol* 2000;156:393-8.
- Clark RA. Wound repair. Overview and general considerations. In: Clark RAF, editor. *The Molecular and Cellular Biology of Wound Repair*. New York: Plenum; 1996. p. 3-50.
- Morgan MR, Humphries MJ, Bass MD. Synergistic control of cell adhesion by integrins and syndecans. *Nat Rev Mol Cell Biol* 2007;8:957-69.
- Semenza G. Signal transduction to hypoxia-inducible factor 1. *Biochem Pharmacol* 2002;64:993-8.
- Majima M, Hayashi I, Muramatsu M, Katada J, Yamashina S, Katori M. Cyclo-oxygenase-2 enhances basic fibroblast growth factor-induced angiogenesis through induction of vascular endothelial growth factor in rat sponge implants. *Br J Pharmacol* 2000;130:641-9.
- Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. *Nat Med* 2003;9:677-84.
- Miles KA. Perfusion CT for the assessment of tumour vascularity: which protocol? *Br J Radiol* 2003;76:S36-42.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74.
- Matsuoka H, Sisson TH, Nishiuma T, Simon RH. Plasminogen-mediated activation and release of hepatocyte growth factor from extracellular matrix. *Am J Respir Cell Mol Biol* 2006;35:705-13.
- Tsopanoglou NE, Maragoudakis ME. On the mechanism of thrombin-induced angiogenesis. Potentiation of vascular endothelial growth factor activity on endothelial cells by up-regulation of its receptors. *J Biol Chem* 1999;274:23969-76.
- Nguyen M, Arkell J, Jackson CJ. Human endothelial gelatinases and angiogenesis. *Int J Biochem Cell Biol* 2001;33:960-70.
- Hellberg C, Ostman A, Heldin CH. PDGF and vessel maturation. *Recent Results Cancer Res* 2010;180:103-14.
- Pintucci G, Froum S, Pinnell J, Mignatti P, Rafii S, Green D. Trophic effects of platelets on cultured endothelial cells are mediated by platelet-associated fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF). *Thromb Haemost* 2002;88:834-42.
- Li JJ, Huang YQ, Basch R, Karparkin S. Thrombin induces the release of angiotensinogen from platelets. *Thromb Haemost* 2001;85:204-6.
- Nath SG, Raveendran R. An insight into the possibilities of fibroblast growth factor in periodontal regeneration. *J Indian Soc Periodontol* 2014;18:289-92.
- Yoshida S, Yoshida A, Matsui H, Takada Y, Ishibashi T. Involvement of macrophage chemotactic protein-1 and interleukin-1 β during inflammatory but not basic fibroblast growth factor-dependent neovascularization in the mouse cornea. *Lab Invest* 2003;83:927-38.
- Grimm D, Bauer J, Schoenberger J. Blockade of neoangiogenesis, a new and promising technique to control the growth of malignant tumors and their metastases. *Curr Vasc Pharmacol* 2009;7:347-57.
- Lutolf MP, Hubbell JA. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. *Nat Biotechnol* 2005;23:47-55.
- Boote-Wilbraham CA, Tazzyman S, Thompson WD, Stirk CM, Lewis CE. Fibrin fragment E stimulates the proliferation, migration and differentiation of human microvascular endothelial cells *in vitro*. *Angiogenesis* 2001;4:269-75.
- Ji K, Tsirka SE. Inflammation modulates expression of laminin in the central nervous system following ischemic injury. *J Neuroinflammation* 2012;9:159.
- Acker T, Plate KH. Role of hypoxia in tumor angiogenesis-molecular and cellular angiogenic crosstalk. *Cell Tissue Res* 2003;314:145-55.
- Howdieshell TR, Webb WL, Sathyanarayana, McNeil PL. Inhibition of

- inducible nitric oxide synthase results in reductions in wound vascular endothelial growth factor expression, granulation tissue formation, and local perfusion. *Surgery* 2003;133:528-37.
30. Leonardi R, Caltabiano M, Pagano M, Pezzuto V, Loreto C, Palestro G. Detection of vascular endothelial growth factor/vascular permeability factor in periapical lesions. *J Endod* 2003;29:180-3.
31. Smith RS Jr, Gao L, Bledsoe G, Chao L, Chao J. Intermedin is a new angiogenic growth factor. *Am J Physiol Heart Circ Physiol* 2009;297:H1040-7.
32. Inoki I, Shiomi T, Hashimoto G, Enomoto H, Nakamura H, Makino K, Ikeda E, Takata S, Kobayashi K, Okada Y. Connective tissue growth factor binds vascular endothelial growth factor (VEGF) and inhibits VEGF-induced angiogenesis. *FASEB J* 2002;16:219-21.
33. Ma J, Wang Q, Fei T, Han JD, Chen YG. MCP-1 mediates TGF-beta-induced angiogenesis by stimulating vascular smooth muscle cell migration. *Blood* 2007;109:987-94.
34. Korff T, Kimmina S, Martiny-Baron G, Augustin HG. Blood vessel maturation in a 3-dimensional spheroidal coculture model: direct contact with smooth muscle cells regulates endothelial cell quiescence and abrogates VEGF responsiveness. *FASEB J* 2001;15:447-57.
35. Onimaru M, Yonemitsu Y, Fujii T, Tani M, Nakano T, Nakagawa K, Kohno R, Hasegawa M, Nishikawa S, Sueishi K. VEGF-C regulates lymphangiogenesis and capillary stability by regulation of PDGF-B. *Am J Physiol Heart Circ Physiol* 2009;297:H1685-96.
36. Kumar I, Staton CA, Cross SS, Reed MW, Brown NJ. Angiogenesis, vascular endothelial growth factor and its receptors in human surgical wounds. *Br J Surg* 2009;96:1484-91.
37. Darland DC, D'Amore PA. TGF beta is required for the formation of capillary-like structures in three-dimensional cocultures of IOT1/2 and endothelial cells. *Angiogenesis* 2001;4:11-20.
38. McCarty MF, Bielenberg DR, Nilsson MB, Gershenwald JE, Barnhill RL, Ahearne P, Bucana CD, Fidler IJ. Epidermal hyperplasia overlying human melanoma correlates with tumour depth and angiogenesis. *Melanoma Res* 2003;13:379-87.
39. Michaels J 5th, Dobrynsky M, Galiano RD, Bhatt KA, Ashinoff R, Ceradini DJ, Gurtner GC. Topical vascular endothelial growth factor reverses delayed wound healing secondary to angiogenesis inhibitor administration. *Wound Repair Regen* 2005;13:506-12.
40. Lange-Asschenfeldt B, Velasco P, Streif M, Hawighorst T, Pike SE, Tosato G, Detmar M. The angiogenesis inhibitor vasostatin does not impair wound healing at tumor-inhibiting doses. *J Invest Dermatol* 2001;117:1036-41.
41. Van der Bilt JD, Borel Rinkes IH. Surgery and angiogenesis. *Biochim Biophys Acta* 2004;1654:95-104.
42. Hiromatsu Y, Toda S. Mast cells and angiogenesis. *Microsc Res Tech* 2003;60:64-9.
43. Ornitz DM, Itoh N. Fibroblast growth factors. *Genome Biol* 2001;2:REVIEWS3005.
44. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen* 2008;16:585-601.
45. Plum SM, Vu HA, Mercer B, Fogler WE, Fortier AH. Generation of a specific immunological response to FGF-2 does not affect wound healing or reproduction. *Immunopharmacol Immunotoxicol* 2004;26:29-41.
46. Nagy JA, Benjamin L, Zeng H, Dvorak AM, Dvorak HF. Vascular permeability, vascular hyperpermeability and angiogenesis. *Angiogenesis* 2008;11:109-19.
47. Breier G, Blum S, Peli J, Groot M, Wild C, Risau W, Reichmann E. Transforming growth factor-beta and Ras regulate the VEGF/VEGF-receptor system during tumor angiogenesis. *Int J Cancer* 2002;97:142-8.
48. Bates DO, Heald RI, Curry FE, Williams B. Vascular endothelial growth factor increases Rana vascular permeability and compliance by different signalling pathways. *J Physiol* 2001;533:263-72.
49. Failla CM, Odorisio T, Cianfarani F, Schietroma C, Puddu P, Zambruno G. Placenta growth factor is induced in human keratinocytes during wound healing. *J Invest Dermatol* 2000;115:388-95.
50. Hemmerlein B, Kugler A, Ozisik R, Ringert RH, Radzun HJ, Thelen P. Vascular endothelial growth factor expression, angiogenesis, and necrosis in renal cell carcinomas. *Virchows Arch* 2001;439:645-52.
51. Zachary I, Gliki G. Signaling transduction mechanisms mediating biological actions of the vascular endothelial growth factor family. *Cardiovasc Res* 2001;49:568-81.
52. Efron PA, Moldawer LL. Cytokines and wound healing: the role of cytokine and anticytokine therapy in the repair response. *J Burn Care Rehabil* 2004;25:149-60.
53. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003;9:669-76.
54. Bates DO, Harper SJ. Regulation of vascular permeability by vascular endothelial growth factors. *Vascul Pharmacol* 2002;39:225-37.
55. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004;25:S81-611.
56. Kessler T, Fehrmann F, Bieker R, Berdel WE, Mesters RM. Vascular endothelial growth factor and its receptor as drug targets in hematological malignancies. *Curr Drug Targets* 2007;8:257-68.
57. Roth D, Piekarek M, Paulsson M, Christ H, Bloch W, Krieg T, Davidson JM, Eming SA. Plasmin modulates vascular endothelial growth factor-A-mediated angiogenesis during wound repair. *Am J Pathol* 2006;168:670-84.
58. Primo L, Seano G, Roca C, Maione F, Gagliardi PA, Sessa R, Martinelli M, Giraudo E, di Blasio L, Bussolino F. Increased expression of alpha6 integrin in endothelial cells unveils a proangiogenic role for basement membrane. *Cancer Res* 2010;70:5759-69.
59. Rao X, Zhong J, Zhang S, Zhang Y, Yu Q, Yang P, Wang MH, Fulton DJ, Shi H, Dong Z, Wang D, Wang CY. Loss of methyl-CpG-binding domain protein 2 enhances endothelial angiogenesis and protects mice against hind-limb ischemic injury. *Circulation* 2011;123:2964-74.
60. Brunner G, Blakytyn R. Extracellular regulation of TGF-beta activity in wound repair: growth factor latency as a sensor mechanism for injury. *Thromb Haemost* 2004;92:253-61.
61. Verrecchia F, Mauviel A. Transforming growth factor-beta and fibrosis. *World J Gastroenterol* 2007;13:3056-62.
62. Tsigkos S, Koutsilieris M, Papapetropoulos A. Angiopoietins in angiogenesis and beyond. *Expert Opin Investig Drugs* 2003;12:933-41.
63. Solovyan VT, Keski-Oja J. Apoptosis of human endothelial cells is accompanied by proteolytic processing of latent TGF-beta binding proteins and activation of TGF-beta. *Cell Death Differ* 2005;12:815-26.
64. Iddamalga A, Le QT, Ito K, Tanaka K, Kojima H, Kido H. Mast cell tryptase and photoaging: possible involvement in the degradation of extra cellular matrix and basement membrane proteins. *Arch Dermatol Res* 2008;300 Suppl 1:S69-76.
65. Martin A, Komada MR, Sane DC. Abnormal angiogenesis in diabetes mellitus. *Med Res Rev* 2003;23:117-45.
66. Brem H, Jacobs T, Vileikyte L, Weinberger S, Gibber M, Gill K, Tarnovskaya A, Entero H, Boulton AJ. Wound-healing protocols for diabetic foot and pressure ulcers. *Surg Technol Int* 2003;11:85-92.
67. Keswani SG, Katz AB, Lim FY, Zoltick P, Radu A, Alaaee D, Herlyn M, Crombleholme TM. Adenoviral mediated gene transfer of PDGF-B enhances wound healing in type I and type II diabetic wounds. *Wound Repair Regen* 2004;12:497-504.
68. Altavilla D, Saitta A, Cucinotta D, Galeano M, Deodato B, Colonna M, Torre V, Russo G, Sardella A, Urna G, Campo GM, Cavallari V, Squadrito G, Squadrito F. Inhibition of lipid peroxidation restores impaired vascular endothelial growth factor expression and stimulates wound healing and angiogenesis in the genetically diabetic mouse. *Diabetes* 2001;50:667-74.
69. Wicke C, Halliday B, Allen D, Roche NS, Scheuenstuhl H, Spencer MM, Roberts AB, Hunt TK. Effects of steroids and retinoids on wound healing. *Arch Surg* 2000;135:1265-70.
70. Peplow PV, Baxter GD. Gene expression and release of growth factors during delayed wound healing: a review of studies in diabetic animals and possible combined laser phototherapy and growth factor treatment to enhance healing. *Photomed Laser Surg* 2012;30:617-36.
71. Stavrou D. Neovascularisation in wound healing. *J Wound Care* 2008;17:298-300, 2.
72. Johnson KE, Wilgus TA. Vascular endothelial growth factor and angiogenesis in the regulation of cutaneous wound repair. *Adv Wound Care (New Rochelle)* 2014;3:647-61.
73. Hoffman M, Monroe DM. Wound healing in haemophilia-breaking the vicious cycle. *Haemophilia* 2010;16 Suppl 3:13-8.
74. Goova MT, Li J, Kislinger T, Qu W, Lu Y, Bucciarelli LG, Nowygrod S, Wolf BM, Caliste X, Yan SF, Stern DM, Schmidt AM. Blockade of receptor for advanced glycation end-products restores effective wound healing in diabetic mice. *Am J Pathol* 2001;159:513-25.
75. Corral CJ, Siddiqui A, Wu L, Farrell CL, Lyons D, Mustoe TA. Vascular endothelial growth factor is more important than basic fibroblastic growth factor during ischemic wound healing. *Arch Surg* 1999;134:200-5.
76. Howdieshell TR, Callaway D, Webb WL, Gaines MD, Procter CD Jr, Sathyanarayana, Pollock JS, Brock TL, McNeil PL. Antibody neutralization of vascular endothelial growth factor inhibits wound granulation tissue formation. *J Surg Res* 2001;96:173-82.
77. Lerman OZ, Galiano RD, Armour M, Levine JP, Gurtner GC. Cellular dysfunction in the diabetic fibroblast: impairment in migration, vascular

- endothelial growth factor production, and response to hypoxia. *Am J Pathol* 2003;162:303-12.
78. Galiano RD, Tepper OM, Pelo CR, Bhatt KA, Callaghan M, Bastidas N, Bunting S, Steinmetz HG, Gurtner GC. Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells. *Am J Pathol* 2004;164:1935-47.
 79. Weinheimer-Haus EM, Judex S, Ennis WJ, Koh TJ. Low-intensity vibration improves angiogenesis and wound healing in diabetic mice. *PLoS One* 2014;9:e91355.
 80. Franzeck UK, Haselbach P, Speiser D, Bollinger A. Microangiopathy of cutaneous blood and lymphatic capillaries in chronic venous insufficiency (CVI). *Yale J Biol Med* 1993;66:37-46.
 81. Jünger M, Steins A, Hahn M, Häfner HM. Microcirculatory dysfunction in chronic venous insufficiency (CVI). *Microcirculation* 2000;7:53-12.
 82. Shoab SS, Scurr JH, Coleridge-Smith PD. Plasma VEGF as a marker of therapy in patients with chronic venous disease treated with oral micronised flavonoid fraction-a pilot study. *Eur J Vasc Endovasc Surg* 1999;18:334-8.
 83. Oahues N, Philips TJ. Leg ulcers. *Curr Probl Dermatol* 1995;7:109-42.
 84. Moosa HH, Falanga V, Steed DL, Makaroun MS, Peitzman AB, Eaglstein WH, Webster MW. Oxygen diffusion in chronic venous ulceration. *J Cardiovasc Surg (Torino)* 1987;28:464-7.
 85. Falanga V, Moosa HH, Nemeth AJ, Alstadt SP, Eaglstein WH. Dermal pericapillary fibrin in venous disease and venous ulceration. *Arch Dermatol* 1987;123:620-3.
 86. Weckroth M, Vaheri A, Virolainen S, Saarialho-Kere U, Jahkola T, Sirén V. Epithelial tissue-type plasminogen activator expression, unlike that of urokinase, its receptor, and plasminogen activator inhibitor-1, is increased in chronic venous ulcers. *Br J Dermatol* 2004;151:1189-96.
 87. Higley HR, Ksander GA, Gerhardt CO, Falanga V. Extravasation of macromolecules and possible trapping of transforming growth factor-beta in venous ulceration. *Br J Dermatol* 1995;132:79-85.
 88. Trent JT, Falabella A, Eaglstein WH, Kirsner RS. Venous ulcers: pathophysiology and treatment options. *Ostomy Wound Manage* 2005;51:38-54.
 89. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* 2003;63:71-100.
 90. Sundberg C, Nagy JA, Brown LF, Feng D, Eckelhoefer IA, Manseau EJ, Dvorak AM, Dvorak HF. Glomeruloid microvascular proliferation follows adenoviral vascular permeability factor/vascular endothelial growth factor-164 gene delivery. *Am J Pathol* 2001;158:1145-60.
 91. McCarty SM, Cochrane CA, Clegg PD, Percival SL. The role of endogenous and exogenous enzymes in chronic wounds: a focus on the implications of aberrant levels of both host and bacterial proteases in wound healing. *Wound Repair Regen* 2012;20:125-36.
 92. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE Jr, Taylor LM. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996;94:3026-49.
 93. Konya H, Miuchi M, Satani K, Matsutani S, Tsunoda T, Yano Y, Katsuno T, Hamaguchi T, Miyagawa J, Namba M. Hepatocyte growth factor, a biomarker of macroangiopathy in diabetes mellitus. *World J Diabetes* 2014;5:678-88.
 94. Baumgartner I, Pieczek A, Manor O, Blair R, Kearney M, Walsh K, Isner JM. Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation* 1998;97:1114-23.
 95. Lawall H, Bramlage P, Amann B. Stem cell and progenitor cell therapy in peripheral artery disease. A critical appraisal. *Thromb Haemost* 2010;103:696-709.
 96. Eming SA, Brachvogel B, Odorisio T, Koch M. Regulation of angiogenesis: wound healing as a model. *Prog Histochem Cytochem* 2007;42:115-70.
 97. Bauer SM, Bauer RJ, Velazquez OC. Angiogenesis, vasculogenesis, and induction of healing in chronic wounds. *Vasc Endovascular Surg* 2005;39:293-306.
 98. Chaplain M, Anderson A. Mathematical modelling of tumour-induced angiogenesis: network growth and structure. *Cancer Treat Res* 2004;117:51-75.

Current concepts in the physiology of adult wound healing

Friji Meethale Thiruvoth, Devi Prasad Mohapatra, Dinesh Kumar Sivakumar, Ravi Kumar Chittoria, Vijayaraghavan Nandhagopal

Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India.

Address for correspondence: Dr. Friji Meethale Thiruvoth, Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India. E-mail: frijimt@gmail.com

ABSTRACT

Wound healing requires a complex interaction and coordination of different cells and molecules. Any alteration in these highly coordinated events can lead to either delayed or excessive healing. This review provides an overview of adult wound healing physiology. A review of the literature focused on wound healing physiology and current advances in wound healing was conducted using the online MEDLINE/PubMed database. The aim of this review was to inspire further investigation into wound healing physiology that will ultimately translate into improved patient care.

Key words:

Cytokine, growth factor, inflammation, wound healing

INTRODUCTION

Wound healing without complications is critical to the survival, as it restores the integrity of the skin and protects the individual from infection and dehydration. Adult wound healing involves a well-orchestrated series of events leading to the repair of injured tissues, resulting in scar formation. Healing of acute wounds, triggered by tissue injury, consists of overlapping and highly coordinated phases of hemostasis, inflammation, proliferation and remodeling. When a breach of the skin's integrity occurs, hemostasis is initiated by platelets through fibrin clot formation. Platelets also release various mediators of wound healing to attract macrophages and fibroblasts to the site of tissue injury.^[1] The inflammatory phase begins with the arrival of neutrophils followed later by macrophages and lymphocytes at the wound site. The proliferative phase is characterized by new blood vessel formation (angiogenesis), synthesis of extracellular matrix (ECM) components and re-epithelialization.^[2] Following the proliferative phase,

collagen remodeling begins, along with vascular maturity and regression; this process typically lasts 6-24 months from the time of injury^[1] [Figure 1].

The wound healing cascade may be arrested in any of these phases, leading to the formation of a chronic nonhealing wound. Many mediators including inflammatory cells, growth factors, proteases such as matrix metalloproteinases (MMPs) and cellular and extracellular elements play important roles in the process of wound healing. Alterations in one or more of these components may lead to the impaired healing.^[2] Wound healing can also be negatively influenced by many exogenous factors, including concurrent diseases, such as diabetes, renal failure, malnutrition, smoking, radiation exposure, infection and an immunocompromised state. In the presence of these factors, wounds can fail to heal adequately, resulting in chronic wound formation.^[3] The wound healing process can occasionally go into overdrive,

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Thiruvoth FM, Mohapatra DP, Sivakumar DK, Chittoria RK, Nandhagopal V. Current concepts in the physiology of adult wound healing. *Plast Aesthet Res* 2015;2:250-6.

Received: 12-01-2015; **Accepted:** 27-02-2015

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.158851

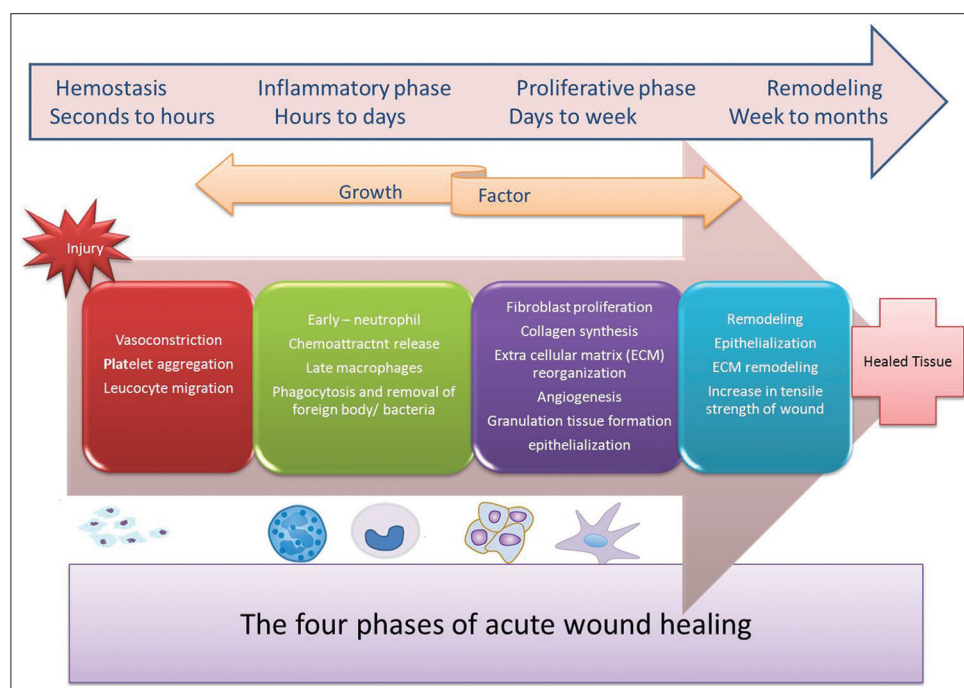


Figure 1: Distinct and overlapping phases of wound healing

resulting in excessive healing and the formation of fibroproliferative scar-like keloids and hypertrophic scars.^[4] This review provides a general overview of the physiology of adult wound healing, focusing specifically on how recent advances could translate into improved clinical outcomes.

HEMOSTASIS

Acute wounds cause vascular injury and bleeding from the wound, and the immediate priority is to prevent blood loss by vasoconstriction and formation of a blood clot to seal the vessel. Hemostasis is initiated by the exposure of blood components to the subendothelial layers of the vessel wall. Platelets adhere, aggregate and form the initial hemostatic plug. The coagulation and complement cascades are then initiated. Within the tissue, prothrombin is activated to form thrombin, which then cleaves fibrinogen to generate fibrin. Along with platelets and the plasma fibronectin, fibrin forms the clot.

The blood clot is made up primarily of cross-linked fibrin, cells such as erythrocytes and platelets, as well as other ECM proteins such as fibronectin, vitronectin and thrombospondin.^[5] In addition to containment of blood loss, the blood clot serves as a first defense against microbial invasion and a provisional matrix for the homing of inflammatory cells.^[5] The adhesiveness of platelets is mediated by activated integrin receptors on their surface.^[6,7] The platelets in the clot undergo degranulation, releasing potent chemoattractants for inflammatory cells, activation factors for local fibroblasts and endothelial cells and vasoconstrictors, such as chemokine (C-C motif) ligand 5 (CCL5), thrombin, transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).^[5] CCL5 is one of the most potent monocyte chemoattractants

released by platelets after injury. Thrombin, released by platelets at the wound site, is an early mediator of clot development.^[8] Thrombin also induces the release of pro-inflammatory cytokines like CCL2, interleukin-6 (IL-6) and IL-8 by endothelial cells. These cytokines induce monocyte chemotaxis.^[9] Of the injury response chemokines, chemokine (C-X-C motif) ligand 4 (CXCL4) participates in the coagulation process and prevents the premature development of blood vessels.^[10] The degradation of fibrin and subsequent activation of the complement system play a crucial role in mounting the inflammatory process, as well as in facilitating wound angiogenesis and stromal cell proliferation. Fibrin binds to integrin CD11b/CD18 on infiltrating monocytes and neutrophils. It also binds to fibroblast growth factor-2 (FGF-2) and VEGF that help the wound tissue vascularize. In addition, fibrin binds to insulin-like growth factor-1 (IGF-1) and promotes stromal cell proliferation.^[5,11,12] Under thrombocytopenic conditions, macrophages and T cells at the wound site compensate for the lack of PDGFs and initiation of the inflammatory phase.^[13]

INFLAMMATION

The inflammatory process involves the recruitment of neutrophils, macrophages, and lymphocytes. After hemostasis, local vessels dilate secondarily to the effects of the coagulation and complement cascades. Bradykinin (generated by the coagulation cascade) and C3a and C5a anaphylatoxins (generated by the complement cascade) increase blood vessel permeability and attract neutrophils and monocytes to the wound.^[14] The C3a and C5a anaphylatoxins also stimulate the release of histamine and leukotrienes from mast cells. The local endothelial cells then break cell-to-cell contact and increase permeability, enhancing the margination of inflammatory cells at the

wound site.^[15] The initial population of white blood cells in the wound is composed of neutrophils. Thrombin and IL-8 stimulate endothelial permeability through the modulations of adherens-junction endothelial cell adhesion and cell contraction, thereby facilitating leukocyte exit from the circulation.^[16,17] Within the wound, neutrophils employ various strategies to kill bacteria and decontaminate the wound, including the secretion of proteases and antimicrobial peptides, as well as the generation of reactive oxygen intermediates via the respiratory burst.^[18] In the absence of inflammatory mediators, neutrophils will undergo spontaneous apoptosis. The apoptosis is mediated by cathepsin D release from neutrophil granules, which then facilitates the cleavage and activation of caspase 8, ultimately resulting in caspase 3 activation, DNA fragmentation and apoptosis.^[19] In the absence of neutrophils, wound site macrophages lack guidance in conducting the healing process.^[20] Although neutrophils play a role in decreasing infection during wound healing, their absence does not prevent the overall progress of wound healing.^[21] However, their prolonged presence in the wound may be a factor in the conversion of acute wounds into nonhealing chronic wounds.

Within two to three days, monocytes become the predominant inflammatory cell population in the wound. Monocyte chemotaxis to the wound occurs via CC chemokines like CCL2. The chemokines can be released by neutrophils, by the monocytes themselves and by keratinocytes at different stages of healing.^[22-24] Circulating monocytes and mast cells are attracted to and infiltrate the wound site.^[1,25] Within the wound, monocytes differentiate into macrophages. Macrophages in turn remove apoptotic neutrophils and other dead cells, function as antigen-presenting cells, and secrete cytokines and multiple peptide growth factors.^[10] Phagocytosis of the apoptotic neutrophils by macrophages then leads to removal of chemokines from the area of inflammation, preventing further leukocyte influx.^[10] Several cytokines and growth factors are known to be secreted by macrophages.^[26] Such growth factors include TGF- β , TGF- α , basic FGF (bFGF), VEGF and PDGF. These growth factors activate and attract local endothelial cells, fibroblasts and keratinocytes, and enable wound healing by causing cell proliferation and synthesis of ECM and inducing angiogenesis VEGF,^[27-30] which stimulates angiogenesis, also stimulates the macrophages to express LIGHT, a member of the tumor necrosis factor alpha (TNF- α) family of cytokines, which binds to lymphotoxin- β receptor and induces macrophage death.^[31]

Macrophages play a crucial role in enabling wound healing. Macrophage depletion is known to markedly impair wound closure.^[27,32] In a landmark study, Leibovich and Ross^[33] demonstrated that the antimacrophage serum combined with hydrocortisone diminished the accumulation of macrophages in healing skin wounds of adult guinea pigs. Such depletion resulted in impaired disposal of damaged tissue and provisional matrix, compromised fibroblast count, and delayed healing. Inflammatory responses

elicited by injury are only helpful to the healing process if they are timely and transient. However, the inflammation is not essential for skin wound healing. Martin *et al.*^[34] has shown that the PU.1 null mouse, which is devoid of both macrophages and neutrophils, healed both incisional and excisional wounds at statistically similar rates to wild-type littermates, but without scar formation. The cytokine and growth-factor profiles at the wound site in the PU.1 null mouse differed from those of the wild-type. As a result, cell death was reduced, and scar formation did not occur.^[34] Studies have focused on platelets and mast cells as targets, and have shown that neither of these mediators is essential to effective wound repair. This further suggests that a dampened or modified inflammatory response could reduce scar formation.^[13,35] Impairment of macrophage function at the wound site derails the resolution of inflammation. A persistent inflammatory state of diabetic wound macrophages is caused by impairment in the ability of these cells to phagocytose apoptotic cells at the wound site, in turn preventing the switch from M1 to M2 phenotype.^[36] Prolonged inflammation may not only compromise wound closure but may also worsen scar outcomes.^[37,38] Lipid mediators, such as the lipoxins, resolvins, protectins and maresins, have emerged as a novel genus of potent and stereoselective players that counter regulate excessive acute inflammation and stimulate molecular and cellular events that define resolution.^[39] The production and activity of several proteases including metalloproteinase, serine proteases and neutrophil elastases which are tightly regulated in acute wound healing may be altered in chronic wounds.^[1] For example, non-healing human wound fluid and tissue have increased protease activity, which rapidly degrades exogenously applied peptide growth factors.^[40,41] Products targeting excessive protease activity such as protease-scavenging matrices (e.g. Promogran), selective inhibitors or specific antibodies may be useful in the treatment of chronic wounds refractory to conventional treatments.^[42,43]

The lymphocytes are the last type of leukocytes to arrive at the wound site. The lymphocytes exert a specific response against microbes and other foreign material in the wound: B-lymphocytes via antibodies and the T-lymphocytes through production of cytokines and stimulation of cytolytic activity. Lymphocyte-induced inflammation is then resolved by apoptosis when interferon (IFN)- γ and TNF- α are produced at the wound site.^[10] Mast cells also appear during the later part of the inflammatory phase, but their function remains unclear. Impaired wound healing has been reported in mast cell-deficient mice.^[44] Mast cells have also been implicated in skin wound fibrosis.^[45,46] Recently, the role of mast cells in wound healing has become an area of intense research because of a correlation between mast cells and both keloids and hypertrophic scars.^[45,46]

PROLIFERATION PHASE

The proliferative phase of wound healing is accepted to start around two days after injury and typically lasts up

to three weeks in a healing cutaneous wound. This phase overlaps with the inflammatory phase, beginning with the degradation of the initial fibrin-platelet matrix and invasion of fibroblasts and endothelial cells. Proteases of the serine, cysteine and MMP families are secreted to facilitate cellular migration through the fibrin clot and provisional matrix.^[47-50] The major events of this phase include the influx of fibroblasts, ECM deposition, formation of new blood vessels and re-epithelialization.

Fibroblasts are the key type of cells in this phase of healing and become the predominant cell type by three to five days after injury. Macrophages and mast cells release growth factors, including PDGF and TGF- β , that stimulate fibroblast activation.^[25] The fibroblasts proliferate and produce the matrix proteins fibronectin, hyaluronic acid, collagen and proteoglycans, all of which help to construct the new ECM and a platform for keratinocyte migration.^[1,14] The provisional fibrin matrix is gradually replaced by granulation tissue.

Granulation tissue is a dense conglomeration of blood vessels, macrophages and fibroblasts embedded within a loose matrix of fibronectin, hyaluronic acid and collagen. Granulation tissue begins to appear in human wounds by about four days after injury. During granulation tissue formation, new blood vessels develop from preexisting vessels (angiogenesis). Angiogenic factors are secreted by fibroblasts and macrophages (e.g. VEGF, basic FGF, angiopoietin1 and thrombospondin), keratinocytes (e.g. CXCL8 and VEGF) and endothelial cells themselves (e.g. CXCL8 and VEGF).^[51-54] Integrin $\alpha\text{v}\beta3$ at the leading capillary tip is a prerequisite for endothelial growth, and is a promising therapeutic target for angiogenesis.^[55] Blocking these processes with angiogenesis inhibitors impairs wound healing and can be corrected with growth factors such as VEGF.^[51] Over time, the fibrin provisional matrix is replaced with type III collagen, which in turn is replaced by the type I collagen during the remodeling phase. At least twenty-eight different types of collagen are currently known.^[56] Most collagen types in the ECM are synthesized by fibroblasts, however, some types are synthesized by keratinocytes.^[57]

Approximately four days after injury, myofibroblasts appear in the wound.^[58] TGF- β and CXCL8 promote the differentiation of fibroblasts in the granulation tissue into myofibroblasts.^[48,59,60] Myofibroblast differentiation also requires an interaction with cellular fibronectin containing the extra domain-A domain. Inhibition of either fibronectin or the corresponding integrin receptors prevents TGF- β 1-mediated myofibroblast differentiation.^[61,62] Myofibroblasts exert their contractile forces by focal adhesion contacts that link the intracellular cytoskeleton to the ECM. *In vitro* experiments have shown higher contractile forces of keratinocytes compared with fibroblasts.^[63]

Re-epithelialization is an important process during wound healing that starts in the early phase of healing. Platelets in the early wound release epidermal growth factor (EGF) and TGF- β stimulate the keratinocytes at the wound edge to proliferate and migrate to cover the wound. Cytokines

PDGF, TNF- α , FGF, keratinocyte growth factor and CXCL8 produced by neutrophils, macrophages, endothelial cells and fibroblasts, maintain the proliferation and migration of keratinocytes which in turn induces wound re-epithelialization.^[22,64-66] During re-epithelialization, the keratinocytes migrate beneath the provisional ECM. MMP release keratinocytes from their substratum and help in the migration through the matrix and promotion of re-epithelialization.^[67-69] Wound treatment with a broad-spectrum metalloproteinase inhibitor significantly delays re-epithelialization *in vitro* and *in vivo*.^[70,71] Wound re-epithelialization also requires the activity of various proteases, including the serine protease plasmin. Re-epithelialization is delayed in plasminogen-deficient mice, due to the inability of keratinocytes to degrade and thus migrate through the fibrin matrix and the underlying dermal tissue, whereas mice deficient in both plasminogen and fibrinogen exhibit more normal healing.^[72,73] After the re-establishment of the epithelial layer, keratinocytes and fibroblasts secrete type IV collagen to form the basement membrane.^[74] The keratinocytes undergo division and become columnar to restore the epidermal layer and reform a barrier to infection and moisture loss.

The dysregulation of the proliferative phase is believed to underlie the pathophysiology of chronic wound and fibrotic disorders such as hypertrophic scarring and keloids. A randomized controlled trial in patients with diabetic neuropathic foot ulcers showed topical PDGF to be superior to placebo in promoting healing.^[75] VEGF gene transfer was effective in increasing vascularity in ischemic leg ulcers.^[76] Among cytokines and growth factors, the possible targets for promotion of wound healing include TNF- α , PDGF, FGF, VEGF, IGF-1 and EGF.^[77-80] Understanding the signals for halting the proliferative phase will help developing new therapeutics for acute wound healing.^[51]

REMODELING PHASE

The remodeling of wound tissue occurs over a prolonged time and may last up to 1 year.^[51] It involves ECM turnover coupled with a significant decrease in cellularity. The decline in cellularity results from the apoptosis of residual inflammatory cells and myofibroblasts as well as regression of the neovasculature.^[59] In humans, remodeling is characterized by both wound contraction and collagen remodeling. The balance of collagen metabolism is in part determined by the regulation of MMP activity.^[81] The process of wound contraction is produced by wound myofibroblasts. While remodeling, wounds gradually become stronger with time. Wound tensile strength increases rapidly from 1 to 8 weeks after wounding and correlates with collagen cross-linking by lysyl oxidase.^[82] The tensile strength of wounded skin reaches at best only approximately 80% that of unwounded skin, but can be increased by synthetic MMP inhibitors.^[83,84] Scar formation is the final outcome of wound repair in children and adults.

New therapeutic strategies can be tried to reduce an esthetically unacceptable scar appearance. Treatment with TGF- β 3 formulations and neutralizing antibodies

to TGF- β as well as solutions that decrease the activity of connexin 43, a mediator of TGF- β signaling, has been shown to reduce the inflammatory response and scar formation.^[85,86] Evidence of success using TGF- β -related strategies was provided by a study showing that the exogenous addition to wounds of fibromodulin, a TGF- β modulator, reduces scar.^[87] Decorin is a small chondroitin/dermatan sulfate proteoglycan that limits the duration of TGF- β influence on inflammation and tissue repair, promoting regenerative repair and limiting tissue fibrosis.^[88] Other novel strategies include the application of antifibrotic human recombinant growth factors and cytokines, anti-inflammatory substances, protease inhibitors and molecules that interfere with profibrotic cytokine function (e.g. TGF- β) and collagen synthesis at the wound site.^[89]

FETAL WOUND HEALING

Fetal wound healing is an area of great interest because it is characterized by scar-less, regenerative wound healing. This process is age-dependent, like postnatal healing, wounds in third-trimester cause scarring.^[90] The exact mechanism responsible for scar-less healing in the first and second trimesters is not yet clearly understood. The proposed mechanisms include decreased inflammation, unique properties of fetal cells, altered cytokine milieu, variable gene expression and ECM deposition.^[91] Recent fields of research revolve around the role of TGF, IL-10 and mast cells. King *et al.*^[92] described a major role for IL-10 in scar-less wound healing. The authors propose a “cytokine hypothesis” centered on the anti-inflammatory properties of IL-10. IL-10 protects against excess deposition of collagen, maintains elevated hyaluronic levels, enhances fibroblast function, prevents differentiation of fibroblast to myofibroblasts and increases survival of endothelial progenitor cells and angiogenesis.^[92] Research in a mouse model demonstrated the scarring potential of mast cells in fetal wounds. In early fetal life (day 15), scar-less wounds were associated with a lesser number of mast cells with reduced degranulation as compared to later scarring wounds.^[93] Another factor implicated in fetal wound healing is the growth factor TGF- β . Of the three isoforms, TGF- β 1 is responsible for fibrosis. TGF- β 3 isoform is the predominant isotype in fetal wound healing, and altered profiling of the isoform may be a factor responsible for scarless healing. Other additional mechanisms include mediators of TGF pathway such as connective tissue growth factor, proteoglycan, decorin and P311.^[94]

ROLE OF STEM CELLS IN WOUND HEALING

Stem cells are a specialized group of cells with the potential for self-renewal, as well as the ability to differentiate into various cell lineages. Stem cells can be classified according to their origin (embryonic, fetal and adult) or based on the differentiation potential (totipotent, pluripotent, multipotent and unipotent).^[95] Due to the ease of

availability and fewer ethical issues, adult stem cells are the most commonly used type of stem cells in medical practice.

Mesenchymal stem cells are derived from bone marrow, adipose tissue, umbilical cord, periosteum, tendons, muscle and skin.^[96] The most commonly used source is adipose tissue. Stem cells affect all stages of wound healing. They have significant anti-inflammatory and immunomodulatory effects in the inflammation phase of healing.^[97] In the proliferative phase, they also stimulate fibroblasts, keratinocytes and endothelial cells, thereby accelerating wound closure. Uysal *et al.*^[98] demonstrated that wound healing time was reduced in rats treated by patchy skin grafts and mesenchymal stem cells. In addition, wound contraction was reduced, angiogenesis was increased, epithelialization progressed rapidly.^[99]

Stem cell therapy can be administered either topically or systemically. Falanga *et al.*^[100] demonstrated a topical application of mesenchymal stem cells with either fibrinogen or thrombin applied to chronic wounds in the form of a spray. This spray is converted into a gel form over the wound and helps in retaining the stem cells over the wound.^[100] To improve the retention of stem cells in the wound, cells are now applied on an adequate support/scaffold-like collagen, skin substitutes. This helps in maintaining the viability of the cells and facilitates migration in the wound bed.^[101]

CONCLUSION

Cutaneous wound healing is a complex and dynamic biological process requiring the interaction and coordination of many different cell types and molecules, including growth factors and cytokines. Tremendous strides have been made in delineating the myriad of factors involved in normal and delayed/excessive healing. However, this increased understanding has not led to significant advances in patient care. Administration of exogenous growth factors and cytokines has shown promise in improving healing results in wounds. As wound healing involves multiple molecular mechanisms, no single agent therapy is likely to be successful in accelerating or modulating wound healing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med* 1999;341:738-46.
2. Enoch S, Grey JE, Harding KG. Recent advances and emerging treatments. *BMJ* 2006;332:962-5.
3. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res* 2010;89:219-29.
4. Köse O, Waseem A. Keloids and hypertrophic scars: are they two different sides of the same coin? *Dermatol Surg* 2008;34:336-46.
5. Sen CK, Roy S. Wound healing. In: Rodriguez E, Losee J, Neligan PC, editors. *Plastic Surgery: Craniofacial, Head and Neck Surgery and Pediatric Plastic Surgery*. 3rd ed. Vol. 3. Philadelphia: Saunders; 2012. p. 240-66.

6. Bennett JS, Berger BW, Billings PC. The structure and function of platelet integrins. *J Thromb Haemost* 2009;7 Suppl 1:200-5.
7. Suzuki-Inoue K. Activation and inhibitory mechanisms of blood platelets. *Nihon Rinsho* 2014;72:1212-7.
8. He S, Blombäck M, Bark N, Johnsson H, Wallén NH. The direct thrombin inhibitors (argatroban, bivalirudin and lepirudin) and the indirect Xa-inhibitor (danaparoid) increase fibrin network porosity and thus facilitate fibrinolysis. *Thromb Haemost* 2010;103:1076-84.
9. Marin V, Montero-Julian FA, Grès S, Boulay V, Bongrand P, Farnarier C, Kaplanski G. The IL-6-soluble IL-6Ralpha autocrine loop of endothelial activation as an intermediate between acute and chronic inflammation: an experimental model involving thrombin. *J Immunol* 2001;167:3435-42.
10. Martins-Green M, Petreaca M, Wang L. Chemokines and their receptors are key players in the orchestra that regulates wound healing. *Adv Wound Care (New Rochelle)* 2013;2:327-47.
11. Sahni A, Odrlić T, Francis CW. Binding of basic fibroblast growth factor to fibrinogen and fibrin. *J Biol Chem* 1998;273:7554-9.
12. Tuan TL, Wu H, Huang EY, Chong SS, Laug W, Messadi D, Kelly P, Le A. Increased plasminogen activator inhibitor-1 in keloid fibroblasts may account for their elevated collagen accumulation in fibrin gel cultures. *Am J Pathol* 2003;162:1579-89.
13. Szpaderska AM, Egozi EI, Gamelli RL, DiPietro LA. The effect of thrombocytopenia on dermal wound healing. *J Invest Dermatol* 2003;120:1130-7.
14. Mirastschijski U, Jokuszies A, Vogt PM. Skin wound healing: repair biology, wound and scar treatment. In: Rodriguez E, Losee J, Neligan PC, editors. *Plastic Surgery: Craniofacial, Head and Neck Surgery and Pediatric Plastic Surgery*. 3rd ed. Vol. 3. Philadelphia: Elsevier; 2012. p. 268-96.
15. Roberts HR, Tabares AH. Overview of the coagulation reactions. In: High KA, Roberts HR, editors. *Molecular Basis of Thrombosis and Hemostasis*. New York: Marcel Dekker; 1995. p. 35-50.
16. Petreaca ML, Yao M, Liu Y, Defea K, Martins-Green M. Transactivation of vascular endothelial growth factor receptor-2 by interleukin-8 (IL-8/CXCL8) is required for IL-8/CXCL8-induced endothelial permeability. *Mol Biol Cell* 2007;18:5014-23.
17. Schraufstatter IU, Chung J, Burger M. IL-8 activates endothelial cell CXCR1 and CXCR2 through Rho and Rac signaling pathways. *Am J Physiol Lung Cell Mol Physiol* 2001;280:L1094-103.
18. Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol* 2006;6:173-82.
19. Conus S, Perozzo R, Reinheckel T, Peters C, Scapozza L, Yousefi S, Simon HU. Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation. *J Exp Med* 2008;205:685-98.
20. Peters T, Sindrilariu A, Hinz B, Hinrichs R, Menke A, Al-Azzeh EA, Holzwarth K, Oreshkova T, Wang H, Kess D, Walzog B, Sulyok S, Sunderkötter C, Friedrich W, Wlaschek M, Krieg T, Scharffetter-Kochanek K. Wound-healing defect of CD18(-/-) mice due to a decrease in TGF-beta1 and myofibroblast differentiation. *EMBO J* 2005;24:3400-10.
21. Simpson DM, Ross R. The neutrophilic leukocyte in wound repair a study with antineutrophil serum. *J Clin Invest* 1972;51:2009-23.
22. Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. *J Leukoc Biol* 2001;69:513-21.
23. DiPietro LA, Polverini PJ, Rahbe SM, Kovacs EJ. Modulation of JE/MCP-1 expression in dermal wound repair. *Am J Pathol* 1995;146:868-75.
24. Wetzler C, Kämpfer H, Pfeilschifter J, Frank S. Keratinocyte-derived chemotactic cytokines: expressional modulation by nitric oxide *in vitro* and during cutaneous wound repair *in vivo*. *Biochem Biophys Res Commun* 2000;274:689-96.
25. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends Cell Biol* 2005;15:599-607.
26. Novak ML, Koh TJ. Phenotypic transitions of macrophages orchestrate tissue repair. *Am J Pathol* 2013;183:1352-63.
27. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol* 2007;127:514-25.
28. Eming SA, Werner S, Bugnon P, Wickenhauser C, Siewe L, Utermöhlen O, Davidson JM, Krieg T, Roers A. Accelerated wound closure in mice deficient for interleukin-10. *Am J Pathol* 2007;170:188-202.
29. Miao M, Yuan B, Mani R, Lu S. Macrophage activation dysfunction in impaired wound healing: a potential therapeutic target. *Int J Low Extrem Wounds* 2013;12:239-41.
30. Sindrilariu A, Scharffetter-Kochanek K. Disclosure of the culprits: macrophages-versatile regulators of wound healing. *Adv Wound Care (New Rochelle)* 2013;2:357-68.
31. Petreaca ML, Yao M, Ware C, Martins-Green MM. Vascular endothelial growth factor promotes macrophage apoptosis through stimulation of tumor necrosis factor superfamily member 14 (TNFSF14/LIGHT). *Wound Repair Regen* 2008;16:602-14.
32. DiPietro LA. Wound healing: the role of the macrophage and other immune cells. *Shock* 1995;4:233-40.
33. Leibovich SJ, Ross R. The role of the macrophage in wound repair. A study with hydrocortisone and antimacrophage serum. *Am J Pathol* 1975;78:71-100.
34. Martin P, D'Souza D, Martin J, Grose R, Cooper L, Maki R, McKercher SR. Wound healing in the PU.1 null mouse: tissue repair is not dependent on inflammatory cells. *Curr Biol* 2003;13:1122-8.
35. Egozi EI, Ferreira AM, Burns AL, Gamelli RL, DiPietro LA. Mast cells modulate the inflammatory but not the proliferative response in healing wounds. *Wound Repair Regen* 2003;11:46-54.
36. Khanna S, Biswas S, Shang Y, Collard E, Azad A, Kauh C, Bhaskar V, Gordillo GM, Sen CK, Roy S. Macrophage dysfunction impairs resolution of inflammation in the wounds of diabetic mice. *PLoS One* 2010;5:e9539.
37. Gordon A, Kozin ED, Keswani SG, Vaikunth SS, Katz AB, Zoltick PW, Favata M, Radu AP, Soslowsky LJ, Herlyn M, Crombleholme TM. Permissive environment in postnatal wounds induced by adenoviral-mediated overexpression of the anti-inflammatory cytokine interleukin-10 prevents scar formation. *Wound Repair Regen* 2008;16:70-9.
38. Li P, Liu P, Xiong RP, Chen XY, Zhao Y, Lu WP, Liu X, Ning YL, Yang N, Zhou YG. Ski, a modulator of wound healing and scar formation in the rat skin and rabbit ear. *J Pathol* 2011;223:659-71.
39. Spite M, Serhan CN. Novel lipid mediators promote resolution of acute inflammation: impact of aspirin and statins. *Circ Res* 2010;107:1170-84.
40. Mirastschijski U, Impola U, Jahkola T, Karlsmark T, AGren MS, Saarialho-Kere U. Ectopic localization of matrix metalloproteinase-9 in chronic cutaneous wounds. *Hum Pathol* 2002;33:355-64.
41. Yager DR, Nwomeh BC. The proteolytic environment of chronic wounds. *Wound Repair Regen* 1999;7:433-41.
42. Enoch S, Grey JE, Harding KG. ABC of wound healing. Non-surgical and drug treatments. *BMJ* 2006;332:900-3.
43. Fray MJ, Dickinson RP, Huggins JP, Occlleston NL. A potent, selective inhibitor of matrix metalloproteinase-3 for the topical treatment of chronic dermal ulcers. *J Med Chem* 2003;46:3514-25.
44. Shiota N, Nishikori Y, Kakizoe E, Shimoura K, Niibayashi T, Shimbori C, Tanaka T, Okunishi H. Pathophysiological role of skin mast cells in wound healing after scald injury: study with mast cell-deficient W/W^v (V) mice. *Int Arch Allergy Immunol* 2010;151:80-8.
45. Gallant-Behm CL, Hildebrand KA, Hart DA. The mast cell stabilizer ketotifen prevents development of excessive skin wound contraction and fibrosis in red Duroc pigs. *Wound Repair Regen* 2008;16:226-33.
46. Noli C, Miolo A. The mast cell in wound healing. *Vet Dermatol* 2001;12:303-13.
47. Lund LR, Romer J, Bugge TH, Nielsen BS, Frandsen TL, Degen JL, Stephens RV, Danø K. Functional overlap between two classes of matrix-degrading proteases in wound healing. *EMBO J* 1999;18:4645-56.
48. Mirastschijski U, Schnabel R, Claes J, Schneider W, Agren MS, Haaksma C, Tomasek JJ. Matrix metalloproteinase inhibition delays wound healing and blocks the latent transforming growth factor-beta1-promoted myofibroblast formation and function. *Wound Repair Regen* 2010;18:223-34.
49. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol* 2001;17:463-516.
50. Brix K, Dunkhorst A, Mayer K, Jordans S. Cysteine cathepsins: cellular roadmap to different functions. *Biochimie* 2008;90:194-207.
51. Gurtner GC. Wound healing: normal and abnormal. In: Thorne CH, Bartlett SP, Beasley RW, Aston SJ, Gurtner GC, Spear SL, editors. *Grabb and Smith's Plastic Surgery*. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 15-22.
52. Johnson KE, Wilgus TA. Vascular endothelial growth factor and angiogenesis in the regulation of cutaneous wound repair. *Adv Wound Care (New Rochelle)* 2014;3:647-61.
53. Cao PF, Xu YB, Tang JM, Yang RH, Liu XS. HOXA9 regulates angiogenesis in human hypertrophic scars: induction of VEGF secretion by epidermal stem cells. *Int J Clin Exp Pathol* 2014;7:2998-3007.
54. Kazemi-Lomedasht F, Behdani M, Bagheri KP, Habibi-Anbouhi M, Abolhassani M, Arezumand R, Shahbazzadeh D, Mirzahoseini H. Inhibition of angiogenesis in human endothelial cell using VEGF specific nanobody. *Mol Immunol* 2015;65:58-67.
55. Li YJ, Li XH, Wang LF, Kuang X, Hang ZX, Deng Y, Du JR. Therapeutic efficacy of a novel non-peptide $\alpha\beta 3$ integrin antagonist for pathological retinal angiogenesis in mice. *Exp Eye Res* 2014;129:119-26.
56. Mienaltowski MJ, Birk DE. Structure, physiology, and biochemistry of collagens. *Adv Exp Med Biol* 2014;802:5-29.

57. Nyström A, Velati D, Mittapalli VR, Fritsch A, Kern JS, Bruckner-Tuderman L. Collagen VII plays a dual role in wound healing. *J Clin Invest* 2013;123:3498-509.
58. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol* 2002;3:349-63.
59. Desmoulière A, Chaponnier C, Gabbiani G. Tissue repair, contraction, and the myofibroblast. *Wound Repair Regen* 2005;13:7-12.
60. Feugate JE, Li Q, Wong L, Martins-Green M. The cxc chemokine cCAF stimulates differentiation of fibroblasts into myofibroblasts and accelerates wound closure. *J Cell Biol* 2002;156:161-72.
61. Kato R, Kamiya S, Ueki M, Yajima H, Ishii T, Nakamura H, Katayama T, Fukai F. The fibronectin-derived antiadhesive peptides suppress the myofibroblastic conversion of rat hepatic stellate cells. *Exp Cell Res* 2001;265:54-63.
62. Darby IA, Laverdet B, Bonté F, Desmoulière A. Fibroblasts and myofibroblasts in wound healing. *Clin Cosmet Investig Dermatol* 2014;7:301-11.
63. Wall IB, Bhadal N, Broad S, Whawell SA, Mudera V, Lewis MP. Force generation and protease gene expression in organotypic co-cultures of fibroblasts and keratinocytes. *J Tissue Eng Regen Med* 2009;3:647-50.
64. Shah JM, Omar E, Pai DR, Sood S. Cellular events and biomarkers of wound healing. *Indian J Plast Surg* 2012;45:220-8.
65. Takehara K. Growth regulation of skin fibroblasts. *J Dermatol Sci* 2000;24 Suppl 1:S70-7.
66. Werner S, Krieg T, Smola H. Keratinocyte-fibroblast interactions in wound healing. *J Invest Dermatol* 2007;127:998-1008.
67. Fu X, Xu M, Liu J, Qi Y, Li S, Wang H. Regulation of migratory activity of human keratinocytes by topography of multiscale collagen-containing nanofibrous matrices. *Biomaterials* 2014;35:1496-506.
68. Stevens LJ, Page-McCaw A. A secreted MMP is required for reepithelialization during wound healing. *Mol Biol Cell* 2012;23:1068-79.
69. Dumin JA, Dickeson SK, Stricker TP, Bhattacharyya-Pakrasi M, Roby JD, Santoro SA, Parks WC. Pro-collagenase-1 (matrix metalloproteinase-1) binds the alpha(2) beta(1) integrin upon release from keratinocytes migrating on type I collagen. *J Biol Chem* 2001;276:29368-74.
70. Mirastschijski U, Haaksma CJ, Tomasek JJ, Agren MS. Matrix metalloproteinase inhibitor GM 6001 attenuates keratinocyte migration, contraction and myofibroblast formation in skin wounds. *Exp Cell Res* 2004;299:465-75.
71. Mirastschijski U, Impola U, Karsdal MA, Saarialho-Kere U, Agren MS. Matrix metalloproteinase inhibitor BB-3103 unlike the serine proteinase inhibitor aprotinin abrogates epidermal healing of human skin wounds ex vivo. *J Invest Dermatol* 2002;118:55-64.
72. Frössing S, Rønø B, Hald A, Rømer J, Lund LR. Skin wound healing in MMP2-deficient and MMP2/plasminogen double-deficient mice. *Exp Dermatol* 2010;19:e234-40.
73. Green KA, Almholt K, Ploug M, Rønø B, Castellino FJ, Johnsen M, Bugge TH, Rømer J, Lund LR. Profibrinolytic effects of metalloproteinases during skin wound healing in the absence of plasminogen. *J Invest Dermatol* 2008;128:2092-101.
74. Wojtowicz AM, Oliveira S, Carlson MW, Zawadzka A, Rousseau CF, Baksh D. The importance of both fibroblasts and keratinocytes in a bilayered living cellular construct used in wound healing. *Wound Repair Regen* 2014;22:246-55.
75. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plast Reconstr Surg* 2006;117:S143-9.
76. Mäkinen K, Manninen H, Hedman M, Matsi P, Mussalo H, Alhava E, Ylä-Herttuala S. Increased vascularity detected by digital subtraction angiography after VEGF gene transfer to human lower limb artery: a randomized, placebo-controlled, double-blinded phase II study. *Mol Ther* 2002;6:127-33.
77. Greaves NS, Ashcroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. *J Dermatol Sci* 2013;72:206-17.
78. Kang HC, Ahn SD, Choi DH, Kang MK, Chung WK, Wu HG. The safety and efficacy of EGF-based cream for the prevention of radiotherapy-induced skin injury: results from a multicenter observational study. *Radiat Oncol J* 2014;32:156-62.
79. Singla S, Garg R, Kumar A, Gill C. Efficacy of topical application of beta urogastrone (recombinant human epidermal growth factor) in Wagner's Grade 1 and 2 diabetic foot ulcers: comparative analysis of 50 patients. *J Nat Sci Biol Med* 2014;5:273-7.
80. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen* 2014;22:569-78.
81. Toriseva M, Kähäri VM. Proteinases in cutaneous wound healing. *Cell Mol Life Sci* 2009;66:203-24.
82. Lau YK, Gobin AM, West JL. Overexpression of lysyl oxidase to increase matrix crosslinking and improve tissue strength in dermal wound healing. *Ann Biomed Eng* 2006;34:1239-46.
83. Gurtner GC, Wong VW. Wound healing: normal and abnormal. In: Thorne CH, Gurtner GC, Chung K, Gosain A, Mehrara B, Rubin P, Spear SL, editors. *Grabb and Smith's Plastic Surgery*. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2013. p. 13-9.
84. Levenson SM, Geever EF, Crowley LV, Oates JF 3rd, Berard CW, Rosen H. The healing of rat skin wounds. *Ann Surg* 1965;161:293-308.
85. Witte MB, Thornton FJ, Kiyama T, Efron DT, Schulz GS, Moldawer LL, Barbul A. Metalloproteinase inhibitors and wound healing: a novel enhancer of wound strength. *Surgery* 1998;124:464-70.
86. Viera MH, Vivas AC, Berman B. Update on keloid management: clinical and basic science advances. *Adv Wound Care (New Rochelle)* 2012;1:200-06.
87. Rhett JM, Ghatnekar GS, Palatinus JA, O'Quinn M, Yost MJ, Gourdie RG. Novel therapies for scar reduction and regenerative healing of skin wounds. *Trends Biotechnol* 2008;26:173-80.
88. Soo C, Hu FY, Zhang X, Wang Y, Beanes SR, Lorenz HP, Hedrick MH, Mackool RJ, Plas A, Kim SJ, Longaker MT, Freymiller E, Ting K. Differential expression of fibromodulin, a transforming growth factor-beta modulator, in fetal skin development and scarless repair. *Am J Pathol* 2000;157:423-33.
89. Järveläinen H, Puolakkainen P, Pakkanen S, Brown EL, Höök M, Iozzo RV, Sage EH, Wight TN. A role for decorin in cutaneous wound healing and angiogenesis. *Wound Repair Regen* 2006;14:443-52.
90. Occleston NL, O'Kane S, Goldspink N, Ferguson MW. New therapeutics for the prevention and reduction of scarring. *Drug Discov Today* 2008;13:973-81.
91. Wilgus TA. Regenerative healing in fetal skin: a review of the literature. *Ostomy Wound Manage* 2007;53:16-31.
92. King A, Balaji S, Le LD, Crombleholme TM, Keswani SG. Regenerative wound healing: the role of interleukin-10. *Adv Wound Care (New Rochelle)* 2014;3:315-23.
93. Lo DD, Zimmermann AS, Nauta A, Longaker MT, Lorenz HP. Scarless fetal skin wound healing update. *Birth Defects Res C Embryo Today* 2012;96:237-47.
94. Wulff BC, Parent AE, Meleski MA, DiPietro LA, Schrementi ME, Wilgus TA. Mast cells contribute to scar formation during fetal wound healing. *J Invest Dermatol* 2012;132:458-65.
95. Penn JW, Grobbelaar AO, Rolfe KJ. The role of the TGF-β family in wound healing, burns and scarring: a review. *Int J Burns Trauma* 2012;2:18-28.
96. Kozlik M, Wójcicki P. The use of stem cells in plastic and reconstructive surgery. *Adv Clin Exp Med* 2014;23:1011-7.
97. da Silva Meirelles L, Caplan AI, Nardi NB. In search of the *in vivo* identity of mesenchymal stem cells. *Stem Cells* 2008;26:2287-99.
98. Uysal CA, Tobita M, Hyakusoku H, Mizuno H. The effect of bone-marrow-derived stem cells and adipose-derived stem cells on wound contraction and epithelialization. *Adv Wound Care (New Rochelle)* 2014;3:405-13.
99. Singer NG, Caplan AI. Mesenchymal stem cells: mechanisms of inflammation. *Annu Rev Pathol* 2011;6:457-78.
100. Falanga V, Iwamoto S, Chartier M, Yufit T, Butmarc J, Kouttab N, Shrayr D, Carson P. Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. *Tissue Eng* 2007;13:1299-312.
101. Sorrell JM, Caplan AI. Topical delivery of mesenchymal stem cells and their function in wounds. *Stem Cell Res Ther* 2010;1:30.

Effect of limited access dressing on surface pH of chronic wounds

Pramod Kumar^{1,2}, Thittamaranahalli Muguregowda Honnegowda²

¹Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

²Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India.

Address for correspondence: Dr. Pramod Kumar, Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia. E-mail: pkumar86@hotmail.com

ABSTRACT

Aim: Changes in the pH of chronic wounds can inhibit the optimal activity of various enzymes in the wound environment, thereby delaying wound healing. The aim of the present study is to monitor the effect of limited access dressing (LAD) on the pH on the surface of chronic wounds. **Methods:** A total of 140 patients with chronic wounds of more than 4 weeks duration were divided into two groups by simple randomization: a LAD group ($n = 64$) and a conventional dressing group ($n = 76$). Fifty-six participants (22 in the LAD group and 34 in the conventional dressing group) were lost to follow-up or withdrawn from the study. **Results:** In the LAD group ($n = 42$), the mean age was 38.3 ± 10.56 years (range: 12-60 years), and the mean wound size at the time of admission was 28 cm^2 (range: 19-40 cm^2). In the conventional dressing group ($n = 42$), the mean age was 35.3 ± 14.0 years (range: 17-65 years), and the mean wound size at the time of admission was 26 cm^2 (range: 18-39 cm^2). Patients treated with LAD showed a significant decrease in the mean \pm standard deviation pH when compared with the conventional dressing group (0.83 ± 0.52 vs. 0.41 ± 0.26 , $P = 0.048$). **Conclusion:** LAD reduces the chronic wound surface pH to a level required for the optimal function of various enzymes. This could be a factor that exerts a beneficial effect on wound healing.

Key words:

Chronic wounds, limited access dressing, negative pressure wound therapy, wound surface pH

INTRODUCTION

Chronic nonhealing wounds continues to pose a treatment challenge to the clinician.^[1-3] Several enzymatic reactions in the wound environment are governed by the wound pH. Chronic nonhealing wounds may occur secondary to an elevated alkaline pH.^[4] Very few studies have investigated the relationship between wound pH and the healing of chronic wounds. A study by Leveen *et al.*^[5] established that weakly acidic wound environments significantly inhibit protease activity and may potentially promote wound healing. A subsequent comprehensive review by Schneider *et al.*^[6] and Percival *et al.*^[7] showed that pH is

an influential factor in the healing process, as an acidic environment favors wound healing. The pH of the wound surface may change due to various factors including infection, oxygenation and topical applications of various dressing materials. Modulation of the wound pH may therefore change the direction of wound healing. There were no studies in the literature evaluating the role of negative pressure wound therapy in modulating wound pH.

Limited access dressing (LAD), a relatively new technique that combines negative pressure and moist wound

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kumar P, Honnegowda TM. Effect of limited access dressing on surface pH of chronic wounds. *Plast Aesthet Res* 2015;2:257-60.

Received: 30-01-2015; **Accepted:** 27-07-2015

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.165449

dressings, has been shown to have a positive effect on wound healing.^[8] The aim of the present study is to determine the effect of LAD on wound surface pH.

METHODS

Ethical issues

This randomized control trial was carried out in the Burns and Plastic Surgery Department of Kasturba Medical College and Hospital, Manipal, Keanataka, India. The study protocol was reviewed and approved by the Institutional Ethics Committee. The study was conducted as per approved protocol after obtaining informed consent from all patients.

Study design and randomization

Two hundred and fifteen patients with chronic wounds of more than 4 weeks duration were screened in the study. Patients were evaluated for inclusion criteria (nonhealing chronic wounds) and exclusion criteria (collagen disorders, diabetes, leprosy, cirrhosis, HIV and pregnancy), and 140 patients were enrolled in the study. Simple randomization was performed (www.random.org; random number table was prepared) with assigned numbers and treatment sealed in opaque envelopes.

One hundred and forty patients with a mean age of 36.86 ± 12.4 years (range: 12-65 years) were randomized and assigned to the LAD group ($n = 64$) or the conventional dressing group ($n = 76$) by simple randomization [Figure 1].

Of 140 patients, 56 participants (22 in the LAD group and 34 in the conventional dressing group) were lost to follow-up or withdrawn from the study. Of 42 patients in the LAD group, 22 (52%) were women, and 20 (48%) were men. In the conventional dressing group, of 42 patients, 18 (42.8%) were women, and 24 (57.1%) were men [Figure 1].

In the LAD group, the mean age was 38.3 ± 10.56 years (range: 12-60 years), and the mean wound size at the time of admission was 28 cm^2 (range: 19-40 cm^2). In the conventional dressing group, the mean age was 35.3 ± 14.0 years (range: 17-65 years), and the mean wound size at the time of admission was 26 cm^2 (range: 18-39 cm^2) [Table 1].

Patients in the LAD group were treated with intermittent negative pressure.^[8] In the conventional closed dressing group, patients were dressed daily with 5% povidone-iodine solution soaked gauze. The wounds of both groups were washed daily.

Assessment of wound surface pH

The surface pH was measured by a pH paper strip (Merck, Mumbai, India) placed on the surface of the wound with care taken to ensure accuracy.^[9]

Statistical analysis

Data obtained from both groups were analyzed using the Student's *t*-test SPSS, 15th version, SPSS Inc., Chicago. The data (mean \pm SD) were compared between the two groups. A $P < 0.05$ was taken as statistically significant.

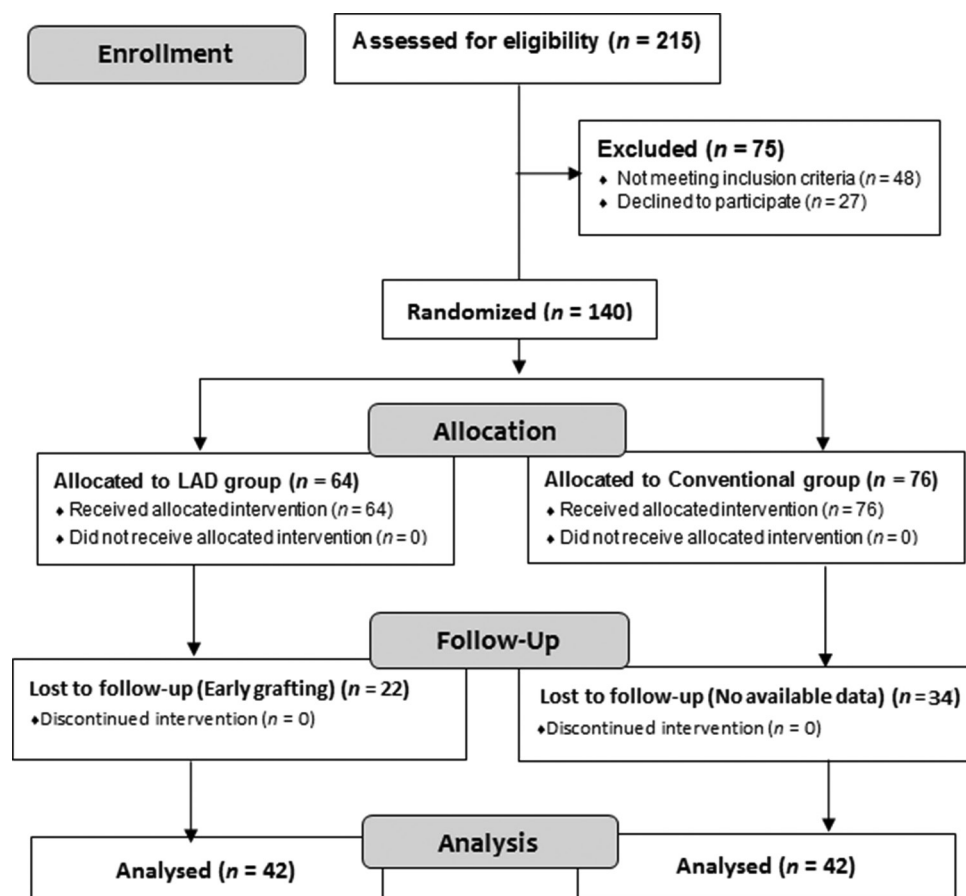


Figure 1: Consort flowchart

RESULTS

In total, 215 patients were screened, 140 patients were randomized, of whom 64 were assigned to the LAD group and 76 to the conventional group [Figure 1]. Of the 56 participants, 22 in the LAD group and 34 in the conventional dressing group were lost to follow-up or withdrawn from the study. The results of wound surface pH in chronic ulcer patients of the LAD group as compared to that of the conventional dressing group shown in Table 2.

DISCUSSION

The acidity and alkalinity are measured by pH value, that is, pH is a measurement of the concentration of H^+ in the body. It ranges from 1 to 14, with pure water at a pH of 7 to be considered neutral. Acidic solution has a pH of less than 7 and basic or alkaline solutions have a pH more than 7. Body pH can be tested using litmus paper immersed in saliva or urine. Even a minor variation in the concentration of H^+ can alter the rate of many biochemical processes. Body pH can change secondary to diet, consumption of chemicals, exercise and various diseases altering the metabolism of body. Topical applications may change the body surface pH. Wound healing is regulated by complex chemical processes mediated by various enzymes and hormones. Hence, various intrinsic and extrinsic factors may influence the pH of the wound environment, leading to alterations in the healing process. Therefore, events in wound healing including vasodilation, inflammation, release of oxygen into the wound bed, protease activity and the release and effects of bacterial toxins may be significantly influenced by the pH of the wound. The pH of body fluids and tissues is stabilized by various protein buffering systems. Hydrogen ions bind to protein molecules or bound hydrogen ions are released, changing their concentration in the body's tissues and fluids. Intracellular buffers such as hemoglobin in its

reduced form act as good buffering agents of the body. Hemostasis, inflammation, proliferation and remodeling are the four overlapping phases of wound healing. Altered or impaired healing of chronic wounds is the result of an interruption in the various processes of these four phases of wound healing. Changes in the pH of the wound surface may be induced by application of topical preparations that influence the cellular events in wound healing. Subjective evaluation of the wound bed is performed by clinicians when making clinical decisions regarding management. A simple system for monitoring wound pH may provide an objective method for clinicians when deciding upon the course of treatment.^[10]

The pH environment of chronic wounds has been recorded within the range of 7.15-8.9.^[11-13] Both acute and chronic wounds with an elevated alkaline pH have demonstrated lower rates of healing than wounds in which the pH is closer to neutral.^[5,10,14] Chronic wounds exhibit excessive breakdown of the extracellular matrix, and this occurs more readily when the wound has an alkaline pH^[14,15] which may contribute to nonhealing ulcers. A study by Greener *et al.*^[15] showed that every protease shows peak enzyme activity at certain pH levels, where the protein is broken down more rapidly than at other pH values. For example, cathepsins G has peak activity at pH 7.0, elastase at 8.0, matrix metalloproteinases 2 (MMP-2) at 8.0, and neutrophil elastase at 8.3. The shift of the pH in a wound environment from alkaline to acidic favors the production of healthy granulation tissue by decreasing the growth of bacteria and MMPs.^[15] The alteration of surface pH of wounds by the use of topical preparations has been used to promote healing.^[16,17] In the present study, the wound surface pH of LAD vs. conventional dressing on day 0 was (mean \pm SD) 8.33 ± 0.35 vs. 8.31 ± 0.38 . On day 10, the mean wound surface pH (\pm SD) in the LAD vs. conventional dressing group was 7.5 ± 0.43 vs. 7.9 ± 0.47 . The decrease in the mean wound surface pH (\pm SD) after 10 days of treatment in the LAD group was 0.83 ± 0.52 while in the conventional dressing group, it was 0.41 ± 0.26 ($P = 0.048$).

LAD is a newer method of dressing which combines the principles of both negative pressure and moist wound healing. It utilizes a definite intermittent negative pressure regimen of 30 min of negative pressure followed by a rest period of 3.5 h. During the period without negative pressure, the LAD acts as a moist wound dressing. The wound bed preparation period has been shown to be reduced in LAD as compared to conventional dressings.^[8] Also, the percentage of graft take under LAD has been shown to be higher.^[8] LADs have been shown to

Table 1: Patient demographics and wound characterization at baseline

	LAD group	Conventional group
Number of patients	42	42
Age, years (mean \pm SD, range)	38.3 ± 10.56 , 12-60 years	35.3 ± 14.0 , 17-65 years
Mean wound size (cm ²)	28 (range: 19-40)	26 (range: 18-39)
Female (%)	52	42.8
Male (%)	48	57.1

SD: Standard deviation, LAD: Limited access dressing

Table 2: Results of wound surface pH in the LAD (n = 42) and conventional dressing group (n = 42)

Parameters	Mean \pm SD						P
	LAD group (n = 42)			Conventional dressing group (n = 42)			
	Day 0	Day 10	Day (0-10)	Day 0	Day 10	Day (0-10)	
Wound surface pH	8.33 \pm 0.35	7.5 \pm 0.43	0.83 \pm 0.52	8.31 \pm 0.38	7.9 \pm 0.47	0.41 \pm 0.26	0.048

SD: Standard deviation, LAD: Limited access dressing

have a faster rate of healing for both chronic and acute wounds.^[8] In the present study, a significant decrease in the wound surface pH of chronic wounds ($P = 0.048$) was noted in patients treated with the LAD as compared with the conventional group. The lower pH may be one of the factors responsible for improved wound healing with LAD as experienced clinically.^[18-21] Lower systemic toxic symptoms in patients treated by LAD may be due to reduced activity of bacteria and bacterial toxins under the influence of a lower pH.

In conclusion, the study showed a reduction in the wound pH in LAD treated patients as compared to those who received a conventional dressing treatment. Lowering the pH in chronic wounds may accelerate wound healing by reestablishing equilibrium in the wound bed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J (Clin Res Ed)* 1985;290:1855-6.
2. Nelzen O, Bergqvist D, Lindhagen A. The prevalence of lower-limb ulceration has been underestimated: results of a validated population questionnaire. *Br J Surg* 1996;83:255-8.
3. O'Brien JF, Grace PA, Perry JJ, Burke PE. Prevalence and aetiology of leg ulcers in Ireland. *Ir J Med Sci* 2000;169:110-2.
4. Ye RC. The relationship of pH of the granulation tissue and the take of the skin graft. *Plast Reconstr Surg* 1957;19:213-7.
5. Leveen HH, Falk G, Borek B, Diaz C, Lynfield Y, Wynkoop BJ, Mabunda GA, Rubricius JL, Christoudias GC. Chemical acidification of wounds: an adjuvant to healing and the unfavorable action of alkalinity and ammonia. *Ann Surg* 1973;178:745-53.
6. Schneider LA, Korber A, Grabbe S, Dissemmond J. Influence of pH on wound-healing: a new perspective for wound-therapy? *Arch Dermatol Res* 2007;298:413-20.
7. Percival SL, McCarty S, Hunt JA, Woods EJ. The effects of pH on wound healing, biofilms and antimicrobial efficacy. *Wound Repair Regen* 2014;22:174-86.
8. Kumar P. Exploiting potency of negative pressure in wound dressing using limited access dressing and suction-assisted dressing. *Indian J Plast Surg* 2012;45:302-15.
9. Shukla VK, Shukla D, Tiwary SK, Aqrawal S, Rastoqi A. Evaluation of pH measurement as a method of wound assessment. *J Wound Care* 2007;16:291-4.
10. Gethin G. The significance of surface pH in chronic wounds. *Wounds UK* 2007;3:52-6.
11. Wilson IA, Henry M, Quill RD, Byrne PJ. The pH of varicose ulcer surfaces and its relationship to healing. *Vasa* 1979;8:339-42.
12. Tsukada K, Tokunaga K, Iwama T, Mishima Y. The pH changes of pressure ulcers related to the healing process of wounds. *Wounds* 1992;4:16-20.
13. Romanelli M, Schipani E, Piaggese A, Barachini P. Evaluation of surface pH on venous leg ulcers under allevyn dressings. In: International Congress and Symposium Series-Royal Society of Medicine, editors. Evidence-based Woundcare. Proceedings of a Conference Sponsored by Smith and Nephew; 1997 November, 17, UK. London: Royal Society of Medicine Press; 1998. p. 57-60.
14. Roberts G, Hammad L, Creevy J, Shearman C, Mani R. Physical changes in dermal tissues around chronic venous ulcers. In: Proceedings of the European Conference on Advances in Wound Management; 1997 November, 18-20. Harrogate, UK. London: EMAP Healthcare Ltd.; 1998. p. 104-5.
15. Greener B, Hughes AA, Bannister NP, Douglass J. Proteases and pH in chronic wounds. *J Wound Care* 2005;14:59-61.
16. Gethin GT, Cowman S, Conroy RM. The impact of Manuka honey dressings on the surface pH of chronic wounds. *Int Wound J* 2008;5:185-94.
17. Molan PC. Re-introducing honey in the management of wounds and ulcers-theory and practice. *Ostomy Wound Manage* 2002;48:28-40.
18. Kumar PP, Sharma A. The limited access dressing for damage control in trauma patients. *Wounds* 2010;22:188-92.
19. Sreenivas T, Nandish Kumar KC, Menon J, Nataraj AR. Calcific myonecrosis of the leg treated by debridement and limited access dressing. *Int Low Extrem Wounds* 2013;12:44-9.
20. Friji MT, Mohapatra DP, Chittoria RK, Dinesh Kumar S, Ashokan A, Vijayaraghavan N. Use of urine collection bag as an alternative of custom-made plastic bag for limited access dressing (LAD). *J Soc Wound Care Res* 2013;6:36-9.
21. Chittoria RK, Kumar P, Bajaj SP, Singh AK, Gupta DK. General clinical guidelines for wound management: redefining acronym SWCR. *J Soc Wound Care Res* 2014;7:2-7.

Computer assessment of the composition of a generic wound by image processing

Rohit Nayak¹, Pramod Kumar^{2,3}, Ramesh R. Galigekere⁴

¹Department of Electrical and Computer Engineering, University of Rochester, Rochester, NY 14623, USA.

²Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

³Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁴Department of Biomedical Engineering, Manipal Institute of Technology, Manipal University, Manipal 576104, Karnataka, India.

Address for correspondence: Dr. Ramesh R. Galigekere, Department of Biomedical Engineering, Manipal Institute of Technology, Manipal University, Manipal 576104, Karnataka, India. E-mail: ramesh.galigekere@manipal.edu

ABSTRACT

Aim: This paper addresses the assessment of the composition of a general wound, in terms of all identifiable categories of tissue and pigmentation in an attempt to improve accuracy in assessing and monitoring wound health. **Materials and Methods:** A knowledgebase of clusters was built into the hue, saturation and intensity (HSI) color space and then used for assessing wound composition. Based on the observation that the clusters are fairly distinct, two different algorithms, that is, Mahalanobis distance (MD) based and the rotated coordinate system (RCS) method, were used for classification. These methods exploit the shape, spread, and orientation of each cluster. **Results:** The clusters in the HSI color space, built from about 9,000 (calibrated) pixels from 48 images of various wound beds, showed 8 fairly distinct regions. The inter-cluster distances were consistent with the visual appearance. The efficacy of the MD and RCS based methods in 120 experiments taken from a set of 15 test images (in terms of average percent-match) was found to be 91.55 and 93.71, respectively. **Conclusion:** Our investigations established eight categories of tissue and pigmentation in wound beds. These findings help to determine the stage of wound healing more accurately and comprehensively than typically permitted through use of the 4-color model reported in the literature for addressing specific wound types.

Key words:

Wound composition, color-image processing, hue, saturation and intensity model, classification, Mahalanobis distance, rotated coordinate system method

INTRODUCTION

Accurate assessment of wound health is essential in the reduction of morbidity and mortality, which in turn reduces the cost of health care. Factors characterizing the health of a wound include its composition in terms of tissue type, pigmentation (with a one-to-one correspondence to distinct colors), size (area, depth, and volume), shape, regularity and texture. Traditionally, wound composition has been assessed by visual inspection, which is subjective, tedious

and limited in precision and consistency. A computerized system for assessment and documentation of the evolution of a wound is useful in providing a better understanding of wounds, the healing process, and validation of treatment protocols, and wound care products.

Color composition is the most important factor in determining the status of a wound, and its computerized

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165444

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Nayak R, Kumar P, Galigekere RR. Computer assessment of the composition of a generic wound by image processing. *Plast Aesthet Res* 2015;2:261-5.

Received: 15-12-2014; **Accepted:** 08-07-2015

assessment has been an active area of research. Arnqvist *et al.*^[1] addressed segmenting secondary healing ulcers based on the 3-color (RYK) model: red (R) granulation, yellow (Y) necroses and black (K) necrotic eschar. Herbin *et al.*,^[2] in their study on the effect of a new drug on wound kinetics, used color information (red and green) to distinguish a wound from normal skin in estimating the area of the wound, and proposed a color index to quantify healing on uniformly colored, artificially created blisters. However, natural wounds are generally more complex with highly variegated coloring.^[3] The use of color information, rather than size, to assess healing and guide clinicians in their choice of wound care products, was stressed by Mekkes and Westerhof.^[4] The approach taken by Mekkes and Westerhof^[4] in their study of wound debridement based on video images, uses the RYK model. Jones and Plassmann^[5] used the same model along with an “unclassified” category in their description of skin ulcers. Hansen *et al.*^[6] applied the hue, saturation and intensity (HSI) model to classify wound severity in an animal model within 30 min following injury. Wounds were classified as mild, moderate or severe, based on differences in color. Berris and Sangwine^[7] used the RGB model, in a study of pressure ulcers, to assess the content in terms of the three tissue types (BYR model). Hoppe *et al.*^[8] highlighted the inadequacy of the RGB model, and used the HSI model to grade leg ulcers in terms of the quantity of slough. They also investigated the variability of color attributes (only red was considered) due to differences in lighting conditions and found hue to be the least variant. Oduncu *et al.*^[9] also used the HSI model to assess the amount of slough in leg ulcers. Varedas *et al.*^[10] developed a method very specific to pressure ulcers for classifying healthy and nonhealthy skin, with four tissue types for the latter, their method involves several preprocessing steps for the extraction of color and texture parameters. Wannous *et al.*^[11] studied the variability arising from image capture from different sources under different conditions, they too considered only three tissue types. Dorileo *et al.*^[12] added white (W, representing hyperkeratosis) to the RYK model, for analyzing dermatological ulcers. In the same context, the use of texture parameters was proposed by Pereira *et al.*^[13] to improve the performance of classification. The authors previously presented initial results showing the presence of eight tissue types and pigmentation, with a one-to-one correspondence to distinct colors.^[14] Subsequently, Veredas *et al.*,^[15] in their elaborate work on pressure ulcers based on four tissue-types (with the skin regarded as the fifth), have emphasized the necessity for precise evaluation. Recently, Mukherjee *et al.*^[16] presented results using a three-color model with textures.

Thus, while the importance of color in representing wound composition is well-recognized, only three to four categories and colors have been used to date in the analysis of specific types of wounds. However, wounds evolve over time, with specific types of tissue and pigmentation with eight identifiable colors which represent healing, necrosis and/or infection.^[14] This theory is also supported by observations in a recent paper by

Veredas *et al.*^[15] Finally, other authors have indicated that an unaccounted color may appear in a wound bed and affect classification.^[17]

The current study proposes that an eight-color model would more comprehensively represent wound composition, evolution and changes due to infection. This would assist in the development of a comprehensive algorithm for all wounds, rather than a specific wound type (e.g. pressure ulcers). Thus, in the interest of improving the accuracy of assessment for general wounds, the authors discuss a knowledge base of clusters associated with the eight categories in an appropriate color space. The results of a classification algorithm which take into account the information about the shape, spread and orientation of each cluster, through its covariance matrix, are presented.^[18] In addition, the results of the “rotated coordinate system (RCS)” method, which also makes use of cluster shapes, are delineated.^[19]

MATERIALS AND METHODS

The procedure for computer assessment of wound composition based on colors of tissue and pigmentation involves (a) choosing an appropriate color model, (b) building the knowledge base in the chosen space, and (c) classification of regions in the given wound.

The color model

Although R, G and B are the considered the “primary colors” of light, the RGB model is more useful in the generation of color rather than analysis.^[18] An alternative is the HSI model, wherein hue (*H*) describes pure color, saturation (*S*) is the “degree of dilution from purity” by white light, and *I* is the intensity (decoupled from color information). Color in RGB-format can be converted to the HSI version by suitable transformations.^[18] Since hue is quantified in terms of the angle from the “red”-axis in the HSI space, it suffers discontinuity at 0 (located at the mid-point of the interval representing the red hue). To circumvent this problem, the hue range was shifted, as was suggested in the previous study.^[20]

$$H = \begin{cases} 360 - H, & H \in [250, 360) \\ H + 110, & H \in [0, 250) \end{cases} \quad (1)$$

The choice of the origin at $H = 250$ is guided by the fact that minimal tissue was found in the range of 250 ± 60 . We refer to this as the modified HSI space.

Procedure for assessing wound composition

The algorithm for determining the wound status in terms of tissue types and pigmentation consists of two phases, as described in the following.

Building the knowledge base

The eight categories of tissue and pigmentation of interest include: (1) healthy granulation tissue (HGT), (2) unhealthy granulation tissue (UGT), (3) whitish slough, (4) yellowish-green pigmentation (G_1), (5) bluish-green pigmentation (G_2), (6) fat (F), (7) brown necrotic tissue (BNT), and (8) black necrotic tissue or gangrene (Ga). A sample of each, pertaining to each of the eight categories, was

selected randomly from various wounds and is displayed in Figure 1 for the purpose of illustration.

The concept of identifying the tissue types based on pigmentation involves first building a reference base, that is, a labeled set of clusters in the HSI space, based on a large number of pixels per category from many wound images as judged by an experienced plastic surgeon. Prior to calculating the HSI parameters, the RGB components must be calibrated to account for variations due to "local" or "global" factors.^[11] Local variations occur due to variations in the angle and the distance of the camera from the wound. Global variation arises due to factors like ambient light. All of the wound images were taken by the same camera under similar conditions. Ignoring local variations, the RGB components have been calibrated for global variations, as suggested by Wannous *et al.*^[11] by exploiting the white patches available in the vicinity of the wound in some of the images. The corrected values were used to compute the values of *H*, *S*, and *I*. Each pixel within the wound is represented by a 3-element vector (a point) in the HSI space. Points corresponding to a given tissue type or pigmentation, as decided by an expert based on its color, form a cluster.

Classification

Classification by distance-based approaches is considered as the clusters were found to be fairly distinct.

The first approach is based on the Mahalanobis distance (MD).^[21] This measure recognizes that some variables may suffer larger variance than the others due to differences in numerical values, variances and their inter-relationships (if any). Indeed, MD takes into account the shape of each of the clusters, information about which is embedded in the covariance matrix. The expression for MD between the observation vector *x* and a cluster "i" with mean μ_i and covariance matrix C_i , is given by:

$$d^2(x, \mu_i) = (x - \mu_i)^T C_i^{-1} (x - \mu_i) \quad (2)$$

Note that the contours of constant density (three-dimensional histogram) are hyperellipsoids of constant MD from μ_i .^[22]

Another method, the RCS method, is considered based on its philosophy, its success in machine vision applications,^[19] and for the sake of comparison. It uses a metric derived by transforming the coordinates of the cluster space, such that the intra-class samples are clustered closely, and inter-class samples are separated. The transformation involves rotation and scaling of the axes, such that one

axis lies along that of minimum variance and another along that of the maximum. The optimum rotated coordinate axes may be shown to lie in the directions of the orthogonal eigenvectors of C_i , and scaled by the inverse of the respective eigenvalues. The theoretical considerations outlined in the preceding result in the following distance metric between the observation-vector *x* and a cluster "i" with mean μ_i :

$$d^2(x, \mu_i) = (\prod_{j=1}^3 \sqrt{\lambda_j})^2 \left\{ \sum_{k=1}^3 \frac{[(x - \mu_i)^T e_k]^2}{\lambda_k} + 3 \right\} \quad (3)$$

Where e_k and γ_k are the k^{th} eigenvectors and the eigenvalue of C_i . Note that γ_k happens to be the variance of the sample points in the direction of e_k . Scaling the transformed axes by the inverse of the respective eigenvalues is, therefore, logical. The relation of this approach to statistical decision theory is seen when one notes that the minimum (Euclidean) distance classification in the new space amounts to maximum likelihood classification after fitting Gaussian density to the data.^[19]

Classification of a color pixel specified by the vector *x* of HSI values is performed by assigning it to the cluster having the smallest value of $d(x, \mu_i)$

RESULTS

The reference clusters were built by using 48 reference images of chronic wounds of various types, acquired under daylight, by a digital camera (Sony DSC P9) with flash. About 9,000 pixels (>1,000/category) were assigned to one of the eight categories. Samples of the eight types of tissue and pigmentation are displayed in Figure 1. The calibrated RGB values of each of the pixels were recorded against the category. The calibration factors were 1.0162 (red), 1 (green) and 1.016 (blue). After rejecting the pixels (with *I* > 233) associated with reflections from flash, the values of *H*, *S* and *I*, associated with each pixel, were computed, and that of *H* was modified (as per Equation 1).

Views of the clusters in two different orientations are displayed in Figure 2. It is very important to observe the presence of eight clusters and that they are fairly distinct. HGT and UGT lie within a narrow hue (red) but spread only over saturation. Not surprisingly, they are close to each other. In fact, the appearance or disappearance of various colors over time allows one to assess the evolution of the wound toward a state of healing or otherwise. To assist in a quantitative understanding of the clusters, the values of inter-cluster distance are displayed in Table 1. The inter-cluster distance,^[23] based on the MD measure, between clusters *i* and *j*, is given by:

$$d_{ij}^2(x_i, x_j) = (x_i - x_j)^T C_{ij}^{-1} (x_i - x_j) \quad (4)$$

where x_i and x_j are the means of the clusters *i* and *j*, respectively, and C_{ij} is the pooled covariance matrix. The pooled covariance matrix was computed based on the data associated with both of the clusters *i* and *j* (considered as one group), rather than considering it to be a weighted average of the covariance matrices associated with the



Figure 1: A sample each, of the eight categories of tissue types/pigmentation, selected randomly from various wound-beds

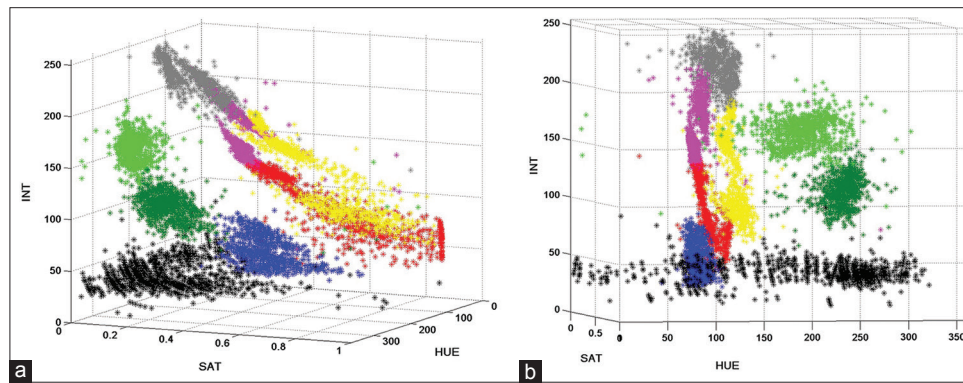


Figure 2: (a) A view of the three-dimensional clusters in the hue, saturation, and intensity space, showing various tissue-categories; (b) another view of the clusters in the hue, saturation, and intensity space from a different orientation. These two views show all the tissue categories, and that the clusters are fairly distinct

Table 1: Values of inter-cluster MD in the HSI space

	HGT	UGT	WS	G ₁	G ₂	F	BNT	Ga
HGT	0	2.69	3.73	3.7	3.95	3.43	3.54	3.88
UGT	2.69	0	3.26	3.71	3.95	3.03	3.67	3.94
WS	3.73	3.26	0	3.61	3.95	3.09	3.92	4.15
G ₁	3.7	3.71	3.61	0	3.3	3.69	3.84	3.93
G ₂	3.95	3.95	3.95	3.3	0	3.94	3.94	3.86
F	3.43	3.03	3.09	3.69	3.94	0	3.7	3.93
BNT	3.54	3.67	3.92	3.84	3.94	3.7	0	3.01
Ga	3.88	3.94	4.15	3.93	3.86	3.93	3.01	0

HIS: Hue, saturation, and intensity, MD: Mahalanobis distance, HGT: Healthy granulation tissue, UGT: Unhealthy granulation tissue, WS: Whitish slough, G₁: Yellowish green pigmentation, G₂: Bluish green pigmentation, F: Fat, BNT: Brown necrotic tissue, Ga: Gangrene

individual clusters, as suggested by Hertzog period.^[24] The distances agree with the visual (geometric) separations. The distance between HGT and UGTs is the smallest. The cluster associated with UGT appears to consist of two lobes, though over a narrow range of hue, because the color associated with the unhealthy bed can vary slightly due to poor vascularity, infections, *etc.* Clinically, considering UGT to consist of two clusters is therefore unnecessary. Instead, this is addressed mathematically through an algorithm that exploits cluster shape.

To test the efficacy of the proposed algorithms, a set of 15 test images were used to perform 120 experiments (15/category). Each experiment began with the selection of a relatively homogenous region of interest (ROI), selected randomly from the test images. A visual estimate of the composition (in terms of the percentage of the main tissue/pigmentation) was declared by one author who was blinded to the selection of the ROI. The ROI was subjected to estimation of its composition by the algorithms described in this paper. The performance of the algorithm in terms of accuracy of the estimates is defined by:

$$\%Match = \left[1 - \frac{1}{N_{exp}} \sum_{i=1}^{N_{exp}} |E_{Vi} - E_{Ci}| \right] \times 100 \quad (5)$$

where E_{Vi} and E_{Ci} are the fractional estimates (visual and computer-assisted) of the tissue and pigmentation composition, and N_{exp} is the number of experiments

(15 in this case). The values of $\%Match$ were computed using both methods and Table 2 lists the values obtained. The relatively poor performance with respect to UGT and Ga may be attributed to the absence of a tight cluster in the first case, and a large spread in the second. Indeed, both are difficult to judge visually; UGT is close to HGT in color, and Ga is very dark to allow easy identification of its hue. To understand the behavior quantitatively, the inter-cluster MDs were calculated as listed in Table 1. One may observe that the distances between HGT and UGT, Ga and BNT, are relatively small.

DISCUSSION

In this paper, there was no attempt to refine the cluster structure in the HSI space, by breaking apparently disjointed clusters or joining those close to each other, as reported by Nayak *et al.*^[14] Modifying the clusters is not meaningful, as some color spread is natural.^[2] Such variations are captured in the cluster shapes and are incorporated in the algorithms proposed in this paper. Although we experimented with the inter-quartile range, retaining central tendencies, and the improvement in the accuracy of classification was not significant.^[20]

There are some limitations in the presented study. As reported, a modified HSI space was used, which involves a shift of the origin. This approach suggested by Hoppe *et al.*^[8] ensures a continuous value for hue, which is used as a parameter. The choice of the origin and the minimal range of hues was based on empirical observations of data involving nearly 9,000 pixels. While there could be some change in the precise values attributed to the camera and ambience, color calibration can account for such variations. Indeed, variation associated with the range of hues is minimal in comparison with the other parameters.^[8] However, it would be interesting to find an approach to determine the values of the parameters to facilitate a shift of the origin. Further, simulated images and varying ambience could be used to test the efficacy of the values derived by such a method.

To validate the algorithms, randomly selected and blinded ROIs were used to mitigate bias. Nevertheless, the approach presented has limitations; specifically, it

Table 2: %Match of the visual and computer assessments, for various categories of tissue and pigmentation

Tissue/pigmentation category	MD	RCS
HGT	100	100
UGT	76.6	89.99
WS	80.5	94.60
G ₁	98.4	95.75
G ₂	89.3	92.26
F	96.1	98.11
BNT	98.2	100
Ga	93.3	78.94

MD: The method based on Mahalanobis distance, RCS: The rotated coordinate system method, HGT: Healthy granulation tissue, UGT: Unhealthy granulation tissue, WS: Whitish slough, G₁: Yellowish green pigmentation, G₂: Bluish green pigmentation, F: Fat, BNT: Brown necrotic tissue, Ga: Gangrene

would be useful to take a consensus of multiple operators for segmenting clusters for training, and use different operators for selecting ROIs for a more robust validation of the algorithms.

In conclusion, this paper establishes eight categories of color due to tissue types and pigmentation, more than those based on the commonly used 4-color model. The results were based on a knowledge base built using the one-to-one correspondence between tissue types pigmentation, and color. The (modified) HSI model was used because it better represents the physician's perception of color, in addition, to resolving the information into eight useful categories. The resulting eight categories provide a better representation and assessment of wound health and minimize error in judgment due to misclassification of unidentified tissue types and pigmentation. Segmentation of wounds would be very useful for monitoring and objective recording of various phases of wound healing and the response to treatment protocols.

Acknowledgments

We are grateful to the critical remarks and suggestions of the reviewers, who have gone through the material in great detail. The data reported in this paper were collected by the second author while he was the Head of the Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal University, Manipal.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Arnqvist J, Hellgren L, Vincent J. Semiautomatic Classification of Secondary Healing Ulcers in Multispectral Images. Proceedings of 9th International Conference on Pattern Recognition, 1988 November, 14-17. Rome, New York: IEEE; 1988. p. 459-61.

2. Herbin M, Bon FX, Venot A, Jeanlouis F, Dubertret ML, Dubertret L, Strauch G. Assessment of healing kinetics through true color image processing. *IEEE Trans Med Imaging* 1993;12:39-43.
3. Berris WP, Sangwine SJ. Automatic Quantitative Analysis of Healing Skin Wounds Using Colour Digital Image Processing. *World Wide Wounds*, 1997; Available from: <http://www.worldwidewounds.com/1997/july/Berris/Berris.html>. [Last accessed on 2015 Apr 12].
4. Mekkes JR, Westerhof W. Image processing in the study of wound healing. *Clin Dermatol* 1995;13:401-7.
5. Jones BF, Plassmann P. An instrument to measure the dimensions of skin wounds. *IEEE Trans Biomed Eng* 1995;42:464-70.
6. Hansen GL, Sparrow EM, Kokate JY, Leland KJ, Iazzo PA. Wound status evaluation using color image processing. *IEEE Trans Med Imaging* 1997;16:78-86.
7. Berris WP, Sangwine SJ. A Colour Histogram Clustering Technique for Tissue Analysis of Healing Skin Wounds. Proceedings of the 6th International Conference on Image Processing and its Applications, 1997 July 14-17. Vol. 2. Dublin, New York: IET; 1997. p. 693-7.
8. Hoppe A, Wertheim D, Melhuish J, Morris H, Harding KG, Williams RJ. Computer Assisted Assessment of Wound Appearance Using Digital Imaging. In: Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2001 October, 25-28. Istanbul, Turkey; 2001. p. 2595-7.
9. Oduncu H, Hoppe A, Clark M, Williams RJ, Harding KG. Analysis of skin wound images using digital color image processing: a preliminary communication. *Int J Low Extrem Wounds* 2004;3:151-6.
10. Varedas FJ, Mesa H, Morente L. A hybrid learning approach to tissue recognition in wound images. *Int J Intell Comput Cybern* 2009;2:327-47.
11. Wannous H, Trelluillet S, Lucas Y. Robust tissue classification for reproducible wound assessment in telemedicine environments. *J Electron Imaging* 2010;19:1-9.
12. Dorileo EAG, Frade MAC, Rangayyan RM, Azevedo Marques PM. "Segmentation and Analysis of Tissue Composition of Dermatological Ulcers", Proceedings of the Canadian Conference on Electrical and Computer Engineering, Calgary, Canada, May 2010. p. 1-4.
13. Pereira SM, Frade MA, Rangayyan RM, Marques PM. Classification of Dermatological Ulcers Based on Tissue Composition and Color Texture Features. Proceedings of the 4th International Symposium on Applied Sciences in Biomedical and Communication Technologies, 2011 October 26-29. Barcelona, Spain. New York: ACM; 2011. <http://dl.acm.org/citation.cfm?id=2093766&preflayout=tab>s. [Last accessed on 2015 Aug 27].
14. Nayak R, Kumar P, Galigekere RR. Towards a Comprehensive Assessment of Wound Composition by Color Image Processing. Proceedings of the 4th International Conference on Image Processing, 2009 November 7-10. Cairo, Egypt, New York: IEEE; 2009. p. 4185-8.
15. Varedas F, Mesa H, Morente L. Binary classification on wound images with neural networks and bayesian classifiers. *IEEE Trans Med Imaging* 2010;29:410-27.
16. Mukherjee R, Manohar DD, Das DK, Achar A, Mitra A, Chakraborty C. Automated tissue classification framework for reproducible chronic wound assessment. *Biomed Res Int* 2014;2014:851582.
17. Kolesnik M, Fexa A. How Robust is SVM Wound Segmentation? Proceedings of the 7th Nordic Symposium on Signal Processing, 2006 June, 7-9. Reykjavik, New York: IEEE; 2006. p. 50-3.
18. Gonzalez RC, Woods RE. Digital Image Processing. 3rd ed. Delhi: Prentice Hall; 2007.
19. Dubois SR, Glanz FH. An autoregressive model approach to two-dimensional shape classification. *IEEE Trans Pattern Anal Mach Intell* 1986;8:55-66.
20. Herbin M, Venot A, Devaux JY, Piette C. Color quantitation through image processing in dermatology. *IEEE Trans Med Imaging* 1990;9:262-9.
21. Raykov T, Marcoulides GA. An Introduction to Applied Multivariate Analysis. New York: Routledge Taylor and Francis Group; 2008.
22. Duda RO, Hart PE, Stork DG. Pattern Classification. 2nd ed. Hoboken: Wiley; 2001.
23. Gashaw A, Mohammed H, Singh H. Genetic divergence in selected durum wheat genotypes of Ethiopian plasm. *Afr Crop Sci J* 2007;15:67-72.
24. Hertzog C. On pooling covariance matrices for multivariate analysis. *Educ Psychol Meas* 1986;46:349-52.

A comparative study to evaluate the effect of limited access dressing on diabetic ulcers

Thittamaranahalli Muguregowda Honnegowda¹, Pramod Kumar^{1,2}, Krishnananda Prabhu³, Ashwini Kumar⁴, Pragna Rao³, E. G. Padmanabha Udupa³, Shobha Kamath³, Antony Sylvan D' Souza⁵, Krishna Kishore Mahato⁶

¹Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India.

²Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

³Department of Biochemistry, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁴Department of Forensic Medicine, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁵Department of Anatomy, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁶Department of Biophysics, School of Life Sciences, Manipal 576104, Karnataka, India.

Address for correspondence: Dr. Thittamaranahalli Muguregowda Honnegowda, Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India. E-mail: honnegowda33@gmail.com

ABSTRACT

Aim: Emerging evidence favors the important role of antioxidants, matrix metalloproteinases (MMPs), and nitric oxide (NO) in the healing of diabetic wounds. There is a lack of substantial evidence regarding the effects of negative pressure on antioxidants, MMPs and NO in chronic wounds associated with diabetes. **Methods:** A total of 55 type 2 diabetic patients with leg ulcers were divided into 2 groups: a limited access dressing (LAD) group ($n = 27$) and a conventional dressing group ($n = 28$). Levels of hydroxyproline, total protein, MMP-2 and MMP-9, NO and antioxidants including reduced glutathione (GSH) and the oxidative biomarker malondialdehyde (MDA) were measured in the granulation tissue at days 0 and 10. Changes in levels between the LAD and conventional groups were determined by the Student's *t*-test. **Results:** After 10 days of treatment, the LAD *vs.* conventional dressing group showed increase in the levels of hydroxyproline (mean \pm standard deviation = 55.2 ± 25.1 *vs.* 29.2 ± 1 , $P < 0.05$), total protein (12.8 ± 6.5 *vs.* 8.34 ± 3.2 , $P < 0.05$), NO (1.13 ± 0.52 *vs.* 0.66 ± 0.43 , $P < 0.05$), GSH (7.0 ± 2.4 *vs.* 6.6 ± 2.2 , $P < 0.05$) and decrease in MMP-2 (0.47 ± 0.33 *vs.* 0.62 ± 0.30 , $P < 0.05$), MMP-9 (0.32 ± 0.20 *vs.* 0.53 ± 0.39 , $P < 0.05$) and MDA (6.8 ± 2.3 *vs.* 10.4 ± 3.4 , $P < 0.05$). **Conclusion:** When compared to conventional dressings, LAD induces biochemical changes by significantly increasing the levels of hydroxyproline, total protein, NO and antioxidants levels, and significantly reducing MMPs (MMP-2 and MMP-9) and an oxidative biomarker in diabetic wounds. These biochemical changes are thought to favor diabetic wound healing.

Key words:

Antioxidants, diabetic wounds, hydroxyproline, limited access dressing, matrix metalloproteinases, nitric oxide, reactive oxygen species and oxidative stress biomarker, total protein

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Honnegowda TM, Kumar P, Prabhu K, Kumar A, Rao P, Padmanabha Udupa EG, Kamath S, D' Souza AS, Mahato KK. A comparative study to evaluate the effect of limited access dressing on diabetic ulcers. *Plast Aesthet Res* 2015;2:266-71.

Received: 02-05-2015; **Accepted:** 28-06-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165448

INTRODUCTION

Wound healing is a self-regulated physiological process of cell regeneration which occurs without any external stimuli. This is accomplished by the stages of fibroplasia, angiogenesis, and migration of fibroblasts, endothelial, and epithelial cells, finally leading to the wound contraction.^[1] Inflammation is a vital and protective response instigated by injured cells at the wound site which begins the process of tissue repair.^[2] In response to inflammation, reactive oxygen species (ROS) such as free radicals (superoxide anion radical: O_2^-) and nonradical hydrogen peroxide (H_2O_2), are generated continuously until inflammation subsides.^[3] Free radicals and their scavenging systems play an important role in normal and delayed wound healing.^[4,5]

Delayed healing of diabetic wounds is characterized by an increase in matrix metalloproteinases (MMPs), a decrease in the tissue inhibitors of metalloproteinases (TIMPs),^[6] and an altered magnitude of free radical generation and disposal.^[7] An imbalance between oxidant and antioxidant defense mechanisms leads to oxidative stress resulting in lipid peroxidation, DNA damage, and inactivation of free radical scavenger enzymes.^[8] This leads to tissue damage and impairs the healing process in diabetic wounds with reduced angiogenesis, altered proliferation of fibroblasts, reduced fibroblast migration, inadequate collagen deposition, advanced glycation, and abnormal mitochondrial function.^[9-11]

Nitric oxide (NO) is a mediator which plays an important role in wound healing and has been implicated in diabetic wounds. Reduced levels can cause alterations in vascular permeability and a reduction of capillary flow causing oxidative stress.^[12] Antioxidants such as reduced glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT), and thiol (-SH) prevent the generation and action of ROS. Hence, antioxidants that provide potential mechanisms for wound healing can ameliorate diabetic complications by both significantly preventing tissue damage and stimulating the wound healing process.^[13,14]

Several studies have demonstrated the negative role of free radicals on wound healing; reduction of persistent inflammation; and elimination of free radicals may improve healing in diabetic wounds.^[15] Although advanced technologies have been developed for the treatment of diabetic wounds, outcomes have been poor. Negative pressure wound therapy (NPWT) has emerged as a treatment for complex wounds. This is a noninvasive system which creates a localized and controlled sub atmospheric pressure environment. Wound healing by delayed primary or secondary intention is promoted by the creation of a moist wound environment which prepares the wound bed for closure, reduces edema, and promotes the formation and perfusion of granulation tissue.^[16,17] The clinical evidence supporting the use of continuous NPWT on diabetic wounds has been based largely on clinician perception, case series, small cohort studies, and weakly powered randomized trials that

constitute a substantial number of publications but an overall low amount of evidence. Evidence is lacking on the use of an intermittent negative pressure dressing which would be more economical and clinically acceptable^[17] than the use of continuous NPWT.

The present study evaluates the role of intermittent negative pressure using limited access dressing (LAD) (a cycle of 30 min of suction and 3.5 h of rest) on diabetic wounds by measuring and comparing the levels of hydroxyproline, total protein, NO, antioxidants (GSH), and an oxidative biomarker malondialdehyde (MDA) in the granulation tissue of type 2 diabetes mellitus ulcer patients.

METHODS

Ethical approval and informed consent

This prospective randomized controlled trial study was carried out in the Department of Plastic Surgery, Kasturba Hospital, Manipal. The Institutional Ethics Committee reviewed and approved the study protocol. Written informed consent was obtained from all patients or their next of kin prior to inclusion in the study.

Study design

Patients were diagnosed on the basis of history, physical examination, and biochemical investigation. Seventy-five patients more than 40 years of age (mean age: 56 years) suffering from chronic diabetic wounds with insulin-controlled diabetes were enrolled in the study. After evaluation for inclusion (diabetic leg ulcers) and exclusion criteria (collagen disorders, leprosy, pregnancy, cirrhosis, and HIV positive status), 55 patients were randomized of whom 27 were assigned to the LAD group and 28 were assigned to the conventional dressing group. Biopsies were taken from both groups on day 0 of the study. The LAD group patients were treated with intermittent negative pressure and a moist wound environment, and wounds were washed daily with a solution of povidone-iodine. Conventional dressing group patients were dressed daily with 5% povidone-iodine solution soaked gauze. On day 10, granulation tissue biopsies were taken from both groups and subjected to biochemical study by an investigator blinded to the clinical data.

Randomization

Patients were randomized by generating tables of random numbers through www.random.org. Numbers were assigned to a treatment group and sealed in opaque envelopes containing labeled paper with the treatment and the patient's ID.

Chemicals

All chemical used were of analytical grade. Standard L-hydroxyproline, bovine serum albumin (BSA), standard GSH, 1-chloro-2,4-dinitrobenzene, and cumene H_2O_2 were purchased from Sigma-Aldrich (St. Louis, MO, USA). Thiobarbituric acid (TBA), trichloroacetic acid (TCA), 1,1,3,3-tetramethoxypropane N-ethylmaleimide (NEM), and orthophosphoric acid were purchased from S.D. Fine-Chemicals Ltd. (Boisar, India).

Tissue preparation for assays

Tissue preparation for hydroxyproline estimation

The granulation tissue specimens were dried at 60°C for 24 h and then were weighed and kept in glass-stoppered test tubes. 6N HCl was added to each tube for a total of 40 mg of dried granulation tissue per ml of acid. The tubes were kept in boiling water bath for a total of 24 h (12 h and each for 2 days) for hydrolysis. The hydrolysate was then cooled, and the excess acid was neutralized by 10N sodium hydroxide (NaOH) using phenolphthalein/methyl red as an indicator. The volume of neutral hydrolysate was diluted with distilled water to a concentration of 20 mg/mL of dried granulation tissue in the final hydrolysate. The hydrolysate was used to estimate the level of hydroxyproline.^[18]

Tissue preparation for estimation of antioxidants and oxidative biomarkers

The wet weight of the granulation tissue samples was noted and homogenized by a Rotex homogenizer in ice-cold 0.2 M phosphate buffer (pH 7.4). Homogenates were centrifuged at 15,000 rpm for 30 min in a cooling centrifuge, and the supernatant was then used to determine total protein, GSH, and an oxidative biomarker (MDA).

For the MMP-2 assay, the granulation tissue was rinsed in ice-cold phosphate buffer saline (PBS) (0.1 mol/L, pH 7.0-7.2) to remove all traces of excess blood and weighed prior to homogenization. The tissues were minced into small pieces and homogenized on ice in 5 mL of PBS. The resulting suspension was sonicated with an ultrasonic cell disrupter or subjected to two freeze-thaw cycles to further break the cell membranes. The homogenates were then centrifuged for 5 min at 50 g, removing the supernatant and aliquot store at no more than -80°C.

For the NO assay, the tissue was homogenized in an isotonic solution of PBS containing 10 mM of NEM and 2.5 mmol ethylenediaminetetraacetic acid (EDTA). The addition of NEM/EDTA blocks the SH-groups while inhibiting the transition of metal-catalyzed trans-nitrosation reactions, preventing artificial nitrosation and thiolate- and ascorbate-mediated degradation of endogenous Nitrosothiols and nitrite (NO_2^-). The protein concentration was determined according to Lowry *et al.*^[19] using purified BSA as the standard.

Estimation of biochemical parameters

Hydroxyproline

The dried tissue was added to 10 mL of 6N HCl and stored at 110°C for 24 h. The neutralized acid hydrolysate of the dry tissue was used to determine the level of hydroxyproline. The reaction mixture contains 0.05 M copper sulfate, 2.5N NaOH, 6% H_2O_2 , 3N sulfuric acid, and 5% p-dimethylaminobenzaldehyde using L-hydroxyproline as the standard. Absorbance was measured at 540 nm and expressed as $\mu\text{g}/\text{mg}$ of dry tissue weight.^[18]

Total protein

The total protein content of the wound tissue homogenate was determined according to the method of Lowry *et al.*^[19] Absorbance was measured at 540 nm and expressed in mg/g of tissue. Standards were treated similarly using BSA at concentrations of 0, 20, 40, 60, 80, and 100 $\mu\text{g}/\text{mL}$ in 0.1 M phosphate buffer at pH 7.4.

Matrix metalloproteinase-2 and -9

A total of 100 mg of tissue was homogenized in 1 mL of ice-cold lysis buffer. Subsequently, homogenates were centrifuged at 3,000 g for 5 min at 4°C, and supernatants were stored at -80°C until use. MMP-2 and MMP-9 were measured using prefabricated ELISA kits, according to manufacturer protocol (R and D Systems, USCN Life Science Inc., USA). Plates were read at 450 nm and 540 nm, and concentrations were calculated using a 4-point standard curve and expressed as ng/mg of protein.^[20]

Nitric oxide estimation

The level of NO was estimated as NO_2^- , an NO metabolite in tissue samples. NO is a highly reactive free radical gas which is a ready oxidizer and remains stored in tissues as nitrates (NO_3^-) or NO_2^- . Thus, NO concentration can be estimated by measuring concentrations of NO_3^- and NO_2^- in combination. The simplest technique is to monitor the reduction of NO_3^- to NO_2^- by nitrate reductase or a metallic catalyst, followed by the colorimetric Griess reaction to measure NO_2^- levels (nitrite levels).

Sample NO_2^- levels were estimated by a colorimetric assay which is based on the Griess reaction. Using a two-step diazotization reaction, acidified NO_2^- produces a nitrosating agent which reacts with sulfa nitric acid to produce the diazonium ion. This ion is then coupled to N-(1-naphthyl) ethylenediamine dihydrochloride to form a red azo derivative which is measured at 550 nm using a spectrophotometer. The concentrations of NO_2^- are calculated from a standard curve established with serial dilutions of sodium NO_2^- .^[21]

Glutathione estimation

The reaction mixture was prepared by adding 80 μL of tissue supernatant to 0.9 mL of 0.2 M sodium phosphate buffer of pH 7.00 and 20 μL of 10 mM 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) solution. The yellow-colored substance formed by the reaction of GSH and DTNB was measured at 412 nm. The results were expressed as GSH $\mu\text{mol}/\text{mg}$ protein.^[22]

Malondialdehyde

The MDA levels of wound tissue homogenate were measured according to the method of Ohkawa *et al.*^[23] To 0.1 mL of the test sample, 1 mL of 10% TCA and 1 mL of 0.67% TBA were added and then heated in a boiling water bath at 100°C for 30 min. The mixture was cooled under tap water and centrifuged at 12,000 rpm for 10 min. Clear supernatant was determined by the absorbance at 535 nm and expressed as nmol/mg protein.

Statistical analysis

Statistical analysis for biochemical parameters was performed by Student's *t*-test, and data were expressed as

mean \pm standard deviation (SD). $P < 0.05$ was considered to be significant, when appropriate, statistical uncertainty was expressed by 95% confidence levels.

RESULTS

A total of 75 patients were enrolled of which 55 patients were randomized; with 27 patients assigned to the LAD group and 28 patients assigned to the conventional group [Figure 1]. Five participants were lost to follow-up (two in the LAD and three in the conventional group) before the biopsies could be taken. The results of hydroxyproline, total protein, MMP-2 and MMP-9, GSH, NO, and MDA levels in diabetic ulcers are shown [Table 1].

Hydroxyproline

After 10 days of treatment, the LAD group had significantly higher hydroxyproline level (mean \pm SD = 55.2 ± 25.1 μ g/mg dry tissue weight) than the conventional group (29.2 ± 13.5 μ g/mg dry tissue weight), $P = 0.000$.

Total protein

After 10 days of treatment, the LAD group had significantly higher total protein levels (mean \pm SD = 12.8 ± 6.5 mg/g wet tissue weight) than

the conventional group (8.34 ± 3.2 mg/g wet tissue weight), $P = 0.011$.

Matrix metalloproteinases-2 and matrix metalloproteinases-9

After 10 days of treatment, MMP-2 (0.47 ± 0.33 ng/mg tissue protein, $P = 0.041$) and MMP-9 levels (0.32 ± 0.20 ng/mg tissue protein, $P = 0.037$) in LAD group were significantly lower than the conventional group MMP-2 (0.62 ± 0.30 ng/mg tissue protein) and MMP-9 (0.53 ± 0.39 ng/mg tissue protein).

Nitric oxide

After 10 days of treatment, the LAD group had a significantly high total protein level (mean \pm SD = 1.13 ± 0.52 nmol/mg protein) than the conventional group (0.66 ± 0.43 nmol/mg protein), $P = 0.019$.

Reduced glutathione

After 10 days of treatment, antioxidant (reduced GSH) levels in the LAD group were significantly higher (mean \pm SD = 7.0 ± 2.4 μ mol/mg protein) as compared to those in the conventional dressing group (6.6 ± 2.2 μ mol/mg protein), $P = 0.044$.

Malondialdehyde

After 10 days of treatment, MDA levels were significantly higher in the conventional dressing group (mean \pm SD = 10.4 ± 3.4 nmol/mg protein) as compared to the LAD group (6.8 ± 2.3 nmol/mg protein), $P = 0.024$.

DISCUSSION

Diabetes is a multisystem disorder which induces physiological changes in tissues and cells that impair the normal healing process. Diabetic wounds can have prolonged periods in the inflammatory phase of healing, with a continuous influx of neutrophils that release cytotoxic enzymes, free radicals, and inflammatory mediators, causing extensive collateral damage to the surrounding tissue.^[24-26]

In the treatment of diabetic ulcers, the NPWT wound dressing provides faster wound resolution as compared to gauze dressings. NPWT may be beneficial in the treatment of nonhealing diabetic wounds of the lower

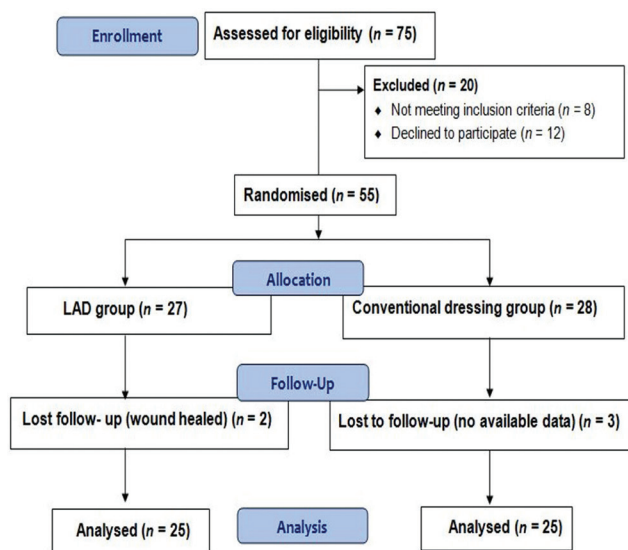


Figure 1: Consort flow chart

Table 1: Results of hydroxyproline, total protein, MMP-2 and MMP-9, NO, GSH, and MDA levels in granulation tissue of diabetic ulcer in LAD group and conventional dressing group

Parameters	Mean ± SD						P
	LAD group			Conventional dressing group			
	Day 0	Day 10	Day (0-10)	Day 0	Day 10	Day (0-10)	
Hydroxyproline (µg/mg of dry weight of tissue)	46.9 ± 16.0	100 ± 6.6	55.2 ± 25.1	51.5 ± 10.9	80.7 ± 15.6	29.2 ± 13.5	0.000
Total protein (mg/g of wet weight tissue)	11.7 ± 3.2	24.3 ± 5.9	12.8 ± 6.5	12.0 ± 2.6	20.6 ± 4.8	8.34 ± 3.2	0.011
MMP-2 (ng/mg tissue protein)	0.95 ± 0.20	0.48 ± 0.42	0.47 ± 0.33	0.97 ± 0.52	0.35 ± 0.49	0.62 ± 0.30	0.041
MMP-9 (ng/mg tissue protein)	0.87 ± 0.54	0.55 ± 0.25	0.32 ± 0.20	0.93 ± 0.22	0.40 ± 0.32	0.53 ± 0.39	0.037
NO (nmol/mg protein)	2.0 ± 1.42	3.13 ± 1.3	1.13 ± 0.52	2.74 ± 1.4	3.4 ± 1.44	0.66 ± 0.43	0.019
GSH (µmol/mg protein)	16.1 ± 4.3	23.1 ± 3.3	7.0 ± 2.4	14.9 ± 3.5	21.5 ± 3.79	6.6 ± 2.2	0.044
MDA (nmol/mg protein)	19.3 ± 3.8	12.5 ± 4.8	6.8 ± 2.3	19.9 ± 4.5	9.5 ± 4.5	10.4 ± 3.4	0.024

MMP: Matrix metalloproteinase, NO: Nitric oxide, GSH: Glutathione, MDA: Malondialdehyde, LAD: Limited access dressing, SD: Standard deviation

extremity.^[27] The intermittent negative pressure regimen used in LAD has been shown to be an economical and effective alternative in treating traumatic wounds.^[28,29]

Evidence shows that increased oxidative stress causes delayed wound healing in diabetics with altered antioxidant enzyme activities.^[30] Various studies^[31,32] have shown a significant reduction in collagen content in the granulation tissue of diabetic animals. The authors of these studies have proposed that the decreased collagen levels seen in diabetic wounds are likely in response to an altered extracellular environment (i.e. hyperglycemia, persistent inflammation, excess H_2O_2 and free radical production, and low levels of antioxidants). Collagen is the major component of extracellular tissue which provides support and strength. It is measured by monitoring the concentration of hydroxyproline, that is, synthesized by fibroblasts^[33] and is vulnerable to the effects of free radicals. In the present study, after 10 days of therapy, the mean level of hydroxyproline (\pm SD) was significantly higher in the LAD group as compared to that of the conventional dressing group (LAD vs. conventional = 55.2 ± 25.1 vs. 29.2 ± 13.5 μ g/mg of dry weight of tissue, $P = 0.000$). The concentration of protein found in the wound's granulation tissue was higher in the LAD group (12.8 ± 6.5 mg/g wet tissue weight) than in the conventional group (8.34 ± 3.2 mg/g wet tissue weight), $P = 0.011$.

In a study by Lobmann *et al.*,^[34] higher concentrations of the MMP-2 and MMP-9, in conjunction with lower concentrations of TIMP-2, were found in tissue biopsies of diabetic wounds as compared to healthy controls.^[34] Another study by Liu *et al.*^[35] showed that high MMP-9 levels were indicative of poor wound healing in diabetics. In the present study, significant decreases in the concentrations of MMP-2 (0.47 ± 0.33 ng/mg tissue protein, $P = 0.041$) and MMP-9 (0.32 ± 0.20 ng/mg tissue protein, $P = 0.037$) were observed in the LAD group versus the conventional group after 10 days of treatment.

Normal physiological amounts of NO act as a mediator for moderate vasodilatation and are required to increase blood flow and vascular permeability. Endothelial dysfunction and decreased NO production are observed in diabetic patients with a consequent delay in wound healing due to decreased tissue perfusion.^[36] After 10 days of therapy, the mean level of NO (\pm SD) was significantly higher in the LAD group as compared to that in the conventional dressing group (LAD vs. conventional = 1.13 ± 0.52 vs. 0.66 ± 0.43 nmol/mg protein; $P = 0.019$).

Decreased levels of the enzymatic antioxidants, GPx, CAT, and GSH may contribute to diminished defense mechanisms against free radical overload in diabetic wounds.^[37] Antioxidants hasten the process of wound healing by destroying free radicals.^[38] In the present study, after 10 days of treatment, the levels of antioxidants in granulation tissue were significantly higher in the LAD group as compared to the conventional dressing group (LAD vs. conventional = 7.0 ± 2.4 vs. 6.6 ± 2.2 μ mol/mg protein, $P = 0.044$). Lipid peroxidation is an important

pathophysiological event in diabetes.^[39] It is well known that MDA from lipid peroxidation reacts with DNA bases and induces mutagenic lesions.^[40] In the present study, after 10 days of therapy, the mean level of MDA (\pm SD) was significantly less in the LAD group than in the conventional dressing group (LAD vs. conventional = 6.8 ± 2.3 vs. 10.4 ± 3.4 nmol/mg protein, $P = 0.024$).

In conclusion, LAD (intermittent NPWT and moist wound dressing) exerts a beneficial effect on diabetic wound healing as seen by a significant increase in the levels of hydroxyproline, total protein, NO, antioxidants, a decrease in MMP-2 and MMP-9, and oxidative biomarkers (MDA) as compared to conventional dressings.

The use of intermittent NPWT using LAD may be an effective alternative therapy used to achieve faster granulation of the wound bed in diabetic ulcers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med* 1999;341:738-46.
2. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol* 2007;127:514-25.
3. Khodr B, Khalil Z. Modulation of inflammation by reactive oxygen species: implications for aging and tissue repair. *Free Radic Biol Med* 2001;30:1-8.
4. Hallberg CK, Trocme SD, Ansari NH. Acceleration of corneal wound healing in diabetic rats by the antioxidant Trolox. *Res Commun Mol Pathol Pharmacol* 1996;93:3-12.
5. McDaniel DH, Ash K, Lord J, Newman J, Zukowski M. Accelerated laser resurfacing wound healing using a triad of topical antioxidants. *Dermatol Surg* 1998;24:661-4.
6. Madlener M, Parks WC, Werner S. Matrix metalloproteinases and their physiological inhibitors (TIMPs) are differentially expressed during excisional skin wound repair. *Exp Cell Res* 1998;242:201-10.
7. Kakkar R, Kalra J, Mantha SV, Prasad K. Lipid peroxidation and activity of antioxidant enzymes in diabetic rats. *Mol Cell Biochem* 1995;151:113-9.
8. Wiseman H, Halliwell B. Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer. *Biochem J* 1996;313:17-29.
9. Sivitz WI, Yorek MA. Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. *Antioxid Redox Signal* 2010;12:537-77.
10. Rolo AP, Palmeira CM. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. *Toxicol Appl Pharmacol* 2006;212:167-78.
11. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res* 2010;89:219-29.
12. Hsu WT, Tsai LY, Lin SK, Hsiao JK, Chen BH. Effects of diabetes duration and glycemic control on free radicals in children with type I diabetes mellitus. *Ann Clin Lab Sci* 2006;36:174-8.
13. Flora SJ. Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure. *Oxid Med Cell Longev* 2009;2:191-206.
14. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 2007;39:44-84.
15. Honnegowda TM, Kumar P, Udupa P, Rao P, Bhandary S, Mahato KK, Sharan A, Mayya SS. Effect of limited access dressing on hydroxyproline and enzymatic antioxidant status in nonhealing chronic ulcers. *Indian J Plast Surg* 2014;47:216-20.
16. Polack G, McCray V, Tyner T, Kane S, Vu K, Yamaguchi K Jr, Merriman J, Ishimoto M, Hasson A, Sian K, Yamaguchi KT. Accelerated wound closure in a

- diabetic mouse model after exposure to phenanthrenequinone. *Ann Plast Surg* 2013;70:720-5.
17. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008;31:631-66.
 18. Neuman RE, Logan MA. The determination of collagen and elastin in tissues. *J Biol Chem* 1950;86:549-56.
 19. Lowry OH, Rosebrough MH, Farr L, Randell RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951;193:265-75.
 20. Young PK, Grinnell F. Metalloproteinase activation cascade after burn injury: a longitudinal analysis of the human wound environment. *J Invest Dermatol* 1994;103:660-4.
 21. Green LC, Wagner DA, Glogowski J, Skipper PL, Wishnok JS, Tannenbaum SR. Analysis of nitrate, nitrite, and [15N]nitrate in biological fluids. *Anal Biochem* 1982;126:131-8.
 22. Beutler E, Duron O, Kefly BM. Improved method for the determination of blood glutathione. *J Lab Clin Med* 1963;61:882-8.
 23. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem* 1979;95:351-8.
 24. Abd-El-Aleem SA, Ferguson MW, Appleton I, Kairsingh S, Jude EB, Jones K, McCollum CN, Ireland GW. Expression of nitric oxide synthase isoforms and arginase in normal human skin and chronic venous leg ulcers. *J Pathol* 2000;191:434-42.
 25. Rojkind M, Domínguez-Rosales JA, Nieto N, Greenwel P. Role of hydrogen peroxide and oxidative stress in healing responses. *Cell Mol Life Sci* 2002;59:1872-91.
 26. Moseley R, Hilton JR, Waddington RJ, Harding KG, Stephens P, Thomas DW. Comparison of oxidative stress biomarker profiles between acute and chronic wound environments. *Wound Repair Regen* 2004;12:419-29.
 27. Joseph E, Hamori CA, Bergman S, Roaf E, Swann NF, Anastasi GW. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. *Wounds* 2000;12:60-7.
 28. Kumar P. Exploiting potency of negative pressure in wound dressing using limited access dressing and suction-assisted dressing. *Indian J Plast Surg* 2012;45:302-15.
 29. Kumar P, Sharma A. The limited access dressing for damage control in trauma patients. *Wounds* 2010;22:188-92.
 30. Rasik AM, Shukla A. Antioxidant status in delayed healing type of wounds. *Int J Exp Pathol* 2000;81:257-63.
 31. Tengrup I, Hallmans G, Agren MS. Granulation tissue formation and metabolism of zinc and copper in alloxan-diabetic rats. *Scand J Plast Reconstr Surg Hand Surg* 1988;22:41-5.
 32. Spanheimer RG, Umpierrez GE, Stumpf V. Decreased collagen production in diabetic rats. *Diabetes* 1988;37:371-6.
 33. Honnegowda TM, Kumar P, Padmanabha Udupa EG, Sharan A, Singh R, Prasad HK, Rao P. Effects of limited access dressing in chronic wounds: a biochemical and histological study. *Indian J Plast Surg* 2015;48:22-8.
 34. Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schiweck S, Lehnert H. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. *Diabetologia* 2002;45:1011-6.
 35. Liu Y, Min D, Bolton T, Nubé V, Twigg SM, Yue DK, McLennan SV. Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers. *Diabetes Care* 2009;32:117-9.
 36. Boykin JV Jr. Wound nitric oxide bioactivity: a promising diagnostic indicator for diabetic foot ulcer management. *J Wound Ostomy Continence Nurs* 2010;37:25-32.
 37. Johansen JS, Harris AK, Rychly DJ, Ergul A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. *Cardiovasc Diabetol* 2005;4:5.
 38. Honório-França AC, Marins CM, Boldrini F, França EL. Evaluation of hypoglycemic activity and healing of extract from amongst bark of "Quina do Cerrado" (*Strychnos pseudoquina* ST.HILL). *Acta Cir Bras* 2008;23:504-10.
 39. Ceriello A, Quatraro A, Caretta F, Varano R, Giugliano D. Evidence for a possible role of oxygen free radicals in the abnormal functional arterial vasomotion in insulin dependent diabetes. *Diabete Metab* 1990;16:318-22.
 40. Al-Bayat F, Ameen Abdulla M. A comparison of wound healing rate following treatment with aftamed and chlorine dioxide gels in streptozotocin-induced diabetic rats. *Evid Based Complement Alternat Med* 2012;2012:468764.

Histopathological study of chronic wounds modulated by intermittent negative pressure therapy under limited access dressing

Thittamaranahalli Muguregowda Honnegowda¹, Pramod Kumar^{1,2}, Rekha Singh³, Swarna Shivakumar⁴, Pragna Rao⁵, Hemanth K. Prasad⁵, Sudesh Kumar⁶, Udaya Kumar⁶, Echalasara Govindarama Padmanabha Udupa⁵

¹Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India.

²Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

³Department of Pathology, Vydehi Institute of Medical Sciences and Research Center, Bengaluru 560066, Karnataka, India.

⁴Department of Pathology, Apollo Hospitals, Bengaluru 560066, Karnataka, India.

⁵Department of Biochemistry, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁶Department of Surgery, Government District Hospital, Udupi 576101, Karnataka, India.

Address for correspondence: Dr. Thittamaranahalli Muguregowda Honnegowda, Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India. E-mail: honnegowda33@gmail.com

ABSTRACT

Aim: Negative pressure wound therapy (NPWT) has achieved widespread success in the treatment of chronic wounds. However, its effects have been only partially explored, and investigations have generally concentrated on the wound-dressing interface; a detailed histopathological description of the evolution of wounds under NPWT is still lacking. The present study was performed to investigate the effect of a limited access dressing (LAD) which exerts intermittent NPWT in a moist environment on chronic wounds. **Methods:** A total of 140 patients were randomized into 2 groups: LAD group ($n = 64$) and conventional dressing group ($n = 76$). By histopathological analysis of the granulation tissue, the amount of inflammatory infiltrate, necrotic tissue, angiogenesis, and extracellular matrix (ECM) deposition was studied and compared to determine healing between the 2 groups. **Results:** After 10 days of treatment, histopathological analysis showed a significant decrease in necrotic tissue with LAD compared to the conventional dressing group (mean \pm standard error, 11.5 ± 0.48 vs. 10.1 ± 0.30 , $P = 0.007$), the number of inflammatory cells (12.6 ± 0.60 vs. 8.63 ± 0.35 , $P = 0.018$), a significant increase in new blood vessels (12.8 ± 0.58 vs. 9.3 ± 0.29 , $P = 0.005$) and ECM deposit (13.3 ± 0.50 vs. 9.6 ± 0.24 , $P = 0.001$). **Conclusion:** LAD exerts its beneficial effects on chronic wound healing by decreasing the amount of necrotic tissue and inflammatory cells while increasing the amount of ECM deposition and angiogenesis.

Key words:

Angiogenesis, chronic wounds, extracellular matrix, granulation tissue, inflammatory cell, limited access dressing, necrotic tissue, negative pressure wound therapy

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Honnegowda TM, Kumar P, Singh R, Shivakumar S, Rao P, Prasad HK, Kumar S, Kumar U, Udupa EG. Histopathological study of chronic wounds modulated by intermittent negative pressure therapy under limited access dressing. *Plast Aesthet Res* 2015;2:272-6.

Received: 20-11-2014; **Accepted:** 28-01-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.156993

INTRODUCTION

Negative pressure wound therapy (NPWT) is a bio-stimulating treatment for chronic wounds. In recent years, it has become one of the most frequently adopted treatments for complex wounds worldwide. While it is generally believed that NPWT improves wound healing and is cost-effective, there is a persistent demand for scientific evidence.

Several recent studies support the use of NPWT to enhance wound healing by removing excess extracellular fluid and decreasing tissue edema, which leads to increased blood flow^[1] and stabilization of the wound environment. A reduction in systemic (e.g. interleukins, monocytes) and local mediators of inflammation has been demonstrated in experimental models,^[2] while decreased matrix metalloproteinase activity^[3] and bacterial burden have been documented clinically.^[4] *In vivo*, NPWT has been shown to increase fibroblast proliferation and migration, collagen organization, and to increase the expression of vascular endothelial growth factor and fibroblast growth factor-2, thereby enhancing wound healing.^[5]

Limited access dressings (LADs) have been shown to be more effective in the treatment of chronic wounds.^[6] The present study evaluates the role of intermittent negative pressure in a moist environment using LAD (cycle of 30-min suction and 3.5-h rest) on chronic wounds by quantitative and comparative analysis of histopathological parameters including the amount of necrotic tissue, the number of inflammatory cells, extent of angiogenesis, and the level of extracellular matrix (ECM) deposit.

METHODS

Ethical approval and informed consent

This prospective randomized study was carried out in the Department of Plastic Surgery and Burns, Kasturba Medical College and Hospital, Manipal, India. The Institutional Ethics Committee reviewed and approved the study protocol. Informed consent was obtained from all patients or their next of kin (as applicable) before inclusion into the study.

Clinical study design

Two hundred and fifteen patients with chronic wounds of more than 4 weeks duration were enrolled and assessed for eligibility. After examination of inclusion criteria (nonhealing chronic wounds, 12-65 years of age) and exclusion criteria (collagen disorders, diabetes, leprosy, liver cirrhosis, HIV positive status, and pregnant women), 140 patients were randomized into the LAD group ($n = 64$) or conventional dressing group ($n = 76$) [Figure 1]. In the LAD group, the mean age was 38.3 ± 10.56 years (range: 12-60 years), with a mean wound size at the time of admission of 19 cm^2 (range: 28-40 cm^2). In the conventional dressing group, the mean age was 35.3 ± 14.0 years (range: 17-65 years) with a mean wound size at the time of admission of 18 cm^2 (range: 26-39 cm^2) [Table 1].

The LAD group was treated with intermittent negative pressure in a moist environment. The conventional closed dressing group was treated with daily dressing changes using a squeezed 5% povidone-iodine gauze which is a routine protocol in our burn unit.^[7]

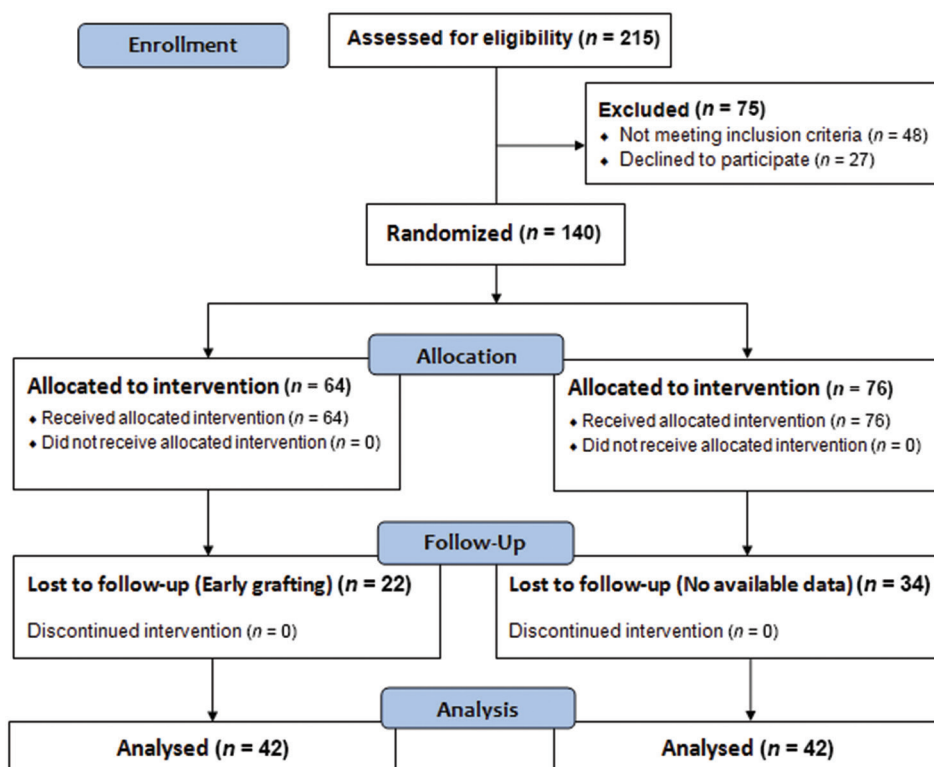


Figure 1: Consort flow chart

Wounds were washed daily both the LAD group and the conventional group prior to dressing with 5% povidone-iodine solution. Of these 140 patients, 56 participants (22 in the LAD group and 34 in the conventional dressing group) were lost to follow-up. Of 42 patients in the LAD group, 22 (52%) were women, and 20 (48%) were men. In the conventional dressing group, 18 (42.8%) were women, and 24 (57.1%) were men. Biopsies were taken on days 0 and 10 and were analyzed for the histopathologic parameters under study.

Randomization

Patients were randomized by generating tables of random numbers through www.random.org. Numbers were assigned to a treatment group and sealed in opaque envelopes containing labeled paper with the treatment and patient ID.

Tissue preparation for histopathologic study

Wound biopsies performed on days 0 and 10 were collected, fixed in 10% formalin, dehydrated through an increasing alcohol series (50%, 70%, 90%, and 100%), cleared in xylene and embedded (Leica EG1150 H) in paraffin wax (melting point 56°C). Serial sections of 5 µm thickness were cut using a microtome (Leica RM2255) and were stained with hematoxylin-eosin (Sigma-Aldrich, MO, USA). Each section was evaluated in 8 microscopic fields (×100) under light microscopy (Olympus PM20). Histopathology slides were graded using a modified 0-4 Ehrlich and Hunt numerical scale, and modified and internally validated in our laboratory on a scale of 1-3, with 1 representing necrosis, 2 representing inflammatory cell infiltration (white blood cell and fibroblast count), and 3 representing ECM deposition. We used a 5-point scale to evaluate the presence of necrosis and inflammatory cell infiltration (0, no evidence; 1, occasional evidence; 2, light scattering; 3, abundant evidence; 4, confluent cell) as previously described,^[8] and used a 4-point scale to evaluate the presence of ECM deposition (0, no evidence; 1, little ECM deposition; 2, moderate ECM deposition; 3, confluent ECM deposition) as previously described.^[8] In determining the degree of angiogenesis, only mature vessels were counted and identified by the presence of erythrocytes in their lumen.^[9] The score was assigned by 2 investigators. The code describing the specific treatment received by the patient was broken after scoring had been completed by the investigators.

Table 1: Patient demographics and baseline wound characterization

Details	LAD group	Conventional group
Number of patients	42	42
Age, years (mean ± SD, range)	(38.3 ± 10.56, 12-60)	(35.3 ± 14.0, 17-65)
Mean wound size (cm ²)	28 (range: 19-40)	26 (range: 18-39)
Female (%)	52	42.8
Male (%)	48	57.1

LAD: Limited access dressing, SD: Standard deviation

Statistical analysis

Statistical analysis was performed using the student's *t*-test for comparisons between groups (SPSS, 15th version (233 South Wacker Drive, 11th Floor, Chicago)). The data were expressed as mean ± standard error (SE). *P* < 0.05 was considered to be significant. When appropriate, statistical uncertainty was expressed with 95% confidence levels.

RESULTS

On day 0, both the LAD and conventional groups showed necrotic tissue with increased inflammatory infiltrates [Figures 2A and 3A]. On day 10, the LAD group [Figure 2B] showed an increase in ECM deposition and angiogenesis with a decrease in inflammatory infiltrate when compared to the conventional group [Figure 3B]. The results of the histopathologic scoring are shown in Table 2. Histopathology revealed that in LAD group after 10 days of treatment, the scores of necrotic tissue (*P* = 0.007) and inflammatory cell infiltrate (*P* = 0.018) were significantly lower than those of the conventional treatment group. The score of ECM deposits and number of blood vessels on day 0 were not well-defined in either group, but on day 10 ECM deposits (*P* = 0.001) and number of blood vessel (*P* = 0.005) were significantly higher in the LAD group than in the conventional group [Table 2, Figure 4].

DISCUSSION

Wound healing is a complex and dynamic process which involves cell-cell interactions and cell-matrix interaction. The proliferative phase of wound healing is marked by angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction resulting in less scar tissue.^[10]

A study by Nain *et al.*^[11] showed a decrease in the amount of necrotic tissue in chronic wounds treated with NPWT. Histopathological analysis showed significantly less necrotic tissue in the LAD group compared to a conventional dressing group after 10 days of treatment (mean ± SE, 11.5 ± 0.48 vs. 10.1 ± 0.30, *P* = 0.007). The ECM is made up of collagen fibers and glycosaminoglycans,

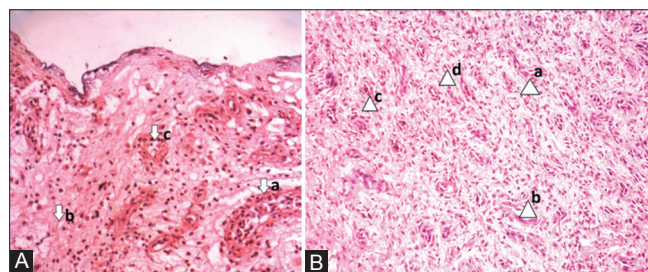


Figure 2: Histopathology of granulation tissue on days 0 and 10 in the limited access dressing (LAD) group. A: (a) LAD group - day 0 - (arrow) abundant inflammatory cells, (b) poorly developed matrix, (c) minimal blood capillaries. (photographed with an Olympus PM20 photomicroscope ×20); B: (a) LAD group - day 10 - (arrow) increased number of fibroblast cells, (b) fewer inflammatory cells, (c) increased proliferating blood capillaries, (d) collagen bundles organized well between the cells (photographed with an Olympus PM20 photomicroscope ×20)

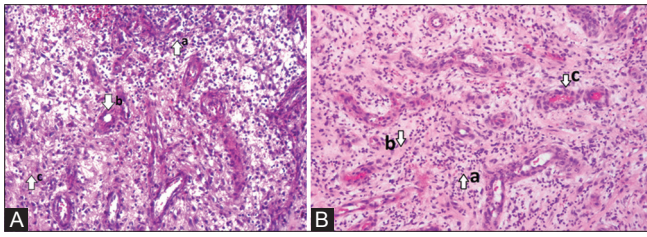


Figure 3: Histopathology of granulation tissue on days 0 and 10 in the conventional group. A: (a) Conventional group - day 0 - (arrow) abundant inflammatory cells, (b) minimal blood capillaries, (c) poor matrix (photographed with an Olympus PM20 photomicroscope $\times 20$); B: (a) Conventional group - day 10 - (arrow) More number of fibroblast cells, (b) poorly developed matrix with a minimal number of fibroblasts, (c) minimal blood capillaries. (photographed with an Olympus PM20 photomicroscope $\times 20$)

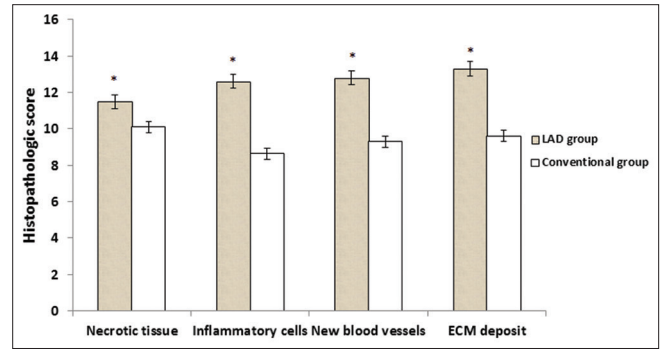


Figure 4: Histopathologic scores of necrotic tissue, inflammatory cells, new blood vessels, and extracellular matrix deposit in limited access dressing versus conventional groups (mean \pm SE, $P < 0.05$)

Table 2: Histopathologic scores of LAD and conventional groups

Parameters	(n = 42) (mean ± SE)						P
	LAD group			Conventional dressing group			
	Day 0	Day 10	Day (0-10)	Day 0	Day 10	Day (0-10)	
Necrotic tissue	25.5 ± 0.86	14.0 ± 0.39	11.5 ± 0.48	26.1 ± 0.76	16.0 ± 0.46	10.1 ± 0.30	0.007*
Inflammatory cells	25.0 ± 0.74	12.4 ± 0.45	12.6 ± 0.60	17.0 ± 0.34	8.37 ± 0.35	8.63 ± 0.35	0.018*
New blood vessels	8.3 ± 0.45	21.1 ± 0.63	12.8 ± 0.58	8.0 ± 0.24	17.3 ± 0.56	9.3 ± 0.29	0.005*
ECM deposit	9.7 ± 0.67	23.0 ± 0.78	13.3 ± 0.50	8.4 ± 0.29	18.0 ± 0.46	9.6 ± 0.24	0.001*

Each parameter was assessed individually in 8 microscopic fields per slide. The scores of the 8 microscopic fields were totaled, and the mean \pm SE were calculated, respectively; * $P < 0.05$ significant difference. Histological scales: 0, no evidence; 1, occasional evidence; 2, light scattering; 3, abundant evidence, and 4, confluent cells or fibers. LAD: Limited access dressing, SE: Standard error, ECM: Extracellular matrix

which form the principal component of connective tissue and play a central role in wound healing by providing a structural framework for regenerating tissue.^[12]

Borgquist *et al.*^[13] showed that chronic wounds treated with NPWT promote the formation of granulation tissue with an increase in ECM. After 10 days of treatment, there was a significant increase in the ECM deposit of a LAD group compared to a conventional group (mean \pm SE, 13.3 \pm 0.50 vs. 9.6 \pm 0.24, $P = 0.001$).

Angiogenesis improves circulation to the wound bed by providing oxygen and essential nutrients for the healing process.^[14] Xia *et al.*^[15] conducted a study on chronic wounds treated with NPWT, and showed that NPWT-treated wounds had increased angiogenesis and blood flow, with the number of new blood vessels significantly higher in a LAD group when compared to a conventional dressing group (mean \pm SE, 12.8 \pm 0.58 vs. 9.3 \pm 0.29, $P = 0.005$).

Huang *et al.*^[16] showed that NPWT promotes healing by modulating inflammation and cell migration. There were significantly fewer inflammatory cells in a LAD group as compared to a conventional dressing group (mean \pm SE, 12.6 \pm 0.60 vs. 8.63 \pm 0.35, $P = 0.018$).

In conclusion, the present study demonstrates that intermittent NPWT in a moist environment with a LAD to chronic wounds accelerates the rate of wound healing by significantly increasing ECM deposits and the formation of new blood vessels while decreasing the number of inflammatory cells and the amount of necrotic tissue.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Rahmanian-Schwarz A, Willkomm LM, Gonser P, Hirt B, Schaller HE. A novel option in negative pressure wound therapy (NPWT) for chronic and acute wound care. *Burns* 2012;38:573-7.
2. Norbury K, Kieswetter K. Vacuum-assisted closure therapy attenuates the inflammatory response in porcine acute wound healing model. *Wounds* 2007;19:97-106.
3. Greene AK, Puder M, Roy R, Arsenaault D, Kwei S, Moses MA, Orgill DP. Microdeformational wound therapy: effects on angiogenesis and matrix metalloproteinases in chronic wounds of 3 debilitated patients. *Ann Plast Surg* 2006;56:418-22.
4. Mouës CM, Vos MC, van den Bemd GJ, Stijnen T, Hovius SE. Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. *Wound Repair Regen* 2004;12:11-7.
5. Jacobs S, Simhaee DA, Marsano A, Fomovsky GM, Niedt G, Wu JK. Efficacy and mechanisms of vacuum-assisted closure (VAC) therapy in promoting wound healing: a rodent model. *J Plast Reconstr Aesthet Surg* 2009;62:1331-8.
6. Kumar P. Exploiting potency of negative pressure in wound dressing using limited access dressing and suction-assisted dressing. *Indian J Plast Surg* 2012;45:302-15.
7. Balin AK, Pratt L. Dilute povidone-iodine solutions inhibit human skin fibroblast growth. *Dermatol Surg* 2002;28:210-4.
8. Turan M, Saraydın SU, Bulut HE, Elagöz S, Cetinkaya O, Karadayi K, Canbay E, Sen M. Do vascular endothelial growth factor and basic fibroblast growth factor promote phenytoin's wound healing effect in rat? An immunohistochemical and histopathologic study. *Dermatol Surg* 2004;30:1303-9.
9. Galeano M, Altavilla D, Cucinotta D, Russo GT, Calò M, Bitto A, Marini H, Marini R, Adamo EB, Seminara P, Minutoli L, Torre V, Squadrito F. Recombinant human erythropoietin stimulates angiogenesis and wound healing in the genetically diabetic mouse. *Diabetes* 2004;53:2509-17.

10. Al-Bayaty F, Abdulla MA. A comparison of wound healing rate following treatment with aloe vera and chlorine dioxide gels in streptozotocin-induced diabetic rats. *Evid Based Complement Alternat Med* 2012;2012:468764.
11. Nain PS, Uppal SK, Garg R, Bajaj K, Garg S. Role of negative pressure wound therapy in healing of diabetic foot ulcers. *J Surg Tech Case Rep* 2011;3:17-22.
12. Abdulla MA, Ahmed KA, Ali HM, Noor SM, Ismail S. Wound healing activities of *Rafflesia hasseltii* extract in rats. *J Clin Biochem Nutr* 2009;45:304-8.
13. Borgquist O, Ingemansson R, Malmström M. The effect of intermittent and variable negative pressure wound therapy on wound edge microvascular blood flow. *Ostomy Wound Manage* 2010;56:60-7.
14. Suguna L, Sivakumar P, Chandrakasan G. Effects of *Centella asiatica* extract on dermal wound healing in rats. *Indian J Exp Biol* 1996;34:1208-11.
15. Xia CY, Yu AX, Qi B, Zhou M, Li ZH, Wang WY. Analysis of blood flow and local expression of angiogenesis-associated growth factors in infected wounds treated with negative pressure wound therapy. *Mol Med Rep* 2014;9:1749-54.
16. Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014;51:301-31.

Role of jet force technology in wound management

Vijayaraghavan Nandhagopal, Ravi Kumar Chittoria, Devi Prasad Mohapatra, Friji Meethale Thiruvoth, Dinesh Kumar Shivakumar, Arjun Ashokan

Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India.

Address for correspondence: Dr. Ravi Kumar Chittoria, Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India. E-mail: drchittoria@yahoo.com

ABSTRACT

Aim: The aim was to study the role of jet force technology (JFT) in wound management. **Methods:** This is a retrospective analysis of 18 cases of chronic nonhealing wounds in which JFT was used. Chronic wounds which had already undergone surgical debridement but which were not ready for reconstruction (skin graft/flap) secondary to a persistent bacterial load or infection (tissue culture positive) were included in the study. Patients were divided into two groups. Group 1 included those patients who were poor candidates for anesthesia or who refused for reconstruction and were managed with JFT only. Group 2 included those patients who were cleared for anesthesia and who were managed with JFT and skin graft or flap coverage. The time to negative wound cultures after JFT and the total duration of healing were noted. **Results:** In both the groups, all tissue culture positive chronic wounds became negative after 2 ± 1 weeks and were ready for reconstruction. In Group 1 (6 patients), the wounds completely healed in 5-6 weeks with JFT only. In Group 2 (12 patients), the wounds completely healed in 3-4 weeks with JFT and skin graft/flap. **Conclusion:** Hydrotherapy with JFT helps in the removal of contaminants, debris, and microbial colonization of the wound leading to spontaneous wound healing and facilitating wound bed preparation for wound coverage by a skin graft or flap.

Key words:

Chronic wounds, debridement, hydrotherapy, jet force technology

INTRODUCTION

Normal wound healing is a complex array of multiple processes which is characterized by three overlapping phases: inflammatory, proliferative and remodeling.^[1] Infection and debris are one of the important and common impediments to wound healing. Wound healing is possible only when bacterial counts are maintained at a concentration of 100,000 organisms per gram or less.^[2] The presence of eschar, scab or foreign bodies also act as impediments to wound healing.^[3] Irrigating the wounds

under pressure (hydrotherapy) removes debris and reduces the bacterial content (bioburden), assisting in wound healing.^[3]

Jet force technology (JFT) is a type of continuous hydrotherapy, which transforms saline and oxygen into microdroplets, which are accelerated to supersonic speeds to remove dead or poorly healing tissue from a wound surface. On a review of the current literature, no articles on JFT were found. This article presents the

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Nandhagopal V, Chittoria RK, Mohapatra DP, Thiruvoth FM, Shivakumar DK, Ashokan A. Role of jet force technology in wound management. *Plast Aesthet Res* 2015;2:277-81.

Received: 28-11-2014; **Accepted:** 11-06-2015

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.165441

authors' experience of JFT in the management of chronic wounds.

SUBJECTS AND METHODS

This is a retrospective study of patients with chronic nonhealing wounds in whom JFT was used in the Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India from November 2013 to October 2014. Patients of all age groups and both genders with chronic nonhealing wounds (> 3 months duration) of different etiologies which had undergone surgical debridement but were not ready for reconstruction due to debris and infection were included in the study. Eighteen patients matched the inclusion criteria. Informed consent was obtained. Details including age, gender, etiology, duration of wound, site, size, co-morbid factors, type of organism grown in tissue culture prior to JFT, duration to negative cultures following JFT, and duration until wound healing were recorded in the study *proforma*. The wound score was documented using the Bates Jansen Wound Assessment Tool.^[4] Wound measurements were recorded by Digital Planimetry using Image-J Software (National Institutes of Health).^[5] Wound score and measurements were recorded at each dressing changes. Patients were evaluated for medical clearance for anesthesia. Wound tissue cultures were sent prior to beginning JFT and weekly thereafter. JFT hydrotherapy and dressing changes were performed when the wound dressings were noted to be soaked. No systemic antibiotic therapy was required in any of the cases. Only saline moist dressings were used. JFT hydrotherapy was performed using a disposable JFT cannula (Tav Tech Ltd., Israel) which costs INR 2880/- [Figures 1 and 2]. All JFT procedures were done at the bedside without the need for anesthesia. The JFT cannula has two ports, one for the oxygen line and the other for connection to a saline bag. The pressure generated depends upon the flow rate of oxygen (9 L/min-4 PSI, 11 L/min-6 PSI, 13 L/min-9 PSI, 15 L/min-12 PSI). All patients tolerated the JFT procedure well. When the dressing became soaked, JFT with a moist saline dressing was done. In Group 1, only JFT



Figure 1: JET cannula. JFT: jet force technology

was used. In Group 2, once the tissue cultures became negative, the wound was covered with a skin graft or flap.

RESULTS

In our study cohort ($n = 18$ patients), the age of the patients ranged from 23 years to 75 years (mean: 49.32 years). In Group 1, the mean age was 55.2 years and 46.5 years in Group 2. There were more men than women with a ratio of 2.4:1. The most common site for chronic wounds was the lower extremity. The most common etiology was a diabetic ulcer, followed by a posttraumatic region of excoriation. The size of the wounds varied from 3 cm × 2 cm to 20 cm × 10 cm. The mean Bates-Jansen wound score was 33 ± 1 in Group 1 and 36 ± 1 in Group 2. The mean wound area in Group 1 was 42.6 cm² and 55.4 cm² in Group 2. In both groups, all wounds were culture positive for polymicrobial growth. In both groups, the most common organism cultured was *Pseudomonas aeruginosa* followed by *Staphylococcus aureus*. In Group 1, tissue cultures became negative after a mean duration of 2.17 weeks, whereas in Group 2, tissue cultures became negative after a mean duration of 2.34 weeks. On combining of both groups (18 patients), the wounds required 2.25 weeks to become culture negative. The mean number of JFT sessions in Group 1 was 3.67, while the mean number of JFT sessions in Group 2 was 4.58. In Group 1 (6 patients) managed by JFT alone, the mean duration to complete healing was 4 weeks. In Group 2 (12 patients) managed by JFT and split skin graft/flap, the mean duration to complete healing was 3.25 weeks [Tables 1 and 2, Figures 3-5]. Only group 2 received flap or graft. So graft loss or flap necrosis applies only to Group 2.

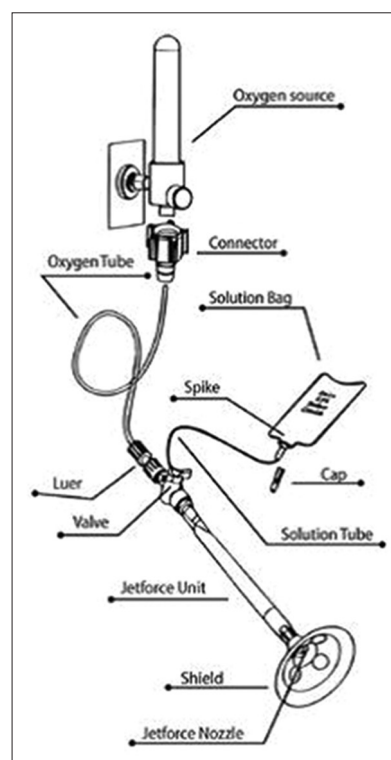


Figure 2: Demonstration of parts of JET cannula. JFT: jet force technology

Table 1: Summary of Group 1 patients

Age (years)	Gender	Etiology and site	Size (cm ²)	Total duration for tissue culture to become negative after JFT	Total number of sessions of JFT	Method of healing	Total duration of wound healing (in weeks)
70	Male	Postinfective (cellulitis) raw area left ankle	7 × 6.5	2	4	JFT only	4
42	Male	Posttraumatic ulcer right heel	7 × 6	2	2	JFT only	4
75	Female	Sacral pressure sore (grade 3)	5 × 7	2	3	JFT only	5
61	Male	Diabetic foot ulcer	4 × 4	2	4	JFT only	3
60	Male	Posttraumatic raw area right leg	4 × 4	2	4	JFT only	2
23	Male	Sacral pressure sore (grade 4)	15 × 10	3	5	JFT only	6

JFT: Jet force technology

Table 2: Summary of Group 2 patients

Age (years)	Gender	Etiology and site	Size (cm ²)	Total duration for tissue culture to become negative after JFT	Total number of sessions of JFT	Method of healing (JFT + SSG/flap)	Total duration of wound healing (in weeks)
36	Male	Posttraumatic raw area left foot with osteomyelitis	15 × 10	3	8	JFT + SSG	3
52	Female	Diabetic foot ulcer	3 × 3	1	2	JFT + flap	2
65	Male	Post pacemaker implant infected nonhealing ulcer left chest wall	4 × 3	2	4	JFT + flap	3
47	Female	Diabetic foot ulcer	5 × 4	3	7	JFT + flap	4
45	Male	Posttraumatic raw area left forearm	12 × 5	3	4	JFT + SSG	2
32	Male	Postelectric burn raw area	8 × 7	3	6	JFT + SSG	3
72	Male	Trophic ulcer right heel	3 × 2	1	2	JFT + SSG	2
31	Female	Nonhealing varicose ulcer left ankle	15 × 7	3	5	JFT + SSG	5
54	Male	Nonhealing diabetic ulcer left leg	3 × 2	2	3	JFT + SSG	2
24	Male	Ischial pressure sore Grade 4	5 × 5	2	3	JFT + flap	4
48	Female	Carcinoma left buccal mucosa postfailed free alt and PMMC flap with orocutaneous fistula	20 × 10	3	6	JFT + flap	5
52	Male	Sacral pressure sore Grade 4	10 × 8	2	5	JFT + SSG	4

JFT: Jet force technology, SSG: Split skin graft, PMMC: Pectoralis major myocutaneous

**Figure 3: At admission**

DISCUSSION

The healing of any wound proceeds through the following phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution. The end result of wound healing is determined by the interplay of these functions in a proper sequence at an appropriate intensity for a specified

duration of time.^[6] Local wound infection and foreign bodies affect healing by prolonging the inflammatory phase. If the bacterial count in the wound exceeds 10⁵ organisms per gram of tissue or if beta-hemolytic *Streptococcus* is present, the wound will not heal by any means, including flap coverage, skin grafting, or primary suturing.^[7] The common terms used to describe the processes used to remove factors detrimental to wound healing are “cleansing” and “debridement”. Cleansing describes the process in which fluid is utilized to remove cellular debris and residue from the wound surface or exudate or wound care products.^[8] Debridement refers to the application of mechanical force or chemicals to remove any adherent particles from a wound.^[9]

Wound cleansing is an integral part of the management of acute traumatic wounds as well as chronic wounds. Hydrotherapy is one of the oldest adjuvant therapies still in use today. Hydrotherapy is the use of water or saline under pressure to mechanically remove microscopic debris and bacteria. There are two types of hydrotherapy commonly practiced, whirlpool and pulsed lavage therapy. Whirlpool therapy supports wound healing by debriding the wound, warming the injured extremity,



Figure 4: JFT procedure. JFT: jet force technology

and providing buoyancy and gentle limb resistance for physical therapy.^[10] However, whirlpool treatments have fallen out of favor secondary to the risk of nosocomial contamination and transmission of virulent infections.^[11,12] Wound cleansing involves the process of selection of both a wound cleansing solution and a mechanical means for delivering that solution to the wound. The methods for wound irrigation can be broadly classified into two types, including continuous and pulsed irrigation. The delivery of an uninterrupted stream of irrigant to the wound's surface is termed "continuous irrigation". The system of intermittent or interrupted delivery of irrigant to the wound's surface is referred to as the "pulsed irrigation" technique. Recently, the use of pulsed lavage has begun to replace whirlpool therapy. Mechanical forces are used to rid the wound of bacteria and other particulate matter retained on the wound surface by adhesive forces. Under most circumstances, debridement alone will reduce bacterial load with the added benefit of removing necrotic tissue which would otherwise increase inflammation and delay healing.^[13] If cleansing is required, an appropriate solution should be selected to optimize the healing process and minimize the risk of damage to viable tissue.^[14] The recommendation for irrigation pressure ranges from 4 to 15 PSI. When pressures < 4 PSI are used there is insufficient pressure to remove surface pathogens and debris. Irrigation pressures > 15 PSI have been noted to cause wound trauma and drive bacteria into wounds.^[15] It is thought that pulsed lavage encourages the growth of healthy, granulating tissue.^[16] The goal is to remove unwanted tissue without disturbing the healthy tissue. The forces holding bacterial particles on the wound's surface are capillary, molecular and electrostatic. Madden *et al.*^[17] proposed three types of forces that could be used to remove bacteria from the wound's surface: direct mechanical contact (e.g. scrubbing), inertial forces and fluid dynamic forces. Fluid dynamic forces are the effective forces in wound irrigation using pulsed lavage. The high-powered water jet is a unique device when compared to the pulse irrigator, which is a low-energy water jet. The advantage is the ability to focus a high-powered stream of water into a high-energy cutting implement. The mechanism of action of this



Figure 5: After complete healing with JFT and split skin graft. JFT: jet force technology

hydro jet is the Venturi effect. A jet of saline, propelled by a power console, travels across the operating window of a hand-held piece, and then into a suction collector. This pressurized saline stream functions like a knife. The saline beam is aimed parallel to the wound, allowing the cutting mechanism to perform a highly controlled form of tangential excision.^[18] It is also used as pulsed lavage in wound cleansing.^[19]

JFT is a type of hydrotherapy which uses a disposable cannula (Israel), saline, and oxygen under pressure to mechanically remove mechanically debris and bacteria. Utilizing a unique triple nozzle, JFT is one of the simplest, most efficient, and effective methods of achieving fast and virtually painless debridement when compared to other mechanical debridement methods. JFT is the comprehensive innovation for cleansing and debridement. By using compressed oxygen combined with a minimal amount of saline solution, JFT quickly and effectively debrides wounds without the mess of traditional methods. JFT supersedes other equipment which is more complicated to operate and replaces more expensive methods of debridement. It is ideal for use at the bedside without the need for anesthesia in patients who are not medically stable for anesthesia or who have refused surgery. In our study, it was useful in both groups of patients. The current study's limitations include its small sample size, the lack of statistical analysis, the absence of controls, and the lack of testing utility against other infectious organisms including like fungi, anaerobes and biofilms.

In conclusion, hydrotherapy with JFT helps to remove contaminants, debris, and microbial colonization of the wound leading to spontaneous wound healing or facilitating wound bed preparation for wound coverage by a skin graft or flap.

Financial support and sponsorship

The department of Plastic Surgery, JIPMER, Pondicherry, India.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Serhan CN, Chiang N. Novel endogenous small molecules as the checkpoint controllers in inflammation and resolution: entrée for resolomics. *Rheum Dis Clin North Am* 2004;30:69-95.
2. Robson MC, Heggers JP. Bacterial quantification of open wounds. *Mil Med* 1969;134:19-24.
3. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature* 1962;193:293-4.
4. Harris C, Bates-Jensen B, Parslow N, Raizman R, Singh M, Ketchen R. Bates-Jensen wound assessment tool: pictorial guide validation project. *J Wound Ostomy Continence Nurs* 2010;37:253-9.
5. Shetty R, Sreekar H, Lamba S, Gupta AK. A novel and accurate technique of photographic wound measurement. *Indian J Plast Surg* 2012;45:425-9.
6. Gosain A, DiPietro LA. Aging and wound healing. *World J Surg* 2004;28:321-6.
7. Robson MC. Wound infection. A failure of wound healing caused by an imbalance of bacteria. *Surg Clin North Am* 1997;77:637-50.
8. Rodeheaver GT. Pressure ulcer debridement and cleansing: a review of current literature. *Ostomy Wound Manage* 1999;45:80S-5S.
9. Feedar JA. Clinical management of chronic wounds. In: McCulloch JM, Kloth LC, Feedar JA, editors. *Wound Healing: Alternatives in Management*. 2nd ed. Philadelphia: FA Davis Co.; 1995. p. 137-85.
10. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation. *Ann Plast Surg* 2003;51:210-8.
11. Simor AE, Lee M, Vearncombe M, Jones-Paul L, Barry C, Gomez M, Fish JS, Cartotto RC, Palmer R, Louie M. An outbreak due to multiresistant *Acinetobacter baumannii* in a burn unit: risk factors for acquisition and management. *Infect Control Hosp Epidemiol* 2002;23:261-7.
12. Berrouane YF, McNutt LA, Buschelman BJ, Rhomberg PR, Sanford MD, Hollis RJ, Pfaller MA, Herwaldt LA. Outbreak of severe *Pseudomonas aeruginosa* infections caused by a contaminated drain in a whirlpool bathtub. *Clin Infect Dis* 2000;31:1331-7.
13. Thomas GW, Rael LT, Bar-Or R, Shimonkevitz R, Mains CW, Slone DS, Craun ML, Bar-Or D. Mechanisms of delayed wound healing by commonly used antiseptics. *J Trauma* 2009;66:82-90.
14. Main RC. Should chlorhexidine gluconate be used in wound cleansing? *J Wound Care* 2008;17:112-4.
15. Bergstrom N, Allman RM, Alvarez OM, Bennett MA, Carlson CE, Frantz RA, Garber SL, Jackson BS, Kaminski MV, Kemp MG, Krouskop TA, Lewis VL, Maklebust J, Margolis DJ, Marvel EM, Reger SI, Rodeheaver GT, Salcido R, Xakellis GC, Yarkony GM. Treatment of Pressure Ulcers: clinical Practice Guideline No. 15. Rockville, Md: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994. p. 6-7, 47-53.
16. Haynes LJ, Brown MH, Handley BC. Comparison of Pulsavac and sterile whirlpool regarding the promotion of tissue granulation. *Phys Ther* 1994;74:S4.
17. Madden J, Edlich RF, Schauerhamer R, Prusak M, Borner J, Wangenstein OH. Application of principles of fluid dynamics to surgical wound irrigation. *Curr Top Surg Res* 1971;3:85-93.
18. Granick MS, Jacoby M, Norruthrun S, Datsishvili RO, Ganchi PA. Clinical and economic impact of hydrosurgical debridement on chronic wounds. *Wounds* 2006;18:35-9.
19. Luedtke-Hoffmann KA, Schafer DS. Pulsed lavage in wound cleansing. *Phys Ther* 2000;80:292-300.

Acellular micronized extracellular matrix and occlusive dressings for open fingertip injuries

Stephanie E. Dreifuss¹, Ronit Wollstein^{1,2}, Stephen F. Badylak¹, Peter J. Rubin¹

¹Department of Plastic and Reconstructive Surgery, University of Pittsburgh, Pittsburgh, PA 15261, USA.

²Department of Orthopedic Surgery, Technion Medical School, Haifa 3200003, Israel.

Address for correspondence: Prof. Ronit Wollstein, Department of Plastic and Reconstructive Surgery, University of Pittsburgh, Pittsburgh, PA 15261, USA. E-mail: ronitwollstein@gmail.com

Sir,

Fingertip amputation injuries compromise the sensation, function, and appearance of the hand. They are often exquisitely painful and take a substantial amount of time to heal, causing significant functional disability. Conservative management of these injuries may result in decreased range of motion, hypo- or hyperesthesia, loss of pulp contour, scarring, and other long-term sequelae.^[1,2] In addition, they may prolong patient discomfort with dressing changes, hindering adherence with wound therapy regimens, especially in the presence of multiple finger injuries.

Both acellular and cellular bioscaffolds have been employed in conjunction with wound dressing techniques. These biologically active materials supply extracellular matrix proteins, deliver growth factors, and recruit differentiated cells to the wound site.^[3,4] Furthermore, they aim to address the issue of pain associated with debriding dressings. The efficacy of cellular materials is limited by their reduced shelf life, risk of the immune response, increased regulation and high cost. Acellular materials, however, do not face these limitations.

We present a series of 8 patients (6 males and 2 females, average age: 40.8 ± 18.8 years) with fingertip amputations treated with Particulate Extracellular Matrix, or P-ECM (ACell Inc., Columbia, MD), an acellular, sterile, porcine-derived, naturally occurring, lyophilized and extracellular matrix material. There were 11 fingers treated. Injuries in these patients involved fingertip pulp

only, pulp and nail bed, or pulp, nail bed, and distal phalanx. All patients in the series were followed until complete wound healing, which occurred within an average of 7 weeks.

The wound care regimen for all patients involved removal of dressings, gentle sterile saline rinse, application of additional P-ECM powder, and redressing with nonadherent petrolatum gauze and cotton gauze fingertip bandage. The P-ECM was not completely removed with each dressing change but allowed to form a crystallized layer over the wound.

All patients rated the comfort of P-ECM treatment as 5 on a 5-point scale, citing a soothing effect upon changing dressings. Ease of use was rated as 4.2 out of 5 for patients who had another individual apply the treatment, while patients commented on the difficulty of independently treating and dressing their own fingertip wounds. Moreover, patients reported satisfaction with the appearance and function of their fingertips in comparison with normal digits. All patients noted a subjective recovery of pressure sensation, the light touch, and temperature sensation, comparable to their uninjured digits. There were no complications associated with the use of P-ECM in our series.

The P-ECM powder has an advantage of being applied every other day. Furthermore, application and maintenance are simple and comfortable for patients.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Dreifuss SE, Wollstein R, Badylak SF, Rubin PJ. Acellular micronized extracellular matrix and occlusive dressings for open fingertip injuries. *Plast Aesthet Res* 2015;2:282-3.

Received: 23-11-2014; **Accepted:** 03-01-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.156994

This is especially true for patients with multiple fingertip amputations in which dressing changes may be a painful ordeal. Like all treatments that allow for wound healing by secondary intention, the P-ECM technique requires that a patient adequately understand the treatment protocol and correctly apply the powder every other day. Therefore, it is important to consider patient adherence and availability of an individual who can aid in treatment application, patient's access to sterile saline and wound dressing materials, and motivation to adhere to treatment regimen.

This series demonstrates that the use of P-ECM is comparable to other treatment options for fingertip amputations. Its use was not compared to healing by secondary intention or any surgical procedures. At this time, there is no clear justification for its use in fingertip amputations, but perhaps it should be kept in our toolbox for the treatment of fingertip injuries, especially when there are multiple fingers involved. Study is necessary to

examine the advantages, disadvantages and to define the indications for its use.

Acknowledgment

P-ECM powder was provided by ACell, Inc., Columbia, MD.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yeo CJ, Sebastin SJ, Chong AK. Fingertip injuries. *Singapore Med J* 2010;51:78-86.
2. Fassler PR. Fingertip Injuries: evaluation and treatment. *J Am Acad Orthop Surg* 1996;4:84-92.
3. Rivera AE, Spencer JM. Clinical aspects of full-thickness wound healing. *Clin Dermatol* 2007;25:39-48.
4. Lazic T, Falanga V. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg* 2011;127 Suppl 1:S75-90.

Corticosteroid - an uncertainty in management of sepsis

Kanica Yashi

Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA 15232, USA.

Address for correspondence: Dr. Kanica Yashi, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA 15232, USA.

E-mail: kay42@pitt.edu

Sir,

The purpose of this letter is to review the literature and bring the facts related to ambiguity in the use of corticosteroid in the management of sepsis.

Sepsis is defined as systemic response to infection and is diagnosed as per ACCS/SCCP consensus conference committee, 1992 guidelines.^[1] Progression of sepsis to septic shock is caused by series of immune responses.^[2] For many decades in the past steroids have been used in the management of sepsis but there has been an ambiguity in their use in septic shock, doses, duration of therapy effectiveness. However, recent studies have shown it to be effective in septic shock associated with “relative adrenal insufficiency”.^[3] Cortisol increases at times of physiological stresses (e.g. sepsis, major injury, surgery, burns) due to activation of the hypothalamus pituitary axis. Suboptimal cortisol production during the septic shock has been termed as relative adrenal insufficiency and has been related to increased mortality in patients with sepsis but its actual existence remains controversial. The biochemical diagnosis of adrenal insufficiency by adrenocorticotrophic hormone (ACTH) tests were thought to be unreliable in critically ill patients. Also, measuring total cortisol may not be accurate in severely ill patients due to fluctuating levels of cortisol binding globulins.^[4,5]

Several studies are available that provides clinical evidences related to the use of corticosteroids in sepsis. The French trial,^[6] in a randomized control trial on 229 patients, revealed that there was reduction in 28-day mortality on treatment with low dose corticosteroids (LDCs). Those who responded to ACTH stimulation test (maximum increase in serum cortisol of $> 9 \mu\text{g/L}$) did not show

any significant difference in 28-day mortality. The median time to vasopressor withdrawal and shock reversal was 9 days in the placebo group and was 7 days in treatment group ($P = 0.01$).^[3,4] The strength of the study was the big sample size and the randomization, however, the use of both glucocorticoid and a mineralocorticoid was a marked weakness making distinctions between the effects of each drug difficult.^[1]

Keh *et al.*^[7] performed a randomized double blinded placebo controlled crossover trial on 40 patients with septic shock to investigate the effects of LDC (100 mg bolus followed by 10 mg/h for the rest of 3 days) on immunologic parameters and hemodynamic parameters. It was seen that plasma cortisol levels increased to 5 folds in each group and were associated with stabilization of hemodynamic parameters. After 24 h of administration of corticosteroid the plasma concentration of interleukin-6 (IL-6), IL-8, IL-10 and tumor necrosis factor (TNF-1) and TNF-2 were significantly lower in the first group (received hydrocortisone) compared to the second one (did not receive hydrocortisone) ($P = 0.01$).

The strength of the study was that each patient received the intervention and served as his or her own control. However, the study was limited by the fact that hypothalamic-pituitary-adrenal axis was not addressed in this study.^[1]

CORTICUS^[8] has evaluated the efficacy of LDC in a broad population of patients (regardless of adrenal function) within 72 h of onset of shock. A total of 499 patients were randomized to treatment (50 mg hydrocortisone bolus every 6 h for 5 days, then 50 mg hydrocortisone every

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165442

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Yashi K. Corticosteroid - an uncertainty in management of sepsis. *Plast Aesthet Res* 2015;2:284-5.

Received: 28-11-2014; **Accepted:** 19-01-2015

12 h for 3 days and finally 50 mg hydrocortisone every 24 h for 3 days)^[9] or placebo groups. The results indicated no significant difference in mortality between treatment and the placebo group. But shock reversal was achieved more quickly in treatment group compared to the placebo group, regardless of the adrenal function ($P = 0.001$). However, the proportion of patients, in whom shock reversal was achieved, was similar between the 2 groups. There was also evidence of increased risk of superinfection in treatment group (combined odds ratio: 1.37; 95% confidence interval: 1.05-1.79). The strength of the study was its large sample size, randomization and power of study was 80%. The limitation of this study is that the treatment group received steroids as late as 72 h. Earlier studies have shown that steroids have been beneficial only if given early (< 8 h).^[9]

All meta-analysis confirmed improved shock reversal with LDC use.^[3] Subsequent analysis found that severely ill patients were more likely to benefit from corticosteroid therapy. One analysis suggested that it may be harmful in less ill patients.^[3]

While on steroids, according to a previous study done,^[10] there was a certain increase in side effects of secondary infections, gastrointestinal bleeding and increased blood glucose. However, these problems could be due to terminal illness. This probably indicates the need for a larger clinical trial.^[2]

Current recommendations^[3,11,12] suggest:

- Administering intravenous corticosteroid therapy (200-300 mg/day) to adult patients with severe septic shock (defined as a systolic blood pressure less than 90 mmHg for more than 1 h despite both adequate fluid resuscitation and vasopressor administration);
- Not administering the corticosteroid to patients without shock or patients with less severe shock (defined as those in whom fluid resuscitation and vasopressor therapy have restored hemodynamic instability);
- ACTH test prior to administering steroids in sepsis is not recommended;
- Typically administer hydrocortisone for 57 days and taper the dose as guided by the clinical response.

The impairment of hypothalamic-pituitary-adrenal axis in sepsis has not been resolved yet.

The most uniform finding by almost all trials is that corticosteroid may accelerate shock reversal. At this time, the most supported view is LDC should be administered to those patients who are in septic

shock and unresponsive to fluids and vasopressor administration.

Review of the literature indicates the need to conduct carefully planned clinical trials to resolve controversies and to provide a more reliable result.^[13]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644-55.
2. Yarema TC, Yost S. Low-dose corticosteroids to treat septic shock: a critical literature review. *Crit Care Nurse* 2011;31:16-26.
3. Gesensway D. Why steroids are making a comeback for treating septic shock. *Today's Hospitalist* 2006;5. Available from: http://www.todayshospitalist.com/index.php?b=articles_read&cnt=176. [Last accessed on 2014 Jun 02].
4. David KA, Mancebo J. Corticosteroid Therapy in septic shock. *UpToDate* 2014;1. Available from: <http://www.uptodate.com/contents/corticosteroid-therapy-in-septic-shock>. [Last accessed on 2015 Jan 11].
5. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med* 2004;350:1629-38.
6. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
7. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003;167:512-20.
8. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-24.
9. Toma A, Stone A, Green RS, Gray S. Steroids for patients in septic shock: the results of the CORTICUS trial. *CJEM* 2011;13:273-6.
10. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, Fisher CJ Jr. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995;23:1430-9.
11. Gandhi NR, Asudani DG. What is the role of steroids in septic shock? *Hospitalist* 2012;5. Available from: <http://www.the-hospitalist.org/article/what-is-the-role-of-steroids-in-septic-shock/>. [Last accessed on 2015 Jan 11].
12. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
13. Vincent JL. Steroids in sepsis: another swing of the pendulum in our clinical trials. *Crit Care* 2008;12:141.

Morphometry of subcutaneous fat lobules of the abdomen and its implication in obesity

Arvind K. Pandey¹, Pramod Kumar^{2,3}, Kodavoor Shrinivas Aithal⁴, Rama Kotian Sushma¹, Antony Sylvan D'Souza¹

¹Department of Anatomy, Kasturba Medical College, Manipal University, Manipal, Udupi 576104, Karnataka, India.

²Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia.

³Department of Plastic Surgery and Burns, Kasturba Medical College, Manipal 576104, Karnataka, India.

⁴Department of Physics, MIT, Manipal University, Manipal, Udupi 576104, Karnataka, India.

Address for correspondence: Dr. Pramod Kumar, Department of Plastic Surgery, King Abdulaziz Specialist Hospital, Sakaka 42421, Al-Jouf, Saudi Arabia. E-mail: pkumar86@hotmail.com

ABSTRACT

Aim: The subcutaneous fat in the lower abdomen (LA) is more resistant to resorption as compared to the upper abdomen (UA). Males and females have variability in fat deposition and resorption in the abdominal region. Hence, there could be a difference in morphology of fat cells of these regions. The present study aims to identify the differences in morphology of subcutaneous fat lobules of upper and LA. **Methods:** Subcutaneous fat samples were collected from upper and LA of 40 cadavers (33 males and 7 females). The shape, the arrangement, and the color of superficial and deep subcutaneous fat lobules were observed. The height and width were recorded for larger fat lobules. **Results:** There was a difference in the color, shape, size, and arrangement of the fat lobules between the two locations. Height ($P = 0.042$) and width ($P = 0.008$) of deep subcutaneous fat of LA were significantly larger than the UA in males while the height of superficial fat ($P = 0.016$) was significantly larger in LA than the UA in females. Height of the deep fat of UA ($P = 0.018$) and width of deep fat of the LA ($P = 0.020$) were significantly larger in females as compared to males. **Conclusion:** There was a significant difference in the morphology of the superficial and deep subcutaneous fat based on location and gender of the patient.

Key words:

Abdomen, morphometry, obesity, resorption, subcutaneous fat

INTRODUCTION

The development of liposuction and lipectomy in reconstructive surgery has enhanced interest in the study of superficial fascia and subcutaneous fat deposits of the abdomen.^[1-3] Furthermore, a strong relationship exists between obesity, insulin resistance, and cardiometabolic risk factors.^[4-7]

Subcutaneous tissue constitutes 85% of total adipose tissue mass and visceral fat constitutes the remaining 15%.^[8] Subcutaneous fat in adults is called white fat and its quantitative distribution is variable in different sexes.^[9,10]

There are two distinct types of subcutaneous fat: superficial and deep.^[8] The superficial fat exists between the skin

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Pandey AK, Kumar P, Aithal KS, Sushma RK, D'Souza AS. Morphometry of subcutaneous fat lobules of the abdomen and its implication in obesity. *Plast Aesthet Res* 2015;2:286-9.

Received: 05-12-2014; **Accepted:** 12-01-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165443

and the superficial fascia whereas the deep fat occupies the area between the superficial fascia and the muscles. Superficial layer is richly vascularized and results in cellulite formation when it is hypertrophied. The deep layer of fat is called localized fat deposit (LFD) when it is hypertrophied. LFD is excessive bulge producing contour deformity of the region.^[11] The subcutaneous fat deposits in the lower abdomen (LA) do not get absorbed easily by dieting and exercise, compared to the upper abdomen (UA).

The present study was carried to find the difference in morphology of subcutaneous fat lobules, as an initial step to explore the different re-absorption pattern of deposited fat different location of abdomen and different gender.

METHODS

This study included 40 fresh (within 6-10 h after death) adult cadavers (33 males and 7 females) of age varied between 18 and 70 years collected from the Department of Forensic Medicine, Kasturba Medical College, Manipal. All cadavers (<10 h after death) of body mass index more than 19.5 were included in this study. None of the cases had lipodistrophies or any kind of hormonal imbalance that causes abnormal fat accumulation.

This study was approved by the Institutional Human Ethics Committee (IEC 111/2009).

Data collection

Samples of the subcutaneous fat lobules were collected from UA (3 cm above the umbilicus) and LA (3 cm below the umbilicus) at the mid-clavicular line. The shape, arrangement, and color of the superficial and deep subcutaneous fat lobules were observed and recorded. The larger fat lobules (in width and height) in the region under study were identified, and their height and width were noted. The maximum distance between the upper and lower end of the fat lobule was considered as the height while the maximum distance between the anterior and posterior part of the lobule was considered as the width [Figure 1]. The readings of maximum height and width were taken at the accuracy of 10 μ m using metal casing Electronic Digital

Calipers (series-sc02, Guilin Gunglv measuring instrument Co. Ltd., Guilin, China); and the average readings of 3 larger lobules was calculated for further analysis.

Statistical analysis was performed using the SPSS 15 package (SPSS, IBM Company). Data were expressed as mean \pm standard deviation (SD) and 95% confidence interval. Paired sample *t*-test was applied for comparing UA and LA parameters in each sex. Independent sample *t*-test was applied for comparing the parameters between males and females. In addition, Pearson's correlation test was applied to correlate the parameters of the upper and LA. $P < 0.05$ was considered as statistically significant.

RESULTS

There was a difference in the color, shape, size, and arrangement of the fat lobules at different locations. Subcutaneous fat of the UA was dark yellowish in color whereas LA subcutaneous fat was yellowish in color, and deeper fat lobules were pale yellow [Figure 2].

The fat lobules from the superficial layer were elongated and arranged perpendicular to the skin. The fat lobules from deeper layers of UA were rounded in shape whereas the fat lobules from LA were elongated and arranged perpendicular to the skin. Most dependent (lowest in standing position) lobules were larger in size (both in height and width).

Height ($P = 0.042$) and width ($P = 0.008$) of deep fat of LA were significantly more than UA in males [Table 1] while the height of superficial fat ($P = 0.016$) was significantly more in LA than the UA in females [Table 2].

Independent sample *t*-test was applied to compare the means of width and height of fat lobules-in males and females. The height of deep fat of UA ($P = 0.018$) and width of deep fat of LA ($P = 0.020$) were significantly larger in females than males.

Pearson correlation between height ($r = 0.403$, $P = 0.010$) and width ($r = 0.585$, $P < 0.01$) of the superficial fat of

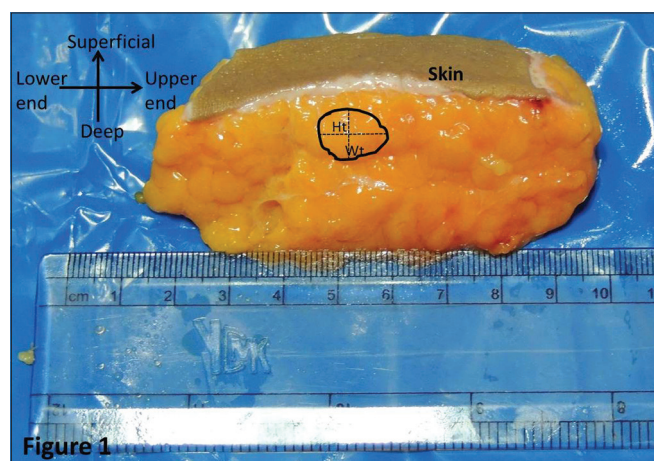


Figure 1: The schematic representation of the measurements of a fat lobule. Height (Ht): the maximum distance between the upper and lower end of the fat lobule; Width (Wt): the maximum distance between the anterior and posterior part of the lobule

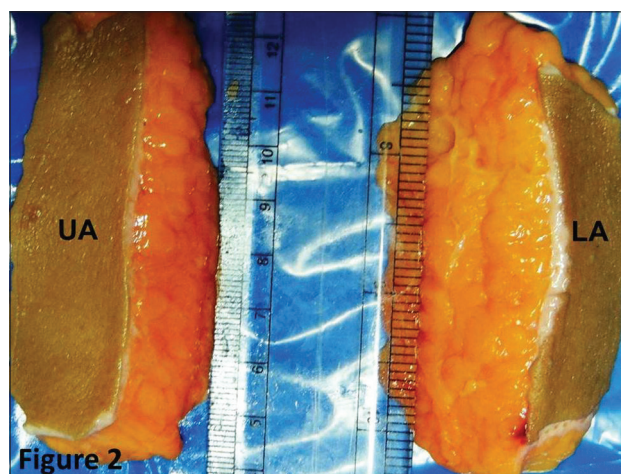


Figure 2: The subcutaneous fat of upper and lower abdomen. Subcutaneous fat of the UA was dark yellowish in color whereas in the LA, subcutaneous fat was yellowish in color. UA: Upper abdomen, LA: Lower abdomen

Table 1: Morphometry of subcutaneous fat lobules in males

Parameters (cm)	Mean \pm SD		Paired <i>t</i>	<i>P</i>	95% CI of difference	
	Lower abdomen	Upper abdomen			Lower	Upper
Height of superficial subcutaneous fat	0.706 \pm 0.213	0.648 \pm 0.187	1.394	0.173	-0.026	0.141
Width of superficial subcutaneous fat	0.570 \pm 0.168	0.509 \pm 0.186	1.991	0.055	-0.001	0.122
Height of deep subcutaneous fat	0.824 \pm 0.225	0.730 \pm 0.227	2.117	0.042	0.003	0.184
Width of deep subcutaneous fat	0.782 \pm 0.222	0.639 \pm 0.2449	2.848	0.008	0.040	0.244

SD: Standard deviation, CI: Confidence interval

Table 2: Morphometry of subcutaneous fat lobules in females

Parameters (cm)	Mean \pm SD		Paired <i>t</i>	<i>P</i>	95% CI of difference	
	Lower abdomen	Upper abdomen			Lower	Upper
Height of superficial subcutaneous fat	0.743 \pm 0.229	0.600 \pm 0.216	3.333	0.016	0.038	0.247
Width of superficial subcutaneous fat	0.657 \pm 0.171	0.629 \pm 0.205	0.603	0.569	-0.087	0.144
Height of deep subcutaneous fat	1.014 \pm 0.261	0.971 \pm 0.269	0.528	0.617	-0.155	0.241
Width of deep subcutaneous fat	1.00 \pm 0.173	0.771 \pm 0.236	2.359	0.056	-0.008	0.465

SD: Standard deviation, CI: Confidence interval

the upper and LA revealed significant (2-tailed) positive correlation. The height ($r = 0.491$, $P = 0.001$) of the deep fat of the upper and LA showed a positive correlation while the width ($r = 0.301$, $P = 0.059$) of the deep fat of the upper and LA did not show positive correlation.

DISCUSSION

Superficial fat layer is richly vascularized, and when hypertrophied, it is responsible for cellulite. Embryologically it arises from the hypodermis of the integument. Hypertrophy of the deep layer of fat is unsightly and called LFD. LFDs are often difficult to lose by exercise and diet.^[11]

The superficial layer comprises of tightly packed adipocytes supported by dense fibrous network whereas the deep layer constitutes of loosely arranged adipocytes. Varied blood supply of the two layers was also reported.^[12,13] The superficial epigastric arteries (a branch of the femoral artery) supply to the superficial layers, veins drain into the femoral veins via the saphenous hiatus. Inferior epigastric and deep circumflex iliac arteries (branches of the external iliac artery) and the superior epigastric artery (a branch of the internal thoracic artery) supplies to the deep layer.^[14]

In the present study, the color, shape, size and arrangement of fat lobules were different at different regions of the abdomen and these were in agreement with those reported by Yves.^[11] Although authors have mentioned the variability in the measurement (height or width) of the fat lobules, an extensive attempt was not made to study the differences in the superficial and deep fat of the upper and LA.

Current study revealed that the height (0.824 ± 0.225 vs. 0.730 ± 0.227 , $P = 0.042$) and width (0.782 ± 0.222 vs.

0.639 ± 0.2449 , $P = 0.008$) of the deep subcutaneous fat of the LA was significantly more than that in the UA in males. Whereas in females, the height of the superficial fat (0.743 ± 0.229 vs. 0.600 ± 0.216 , $P = 0.016$) was significantly larger in the LA than in the UA [Tables 1 and 2].

The height of deep fat of UA (0.971 ± 0.269 vs. 0.730 ± 0.227 , $P = 0.018$) and width of deep fat of LA (1.00 ± 0.173 vs. 0.782 ± 0.222 , $P = 0.020$) were significantly more in females than males. This may be the reason for an increase in lower abdominal girth with weight gain in females. Our findings thus support observations concluded by Champe and Harvey.^[15] He Q *et al.*^[16] suggested that superficial and deep subcutaneous compartments may differ in the rate of fat deposition, lipolysis or both.

Even though *in vivo* signals and the pathways regulating lipid metabolism are more complex than those in a controlled *in vitro* study, the metabolic difference in the superficial and deep compartments may lead to varied rates of gain and loss. This may be due to changes in energy intake or other factors.

Accumulation of subcutaneous fat depicts the normal physiological buffer for high caloric diet with limited physical activity. This acts as a metabolic sink to store excess free fatty acids and glycerol as triglycerides in adipocytes.^[17]

Illouz^[1] defined the resistant nature (to absorption) of the abdominal LFD and showed that the anatomy of fat lobules and its arrangement differ in different areas of the abdomen. The LFD in the central region of the abdomen is less resistant to resorption of fat and is strongly correlated with cardiovascular diseases.^[5] The present study on the morphometry of the superficial and deep subcutaneous fat in the upper and lower regions of the abdomen and in males and females reveals a significant

difference in morphology of fat cells between the two regions and genders. Further studies are required to correlate anatomical variations with varied behavior of fat in different locations of body and gender types.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Illouz YG. History and current concepts of lipoplasty. *Clin Plast Surg* 1996;23:721-30.
2. Fodor PB. Reflections on lipoplasty: history and personal experience. *Aesthet Surg J* 2009;29:226-31.
3. Matarasso A. Traditional abdominoplasty. *Clin Plast Surg* 2010;37:415-37.
4. Despre's JP. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. *Eur Heart J Suppl* 2006;8:B4-12.
5. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.
6. Gorter PM, Olijhoek JK, van der Graaf Y, Algra A, Rabelink TJ, Visseren FL, SMART Study Group. Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. *Atherosclerosis* 2004;173:363-9.
7. Sönmez K, Akçakoyun M, Akçay A, Demir D, Duran NE, Gençbay M, Degertekin M, Turan F. Which method should be used to determine the obesity, in patients with coronary artery disease? (body mass index, waist circumference or waist-hip ratio). *Int J Obes Relat Metab Disord* 2003;27:341-6.
8. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, Mohammed BS. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004;350:2549-57.
9. Vague J. Sexual differentiation. A determinant factor of the forms of obesity 1947. *Obes Res* 1996;4:201-3.
10. Bahman T. Suction lipectomy and body sculpturing. Maryland heights. St. Louis: Mosby Year Company; 1986. p. 19-20.
11. Yves I. Body Sculpturing by Lipoplasty. Edinburgh: Churchill Livingstone; 1989. p. 29-32, 51.
12. Lee Y, Hong JJ, Bang C. Dual-plane lipoplasty for the superficial and deep layers. *Plast Reconstr Surg* 1999;104:1877-84.
13. El-Mrakby HH, Milner RH. Bimodal distribution of the blood supply to lower abdominal fat: histological study of the microcirculation of the lower abdominal wall. *Ann Plast Surg* 2003;50:165-70.
14. Ahluwalia HS, Burger JP, Quinn TH. Anatomy of the anterior abdominal wall. *Oper Tech Gen Surg* 2004;6:147-55.
15. Harvey RA, Ferrier DR. Lippincott's Illustrated Reviews: Biochemistry. 5th ed. Philadelphia: Lippincott William and Wilkins; 2011. p. 350.
16. He Q, Engelson ES, Kotler DP. A comparison of abdominal subcutaneous adipose tissue pattern in obese and lean HIV-infected women. *J Nutr* 2005;135:53-7.
17. Freedland ES. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. *Nutr Metab (Lond)* 2004;1:12.

Ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome: a rare entity

Samrat Sabhlok¹, Sobhan Mishra², Ramanupam Tripathy², Deepthi Mony³

¹Department of Oral and Maxillofacial Surgery, Dr. D. Y. Patil Dental College and Hospital, Pune 411018, Maharashtra, India.

²Department of Oral and Maxillofacial Surgery, Institute of Dental Sciences, Bhubaneswar, Odisha 751003, India.

³Consultant Oral and Maxillofacial Surgeon, Navi Mumbai 400706, Maharashtra, India.

Address for correspondence: Dr. Samrat Sabhlok, Department of Oral and Maxillofacial Surgery, Dr. D. Y. Patil Dental College and Hospital, Pune 411018, Maharashtra, India. E-mail: samratsabhlok@yahoo.com

ABSTRACT

Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome is a rare congenital anomaly of inherited origin and varying clinical features. This syndrome has three main symptoms, which display variable expression and penetrance. The management of this syndrome is challenging, with few reports in the medical literature. We present a case of a 22-year-old boy with EEC syndrome and offer insight into current knowledge about this syndrome.

Key words:

Cleft lip and palate, ectodermal dysplasia, ectrodactyly

INTRODUCTION

Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome applies to a triad of inherited congenital anomalies including ectrodactyly (lobster claw deformities of the hands/feet), ectodermal dysplasia (ED) (fine, short hair, absent eyebrows and eyelashes, dystrophic nails, diffuse scaling and palmoplantar keratoderma) and cleft lip with or without cleft palate.^[1] The syndrome was first documented in a tribe from German Guyana in South America, in 1770 while Eckholdt and Martens described the syndrome for the 1st time in 1804.^[2] In 1936, Cockayne described a pedigree of two generations with split hands and feet, cleft lip and palate and dacryocystitis. Subsequently, Walker and Clodius described three pedigrees with complete unilateral or bilateral clefts of the primary and secondary palate associated with lobster claw hands and feet and malfunction of the lacrimal system.^[3] In 1970, Rudiger and associates described the rare combination of ectrodactyly (lobster claw deformity), ED

(with atresia of the nasolacrimal duct) and cleft lip with or without cleft palate, terming it EEC syndrome.^[4]

It is a rare syndrome, with the frequency of ectrodactyly at 1.5/100,000 live births and 1/100,000 live births for cleft palate with or without a cleft lip.^[5] The occurrence of all three disorders in one, that is, ectrodactyly, ectodermal dysplasia, and cleft lip/palate, is reported to be approximately 1.5/100 million.^[6]

EEC syndrome shows an autosomal dominant inheritance pattern with variable expressivity and incomplete penetrance, although autosomal recessive inheritance has also been reported.^[7]

The responsible gene has been identified as the *p63* gene, which is essential for limb formation and epidermal morphogenesis including adnexa (teeth, hair, mammary and prostate glands).^[8] The mutation of this gene accounts for most, if not all, cases of the classic EEC syndrome.^[6]

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Sabhlok S, Mishra S, Tripathy R, Mony D. Ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome: a rare entity. *Plast Aesthet Res* 2015;2:290-3.

Received: 01-04-2015; **Accepted:** 10-07-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165446

There are a wide array of features noted in association with the syndrome, including genitourinary defects, mental retardation, midface hypoplasia, auricular anomalies, hypopigmentation of the skin, an increased number of nevocellular nevi,^[4] conductive hearing loss,^[3] nipple abnormalities, lumbar lordosis, short stature,^[9] glaucoma, and blindness.^[10]

The cosmetic aspects of EEC can have a tremendous impact on quality of life. The facial and limb differences can be socially isolating and physically challenging for both children and adults.

There are a few cases of EEC syndrome reported in the literature, with variable presentation. Here, we offer an insight into the diagnosis and management of EEC syndrome through the presentation of a case.

CASE REPORT

A 22-year-old man presented to our unit with a chief complaint of cleft lip and cleft palate. There was no family history of any such deformity.

On physical examination, the patient had a wide left unilateral complete cleft lip and palate [Figure 1]. Clinical features show shortening of the philtral height, shortened columella, the flattened alar dome on the cleft side and alar rim distortion, which reduced the apparent height of the columella.

The examination of the upper extremities was remarkable for ectrodactyly. The right hand showed clefting between the second and fourth digits with the absence of the third digit. The left hand showed clefting in the same region with a deformity between the second and fourth digits and absence of the third digit [Figure 2]. The lower extremities were remarkable for ectrodactyly of the right foot with clefting present between the great toe and third digit of the right foot and absence of the second digit [Figure 3].

The scalp, hair and eyebrows were light, short, thin, brittle and kinky. There was no dermatitis of the scalp. The eyebrows were especially sparse in their lateral halves. The patient's skin was significantly thickened and dry, especially on the extremities, with ridged and brittle toenails. The parents reported that he seldom sweated. The evaluation of the patient's psychomotor development showed moderate retardation. The speech disorder was attributed to both his anatomical lip and palate impairment and psychomotor retardation. The ophthalmological examination revealed no abnormality and no epiphora. Audiometric analysis showed no conduction blockade.

The intraoral examination was notable for a complete cleft palate. There were multiple carious and missing teeth. An orthopantomograph revealed a wide alveolar cleft in the left maxilla in the region of the left incisor and canine. Radiographic examination of the hands revealed a fusion of the metacarpals and phalanges of the first and second digits and a deformity of the third metacarpal of the right

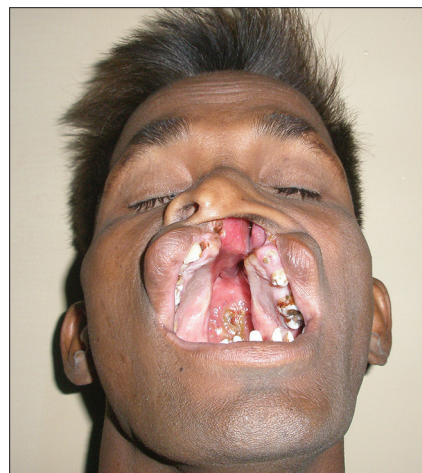


Figure 1: Wide left unilateral complete cleft lip and palate



Figure 2: Upper extremities showing ectrodactyly



Figure 3: Clefting present in between the great toe and the third digit of the right foot

hand. The left hand revealed a deformity of the phalanges of the second digit, with fusion and deformity of the third and fourth digits [Figure 4]. The right foot shows a deformity of the second metatarsal and the absence of phalanges of the second digit [Figure 5].

The patient was taken to the operating room for repair of the cleft lip and palate under general anesthesia. The cleft lip was repaired with use of the Millard incision, and the palate was repaired using the Bardach two flap

palatoplasty technique. The patient reported for follow-up on a regular basis for a period of six months [Figure 6]. The hypernasal quality of the voice did not improve following palatoplasty. Although speech therapy was prescribed, the patient did not return for treatment.

DISCUSSION

EEC syndrome is a rare autosomal dominant multiple congenital anomaly syndromes with variable expression. Disease-causing mutations have been identified in the *p63*



Figure 4: Radiograph of upper extremities showing ectrodactyly

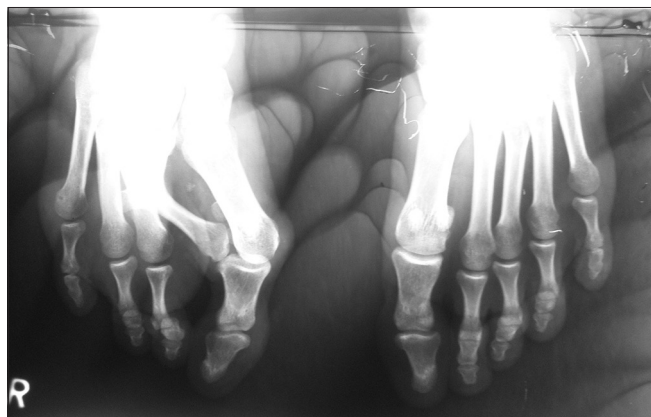


Figure 5: Radiograph of lower extremity showing deformity of the second metatarsal and the absence of phalanges of the second digit



Figure 6: Six months postoperative

gene, a homolog of the *p53* tumor suppressor gene. The *p63* produces a protein, which is essential for ectodermal development. The mutation is thought to affect *p63* binding to DNA, resulting in abnormal ectodermal development.^[11,12] The *p63* is expressed in the ectodermal surfaces of the limb buds. Limb truncations are due to a failure to maintain the apical ectodermal ridge, a stratified epithelium essential for limb development. The *p63* is critical for maintaining the progenitor-cell populations necessary for epithelial development and morphogenesis.^[13]

There are three types of EEC syndrome, with gene loci identified as follows:

- EEC syndrome type 1 (Mendelian Inheritance in Man (MIM) 129900)-7q11.2-q21.3;
- EEC syndrome type 2 (MIM 602077)-chromosome 19;
- EEC syndrome type 3 (MIM 604292)-3q27.

Different combinations of ectodermal dysplasia, orofacial clefting and limb malformation are seen in five different syndromes: EEC syndrome (most common, OMIM 604292), ankyloblepharon-ectodermal defect-cleft lip/palate syndrome (AEC, OMIM 106260), limb mammary syndrome (LMS, OMIM 603543), acro-dermato-ungual-lacrima-tooth syndrome (adult, OMIM 103285), and Rapp-Hodgkin syndrome (RHS, OMIM 129400).^[14] The term ectrodactyly originates from the Greek “*ektroma*” (abortion) and “*daktylos*” (finger). In 1829, von Walter described the characteristic crab foot, which Cruveilhier later coined the “lobster foot”.^[1] Ectrodactyly, cleft foot, lobster foot and crab-claw foot are synonyms expressing the absence of, to a greater or lesser degree, the central digits and metacarpals or metatarsals of the feet and hands, respectively. The first and fifth rays are generally present, although sometimes the first is hypertrophied. The usual presentation involves the hands and feet bilaterally.^[1] Our case demonstrated ectrodactyly of both hands and the right foot. According to Blauth and Borissh^[15] six level radiographic classification of cleft feet, the right foot is Grade II, as there are five metatarsals, which are partially hypoplastic or synostotic with other metatarsals or phalanges. The second or third ray is always affected, and at least one toe is absent.

ED syndrome requires involvement from the birth of hair, skin, teeth or nails without progression of the condition. The signs of ED were seen in the present case as the hair was brittle but not sparse. The anodontia noted in the maxillary arch may have been secondary to the cleft palate, however, the anodontia of the mandibular arch could be attributed to ED. The toenails were ridged, thick and brittle. The patient's skin was pigmented and prone to rashes.

Making a diagnosis of ED is challenging as any ectodermal derivative may be involved in varying degrees, and other systems may also be affected. To circumvent this problem, Freire-Maia and Pinheiro designed a classification system, which contains over 100 clinically distinct conditions.^[9,15,16] Freire-Maia and Pinheiro based their definition on four “classical signs” associated with ED: trichodysplasia,

dental defects, onychodysplasia and dyshidrosis. Group A includes those disorders with signs affecting at least two of the classical structures: (1) hair, (2) teeth, (3) nails, and (4) sweat glands. Group B includes disorders involving one of the classical signs associated with another ectodermal sign. "Pure" ED is characterized by only ectodermal signs while ED syndrome combines ectodermal signs and other malformations.^[17]

Several clinical syndromes are characterized by ED in association with clefting of the lip and/or palate. The three most commonly recognized are (1) EEC syndrome (ED, ectrodactyly, cleft lip/palate); (2) Rapp-Hodgkin syndrome with ED, cleft lip/palate, and midfacial hypoplasia; and (3) Hay-Wells or AEC syndrome.^[18]

Clinical expression of the components of this syndrome is very diverse. The cases of EEC syndrome without cleft lip or cleft palate have been reported.^[19] The patient presented in the above report showed unilateral complete cleft lip and palate, which was the primary motivation for seeking treatment. The frequency of presentation of the different manifestations is as follows: ectodermal dysplasia (10-100%), lacrimal duct alterations (70-96.5%), ectrodactyly (78-88%), cleft lip/palate (58-88%), urogenital alterations (15-55%), deafness (8-28%) and mental retardation (1-16%).^[20-22]

EEC syndrome can be diagnosed prenatally by ultrasound, which detects the structural abnormalities associated with the syndrome including cleft lip, cleft palate, kidney abnormalities and limb abnormalities. Prenatal DNA testing can be done by chorionic villi sampling or amniocentesis. Mutation of the *p63* gene is diagnostic for EEC syndrome.

Although there is no specific cure for EEC syndrome, there are many treatments available for the various symptoms. Our patient's main concern was his wide cleft lip and palate for which he underwent surgical repair. In most patients, the cleft lip and palate are surgically repaired early in life to address the issues with nutrition and speech. However, many patients appear to adapt well to the limb deformities of EEC syndrome. From a dental viewpoint, the dentition should be preserved as long as possible by restoring the teeth. Saliva^[23] substitutes can be used in cases of severe xerostomia.

The above patient was not extremely concerned about the malformation of his hands or feet. The Grade II ectrodactyly of his feet did not affect his gait or the fit of his shoes, but gait problems are seen in Grades III or greater. Treatment of the foot malformation brings the size of the foot into the normal range, fills the cleft, corrects the secondary deformities and maintains good function.^[1]

In conclusion, the ideal treatment plan includes early diagnosis and a multidisciplinary approach. An endeavor should be made to establish a protocol for the treatment of EEC syndrome to minimize progression of the deformities.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pêna DA, Nova AM, Pêna JA, Ruiz SH. Cleft foot and ectrodactyly-ectodermic dysplasia-cleft lip/palate syndrome review of the literature and report of two new cases. *Foot* 2004;14:221-6.
2. South AP, Ashton GH, Willoughby C, Ellis IH, Bleck O, Hamada T, Mannion G, Wessagowit V, Hashimoto T, Eady RA, McGrath JA. EEC (Ectrodactyly, 3. 3. Ectodermal dysplasia, Clefting) syndrome: heterozygous mutation in the *p63* gene (R279H) and DNA-based prenatal diagnosis. *Br J Dermatol* 2002;146:216-20.
3. Robinson GC, Wildervanek LS, Chiang TP. Ectrodactyly, ectodermal dysplasia, and cleft lip-palate syndrome. Its association with conductive hearing loss. *J Pediatr* 1973;82:107-9.
4. Rüdiger RA, Haase W, Passarge E. Association of ectrodactyly, ectodermal dysplasia, and cleft lip-palate. *Am J Dis Child* 1970;120:160-3.
5. Marwaha M, Nanda KD. Ectrodactyly, ectodermal dysplasia, cleft lip, and palate (EEC syndrome). *Contemp Clin Dent* 2012;3:205-20.
6. Oğur G, Yüksel M. Association of syndactyly, ectodermal dysplasia, and cleft lip and palate: report of two sibs from Turkey. *J Med Genet* 1988;25:37-40.
7. Brunner HG, Hamel BC, van Bokhoven H. The *p63* gene in EEC and other syndromes. *J Med Genet* 2002;39:377-81.
8. Balci S, Engiz O, Okten G, Sipahier M, Gursu G, Kandemir B. A 19-year follow-up of a patient with type 3 ectrodactyly-ectodermal dysplasia-clefting syndrome who developed non-Hodgkin lymphoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:e91-5.
9. Soekarman D, Fryns JP. Hypohidrotic ectodermal dysplasia, central nervous system malformation, and distinct facial features: confirmation of a distinct entity? *J Med Genet* 1992;30:245-7.
10. Rosenberg JB, Butrus S, Bazemore MG. Ectrodactyly-ectodermal dysplasia-clefting syndrome causing blindness in a child. *JAAPOS* 2011;15:80-2.
11. Celli J, Duijf P, Hamel BC, Bamshad M, Kramer B, Smits AP, Newbury-Ecob R, Hennekam RC, van Buggenhout G, van Haeringen A, Woods CG, van Essen AJ, de Waal R, Vriend G, Haber DA, Yang A, McKeon F, Brunner HG, van Bokhoven H. Heterozygous germline mutations in the *p53* homolog *p63* are the cause of EEC syndrome. *Cell* 1999;99:143-53.
12. Levrero M, De Laurenzi V, Costanzo A, Gong J, Wang JY, Melino G. The *p53/p63/p73* family of transcription factors: overlapping and distinct functions. *J Cell Sci* 2000;113:1661-70.
13. Yang A, Schweitzer R, Sun D, Kaghad M, Walker N, Bronson RT, Tabin C, Sharpe A, Caput D, Crum C, McKeon F. *p63* is essential for regenerative proliferation in limb, craniofacial and epithelial development. *Nature* 1999;398:714-8.
14. Agrawal A, Agrawal R, Singh R, Agrawal R, Agrawal S. Lobster claw deformity. *Indian J Dent Res* 2014;25:243-7.
15. Blauth W, Borisch NC. Cleft feet. Proposals for a new classification based on roentgenographic morphology. *Clin Orthop Relat Res* 1990;258:41-8.
16. Freire-Maia N, Pinheiro M. Ectodermal Dysplasias: a Clinical and Genetic Study. New York: Alan R Liss; 1984. p. 172-3.
17. Freire-Maia N. Ectodermal dysplasias. *Hum Hered* 1971;21:309-12.
18. Fosko SW, Stenn KS, Bologna JL. Ectodermal dysplasias associated with clefting: significance of scalp dermatitis. *J Am Acad Dermatol* 1992;27:249-56.
19. Thakkar S, Marfatia Y. EEC syndrome sans clefting: variable clinical presentations in a family. *Indian J Dermatol Venereol Leprol* 2007;73:46-8.
20. Dipak NK, Sheikh S, Srinivasan A. EEC (Ectrodactyly-ectodermal dysplasia clefting) syndrome in a Newly Born Baby. *Int J Integr Med Sci* 2015;2:87-9.
21. Rodini ES, Richieri-Costa A. EEC Syndrome: report on 20 new patients, clinical and genetic considerations. *Am J Med Genet* 1990;37:42-53.
22. Koul M, Dwivedi R, Upadhyay V. Ectrodactyly-ectodermal dysplasia clefting syndrome (EEC syndrome). *J Oral Biol Craniofac Res* 2014;4:135-9.
23. Dhar RS, Bora A. Ectrodactyly-ectodermal dysplasia-cleft lip and palate syndrome. *J Indian Soc Pedod Prev Dent* 2014;32:346-9.

A massive dentigerous cyst of the mandible in a young patient: a case report

Gururaj Arakeri¹, Kirthi Kumar Rai², Hosadurga Rudraswami Shivakumar²,
Shahanavaj I. Khaji³

¹Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur 584101, Karnataka, India.

²Department of Oral Maxillofacial Surgery, Bapuji Dental College and Hospital, Davangere 577004, Karnataka, India.

³Department of Oral and Maxillofacial Surgery, Tatyasaheb Kore Dental College and Research Centre, Kolhapur 416137, Maharashtra, India.

Address for correspondence: Dr. Gururaj Arakeri, Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur 584101, Karnataka, India. E-mail: gururaj.arakeri@gmail.com

ABSTRACT

Cysts of the jaw present as swellings of jaws and midface. Of the different varieties, the dentigerous cyst is the most common type of noninflammatory odontogenic cyst and the frequent cause of a lytic lesion associated with an impacted tooth. The cyst develops from epithelial remnants of the tooth forming organ. The obstruction of venous flow due to compression of tooth follicle by developing tooth causes fluid accumulation between the follicular epithelium and the crown of the developing or unerupted tooth resulting in a cyst. Most small dentigerous cysts manifest in early age, usually as an incidental discovery in radiographic examinations. However, they can grow extremely large, asymptotically, and remain undetected until they enlarge enough, causing bony expansion and asymptomatic facial swelling. We present a challenging case of massive dentigerous cyst in a 13-year-old female child involving half of the mandible, which was successfully treated with conservative therapy. This case report illustrates the effectiveness of simplified surgical treatment for a large dentigerous cyst in the mixed dentition period.

Key words:

Conservative therapy, cyst, massive dentigerous cyst

INTRODUCTION

In general, cysts of the jaw commonly present as swellings of the jaws and the midface. A *sine qua non* for the development of a dentigerous cyst is usually an unerupted tooth. The frequency of dentigerous cyst formation has been calculated as 1.44 in every 100 unerupted teeth.^[1-3]

Dentigerous cysts occur over a wide age range with a peak frequency in the second to fourth decades and are the second most common odontogenic cysts after radicular

cysts, accounting for approximately 24% of all true cysts in the jaws.^[4-6]

Clinically, it is often asymptomatic; it is discovered as an incidental radiographic finding or when acute inflammation, infection or swelling develops^[7-9] where it appears as a well circumscribed, unilocular, usually symmetric radiolucency around the crown of an impacted tooth. As normal follicular space is 3-4 mm, a dentigerous cyst can be suspected when the space

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Arakeri G, Rai KK, Shivakumar HR, Khaji SI. A massive dentigerous cyst of the mandible in a young patient: a case report. *Plast Aesthet Res* 2015;2:294-8.

Received: 22-11-2014; **Accepted:** 14-07-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.165439

is more than 5 mm.^[1] These cysts may also convert into ameloblastomas, mucoepidermoid carcinoma and squamous cell carcinoma.^[10]

The growth rate may be quite rapid, with lesions growing up to 5 cm in diameter in 3-4 years. It can, however, become extremely large and is sometimes associated with cortical expansion and erosion.^[3] The expansion of these cysts is usually related to an increase in the osmolality resulting from passage of inflammatory cells and desquamated epithelial cells into the cystic lumen.^[11]

We report a challenging case of massive dentigerous cyst involving the whole half of the mandible, which was successfully treated with conservative therapy. This report also illustrates a simplified surgical treatment for a large dentigerous cyst in the mixed dentition period.

CASE REPORT

A 13-year-old female child reported to the Department of Oral, Maxillofacial Surgery of Bapuji Dental College and Hospital, Davangere with a chief complaint of swelling over the left lower third of the face. The swelling was gradual and progressive as noted by the patient till the time of presentation [Figure 1]. There was no history of trauma. No episode of pain or discharge from the site was reported by the patient.

Patient was subjected to routine general systemic examination. She had no relevant past and present medical history. There was no history of cachexia or weight loss. Patient reported no contributory significant dental history. Local examination revealed an extraoral solitary swelling, which was oval in shape measuring about 5 cm × 4.5 cm. Swelling extended superiorly from the zygomatic arch region to 1 cm below the inferior border of the mandible inferiorly. Anteroposteriorly, it was extended about 3 cm from the tragus of the ear to the oral commissure. On palpation, the swelling was bony hard in consistency with a smooth surface. It was nontender with no pulsations; no egg-shell crackling was evident. Overlying skin was pinchable with no rise in local temperature and no secondary changes were evident. The patient had normal functioning cranial nerves V and VII. Lymph node examination ruled out the presence of any pathology with the nodes.

The patient had a maximal interincisal opening of 35 mm. Teeth present were the second molar to second molar in the maxilla, and she had clinically missing both of the third molars. In the mandible, both the third molars as well as the second molar on the left side were absent. Lingual and buccal cortical expansion on the left side was evident.

Routine hematological investigations revealed normal values. The swelling was aspirated using a large bore needle and the straw-colored fluid revealed a high protein content of 5.1 g/100 mL.

Orthopantomogram [Figure 2] showed an expansile radiolucent lesion involving the left body, the ramus, condyle and coronoid processes measuring approximately

3.0 cm × 4.5 cm in size. The erupting left lower third molar was displaced and lying in close proximity to that of the sigmoid notch and the crown of the tooth was involved in the lesion. Second molar on the same side was also impacted wherein the lesion had encompassed the entire tooth. Gross thinning of both the cortices was noted in relation to the lesion and no definitive resorption of the root of any tooth was seen. Lesion was extending anteriorly to the root of left canine. Coronal and axial computed tomography (CT) scans [Figure 3] revealed almost symmetrical expansion of the medial and lateral cortices of the left condyle and also that of the ramus. No temporal bone involvement was seen.

Considering the factors such as age, site, as well as the high regenerative capacity of the musculo-periosteal



Figure 1: Preoperative profile



Figure 2: Preoperative orthopantomogram

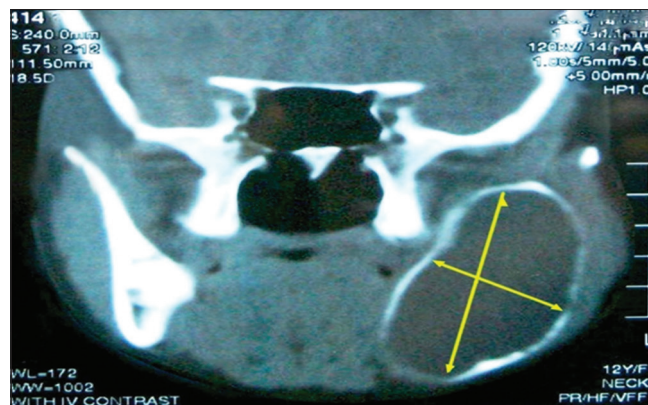


Figure 3: Preoperative CT scan

capsule of the growing child, it was planned to treat the lesion with simple enucleation procedure.

Under general anesthesia, an intraoral incision was placed along the anterior border of the ramus and the coronoid process and lateral surface of the mandible were denuded [Figure 4]. The lesion was enucleated in total [Figures 5 and 6] along with the third molar. Extraction of the impacted second molar was carried out, and Carnoy's solution was applied along the entire bed of the lesion. Inferior alveolar nerve was preserved by applying Vaseline jelly [Figure 5]. Wire eyelets were placed on both sides and watertight wound closure was achieved using layered suturing. Intermaxillary fixation (IMF) was done on the first postoperative day (for 8 weeks) to maintain intercondylar distance. Her postoperative course was uneventful.

Histopathologic examination revealed the presence of a cystic lining and connective tissue capsule. The epithelial lining consisted of nonkeratinized 2-4 layers of flattened epithelial cells. The epithelial and connective tissue interface was flattened. The fibrous connective tissue wall was composed of dense collagen fibers and revealed islands of odontogenic epithelial rests, chronic inflammatory cells, chiefly plasma cells, and lymphocytes. All the features suggested a dentigerous cyst.

Patient was discharged on the 10th postoperative day with IMF and advised regular follow-up (2 weeks interval). On

8th week, IMF was released. As per our protocol, CT scans (both axial and coronal view) and radiographs were taken at regular intervals and evaluated. Radiographic follow-up revealed sufficient bone filling with increased bone density from the margin to the center of the defect when compared with the preoperative scans and radiographs [Figures 7-10].

DISCUSSION

Therapy for a cyst is determined by its etiology and localization, which, on the one hand, means that the causal tooth must be treated or removed and on the other that the cystic lining, which secretes the cystic content, must be excised.^[12] This statement fits well with the treatment characteristics of a dentigerous cyst.

Among various surgical treatment modalities to treat a dentigerous cyst, enucleation of the cyst is the most widely accepted procedure. Marsupialization is another treatment modality, which is usually employed for large dentigerous cysts due to its significant size, possibility of destruction of the surrounding tissue and concern for the potential of a pathologic fracture.^[13]

Dentigerous cyst is more common in the third and fourth decades^[14] and most of the surgical modality can be justified

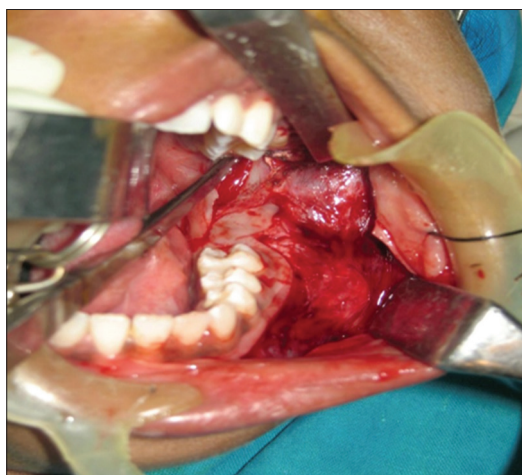


Figure 4: Intra oral exposure of cystic lesion



Figure 5: After enucleation inferior alveolar neurovascular bundle preserved



Figure 6: Enucleated specimen



Figure 7: Three months post operative profile



Figure 8: Three months post operative occlusal view (intact)



Figure 9: Three months CT scan showing bone filling in the defect

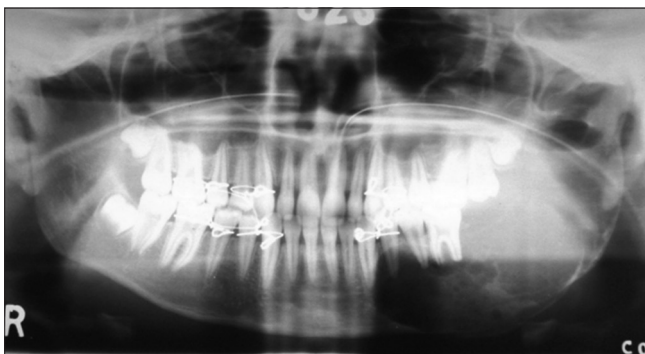


Figure 10: Three months post operative orthopantomogram showing successful bone regeneration

in those instances where jaws have completed the growth. But, choosing a treatment modality becomes critical when young growing jaws suffer a massive lesion. In the present case, the patient was only 13 years old at the time of presentation. Any radical approach may result in severe mutilation of the jaw along with the loss of its function.

In such situations proper decision making in selecting the appropriate treatment modality plays a crucial role in the prognosis of the overall therapy. For the present case, we had considered all possible modalities by taking into account the factors such as age, gender, location, size as well as the patient's socioeconomic status.

Although the well-considered modality, marsupialization satisfies certain therapeutic requirements in such large lesions, it has significant drawbacks such as slow healing and cicatrization.^[12] Moreover, this procedure is hard to rely on when treating a dentigerous cyst because it is difficult to maintain patency in a bony lesion. Also, a lateral window could drive the developing permanent dentition toward ectopic eruption, resulting in malocclusion and creating a potential need for further interceptive orthodontics.^[7-9]

However, the treatment, prognosis and cure rates in such large dentigerous cysts are all dependent upon the various factors such as growth characteristics, anatomic site, clinical extent size, age, gender, *etc.*

Various studies have shown predictable spontaneous bone regeneration in young patients after enucleation of such large cysts. Many authors believe that bone grafting in young patients should be considered carefully and in most of the instances it is unnecessary.^[11]

In view of the aforementioned, we preferred cystectomy rather a radical procedure, which may otherwise usually recommended in such large cysts. In our opinion, a radical treatment in a growing child might result in severe mutilation. Therefore, we would opine that it is always advisable to be conservative in such scenarios.

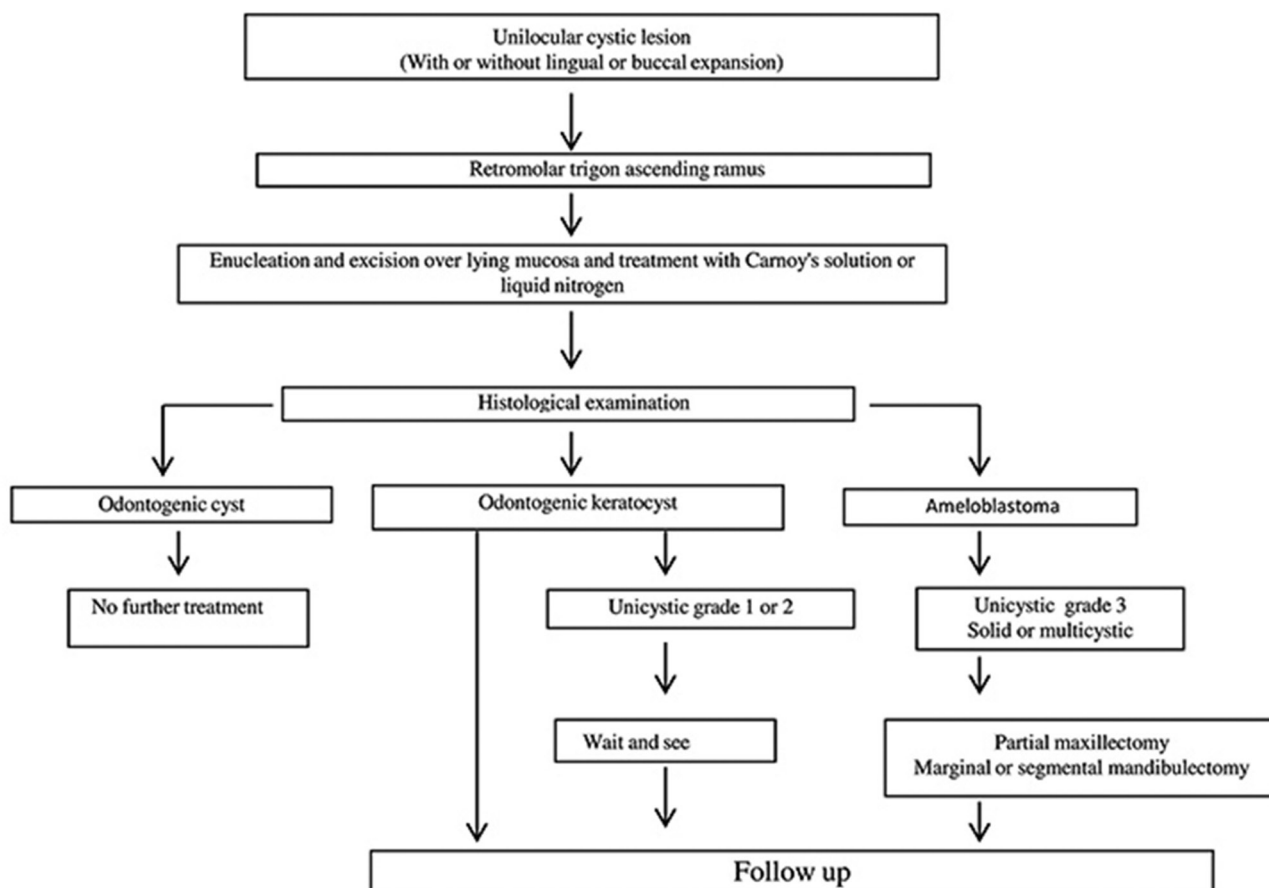
But, many authors differ in their opinion with regard to enucleation of large dentigerous cysts. This is largely due to the fact that larger cystic cavities lack organization of a blood clot and formation of new bone is questionable.^[12] A blood clot in a devitalized area is a great risk, as it can easily become infected and may lead to the unwanted consequences of local inflammation. There is also possibility of nerve damage and incomplete removal of cystic lining due to the encompassment of the roots of the posterior teeth by the cyst.^[12]

However, in a large case series study^[15] [Figure 11] a decision tree for treating large unilocular cysts of the jaws has been suggested. The authors recommended enucleation for all the unilocular cysts irrespective of its size followed by chemical cauterization. They also deferred biopsy prior to a definitive surgical procedure as a valid practice. This is because the wound created by biopsy may impede clean first-hand surgical procedure with regards to tissue planes and wound infection.^[15,16]

We strongly agree with the tenet and further believe that watertight primary closures followed by unstressed jaw movements are crucial for uneventful bone regeneration after enucleation therapy.

In our case, there was an intact lower basal bone, which favored the enucleation therapy. Postoperative maintenance such as sustaining intercondylar distance, avoiding jaw stress by IMF for eight weeks, and using liquid diet subsequently contributed equally for the success of this therapy. However, this type of cases demands a long-term follow-up to monitor for any recurrence.

The above-described approach will certainly prevent the aggressive radical treatment protocol, which would



(Adapted from : K.A.O.M. Chapelle et al. Rational approach to diagnosis & treatment of ameloblastomas & odontogenic keratocysts. Br J Oral Maxillofac Surg 2004;42: 381-390.)

Figure 11: Decision tree for unilocular cystic lesion in mandibular third molar area that tends to extend in the ascending ramus

be taxing both to the patient as well as surgical team. Therefore, in such cases conservative treatment does have a far better advantage to minimize the postoperative morbidity. In our opinion, this method of treatment would stand us a chance of a radical option if need arises in the course of patient follow-up.

We have observed in our present case, the therapy enucleation alone may holds well in such young aged patients provided the proper preoperative diagnosis and meticulous surgery is carried out. Conversely, the technique chosen largely depends on the surgeon, as even the best technique will not be satisfactory if incorrectly carried out and our case is not an exception.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ko KS, Dover DG, Jordan RC. Bilateral dentigerous cysts-report of an unusual case and review of literature. *J Can Dent Assoc* 1999;65:49-51.
2. Freitas DQ, Tempest LM, Sicoli E, Lopes-Neto FC. Bilateral dentigerous cysts: review of the literature and report of an unusual case. *Dentomaxillofac Radiol* 2006;35:464-8.
3. Ustuner E, Fitoz S, Atasoy C, Erden I, Akyar S. Bilateral maxillary dentigerous cysts: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95:632-5.
4. Benn A, Altini M. Dentigerous cysts of inflammatory origin. A clinicopathologic study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;81:203-9.
5. Demirkol M, Ege B, Yanik S, Aras MH, Ay S. Clinicopathological study of jaw cysts in southeast region of Turkey. *Eur J Dent* 2014;8:107-11.
6. Al Sheddi MA. Odontogenic cysts. A clinicopathological study. *Saudi Med J* 2012;33:304-8.
7. Ziccardi VB, Eggleston TI, Schneider RE. Using fenestration technique to treat a large dentigerous cyst. *J Am Dent Assoc* 1997;128:201-5.
8. Marwah N, Bishen KA, Prabha V, Goenka P. A conservative approach in the management of inflammatory dentigerous cyst in transitional dentition: a case report. *J Mass Dent Soc* 2012;61:18-21.
9. Bozdogan E, Cankaya B, Gencay K, Aktoren O. Conservative management of a large dentigerous cyst in a 6-year-old girl: a case report. *J Dent Child (Chic)* 2011;78:163-7.
10. Gulbranson SH, Wolfrey JD, Raines JM, McNally BP. Squamous cell carcinoma arising in a dentigerous cyst in a 16-month-old girl. *Otolaryngol Head Neck Surg* 2002;127:463-4.
11. Meara JG, Brown MT, Caradonna D, Varvares MA. Massive, destructive, dentigerous cyst: a case report. *Otolaryngol Head Neck Surg* 1996;115:141-4.
12. Sokler K, Sandev S, Grgurevic J. Surgical treatment of large mandibular cysts. *Acta Stomatol Croat* 2001;35:253-7.
13. Lung KE, Ganatra S, Robinson CE. Multiple multilocular dentigerous cysts with intraosseous and extraosseous third molar displacement: a case report. *Oral Health* 2006;6:20-9.
14. Isser DK, Das S. Dentigerous cyst in a young boy. *Indian J Otolaryngol Head Neck Surg* 2002;54:44-5.
15. Chapelle KA, Stoelinga PJ, Wilde PC, Brouns JJ, Voorsmit RA. Rational approach to diagnosis and treatment of ameloblastomas and odontogenic keratocysts. *Br J Oral Maxillofac Surg* 2004;42:381-90.
16. Pogrel MA, Montes DM. Is there a role for enucleation in the management of ameloblastoma? *Int J Oral Maxillofac Surg* 2009;38:807-12.

A simple postoperative oral physiotherapy aid for edentulous patients with oral submucous fibrosis

Ankita Vastani¹, Anisha Maria¹, Nishant Chourasia¹, Ambika Shrivastava Gupta²

¹Department of Oral and Maxillofacial Surgery, Rishiraj College of Dental Sciences and Research Centre, Bhopal 462036, Madhya Pradesh, India.

²Department of Prosthodontics, Rishiraj College of Dental Sciences and Research Centre, Bhopal 462036, Madhya Pradesh, India.

Address for correspondence: Dr. Ankita Vastani, Department of Oral and Maxillofacial Surgery, Rishiraj College of Dental Sciences and Research Centre, Bhopal 462036, Madhya Pradesh, India. E-mail: ankitavastani@gmail.com.

Sir,

Oral submucous fibrosis is a chronic inflammatory disease, which results in progressive juxta-epithelial fibrosis of the oral soft tissues and can cause increasing difficulty in chewing, swallowing, speaking and mouth opening.^[1] Management of the disease, being medical or surgical, poses a great challenge because of the tendency to recur or undergo malignant transformation.

For the management of oral submucous fibrosis, our institution follows a protocol. This includes bilateral surgical release of fibrous bands, bilateral coronoidectomy, extraction of all third molars and reconstruction of intraoral defects using the buccal pad of fat and vigorous postoperative oral physiotherapy with mouth gags.

Application of interocclusal forces to achieve adequate mouth opening forms an integral part of the treatment of oral submucous fibrosis.^[2] The oral physiotherapy aids that are currently in use, range from wooden spatulas to mouth gags (such as Heister or Ferguson). Patients with good dentition are amenable to the application of such forces but in edentulous patients, the forces get directly transmitted to the atrophic ridges rendering them vulnerable to fracture and soft tissue injury.^[2]

Custom made occlusal splints with grooves (for seating of a mouth gag) have already been described as an adjunct to oral submucous fibrosis surgery.^[1-3] In this letter, we describe oral stents with occlusal rims without grooves,

aimed for oral physiotherapy in patients without the use of a mouth gag.

This technique involves taking impressions of the maxillary and mandibular edentulous areas using perforated trays. Customized special trays are then fabricated and border molding is performed. Next, these trays are used to make impressions to create heat cure denture bases with occlusal rims on the mandibular denture base [Figure 1]. These denture bases are seated in the patient's mouth [Figure 2] and vertical height of the occlusal rim can be adjusted chair side. If more vertical height is required, then acrylic can be added on the maxillary base plate. The purpose of adding the occlusal rims on denture bases is to maintain mouth opening without having to rely on patient's compliance to actively open the mouth. The patients are supposed to wear these dentures when they want to perform physiotherapy. These dentures are economical, easy to maneuver by the



Figure 1: Heat cure acrylic resin denture bases with occlusal rims

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.165447

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

How to cite this article: Vastani A, Maria A, Chourasia N, Gupta AS. A simple postoperative oral physiotherapy aid for edentulous patients with oral submucous fibrosis. *Plast Aesthet Res* 2015;2:299-300.

Received: 23-04-2015; **Accepted:** 18-05-2015



Figure 2: Dentures seated in the patient's mouth, forcing the mouth to be opened in this position

patient himself/herself, comfortable and maintenance free. After the tissues heal, procedures for permanent dentures (with teeth) can be performed.

To conclude, this letter described a simple postoperative oral physiotherapy aid for edentulous patients undergoing oral submucous fibrosis surgery. It is the authors hope that it could be beneficial to the surgical community and patients suffering from this condition.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Le PV, Gornitsky M, Domanowski G. Oral stent as treatment adjunct for oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;81:48-50.
2. Mahajan AD, Tatu RJ, Shenoy NA, Sharma VS. Surgical management of oral submucous fibrosis in an edentulous patient: a procedural challenge. *Natl J Maxillofac Surg* 2010;1:161-3.
3. Rai A, Bhola N, Agrawal B, Rai N. A modified technique for postoperative physiotherapy in edentulous patients. *J Maxillofac Oral Surg* 2012;11:247-8.

Lift of cheek and neck: technical notes

Maurice Yves Mommaerts

European Face Centre, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.

Address for correspondence: Prof. Maurice Yves Mommaerts, European Face Centre, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. E-mail: maurice.mommaerts@uzbrussel.be

INTRODUCTION

Because alternatives exist for the full facelift (rhytidectomy), this procedure has become less popular overtime. In the past, forehead wrinkles were addressed with coronal^[1,2] and endoscopically assisted forehead lift^[3] procedures. Today, botulinum toxin and hyaluronic acid fillers are used for this purpose because they are more effective and result in less downtime. Lateral brow sag can be corrected by using the Fogli^[4] and Knize^[5] browlift techniques, Endotine[®] browlift^[6] or sub-brow fat augmentation.^[7] The pretrichial incision is occasionally chosen, typically in facial feminization surgery, which includes supraorbital rim contouring and scalp advancement.^[8] Although indications for facelift surgery remain, they are limited. A more recent approach to restoring a youthful appearance to the midface involves volume augmentation, although this is questionable.^[9] Facial aging is thought to be primarily due to gravitational sagging because of the loss of collagenous support [Figure 1]; however, fillers provide more predictable results than lifting in this area. Furthermore, hyaluronic acid fillers are more predictable than micro fat grafting^[10] and are safer to use around the eyes.^[11] The lifting of tissues is more useful in the lower face (caudal extension of nasolabial folds and grooves, labiomental folds and grooves and jowls disrupting the jaw line) and neck (platysmal bands, skin excess). Hence, “cheek and neck lift” or “buccocervical lift” may be more appropriate terms for this type of procedure.

This article describes important features of facelift surgery as performed by the author. All patients involved in this article agreed to have their facial pictures published and signed the consent form. The proper sequence of steps is explained in the last section.

MINIMAL SEDATION

For all patients, reduction of anxiety and mild hypnosis are achieved with the oral administration of 1 mg lorazepam, along with the 100 mg of diclofenac, 1 g of paracetamol, 2 g of penicillin and 32 mg of methylprednisolone given 1 h prior to the procedure. Lorazepam has a half-life of 9-16 h,^[12] which helps the patient to remain calm and normotensive postoperatively. Because pain occurs only with injection of the local anesthetic intravenously solution along the skin incision line, midazolam is given 2 min prior to the administration of local anesthetic for those patients who are anxious IV or agitated; oriented and calm patients may not require sedation. Midazolam is given by slow intravenous injection, starting with a test dose of 0.1 mg and slowly delivering a total dose of 2-6 mg (depending on body weight) over 2 min. During this time the skin is marked for the incision and prepping and draping are performed. The half-life of midazolam is 2-6 h.^[13] The goal is to achieve a co-operative, oriented and calm state (level 2 on the Ramsey Scale of Sedation).^[14] The patient should still be able to respond normally to verbal stimuli (i.e. minimal sedation on the American Society of Anesthesiologists scale of sedation); however, if moderate or conscious sedation is reached (i.e. purposeful response to verbal/tactile stimulation), this state will not last longer than 20 min.

INFILTRATION ANESTHESIA USING THE WHITACRE SPINAL NEEDLE

The aim is to numb the area and provide a bloodless surgical field, defined by the marked dissection area, including the skin and superficial muscular aponeurotic

Video Available on: www.parjournal.net

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.169502

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Mommaerts MY. Lift of cheek and neck: technical notes. *Plast Aesthet Res* 2015;2:301-8.

Received: 30-05-2015; **Accepted:** 08-09-2015

system (SMAS). The first step is to achieve a superficial, cephalad cervical plexus block, aiming for the lesser occipital nerve, great auricular nerve and transverse cervical nerve rather than the inferiorly running nerves of the punctum nervosum. An aliquot of 3% lidocaine (one 1.8 mL carpule) with norepinephrine (1:100,000) is placed at the punctum nervosum, which is located at the posterior aspect of the sternocleidomastoid (SCM) muscle, midway between the mastoid process and the transverse process of C6 [Figure 2]. The second step is to infiltrate the periauricular incision line using 2 carpules of lidocaine and a serial puncture technique. The third step involves the infiltration of the dissection area using a Whitacre epidural cannula and the super wet technique with a modified Klein solution consisting of one 20 mL vial of lidocaine (2%) with epinephrine (1:100,000) and two vials of 0.9% sodium chloride (normal saline).^[15] The 25-gauge 3.5 inch Whitacre spinal needle (Becton, Dickinson and Company, NJ, USA) has a pencil tip and lateral opening, which spreads the subcutaneous tissues without cutting nerves and vessels. With a little pressure, it is inserted into the area infiltrated in step 2. The area can then be anesthetized painlessly by slowly sliding the cannula in the subcutaneous fat plane, continuously delivering the small amounts of the anesthetic solution [Video 1].

Whereas the tumescent technique uses a large volume of dilute solution to stretch the skin taut, the super wet technique injects less than half the volume required for the tumescent technique, 40 mL suffices to infiltrate both sides.

MICRO-LIPOSUCTION

As we age, the loss of fibrous support, endocrine changes, a sedentary life style and excess caloric intake result in fat pockets in the cheek and the anterior neck becoming more voluminous and delineated. Disruption of the jaw line by jowling is often the first sign that leads patients to consider a cosmetic procedure, and submental lipodystrophy is hereditary in some individuals. Because a skin-only facelift cannot alter these signs of aging, submental liposuction is carried out prior to the lateral work, requiring another 20 mL of simplified Klein solution. Central lipodystrophy is accessed by a 2-mm incision with a number 11 blade anterior to the submental crease. A Becker grater round cannula (2.7 mm diameter, Wells Johnson Company, Tucson, AZ, USA) [Figure 3] is connected to a 10 mL disposable syringe with a luer lock and introduced without suction to dissect the subcutaneous plane at the supraplatysmal level. It is easy to inadvertently enter the subplatysmal plane, leading to disruption of the capsule of the submandibular gland with subsequent ptosis or injury to the marginal branch of the facial nerve. After determining the appropriate plane, the syringe plunger is withdrawn to create a 2-mL space. Just posterior to the central stab incision, a cannula with an open tip is used to maintain negative pressure in the syringe, with the tip close to the exit site. Rapid movements are required [Video 2].

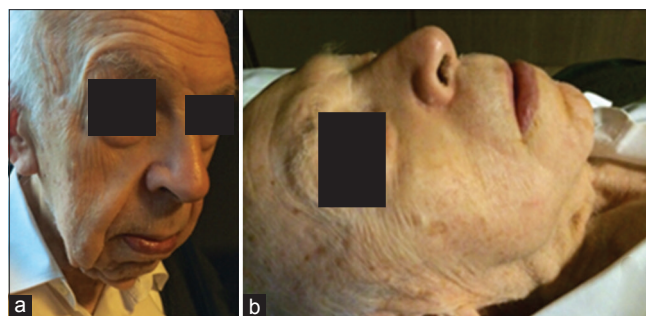


Figure 1: Effect of gravity (position) on the facial soft tissues of an 86-year-old man in upright (a) and prone (b) positions; the photo in (b) was rotated 90° for comparison with the photo in (a) to show the effects of gravity on the midface, revealing that the aged appearance results not only from fat atrophy but also from gravity

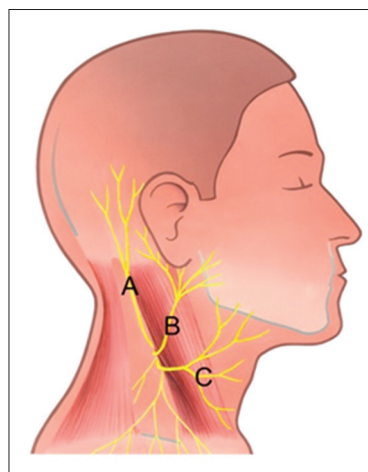


Figure 2: Punctum nervosum with the branches. A: lesser occipital nerve; B: great auricular nerve; and C: transverse cervical nerve



Figure 3: A 2.7 mm Becker grater round cannula with multiple perforations (1 mm diameter)

Surgical removal of the jowl fat is essential for the lifting procedure. This may be performed by Metzenbaum scissors or by open liposuction with a Becker grater cannula, after elevating the skin flap [Figure 4]. However, closed liposuction through a 2-mm stab incision anterior to the earlobe can be used to avoid irregularities, hematomas and damage to the marginal branch of cranial nerve VII. Counter pressure is important, but also leaving a layer of fat on the undersurface of the dermis [Video 3].

BAKER SMASECTOMY

Traction on low suspension sutures provides a strong

lifting effect to the neck compared to the high suspension of the SMAS flap used in a classic facelift. The disadvantage is that the purse string formed by plication of the SMAS can result in preauricular fullness in heavier patients. The lateral SMAS ectomy^[16] offers a solution [Figure 5]. Excision of a portion of the SMAS overlying the anterior section of the parotid gland secures the mobile anterior SMAS to the fixed portion of the superficial fascia. The long axis of the lentoid incision is oriented such that the vectors of elevation following SMAS closure lie perpendicular to the nasolabial fold. This procedure avoids extensive SMAS flap dissection and elevation, which risks damage to the buccal branches of cranial nerve VII and tearing of the flap. In addition, lateral bulkiness is addressed.

DANGER ZONES

Because the SMAS and platysma muscle are not elevated, and liposuction is preferred to lipectomy, there is no risk of injury to branches of the facial nerve. However, injury to the great auricular nerve can lead to a painful neuroma. Dissection of the skin flap overlying the mastoid fascia and under the earlobe should be confined to the reticular layer of the dermis. Sensation in the earlobe should return to normal or near normal by one week. In case of neuralgia, repeated injections with ropivacaine or betamethasone may be helpful.

Laceration of the facial vein [Figure 6] leads to bleeding, ecchymosis and sometimes hematoma. Coagula can lead to oozing because of fibrinolysis. They are difficult to remove because dissection of the tissue planes is required; following evacuation the epidermis appears lax and pigmented for a prolonged period. Vein laceration can be prevented by using Metzenbaum scissors, keeping the tips parallel to the skin surface and remaining in contact with the reticular dermis. Retrieving the vein stump after complete resection can be difficult as it retracts, and for this reason, bipolar coagulation is used. The vein may also be punctured by a suture needle when weaving the loops (the weaving is done with a sertix suture: suture and needle).

ALPHA AND OMEGA OF THE INCISION, CURVES, DOG-EARS

Scalp extension to create sideburns, which are beveled as described by Frechet^[17] and scalloped as described by Camirand and Doucet,^[18] opens the superior tunnel in a manner that allows for suspension of the SMAS to the temporalis fascia [Figure 7a].^[19] However, the result is a visible scar that cannot be erased [Figure 7b]. Attempts at correction will thin the sideburn hair and make the area less attractive. As mentioned in section one, the approach to the midface involves volume augmentation rather than lifting. The temporal extension does not improve the result.

The author recommends that the incision begins where the anterior helix separates from the preauricular skin and becomes the superior helix of the pinna. Depending



Figure 4: Open-sky liposuction of the jowls

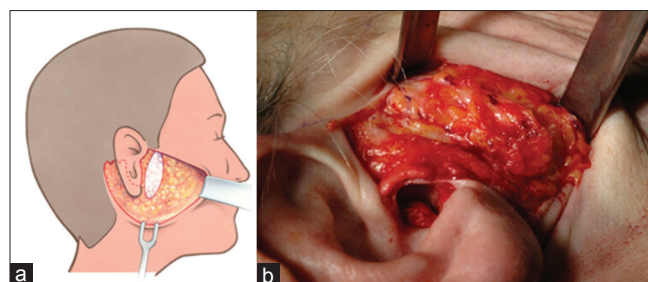


Figure 5: Lateral SMAS ectomy, as described by Baker (2,000). (a) Schematic diagram; (b) intraoperative photograph. Resorbable 4-0 Vicryl placed after resection

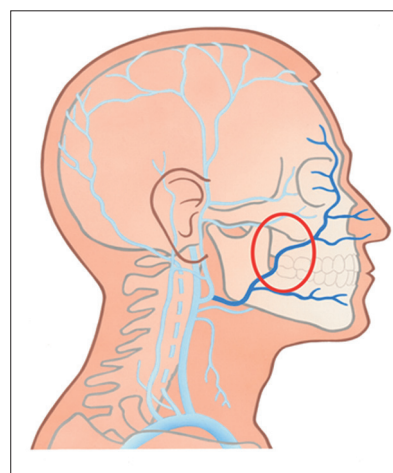


Figure 6: The facial vein (darker blue) at the edge of the dissection area (red oval) is difficult to visualize and may, therefore, be accidentally nicked, resulting in bleeding

upon the vector, the amount of lift and skin elasticity, the dog-ear may be small or substantial. Cephalad undermining is attempted first and is generally effective. Otherwise, an infra-sideburn incision, as described by Knize [Figure 8],^[5,20] or a 1-cm hockey stick extension can be used while keeping the scar hidden behind the sideburn.

The incision descends in front of the inferior crus and at the inner aspect of the tragus [Video 4]. The cartilage should not be notched as this will be visible after healing. The incision runs just anterior to the earlobe and curves around its attachment. After bipolar coagulation, the

superior subcutaneous tunnel is prepared. The incision then runs behind the pinna in the cephalad direction to the conchal cartilage; the scar will contract and be pulled down into the groove. If the incision is inadvertently placed in the auriculomastoid groove, the scar will be pulled into the visible mastoid area. The incision becomes horizontal at the level of the external auditory canal and then is scalloped, curving cephalad [Figure 9]. It should generally not extend into the occipital hairline, but if it does, it curves caudally again. The scalloped incision is beveled according to the method of Frechet, in the area of hair-bearing skin. The scalloped incision developed by Camirand and Doucet^[18] aids tremendously in dealing with the retroauricular dog-ear. After removing excess skin, the straight long excision edge of the flap is sutured into the scalloped edge, from back to the front, keeping the hairline intact.

LOW SUSPENSION VERSUS HIGH SUSPENSION

Patients often simulate the effects they wish to obtain in front of the bathroom mirror by manually pressing up the droopy skin, fat compartments and SMAS [Figure 10].

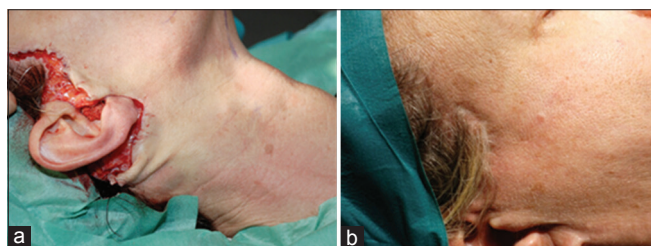


Figure 7: (a) Revision of a previous minimal access cranial suspension lift prompted scar revision. An extension in the sideburn area was of particular concern to the patient. This long incision provides ample exposure and is certainly more comfortable for the surgeon; (b) the presideburn extension of the "short scar" minimal access cranial suspension lift incision can produce a visible scar. The incisions are altogether as long as those of the classic approach with retroauricular (invisible) extensions

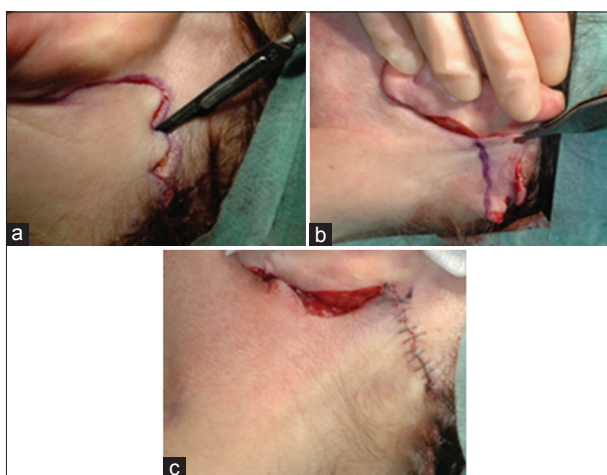


Figure 9: The scalloped incision described by Camirand and Doucet deals with the retroauricular dog-ear in an efficient way. Suturing is performed from back to the front to prevent hairline displacement, avoiding folds in the lower part of the retroauricular skin flap. (a) Scalloped design; (b) straight excision; (c) the longer straight lower margin now fits into the scallops of the upper margin

The 3 (sometimes 2 or 4) low suture suspension loops and 3 high suspension sutures are made of the resorbable material. The loops are woven in the SMAS layer and provide a mild purse string action that should be taken into clinical consideration [Video 5].

The inferior low reaching suspension suture picks up the posterior edge of the platysma at a point 1.5 cm anterior to the SCM muscle and 3 cm below the mandibular border, where the sliding plane between the platysma and deep cervical structures^[21] allows lifting without dissection [Figure 11].^[22] Labbé *et al.*^[22] suspend the platysma and SMAS to the temporoparotid fascia described by Lore,^[23] which is located immediately in the front of the intertragal incisura and at least 2 cm from the facial nerve trunk.^[24] The fascia is a highly resistant point of anchorage for the 2-0 polydioxanone (PDS) suspension suture. In heavy patients, the purse string plication of the platysma and SMAS obliterates the interval between the posterior mandibular border and SCM muscle, an aesthetically important zone [Figure 12]. The author proposes that a suspension suture be placed under the SCM muscle



Figure 8: The infra-sideburn technique described by Knize involves a downward extension of the hockey stick design

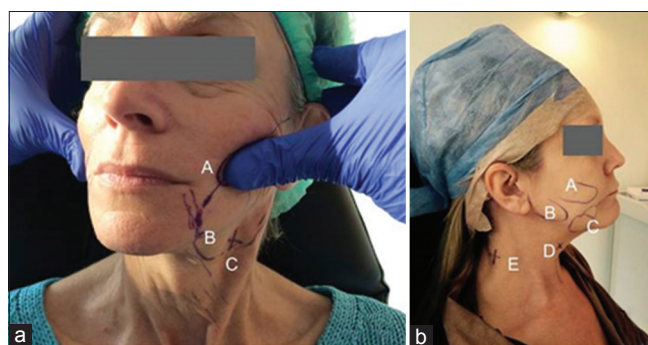


Figure 10: The position of the loops and hence the extension of the subcutaneous dissection is guided by manually simulating correction at the melolabial and mentolabial folds. The platysma is lifted after pinching it through the skin. (a) The face is lifted to undo the melolabial fold. A indicates marking around the thumb; B indicates marking at the mentolabial fold; C indicates where the platysma requires elevation (marked with an "X"). Dissection extends around the markings; (b) A and B indicate placement of the loops that lift the melolabial and mentolabial folds. In this case, the dissection could be minimal; C indicates micro-liposuction; D indicates platysma elevation; E indicates the punctum nervosum

to suspend the platysma to the mastoid fascia. This can be achieved by lifting the SCM muscle with one hand and sliding a mandibular awl beneath it in an anterior direction [Video 6]. The PDS suture is picked up by the awl, pulled posteriorly and knotted to the mastoid fascia using a widow needle [Figure 13]. The PDS suture requires many knots to hold. The volume and ends of the suture may cause pain when they press on the skin, such as during sleep. In addition, the ends may pierce the skin and cause painful inflammation. Suturing the surrounding tissues on the top of the knots with a 4-0 Vicryl suture can prevent this problem.

The 2-0 PDS purse string suture that is woven into the SMAS and picks up the remaining fat in the jowl area is suspended to the temporoparotid fascia described by Lore. The same procedure is used for the 2-0 PDS suture loops picking up the lower side of the nasolabial fold, which smooth the nasolabial groove and provide a moderate lift to the malar prominence. However, this effect does not appear to be maintained over time.

The high suspension is achieved by suturing the dermis in the pretragal area down to the parotid fascia using 4-0 Vicryl, with one stitch above and one stitch below the level of the tragus. Another useful high suspension maneuver was demonstrated by Dr. Heinz Bull at during the 2006 meeting of the German Association for Aesthetic Surgery in Düsseldorf. Using this technique, the skin flap is fixed to the conchal cartilage under the earlobe to prevent a pixie ear deformity. The 4-0 Vicryl includes tissue from both the dermis and the cartilage [Figure 14].

In regard to low suspension sutures, Hoefflin^[25] observed that “pulling on the SMAS is like repositioning a living room sofa by pulling on the carpet. It’s easier to just pick up the sofa and position it where you want it”. The

procedure described herein can therefore, be considered to be a repositioning of both the SMAS and fat.

The so-called “short scar” SMAS lift,^[19] with a strictly vertical vector, is not so short. The scar is quite long because it requires an extra skin excision in the lower eyelid [Figure 15a and c] and vertical pleating in the neck [Figure 15b] with difficult undermining in the retroauricular area and an extra posterior hairline incision. The total length of these “short scar” incisions averages 13 cm, whereas the currently proposed procedure uses an incision with an average length of 11 cm.

MAINTAINING TRAGUS AND EARLOBE POSITION

Trimming of the preauricular skin should be conservative because the pretragal high suture suspension creates tension on the tragal cartilage via the SMAS. Visibility of the external auditory canal is not aesthetically pleasing. The dermis overlying the tragal cartilage is trimmed over 1.5 cm to recreate the pretragal groove [Figure 16]. Otherwise, the flat appearance of the surface in front of

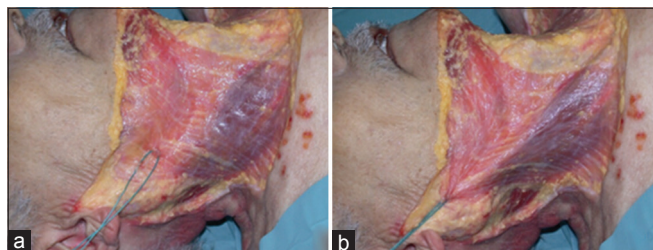


Figure 11: The platysma is more mobile a few centimeters in front of the sternocleidomastoid muscle than directly on top of it.^[21] (a) Prior to elevating the platysma with the suture loop; (b) after sliding the platysma along the superficial layer of the deep cervical fascia. Courtesy of Dr. Daniel Labbé, Caen, France

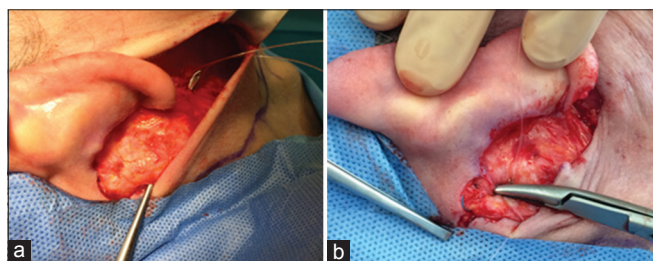


Figure 13: Platysma suspension. (a) A mandibular awl is used to lift the platysma under the sternocleidomastoid muscle; (b) suspension at the mastoid periosteum

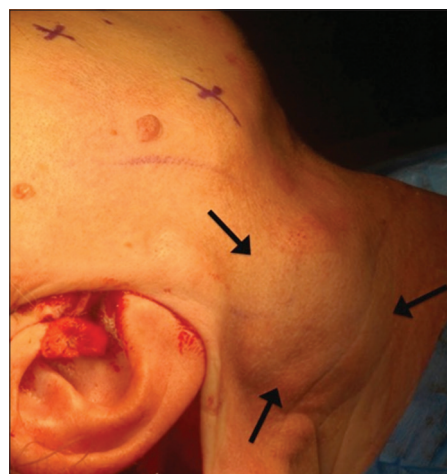


Figure 12: When sutured at the temporoparotid fascia as described by Lore, the platysma and subcutaneous fat bulge in the superolateral esthetic zone

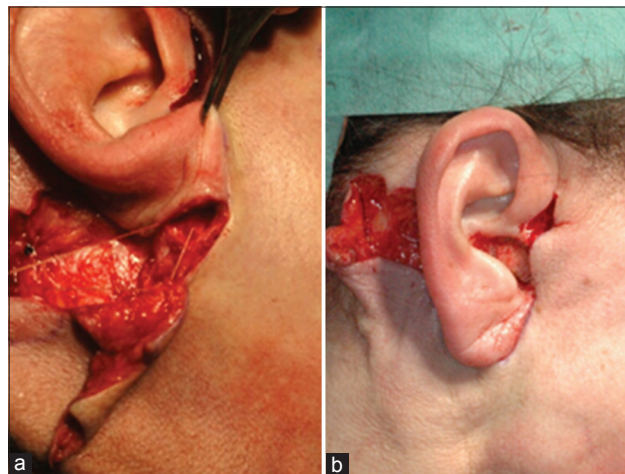


Figure 14: Suspension of the skin flap to the ear. (a) High suspension of dermis to the conchal cartilage using a 4-0 Vicryl suture; (b) the earlobe is pushed upward and backward

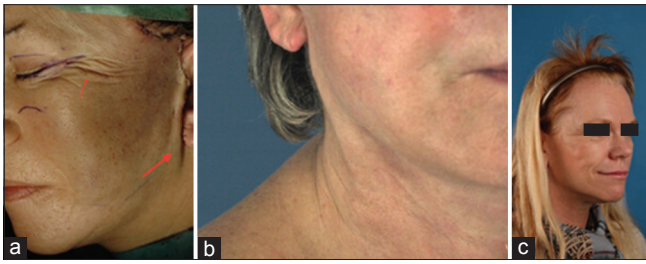


Figure 15: Complications of the vertical vector lift.^[19] (a) Vertical pleating (large arrow) and lower eyelid skin excess (small arrow). The latter is corrected by pinch blepharoplasty, which requires a 2-cm incision; (b) patient treated *alio loco*, presenting with vertical pleating in the neck; (c) patient treated *alio loco* presenting with excess skin in the lower eyelid

the tragus can indicate that a facelift has been performed. In men, the hair follicles should be meticulously trimmed, taking into consideration the desired sideburn shape and the fact that shaving the tragus (and under the earlobe) is a nuisance and may lead to repeated bleeding. Two 4-0 Vicryl sutures in this location will support lifting and shaping of the pretragal fovea.

Trimming under the earlobe should also be conservative. The anterior skin flap created during the resection of excess skin can usually be pulled behind the earlobe to determine how much needs to be resected. Because the earlobe will be pulled forward and downward by gravity and collagen contraction during the first few weeks following surgery, the shape of the skin flap should push the earlobe upward and backward [Figure 14].

Skin closure with 5-0 nylon starts at the superior end of the incision and continues down to the earlobe, stopping behind the earlobe and repositioning it upward and backward.

FIBRIN GLUE

The use of vacuum drains and extensive bandaging is not recommended. Fibrin glue spray is preferred to prevent hematomas, ecchymosis, seromas and discharge [Video 7]. The sealant should be applied while the wound is still open (0.5 mL each side) to allow air to escape and prevent venous air embolism. The wound bed is dried by introducing a suction drain connected to the central vacuum system under the skin flap before skin suturing.

LIP AND EARLOBE REDUCTION

Whereas a turkey gobbler neck and lower eyelid bags are spotted quickly and addressed with blepharoplasty and liposuction, long upper lips and earlobes are often overlooked.^[26] A long upper lip (and low lower lip) expose the lower teeth when smiling, a typical sign of aging. Pendulous earlobes can result from wearing heavy jewelry over many decades.

Upper lip reduction and nasal tip lift are accomplished by a modification^[27] of the “double duck” procedure,^[28] which is a modification of Austin^[26] sub-nasal buffalo horn excision. This procedure involves a sub-alar

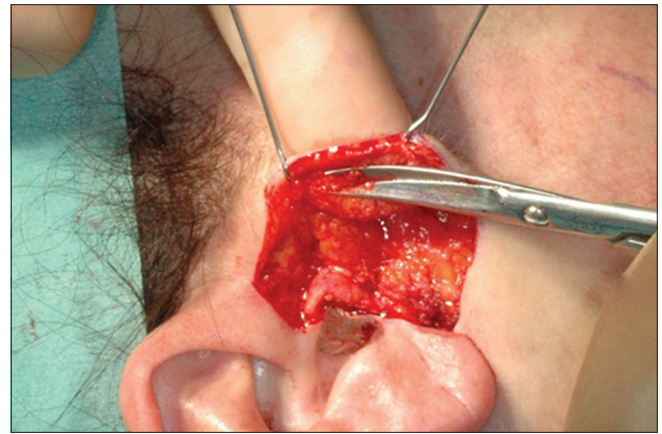


Figure 16: Creating the pretragal fovea. Trimming the flap to the dermis

crescent-shaped skin excision which continues into the membranous septum and which may be reduced in height if the nasolabial angle requires sharpening and a hanging columella is present. Otherwise, a full transfixion incision divides the medial crural footplates and the caudal septum. The dermis of the central lip is then suspended to it with a 4-0 PDS suture. The columella can then slide upward slightly with the footplates for the elevation of the nasal tip [Figure 17].

Earlobe reduction can be performed with marginal excision and fine sutures, although removal of a full-thickness medially based wedge produces better results. The facial skin flap is pulled up behind the newly formed earlobe to allow for proper cephalad repositioning [Figures 18 and 19].

Recommended sequence

- Premedicate
- Mark locations of the suspension loops and extent of dissection
- Secure intravenous access
- Prep and drape
- Mark incision lines
- Intravenous sedation
- Infiltrate of local anesthetic in the anterior neck for submental liposuction
- Perform submental liposuction
- Perform nerve block anesthesia and infiltrate local anesthetic
- Perform liposuction of jowl
- Incise and elevate pre-and post-auricular flaps and connect pockets
- Perform lateral SMAS ectomy
- Weave suspension sutures into the nasolabial fold, jowl area and platysma
- Fixate platysma to the substernomastoid region with a 2-0 PDS suture, followed by over-suturing with 4-0 Vicryl suture
- Knot the remaining suspension sutures onto the temporoparotid fascia, as described by Lore^[23]
- Mark and excise of excess skin in the preauricular region
- Trim pretragal subcutaneous sutures, and place high suspension suture to shape the pretragal fovea and drape the skin



Figure 17: The “double duck” procedure with full transfixion incision lifts the nasal tip and can correct a hanging columella by resection of the membranous septum



Figure 18: Earlobe reduction. Triangular excision and upward rotation of the lower earlobe flap. Suturing is performed, and a new perforation allows for secondary epithelialization on a 0.4 mm titanium wire (cut short at the end)



Figure 19: (a) Before buccocervical lift and earlobe reduction; (b) six months after the procedures

- Suspend the dermis to the conchal cartilage
- Place a Redon drain under the skin flap
- Suture the preauricular skin
- Excise excess postauricular skin
- Place high suspension suture to drape the postauricular flap provisionally

- Remove the Redon drain and apply fibrin glue spray
- Suture the postauricular skin
- Apply a pressure dressing with gauze behind the earlobes.

Products required

Xylonor (30 mg/mL) + 0.04 mg/mL noradrenaline 1.8 mL (Septodont, Saint-Maur-des-Fossés, France).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Rafaty FM, Brennan HG. Current concepts of browpexy. *Arch Otolaryngol* 1983;109:152-4.
2. Mommaerts MY, Abeloos JS, De Clercq CA, Neyt LF. Brow and forehead lift with cranial suspension. Technical note. *J Craniomaxillofac Surg* 1994;22:33-6.
3. Isse BG. Endoscopic facial rejuvenation: endoforehead, the functional lift. Case reports. *Aesthetic Plast Surg* 1994;18:21-9.
4. Fogli AL. Temporal lift by galeapexy. A review of 270 cases. *Aesthetic Plast Surg* 2003;27:159-65.
5. Knize DM. The Forehead and Temporal Fossa. Philadelphia: Lippincott Williams and Wilkins; 2001.
6. Stevens WG, Apfelberg DB, Stoker DA, Schantz SA. The endotine: a new biodegradable fixation device for endoscopic forehead lifts. *Aesthet Surg J* 2003;23:103-7.
7. Lam S, Glassgold MJ, Glasgold RA. Complementary Fat Grafting. Philadelphia: Lippincott, Williams and Wilkins; 2006.
8. Altman K. Facial feminization surgery: current state of the art. *Int J Oral Maxillofac Surg* 2012;41:885-94.
9. Wan D, Amirlak B, Rohrich R, Davis K. The clinical importance of the fat compartments in midfacial aging. *Plast Reconstr Surg Glob Open* 2014;1:e92.
10. Geissler PJ, Davis K, Roostaeian J, Unger J, Huang J, Rohrich RJ. Improving fat transfer viability: the role of aging, body mass index, and harvest site. *Plast Reconstr Surg* 2014;134:227-32.
11. Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. *Plast Reconstr Surg* 2014;134:1197-201.
12. Greenblatt DJ, Shader RI, Franke K, MacLaughlin DS, Harmatz JS, Allen MD, Werner A, Woo E. Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. *J Pharm Sci* 1999;68:57-63.
13. Kanto JH. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 1985;5:138-55.
14. Ramsay MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J* 1974;2:656-9.
15. Klein JA. Anesthetic formulation of tumescent solutions. *Dermatol Clin* 1999;17:751-9.
16. Baker D. Rhytidectomy with lateral SMASectomy. *Facial Plast Surg* 2000;16:209-13.
17. Frechet P. Minimal scars for scalp surgery. *Dermatol Surg* 2007;33:45-55.
18. Camirand A, Doucet J. A comparison between parallel hairline incisions and perpendicular incisions when performing a face lift. *Plast Reconstr Surg* 1997;99:10-15.
19. Tonnard P, Verpaele A. Short-scar Face Lift. Operative Strategies and Techniques. St. Louis: Quality Medical Publishing; 2007.

20. Knize DM. Periauricularface lift incisions and the auricular anchor. *Plast Reconstr Surg* 1999;104:1508-20.
21. Gardetto A, Dabernig J, Rainer C, Piegger J, Piza-Katzer H, Fritsch H. Does a superficial musculoaponeurotic system exist in the face and neck? An anatomical study by the tissue plastination technique. *Plast Reconstr Surg* 2003;111:664-72.
22. Labbé D, Franco RG, Nicolas J. Platysma suspension and platysmaplasty during neck lift: anatomical study and analysis of 30 cases. *Plast Reconstr Surg* 2006;117:2001-7.
23. Lore JM. *An Atlas of Head and Neck Surgery*. 2nd ed. Philadelphia: Saunders; 1973.
24. O'Brien JX, Rozen WM, Whitaker IS, Ashton MW. Lore's fascia and the platysma-auricular ligament are distinct structures. *J Plast Reconstr Aesthet Surg* 2012;65:e241-5.
25. Hoefflin S. Facial rejuvenation-my personal evolution. *Aesthet Surg J* 1998;18:286-9.
26. Austin HW. The lip lift. *Plast Reconstr Surg* 1986;77:990-4.
27. Cardim VL, Salomons RL, De Faria Valle R, De Souza JO, De Lima ES. "Double duck" nasolabial lifting. *Rev Bras Cir Plást* 2011;26:466-71.
28. Mommaerts MY, editor. Lip lift. In: *The Surgical Art of Facial Makeover. Planning and Operative Techniques*. Vol. I. Sint-Martens-Latem: Orthoface R and D; 2013. p. 291-4.

Peripheral nerve injuries

Katerina Anesti¹, Paul Caine²

¹Department of Plastic Surgery, Royal Devon and Exeter NHS Foundation Trust, Exeter, EX2 5DW, UK.

²Department of Plastic Surgery, St Andrew's Centre, Mid Essex NHS Trust, Chelmsford, CM1 7ET, UK.

Address for correspondence: Miss. Katerina Anesti, Department of Plastic Surgery, Royal Devon and Exeter NHS Foundation Trust, Exeter, EX2 5DW, UK. E-mail: katanest@doctors.org.uk

Nerve injuries caused by medical interventions (iatrogenic lesions) can complicate procedures and affect any part of the peripheral nervous system. Available data are fragmentary and little information is accessible on the overall incidence of iatrogenic nerve lesions that ranges from 1.5% to 15%.^[1,2] Major drawbacks are the limited number of patients studied and the incomplete and subjective assessment of nerve function. The potential for iatrogenic injuries in the course of any surgical procedure should be thoroughly appreciated by all surgeons and they should be familiar with early diagnostic steps for detecting these lesions. The importance of prompt diagnosis and adequate treatment of iatrogenic nerve injuries for optimal functional recovery should be stressed. Excellent results can be obtained if certain diagnostic and surgical principles are followed.

Iatrogenic injuries during surgery are becoming more widely documented as we begin to see surges in insurance claims. A review of insurance claims filed by patients who had undergone otorhinolaryngological procedures in Finland found a total of 422 claims over a 4-year-period. Iatrogenic nerve injury accounted for 30 patients; 10 patients suffered facial nerve damage (secondary to ear and parotid gland surgery) and 10 suffered trigeminal nerve injury (secondary to maxillary sinus surgery).^[1] A series by Kretschmer *et al.*^[2] looking at 722 patients with peripheral nerve trauma found that approximately 17.4% were iatrogenic injuries with the majority (94%) being secondary to a surgical procedure. Seventeen percent of injuries occurred to the median nerve, 16% to the accessory, 13% to the radial and common peroneal, 8.5% to the ulnar and 5% to the femoral nerves, respectively.^[3] Spinal accessory nerve injuries resulting from medical intervention have been quoted as high as 94%^[4] and figures of 60% and 25.2% for femoral

and sciatic nerve injuries, respectively.^[5,6] Topuz *et al.*^[7] attributed sciatic nerve damage to intragluteal injections in approximately 40% of their patients. The high risk procedures that often result in peripheral nerve damage include: osteosynthesis, arthrodesis, posterior triangle lymph node biopsies, carpal tunnel release, surgery for varicose veins, baker cyst excision and inguinal herniorrhaphy.^[8]

The use of pneumatic surgical tourniquets is a key in providing a bloodless environment in distal extremities. They also have a crucial role in the application of regional anesthesia. However, they can result in complications including: skin damage, nerve and vascular injury and also postoperative swelling. Nerve injury related to tourniquets results from two pathological processes: mechanical compression and neural ischemia. Horlocker *et al.*^[9] found there to be a three-fold increase in risk of nerve damage for every 30 min increase in tourniquet inflation time. Tourniquet related nerve injury is widely documented in the literature,^[10] however, permanent femoral nerve injury secondary to tourniquet use is sparsely reported. Mingo-Robinet reported a permanent femoral nerve palsy secondary to tourniquet use in patella fracture surgery.^[11]

It has been documented in the literature that iatrogenic nerve injury can arise from enucleation of peripheral schwannomas by both an extra and intracapsular approach. The reported incidence of iatrogenic injury has been found to range from 13% of cases for motor deficit^[12] up to 50% for sensory deficit.^[13] Park *et al.*^[14] reported values as high as 73% of new neurological deficit after enucleation. A review of nerves injured and the length of neurological deficit was carried out by Date *et al.*^[15] Upper limb nerves were affected and included: the radial

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.169500

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Anesti K, Caine P. Peripheral nerve injuries. *Plast Aesthet Res* 2015;2:309-10.

Received: 03-05-2015; **Accepted:** 06-09-2015

nerve in 2 patients, median nerve in 3, ulnar nerve in 5 and musculocutaneous in 1. Lower limb nerves were also affected: tibial in 13 patients, peroneal in 8, and the femoral, obturator and sciatic nerve in 3 individual patients. The degree of neurological deficit was graded according to persistence of symptoms. The review found that 22 patients developed sensory changes resolving within 6 months (Medical Research Council [MRC] motor grading system Grade 1)^[16] and 10 patients where the deficit took in excess of 6 months to recover (MRC Grade 2). After a total of 48 months follow-up there were 4 patients in which the motor deficit or paresthesia had not recovered (MRC Grade 3). The nerves affected in these 4 patients included the median, ulnar and tibial. Of the 11 patients with schwannomas arising from the upper extremity nerve three had not recovered function by the end of follow-up. Five patients with ulnar nerve damage showed Grade 3 motor palsy with reduced abduction of the little finger. Of the 24 patients with lower limb schwannomas only 3 developed a Grade 3 motor deficit. Knight *et al.*^[17] found 28 patients to have neurological deficit and/or pain after excision of schwannomas. Factors to try to reduce the neurological deficit include; avoiding unnecessary biopsy, air tourniquet use for good vision under microscope, intracapsular approach, limited incision of the epineurium, atraumatic dissection, no *en bloc* resection if traumatic, adequate drainage to prevent hematoma formation and to raise the affected limb. Simon *et al.*^[18] in a case series of 2 patients reported the benefit of using high resolution ultrasonography prior to nerve sheath tumor resection to identify normal nerve tissue.

In summary, iatrogenic nerve lesions require early clinical and electrophysiological testing and prompt referral to specialized centers for timely treatment. In cases of nerve discontinuity and acute nerve compression, surgical intervention is indicated immediately. In all other cases, 6-12 weeks after the iatrogenic lesion, primary surgery should be considered if no significant spontaneous recovery is observed. Neurapraxia carries a good prognosis, but if diagnosis is in doubt, delay may cause continuing compression or ischemia, which will result in worsening of the nerve lesion to axonotmesis or even neurotmesis. Furthermore, when dealing with traumatic neuropathies, adequate pain management is likely to have a strong positive influence in the prognosis of these patients, both in terms of improving their quality of life and functional recovery. The role of aggressive physiotherapy with motor and sensory re-education will facilitate rehabilitation and useful functional restoration. It seems imperative to know more about long-term function and quality of life, since these injuries may lead to severe psychological distress.

In conclusion, iatrogenic nerve injuries constitute a complex, multifactorial problem, which cannot be resolved by surgery alone. The management should embrace prevention, early diagnosis and appropriate treatment with rehabilitation, psychological support and control of pain. This warrants the highest quality of care in nerve reconstruction.

Complications should be referred and dealt with promptly by experienced surgeons with adequate microsurgical training, to ensure best chances for successful outcome. In addition, when nerve damage is caused by medical intervention, legal issues may ensue. The importance of preoperative counseling about the potential injury and precise documentation of intraoperative and postoperative findings cannot be overemphasized. This will facilitate postoperative discussion of any surgical complication.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Lehtivouri T, Palonen R, Mussalo-Rauhamaa H, Holi T, Henriksson M, Aaltonen LM. Otorhinolaryngological patient injuries in Finland. *Laryngoscope* 2013;123:2397-400.
- Kretschmer T, Antoniadis G, Braun V, Rath SA, Richter HP. Evaluation of iatrogenic lesions in 722 surgically treated cases of peripheral nerve trauma. *J Neurosurg* 2001;94:905-12.
- Antoniadis G, Kretschmer T, Pedro MT, König RW, Heinen CP, Richter HP. Iatrogenic nerve injuries: prevalence, diagnosis and treatment. *Dtsch Arztebl Int* 2014;111:273-9.
- Kim DH, Cho YJ, Tiel RL, Kline DG. Surgical outcomes of l1l1 spinal accessory nerve injuries. *Neurosurgery* 2003;53:1106-12.
- Kim DH, Murovic JA, Tiel R, Kline DG. Management and outcomes in 353 surgically treated sciatic nerve lesions. *J Neurosurg* 2004;101:8-17.
- Kim DH, Murovic JA, Tiel RL, Kline D. Intrapelvic and thigh-level femoral nerve lesions: management and outcomes in 119 surgically treated cases. *J Neurosurg* 2004;100:989-96.
- Topuz K, Kutlay M, Simsek H, Atabey C, Demircan M, Senol Güney M. Early surgical treatment protocol for sciatic nerve injury due to injection—a retrospective study. *Br J Neurosurg* 2011;5:509-15.
- Stöhr M. Iatrogenic nerve lesions. Injection, operation, storage, radiotherapy. 2nd ed. Stuttgart: Thieme; 1996. p. 131-91.
- Horlocker TT, Hebl JR, Gali B, Jankowski CJ, Burkle CM, Berry DJ, Zepeda FA, Stevens SR, Schroeder DR. Anesthetic, patient, and surgical risk factors for neurologic complications after prolonged total tourniquet time during total knee arthroplasty. *Anesth Analg* 2006;102:950-5.
- Kornbluth ID, Freedman MK, Sher L, Frederick RW. Femoral, saphenous nerve palsy after tourniquet use: a case report. *Arch Phys Med Rehabil* 2003;84:909-11.
- Mingo-Robinet J, Castañeda-Cabrero C, Alvarez V, León Alonso-Cortés JM, Monge-Casares E. Tourniquet-related iatrogenic femoral nerve palsy after knee surgery: case report and review of the literature. *Case Rep Orthop* 2013;2013:368290.
- Donner TR, Voorhies RM, Kline DG. Neural sheath tumors of major nerves. *J Neurosurg* 1994;81:362-73.
- Oberle J, Kahamba J, Richter HP. Peripheral nerve schwannomas – An analysis of 16 patients. *Acta Neurochir (Wien)* 1997;139:949-53.
- Park MJ, Seo KN, Kang HJ. Neurological deficit after surgical enucleation of schwannomas of the upper limb. *J Bone Joint Surg Br* 2009;91:1482-6.
- Date R, Muramatsu K, Ihara K, Taguchi T. Advantages of intra-capsular micro-enucleation of schwannoma arising from extremities. *Acta Neurochir (Wien)* 2012;154:173-8.
- Medical Research Council Scale. Aids to examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationery Office; 1976.
- Knight DM, Birch R, Pringle J. Benign solitary schwannomas: a review of 234 cases. *J Bone Joint Surg Br* 2007;89:382-7.
- Simon NG, Cage T, Narvid J, Noss R, Chin C, Kliot M. High-resolution ultrasonography and diffusion tensor tractography map normal nerve fascicles in relation to schwannoma tissue prior to resection. *J Neurosurg* 2014;120:1113-7.

Free deep inferior epigastric perforator flap after abdominal liposuction: reconsidering a contraindication

Peter James Mankowski, Jonathan Kanevsky, Anne-Sophie Lessard, Teanoosh Zadeh

Division of Plastic and Reconstructive Surgery, McGill University Health Centre, Montreal, Quebec H3G 1B3, Canada.

Address for correspondence: Mr. Peter James Mankowski, Division of Plastic and Reconstructive Surgery, McGill University Health Centre, Montreal, Quebec H3G 1B3, Canada. E-mail: peter.mankowski@mail.mcgill.ca

ABSTRACT

Autologous breast reconstruction with perforators has been previously avoided in tissues that have undergone liposuction. We present a case series and literature review of breast reconstruction with deep inferior epigastric perforator (DIEP) flaps after abdominal wall liposuction. An MEDLINE search was performed for all relevant articles describing breast reconstruction with DIEP flap technique following the abdominal wall liposuction. Key search words used included "DIEP", "DIEAP", "deep inferior epigastric perforator", "liposuction" and "free flap". All published data on the topic from 1965 to December 2014 were reviewed. Articles were assessed for reports of clinical cases, complications, age, liposuction amount, time since liposuction and number of perforators for comparison. We have also presented 2 patients who underwent a DIEP procedure with a previous history of liposuction. Eight cases of autologous breast reconstruction using a DIEP flap after liposuction were identified in the literature in addition to the presented cases. The preoperative and postoperative course was uneventful in all cases except one patient who had a mild cellulitis managed with antibiotics and a second patient with a drainable hematoma. The average age was 52 years \pm 6.4 years old, one perforator was used in all cases except one where 2 were used, and the average amount of total liposuction was 1,084 mL. No major complications were reported. Previous liposuction is not an absolute contraindication for free-flap breast reconstruction. Preoperative management should include evaluation of suitable perforators by duplex ultrasound or computed tomography angiography. Larger case series are needed to better understand the safety of perforator flaps after liposuction.

Key words:

Breast reconstruction, deep inferior epigastric perforator, flap, liposuction

INTRODUCTION

Over the past decade, there has been an increase in breast reconstruction among women who have previously had liposuction.^[1] Raising a perforator flap is generally contraindicated after abdominal liposuction due to possible damage of the perforators that supply the flap's vascularity.^[2] Numerous articles have already

demonstrated successful breast reconstruction with a transverse rectus abdominis myocutaneous flap after liposuction; however, there is a paucity of data on breast reconstruction using a deep inferior epigastric perforator (DIEP) flap after liposuction.^[3-6] Our experience

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Mankowski PJ, Kanevsky J, Lessard AS, Zadeh T. Free deep inferior epigastric perforator flap after abdominal liposuction: reconsidering a contraindication. *Plast Aesthet Res* 2015;2:311-4.

Received: 19-07-2015; **Accepted:** 29-09-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.169504

of breast reconstruction with DIEP flap after abdominal wall liposuction will be demonstrated in addition to a literature review.

METHODS

An MEDLINE search was performed for all relevant articles describing the breast reconstruction with DIEP flap technique following abdominal wall liposuction. This study includes all published data on the topic from 1965 to December 2014. The PubMed database of the National Center for Biotechnology Information, National Library of Medicine (Bethesda, Maryland, USA), was used to collect reports using the keywords “DIEP”, “DIEAP”, “deep inferior epigastric perforator”, “liposuction” and “free flap”. All articles were reviewed for reports of clinical cases including complications, age, liposuction amount, time since liposuction and the number of perforators for comparison.

RESULTS

A total of 8 cases of autologous breast reconstruction using a DIEP flap after liposuction were identified in the literature review in addition to the 2 cases we present here. A study by De Frene *et al.*^[7] describes five consecutive cases, and Jandali *et al.*^[1] reports one case. In addition, Farid *et al.*^[8] reported 2 cases involving DIEP flap breast reconstruction after multiple liposuction procedures. The results of these studies including our cases are summarized in Table 1. The preoperative and postoperative course for all prior liposuction cases was uneventful except for our 2 patients: one who had a mild cellulitis that resolved with appropriate therapy without any compromise of the flap and another who experienced a hematoma which was subsequently drained. The average patient age was 52.2 years \pm 6.4 years old, and one perforator was used in all cases except one report where two were used. Of the reported cases, the average amount of liposuction collected was 1,084 mL. Two minor complications out of the total 10 cases were a mild cellulitis and a postoperative stable hematoma. No major complications were reported.

Case 1

A 50-year-old, nonsmoker, female underwent a left sided mastectomy for invasive ductal carcinoma. Conventional

abdominal liposuction was performed 5 years before the original diagnosis of breast cancer. Three years after the mastectomy, the patient underwent autologous breast reconstruction with a DIEP flap. The patient was evaluated preoperatively for suitable perforators by computed tomography (CT) angiography and duplex ultrasound. Examination revealed appropriate perforator vessels and extensive fibrosis throughout the subcutaneous tissue caused by the previous liposuction. The patient underwent delayed unilateral breast reconstruction with a free DIEP flap. The postoperative course was complicated by a mild cellulitis that was successfully treated with antibiotics and no damage resulted to the flap [Figure 1].

Case 2

A 59-year-old, smoker, female with breast cancer underwent a right mastectomy in 1998 followed by implant-based reconstruction the same year. She later underwent radiation therapy and subsequently developed severe capsular contracture [Figure 2]. In 2012, she underwent right breast capsulectomy and reconstruction with DIEP flap. Eighteen years earlier, the patient had undergone conventional abdominal liposuction. The patient was evaluated preoperatively for suitable perforators by CT angiography and duplex ultrasound. Examination revealed appropriate perforator vessels. Three days following the DIEP flap procedure the patient developed a hematoma that was evacuated and the patient had a stable postoperative course without any flap compromise.

DISCUSSION

Previous literature suggests that harvesting perforator flaps from liposuctioned donor sites may not necessarily be a contraindication to free-flap breast reconstruction.^[5,7] The largest reported series of DIEP flaps after liposuction was published by De Frene *et al.*^[7] with five successful cases of breast reconstruction. The DIEP flap, introduced by Itoh and Arai^[9] and Koshima and Soeda^[10] and popularized by Allen and Treece,^[11] Blondeel and Boeckx,^[12] and Blondeel^[13] has been described as the most appropriate way to reconstruct a breast to minimize donor morbidity.^[6,14,15] The effect of liposuction on a free flap donor site months or years before flap transfer remains to be clarified.

Table 1: Summary of studies performing DIEP reconstruction in patients who have had previous liposuction

Study	Age	Number of perforators	Liposuction (mL)	Years after liposuction	Complications
Jandali <i>et al.</i> ^[1]	42	2	Not reported	9	None
Farid <i>et al.</i> ^[8]	57	1	240 + 300 + 300	1.33	None
	54	1	100 to 160 × 5	0.5	None
De Frene <i>et al.</i> ^[7]	52	1	1,300	4	None
	58	1	1,000	11	None
	41	1	1,100	9	None
	52	1	1,500	6.5	None
	57	1	1,200	4	None
Our study	50	1	Not reported	5	Mild cellulitis
	59	2	Not reported	18	Hematoma

DIEP: Deep inferior epigastric perforator

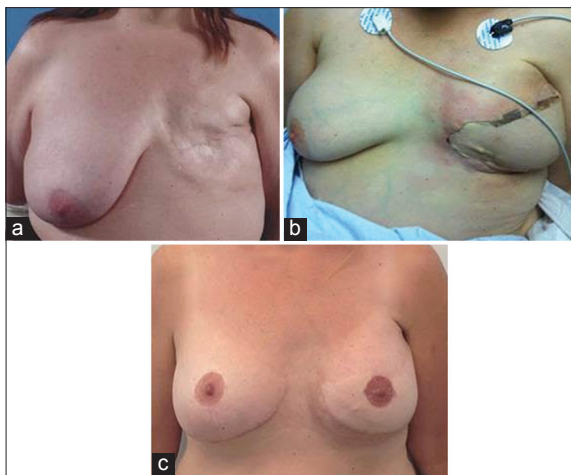


Figure 1: Case 1, patient before (a) and after (b), deep inferior epigastric perforator procedure with evidence of mild cellulitis surrounding the flap; (c) patient at 2 years follow-up after additional nipple reconstructive produces and extensive weight loss

Previous literature has shown conflicting evidence regarding the effect of liposuction on donor tissue, specifically, perforator vessels. Teimourian and Kroll^[16] reported that neurovascular bundles remain intact following conventional liposuction on examination with subcutaneous endoscopy. However, a study by Ozcan *et al.*^[17] demonstrated that flap necrosis is directly related to the number of suction passes of a cannula accompanied by a vacuum. Inceoglu *et al.*^[18] reported a 57.8% decrease in the number of perforators in abdominal subcutaneous tissue 3 months after liposuction using duplex ultrasound. Despite the reported decrease in the number of perforators, Ribuffo *et al.*^[5] demonstrated that perforator arteries regenerate up to 40% of their original diameter after liposuction. This evidence suggests that the liposuction technique may influence the degree to which perforator vessels are damaged and the outcome of the flap.

It should be possible to minimize patient complications associated with free-flap breast reconstruction after liposuction through modification of the initial liposuction procedure and decreasing trauma to perforators during liposuction. The variability in a number of perforators after liposuction is likely related to factors such as the cannula used, the number of passes, strength of suction and operator force and technique. An ultrasound-assisted liposuction technique described by Zocchi^[19] showed less damage to neurovascular structures. However, these findings were later opposed by a study which compared conventional versus ultrasonic liposuction.^[2] Salgarello *et al.*^[20] suggest employing a superficial subdermal liposuction technique to maintain perforator viability. Overall, a refined technique or protocol for liposuction in future free flap donor areas may improve patient outcome.

There are inherent difficulties in choosing when to use a technique to maximize perforator viability. For example, it is not possible to predict which patients will require autologous breast reconstruction with a free flap at the time of abdominal liposuction. Furthermore, patients may have breast reconstruction with a different surgeon than the one who performed the liposuction, creating

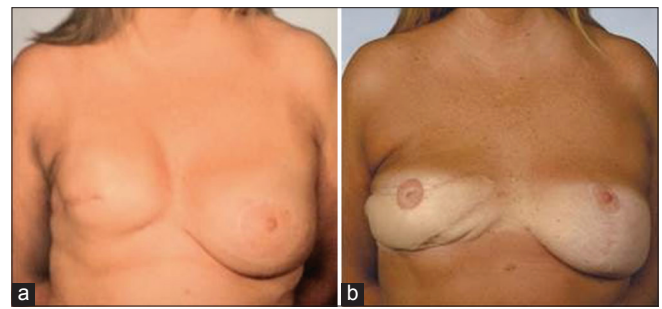


Figure 2: Case 2, (a) Patient prior to breast reconstruction with severe capsular contracture; (b) after DIEP flap procedure. DIEP: Deep inferior epigastric perforator

a challenge for the surgeon to predict the adequacy of perforators in the future donor site. As noted by Wes *et al.*,^[21] breast reconstructive in the context of previous abdominal surgery therefore requires a thorough preoperative evaluation to prevent flap morbidity. Specifically in the context of liposuction, duplex ultrasound and CT angiography will help identify perforator viability to reduce procedural complications. The use of color duplex examination as a preoperative guide is reported to have a true-positive rate of 96.2% and a positive predictive value of 100% in the hands of an experienced sonographer.^[22] The use of CT angiography as a preoperative methodology was reinforced by both Bank *et al.*^[23] and Rozen *et al.*^[24] to confirm perforator presence and communication for facilitating DIEP flap paddle design in postabdominal procedure patients. Rozen *et al.*^[24] highlighted the benefit of preoperative CT flap design as a method for identifying perforators resulted from neovascularization offering additional possibilities for DIEP harvesting. Other techniques such as flap perfusion mapping may be useful when the surgeon needs to know the integrity of vessels that are too small to image with standard angiographic techniques preoperatively.^[25] In addition, Masia *et al.*^[26] described multidetector-row CT, an imaging modality that allows for interpretation of a virtual anatomic dissection in three dimensions with very high spatial resolution. Intraoperative laser angiography using the SPY system has been shown to be beneficial for assessing tissue perfusion during flap elevation.^[27] Application of SPY laser angiography decreases the incidence skip necrosis in postmastectomy reconstruction and the rate of reoperation due to of perfusion related complications.^[28] Finally, Farid *et al.*^[8] prefer MR angiography to CT angiography to avoid reliance on intravenous contrast and to reduce patient exposure to radiation. Appropriate application of these techniques for perforator evaluation including CT, ultrasound, or perfusion mapping may improve the outcome of patients undergoing DIEP after abdominal liposuction

CONCLUSION

We have demonstrated two cases, in addition to the previously reported literature that suggest previous conventional liposuction is not an absolute contraindication for free-flap breast reconstruction. Preoperative management of the patient should include thorough evaluation of suitable

perforators by duplex ultrasound or CT angiography. In patients with history of liposuction to the lower abdomen, a classification system would be of clinical utility in guiding the selection of the ideal technique for breast reconstruction. Larger case series are needed to better understand the safety of perforator flaps after liposuction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Jandali S, Nelson JA, Wu LC, Serletti JM. Free transverse rectus abdominis myocutaneous flap for breast reconstruction in patients with prior abdominal contouring procedures. *J Reconstr Microsurg* 2010;26:607-14.
- Blondeel PN, Derks D, Roche N, Van Landuyt KH, Monstrey SJ. The effect of ultrasound-assisted liposuction and conventional liposuction on the perforator vessels in the lower abdominal wall. *Br J Plast Surg* 2003;56:266-71.
- Hess CL, Gartside RL, Ganz JC. TRAM flap breast reconstruction after abdominal liposuction. *Ann Plast Surg* 2004;53:166-9.
- Karanas YL, Santoro TD, Da Lio AL, Shaw WW. Free TRAM flap breast reconstruction after abdominal liposuction. *Plast Reconstr Surg* 2003;112:1851-4.
- Ribuffo D, Marcellino M, Barnett GR, Houseman ND, Scuderi N. Breast reconstruction with abdominal flaps after abdominoplasties. *Plast Reconstr Surg* 2001;108:1604-8.
- Tachi M, Yamada A. Choice of flaps for breast reconstruction. *Int J Clin Oncol* 2005;10:289-97.
- De Frene B, Van Landuyt K, Hamdi M, Blondeel P, Roche N, Voet D, Monstrey S. Free DIEAP and SGAP flap breast reconstruction after abdominal/gluteal liposuction. *J Plast Reconstr Aesthet Surg* 2006;59:1031-6.
- Farid M, Nicholson S, Kotwal A, Akali A. DIEP breast reconstruction following multiple abdominal liposuction procedures. *Eplasty* 2014;14:e47.
- Itoh Y, Arai K. The deep inferior epigastric artery free skin flap: anatomic study and clinical application. *Plast Reconstr Surg* 1993;91:853-63.
- Koshima I, Soeda S. Inferior epigastric artery skin flaps without rectus abdominis muscle. *Br J Plast Surg* 1989;42:645-8.
- Allen RJ, Treece P. Deep inferior epigastric perforator flap for breast reconstruction. *Ann Plast Surg* 1994;32:32-8.
- Blondeel PN, Boeckx WD. Refinements in free flap breast reconstruction: the free bilateral deep inferior epigastric perforator flap anastomosed to the internal mammary artery. *Br J Plast Surg* 1994;47:495-501.
- Blondeel PN. One hundred free DIEP flap breast reconstructions: a personal experience. *Br J Plast Surg* 1999;52:104-11.
- Arnez ZM, Pogorelec D, Planinsek F, Ahcan U. Breast reconstruction by the free transverse gracilis (TUG) flap. *Br J Plast Surg* 2004;57:20-6.
- Hamdi M, Weiler-Mithoff EM, Webster MH. Deep inferior epigastric perforator flap in breast reconstruction: experience with the first 50 flaps. *Plast Reconstr Surg* 1999;103:86-95.
- Teimourian B, Kroll SS. Subcutaneous endoscopy in suction lipectomy. *Plast Reconstr Surg* 1984;74:708-11.
- Ozcan G, Shenaq S, Baldwin B, Spira M. The trauma of suction-assisted lipectomy cannula on flap circulation in rats. *Plast Reconstr Surg* 1991;88:250-8.
- İnceoğlu S, Özdemir H, İnceoğlu F, Demir H, Önal B, Çelebi C. Investigation of the effect of liposuction on the perforator vessels using color Doppler ultrasonography. *Eur J Plast Surg* 1998;21:38-42.
- Zocchi M. Ultrasonic liposculpturing. *Aesthetic Plast Surg* 1992;16:287-98.
- Salgarello M, Barone-Adesi L, Cina A, Farallo E. The effect of liposuction on inferior epigastric perforator vessels: a prospective study with color Doppler sonography. *Ann Plast Surg* 2005;55:346-51.
- Wes AM, Cleveland E, Nelson JA, Fischer JP, Kovach SJ, Kanchwala S, Serletti JM, Wu LC. Do prior abdominal surgeries increase complications in abdominally based breast reconstructions? *Ann Plast Surg* 2015;75:526-33.
- Blondeel PN, Beyens G, Verhaeghe R, Van Landuyt K, Tonnard P, Monstrey SJ, Matton G. Doppler flowmetry in the planning of perforator flaps. *Br J Plast Surg* 1998;51:202-9.
- Bank J, Pavone LA, Seitz IA, Roughton MC, Schechter LS. CASE REPORT case report and review of the literature: deep inferior epigastric perforator flap for breast reconstruction after abdominal recontouring. *Eplasty* 2012;12:e52.
- Rozen WM, Whitaker IS, Ting JW, Ang GG, Acosta R. Deep inferior epigastric artery perforator flap harvest after abdominoplasty with the use of computed tomographic angiography. *Plast Reconstr Surg* 2012;129:198e-200e.
- May JW Jr, Silverman RP, Kaufman JA. Flap perfusion mapping: TRAM flap after abdominal suction-assisted lipectomy. *Plast Reconstr Surg* 1999;104:2278-81.
- Masia J, Clavero JA, Larranaga JR, Alomar X, Pons G, Serret P. Multidetector-row computed tomography in the planning of abdominal perforator flaps. *J Plast Reconstr Aesthet Surg* 2006;59:594-9.
- Gurtner GC, Jones GE, Neligan PC, Newman MI, Phillips BT, Sacks JM, Zenn MR. Intraoperative laser angiography using the SPY system: review of the literature and recommendations for use. *Ann Surg Innov Res* 2013;7:1.
- Duggal CS, Madni T, Losken A. An outcome analysis of intraoperative angiography for postmastectomy breast reconstruction. *Aesthet Surg J* 2014;34:61-5.

Nasal dorsal aesthetic lines and rhinoplasty technical tricks

Alexander Kutubidze

Department of Aesthetic Plastic Surgery, Esthetic Service Clinic, Tbilisi 0171, Georgia.

Address for correspondence: Dr. Alexander Kutubidze, Department of Aesthetic Plastic Surgery, Esthetic Service Clinic, Tbilisi 0171, Georgia.
E-mail: akutubidze@aol.com

ABSTRACT

Rhinoplasty surgery remains one of the most difficult operations of the face. Improving aesthetic appearance and maintaining nasal function are inseparable goals in rhinoplasty surgery, and failure to achieve either of these objectives can be devastating for the patient. After evaluating a variety of rhinoplasty complications, increased attention was devoted to the surgical technique for reconstruction of the dorsal aesthetic lines and nasal tip projection in the patient with a prominent dorsal hump. Based on the modern concept of cartilage conservation, the autospreader flap rotation technique should be considered when dorsal reduction is required. Autospreader flaps are a useful tool in the prevention of postoperative nasal obstruction, segmental (inverted V) appearance, midfacial axial asymmetry and an overdone supratip break. In addition, they assist in preserving ethnicity of the nose when desired. The patient with a long nose, prominent dorsal hump, short nasal bones and low lower lateral cartilages are considered to be an ideal candidate for an autospreader flap.

Key words:

Autospreader flap, nasal aesthetic anatomy, nasal dorsal aesthetic lines, open rhinoplasty, spreader graft

INTRODUCTION

The greatest challenge in primary aesthetic rhinoplasty is the application of advanced anatomical, aesthetic and ethnic principles to an individual case, thereby customizing the procedure to achieve the most natural result for the patient-individualized treatment plan.^[1,2] Specific factors to be noted during the preoperative assessment for the optimization of aesthetic results include the patient's ethnicity, gender, nasofacial aesthetic and any specific requests. The endonasal (closed) and external (open) techniques are the two main techniques used in both primary and secondary rhinoplasty.^[3,4] With both approaches, the goals are to preserve or achieve normal airflow while delivering an aesthetically pleasing and natural permanent long-term result. Multiple studies have reported that nasal obstruction is a relatively common problem in patients

presenting for aesthetic rhinoplasty, with a high prevalence of nasal deviation.^[5] The functions of the nose, specifically respiration, humidification, filtration, temperature regulation and protection, are regulated by the septum, turbinates and nasal valves (internal and external).^[5,6]

Therefore, every rhinoplasty surgeon should cultivate a full understanding of intranasal and external nasal anatomy,^[7] the differential diagnosis for nasal obstruction, and the elements of a complete nasal examination, including nasal endoscopy. In addition, a comprehensive analysis of the face and a broad understanding of the long-term effects of healing forces on the ultimate nasal aesthetic and function are required.^[5] Knowledge of rhinoplasty medical and surgical treatment options and side effects anatomical correlates can assist in anticipating them intraoperatively

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.169495

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kutubidze A. Nasal dorsal aesthetic lines and rhinoplasty technical tricks. *Plast Aesthet Res* 2015;2:315-9.

Received: 21-10-2014; **Accepted:** 22-10-2015

in certain surgical maneuvers. Patient safety is optimized with the use of specific surgical procedures, protocols, specialized instruments and staff training. Endotracheal monitored anesthesia care is preferable and a nasopharyngeal pack can be a useful preventative measure by helping to keep the larynx clear.

THE AESTHETIC ANATOMY OF THE NOSE: DORSAL AESTHETIC LINES

The bony cartilaginous pyramid of the external nose is three-dimensional structure composed of three basic regions: the upper rigid bony third, the middle semi-rigid cartilaginous third and the lower mobile cartilaginous third. Nasal deformities result from the loss of support to this tripod [Figure 1].^[4]

The soft tissue components of the nose include skin, muscles, nerves and vascular tissues. The tissue layers and fibrovascular membranous structures of the skin envelope in the inferior part of the external nose are divided into five layers, which are similar to the structure of the face: epidermis, dermis, superficial fascia, fibromuscular layer and perichondrium. The thin, dynamic musculoaponeurotic layer of the nose is a critical structure of the nose. Preservation of this layer is vital in restoring and retaining nasal function and appearance.^[8-10]

The nasal dorsum connects the radix to the lateral projections of the crura of the lower lateral cartilages (LLCs) by means of two diverging concave lines. These are the nasal dorsal aesthetic lines, which are unbroken extensions of the superciliary ridges [Figure 2]. The radix and supratip regions have thicker soft tissue coverage, while the midvault area contains thinner tissue. The supratip break occurs cephalad to the nasal tip where the contour lines of the nasal dorsum rise toward the tip-defining points. The tip-defining points are composed of two equilateral triangles which extend from the supratip region to the apex of the domes to the columellar lobule angle.^[8,11,12] To achieve a balanced dorsal profile with a supratip break, it is necessary to create a frame with a slightly deeper nasion and tip projection beyond the dorsum.^[10-13] From an aesthetic standpoint, the area from the nasal bridge

to nasal tip should be aligned and straight.^[14,15] Over reduction of the dorsum can change the orbito-nasal relationship with subsequent flattening of the midface.

COMPLICATIONS OF RHINOPLASTY

Clinical manifestations of complications of rhinoplasty and side effects may be classified as functional, aesthetic, or both. A number of technical solutions have been presented.^[4,5,12,16] After a review of these potential complications, specific attention was directed to the surgical technique for reconstruction of nasal tip projection and the dorsal aesthetic lines in the patient with a prominent dorsal hump. Functional insufficiency of the internal nasal valve occurs in conjunction with the inverted V deformity (with disruption of the dorsal aesthetic lines) caused by collapse of the upper lateral cartilages following removal of the dorsal hump. This combined complication can be prevented during component reduction of the dorsal hump by avoiding excessive resection of the upper lateral cartilage as compared with the septum (midvault area) and by placement of spreader grafts.^[17]

The nasal tip presents an exceptional challenge because of its mobility.^[12-15] During dorsal hump reduction when the K-area is disrupted and not aligned with the nasal bridge, it may act as a pivot point; downward and inward rotation of the septal cartilage then becomes possible, disproportionally widen the nasal dorsum and result unnatural look of dorsal aesthetic lines. Protrusion of the anterior septal cartilage can create a polly beak deformity. The polly beak deformity is remarkable for protuberance with a rounded downward pointing tip and fullness of the supratip region. Excess scar tissue in the region of the dorsal septal cartilage or supratip may become apparent once edema has resolved and is more likely to occur in patients with thicker skin. The deformity can be prevented by maintaining adequate tip support through columellar struts. In addition, suturing the subcutaneous tissue of the supratip to the caudal

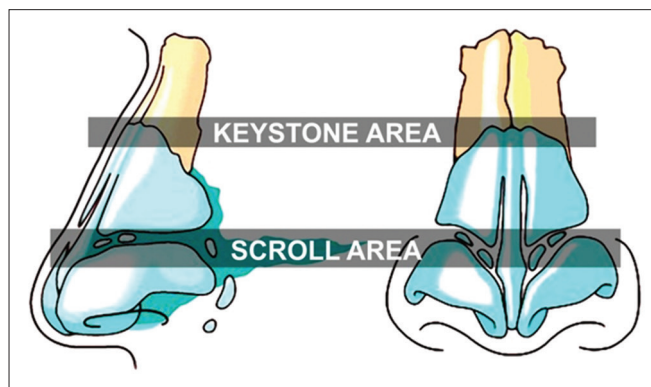


Figure 1: The keystone area, where the nasal bones overlap the upper lateral cartilages and the scroll area, where the lower lateral cartilages overlap the upper lateral cartilages. Restoration of the keystone area anatomical structure during the primary rhinoplasty prevents open roof and inverted V deformities



Figure 2: The dorsal aesthetic lines originate on the supraorbital ridges and pass medially along the glabellar area to converge caudally at the medial canthal ligaments. From there, they usually begin diverging at the keystone area and ultimately conclude at the tip-defining points, which become the highest point in the nasal profile

dorsum and scroll areas eliminates dead space and formation of deep scar tissue, thereby preserving the functional and aesthetic anatomy of the nose.^[10-14]

Systematic and complete analysis of external and internal nasal anatomical regions and knowledge of normal variants are critical factors in creating an appropriate operative plan for a successful rhinoplasty.^[5,6]

THE SURGICAL PLAN AND OPERATIVE STRATEGIES

Open rhinoplasty is an increasingly preferred approach for primary and secondary rhinoplasty in the practices of most experienced rhinoplasty surgeons.^[4] Both approaches provide the surgeon with the ability to successfully perform rhinoplasty, but each has its appropriate anatomical indications, advantages and disadvantages. The most significant advantage of open rhinoplasty approach is improved surgical exposure with better visualization for surgical maneuvers. Direct observation of the underlying bony cartilaginous framework permits accurate diagnosis of nasal deformities, as well as precise manipulation of the dorsum and the nasal tip through a variety of technical maneuvers.^[14-16] Dissection below the musculoaponeurotic layer preserved the major arterial, venous and lymphatic channels.^[6,10] The integrity of the nasal lobule and minor tip support mechanisms can be preserved, preventing future loss of tip projection, and grafts can be fashioned and secured without fear of displacement. This degree of precision can decrease uncontrolled scarring of tissues and lower the rate of revision. Negative consequences of open rhinoplasty include external scarring, occasional prolonged tip edema and longer surgical time. However, the transcolumellar scar typically heals well and is not noticeable. Tip edema generally resolves without negative consequences when using subperichondrial dissection and suturing techniques.^[6,10,14,15]

AUTOSPREADER FLAP TECHNIQUE

Following reduction of the bony and cartilaginous dorsum, spreader grafts can be placed. Sheen's spreader graft concept remains the gold standard for internal valve reconstruction and has been applied for surgical restoration of the disrupted nasal dorsum.^[16,18] The need for a spreader graft is an important consideration during all primary rhinoplasty cases.^[4] Patients with a high, narrow dorsum, a weak middle vault, short nasal bones or a positive Cottle test preoperatively are at higher risk for developing postoperative internal nasal valve dysfunction and resultant nasal airway obstruction.^[6,8,16,18] Traditionally, spreader grafts are fashioned from cartilage taken from the septum or ear.^[16-18] Disadvantages of the use of spreader grafts include increased operative time and donor site morbidity.^[16,18] Postoperative swelling following submucosal dissection of the septum can be both considerable and unpredictable. In all cases, it is

crucial to maintain a 10-15 mm L-strut of cartilage along the nasal dorsum and caudal septum. The width of the nasal dorsum is typically wider after spreader grafts have been applied.^[4,5]

Another option involves the autospreader flap, in which the upper lateral cartilage and septum are preserved. Surgical time is reduced while maintaining the dorsal aesthetic lines and internal valve function.^[16,18] Oneal and Berkowitz were among the first to utilize the upper lateral cartilages as spreader grafts, and they coined the term "spreader flap".^[16,18-20] Gruber *et al.*^[16] subsequently referred to this maneuver as an "autospreader flap".

If a hump is at least 3 mm above the ideal dorsal line, it is usually possible to fold the dissected ends of the upper lateral cartilages as local flaps at their interface with the septum.^[18] The upper lateral cartilage excess can be appreciated following precise reduction of the septum and bony hump. Autospreader flaps are bilaterally interposed between the septum and upper lateral cartilages, including the portion lying under the nasal bones. Where the hump is minimal and folding over the cartilages is not possible, it may be an option to simply return the upper lateral cartilages to the dorsum with suture fixation. With the use of asymmetric mattress sutures, the autospreader flaps are positioned horizontally, abutting the septum instead of being vertically folded and fixed to the septum.^[10,16] Preservation of the dynamic musculoaponeurotic system with its ligamentous connections permits their repair at the time of closure. Repair of Pitanguy's midline ligament using advancement suture allows the surgeon to control tip rotation, enhance projection, and emphasize a supratip break, while reconstruction of the scroll area ligaments provides stability of the internal nasal valve.^[7,10,11] Utilization of the cartilage from the reduced dorsal septum permits successful reshaping of the middle vault and nasal tip. The resected cartilage fragment may also be used as a columellar strut, which thereby allows us to again forego the standard septal harvest, reducing operative time and patient morbidity.^[21] The ideal patient for this technique requires 3 mm or more of dorsal hump reduction, and should not have any breathing problems or septal deviation that would require septal surgery. It is important to identify the patient with a tension tip, as he or she will certainly require maintenance or restoration of tip projection to prevent a polly beak deformity.

The cartilage-conserving concept can be efficient and aesthetic in well-selected patients, but as always anatomical differences will dictate the surgical approach.^[22,23] Upon follow-up, patients demonstrate better postoperative recovery, with much less septal swelling and proportional projection of the dorsal aesthetic lines without over-widening at the K-area. The most common problem encountered is the technique's inability to provide adequate dorsal width when compared to spreader grafts. In addition, the use of an autospreader flap has not been described for special cases such as the crooked nose, small dorsal humps, and in secondary cases. Therefore, relative contraindications to use this

technique include those with a deviated dorsal septum, asymmetric dorsal aesthetic lines, and upper lateral cartilages of insufficient length at caudal end of the septum. This population likely benefit from traditional spreader grafts harvested from the nasal septum, perhaps combined with autospreader flaps. The thickness of free septal grafts can be varied to control asymmetry. In the appropriate patient with nasal axial deviation who also requires a septoplasty, the combined use of autospreader flaps and unilateral or bilateral spreader grafts may be indicated to correct asymmetric dorsal aesthetic lines. Indications for the use of both techniques include widening of the dorsal middle third of the nose (especially in ethnic cases), bridging and strengthening a long, narrow roof of the middle nose in patients with short nasal bones and high LLCs, straightening and stabilizing a dorsally deviated septum, and creating ethnically acceptable dorsal aesthetic lines [Figure 3]. Nasal septal grafts are thicker and stronger, resisting the deforming forces of a deviated septum and thus correcting the curvature.^[18] Autospreader flaps alone may not provide adequate stability when there is associated collapse of the bony sidewalls. In these instances, traditional spreader grafts that extend beyond the keystone are indicated. For cases in which an autospreader flaps cannot provide sufficient width at the anterior septal angle, this area must be supported by spreader grafts [Figure 4].

CONCLUSION

The patient with a long nose, prominent dorsal hump, short nasal bones and low LLCs are good candidates for an autospreader technique [Figure 5]. The technique is simple, reproducible and effective in shaping the dorsum while preserving the function of the internal valve in primary rhinoplasty patients. Subperichondrial dissection of the nasal framework with preservation of the dynamic musculoaponeurotic system and controlled manipulation and repair of ligaments without disturbing the overlying soft tissue allows reshaping and redraping of the nasal aesthetic lines.

The relation between anatomical form and function is of enduring interest in modern aesthetic plastic surgery, being central to our understanding of physiological systems. It provides lessons for engineering design based on advanced anatomical knowledge. For now, limited evidence available in PubMed that shows benefit of using spreader flap technique for correction of dorsal septal deviations.^[24] The use of a spreader flap technique has not been described for special cases with minimal dorsal humps and secondary cases. The spreader architecture rhinoplasty requires wider studies in compare and contrast flap and graft techniques to identify which technology provides the most benefit in terms of outcomes for more durable, consistent, predictable and harmonic results.

Financial support and sponsorship

Nil.

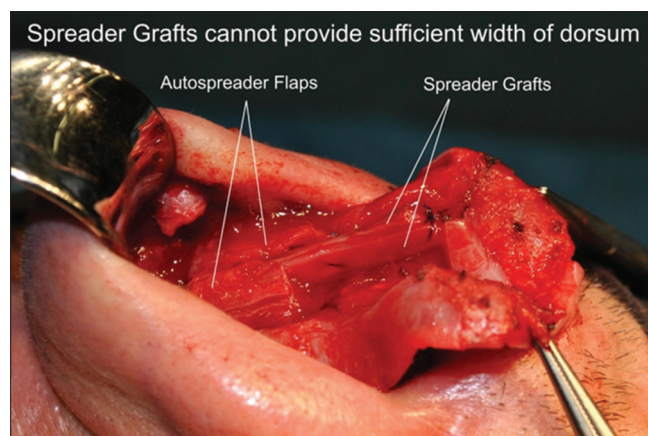


Figure 3: Combination use of the spreading grafting

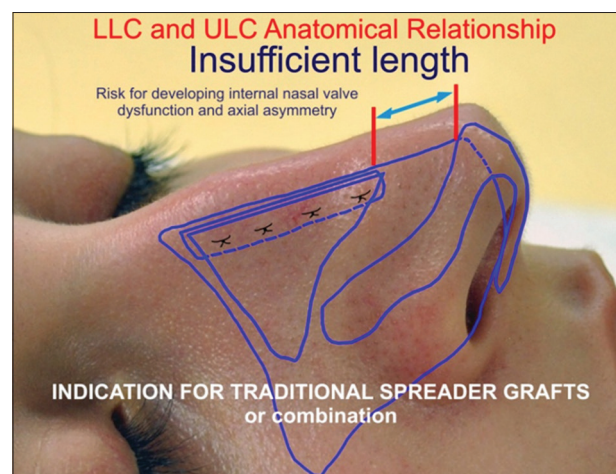


Figure 4: Indication for spreader graft procedure

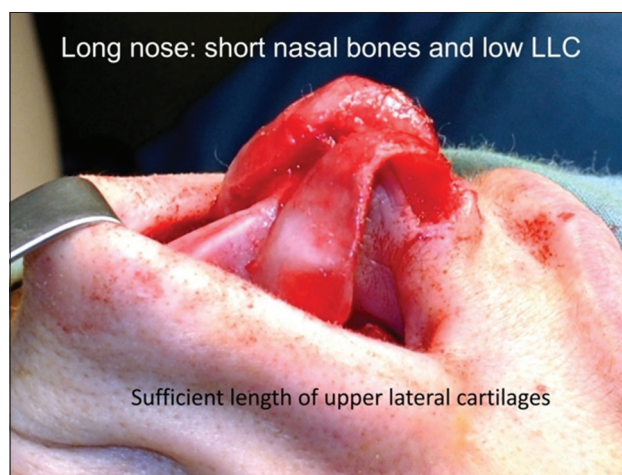


Figure 5: Indication for the autospreader grafting

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nahai F. Your favorite technique: time for a change? *Aesthetic Surg J* 2012;32:900-2.
2. Nahai F. Evidence-based medicine in aesthetic surgery. *Aesthetic Surg J* 2011;31:135-6.
3. Gunter JP, Hackney FL. Clinical assessment and facial analysis. In: Gunter JP, Rohrich RJ, Adams WP Jr, editors. *Dallas Rhinoplasty*:

Nasal Surgery by the Masters. St. Louis: Quality Medical Publishing; 2002. p. 53-71.

4. Sajjadian A, Guyuron B. Primary rhinoplasty. *Aesthetic Surg J* 2010;30:527-39.
5. Becker DG, Ransom E, Guy C, Bloom J. Surgical treatment of nasal obstruction in rhinoplasty. *Aesthetic Surg J* 2010;30:347-78.
6. Guyuron B. Soft tissue functional anatomy of the nose. *Aesthetic Surg J* 2006;26:733-5.
7. Palhazi P, Daniel RK, Kosins AM. The osseocartilaginous vault of the nose: anatomy and surgical observations. *Aesthetic Surg J* 2015;35:242-51.
8. Rohrich RJ, Muzaffar AR, Janis JE. Component dorsal hump reduction: the importance of maintaining dorsal aesthetic lines in rhinoplasty. *Plast Reconstr Surg* 2004;114:1298-308.
9. Wang ZJ, Wang N, Yang HM, Bai SL. Investigation of the layers and vascular density of the soft tissue in the inferior nasal portion. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2007;23:65-8.
10. Cakir B, Oreroglu AR, Dogan T, Akan M. A complete subperichondrial dissection technique for rhinoplasty with management of the nasal ligaments. *Aesthetic Surg J* 2012;32:564-74.
11. Kim SK, Kim JC, Lee KC, Kim HS. Correction of the supratip deformity of the nose. *Aesthetic Surg J* 2012;32:943-55.
12. Guyuron B, DeLuca L, Lash R. Supratip deformity: a closer look. *Plast Reconstr Surg* 2000;105:1140-51.
13. Ponsky D, Eshraghi Y, Guyuron B. The frequency of surgical maneuvers during open rhinoplasty. *Plast Reconstr Surg* 2010;126:240-4.
14. Gruber RP, Weintraub J, Pomerantz J. Suture techniques for the nasal tip. *Aesthetic Surg J* 2008;28:92-100.
15. Daniel RK. Tip refinement grafts: the designer tip. *Aesthetic Surg J* 2009;29:528-37.
16. Gruber RP, Melkun ET, Woodward JF, Perkins SW. Dorsal reduction and spreader flaps. *Aesthetic Surg J* 2011;31:456-64.
17. Sheen JH. Spreader graft: a method of reconstructing the roof of the middle nasal vault following rhinoplasty. *Plast Reconstr Surg* 1984;73:230-9.
18. Byrd HS, Meade RA, Gonyon DL Jr. Using the autospreader flap in primary rhinoplasty. *Plast Reconstr Surg* 2007;119:1897-902.
19. Manavbasi YI, Basaran I. The role of upper lateral cartilage in dorsal reconstruction after hump excision: section I. Spreader flap modification with asymmetric mattress suture and extension of the spreading effect by cartilage graft. *Aesthetic Plast Surg* 2011;35:487-93.
20. Oneal RM, Berkowitz RL. Upper lateral cartilage spreader flaps in rhinoplasty. *Aesthetic Surg J* 1998;18:370-1.
21. Rohrich RJ, Liu JH. The dorsal columellar strut: innovative use of dorsal hump removal for a columellar strut. *Aesthetic Surg J* 2010;30:30-5.
22. Aston SJ. A plastic surgeon's evolution. *IPRAS J* 2011;(6):33-4.
23. Spiro SA, Wolfe SA, Wider TM. The use of the labiocolumellar crease incision in rhinoplasty. *Ann Plast Surg* 1996;37:569-76.
24. Yagmur C, Kelahmetoglu O, Akbas H. Spreader flap correction of dorsal septal deviations. *Aesthetic Surg J* 2015;35:345-8.

Cost-effectiveness of one-stage versus two-stage breast reconstruction in the United Kingdom

Isabel Teo¹, Iman A. Azmy²

¹Department of Plastic Surgery, St John's Hospital at Howden, Livingston, West Lothian EH54 6PP, UK.

²Department of Breast Surgery, Chesterfield Royal Hospital - NHS Foundation Trust, Calow, Chesterfield, Derbyshire S44 5BL, UK.

Address for correspondence: Miss. Isabel Teo, Department of Plastic Surgery, St John's Hospital at Howden, Livingston, West Lothian EH54 6PP, UK. E-mail: isabelteo@hotmail.com

ABSTRACT

Aim: Permanent expanders allow for breast reconstruction as a single stage. These prostheses are more expensive than conventional tissue expanders, but this excess cost is markedly offset as only one operation is required. However, if the revision rate is sufficiently high, then this effect is negated. We aim to compare costs of one-stage *vs.* two-stage reconstruction at a single center, taking into account explantation and unexpected admissions following complications. **Methods:** A retrospective review was carried out on all patients who underwent one-stage and two-stage reconstruction over a 5-year period by a single surgeon. A cost analysis was performed taking into account, explantation and additional admissions. **Results:** One hundred and forty-three one-stage and 45 two-stage procedures were included. The explantation rate for one-stage procedures is 36%, at a mean of 12.9 months postimplantation, the majority of which were exchanged for silicone implants to improve cosmesis. Four (9%) of the two-stage procedures were explanted a mean of 18 months postreconstruction. Overall, one-stage reconstructions were significantly more expensive than the two-stage group ($P = 0.016$). **Conclusion:** There are many benefits of one-stage breast reconstruction. However, it does not appear to be cost-effective when additional admissions for explantation surgery are taken into account.

Key words:

Breast reconstruction, cost-effectiveness, latissimus dorsi flap, McGhan™ 150 expander implant, Natrelle™ 150 expander implant, one-stage breast reconstruction, permanent tissue expanders

INTRODUCTION

One-stage reconstruction was introduced in the 1980s as a valuable addition to the breast reconstruction armamentarium. The first expander implant, the Becker™ Siltex,^[1] came onto the market in 1984, this is a round prosthesis with a saline-filled inner lumen surrounded by a silicone gel, connected to a remote port for injection of saline. These implants provide the volume flexibility

of a saline implant and permit long-term, noninvasive adjustment of breast size. Reconstruction can, therefore, be completed as a single procedure. The implant is placed at the index procedure, expansion achieved with repeat outpatient injections of saline until optimum breast size is reached. The traditional two-stage reconstruction, however, involves two operations, the first involving the

Access this article online

Quick Response Code:



Website:

www.parjournal.net

DOI:

10.4103/2347-9264.169494

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Teo I, Azmy IA. Cost-effectiveness of one-stage versus two-stage breast reconstruction in the United Kingdom. *Plast Aesthet Res* 2015;2:320-5.

Received: 03-01-2015; **Accepted:** 24-09-2015

insertion of the expander and the second to exchange the expander for a fixed volume silicone implant, once the expander has reached its ideal size after outpatient injections.^[2]

The Natrelle™ 150 (previously known as the McGhan™ 150) was introduced in the 1990s. Like the Becker Siltex, it has an inner chamber of saline outer shell of silicone, and a remote port. The main difference is that the Becker Siltex is round, while the Natrelle™ 150 has an anatomical shape, purportedly creating a more natural, teardrop shape. At present, the Natrelle™ 150 and Becker™ range are the only two expander implants on the market, available for one-stage reconstruction, and the Natrelle™ 150 is routinely used at our unit for one-stage reconstruction.

The surgical outcomes of the Natrelle™ 150 expander are well known, with many papers endorsing its good surgical outcomes.^[3-6] However, it is more expensive than a comparative tissue expander [Table 1], but deemed to be cost-effective with many savings derived from a one-stage operation.

The corollary to this is that any unexpected complication resulting in loss or exchange of the implant will effectually result in a two-stage operation. This will incur the cost of a second hospital admission, general anesthetic procedure, and additional implant over and above the excess material cost of the Natrelle™ 150 implant. There is increasing emphasis on good health economics, and to date there has been no cost analysis study analyzing if expander implants are truly cost-effective.

To analyze the costs of one-stage and two-stage breast reconstructions, taking into account unexpected explantation as a complication. This will allow us to evaluate the true cost-effectiveness of one-stage reconstruction at a single institution in the UK.

METHODS

A retrospective case note review was carried out on all patients who had undergone one-stage and two-stage at our unit from 2005 to 2010 by a single oncoplastic surgeon. The Natrelle™ 150 implant is utilized in our hospital for one-stage reconstruction, and the Mentor™ Siltex and Allergan™ 133 expanders for two-stage reconstruction. All the patients received a drain in the breast pocket and remained in hospital until the drains are removed. We do not employ the use of dermal substitutes such as Strattice™. All patients who underwent one-stage and two-stage reconstruction were included in our database, and there was no exclusion criterion.

Cost information was obtained from the financial department and surgical directorate accountant. Each procedure is assigned a Healthcare Resource Group (HRG)^[7] code which determines the costs incurred. Within the National Health Service (NHS), a HRG is a group consisting of patient events that have been deemed to consume a similar level of resource. This cost is based on a maximum number of

days staged as an inpatient, after which each night will incur an excess cost of £131. This is shown in Table 2.

Using this method of data analysis, we analyzed length of stay and costs incurred in all four procedure groups: the Natrelle™ 150 only procedure group; the Natrelle™ 150 and latissimus dorsi (LD) procedure group; the Allergan™ 133 procedure group and Mentor™ Siltex procedure group. We specifically calculated the average costs and length of stay for retained and explanted procedures.

Nonparametric data were analyzed using Chi-squared and Fisher's exact tests. Cost was analyzed using independent sample *t*-test, Kruskal-Wallis and Mann-Whitney *U*-tests. SPSS version-20 was used for all statistical analysis with the assistance of a trust-affiliated statistician.

RESULTS

One hundred and forty-three one-stage procedures and 45 two-stage procedures were performed. All patients' demographics oncological histology, and treatment by procedure are shown in Table 3. Chi-squared analysis and Fisher's exact test were used to compare parameters between these groups. We found that there were a significantly higher number of patients in the one-stage reconstruction group who received radiotherapy compared to the two-stage reconstruction group ($P < 0.01$). This observation is expected as patients who have had radiotherapy are more likely to have a LD flap procedure. It is the senior author's practice to offer permanent expanders in patients who require LD flaps. This allows for greater volume to match the contralateral side and also allows for future alterations, given the unpredictable

Table 1: Typical costs of implants in the UK

Reconstruction	Cost
One-stage reconstruction	
Natrelle™ 150	£975
Two-stage reconstruction	
Expander	£599
Fixed volume implant	£560
Total	£1,159

Table 2: Procedures and stipulated costs according to HRG codes

Procedure	Cost and maximum number of days of inpatient stay
Natrelle™ 150 only reconstruction	£3,402 14 days
Natrelle™ 150 + LD reconstruction	£3,402 14 days
Allergan™ 133 first stage reconstruction	£1,148 6 days
Mentor™ Siltex first stage reconstruction	£3,402 14 days
Exchange of expander/expander implant for fixed volume implant	£1,236 9 days

Additional inpatient stay would incur a daily rate of £131. LD: Latissimus dorsi, HRG: Healthcare Resource Group

Table 3: Patient demographics tumor histology and oncological treatment by procedure

	Natrelle™ 150 only (%)	Natrelle™ 150 + LD (%)	Allergan™ 133 (%)	Mentor™ Siltex (%)
Number of patients	34	92	21	11
Frequency of procedures	45	98	28	17
Mean age at implantation	52.6 (20-73)	51.3 (24-68)	49.4 (21-68)	48.9 (30-61)
Mean BMI	28.0 (21-43)	25.7 (18-43)	27.9 (18-38)	24.5 (21-30)
Smokers	7 (21)	11 (12)	2 (9.5)	1 (9.1)
Diabetes	0	2 (2.2)	1 (4.8)	0
ASA	1 = 13 (38) 2 = 19 (56) 3 = 2 (5.9) 4 = 0	1 = 46 (50) 2 = 42 (46) 3 = 2 (2.2) 4 = 0	1 = 12 (57) 2 = 9 (43) 3 = 0 4 = 0	1 = 4 (36) 2 = 7 (64) 3 = 0 4 = 0
Tumor				
DCIS	21 (47)	53 (54)	13 (47)	10 (59)
Invasive	28 (62)	74 (76)	15 (54)	14 (82)
NPI range	2.14-6.56	2.06-7.20	2.22-5.52	2.01-5.50
Radiotherapy	2 (4.5)	25 (26)	0	0
Chemotherapy	19 (42)	38 (39)	10 (36)	10 (59)
Hormonal	21 (15)	66 (67)	14 (50)	11 (65)
Neoadjuvant	0	4 (4.1)	0	0
Herceptin	3 (2.1)	8 (8.2)	0	1 (5.9)

LD: Latissimus dorsi, BMI: Body mass index, ASA: American Society of Anaesthesiologists, DCIS: Ductal carcinoma *in situ*, NPI: Nottingham prognostic index

degree of LD atrophy that can ensue. Analyzing all the other factors, there was no statistical significant difference between the one-stage procedure group and two-stage procedure group ($P > 0.05$). There were insufficient patients with diabetes to make a valid analysis on this parameter. A Cox regression analysis found that age, body mass index, smoking status, radiotherapy, and American Society of Anaesthesiologist grades were not significantly associated with higher rates of explantation.

Explantation

Explantation is the unanticipated removal or exchange of implants secondary to complications. Fifty-one (36%) of the Natrelle™ 150 implants were explanted an average of 12.9 months after implantation (range: 1-48 months, median: 8.0 months). The majority (40, 79%) were exchanged for fixed volume silicone implants to improve esthetics. Other indications were infection (5, 9.8%), leak (2, 3.9%) and recurrence of cancer (4, 7.8%).

In the two-stage reconstruction group, problems can likewise develop requiring implant removal or exchange with cost implications. Explantation of the final fixed volume silicone implants was analyzed. In the Mentor™ Siltex group, one implant was exchanged for another prosthesis, 18 months later due to implant migration. In the Allergan™ 133 group, three implants were exchanged to improve cosmesis, an average of 19 months after their second stage procedure.

Cost analysis

Forty percentage of Natrelle™ 150 only implants were retained with an average length of inpatient stay of 3.78 days gives an average cost of £3,422, close to the estimated HRG stipulated cost of £3,402. However, 60% of the Natrelle™ 150 only implants were explanted with an average total inpatient stay of 4.22 days. There was a mean unanticipated excess cost of £1,350 in each of these

explanted implants, with the cost of each patient £4,755 instead of the stipulated £3,402. Similar analyses have been performed for the Natrelle™ 150 and LD group, Allergan™ 133 and Mentor™ Siltex groups [Figure 1].

Overall cost was analyzed using a Kruskal-Wallis test (nonparametric equivalent of an ANOVA) and Mann-Whitney *U*-test. This shows that the Allergan™ 133 two-stage procedure is the cheapest reconstructive option ($P < 0.001$). The Mentor™ Siltex and Natrelle™ 150 only procedure are the most expensive options. We used an independent sample *t*-test to compare the combined overall costs of the one-stage procedures to the two-stage procedures and this showed that the one-stage group was significantly more expensive than the planned two-stage group ($P = 0.016$).

DISCUSSION

While the material costs of the Natrelle™ 150 is more expensive than its comparative expander or silicone implant, it is thought to be cost-effective as it eliminates the expenses associated with a second operation. However, any complication resulting in the loss or exchange of this implant will essentially convert a one-stage procedure into a two-stage operation. This includes the additional costs of a second general anesthetic procedure and replacement of the implant in addition to the original costs of the Natrelle™ 150 implant. In today's health economics, where health care providers are increasingly required to rationalize expenses, these cost implications merit investigation.

There are a growing number of studies analyzing the costs of various breast reconstructions.^[8-11] Grover *et al.*^[12] compared five methods of breast reconstruction-autologous flaps with pedicled tissue, autologous flaps with free

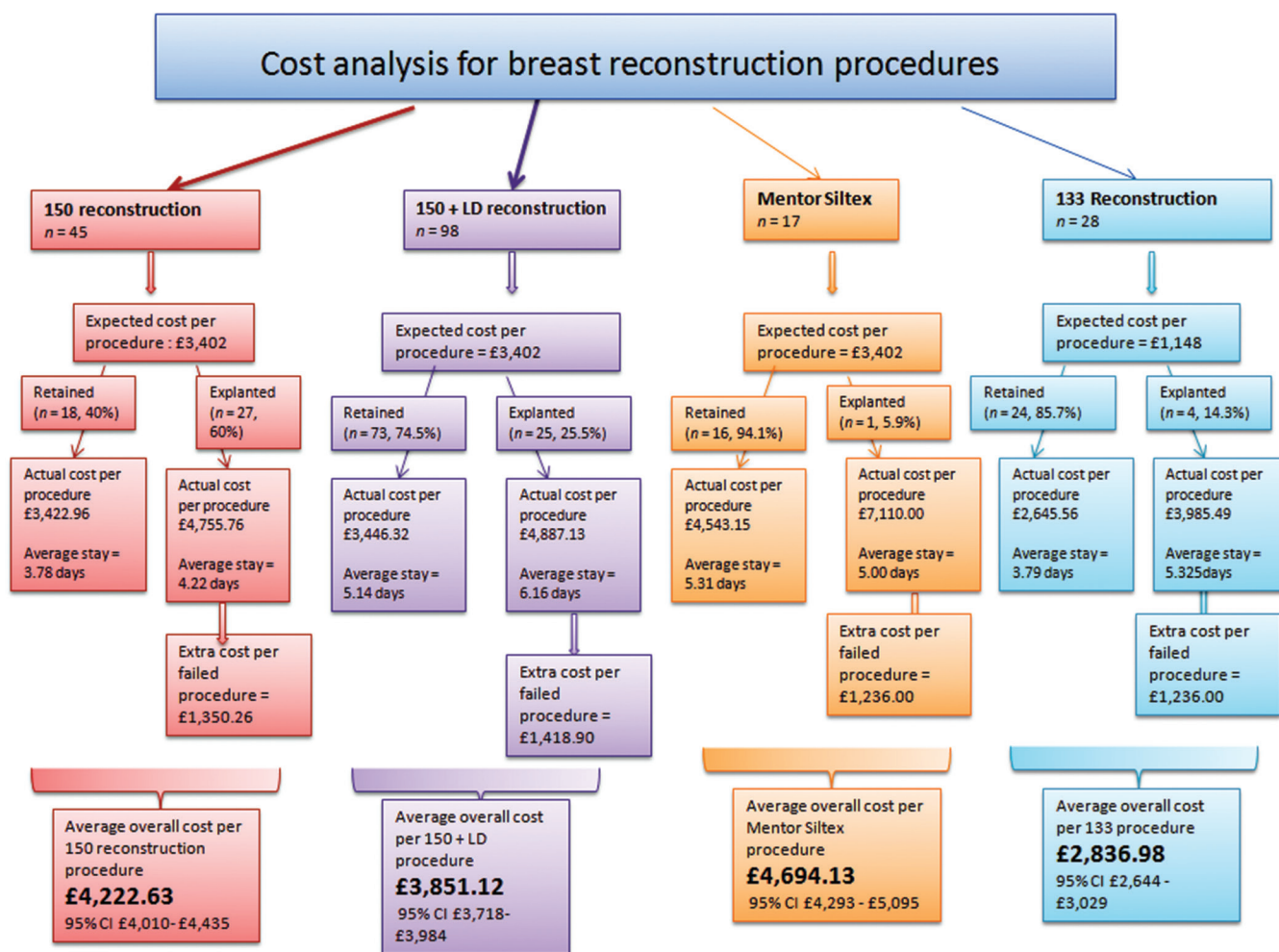


Figure 1: The costs incurred for each type of reconstruction when additional admissions and surgery secondary to explantation are taken into account

tissue, LD flaps with breast implants, expanders with implant exchange and immediate implant placement. They concluded “that autologous pedicled tissue was slightly more cost-effective than free tissue reconstruction”, and that “implant based techniques were not cost-effective”. Damen *et al.*^[13] compared silicone implants, implants preceded by tissue expansion, LD flaps and deep inferior epigastric perforator flaps in 427 patients in a single Dutch center. They found that immediate one-stage reconstructions have lower costs compared with flap procedures and tissue expander reconstructions. To date, there have been no cost analysis solely comparing one-stage and two-stage reconstruction.

At present, there are only two expander implants on the UK market designed for a one-stage reconstruction: the Natrelle™ 150 and the Becker™ Siltex. The Natrelle™ 150 implant is used for one-stage reconstruction at this center because the surgeon has been trained in its use and is most familiar with this product. There is no clear benefit of using one expander implant over the other apart from surgeon or patient preference. In fact, a paper^[14] published in November 2010 compared aesthetic outcome and patient satisfaction between patients who had received the Natrelle™ 150 implant and Becker Siltex implant. Two groups of patients who were all undergoing bilateral, prophylactic mastectomy and

immediate reconstruction were randomly assigned to either the Natrelle™ 150 or Becker™ Siltex implant. Aesthetic outcomes were evaluated by an expert panel who also tried to recognize which implants the breasts were reconstructed with. The results showed that there was no difference between the two groups in terms of symmetry, outcome scores and patient satisfaction. The expert panel guessed the right implant shape in 42% of the Natrelle™ 150 implants and 66% of the round implants.

There have been a number of studies^[15-18] assessing survival of the Becker™ permanent expanders with variable results. Taboada-Suarez *et al.*^[19] reviewed 314 Becker™ permanent expander’s implants in 237 patients, and found “a mean survival time to explantation of 120 months”. Farace *et al.*^[20] found that 77 of Becker™ implants were removed within 5 years in a cohort of 99 patients. Goh *et al.*^[21] found an explantation rate of 25% at a mean follow-up of 64.6 months. There is much less published data on the longevity of the Natrelle™ 150 implant. Gui *et al.*^[22] studied 107 patients with 129 reconstructions with the Natrelle™ 150 and found a low 3.9% explantation rate at a mean of 18 months. Cicchetti *et al.*^[4] analyzed 97 consecutive patients who received a 107 Natrelle™ 150 expander implants and their data show an overall explantation rate of 25% by 6 years. Despite its primary design of permanent expanders being “permanent”,

it is evident from the growing literature that these expander implants are often removed early secondary to complications. Eriksen *et al.*^[23] performed a prospective, randomized study comparing one-stage (Becker 25) and two-stage reconstruction and found that 70% in the one-stage group required revision surgery. They concluded that “the permanent expander method failed significantly as a one-stage procedure”. Similarly, Susarla *et al.*^[24] compared one-stage and two-stage reconstructions and found that the one-stage cohort was “80% more likely to require additional operative revisions” compared to the two-stage group. This is an important consideration not only for economic reasons, but also for patient selection and counseling.

Explantation is the most objective, measurable complication and we looked at this in detail. Our data show an overall explantation rate of 36% at a mean of 12.9 months postimplantation. These results suggest that for a significant proportion of patients undergoing planned one-stage reconstruction, the Natrelle™ 150 has functioned as a temporary expander.

Our analysis of costs involved revealed some surprising findings, in particular, the operation codes, HRG codes and allocated costs. Vastly differing procedures, while using different implants with different expected operating time, are given the same HRG code and costs. For example, the LD and Natrelle™ 150 expander procedure has the same code as the Natrelle™ 150 only procedure, despite the former being much more technically demanding, involving a significantly longer operating time and inpatient hospital stay. The Natrelle™ 150 only procedure and the Natrelle™ Siltex procedure similarly have the same coding, despite the Natrelle™ 150 implant being approximately twice the price of the Natrelle™ Siltex implant and the operation itself being almost identical.

From our discussions with the financial team, many procedures are clustered together under the same coding umbrella as this simplifies costs for the thousands of operations performed in the NHS. Money saved in one operation might be used to cover the excess costs of another operation with underestimated costs. Similar grouping of operations was observed in another hospital in the same region.

We have been very specific in our cost analysis, which only looks at the tariffs and costs of the index procedure length of inpatient stay and explantation as a complication. The benefits of this analysis are relative, simplicity and speed of data acquisition. As mentioned before, the explantation is an objective, measurable complication, and its costs are easy to quantify with a defined HRG code and designated cost.

However, our cost analysis does not accurately represent the overall cost for each patient. We have not included any contralateral procedures such as augmentation, mastopexy or reductions, or subsequent procedures on the ipsilateral side such as nipple reconstruction or tattooing. We have

not included outpatient visits, medications, physiotherapy or any unexpected costs from complications other than explantation. It is not feasible to factor in these additional costs based on a retrospective study. We are interested in the rates of explantation and the cost implications resulting from failed one-stage procedure. Our results show that the cost of one-stage reconstruction at this center is significantly more expensive than two-stage reconstruction.

Cost implications of varying breast reconstructions are an important subject worthy of study and results are highly relevant to clinical practice. While our methodology for cost analysis is objective and transferable, we question if the results reflect the true costs in clinical practice, given the way the coding system is derived.

This is the first study to directly compare the cost of one-stage versus two-stage breast reconstruction. We have found that the one-stage procedure is significantly more expensive than two-stage reconstruction. This is based on a 36% explantation rate, which is comparable to other series showing explantation rates ranging from 25% to 70%. There are many benefits of one-stage breast reconstruction; however, it does not appear to be cost-effective when additional admissions for explantation surgery are taken into account.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Becker H. Breast reconstruction using an inflatable breast implant with detachable reservoir. *Plast Reconstr Surg* 1984;73:678-83.
2. Woods JE, Mangan MA. Breast reconstruction with tissue expanders: obtaining an optimal result. *Ann Plast Surg* 1992;28:390-6.
3. Munhoz AM, Aldrighi C, Montag E, Arruda EG, Aldrighi JM, Filassi JR, Ferreira MC. Periareolar skin-sparing mastectomy and latissimus dorsi flap with biodimensional expander implant reconstruction: surgical planning, outcome, and complications. *Plast Reconstr Surg* 2007;119:1637-49.
4. Cicchetti S, Leone MS, Franchelli S, Santi PL. One-stage breast reconstruction using McGhan Style 150 biodimensional expanders: a review of 107 implants with six years experience. *J Plast Reconstr Aesthet Surg* 2006;59:1037-42.
5. Salgarello M, Seccia A, Eugenio F. Immediate breast reconstruction with anatomical permanent expandable implants after skin sparing mastectomy: aesthetic and technical refinements. *Ann Plast Surg* 2004;52:365-6.
6. Mandrekas AD, Zambakos GJ, Katsantoni PN. Immediate and delayed breast reconstruction with permanent tissue expanders. *Br J Plast Surg* 1995;48:572-8.
7. Health and Social Care Information Centre. Healthcare Resource Groups (HRGs). National Health Service-Connecting for Health. ©UK 2011. Available from: <http://www.hscic.gov.uk/article/2321/HRG4-200809-Reference-Costs-Group-Documentation>. [Last accessed on 2015 Jan 01].
8. Johnson RK, Wright CK, Gandhi A, Charny MC, Barr L. Cost minimisation analysis of using acellular dermal matrix (Strattice™) for breast reconstruction compared with standard techniques. *Eur J Surg Oncol* 2013;39:242-7.
9. Fischer JP, Sieber B, Nelson JA, Cleveland E, Kovach SJ, Wu LC, Kanchwala S, Serletti JM. Comprehensive outcome and cost analysis of free tissue transfer for breast reconstruction: an experience with 1303 flaps. *Plast Reconstr Surg* 2013;131:195-203.
10. Singh NK, Reaven NL, Funk SE. Cost comparison of immediate one-stage and tissue-expander breast reconstructions after mastectomy in commercially insured patients. *Manag Care* 2013;22:36-43.

11. Krishnan NM, Chatterjee A, Rosenkranz KM, Powell SG, Nigriny JF, Vidal DC. The cost-effectiveness of acellular dermal matrix in expander-implant immediate breast reconstruction. *J Plast Reconstr Aesthet Surg* 2014;67:468-76.
12. Grover R, Padula WV, Van Vliet M, Ridgway EB. Comparing five alternative methods of breast reconstruction surgery: a cost-effectiveness analysis. *Plast Reconstr Surg* 2013;132:709e-23e.
13. Damen TH, Wei W, Mureau MA, Tjong-Joe-Wai R, Hofer SO, Essink-Bot ML, Hovius SE, Polinder S. Medium-term cost analysis of breast reconstructions in a single Dutch centre: a comparison of implants, implants preceded by tissue expansion, LD transpositions and DIEP flaps. *J Plast Reconstr Aesthet Surg* 2011;64:1043-53.
14. Gahm J, Edsander-Nord A, Jurell G, Wickman M. No differences in aesthetic outcome or patient satisfaction between anatomically shaped and round expandable implants in bilateral breast reconstruction: a randomized study. *Plast Reconstr Surg* 2010;126:1419-27.
15. Sindali K, Davis M, Mughal M, Orkar KS. The natural history of Becker expandable breast implants: a single-center 10-year experience. *Plast Reconstr Surg* 2013;132:345e-51e.
16. Becker H. The expandable mammary implant. *Plast Reconstr Surg* 1987;79:631-7.
17. Calmilleri IG, Malata CM, Starvrianos S, McLean NR. A review of 120 Becker permanent tissue expanders in reconstruction of the breast. *Br J Plast Surg* 1996;49:346-51.
18. Scuderi N, Alfano C, Campus GV, Rubino C, Chiummariello S, Puddu A, Mazzocchi M. Multicenter study on breast reconstruction outcome using becker implants. *Aesthetic Plast Surg* 2011;35:66-72.
19. Taboada-Suarez A, Brea-García B, Magán-Muñoz F, Couto-González I, González-Álvarez E. Risk factors associated with complication rates of becker-type expander implants in relation to implant survival: review of 314 implants in 237 patients. *Ann Plast Surg* 2014;4.
20. Farace F, Faenza M, Bulla A, Rubino C, Campus GV. Is mammary reconstruction with the anatomical Becker expander a simple procedure? Complications and hidden problems leading to secondary surgical procedures: a follow-up study. *J Plast Reconstr Aesthet Surg* 2013;66:741-6.
21. Goh SC, Thorne AL, Williams G, Laws SA, Rainsbury RM. Breast reconstruction using permanent Becker expander implants: an 18 year experience. *Breast* 2012;21:764-8.
22. Gui GP, Tan SM, Faliakou EC, Choy C, A'Hern R, Ward A. Immediate breast reconstruction using bi-dimensional anatomical permanent expander implants: a prospective analysis of outcome and patient satisfaction. *Plast Reconstr Surg* 2003;111:125-38.
23. Eriksen C, Lindgren EN, Frisell J, Stark B. A prospective randomized study comparing two different expander approaches in implant-based breast reconstruction: one stage versus two stages. *Plast Reconstr Surg* 2012;130:254e-64e.
24. Susarla SM, Ganske I, Helliwell L, Morris D, Eriksson E, Chun YS. Comparison of clinical outcomes and patient satisfaction in immediate single-stage versus two-stage implant-based breast reconstruction. *Plast Reconstr Surg* 2015;135:1e-8e.

First-year experience of a new skin bank in Brazil

Alysson Rogerio Matoski, Clóvis Rodrigo Guimarães Braz Pereira da Silva, Diogo Rodrigues da Silva-Cunha, Luiz Henrique Auerswald Calomeno, Flávia Thaiana Bonato, Marcelus Vinícios Araujo Nigro

Department of Burn and Plastic Surgery, Evangelical University Hospital of Curitiba, Curitiba, Paraná 80730150, Brazil.

Address for correspondence: Dr. Alysson Rogerio Matoski, Department of Burn and Plastic Surgery, Evangelical University Hospital of Curitiba, Curitiba, Paraná 80730150, Brazil. E-mail: alymatoski@yahoo.com.br

ABSTRACT

Aim: To report the 1st year experience of the skin bank opened at the Evangelical University Hospital of Curitiba (HUEC), Brazil in June 2013. **Methods:** A retrospective statistical and epidemiological study was conducted from data obtained from the activities of the HUEC skin bank from June 2013 to August 2014. **Results:** The HUEC skin bank harvested tissue from 45 cadaveric donors (46.6% female and 53.3% male), with an average age of 36.42. The white skin-colored donors represented 91% of donations. Most causes of death were of neurological origin (55.6%). Eighty-one batches were harvested. The bank processed 31,314.63 cm² of skin for transplantation (41 batches), and 38 batches were discarded. The distributed allografts totaled 28,940.82 cm², with tissue from a single donor benefitting up to 5 patients. A total of 52 transplant procedures were performed (66.6% of recipients were male and 33.3% female), burn victims represented 83.3% of the recipients. **Conclusion:** The HUEC skin bank provides skin primarily for victims with severe third-degree burns, mostly men, and who are treated and transplanted in the HUEC as a result of high demand. The successful outcomes highlight the potential use for other clinical indications.

Key words:

Allograft, Brazil, burns, donation, Evangelical University Hospital of Curitiba, skin, skin bank

INTRODUCTION

Burns are an important public health problem.^[1] In Brazil, it is estimated that they are the cause of approximately 1,000,000 accidents per year. Of these, 100,000 patients will require hospital care, and about 2,500 will die directly or indirectly as a result of their injuries.^[2] One of the best ways to treat burn patients is by the use of allografts, which remain the biological dressing of choice and are an important tool. In many cases they can be used for the effective reconstruction of the dermal component.^[3]

Although allografts are primarily used in the treatment of severe burns, they can also be used for many indications, including extensive skin loss, surgical wounds, lower limb ulcers, pyoderma gangrenosum of diabetic feet and bullous diseases. In addition to serving as a barrier against infection, allografts serve as a temporary biological dressing to help control pain, protect deep structures, promote re-epithelialization and restore the important functions of the skin such as thermal regulation and

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Matoski AR, da Silva CR, da Silva-Cunha DR, Calomeno LH, Bonato FT, Nigro MA. First-year experience of a new skin bank in Brazil. *Plast Aesthet Res* 2015;2:326-31.

Received: 20-03-2015; **Accepted:** 06-09-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.169496

control of fluid loss.^[4-7] For these reasons, their use results in a significant reduction in hospital stay and mortality rates, and may generate cost savings.^[4-7]

In 1949, the first skin bank was established by the US Navy. Since then, several other skin banks have been founded, mostly in the USA and Europe and often organized as multi-tissue banks. In 2005, there were approximately 54 active skin banks in the North America.^[5] Currently, there are four skin banks in Brazil, based in São Paulo, Porto Alegre, Recife and Curitiba city.^[7] The latter is the skin bank of the Evangelical University Hospital of Curitiba (HUEC), which officially opened on June 17, 2013 and the activity of which is the focus of this study.

In 2013, the plastic surgery and burns service of the Evangelical Hospital in Curitiba located in Paraná state provided medical attention to approximately 4,500 burn victims of which at least 10% required hospitalization with the potential indication for skin use; this demonstrated the importance of establishing a skin bank within this hospital. The objective of this study is to report the 1st year experience of the Evangelical Hospital of Curitiba skin bank.

METHODS

Retrospective epidemiological and statistical data were collected during the 1st year of operations, from June 2013 to August 2014. The study was approved by the Research Ethics Committee of the Evangelical Beneficent Society of Curitiba, Brazil.

Collected information included two different tissue banking aspects. The first includes data on skin retrieval between June 27, 2013 and June 26, 2014 and the second data set corresponds to skin distribution and transplantation between August 28, 2013 and August 27, 2014.

Data were obtained from analysis of the bank's records of cadaveric (multi-organ/skin tissue) donation and tissue distribution, including a review of the necessary documentation on the cause of death and organ donation.

Inclusion criteria were all medical records of donors of harvested skin and all recipients who received grafts during the 1st year of the bank. There were no exclusion criteria.

The data collected concerning the deceased donors included: age, gender, skin color, cause of death, thickness of retrieved skin tissue (mm), body region from which the skin was removed, number of generated skin batches, hospital where the skin retrieval occurred, date of skin retrieval, area (cm²) of retrieved skin, reason of skin discards when unfit for use and the number of benefited patients from each donor.

As for the skin recipients, collected data included: age, gender, hospital where the allografts were used, donor to recipient ratio, area of allografted skin (cm²), graft release date, body region receiving the allografts and indication for allograft use. In burn victim recipients, additional data

collected included the extent of the burnt region and burn depth.

According to the Brazilian skin donation protocol, the steps are as follows: (1) Paraná State Transplantation Center calls about a potential donor, and the skin bank staff goes to the donor site hospital; (2) a physical examination of the donor is performed to assess the quality of the skin area to be harvested; (3) the donor's medical and family history are screened to elicit any history of (a) ingestion of toxic or illicit drugs; (b) high-risk sexual behavior, recent invasive procedures, malignancies, chronic diseases, death from an unknown cause, infectious disease, immunocompromise and surgical procedures occurring within the prior 12 months; and (c) donor age, which is limited to between 14 years old and 60 years old; (4) blood samples are collected from the donor 72 h prior to cessation of circulation, 12 h after the cessation of blood flow if the body has been kept at room temperature, or up to 24 h after the cessation of blood flow if the body has been cooled to 4 °C ± 2 °C. The tissues cannot be released for use until final results have been obtained. When tests for HIV and hepatitis C virus (HCV) are negative, further testing is performed for RNA detection of HIV and HCV. Mandatory serological donor screening is performed to detect the following: (a) hepatitis B (hepatitis B surface antigen and anti-hepatitis B core), (b) anti-HCV, (c) HIV-1 and HIV-2 (HIV 1 and 2), (d) Chagas disease (anti-*Trypanosoma cruzi*), (e) syphilis (one treponemic or nontreponemic test), (f) human T-lymphotropic virus type I (HTLV-I) and HTLV-II (anti-HTLV I and II), (g) toxoplasmosis (toxoplasma IgG and IgM), and (h) cytomegalovirus (IgG and anti-IgM); (5) the donor is accepted once all laboratory tests have been confirmed to be normal; (6) skin harvest is then performed for a thickness of 0.4-0.8 mm. The skin blade is passed to the nurse who takes swab and inoculates it in thioglycolate broth, amid Sabouraud broth and trypticase soy broth (TSB) respectively, then the nurse dips the blade in 0.9% saline solution twice prior to immersion in glass with glycerol 90%; and (7) the stored skin is processed in a sterile laminar flow hood in 3 phases: Phase 1: skin is removed from the shipping bottle. Then 2 fragments of 0.5 cm × 0.5 cm of each blade are withdrawn for microbiological analysis. Each fragment must be macerated and inoculated in thioglycolate broth, Sabouraud medium, TSB broth and blood culture bottle for aerobic and anerobic germs. The skin blades are stored again in new bottles with glycerol 90% sterile; the vials with the skin in 90% glycerol are placed in water bath at 37 °C for 3 h, then removed from water bath and stored in tissues not released refrigerator; Phase 2: if the first phase microbiological analysis is negative for any germs (waiting time: 15 days) the second phase is performed like the first one; and Phase 3: if the second phase microbiological analysis is negative for any germs (waiting time: 15 days) the third phase is performed like previous phases with removal of excess of glycerol; thereafter, the blades are placed in a sterile plastic bag

and kept refrigerated. The skin is measured and released after the third negative microbiological results.

The batch is discarded should there be positive culture results with any germs in any of the phases. The discarded skin is not counted, as measurements are carried out only following the final phase.

Cryopreservation was not used as the skin was stored in a refrigerator at $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The skin is maintained in a 90% sterile glycerol solution prior to packaging. All allografts were nonmeshed.

RESULTS

In its 1st year of operation, the skin bank of the HUEC retrieved skin tissue from 45 cadaveric donors (46.6% female and 53.3% male) with an average age of 36.4 years (range: 15-60 years).

Most donors were Caucasian (91%); there were no donations from black or yellow skin-colored donors. The most frequent cause of death was of neurological origin, with traumatic brain injury and stroke accounting for 55.6% of cases.

Data related to gender, age, race and cause of death is presented in Table 1 below.

All skin tissue retrievals took place in hospitals within Curitiba city, with 44% in the HUEC, followed by other major trauma hospitals [Table 2].

Regarding the use of donated skin, tissue from 48.9% of donors was released for clinical application. Tissue

from 42.2% of donors had to be discarded secondary to contamination, and 6.7% of tissues were partially discarded. At the end of the period, tissue from one donor (2 batches) was still under quarantine [Table 2]. Eighty-four point four percent of retrievals of skin were from the back and lower limbs, as specified in Table 2.

The total amount of collected skin tissue during the period of evaluation was 31,314.63 cm². The largest amount of retrieved tissue from a single donor totaled 2,453.6 cm² and the lowest amount was 422.2 cm². The obtained average amount was 1,252.59 cm² per donor, as shown in Table 3.

Tissues retrieved from the 45 donors generated 81 processing batches in the 1st year of operation; 41 were of acceptable quality for clinical use, 38 were discarded due to an unacceptable biological burden, and 2 remained in quarantine at the end of the period. Thirty-eight of the batches released for use were transplanted and 3 remained in storage [Table 3].

Fourty-two point one percent of tissue discard was due to detection of coagulase-negative staphylococci. Two batches from a single donor were positive for more than one contaminant. Reasons and contaminants of discarded tissues are specified in Table 3.

As observed in Table 4, tissues from a single donor benefited up to 5 patients. A total of 30 patients received tissue during this period.

Table 1: Skin donors profile

Variable	Descriptive statistics n (%)
Gender	
Female	21 (46.67)
Male	24 (53.33)
Total	45 (100.00)
Age (in years)	
Average (± SD)	36.42 (5)
Maximum	60
Minimum	15
Skin color	
White	41 (91.11)
Brown	4 (8.89)
Cause of death	
Severe TBI	13 (28.89)
Stroke	12 (26.67)
Polytrauma	7 (15.56)
CHF*/respiratory insufficiency	3 (6.67)
WGF†	3 (6.67)
Preeclampsia	1 (2.22)
NW‡	1 (2.22)
Lung cancer	1 (2.22)
HÁ§	1 (2.22)
Chronic pancreatitis	1 (2.22)
Suicide	1 (2.22)
Dissecting aneurysm	1 (2.22)

*Congestive heart failure, †Wound by gunfire, ‡Knife wound, §Heart attack, SD: Standard deviation, TBI: Traumatic brain injury

Table 2: Skin tissue retrieval

Variable	Descriptive statistics [n (%)]
Institution	
Evangelical University Hospital of Curitiba	20 (44.44)
Cajuru University Hospital	8 (17.78)
Workers×Hospital	6 (13.33)
São Vicente Hospital	3 (6.67)
Vitória Hospital	1 (2.22)
Angelina Caron Hospital	1 (2.22)
Pilar Hospital	1 (2.22)
Nations' Hospital	1 (2.22)
Zilda Arns Hospital for Elderly	1 (2.22)
Red Cross Hospital	1 (2.22)
UFPR* Clinical Hospital	1 (2.22)
Vita Batel Hospital	1 (2.22)
Total	45 (100.00)
Donor areas	
Back and legs (anterior and posterior)	38 (84.44)
Lower limbs (anterior and posterior)	5 (11.11)
Abdomen and legs (anterior and posterior)	2 (4.44)
Retrieved tissue outcomes (number of donors)	
All tissues acceptable for use	22 (48.89)
All tissues discarded	19 (42.22)
Partial discard	3 (6.67)
Skin still being processed	1 (2.22)
Areas (in cm ²) of retrieved skins tissue	
Total	31,314.63
Maximum per donor	2,453.60
Minimum per donor	422.20
Average per donor (± SD)	1,252.59 (530.38)

*The Federal University of Paraná, SD: Standard deviation

The average age and sex of tissue recipients is depicted in Table 5.

Thirty patients underwent a total of 52 transplants; 88.5% of the transplants were performed at the HUEC, 7.7% were performed at the Regional University Hospital of Northern Paraná in Londrina city, 2% at the Vita Batel Hospital of Curitiba and 2% at the São Paulo Regional Hospital in Santa Catarina state [Figure 1].

A total allograft area of 28,940.83 cm² was transplanted, with the largest area grafted in a single procedure at 1,816.4 cm² and the smallest at 68 cm². The largest amount of tissue grafted to a single patient was 7,284.75 cm². A single patient could receive skin from up to 10 donors, with an average of 3 donors and a minimum of one donor per surgical intervention [Table 6].

Most patients who received allografts were burn victims, corresponding to 25 patients and 45 skin transplantation procedures. The indications for the other 7 transplants are shown in Figure 2.

Among the burn victims, the vast majority (96%) presented with third-degree burns. The most extensively compromised body surface area was 75% and the lowest 10%, with an average of 38.64% of the total body surface area [Table 7].

The body areas which were transplanted are shown in Table 8.

Table 3: Batches of generated skin

Variable	Descriptive statistics	
	Batch number	Percentage
Quantity (number of batches)		
Approved for distribution		
Transplanted	38	4.91
Stored in the bank	3	3.70
Discarded	38	46.91
In process quarantine	2	2.47
Total	81	100.00
Reasons for batch discard		
Growth of coagulase-negative <i>staphylococci</i>	16	42.11
Growth of <i>bacillus</i>	7	18.42
Gram-positive not <i>Clostridium</i>		
Growth of filamentous <i>Fungi</i>	6	15.79
Growth of positive coagulase <i>Staphylococcus</i>	4	10.53
Growth of <i>Enterococcus</i> spp.	3	7.89
Positive for syphilis	2	5.26
Lung cancer	2	5.26
Total	40	105.26

Table 4: Relation between benefited patients and donors

	<i>n</i>
Total of benefited patients	30
Average of benefited patients per donor (± SD)	2.36 (1.35)
Maximum of patients benefited per donor	5

SD: Standard deviation

DISCUSSION

The HUEC skin bank collected tissue from 45 cadaveric donors during its 1st year of operation. Upon a review of the Brazilian literature, a number of similar collections were noted from another operational skin bank.^[8] The numbers in this study compare favorably with available international data.^[9] Of great importance was the ability of the HUEC skin bank to address the local demand.

The average age of the skin donors was similar to that of the donors of the Helsinki skin bank^[9] but lower than the average age of donors to the Porto Alegre skin bank.^[8] The higher number of younger donors may be justified by the higher mortality rates within this cohort in the city of Curitiba due to traffic accidents and physical assaults, which were 23.2 and 42.1 per 100,000 inhabitants, respectively, according to the information department of Unified Health System (DATASUS 2008).^[10]

An equal number of women and men were donors, despite the number of deaths from external causes in 2012 being 3.36 times higher for males in Curitiba.^[11]

The vast majority of donors in Curitiba were of white-colored skin, justified by a predominantly Caucasian population in the region. According to Database of Unified Health System of Brazilian government (DATASUS)^[11] recordson mortality in Curitiba in 2012, 8,218 white skin people died as compared

Table 5: Recipients profile

Variable	Descriptive statistics <i>n</i> (%)
Gender	
Female	10 (33.33)
Male	20 (66.67)
Total	30 (100.00)
Age	
Average (± SD)	29.09 years (22.72)
Maximum	85 years
Minimum	18 days

SD: Standard deviation

Table 6: Grafted skin

Variable	Descriptive statistics (<i>n</i>)
Transplanted skin area (in cm ²)	
Total	28,940.82
Maximum per surgery	1,816.4
Minimum per surgery	68
Maximum per patient	7,284.75
Minimum per patient	68
Average per surgery	556.55
Average per patient	964.694
Relation between donors × recipients	
Maximum of donors per patient	10
Maximum of donors per surgery	3
Minimum of donors per patient	1
Minimum of donors per surgery	1
Average of donors per patient	1.93
Average of donors per surgery	1.25

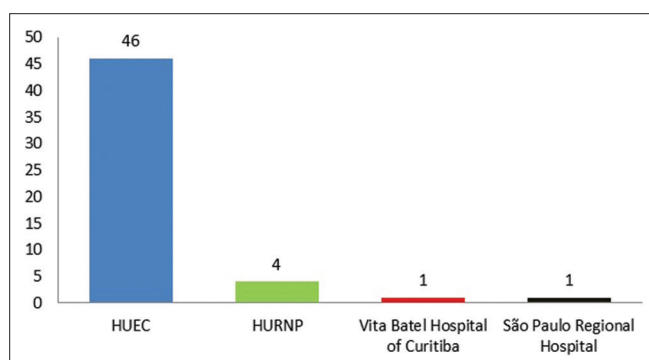


Figure 1: Number of allograft procedures by institution

Table 7: Degree and extension of burns

Variable	Descriptive statistics	
	Patients number	Percentage
Burn depth		
Only third-degree	20	80.00
Second and third-degree	4	16.00
Only deep second degree	1	4.00
Total	25	100.00
Compromised body area (%)		
75	2	8.00
65	1	4.00
56	1	4.00
48	1	4.00
45	7	28.00
40	1	4.00
38	1	4.00
36	1	4.00
35	3	12.00
20	3	12.00
18	1	4.00
15	1	4.00
10	2	8.00

Table 8: Transplanted body areas

Variable	Descriptive statistics n (%)
Allograft region (recipients)	
Lower limb	18 (60.00)
Thorax	18 (60.00)
Upper limb	14 (46.67)
Back	8 (26.67)
Face	7 (23.33)
Cervical	3 (10.00)
Abdomen	2 (6.67)
Perineum	1 (3.33)
Buttocks	1 (3.33)
Genitalia	1 (3.33)

to 257 people with black skin and 59 with yellow skin. Interestingly, there were no black or yellow skin donors, raising the possibility that social, cultural and educational factors within this population cohort may have influenced the consent outcomes for skin donation.

Almost half of the skin donation consents were obtained at the HUEC where the skin bank is located. This outcome

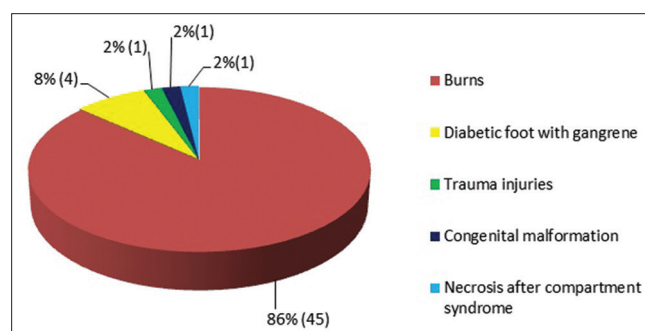


Figure 2: Relation between transplants and allografts reasons

generated some questions: was there a greater awareness of families from potential donors, who were able to observe the care of many burned patients during their own hospital experience? Was the team that approached families of potential donors at the HUEC better prepared to explain skin donation and demystify this procedure, still rarely performed in Brazil? This and possible additional factors should be analyzed to understand why the number of donors in other major trauma hospitals in the region were lower when compared to those from HUEC. Because the offer to donate is provided to the same population, the outcomes could be decisive in increasing the rates of skin donation and transplantation.

During this 1st year of operation, changes were made in the thickness of the retrieved skin. Until February 2014, the grafts harvested were between 0.7 mm and 0.8 mm in thickness. Increased experience in collection and use of the allografts demonstrated that, for better integration, the tissue should have a thickness of 0.4 mm despite the somewhat more complicated and time-consuming manipulation.

The number of discarded tissue batches was high, surpassing by approximately 30% the discard rates at the Porto Alegre skin bank from 2008 to 2012.^[8] In contrast to other national and most international skin banks, the HUEC skin bank protocols did not include exposure of the harvest skin to antibiotics or other disinfecting agents, mainly due to high costs. The data obtained has led to a view of the protocols, in particular, considering that quite a significant number of donors had been hospitalized in the Intensive Care Unit and thus highly manipulated. The goal is to mimic the outcomes of the Helsinki bank, where no batch has been discarded for 8 years.^[9]

On analysis of the skin made available for transplantation, the retrieved skin area amounted to 31,314.63 cm², which is a small number when compared to the skin bank of Helsinki, which scored an average of 44,335 cm² per year from 2001 to 2008.^[9] This was higher than the Clinical Hospital in São Paulo which raised approximately 153,000 cm² of tissue from 2001 to 2006.^[7] Comparing the average area, the HUEC accounted for 1,252.59 cm² of retrieved tissues per donor, a number compatible with that obtained by the bank of Porto Alegre,^[12] but still far below that of the Helsinki bank.

One deviation from acceptance criteria was identified during the retrieval process, when a lung cancer donor

had skin collected, despite this being a contraindication to skin donation. The tissue was subsequently discarded.

As reported by other skin banks, the HUEC skin bank distributed most of its collected tissue to burn victims, corresponding to 25 of the 30 recipients and 86% of transplants performed. This statistic is readily explained by the skin bank's location within a referral center for the treatment of burn patients. Another explanation for these numbers is the relative decreased awareness by other medical specialists whose patients could benefit from the use of skin allografts (e.g. vascular ulcers).

Comparing the Brazilian epidemiology of burn patients, this study found that 80% of recipients experienced exclusively third-degree burn injuries. A different result was obtained by Montes *et al.*^[13] who found that 88.4% of burn patients had only second-degree injuries. This difference is likely secondary to HUEC's treatment of burn victims with deep and large burns. In a literature review of burn victims in Brazil, de Cruz *et al.*^[14] found that the average burnt body surface area was 14.6%. This study demonstrated a higher average of burnt surface area per recipient (38.84%), perhaps because the use of allograft skin was prioritized for critically ill patients with less possibility for autografting.

In this study, it was observed that 28,940.83 cm² of skin was grafted in HUEC with an average of 964.69 cm² per patient; these were higher numbers as compared to the bank of Porto Alegre which sent 35,415 cm² of skin to be grafted onto burn patients nationwide.^[12] This variation may reflect a different indication profile in the hospital burn service, as 88.5% of transplants occurred at our hospital secondary to high demand by locally admitted burn patients.

The HUEC skin bank provided skin for 30 patients. This result is proportional to that of the Porto Alegre skin bank.^[8] Noting that the skin from a single donor benefitted up to 5 patients, with an average of 2.36 recipients per donor, the benefits of a skin bank are clear.

It was observed that the number of retrievals made and the skin area collected by our service was compatible with that seen at other national and international databases, which are in some cases restricted or difficult to access.

Although our use was comparable to these banks, the high disposal rates at our center demonstrate that there is room for improvement in our collection and processing techniques. Techniques including radiosterilization of contaminated tissues, exposure to antibiotics, and better use of the antimicrobial properties of glycerol are being studied for future use to reduce the rate of contaminated tissue.

The HUEC skin bank provided skin primarily for victims of severe third-degree burns, mostly men, who were treated

and transplanted in HUEC. This elevated domestic demand prevented us from sending skin to other regions of the country, highlighting a great need for donations and an improved collection process.

The albeit limited but successful local experience in allograft application for other indications beyond burn care highlights the importance of sharing the potential benefits of allograft availability and use in other medical areas.

A single skin tissue donor can benefit several patients, this should motivate an increase in the profile of skin donation within the public organ and tissue donation campaigns. Both an increased awareness of the importance of donation and the possibility to save several lives, as well as reducing misconceptions of body disfigurement due to skin donation, should be considered.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Roch HJ, Lira SV, de Abreu RN, Xavier ÉP, de Vieira LJ. The profile of accidents by hot liquids in children attended at a reference center in Fortaleza. *Rev Bras Promoção Saúde* 2007;20:86-91.
2. Crisóstomo MR, Serra MC, Gomes DR. Epidemiology of burns. In: Maciel E, Serra MC, editors. *Treaty Burns*. Rio de Janeiro: Atheneu; 2004. p. 31-5.
3. Pianigiani E, Ierardi F, Cherubini Di Simplicio F, Andreassi A. Skin bank organization. *Clin Dermatol* 2005;23:353-6.
4. Fimiani M, Pianigiani E, Di Simplicio FC, Sbrano P, Cuccia A, Pompella G, De Aloe G, Petraglia F. Other uses of homologous skin grafts and skin bank bioproducts. *Clin Dermatol* 2005;23:396-402.
5. Kagan RJ, Robb EC, Plessinger RT. Human skin banking. *Clin Lab Med* 2005;25:587-605.
6. Junqueira JJ, Eras AE, Polo EF, Herson MR, dos Santos VA. Incidence of seropositivity for cytomegalovirus in skin graft donors at the skin bank of the university of the São Paulo Medical School. *J Bras Transplantes* 2007;10:717-9.
7. Schiozer W. Skin banking in Brazil. *Rev Bras Queimaduras* 2012;11:53-5.
8. da Silveira DP, Rech DL, Pretto Neto AS, Martins AL, Ely PB, Chem EM. Skin Bank of Porto Alegre: productivity and donors profiles. *Rev Bras Cir Plást* 2013;28:6.
9. Lindford AJ, Frey I, Vuola J, Koljonen V. Evolving practice of the Helsinki skin bank. *Int Wound J* 2010;7:277-81.
10. Health Information Notebooks, 2010. Brasília: Ministério da Saúde; 2010. Available from: <http://www.tabnet.datasus.gov.br/tabdata/cadernos/pr.htm>. [Last accessed on 2014 Nov 02].
11. System of Mortality Information, 2012. Brasília: Ministério da Saúde; 2012. Available from: <http://www.tabnet.datasus.gov.br/cgi/tabcgi.exe:sim/cnv/obt10pr.def>. [Last accessed on 2015 Jan 07].
12. Minuzzi Filho AC, Chem E, Ely PB, Valiati AA, Fauri M, Cunha TF. Statistics of the santa casa of porto alegre hospital complex skin bank, years 2008-2010. *Rev Bras Cir Plást* 2010;25:93.
13. Montes SF, Barbosa MH, de Sousa Neto AL. Clinical and epidemiological aspects of burned patients hospitalized in a teaching hospital. *Rev Esc Enferm USP* 2011;45:369-73.
14. de Cruz B, Cordovil PB, de Batista K. Epidemiological profile of patients who suffered burns in Brazil: literature review. *Rev Bras Queimaduras* 2012;11:246-50.

Synergistic effect of hyperbaric oxygen preconditioning and hydrogen-rich saline in ameliorating rat flap ischemia/reperfusion injury

Yi-Ding Xiao¹, Yun-Qi Liu², Ming-Zi Zhang¹, You-Bin Wang¹, Yi-Fang Liu², Xue-Mei Ma²

¹Department of Plastic Surgery, Peking Union Medical College Hospital, Dongcheng 100730, Beijing, China.

²College of Life Science and Bioengineering, Beijing University of Technology, Chaoyang 100124, Beijing, China.

Address for correspondence: Dr. You-Bin Wang, Department of Plastic Surgery, Peking Union Medical College Hospital, Dongcheng 100730, Beijing, China. E-mail: wybenz@sina.com

ABSTRACT

Aim: This study was conducted to evaluate the synergistic effects of hyperbaric oxygen (HBO) preconditioning and hydrogen-rich saline (HRS) treatment on skin flap survival and apoptosis in a rat ischemia/reperfusion (IR) skin flap model. **Methods:** Male Sprague-Dawley rats were randomly divided into five groups: one sham surgery group (sham group) and four surgery groups (IR group, HBO group, HRS group, and HBO + HRS group). An extended epigastric adipocutaneous flap (6 cm × 9 cm) was raised over the abdomen in each animal of all five groups. The last four groups underwent 6 h of IR management and were treated, respectively, with normal saline, HBO, HRS (HRS, 0.8 mmol/L), or a combined approach (HBO and HRS). On the 3rd postoperative day, flap survival rate and perfusion condition, apoptotic index, caspase-3 activity, protein expression of pASK1 and Bcl-2/Bax ratio, and Bcl-2 messenger RNA (mRNA) expression were assessed. **Results:** Prior studies have shown the protective effects of HBO and HRS, both of which have been associated with an increase in flap survival. Compared to the IR group, the flaps in the HBO, HRS, and HBO + HRS groups showed better perfusion and a larger survival area with a low number of apoptotic cells, low caspase-3 activity and pASK1 expression, and a high Bcl-2/Bax ratio and Bcl-2 mRNA expression. Of these groups, the HBO + HRS group showed the best flap survival. **Conclusion:** Both HBO and HRS treatments increase the rate of flap survival, while the synergistic application of HBO and HRS showed a higher survival rate as compared to individual treatments of each. The potential regulation of apoptosis with the use of these two modalities may improve skin flap survival.

Key words:

Apoptosis, hydrogen-rich saline, hyperbaric oxygen, ischemia/reperfusion injury, skin flaps

INTRODUCTION

Although the transfer of skin flaps is widely used in wound coverage and reconstruction, soft tissue necrosis

remains a challenging problem. In a report by Chen *et al.*,^[1] 113 cases (9.9%) out of 1,142 free flap operations had

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Xiao YD, Liu YQ, Zhang MZ, Wang YB, Liu YF, Ma XM. Synergistic effect of hyperbaric oxygen preconditioning and hydrogen-rich saline in ameliorating rat flap ischemia/reperfusion injury. *Plast Aesthet Res* 2015;2:332-9.

Received: 24-04-2015; **Accepted:** 27-10-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.169499

complications. Eighty-two percent of these 113 cases demonstrated some form of circulatory compromise within 24 h after surgery.

Postoperative hyperbaric oxygen (HBO) therapy has been used in plastic surgery in the treatment of random skin flaps, axial skin flaps, and flaps with survival problems with satisfactory results.^[2,3] The effect of HBO preconditioning has also been studied in many animal models including stroke^[4] and spinal cord injury.^[5] In a study using a rat skin flap model, HBO preconditioning was found to improve skin flap survival and depress tumor necrosis factor- α (TNF- α) expression in skin tissue.^[6]

In 2007, Ohsawa *et al.*^[7] reported that inhalation of H₂ could selectively mitigate •OH (oxhydryl), generating an antioxidant effect in a rat model of middle cerebral artery occlusion without affecting the signaling of other reactive oxygen species (ROS). Subsequently, H₂ was shown to have protective effects on ischemic/reperfusion (IR) injury in various organs including the liver, heart, kidneys and small intestine.^[8-11] The authors have independently verified this protective effect.^[12]

It is widely accepted that IR injury is a critical factor in flap failure while apoptosis is one important feature of the IR process.^[13,14] In this study, the synergistic effects of HBO preconditioning and hydrogen-rich saline (HRS) treatment were evaluated for their effects on skin flap survival and apoptosis in a rat IR skin flap model.

METHODS

Animals

All protocols were approved by the Committee on Animal Rights Protection of Peking Union Medical College Hospital and were in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals. Adult male Sprague-Dawley (SD) rats weighing 280-320 g were used in this study. The rats were housed in individual cages under standard conditions with 22-25 °C and 12 h of a light-dark cycle. The rats were fed a normal diet with water provided *ad lib* pre- and post-operatively.

Epigastric skin flap preparation

An extended epigastric adipocutaneous flap (6 cm × 9 cm) was raised over the abdomen in each animal.^[12] The left superficial epigastric artery and vein were ligated, and the right was retained as the pedicle. The pedicle artery and vein were occluded with a microvascular clamp and 6 h of skin flap ischemia was induced. The flap was then resutured with a silicone sheet of 0.1 mm deep to it to prevent neovascularization from the wound bed. The clamp was removed, and the flap was reperfused at the end of the ischemic period. Heparin (50,000 U/L in 0.5 mL saline) was injected into the left epigastric artery to avoid thrombus formation prior to ligation.

Hydrogen-rich saline production

Hydrogen was dissolved in normal saline (20 mL) for 20 min with a speed of 0.2 L/min to a supersaturated level. HRS was freshly prepared prior to each use, ensuring that

a concentration of more than 0.8 mmol/L was reached by a needle-type H₂ sensor (Unisense, Aarhus, Denmark).

Experimental protocol and groups

Fifty male SD rats were divided randomly into five groups with 10 animals in each group: (1) a sham-operated group (sham: no IR, HBO, HRS or normal saline injection). Rats in the sham group underwent the same surgery as the rats in the other four groups but without the period of ischemia; (2) IR group: 6 h of ischemia was induced by clamping the right pedicle, followed by an injected intraperitoneally of 5 mL/kg normal saline, 10 min prior to reperfusion; (3) HRS-treated group: 6 h of ischemia was induced by clamping the right pedicle, followed by an intraperitoneally injection of 5 mL/kg HRS, 10 min prior to reperfusion; (4) HBO group: 6 h of ischemia was induced by clamping the right pedicle after HBO preconditioning for 4 times; and (5) HBO and HRS group: 6 h of ischemia was induced by clamping the right pedicle after HBO preconditioning for 4 times. 5 mL/kg HRS was administered by an intraperitoneally injection, 10 min prior to reperfusion.

Hyperbaric oxygen preconditioning

Rats in the HBO and HBO + HRS groups were treated with HBO 2 days before surgery. Treatment included HBO exposure 4 times for 60 min every 12 h (total exposure time of 4 h). 2 L/min of 100% oxygen was supplied continuously at 0.25 MPa during the HBO treatment. Compression and decompression were performed at 5 psi/min. The time at which the HBO chamber pressure reached 0.25 MPa and remained stable was recorded. Calcium carbonate crystals were placed in the chamber to prevent CO₂ accumulation. Flap surgery began 2 h following the final HBO treatment.

Skip flap survival and perfusion evaluation

Skin flap survival was evaluated 72 h after reperfusion by general observation of survival and necrotic phenomena and subsequently confirmed by laser speckle contrast analysis cameras (Perimed AB, Stockholm, Sweden). The surviving and necrotic areas were measured. The percentage of flap survival was defined as the ratio of the surviving area to the original flap area.

To evaluate skin flap perfusion, the rats were secured onto the operative bed such that the entire flap, including part of the normal abdominal skin, was exposed. The PeriScan PSI system (Perimed AB, Stockholm, Sweden) was positioned above the rats, imaging an area of 11 cm × 7.5 cm. The image acquisition rate was 3 Hz and lasted for 3 min. The ambient temperature was maintained between 22 °C and 25 °C during this process. Perfusion of the necrotic and survival areas was analyzed. Vascular flow was measured using perfusion units (PUs).

Rats were sacrificed on the 3rd postoperative day with overdose anesthesia after skin flap survival and perfusion evaluation. The survival flaps were harvested for sampling.

TdT-mediated dUTP-X nick end labeling staining and apoptotic index evaluation

Tissue samples (1 cm² in size) were taken from the proximal areas of the harvested flaps. Samples were sectioned into

smaller pieces and fixed with 4% paraformaldehyde in 0.1 mol/L phosphate buffer. They were then embedded in paraffin, sectioned and mounted onto slides for TdT-mediated dUTP-X nick end labeling (TUNEL) staining.

TUNEL staining was performed using an *in situ* cell death detection kit (Roche, Basel, Switzerland). After being heated to 60 °C and dewaxed, the sections were rehydrated and then incubated in a 20 µg/mL proteinase K working solution for 15 min at room temperature. The slides were rinsed (5 min, 3 times) with phosphate-buffered saline (PBS) and then incubated in a TUNEL reaction mixture for 1 h at 37 °C. The slides were rinsed once again and dried. Converter-POD (anti-fluorescein antibody, Fab fragment from sheep, and conjugated with peroxidase (POD)) was added to the samples for 1 h at 37 °C. The sections were rinsed with PBS and stained with 3,3'-N-diaminobenzidine tetrahydrochloride. Five slide fields were randomly examined using a defined rectangular field area under ×40 magnification. Cells were then counted under ×400 magnification. The apoptotic index (AI) was represented as the percentage of TUNEL-positive cells versus the total number of cell nuclei per field.

Caspase-3 activity assay

Caspase-3 activity was detected using a Fluorometric Assay Kit (Biovision Research Products, Mountain View, CA, USA). Briefly, 50 mg of skin flap tissue was homogenized in ×2 reaction buffer and incubated for 1 h at 37 °C with caspase-3 substrate (DEVD-APC, 1 mM). Substrate cleavage was measured with a spectrofluorometer at 400 nm.

ASK1 and Bcl-2/Bax Western blot

Skin flap tissue (100 mg) was sampled from the proximal, middle and distal regions of the harvested flaps. The samples used for detection were randomly selected from all the samples in each rat in each group to avoid any deviation caused by using different parts of the skin flap samples. Ninety micrograms of total protein were extracted and analyzed from each sample. The protein samples were mixed with loading buffer and boiled at 95 °C for 15 min. The protein samples were then electrophoresed in a 10% dodecyl sulfate-polyacrylamide gel (Bio-Rad, USA) and transferred onto nitrocellulose filter membranes for 1 h at 80 V. The samples were incubated overnight at 4 °C with goat polyclonal actin antibody (1:1,000 dilution, Santa Cruz Biotechnology, Inc., USA), pASK1 antibody (1:500 dilution Cell Signaling Technology, Boston, MA, USA), rabbit anti-Bcl-2 polyclonal antibody (1:1,000 dilution, Chemicon International, Inc., USA), and rabbit anti-Bax polyclonal antibody (1:1,000 dilution, Stressgen Bioreagents, Corp., USA). The proteins were then incubated with horseradish peroxidase-conjugated secondary antibodies diluted at 1:2,500 for 1 h at 37 °C. The blots were then treated with a chemiluminescence detection reagent (Pierce, USA) and exposed to autoradiography film. The bands were then quantified by densitometry.

Quantitative real-time polymerase chain reaction for Bcl-2 messenger RNA

Skin flap tissue (30 mg) was sampled from the proximal, middle and distal areas of the harvested flaps from each

group. The total RNA was extracted from the samples using an RNeasy Fibrous Tissue Mini Kit (Qiagen, Düsseldorf, Germany). One microgram of total RNA was then reversely transcribed into single-stranded complementary DNA with a ProtoScript M-MuLV First Strand cDNA Synthesis Kit (New England Biolabs, Ipswich, MA, USA), according to the manufacturer's instructions. The complementary DNA was then used for real-time polymerase chain reaction (PCR). The process of amplification and quantification were performed with a real-time quantitative PCR system (Agilent, Santa Clara, CA, USA). β -actin was used as the internal control. The PCR protocol was as follows: heating for 2 min at 50 °C, initialization at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s, annealing at 58 °C for 30 s, and extension at 72 °C for 30 s. The primers used in quantitative real-time PCR were Rat Bcl-2 (forward: 5'-AGAACCTTGTGTGACAAATGAGAA-3' and reverse: 5'-TACCCATTAGACA-TATCCAGCTTGA-3') and β -actin (forward: 5'-GGCGGCCAAACAGAAAG-3' and reverse: 5'-CTGAGGGCACGGAGGAT-3').

Statistical analysis

In this study, all data are reported as the mean \pm standard error of the mean (SEM). Significant differences were determined via one-way analysis of variance. Least significant difference *t*-test was used for between-group comparisons. Statistical significance was set at $P < 0.05$. All analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago).

RESULTS

Skin flap survival

Seventy-two hours following reperfusion, necrotic skin flaps were observed and presented as gray areas with little elasticity. In contrast, surviving areas maintained normal elasticity and skin color [Figure 1a]. The highest skin flap survival percentage was observed in the HBO + HRS group (47.70% \pm 12.05%). There were significant differences between the IR (23.30 \pm 6.49%), HRS (36.90% \pm 7.46%), HBO (39.00% \pm 9.14%) and HBO + HRS (47.70% \pm 12.05%) groups (values are the mean \pm SEM, IR vs. HRS, $P < 0.01$; IR vs. HBO, $P < 0.001$; IR vs. HBO + HRS, $P < 0.001$). Among the HBO, HRS and HBO + HRS groups there were significant differences between HBO and HBO + HRS ($P < 0.05$), and HRS and HBO + HRS groups ($P < 0.05$) [Figure 1b].

Skin flap perfusion evaluation

Seventy-two hours following reperfusion, skin flap perfusion stabilized and was analyzed. Skin flap perfusions were 131.10 PU \pm 20.14 PU in the sham group, 26.10 PU \pm 8.09 PU in the IR group, 62.40 PU \pm 14.10 PU in the HBO group, 56.00 PU \pm 25.12 PU in the HRS group and 84.70 PU \pm 13.44 PU in the HBO + HRS group.

A significantly higher blood perfusion was measured in the sham, HBO and HBO + HRS groups. There were statistical differences between the following groups: IR vs. HBO, $P < 0.001$; IR vs. HRS, $P < 0.001$; IR vs. HBO + HRS, $P < 0.001$; HRS vs. HBO + HRS, $P < 0.01$; and HBO vs. HBO + HRS, $P < 0.01$ [Figure 1c].

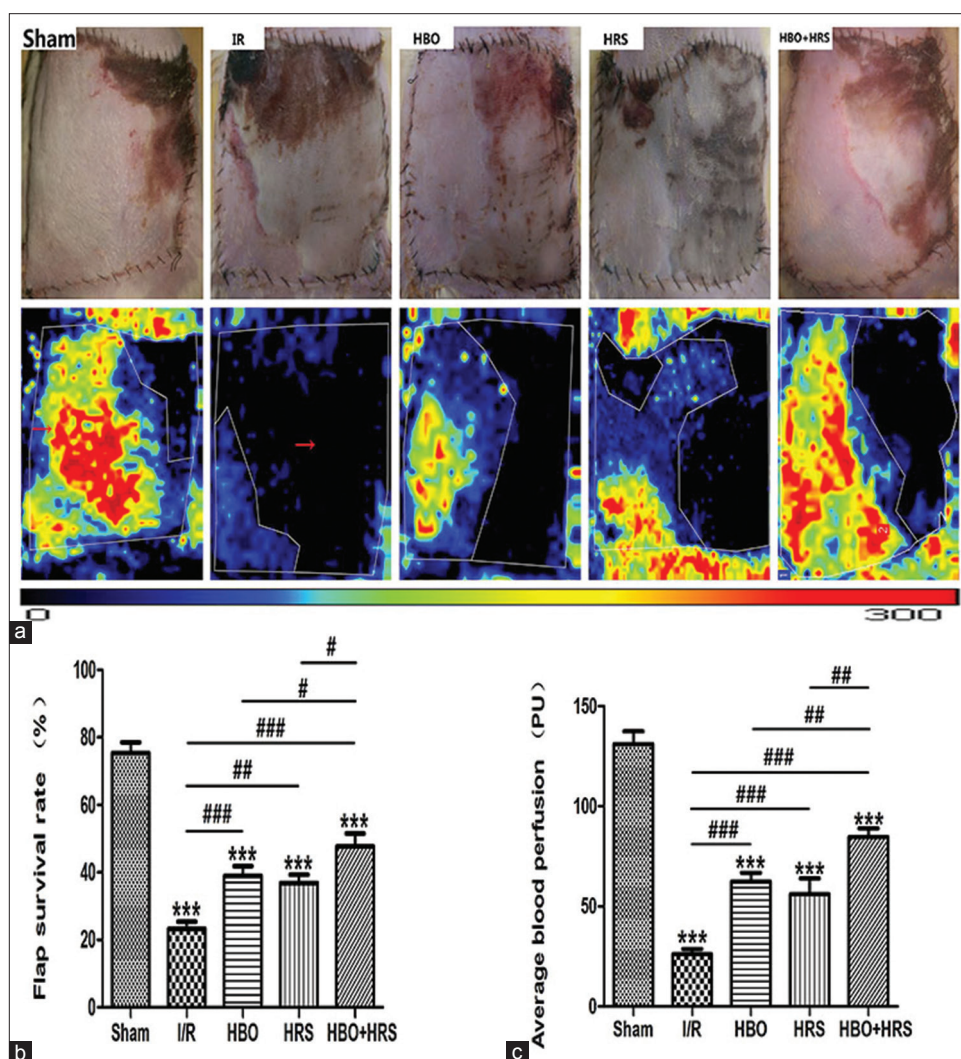


Figure 1: The evaluation of the abdominal skin flaps 72 h following ischemia-reperfusion. Black zones represent the necrotic areas. Red, yellow, and the adjacent blue areas represent surviving areas with rich blood perfusion. (a) Representative photographs of abdominal skin flap microcirculation in the five groups are shown; (b) the survival rate of the total flap area. Flap survival rates were markedly higher in the hyperbaric oxygen, hydrogen-rich saline, and hyperbaric oxygen + hydrogen-rich saline groups; (c) the average blood perfusion of total skin flaps. The hyperbaric oxygen + hydrogen-rich saline group has the greatest blood perfusion among the surgery groups. IR: ischemia reperfusion, HBO: postoperative hyperbaric oxygen, HRS: hydrogen-rich saline

Apoptotic index evaluation

Apoptotic cell death was observed with TUNEL staining [Figure 2a]. The number of apoptotic cells increased in the IR group ($45.85\% \pm 6.64\%$) as compared with the sham group ($8.57\% \pm 4.12\%$). Apoptotic cell number was reduced with HBO preconditioning, HRS and HRS and HBO preconditioning used cooperatively. HRS and HBO preconditioning used cooperatively were more efficient in reducing cell apoptotic death than that of HBO preconditioning or HRS used independently. The AI in HRS was $32.69\% \pm 6.80\%$, in the HBO group was $30.80\% \pm 7.13\%$, and in the HBO + HRS group was $20.24\% \pm 6.90\%$. There were significant differences between each surgical group, (IR vs. HBO, $P < 0.001$; IR vs. HRS, $P < 0.001$; IR vs. HBO + HRS, $P < 0.001$; HBO vs. HBO + HRS, $P < 0.01$; and HRS vs. HBO + HRS, $P < 0.001$) with the exception of HBO versus HRS [Figure 2b].

Caspase-3 activity

Compared to the IR group (1.25 ± 0.26), the caspase-3 relative activity was significantly lower in the HBO (0.59 ± 0.12), HRS (0.53 ± 0.15), and

HBO + HRS (0.36 ± 0.17) groups IR ($P < 0.001$). Significant differences between the HBO + HRS group and the HBO and HRS groups were also found (HBO + HRS vs. HRS, $P < 0.05$; HBO + HRS vs. HBO, $P < 0.01$). However, there was no statistical difference between the HBO and HRS groups [Figure 3].

Western blot for pASK1 and Bcl-2/Bax

The protein expression of pASK1, Bcl-2 and Bax proteins was analyzed by Western blot [Figure 4a]. pASK1 expressed the highest level in the IR group (0.25 ± 0.04) compared with other groups and was significantly decreased in the HBO + HRS group (0.13 ± 0.05) as compared to the IR (0.25 ± 0.04), HRS (0.17 ± 0.04) and HBO (0.18 ± 0.03) groups. Statistical differences were observed in HBO + HRS vs. IR, $P < 0.001$; HRS vs. IR, $P < 0.001$; HBO vs. IR, $P < 0.001$; HBO + HRS vs. HBO, $P < 0.05$; and HBO + HRS vs. HRS, $P < 0.05$ [Figure 4b].

The ratio between the level of Bcl-2 to Bax expression increased in the HBO (2.06 ± 0.49), HRS (2.90 ± 0.65) and HBO + HRS (3.27 ± 0.42) groups. The Bcl-2/Bax

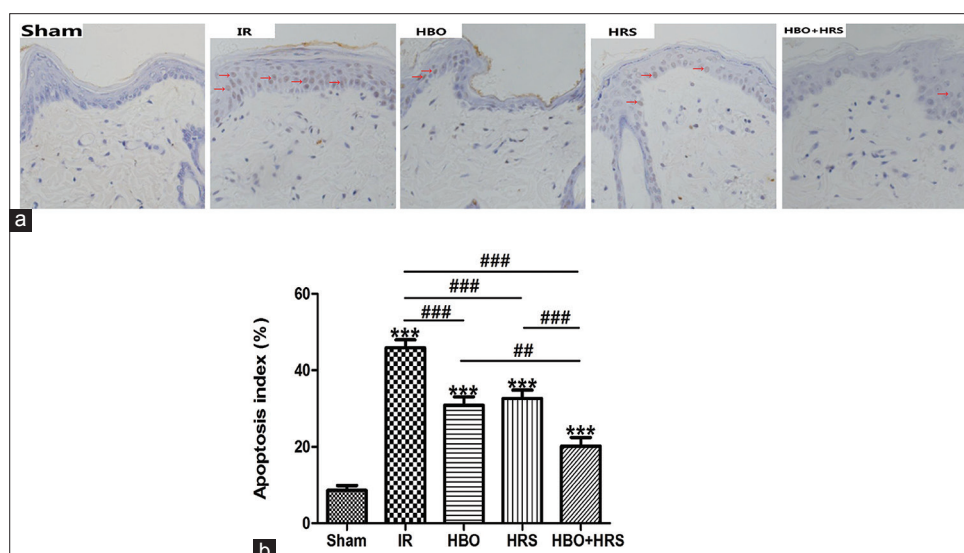


Figure 2: The results of TdT-mediated dUTP-X nick end labeling staining and the apoptosis index 72 h following ischemia-reperfusion. (a) The evaluation of apoptotic cell death by TdT-mediated dUTP-X nick end labeling staining in all groups. Apoptotic cell number was reduced with hyperbaric oxygen preconditioning, hydrogen-rich saline and hydrogen-rich saline and hyperbaric oxygen preconditioning used cooperatively (brown staining indicates apoptotic cells [red arrow]; $\times 200$); (b) the apoptosis index of all groups. The data shown indicate the percentage of TdT-mediated dUTP-X nick end labeling-positive cells and the total cell nuclei per field. Three different slide fields from different skin tissues were counted. TUNEL: TdT-mediated dUTP-X nick end labeling, IR: ischemia reperfusion, HBO: postoperative hyperbaric oxygen, HRS: hydrogen-rich saline

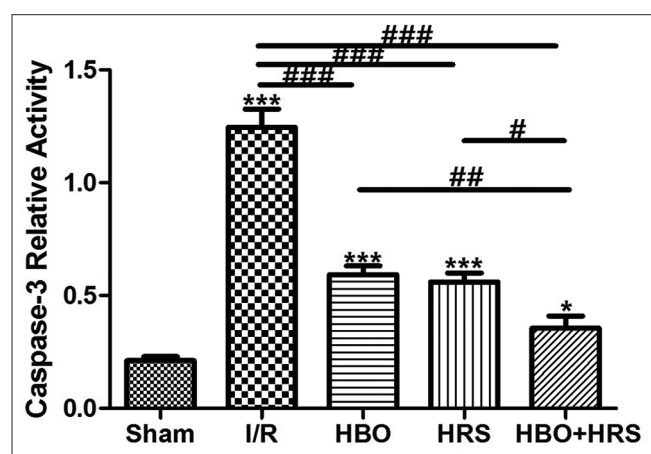


Figure 3: Caspase-3 activity in all groups 72 h following ischemia-reperfusion. Compared to the ischemia-reperfusion group, caspase-3 activity was significantly inhibited in the hyperbaric oxygen, hydrogen-rich saline, and hyperbaric oxygen + hydrogen-rich saline groups. IR: ischemia reperfusion, HBO: postoperative hyperbaric oxygen, HRS: hydrogen-rich saline

ratio in the IR group (0.98 ± 0.40) was the lowest. Statistical differences were observed between HBO + HRS vs. IR, $P < 0.001$; HBO vs. IR, $P < 0.001$; HRS vs. IR, $P < 0.001$; HRS vs. HBO, $P < 0.001$; and HBO + HRS vs. HBO, $P < 0.001$. The highest Bcl-2/Bax ratio was in the HBO + HRS group, but there was no significant difference between the HBO + HRS and HRS groups [Figure 4c].

Bcl-2 messenger RNA expression

The messenger RNA (mRNA) levels in each group were determined with real-time PCR. β -actin was used as a reference gene. Among all groups, the IR group (0.03 ± 0.03) showed the lowest level of Bcl-2 mRNA expression with the exception of the sham group. Among surgery groups, there were significant differences between the IR group and other groups (IR vs. HBO, $P < 0.01$; IR vs. HRS, $P < 0.001$; IR vs. HBO + HRS,

$P < 0.001$). The expression of Bcl-2 mRNA in the HBO + HRS group (0.15 ± 0.05) was higher than in the HBO group (0.08 ± 0.03) and HRS group (0.11 ± 0.05), with statistically significant differences (HBO + HRS vs. HBO, $P < 0.001$; HBO + HRS vs. HRS, $P < 0.05$) [Figure 5].

DISCUSSION

Flap transfer has become a basic albeit challenging technique for all plastic surgeons given the high-risk of flap failure. Even in cases of microsurgical transfer with a stable blood supply, skin flap loss still ranges between 1% and 5% in experienced hands.^[12,15] There are many reasons for partial or total flap loss, including IR injury. During the process of IR injury, flap cells may change their biochemical properties with the induction of apoptosis,^[16] cell shrinkage,^[17] nuclear condensation, and cell death,^[18-20] leading to flap loss.

In clinical work, HBO has been widely used in the treatment of challenging wounds and selected neurological diseases. HBO is considered to be a successful adjunctive therapy for wound healing. In the plastic field, postoperative HBO treatment is commonly used following flap transfer with satisfactory improvement. There has also been research into the protective effect of HBO therapy through preconditioning. Cheng found that HBO reduced cyclooxygenase-2 expression and provided brain protection following ischemia.^[4] The current authors have also examined the effects of HBO preconditioning in a rat skin flap model and found an improvement in flap survival in IR injuries. The mechanisms responsible for its protective effect may be related to attenuation of the inflammatory response and increased flap perfusion.^[6]

Recently, other therapeutic gasses have been studied, in particular, hydrogen. Hydrogen can reach relatively

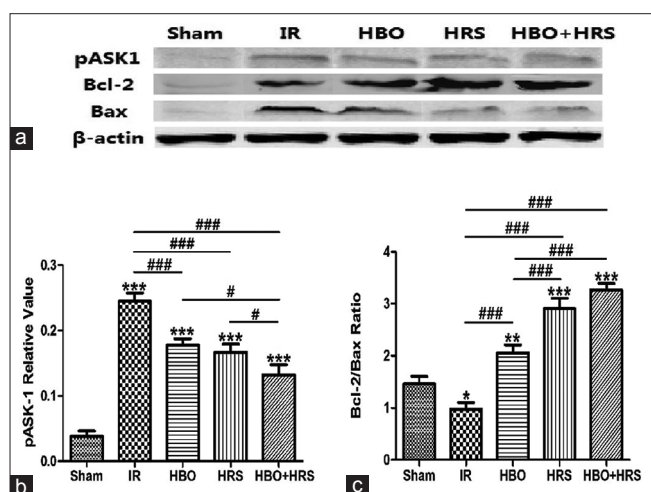


Figure 4: The results of Western blot, pASK1 relative value and Bcl-2/Bax ratio in each group 72 h following ischemia-reperfusion. (a) Representative images of Western blots for pASK1, Bcl-2, and Bax; (b) pASK1 relative values in all groups. Compared to the ischemia-reperfusion group, the expression of pASK1 was significantly reduced in the hyperbaric oxygen, hydrogen-rich saline, and hyperbaric oxygen + hydrogen-rich saline groups; (c) the ratio between Bcl-2 and Bax in all groups. Bcl-2/Bax ratio reveals the highest level in hyperbaric oxygen + hydrogen-rich saline group. IR: ischemia reperfusion, HBO: postoperative hyperbaric oxygen, HRS: hydrogen-rich saline

high concentrations quickly, and excessive hydrogen can be eliminated from the body via breathing, leaving no side effects.^[21] The protective and therapeutic effects of hydrogen in humans have been reported and include such applications as diabetes mellitus type II,^[22] hemodialysis,^[23] inflammatory myopathies,^[24] radiotherapy for liver cancer,^[25] and acute erythematous skin diseases.^[26] Animal research in the rat skin flap model has also been performed to test the protective effect of HRS and has shown that HRS increases the surviving areas of rat abdominal skin flaps while decreasing oxidative stress and inflammation.^[12]

Based on the above theories, this study focused on the combined application of HBO preconditioning and HRS treatment, demonstrating its synergistic effect in protecting a rat skin flap from IR injury by depressing apoptosis. In this study, an abdominal island skin flap IR model was established by ligating the left superficial epigastric artery to investigate cellular and molecular changes following HBO, HRS, and combined treatments. This model was first established by Kuntzsch *et al.*^[27] In his study, an extended (6 cm \times 10 cm) epigastric adipocutaneous flap was harvested, and then the flap was sutured back over a silicon sheet. This flap model has been widely used to study IR injury for the following reasons: first, the flap size is large enough for observation of the survival area. In the sham group, the epigastric artery could only sustain 75.40% \pm 10.01% of the blood supply to the flap; second, with a large flap size, the survival area in each group can be measured scientifically and easily compared. Second, in this model, the flap was supplied by one epigastric artery while other was ligated. A silicon sheet was also used to prevent revascularization. Thus, the blood supply to the model can be easily controlled and manipulated. In this study, several modifications were made including

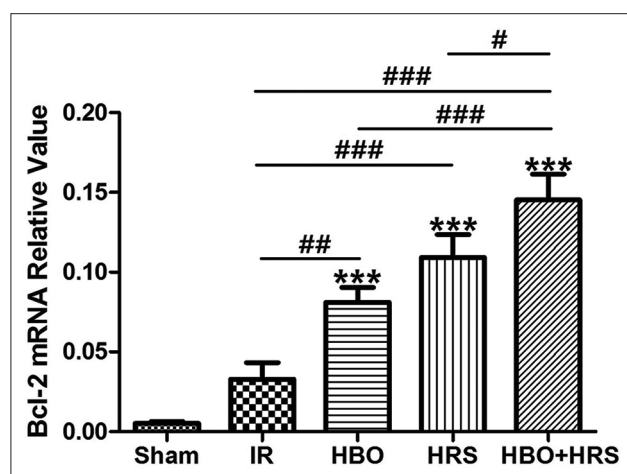


Figure 5: The relative value of Bcl-2 messenger RNA in all groups 72 h following ischemia-reperfusion. Compared to the ischemia-reperfusion group, the hyperbaric oxygen, hydrogen-rich saline, and hyperbaric oxygen + hydrogen-rich saline groups show higher levels of Bcl-2 messenger RNA expression, especially the hyperbaric oxygen + hydrogen-rich saline group. IR: ischemia reperfusion, HBO: postoperative hyperbaric oxygen, HRS: hydrogen-rich saline

the use of an ultrathin silicon sheet (0.1 mm) to avoid revascularization and heparinized saline to avoid thrombus formation.^[12] Analysis of the results showed that skin flaps with HBO preconditioning and HRS treatment have the highest rate of survival in an IR model.

As a new mechanism of inducing cellular IR injury, a TNF- α -induced inflammation via mitochondrial ROS (mtROS) generation has received much attention. mtROS generated by TNF- α can oxidize the reduced thioredoxin-apoptosis signal-regulating kinase 1 complex (Trx [SH] 2-ASK1), and then activate ASK1 and its downstream stress signaling targets including JNK^[28-31] to initiate apoptosis. ASK1 could, therefore, be considered to be a bridge during the apoptotic signaling pathway. One pair of proteins plays a paramount role in regulating apoptosis, specifically the antiapoptotic protein Bcl-2 and the pro-apoptotic protein Bax. The ratio of Bcl-2/Bax determines the cellular direction toward apoptosis.^[32] Caspase-3 plays an important role in increasing the rate of apoptosis. Activated caspase-3 cuts poly (ADP-ribose) polymerase and increase the activity of Ca²⁺/Mg²⁺-dependant endonuclease to destroy DNA molecules.^[33]

In this study, the HBO, HRS and HBO + HRS groups showed low levels of apoptotic. HBO preconditioning and HRS used cooperatively were more efficient in reducing cellular apoptosis than HRS or HBO preconditioning used independently. Caspase-3 could increase the rate of apoptosis. ASK1, as a bridge in the apoptotic process, determines the integrity of the JNK pathway. The caspase-3 activity and pASK1 expression were significantly reduced in the HBO, HRS and HBO + HRS groups. Compared to the HBO and HRS groups, the HBO + HRS group showed the lowest level of caspase-3 activity and pASK1 expression. Bcl-2, a mitochondrial anchoring protein, may prevent apoptosis by acting as an antioxidant.^[34] The Bcl-2/Bax ratio and Bcl-2 mRNA expression were increased among the HBO, HRS and HBO + HRS groups. The Bcl-2/Bax

ratio and Bcl-2 mRNA expression level were higher in the HBO + HRS group than in the HBO or HRS groups.

This study demonstrates the synergistic effect of HBO preconditioning and HRS treatment. By combining the advantages of HBO and HRS, improved flap survival and ischemia tolerance can be used clinically. IR oxygen is not a rare gas and can be readily accessed. However, the application of hydrogen is challenging secondary to its explosive properties and the difficulty of transportation. HRS avoids such problems and can be used in many clinical scenarios. The mechanism of the synergistic effect of HBO preconditioning and HRS treatment have not yet been fully elucidated, and further studies are required. A limitation of this study was the need for an additional IR group with a placebo treatment which would have allowed the comparison of the effects of HBO treatment. With this group, the study would have been more rigorous.

This study showed that compared to an IR group, the rate of skin flap survival is improved, and cellular apoptosis is attenuated secondary to a synergistic effect of HBO preconditioning and HRS treatment.

In conclusion, the synergistic application of HBO and HRS showed a higher flap survival rate, which could be a combined treatment to improve skin flap survival against IR injury.

Financial support and sponsorship

Project supported by the National Natural Science Foundation of China (No. 81171874) and the Beijing Natural Science Foundation (No. 7132169).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Chen KT, Mardini S, Chuang DC, Lin CH, Cheng MH, Lin YT, Huang WC, Tsao CK, Wei FC. Timing of presentation of the first signs of vascular compromise dictates the salvage outcome of free flap. *Plast Reconstr Surg* 2007;120:187-95.
- Zhang T, Gong W, Li Z, Yang S, Zhang K, Yin D, Xu P, Jia T. Efficacy of hyperbaric oxygen on survival of random pattern skin flap in diabetic rats. *Undersea Hyperb Med* 2007;34:335-9.
- Al-Liethy IM, Hanafy AA, Abdel-Aal M, Zaki B. The effect of an extended protocol of hyperbaric oxygen therapy (HBO) on the rat TRAM flap model. *Egypt J Plast Reconstr Surg* 2007;31:7-13.
- Cheng O, Ostrowski RP, Wu B, Liu W, Chen C, Zhang JH. Cyclooxygenase-2 mediates hyperbaric oxygen preconditioning in the rat model of transient global cerebral ischemia. *Stroke* 2011;42:484-90.
- Dong H, Xiong L, Zhu Z, Chen S, Hou L, Sakabe T. Preconditioning with hyperbaric oxygen and hyperoxia induces tolerance against spinal cord ischemia in rabbits. *Anesthesiology* 2002;96:907-12.
- Qi Z, Gao CJ, Wang YB, Ma XM, Zhao L, Liu FJ, Liu XH, Sun XJ, Wang XJ. Effects of hyperbaric oxygen preconditioning on ischemia-reperfusion inflammation and skin flap survival. *Chin Med J (Engl)* 2013;126:3904-9.
- Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med* 2007;13:688-94.
- Fukuda K, Asoh S, Ishikawa M, Yamamoto Y, Ohsawa I, Ohta S. Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. *Biochem Biophys Res Commun* 2007;361:670-4.
- Nakao A, Kaczorowski DJ, Wang Y, Cardinal JS, Buchholz BM, Sugimoto R, Tobita K, Lee S, Toyoda Y, Billiar TR, McCurry KR. Amelioration of rat cardiac cold ischemia/reperfusion injury with inhaled hydrogen or carbon monoxide, or both. *J Heart Lung Transplant* 2010;29:544-53.
- Shingu C, Koga H, Hagiwara S, Matsumoto S, Goto K, Yohoi I, Noguchi T. Hydrogen-rich saline solution attenuates renal ischemia-reperfusion injury. *J Anesth* 2010;24:569-74.
- Buchholz BM, Kaczorowski DJ, Sugimoto R, Yang R, Wang Y, Billiar TR, McCurry KR, Bauer AJ, Nakao A. Hydrogen inhalation ameliorates oxidative stress in transplantation induced intestinal graft injury. *Am J Transplant* 2008;8:2015-24.
- Zhao L, Wang YB, Qin SR, Ma XM, Sun XJ, Wang ML, Zhong RG. Protective effect of hydrogen-rich saline on ischemia/reperfusion injury in rat skin flap. *J Zhejiang Univ Sci B* 2013;14:382-91.
- Wang WZ, Baynosa RC, Zamboni WA. Update on ischemia-reperfusion injury for the plastic surgeon: 2011. *Plast Reconstr Surg* 2011;128:685e-92e.
- van den Heuvel MG, Buurman WA, Bast A, van der Hulst RR. Review: ischaemia-reperfusion injury in flap surgery. *J Plast Reconstr Aesthet Surg* 2008;62:721-6.
- Harder Y, Amon M, Laschke MW, Schramm R, Rucker M, Wettstein R. An old dream revitalized: preconditioning strategies to protect surgical flaps from critical ischemia and ischaemia-reperfusion injury. *J Plast Reconstr Aesthet Surg* 2008;61:503-11.
- Karaaslan O, Ulusoy MG, Kankaya Y, Tiftikcioglu YO, Kocer U, Kankaya D, Karaaslan GM, Tuncer S, Berktaş M. Protective effect of grape seed extract against ischaemia/reperfusion injury in a rat epigastric flap model. *J Plast Reconstr Aesthet Surg* 2010;63:705-10.
- Aydogan H, Gurlek A, Parlakpınar H, Askar I, Bay-Karabulut A, Aydogan N, Fariz A, Acet A. Beneficial effects of caffeic acid phenethyl ester (CAPE) on the ischemia-reperfusion injury in rat skin flaps. *J Plast Reconstr Aesthet Surg* 2007;60:563-8.
- Cetin C, Kose AA, Aral E, Colak O, Ercel C, Karabağlı Y, Alataş O, Eker A. Protective effect of fucoidin (a neutrophil rolling inhibitor) on ischemia reperfusion injury: experimental study in rat epigastric Island flaps. *Ann Plast Surg* 2001;47:540-6.
- Schoenberg MH, Beger HG. Reperfusion injury after intestinal ischemia. *Crit Care Med* 1993;21:1376-86.
- Ozmen S, Ayhan S, Demir Y, Siemionow M, Atabay K. Impact of gradual blood flow increase on ischaemia-reperfusion injury in the rat cremaster microcirculation model. *J Plast Reconstr Aesthet Surg* 2008;61:939-48.
- Chen H, Sun YP, Hu PF, Liu WW, Xiang HG, Li Y, Yan RL, Su N, Ruan CP, Sun XJ, Wang Q. The effects of hydrogen-rich saline on the contractile and structural changes of intestine induced by ischemia-reperfusion in rats. *J Surg Res* 2011;167:316-22.
- Imai S, Kozai H, Matsuda M, Hasegawa G, Obayashi H, Togawa C, Yamamura T, Watanabe K, Miyatani S, Yoshikawa T, Kajiyama S. Intervention with delivery of diabetic meals improves glycemic control in patients with type 2 diabetes mellitus. *J Clin Biochem Nutr* 2008;42:59-63.
- Nakayama M, Nakano H, Hamada H, Itami N, Nakazawa R, Ito S. A novel bioactive haemodialysis system using dissolved dihydrogen (H₂) produced by water electrolysis: a clinical trial. *Nephrol Dial Transplant* 2010;25:3026-33.
- Ito M, Ibi T, Sahashi K, Ichihara M, Ito M, Ohno K. Open-label trial and randomized, double-blind, placebo-controlled, crossover trial of hydrogen-enriched water for mitochondrial and inflammatory myopathies. *Med Gas Res* 2011;1:24.
- Kang KM, Kang YN, Choi IB, Gu Y, Kawamura T, Toyoda Y, Nakao A. Effects of drinking hydrogen-rich water on the quality of life of patients treated with radiotherapy for liver tumors. *Med Gas Res* 2011;1:11.
- Ono H, Nishijima Y, Adachi N, Sakamoto M, Kudo Y, Nakazawa J, Kaneko K, Nakao A. Hydrogen (H₂) treatment for acute erythematous skin diseases. A report of 4 patients with safety data and a non-controlled feasibility study with H₂ concentration measurement on two volunteers. *Med Gas Res* 2012;2:14.
- Kuntscher MV, Schirmbeck EU, Menke H, Klar E, Gebhard MM, Germann G. Ischemic preconditioning by brief extremity ischemia before flap ischemia in a rat model. *Plast Reconstr Surg* 2002;109:2398-404.
- Xue X, Piao JH, Nakajima A, Sakon-Komazawa S, Kojima Y, Mori K, Yagita H, Okumura K, Harding H, Nakano H. Tumor necrosis factor alpha (TNFalpha) induces the unfolded protein response (UPR) in a reactive oxygen species (ROS)-dependent fashion, and the UPR counteracts ROS accumulation by TNFalpha. *J Biol Chem* 2005;280:33917-25.
- Schulze-Osthoff K, Bakker AC, Vanhaesebroeck B, Beyaert R, Jacob WA, Fiers W. Cytotoxic activity of tumor necrosis factor is mediated by early

- damage of mitochondrial functions. Evidence for the involvement of mitochondrial radical generation. *J Biol Chem* 1992;267:5317-23.
30. Goossens V, Grooten J, De Vos K, Fiers W. Direct evidence for tumor necrosis factor-induced mitochondrial reactive oxygen intermediates and their involvement in cytotoxicity. *Proc Natl Acad Sci U S A* 1995;92:8115-9.
 31. Fernández-Checa JC, Kaplowitz N, García-Ruiz C, Colell A, Miranda M, Mari M, Ardite E, Morales A. GSH transport in mitochondria: defense against TNF-induced oxidative stress and alcohol-induced defect. *Am J Physiol* 1997;273:G7-17.
 32. Ayatollahi SA, Ajami M, Reyhanfard H, Asadi Y, Nassiri-Kashani M, Rashighi Firoozabadi M, Davoodi SH, Habibi E, Pazodi-Toroudi H. BCL-2 and bax expression in skin flaps treated with finasteride or azelaic acid. *Iran J Pharm Res* 2012;11:1285-90.
 33. Li CX, Shen SM, Wang LS, Yu Y. Caspase-3-resistant uncleavable form of acidic leucine-rich nuclear phosphoprotein 32B potentiates leukemic cell apoptosis. *Mol Med Rep* 2015;11:2813-8.
 34. Gharib B, Hanna S, Abdollahi OM, Lepidi H, Gardette B, De Reggi M. Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation. *C R Acad Sci III* 2001;324:719-24.

Tissue engineering using mesenchymal stem cells with periosteal wrap for bone defect repair in rabbits

Trung-Hau Lê Thua¹, Dang-Nhat Pham¹, Khanh-Linh Lê¹, Minh-Tuan Lê¹, Quang-Ton-Quyen Nguyen¹, Phan-Huy Nguyen¹, Ngoc-Vu Tran², Ngoc-Luong Nguyen³, Willy Boeckx⁴, Albert Demey⁴

¹Department of Plastic, Reconstructive and Hand Surgery, Center of Orthopaedic and Plastic Surgery, Hue Central Hospital, Hue City 531120, Vietnam.

²Department of Hematology, Hue Central Hospital, Hue City 531120, Vietnam.

³Department of Biology, College of Sciences, Hue University, Hue City 521120, Vietnam.

⁴Department of Plastic Surgery, Brugmann University Hospital, Université libre de Bruxelles, 1020 Brussels, Belgium.

Address for correspondence: Dr. Trung-Hau Lê Thua, Department of Plastic, Reconstructive and Hand Surgery, Center of Orthopaedic and Plastic Surgery, Hue Central Hospital, Hue City 531120, Vietnam. E-mail: donabirini@yahoo.com

ABSTRACT

Aim: Mesenchymal stem cells (MSCs) are an excellent potential source of cells for bone tissue engineering due to their excellent renewal ability and osteogenic differentiation capabilities. This study was designed to evaluate the bone formation properties of a demineralized cancellous bone scaffold seeded with MSCs, with or without periosteum, in a critical size bone defect model in rabbits. **Methods:** Rabbit culture-expanded bone marrow (BM)-MSCs were seeded onto a human demineralized cancellous bone (HDCB) scaffold. Bone defects measuring 15 mm in length were created in each radius. A total of 56 bone defects in 28 rabbits were randomly assigned to one of the 4 groups for scaffold implantation: Group 1: HDCB graft only; Group 2: periosteum-wrapped HDCB graft; Group 3: HDCB graft seeded with BM-MSCs and Group 4: periosteum-wrapped HDCB graft seeded with BM-MSCs. All rabbits were sacrificed 12 weeks after surgery for gross observation, radiological assessment, histological analyses and biomechanical measurements. **Results:** New bone (NB) formation and bone healing were successfully achieved, both radiologically and histologically, on demineralized cancellous bone graft seeded with BM-MSCs. Results were improved when BM-MSCs were associated with periosteum. **Conclusion:** This study demonstrates that repair of bone defects in a rabbit model can be achieved through bone grafting using BM-MSCs, implanted on a demineralized cancellous bone scaffold. The formation of NB was optimized when combined with the preservation of periosteum at the site of injury.

Key words:

Bone defects, bone marrow, bone tissue engineering, mesenchymal stem cells, periosteum

INTRODUCTION

Despite numerous advances in orthopedic and plastic surgery, the repair of bone defects remains challenging. The

most desirable material for bone repair is autologous bone graft, due to its excellent osteoconduction, osteoinduction

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Lê Thua TH, Pham DN, Lê KL, Lê MT, Nguyen QT, Nguyen PH, Tran NV, Nguyen NL, Boeckx W, Demey A. Tissue engineering using mesenchymal stem cells with periosteal wrap for bone defect repair in rabbits. *Plast Aesthet Res* 2015;2:340-5.

Received: 04-04-2015; **Accepted:** 06-09-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.169497

and osteogenesis properties.^[1,2] However, its limitations include additional surgical exposure required for graft harvest, limited bone supply and associated donor site morbidities.^[3,4] Vascularized bone grafts from various locations including the fibula, scapula and iliac crest may be indicated to stimulate bone formation and promote healing. However, harvest requires a complex microsurgery procedure, with the additional risk of including graft necrosis due to vessel thrombosis.^[5,6] Allografts may be a reasonable alternative, as small cancellous allografts can remodel completely. Larger grafts may be incorporated by limited intramembranous bone formation.^[1] However, allografts may increase the risk of infectious disease transmission.

Recent progress in the fields of biotechnology and tissue engineering has offered new options for the repair of traumatic and nontraumatic bone defects. Mesenchymal stem cells (MSCs), which are multipotent adult stem cells of mesodermal origin, have been shown to play a critical role in tissue engineering. MSCs are an excellent potential source of cells for bone tissue engineering due to their excellent renewal ability and osteogenic differentiation capabilities.^[7,8] In addition to the bone marrow (BM), MSCs are also derived from the periosteum. It is well known that the development and regeneration of bone depend on the presence of periosteum and BM.^[9] When transferred to the site of bone damage, MSCs multiply and differentiate into osteoblastic cells, contributing to the production of bone tissues that form a callus at the bone defect site.^[10] Alternatively, bone tissue engineering can be achieved via intramembranous ossification.^[11]

The use of MSCs with an appropriate scaffold has been demonstrated to be promising in guiding bone tissue neof ormation after implantation in the host. Cell repopulation can be achieved either by direct cell loading or indirect cell induction with osteogenic factors.^[12,13] Combining MSCs with appropriate scaffolds has been shown to improve the overall osteoconductivity of the scaffold. The search for an ideal scaffold has led to the development of reconstructive options to engineer new bone (NB) tissue. The ideal scaffold should be biocompatible, noninfectious, resorbable, osteoconductive and osteoinductive.^[14] Demineralized bone matrix (DBM), which is derived from either allogenic or xenogenic bone, is available commercially for clinical application and satisfies some of these requirements.^[4] DBM has been used for several decades in humans for the treatment of nonunion and bone defects following injury or tumor resection. The process of demineralization using hydrochloric acid destroys potential bone forming agents, but also decreases antigenic stimulation and may expose the bone morphogenic protein located within the bone matrix.^[1,4] This study is designed to evaluate the bone formation properties of a demineralized cancellous bone scaffold seeded with allogenic MSCs, with or without periosteum, in a critical sized bone defect model in rabbits.

METHODS

Bone marrow mesenchymal stem cells isolation and expansion

Bone marrow mesenchymal stem cells (BM-MSCs) were isolated from rabbits and cultured as reported previously.^[9,11,13,15] The BM aspirates (5 mL) were obtained from the femurs of 5 rabbits that were 8 weeks old. The BM aspirates were layered over a Ficoll gradient and centrifuged at 2,000 rpm for 20 min at room temperature. Mononuclear cells at the interface were collected and cultured in Dulbecco's Modified Eagle Medium-Low glucose supplemented with 15% fetal bovine serum (FBS), 10 mM L-glutamine, 10 ng/mL epidermal growth factor, 10 ng/mL β -fibroblast growth factor and 1% antibiotic antimycotic solution (10,000 U/mL penicillin, 10 mg/mL streptomycin and 25 μ g amphotericin B) (Sigma-Aldrich, USA). Cultures were maintained in a CO₂ incubator (Shel Lab, USA) at 37 °C and 5% CO₂. The medium was replaced after 3 days and cell layers were washed twice with phosphate-buffered saline to remove nonadherent cells. The passage was carried out when cultures reached 90% confluence using 0.25% trypsin-ethylenediaminetetraacetic acid (Sigma-Aldrich, USA). Cell confluence was normally achieved after 12-14 days.^[14,16-18]

Scaffold materials

Human demineralized cancellous bone (HDCB), which is a type of DBM and has been proven to be usable as scaffold material, was used in this experiment. HDCB was supplied from the Bone Bank at the National Institute of Burns. Fresh bones were aseptically harvested within the first 12 h after being shown to be free of any infectious disease. Bones were treated with H₂O₂, a mixture of methanol/chloroform, hydrochloric acid and phosphate buffer pH 7.4. Subsequently, the bones were dehydrated for 24 h until the water content remaining in the bones was less than 5%. The bones were cut into blocks with dimensions of 1.5 cm \times 0.3 cm \times 0.5 cm. A medullary hole was made in the bone blocks with a diameter of 1.5 mm. The block was packaged and sterilized by gamma irradiation at a dose of 25 kGy. The sterilized bones were then preserved at 4 °C.

Tissue engineered bone graft preparation *in vitro*

Culture-expanded BM-MSCs were seeded evenly onto the HDCB scaffold. DHCB/BM-MSCs were cultured in T flasks (Thermo Scientific Nunc A/S, Denmark) filled with 5 mL DMEM containing 10% FBS and antibiotics. The grafts were placed in a vacuum desiccator and treated at a pressure of 100 torr for 100 s, after which they were incubated at 37 °C, 5% CO₂ for 2 weeks. The medium was replaced every 3 days.^[2,19-21]

Animals and surgical procedure

Twenty-eight male 8-week-old white New Zealand rabbits with a body weight of approximately 1.5 kg from the Experimental Laboratory of the Medical Training and Research Center, Hue Central Hospital, were used for the study. All the experimental study involving animals was approved by the Institutional Animal Care and Use

Committee and the Ethics Committee of the Medical Training and Research Center. The rabbit bone defect model was established as described previously.^[11,13] The rabbit was anesthetized with a combination of intravenous sodium pentobarbital at 20 mg/kg and intramuscular ketamine at 50 mg/kg. The anterolateral side of the forelimb was shaved and sterilized with 10% povidone-iodine. The radius was exposed through a longitudinal incision by gentle retraction of the muscles. An osteotomy gap of 1.5 cm was created in the diaphysis. Periosteum from the excised bone was preserved in the group that would later receive periosteal encapsulation of scaffolds. The ulna was left intact for mechanical stability [Figure 1]. The bone defect was created on both forelimbs of the animals. A total of 56 bone defects within the 28 rabbits were randomly assigned to one of the four groups for scaffold implantation: Group 1: HDCB graft only; Group 2: periosteum-wrapped HDCB graft; Group 3: HDCB graft seeded with BM-MSCs; and Group 4: periosteum-wrapped HDCB graft seeded with BM-MSCs. After implantation, muscle, fascia and skin were separately closed over the defect and no internal or external fixation was used. Forelimbs were postoperatively supported by a carton splint for one week. Each rabbit was administered 400,000 units of penicillin preoperatively on the 1st postoperative day to prevent infection. All rabbits from each group were sacrificed 12 weeks after surgery for gross observation of the growth of callus, radiological assessment, histological analyses and biomechanical measurements.

Gross observation

Following sacrifice, both reconstructed radiuses were harvested and completely cleared from the soft tissues. The status of callus growth, degradation, bone healing and NB formation at the bone graft in the radius were observed.

Radiological assessment

Radius bone specimens in each group were X-rayed for the evaluation of bone formation and remodeling (Titan 2,000, COMED Medical Systems CO. Ltd., Korea). Assessment of NB formation and remodeling was based on the modified Lane and Sandhu radiological scoring system.^[1] Three experts blindly assessed the radiological scores, which were the sum of the scores of bone formation and remodeling. The score for NB formation was assigned as 0 (no NB formation), 1 (less than 25% NB formation),

2 (25-50% NB formation), 3 (50-75% NB formation) or 4 (more than 75% NB formation). The score assigned to the assessment of union was 0 (nonunion), 1 (possible union) or 2 (radiographic union). The proximal and distal unions of the bone graft were separately evaluated. The remodeling score assigned was 0 (no evidence of remodeling) 2 (intramedullary remodeling) or 4 (cortical remodeling). The maximum number of points, which could be achieved, was 10 for each reconstructed bone.

Histological analyses

Fifty-two specimens from the bone graft sites of the radius were successfully fixed with 10% paraformaldehyde, decalcified with sodium formate and embedded in paraffin. Four specimens in Group 1 experienced technical failures. Three sagittal sections were cut with a slow speed saw from each site at the distal, proximal and middle lines of the bone graft. Sections were then prepared and stained with hematoxylin and eosin. The micrographic images from the light microscope were quantified. Images from each section were taken to evaluate the bone formation ratio by a qualified pathologist blinded to the study. The NB formation ratio was calculated by the percentage area of bone tissue within the defect site, and a mean value was determined for each section.

Biomechanical analysis

The specimens of the radius of each group were loaded onto a multifunctional mechanical tester (Instron 5582 Universal Tester, USA) for the performance of a uniaxial compression test. The specimen was placed between compression plates. Force was applied to the specimens at a constant speed of 1 mm/min until fracture occurred. Compressive stress and strain were calculated and plotted. Stress value at the point of yield (load-to-failure) was determined.

Statistical analysis

The data were presented as mean and standard deviation. The Student's *t*-test was performed to compare the difference between the mean values of two groups using Statistical Product and Service Solutions version 15.0 (SPSS, Inc., USA). Differences at a level of $P < 0.05$ were considered to be statistically significant.

RESULTS

The wounds healed completely after one week and the rabbits were noted to regain full movement within two weeks. All the rabbits survived with normal behavior. No complications such as infection or necrosis were recorded prior to sacrifice.

Gross observation

At 12 weeks after surgery, radii implanted in Group 1 showed a small amount of callus and fibrous-like tissue in the interspaces between the defects and grafts. Partial degradation of the HDCB grafts was found. There was a significant amount of callus and bony union filled more than half of the defects in Groups 2 and 3. The HDCB grafts in these groups were almost degraded. In Group 4, good bony union was observed. Bone defects were almost completely remodeled with NB tissue and

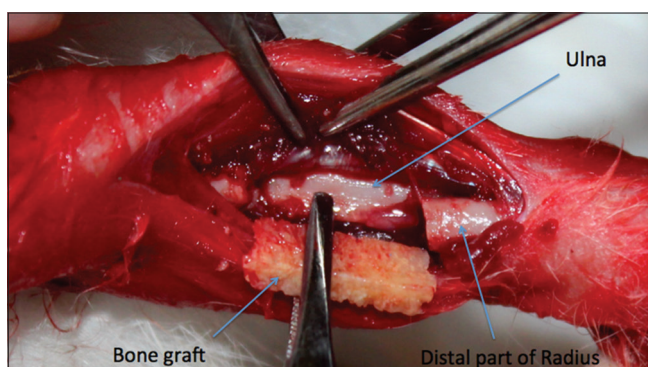


Figure 1: The procedure for the transplantation of cancellous bone graft into the segmental radial defect

the HDCB grafts were completely degraded in this group [Figure 2].

Radiological outcomes

At 3 months postoperatively, there was a small amount of callus formation at the defect gaps in Group 1. NB formation was found to account for over half of the material at the reconstructed bone in Groups 2 and 3. Bone regeneration in the radius in Group 4 was observed to be the best, where callus formation was greatest in comparison to the other groups [Figure 3]. With the radiological score results, the mean score in Group 4 was 8.58 ± 0.64 , which was significantly higher than the other three groups ($P < 0.05$). There was a significant difference between Groups 2 and 3 ($P < 0.05$). The mean scores in Groups 2 and 3 were significantly higher than those in Group 1 ($P < 0.05$) [Table 1].

Histological observations

Inflammation was not observed in the grafted bone segment. Poor NB formation and capillary network were found at the interface between the graft and radius in Group 1. Both ends of the original radius were united with newly regenerated bone in Groups 2 and 3, while the HDCB scaffold was mostly degraded and cortical bone was only observed at the center of the defects. A larger amount of NB was generated along the entire scaffold structure and more capillaries were formed in the area of NB in Group 4. Group 4 showed superior bone union, cancellous bone, cortical bone, marrow formation and capillary formation in comparison to the other groups. Cortical bone was also found along the entire gap of the bone defect, bridging adjacent native bone [Figure 4]. The newly formed bone area in Group 4 increased to $80.5\% \pm 4.96\%$, which was significantly higher when compared with Group 3 ($64.12\% \pm 11.31\%$), Group 2 ($49.79\% \pm 11.69\%$) and Group 1 ($29.6\% \pm 8.33\%$) ($P < 0.05$) [Table 1]. Statistically

significant differences were found between Groups 2 and 3 ($P < 0.05$), while both groups were statistically superior as compared to Group 1 ($P < 0.05$) [Table 1].

Biomechanical testing results

Radii of rabbits with partial or complete union were subjected to biomechanical testing. Results of the biomechanical tests are summarized in Table 1. Group 4 showed the highest compressive strength ($P < 0.05$). Group 3 of HDCB grafts seeded with BM-MSCs showed significantly higher compressive strength than both Groups 1 and 2 ($P < 0.05$). The difference between Groups 1 and 2 was statistically significant ($P < 0.05$) [Table 1].

DISCUSSION

This study demonstrates the presence of NB formation and bone healing, as shown both radiologically and histologically, on demineralized cancellous bone graft seeded with BM-MSCs. Results were improved when BM-MSCs were associated with periosteum.

MSCs, periosteal cells and osteoblasts have all been successfully used for bone tissue engineering.^[4,18] In particular, BM-MSCs play a major role in the repair of bone defects.^[22-25] They are capable of self-replication and differentiation into osteocytes in appropriate culture conditions and can contribute to the regeneration of mesenchymal tissues such as bone.^[3,26] BM-MSCs can be rapidly expanded *ex vivo* without loss of their multi-lineage differentiation potential.^[13] They are readily available and amenable to genetic manipulation. BM-MSCs can, therefore, be viewed as a viable alternative for bone tissue engineering.^[8,11,27,28]

The anatomy of the periosteum, its nutrient transport and its osteoinductive and osteoconductive capacities have been well described.^[29] Periosteum plays a primary role in bridging callus formation and participating in endochondral and intramembranous ossifications in fracture healing.^[30] Previous studies have shown that the

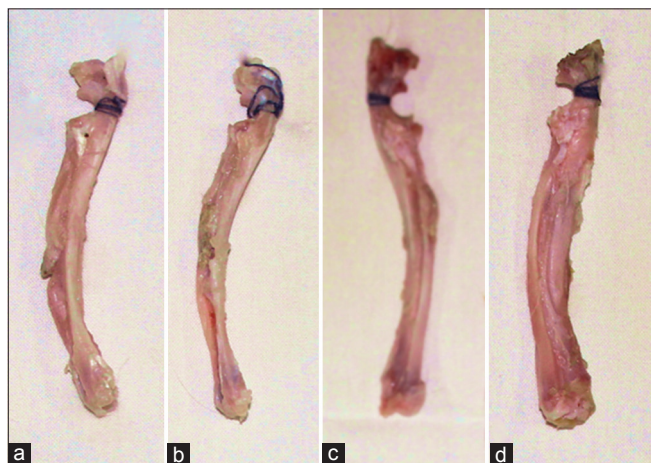


Figure 2: Gross observations of the reconstruction of radius at 3 months after surgery. (a) Small amount of callus and fibrous-like tissue in the interspaces between defect and human demineralized cancellous bone graft in Group 1; (b) callus formed in the defect repair by periosteum-wrapped human demineralized cancellous bone graft in Group 2; (c) significant amount of callus and bony union filled in the defect repair with the human demineralized cancellous bone graft seeded with mesenchymal stem cells in Group 3; (d) complete bone healing in the defect repair by periosteum-wrapped human demineralized cancellous bone graft seeded with bone marrow mesenchymal stem cells in Group 4

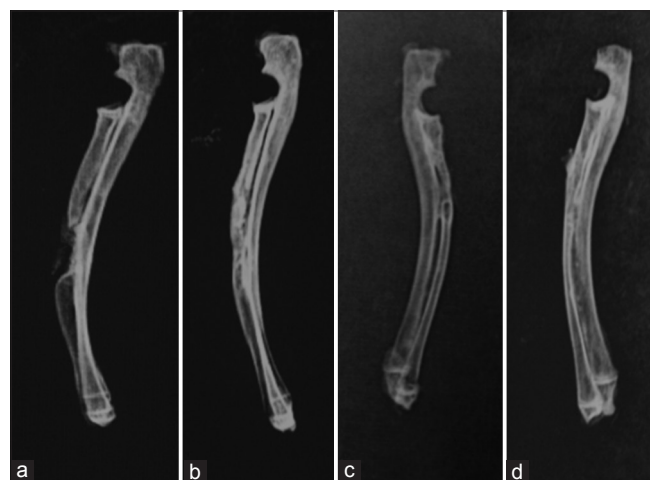


Figure 3: Results of X-ray at the 3 months postoperation. (a) A few calluses at the defect gap in Group 1; (b) significant new bone information at the reconstructed bone in Group 2; (c) more new bone formation between graft and bone tissue in Group 3; (d) almost remodeling of new formed bone along the entire gap of the bone defect in Group 4, and the cortical bone bridged to the adjacent native bone

Table 1: Modified Lane and Sandhu radiological scores, mean new bone formation in Histology (%), and mean compressive strength (MPa) of the rabbit's radius in each group at 3 months after surgery

Group	Scaffold implantation	Mean radiological scores	Mean compressive strength (MPa)	Mean new bone in Histology (%)
1	HDCB only	2.95 ± 0.58	31.14 ± 6.72	29.60 ± 8.33
2	Periosteum-wrapped HDCB	5.57 ± 0.51	73.00 ± 7.20	49.79 ± 11.69
3	HDCB/BM-MSCs	6.41 ± 1.03	80.57 ± 8.50	64.12 ± 11.31
4	Periosteum-wrapped HDCB/ BM-MSCs	8.58 ± 0.64	129.31 ± 5.99	80.50 ± 4.96

HDCB: Human demineralized cancellous bone, BM-MSCs: Bone marrow mesenchymal stem cells

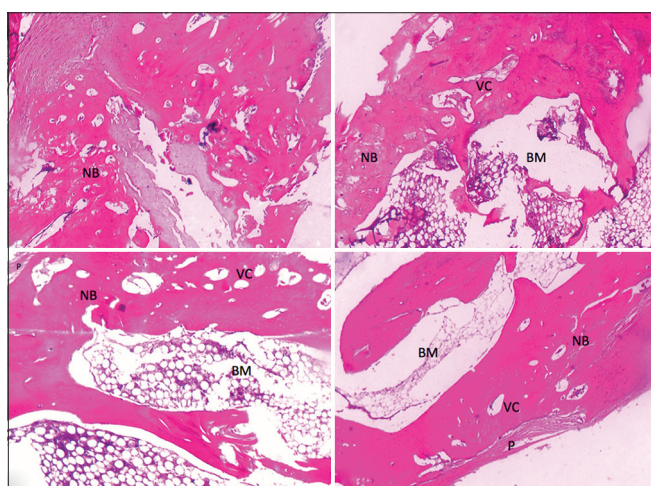


Figure 4: HE stained histological sections from the grafted bone of four groups at 3 months after implantation (original magnification, ×40). NB: New bone, VC: Vascular cavity, BM: Bone marrow, P: Periosteal membrane

inner cambium layer is highly cellular and populated with cells, which influence bone formation and bone repair, including adult mesenchymal skeletal progenitor cells.^[29,31] These progenitor cells proliferate and differentiate into osteoblastic and chondroblastic cells, driving the process of bone repair via either direct intramembranous bone formation or indirect endochondral mechanisms, respectively.^[32] On the contrary, the absence of periosteum reduced by 75%, the number of osteoblasts on devitalized bone graft, which correlated with the poor remodeling activity of the bone graft.^[33] These features indicate that periosteum should be considered to be a structure with regenerative capacity. This suggests the need to restore the essential osteogenic activity of periosteum on bone graft in combination with grafting of MB-MSCs. This approach assists in the early induction of a reparative response by an increase in the formation of a cortical shell around the grafted bone.^[34,35] Agata *et al.*^[34] have also shown that periosteal cells act as progenitor cells with the ability to proliferate and expand. Thus, periosteum-derived cells are another suitable source for bone tissue engineering.

Based on clinical observation, radiologic examination, histological analyses and biomechanical measurements, the current study supports the essential role of periosteum in the process of bone repair. In addition, the regenerative effect of combining BM-MSCs with periosteum showed better outcomes in both the quantity and quality as compared to BM-MSCs alone. Furthermore, the MB-MSCs used in the current study are derived from an allogenic

source, which is more convenient for isolation and expansion when compared with periosteum-derived cells. To further enhance the current bone tissue engineering strategies, a successful cellular replacement for periosteum or tissue-engineered periosteum should be investigated. Zhang *et al.*^[11] previously reported successful regeneration of segmental bone defects in rabbit ulnas using periosteum encapsulated scaffolds seeded with MSCs, with an increase in the newly formed bone area to $80.1\% \pm 9.6\%$. This result is compatible with the results of the current study at $80.5\% \pm 4.96\%$.

Xenogeneic demineralized cancellous bone grafts, which have the advantages of favorable cellular compatibility and histocompatibility as a scaffold, have widely been used for the repair of short bony defects showing the induction of NB formation and good mechanical properties. Osteoinductive structures in demineralized bone graft include a series of low-molecular-weight glycoproteins with bone morphogenetic proteins. These proteins promote chondroblastic differentiation of mesenchymal cells and create NB formation via endochondral osteogenesis.^[1,31,35] The bone formation process increases when decalcification of cortical bone exposes osteoinductive growth factors buried within the mineralized matrix. However, bone grafting has not been successful in the repair of large bone defects.^[13] BM-MSCs, which can be seeded to the HDCB graft for construction of the tissue engineered bone graft, has been suggested as an effective option for the reconstruction of large bone defects.

In the group repaired by periosteum-wrapped HDCB graft seeded with BM-MSCs, bone healing and union were significantly accelerated as compared to the other three groups. Increased density at the graft site and early fusion of cortical bone were observed. In addition to NB formation demonstrated histologically, a significant amount of regenerated capillary vasculature between the NBs was also being observed in a high proportion of grafted bone pores. Zhang *et al.*^[11] reported similar results when incorporating MSCs and periosteum-loaded poly scaffolds. However, our findings have notable differences from the results of Zhang *et al.*^[11] as HDCB/BM-MSCs grafts were significantly superior to periosteum-wrapped HDCB grafts in terms of union rates and capillary density.

For improved biochemical analysis for bone regeneration, a three-point bending test should be performed to evaluate the degree of scaffold integration with the host bone.

In conclusion, this study demonstrates that repair of bone defect in a rabbit model can be achieved through bone grafting using BM-MSCs implanted on a xenogeneic demineralized cancellous bone scaffold. NB formation was optimized with the preservation of the periosteum at the site of injury. The combination of biocompatible material, the ability for self-renewal and differentiation of MSCs with the augmenting effects of periosteum may prove to be an extremely promising approach in the fields of orthopedic and plastic surgery.

Acknowledgment

I acknowledge my colleagues at the Department of Hematology, Hue Central Hospital. I would also like to specially thank Dr. Bui Duc Phu, Dr. Nguyen Duy Thang, Dr. Phan Thi Thuy Hoa, Dr. Phan Hoang Duy, Dr. Dang Cong Thuan and Dr. Frédéric Schuind, for their excellent help and support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bigham-Sadegh A, Shadkhast M, Khalegi MR. Demineralized calf foetal growth plate effects on experimental bone healing in rabbit model. *Vet Arh* 2013;83:525-36.
2. Ng MH, Duski S, Idrus RB, Tan KK, Yusof MR, Low KC, Rose IM, Mohamed Z, Bin Saim A. Repair of segmental load-bearing bone defect by autologous mesenchymal stem cells and plasma-derived fibrin impregnated ceramic block results in early recovery of limb function. *Biomed Res Int* 2014;2014:345910.
3. Fialkov JA, Holy CE, Shoichet MS, Davies JE. *In vivo* bone engineering in a rabbit femur. *J Craniofac Surg* 2003;14:324-32.
4. Kneser U, Schaefer DJ, Polykandriotis E, Horch RE. Tissue engineering of bone: the reconstructive surgeon's point of view. *J Cell Mol Med* 2006;10:7-19.
5. Cao L, Liu X, Liu S, Jiang Y, Zhang X, Zhang C, Zeng B. Experimental repair of segmental bone defects in rabbits by angiopoietin-1 gene transfected MSCs seeded on porous β -TCP scaffolds. *J Biomed Mater Res B Appl Biomater* 2012;100:1229-36.
6. Lê Thua TH, Pham DN, Boeckx W, De Mey A. Vascularized fibular transfer in longstanding and infected large bone defects. *Acta Orthop Belg* 2014;80:50-5.
7. Kanczler JM, Oreffo RO. Osteogenesis and angiogenesis: the potential for engineering bone. *Eur Cell Mater* 2008;15:100-14.
8. Patel DM, Shah J, Srivastava AS. Therapeutic potential of mesenchymal stem cells in regenerative medicine. *Stem Cells Int* 2013;2013:496218.
9. Ai J, Ebrahimi S, Khoshzaban A, Jafarzadeh Kashi TS, Mehrabani D. Tissue engineering using human mineralized bone xenograft and bone marrow mesenchymal stem cells allograft in healing of tibial fracture of experimental rabbit model. *Iran Red Crescent Med J* 2012;14:96-103.
10. Zomorodian E, Baghaban Eslaminejad M. Mesenchymal stem cells as a potent cell source for bone regeneration. *Stem Cells Int* 2012;2012:980353.
11. Zhang X, Qi YY, Zhao TF, Li D, Dai XS, Niu L, He RX. Reconstruction of segmental bone defects in the rabbit ulna using periosteum encapsulated mesenchymal stem cells-loaded poly (lactic-co-glycolic acid) scaffolds. *Chin Med J (Engl)* 2012;125:4031-6.
12. Nooeaid P, Salih V, Beier JP, Boccaccini AR. Osteochondral tissue engineering: scaffolds, stem cells and applications. *J Cell Mol Med* 2012;16:2247-70.
13. Zhao M, Zhou J, Fang T, Dai W, Yin W, Dong J. Repair of bone defect with vascularized tissue engineered bone graft seeded with mesenchymal stem cells in rabbits. *Microsurgery* 2011;31:130-7.
14. Wildemann B, Kadow-Romacker A, Pruss A, Haas NP, Schmidmaier G. Quantification of growth factors in allogenic bone grafts extracted with three different methods. *Cell Tissue Bank* 2007;8:107-14.
15. Chen L, Zhu WM, Fei ZQ, Chen JL, Xiong JY, Zhang JF, Duan L, Huang J, Liu Z, Wang D, Zeng Y. The study on biocompatibility of porous nHA/PLGA composite scaffolds for tissue engineering with rabbit chondrocytes *in vitro*. *Biomed Res Int* 2013;2013:412745.
16. Kon E, Filardo G, Roffi A, Di Martino A, Hamdan M, De Pasqual L, Merli ML, Marcacci M. Bone regeneration with mesenchymal stem cells. *Clin Cases Miner Bone Metab* 2012;9:24-7.
17. Pang L, Hao W, Jiang M, Huang J, Yan Y, Hu Y. Bony defect repair in rabbit using hybrid rapid prototyping polylactic-co-glycolic acid/beta-tricalciumphosphate collagen I/apatite scaffold and bone marrow mesenchymal stem cells. *Indian J Orthop* 2013;47:388-94.
18. Wang X, Wang Y, Gou W, Lu Q, Peng J, Lu S. Role of mesenchymal stem cells in bone regeneration and fracture repair: a review. *Int Orthop* 2013;37:2491-8.
19. Annibali S, Cicconetti A, Cristalli MP, Giordano G, Trisi P, Pilloni A, Ottolenghi L. A comparative morphometric analysis of biodegradable scaffolds as carriers for dental pulp and periosteal stem cells in a model of bone regeneration. *J Craniofac Surg* 2013;24:866-71.
20. Chatterjee A, Renard AJ, Jolink C, van Blitterswijk CA, De Boer J. Streamlining the generation of an osteogenic graft by 3D culture of unprocessed bone marrow on ceramic scaffolds. *J Tissue Eng Regen Med* 2012;6:103-12.
21. Johnson EO, Troupis T, Soucacos PN. Tissue-engineered vascularized bone grafts: basic science and clinical relevance to trauma and reconstructive microsurgery. *Microsurgery* 2011;31:176-82.
22. Zhang W, Zhang F, Shi H, Tan R, Han S, Ye G, Pan S, Sun F, Liu X. Comparisons of rabbit bone marrow mesenchymal stem cell isolation and culture methods *in vitro*. *PLoS One* 2014;9:e88794.
23. Hosseinkhani M, Mehrabani D, Karimfar MH, Bakhtiari S, Manafi A, Shirazi R. Tissue engineered scaffolds in regenerative medicine. *World J Plast Surg* 2014;3:3-7.
24. Li M, Ikehara S. Bone-marrow-derived mesenchymal stem cells for organ repair. *Stem Cells Int* 2013;2013:132642.
25. Ohgushi H. Osteogenically differentiated mesenchymal stem cells and ceramics for bone tissue engineering. *Expert Opin Biol Ther* 2014;14:197-208.
26. Wang B, Sun C, Shao Z, Yang S, Che B, Wu Q, Liu J. Designer self-assembling Peptide nanofiber scaffolds containing link protein N-terminal peptide induce chondrogenesis of rabbit bone marrow stem cells. *Biomed Res Int* 2014;2014:421954.
27. Nakamura O, Kaji Y, Imaizumi Y, Yamagami Y, Yamamoto T. Prefabrication of vascularized bone allograft in a recipient rat using a flow-through vascular pedicle, bone morphogenetic protein, and bisphosphonate. *J Reconstr Microsurg* 2013;29:241-8.
28. Rust PA, Kalsi P, Briggs TW, Cannon SR, Blunn GW. Will mesenchymal stem cells differentiate into osteoblasts on allograft? *Clin Orthop Relat Res* 2007;457:220-6.
29. Colnot C, Zhang X, Knothe Tate ML. Current insights on the regenerative potential of the periosteum: molecular, cellular, and endogenous engineering approaches. *J Orthop Res* 2012;30:1869-78.
30. Lin Z, Fateh A, Salem DM, Intini G. Periosteum: biology and applications in craniofacial bone regeneration. *J Dent Res* 2014;93:109-16.
31. Ferretti C, Mattioli-Belmonte M. Periosteum derived stem cells for regenerative medicine proposals: boosting current knowledge. *World J Stem Cells* 2014;6:266-77.
32. Evans SF, Chang H, Knothe Tate ML. Elucidating multiscale periosteal mechanobiology: a key to unlocking the smart properties and regenerative capacity of the periosteum? *Tissue Eng Part B Rev* 2013;19:147-59.
33. Zhang X, Awad HA, O'Keefe RJ, Goldberg RE, Schwarz EM. A perspective: engineering periosteum for structural bone graft healing. *Clin Orthop Relat Res* 2008;466:1777-87.
34. Agata H, Asahina I, Yamazaki Y, Uchida M, Shinohara Y, Honda MJ, Kagami H, Ueda M. Effective bone engineering with periosteum-derived cells. *J Dent Res* 2007;86:79-83.
35. Chang H, Knothe Tate ML. Concise review: the periosteum: tapping into a reservoir of clinically useful progenitor cells. *Stem Cells Transl Med* 2012;1:480-91.

Transfer of upper trapezius with clavicular segment for restoration of shoulder movements following injury to the brachial plexus

Neeraj Kant Agrawal

Department of Plastic Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, Uttar Pradesh, India.

Address for correspondence: Dr. Neeraj Kant Agrawal, Department of Plastic Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, Uttar Pradesh, India. E-mail: nkagrawal_vns@rediffmail.com

ABSTRACT

Aim: Most brachial plexus palsies occur following high-velocity trauma. The shoulder joint is a large proximal joint which influences the motion of the hand. Transfer of the trapezius muscle is an effective alternative for palsy of the deltoid and supraspinatus muscles. **Methods:** Between 2009 and 2014, 32 patients were treated with modified trapezius muscle transfer in which only the descending fibers along with their attachment to the lateral third of clavicle were used. The clavicle was fixed to the anterolateral surface of the humerus by cancellous screws. The arm was immobilized for 6 weeks. **Results:** All the 32 patients had improved function with stability of the shoulder. The average increase in active abduction was from 7.5° (range: 0°-30°) to 85° (range: 45°-140°), and the mean forward flexion increased from 5.63° (range: 0°-15°) to 55.2° (range: 40°-90°) after a mean follow-up of 8.25 months. Twenty-four of the 32 patients rated the result as good to excellent and were satisfied with the improvement in stability and function. Fifty nine point thirty eight percent patients had Medical Research Council Muscle power 4 after the surgery. **Conclusion:** Transfer of the upper trapezius muscle with a segment of the clavicle segment for a flail shoulder can provide satisfactory function and stability with fewer complications.

Key words:

Brachial plexus, shoulder arthrodesis, trapezius transfer

INTRODUCTION

Restoration of shoulder stability in posttraumatic plexopathy patients is critical in the preservation of distal function.^[1] However, the complexity of management can be frustrating for both patient and surgeon. Primary surgery involves nerve repair, grafting and transfer techniques. Failed operations for the shoulder may require secondary procedures in the form of microneurovascular free-functioning muscle transfer,^[2] tendon transfers and

arthrodesis to improve or restore function. A clear understanding of shoulder anatomy and biomechanics is of paramount importance when using adjacent muscles for transfer.^[3] Options for transfer include the trapezius,^[4,5] pectoralis major^[6] and teres major, latissimus dorsi^[2] and combined biceps and triceps muscles.

The trapezius muscle has been extensively studied and used. Transfer of the trapezius insertion was first described

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Agrawal NK. Transfer of upper trapezius with clavicular segment for restoration of shoulder movements following injury to the brachial plexus. *Plast Aesthet Res* 2015;2:346-9.

Received: 30-05-2015; **Accepted:** 06-09-2015

Access this article online

Quick Response Code:



Website:
www.parjournal.net

DOI:
10.4103/2347-9264.169503

by Mayer^[7] who used a fascia lata graft, albeit with poor results. Bateman's^[4] procedure involved resection of part of the spine of the scapula with the trapezius. This procedure was further modified by Saha,^[5] who also mobilized the upper and middle segments of the trapezius muscle.

The trapezius has three functional segments, consisting of a descending segment which supports the weight of the arm; a transverse segment which retracts the scapula; and an ascending segment which medially rotates and depresses the scapula. Along with the levator scapulae and the serratus anterior, the middle and lower fibers of the trapezius muscle provide shoulder stability for arm movements and for that reason should be spared. The descending fibers which attach to the posterior aspect of the lateral third of the clavicle can be safely used. A more anterolateral fixation on the humerus is expected to abduct and forward flex the arm. Because the clavicle is a superficial bone, it is more amenable to dissection which obviates a more difficult dissection of the scapular spine. The current study was undertaken with the objective of using the descending fibers of the trapezius muscle to evaluate their effect on shoulder movements.

METHODS

Patients with brachial plexus injuries who presented to the outpatient clinic of the Plastic Surgery Department were candidates for the study. A total of 41 patients were evaluated between 2009 and 2014, and 32 patients met inclusion criteria. All patients involved in this article agreed to have their facial pictures published and signed the consent form. The average age of the patients was 23.5 years with a range from 17 years to 42 years. Inclusion criteria were a supple shoulder, passive abduction more than 90°, good adductor muscles, trapezius muscle power more than 4+ and an absence of locoregional injury. Exclusion criteria were dislocation or subluxation of the shoulder, a stiff shoulder, passive abduction less than 90°, weak adductor muscles, a weak trapezius muscle, the presence of a clavicular fracture and injury to the locoregional structures. Patients who had failed previous nerve reconstruction or nerve transfer and patients presenting 2 years or more following injury were the primary candidates for trapezius muscle transfer.

Operative technique

The patient was placed in the supine position with a pillow under the scapula and the neck turned to the opposite side. An incision was made on the anterior border of the trapezius muscle and extended down to the upper 4th of the humerus. The attachments of the upper descending fibers of the trapezius to the posterior border of the lateral 3rd of the clavicle and the attachment of the deltoid muscle to the anterior border of the clavicle were identified. The deltoid attachment was released and the attachment of the trapezius to the lateral clavicle was divided lateral to the coracoclavicular ligament [Figure 1a]. The deep surface of the clavicle was abraded with a bone rasp for bony union between the clavicle and the abraded humerus. The remaining fibers of the trapezius

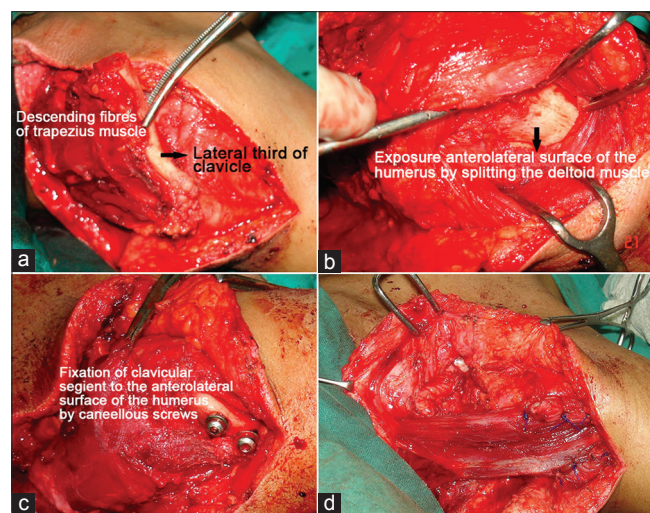


Figure 1: (a) Mobilisation of descending fibres of the trapezius muscle and their insertion on the posterior border of lateral third of clavicle; (b) exposure of anterolateral surface of humerus by splitting the deltoid muscle; (c) fixation of clavicular segment to the anterolateral surface of the humerus by cancellous screws; (d) suturing of deltoid with trapezius and bury the screws

to the acromion and spine of the scapula were left intact. The proximal humerus was exposed by splitting the deltoid longitudinally [Figure 1b] and slightly chiseled out to roughen the anterolateral surface of humerus. The rotator cuff was left untouched. With the humerus held in 90°-100° of abduction, the clavicular fragment with its trapezius insertion was transferred and fixed to the humerus with two 4 mm cancellous screws [Figure 1c]. The deltoid was then sutured over the trapezius with a polypropylene 1-0 suture to render strength to the trapezius and to bury the screws [Figure 1d]. The skin was closed over a suction drain. The arm was splinted in 90°-100° arm abduction. The mean operative time was 112 min. Radiographs were taken on the 2nd postoperative day to assess the position of the screws and the clavicular fragment, and at 3 and 6 weeks to monitor any signs of union. The arm was immobilized for 6 weeks, but assisted and active exercises of the elbow, hand and fingers were initiated on postoperative day one. At one week, the splint was removed and a custom-made airplane splint was applied maintaining the position of abduction. Progressive passive adduction of the arm was started at that time, while active adduction and passive abduction in the supine position were initiated after 21 days. The same exercise was gradually done in the sitting position. After 6 weeks, active abduction and forward flexion were encouraged with splinting between exercises. The patient was evaluated monthly for 3 months and then every 3 months for one year.

RESULTS

In all the 32 patients, the transfer improved both the function and stability of the shoulder [Table 1]. The average increase in active abduction was from 7.5° (range: 0°-30°) to 85° (range: 45°-140°) at a mean follow-up of 8.25 months [Figures 2a and b, Figure 3a and b]. The range of improvement was from 35° to 140°. Mean forward flexion improved from

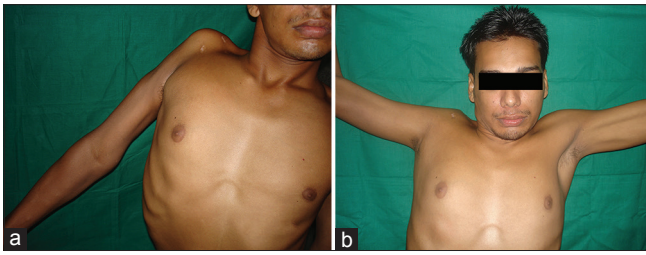


Figure 2: (a) Preoperative photograph of a 20-year-old male who presented 16 months after injury above the right clavicle; (b) postoperative photograph showing 100° of active abduction of the right shoulder

5.63° (range: 0°-15°) to 55.25° (range: 40°-90°), the range of improvement was from 25° to 80°.

Muscle power plays a pivotal role in the day to day activities of a patient. Medical Research Council 4 was encouragingly found in 19 patients (59.38%) after trapezius transfer [Table 2].

The patients' assessment of the results was excellent in 6 cases (18.75%) when active abduction was more than 120°, good in 18 cases (56.25%) when active abduction was 90°-120°, fair in 5 cases (15.63%) when active abduction was 60°-90°, and poor in 3 cases (9.37%) when active abduction was less than 60° [Table 3].

Complications

Two patients were found to have a loose cancellous screw with abduction limited to 35° and 45°, respectively. One patient required eventual removal of the loose screw. Flap necrosis at the suture line was observed in one patient and healed with conservative management.

DISCUSSION

Secondary surgery in brachial plexus palsy is often required for the restoration of shoulder movement^[8] and for the restoration of both analgesia and function. Because the shoulder joint is a large and proximal joint, it is essential for adequate function of distal joints of the upper limb. Local pedicled muscle transfer and glenohumeral arthrodesis remain the mainstay of treatment. With the recent advances in microsurgery, free muscle transfer is also possible.^[2]

Arthrodesis of the shoulder has traditionally been an option in patients with instability secondary to a brachial plexus lesion. However, the surgical technique is difficult, lengthy, and there is no consensus regarding the ideal position for glenohumeral fixation. In addition, the rates of pseudoarthrosis, fracture, residual pain, repositioning of the limb,^[9] and irreversibility of the procedure are significant limiting factors.^[10] However, failure after muscle transfer may be salvaged by shoulder fusion.^[11] Microsurgery is more cumbersome, has a long learning curve, and tension adjustment is not reliable.

The trapezius muscle has previously been used as a donor muscle only with periosteum,^[12] which results in gradual stretching of the muscle and progressive loss of abduction, in trapezius muscle transfer with the spine



Figure 3: (a) Preoperative photograph of a 17-year-old male who had a failed nerve transfer on the right side; (b) postoperative photograph showing 90° of active abduction of the right shoulder

Table 1: Results of modified trapezius transfer (32 patients)

Movements of shoulder	Preoperative	Range	Postoperative	Range
Abduction (°)	7.5	0-30	85	45-140
Forward flexion (°)	5.63	0-15	55.25	40-90
Mean follow-up 8.25 months (6.5-12 months)				

Table 2: Muscle power after transfer (MRC scale)

MRC grade	Number of patients (%)
4	19 (59.38)
2-3	10 (31.25)
0-1	3 (9.37)

MRC: Medical Research Council

Table 3: Satisfaction level of patients and clinical correlation

Subjective opinion of patients	Number of patients (%)	Range of abduction which satisfied the patients (°)
Excellent	6 (18.75)	> 120
Good	18 (56.25)	90-120
Fair	5 (15.63)	60-90
Poor	3 (9.37)	< 60

of the scapula and acromion,^[4] and in mobilization of the upper and middle trapezius muscle with the clavicle, acromion and scapular spine.^[5] The latter two procedures involve extensive, deep and difficult dissection with sacrifice of a significant amount of muscle and bone.

In the technique presented in this paper, only the upper fibers with the lateral clavicle were dissected with good results.

Using Saha's technique, Aziz *et al.*^[13] noted that there was a gain in the abduction of 45.4° following transfer of the acromioclavicular segment. Using the same procedure, Kotwal *et al.*^[14] achieved a gain of 60° of abduction, although the mean level of abduction attained was not mentioned. Conversely, Ruhmann *et al.*^[15] achieved a mean abduction of only 39° with a mean forward flexion of 44°. Severo *et al.*^[10] obtained more encouraging results with a mean postoperative abduction of 75.8° and flexion of 77°. On the contrary, Ragab and El-Sayaed^[16] achieved only 39° of abduction and 32° of flexion. Clearly, the functional

outcome following transfer of the trapezius muscle varies considerably.

The current technique of using the upper descending fibers is easy, quick and reliable with reproducible results and a definite increase in shoulder stability and function. The mean level of abduction of 85° and flexion of 55.2° achieved was encouraging. In 3 of 32 patients, almost 140° of abduction was obtained. In addition, patients were satisfied with fullness in the otherwise atrophic deltoid region, improved forward flexion, a more stable shoulder joint, and decreased heaviness of the upper limb.

Passive shoulder abduction of more than 90° and strong adductors are important prerequisites, and an intensive physiotherapy program should be initiated prior to transfer in order to gain more passive abduction. If adequate abduction is not attained, shoulder arthrodesis is the last resort.

Scar tissue secondary to prior surgery renders the dissection challenging. The use of pillow under the shoulder is recommended to elevate the field of dissection. The pillow should be removed prior to fixation on the humerus lest the transfer be impossible and the incision sutured under tension.

Many patients have osteoporosis of the humerus secondary to disuse following injury to the brachial plexus, creating difficulty in fixation of the clavicle to the humerus. Adequate preparation of the undersurface of the clavicle and anterolateral surface of the humerus is very important, and washers with screws were used in the current study to overcome this problem. Serial radiographs at intervals have been discussed previously. Nonunion was not observed in any cases, although one screw required removal.

Postoperative function depends on the greatest possible tension in the transferred muscle. Proximal mobilization of the trapezius muscle is limited secondary to possible damage to the accessory nerve, which should be identified during dissection. Anterolateral fixation on the humerus is important to achieve forward flexion and internal rotation in addition to the abduction.

Drains should be left in place for one to three days following surgery to prevent late seroma formation and subsequent adhesion of the muscle.

In conclusion, transfer of the upper trapezius muscle with a clavicular segment for a flail shoulder can

provide satisfactory function and stability with fewer complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Terzis JK, Barmptsioti A. Secondary shoulder reconstruction in patients with brachial plexus injuries. *J Plast Reconstr Aesthet Surg* 2011;64:843-53.
2. Chwei-Chin Chuang D. Functioning free muscle transplantation for brachial plexus injury. *Clin Orthop Relat Res* 1995;314:104-11.
3. Elhassan B, Bishop A, Shin A, Spinner R. Shoulder tendon transfer options for adult patients with brachial plexus injury. *J Hand Surg Am* 2010;35:1211-9.
4. Bateman JE. The Shoulder and Environs. St. Louis: CV Mosby; 1955.
5. Saha AK. Surgery of the paralyzed and flail shoulder. *Acta Orthop Scand* 1967;Suppl 97:5-90.
6. Haas SL. Treatment of permanent paralysis of deltoid muscle. *JAMA* 1935;104:99-103.
7. Mayer L. Transplantation of the trapezius for paralysis of the abductors of the arm. *J Bone Joint Surg* 1927;9:412-20.
8. Berger A, Brenner PD. Secondary surgery following brachial plexus injuries. *Microsurgery* 1995;16:43-7.
9. Cofield RH, Briggs BT. Glenohumeral arthrodesis: operative and long-term functional results. *J Bone Joint Surg Am* 1979;61:668-77.
10. Severo AL, Maia PE, Lemos MB, Piluski PC, Lech OL, Fukushima WY. Transfer of the trapezius to the deltoid for the treatment of shoulder instability after lesions of the brachial plexus. *Surg Sci* 2013;4:459-63.
11. Karev A. Trapezius transfer for paralysis of the deltoid. *J Hand Surg (Br)* 1986;11:81-3.
12. Singh AK, Karki D. Modified trapezius transfer technique for restoration of shoulder abduction in brachial plexus injury. *Indian J Plast Surg* 2007;40:39-48.
13. Aziz W, Singer RM, Wolff TW. Transfer of the trapezius for flail shoulder after brachial plexus injury. *J Bone Joint Surg Br* 1990;72:701-4.
14. Kotwal PP, Mittal R, Malhotra R. Trapezius Transfer for deltoid paralysis. *J Bone Joint Surg (Br)* 1998;80:114-16.
15. Ruhmann O, Wirth CJ, Gossé F, Schmolke S. Trapezius transfer after brachial plexus palsy. *J Bone Joint Surg Br* 1998;80:109-13.
16. Ragab RK, El-Sayaed AM. Modified trapezius transfer in brachial plexus palsy. correlation of the surgical outcome with the muscle power. *Bull Alexandria Fac Med* 2008;44:621-7.

High pressure paint gun injury of the index finger: a case report

Memet Yazar¹, Zeliha Gül¹, Ali Can Günenç¹, Sevgi Kurt Yazar², Erol Kozanoğlu³

¹Plastic, Reconstructive and Aesthetic Surgery Clinic, Sisli Etfal Training and Research Hospital, 34371 Istanbul, Turkey.

²Plastic, Reconstructive and Aesthetic Surgery Clinic, Istanbul Training and Research Hospital, 34098 Istanbul, Turkey.

³Plastic, Reconstructive and Aesthetic Surgery Clinic, Istanbul University, Istanbul Medicine Faculty, 34093 Istanbul, Turkey.

Address for correspondence: Dr. Memet Yazar, Plastic, Reconstructive and Aesthetic Surgery Clinic, Sisli Etfal Training and Research Hospital, 34371 Istanbul, Turkey. E-mail: memetyazar@gmail.com

ABSTRACT

Injuries to the hand secondary to high pressure paint guns are considered to be true hand emergencies. These rare injuries may have serious outcomes, and a critical step in their management is extensive debridement performed within the first six hours following injury. For this reason, their diagnosis should not be delayed, and the hand surgeon should be informed immediately to initiate appropriate treatment. In this report, the authors describe a patient who was injured with a chemical paint gun, and whose injury was not diagnosed in the emergency department. The patient subsequently developed tenosynovitis. His treatment is reported herein.

Key words:

Finger injury, high pressure injury, trauma

INTRODUCTION

Hand infections are emergencies of hand surgery that require prompt treatment. The hand is a unique part of the body as it possesses fine compartments with vital structures. Hand infections can accumulate within these compartments through the tendon sheaths and lymphatics, elevating compartmental pressure and progressing to ischemia and necrosis. If the infection spreads to surrounding vital structures, serious functional deficits and even death may occur.^[1-3]

Generally, hand infections can develop following minor trauma such as foreign body penetration and lacerations. In addition, human or animal bites, surgery and intravenous lines may also be associated with infections of the hand.^[4,5] Although injuries due to high pressure injection devices mostly used in manufacturing systems are very rare, they necessitate acute treatment to prevent potentially serious complications.^[6]

In this study, the authors describe a patient who was injured with a chemical paint gun, and whose injury was not initially diagnosed in the emergency department. The patient developed pyogenic tenosynovitis, and his treatment is reported here.

CASE REPORT

A 34-year-old man was referred to our emergency department with the complaints of pain and swelling at the distal phalangeal level of his left index finger. The symptoms began after he was injured with a paint injection gun in a professional setting. The emergency department physicians evaluated the patient and discharged him with prescriptions for oral antibiotics (cefazolin) and analgesics after administration of tetanus prophylaxis. Although

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Yazar M, Gül Z, Günenç AC, Yazar SK, Kozanoğlu E. High pressure paint gun injury of the index finger: a case report. *Plast Aesthet Res* 2015;2:350-2.

Received: 19-04-2015; **Accepted:** 06-09-2015

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.169498

no osseous pathology was detected on his initial radiograph, the radiopaque appearance of the paint could be clearly recognized [Figure 1a and b], demonstrating the high viscosity of the injected material. When the radiograph was evaluated carefully, the paint was noted to have spread proximally through the flexor tendon sheath [Figure 1a and b].

Despite conservative treatment, the pain did not subside, and venous congestion of the finger increased in Figure 2. The patient returned to the emergency department on the following day at which time he was referred to our department with the diagnosis of an infection of the distal phalanx. His examination at that time was remarkable for significant edema of the digit, with an elevated white blood cell count. The differential diagnosis included felon and pyogenic tenosynovitis, and the patient was admitted immediately and taken to the operating room. Mid-lateral incisions were made with findings remarkable for an abscess with a foul odor and tissue necrosis. The pulp was irrigated, dressed and splinted. Cefazolin and gentamicin were ordered for microbial coverage, and dextran 40 and enoxaparin sodium were ordered for circulatory support.

The following day, there were still overt signs of infection, and the patient underwent re-operation. Palmar Z-incisions were made for exposure of the flexor tendon sheaths, and repeat debridement was performed. The paint was found at the level of the proximal phalanx. Both neurodigital bundles and the flexor digitorum profundus tendon were noted to have sustained damage by lysis secondary to the infection [Figure 3a]. The soft tissue and bone were debrided aggressively [Figure 3b], and the deep tissue was sampled for microbiological studies. On the 4th day of hospitalization, cultures revealed mixed Gram-negative bacteria with the growth of *Citrobacter freundii*, *Morganella morganii* and *Proteus vulgaris*. The Department of Infectious Diseases was consulted, and ciprofloxacin and metronidazole were administered per their recommendation. During his stay, the patient was treated with daily povidone-iodine finger baths, the wound dressing was changed daily, and the extremity was elevated continuously. The white blood cell count returned to a normal range by the 10th postoperative day, and the inflammation signs such as swelling and edema subsided. The pulp defect was then reconstructed with a cross-finger flap [Figure 4].

The fingers were attached for 10 days at which time the pedicle was divided. The patient was transferred to physical therapy after recovering from surgery, and eventually returned to his occupation 2 months after the first session of physical therapy. He was evaluated 12 months postinjury with Semmes-Weinstein monofilaments and two-point discrimination tests for sensation. According to these tests, the patient had normal sensation (Semmes-Weinstein: value 2.83, corresponding to green color). Tactile sensation was considered to be good to moderate with two-point discrimination at 6.5 mm. The patient had mild contractures at the proximal

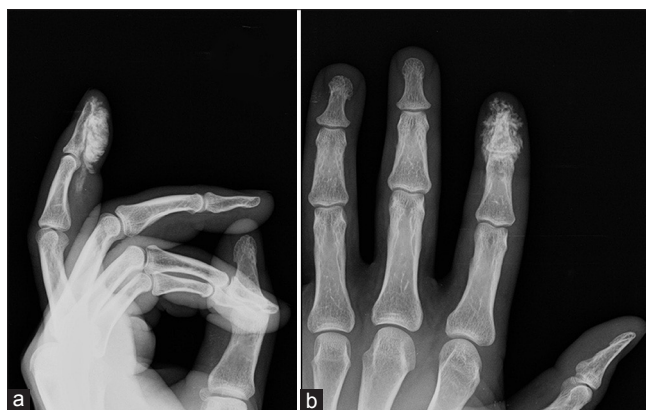


Figure 1: (a) Lateral radiographic view; (b) anteroposterior radiographic view of the patient, the radiopaque appearance of the paint could be recognized clearly



Figure 2: Necrosis of the pulp at the time of referral to the plastic surgery clinic

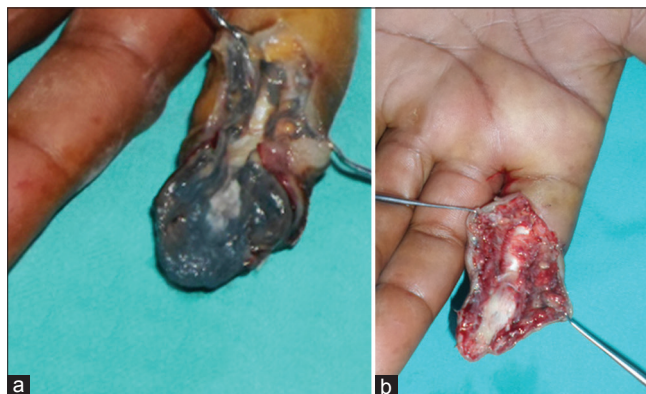


Figure 3: (a) Preoperative view of the paint along the neurovascular bundles and flexor tendon sheaths; (b) the view after debridement

interphalangeal (PIP) and distal interphalangeal (DIP) joints (10°-15° at the PIP and 10° at the DIP).

DISCUSSION

High pressure paint gun injuries of the hand and fingers are very rare, but can progress to amputation. The diagnosis is usually delayed secondary to the benign initial appearance combined with a lack of appropriate clinical knowledge among physicians. Surgical intervention including aggressive



Figure 4: Final postoperative view of the patient after reconstruction with a cross-finger flap

debridement and decompression must be undertaken in the first 6 h to decrease the risk of amputation. Despite aggressive therapy, the risk of amputation ranges from 22% to 48%.^[6] Local necrosis appearing after the first 6 h postinjury may be associated with infection and advancing necrosis which spreads proximally.^[7-9]

In their study, Hogan and Ruland defined the epidemiology of high pressure paint gun injuries.^[10] The majority of the patients were men with a mean age of thirty-five years. The index finger of the nondominant hand was the most frequent injured digit. Tissue damage may be either chemical or mechanical in nature. In general, the injected material creates a small open wound at the entrance point, with the material passing through the tissue and neurovascular structures until it faces resistance. This movement causes traumatic dissection with pressure secondary to the injected fluid potentially causing compartment syndrome. The process advances further with an increase in volume secondary to edema and the inflammation. Because the injected material itself may cause chemical damage, the clinical condition can rapidly deteriorate. All of these factors impair circulation while destroying tissue, increasing the susceptibility to infection. For this reason, a regimen of broad spectrum antibiotics is recommended by most authors. In Hogan and Ruland's study, the microbiological culture was positive with mixed bacteria in forty-two percent of the patients.^[10] Infection can develop even in patients who receive antibiotic therapy. However, their study did not show a statistically significant difference in amputation rates between culture positive and culture negative patients.^[10]

If the patient has been injected with a material other than water or air, debridement must be undertaken within the first 6 h. Local-regional or general anesthesia should be administered because the proximal extent of the injury cannot be known with certainty preoperatively. Digital nerve blocks are not recommended given the risk of increased compression at the fingers. The tourniquet should be applied cautiously to avoid proximal migration

of the injected material. Reconstruction and skin repair can be delayed until a secondary debridement 24-48 h later. Flaps may be utilized in reconstruction following regression of the infection, depending on the condition of the open wound. Although there is controversy regarding their use, steroids may be administered to decrease inflammation. Despite treating 15 patients with steroids, Hogan and Rutland noted that 8 of these patients still required amputation.^[10]

The most significant prognostic factor in high pressure gun injuries is early diagnosis with prompt notification of a hand surgeon. The rate of amputation has been shown to be lower in patients who received debridement of necrotic tissues within the first six hours following injury (58% vs. 88%).^[9] On the other hand, the properties of the injected material are also very important, as injuries with organic solvents (thinner, gasoline, etc.) have a higher risk of amputation than other materials.^[10]

In conclusion, high pressure gun injuries are rare but constitute a true surgical emergency of the hand. The emergency department staff must be educated about such injuries to prevent a delay in diagnosis. As noted above, the most important prognostic factor is aggressive debridement undertaken within the first six hours following injury. For this reason, the hand surgeon must be consulted, broad spectrum antibiotics must be administered promptly, and tissues must be debrided as early as possible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Best RR. An Anatomical and clinical study of infections of the hand. *Ann Surg* 1929;89:359-78.
2. Ki V, Rotstein C. Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. *Can J Infect Dis Med Microbiol* 2007;19:173-84.
3. Rigopoulos N, Dailiana ZH, Varitimidis S, Malizos KN. Closed-space hand infections: diagnostic and treatment considerations. *Orthoped Rev* 2012;4:e19.
4. Clark DC. Common acute hand infections. *Am Fam Physician* 2003;68:2167-76.
5. Bach HG, Steffin B, Chhadia AM, Kovachevich R, Gonzalez MH. Community-associated methicillin-resistant *Staphylococcus aureus* hand infections in an urban setting. *J Hand Surg Am* 2007;32:380-3.
6. Bekler H, Gokce A, Beyzadeoglu T, Parmaksizoglu F. The surgical treatment and outcomes of high-pressure injection injuries of the hand. *J Hand Surg Eur Vol* 2007;32:394-9.
7. Smith GD. High pressure injection injuries. *Trauma* 2005;7:95-103.
8. Öktem F, Özgüder A, Altuntaş N, Bozkurt M, Tellioglu AT. High pressure paint gun injection injury of the hand: a case report. *J Plast Reconstr Aesthet Surg* 2009;62:e157-9.
9. Amsdell SL, Hammert WC. High-Pressure Injection Injuries in the hand: current treatment concept. *Plast Reconstr Surg* 2013;132:e586-91.
10. Hogan CJ, Ruland RT. High-pressure injection injuries to the upper extremity: a review of the literature. *J Orthop Trauma* 2006;20:503-11.

Lacrimal sac rhinosporidiosis

Laxmi Kanta Mishra¹, Sanjeev Gupta², Surya Kanta Pradhan², Manas R. Baisakh³

¹Department of Plastic Surgery, Apollo Hospitals, Bhubaneswar 751005, Orissa, India.

²Department of ENT - Head Neck Surgery, Apollo Hospitals, Bhubaneswar 751005, Orissa, India.

³Department of Pathology, Apollo Hospitals, Bhubaneswar 751005, Orissa, India.

Address for correspondence: Dr. Laxmi Kanta Mishra, Department of Plastic Surgery, Apollo Hospitals, Bhubaneswar 751005, Orissa, India.
E-mail: drlkmishra@rediffmail.com

ABSTRACT

Rhinosporidiosis is caused by the organism *Rhinosporidium seeberi*. It is a rare aquatic protistan parasite. Though more prevalent in Asiatic regions, cases have also been reported in European countries. In India, it mostly affects the southern part. *Rhinosporidium seeberi* most commonly affects the mucous membranes, but can also affect other structures including the larynx, trachea, skin, genitalia, lungs and rectum. The typical presentation is that of a pinkish mass which bleeds profusely. Isolated lacrimal sac rhinosporidiosis is very rare. Computed tomography scans and magnetic resonance imaging are helpful in diagnosis, but histopathological study along with Gomori methenamine silver, periodic acid-Schiff, and potassium chloride are required for confirmation. Its mainstay of treatment is surgery. Prognosis is excellent, but recurrence is not unusual.

Key words:

Computed tomography scan, lacrimal sac, *Rhinosporidium seeberi*, rhinosporidiosis

INTRODUCTION

Rhinosporidiosis is a chronic granulomatous disease affecting the mucous membrane primarily. It is caused by *Rhinosporidium seeberi*.^[1] Previously thought to be a fungus, it is now believed to be a rare aquatic protistan parasite. Rhinosporidiosis is endemic in South India, Sri Lanka, South America and Africa. The most common route of transmission is exposure to the pathogen while bathing in stagnant water pools. It usually presents as a pinkish mass in nose, nasopharynx, oropharynx, conjunctiva, rectum and external genitalia with symptoms depending on the site. Isolated lacrimal sac involvement is very rare. The mainstay of treatment is surgical excision. The authors present a case of isolated lacrimal sac rhinosporidiosis with its surgical management. The patient involved in this article agreed to have his facial pictures published and signed the consent form.

CASE REPORT

A 20-year-old man presented with swelling at the medial canthus of the left eye. He had experienced epiphora for a period of 6 months prior to presentation. There was no history of pain, trauma, bleeding, fever or nasal obstruction. On examination, his general condition was good. There was a soft, nontender, diffuse swelling of 4 cm × 2 cm over the medial canthus of the left eye. Syringing of the lacrimal system was performed and was remarkable for obstruction of the lacrimal sac. The remainder of the ocular examination was normal. Nasal endoscopy and examination of the oropharynx were normal. Routine hematological investigations were normal. Serial axial sections of the paranasal sinuses were performed using computed tomography (CT). Multi-plane reconstructions

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Mishra LK, Gupta S, Pradhan SK, Baisakh MR. Lacrimal sac rhinosporidiosis. *Plast Aesthet Res* 2015;2:353-6.

Received: 16-05-2015; **Accepted:** 13-10-2015

Access this article online	
Quick Response Code:	Website: www.parjournal.net
	DOI: 10.4103/2347-9264.169501

of the images were also studied in addition to screening ultrasonography (USG). A well-defined soft tissue lesion measuring 20 mm × 15 mm in size was noted in the subcutaneous plane at the medial canthus of the left eye at the level of the nasolacrimal sac. The lesion extended into the upper part of the nasolacrimal duct. The lesion was hyperdense with a mean CT attenuation of 48 Hounsfield units (HU) [Figures 1 and 2].

Screening USG showed multiple abnormal vessels with a highly vascular hyperechoic lesion. All the paranasal sinuses were normal. A provisional diagnosis of vascular malformation was made and excision under general anesthesia was planned.

Two percent xylocaine with adrenaline was infiltrated in the region of the medial canthus of the left eye. An elliptical incision was made over the medial canthus of the left eye and extended to the infra-orbital region. The mass was dissected out within the subcutaneous plane and was noted to arise from the lacrimal sac. The mass was soft in consistency, highly vascular and irregular in appearance. The sac could not be preserved during dissection. The lacrimal bone was drilled and silastic tubes were placed from the lacrimal punctum to the nasal

cavity to maintain the lacrimal flow. The medial canthus was repaired and the wound closed in layers. The tissue was sent for histopathology [Figures 3-5].

Pathological sections showed fragments of polypoidal tissue lined by hyperplastic squamous and respiratory mucosa. The underlying stroma showed variable sized round fungal sporangia lined by a thickened wall and many small intraluminal spores. The surrounding tissue showed granuloma formation and infiltration with lymphocytes, plasma cells and eosinophils. The diagnosis was rhinosporidiosis of lacrimal sac [Figures 6 and 7].

The patient was treated with diaminodiphenyl sulfone (Dapsone) 100 mg/day postoperatively for one month. There was no recurrence and the incision healed well with minimal scarring [Figure 8].

DISCUSSION

Rhinosporidiosis was first described in 1900 by Guillermo Seeber who treated a 19-year-old farm worker in Argentina whose breathing was impaired by a nasal mass. Ashworth described the life cycle of the organism in 1923, observing its similarity to the fungal life cycle and renaming it

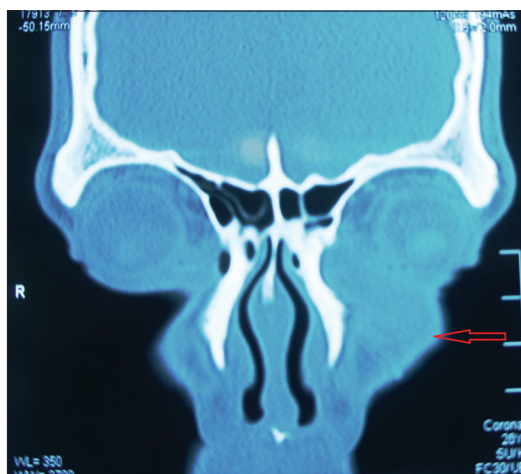


Figure 1: Coronal section of CT scan PNS showing diffuse swelling over left medial canthus and floor of orbit (indicated by arrow). CT: computed tomography, PNS: nose and paranasal sinuses



Figure 2: Axial section of CT scan PNS showing diffuse swelling over left medial canthus and floor of orbit (indicated by arrow). CT: computed tomography, PNS: nose and paranasal sinuses



Figure 3: Preoperative photograph showing medial canthus swelling



Figure 4: Intraoperative photograph showing complete excision and external DCR with silicon tubes *in situ*. DCR: dacryocystorhinostomy



Figure 5: Complete excision specimen



Figure 6: Postoperative photograph after complete healing (three months after surgery)

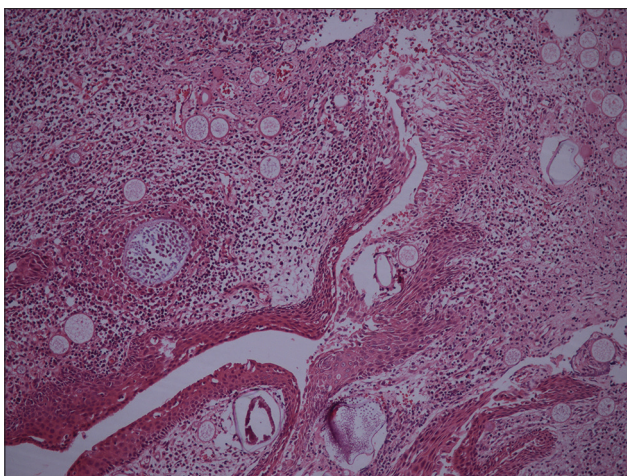


Figure 7: Hematoxylin and eosin stain shows variable size spores with sporangia in the lumen

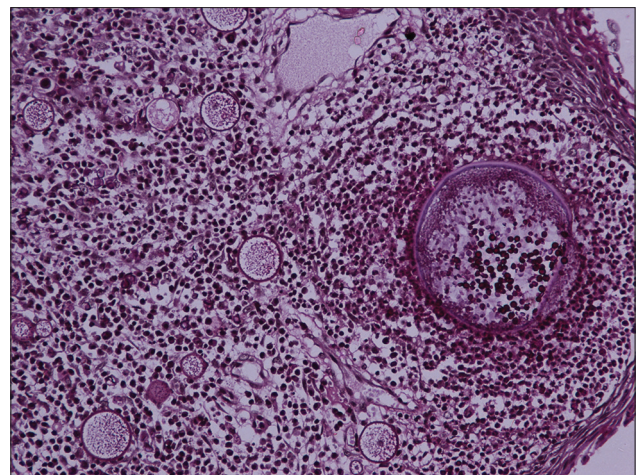


Figure 8: Periodic acid-Schiff stain highlighting the wall of spores

R. seeberi.^[1] Recently, an analysis of the 18S ribosomal ribonucleic acid gene classified it as a protistan parasite and included it in the new class *mesomycetozoea*.^[2] The organism is prevalent in Southern India, Sri Lanka and Southeast Asia, although cases have been reported in South America, Africa and the United States. The most common age group affected is 15-40 years with a predominance in males. The nose and nasopharynx are affected in 70%, while the palpebral conjunctivae and associated structures are affected in 15% of cases.^[3] The mouth, upper airway and eye may also be the sites of disease. Additional sites including the skin, ear, larynx, trachea, bronchi, genitals (vagina, penile urethra or meatus and scrotum), and rectum have also been described.^[4,5] Deep organ involvement with systemic disease has been rarely reported.

Rhinosporidiosis typically presents with sessile or pedunculated polyps, which are occasionally surrounded by whitish spores. Symptoms will depend upon the site affected. Nasal symptoms include nasal obstruction, postnasal drip and bleeding. Ocular symptoms include redness of conjunctiva, itching, epiphora and photophobia. When only the lacrimal sac is affected, it may present as a small, isolated and nontender swelling over the medial

canthus. The reasons for the spread of infection are unclear, and may occur secondary to local inoculation following trauma which progresses with local replication of the organism and associated hyperplastic growth of host tissue and a localized immune response. Nasal and mucosal rhinosporidiosis usually spread by bathing in stagnant fresh water of ponds, lakes or rivers whereas ocular rhinosporidiosis spreads by dust or air.^[5] In cases in which only the lacrimal sac is involved, it is believed that the infection reaches the sac from the nose or eye via the lacrimal canaliculi without affecting the nose or conjunctiva.

CT scan and magnetic resonance imaging can help in diagnosis and in determining the extent of disease by giving moderate to intense enhancement in contrast studies.^[6] However, definitive diagnosis requires microscopy of the biopsy specimen. The oval-shaped sporangia, containing hundreds of endospores, are easily identified under the microscope. Fungal stains including Gomori methenamine silver, periodic acid-Schiff and potassium chloride also help in the diagnosis. Serological tests such as the enzyme-linked immunosorbent assay are used for epidemiological studies.^[7] The differential diagnosis includes condyloma accuminata and hemangioma. Although rhinosporidiosis cannot

generally be treated by medication alone, some studies have shown successful treatment with a long course of dapsone.^[8] Surgical excision with electro-coagulation of the base of the lesion now appears to be the treatment of choice in minimizing the risk of recurrence. Postoperative treatment with dapsone also prevents recurrence, which may have complications including life-threatening dissemination and local secondary bacterial infection.

In conclusion, although rhinosporidiosis is a mucosal disease, it may affect isolated deeper structures including the lacrimal sac, and should be kept as part of the differential diagnosis for all cases with pathology of the lacrimal sac. It is managed mainly by surgical excision although trans-nasal endoscopic excision with dacryocystorhinostomy can be tried in cases with limited disease of the sac. However, more studies of the endoscopic excision are required prior to establish efficacy. Postoperative dapsone treatment can help in the prevention of recurrence. Follow-up is necessary as recurrence is very common.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will

not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ashworth JH. On *Rhinosporidium seeberi* (Wernicke 1903), with special reference to its sporulation and affinities. *Trans R Soc Edinb* 1923;53:301-42.
2. Mendoza L, Taylor JW, Ajello L. The class mesomycetozoea: a heterogeneous group of microorganisms at the animal-fungal boundary. *Annu Rev Microbiol* 2002;56:315-44.
3. Pushker N, Kashyap S, Bajaj MS, Meel R, Sood A, Sharma S, Konkal VL. Primary lacrimal sac rhinosporidiosis with grossly dilated sac and nasolacrimal duct. *Ophthal Plast Reconstr Surg* 2009;25:234-5.
4. Deshpande AH, Agarwal S, Kelkar AA. Primary cutaneous rhinosporidiosis diagnosed on FNAC: a case report with review of literature. *Diagn Cytopathol* 2009;37:125-7.
5. Arora R, Ramachandran V, Raina U, Mehta DK. Oculosporeidiosis in Northern India. *Indian Pediatr* 2001;38:540-3.
6. Prabhu SM, Irodi A, Khiangte HL, Rupa V, Naina P. Imaging features of rhinosporidiosis on contrast CT. *Indian J Radiol Imaging* 2013;23:212-8.
7. Sudasinghe T, Rajapakse RP, Perera NA, Kumarasiri PV, Eriyagama NB, Arseculeratne SN. The regional sero-epidemiology of rhinosporidiosis in Sri Lankan humans and animals. *Acta Trop* 2011;120:72-81.
8. Madke B, Mahajan S, Kharkar V, Chikhalkar S, Khopkar U. Disseminated cutaneous with nasopharyngeal rhinosporidiosis: light microscopy changes following dapsone therapy. *Australas J Dermatol* 2011;52:e4-6.

AUTHOR INSTRUCTIONS

1. Submission Overview

Before you decide to publish with us, please read the following items carefully and make sure that you are well aware of Editorial Policies and the following requirements.

1.1 Topic Suitability

The topic of the manuscript must fit the scope of the journal. Please refer to Aims and Scope for more information.

1.2 Open Access and Copyright

The journal adopts Gold Open Access publishing model since its establishment and has been distributing contents under Attribution 4.0 International License since October 2017, whereas Attribution-NonCommercial-ShareAlike 3.0 Unported had been adopted by then. Please make sure that you are well aware of these policies.

1.3 Publication Fees

Authors are required to pay Article Processing Charges of 499 US Dollars after the manuscript is officially accepted. For more details, please refer to Article Processing Charges.

1.4 Language Editing

All submissions are required to be presented clearly and cohesively in good English. Authors whose first language is not English are advised to have their manuscripts checked or edited by a native English speaker before submission to ensure the high quality of expression. A well-organized manuscript in good English would make the peer review even the whole editorial handling more smooth and efficient.

If needed, authors are recommended to consider the language editing services provided by Charlesworth to ensure that the manuscript is written in correct scientific English before submission. Authors who publish with OAE journals enjoy a special discount for the services of Charlesworth via the following two ways.

- Submit your manuscripts directly at <http://www.charlesworthauthorservices.com/~OAE>;
- Open the link <http://www.charlesworthauthorservices.com/>, and enter Promotion Code “OAE” when you submit.

1.5 Work Funded by the National Institutes of Health

If an accepted manuscript was funded by National Institutes of Health (NIH), the author may inform editors of the NIH funding number. The editors are able to deposit the paper to the NIH Manuscript Submission System on behalf of the author.

2. Submission Preparation

2.1 Cover Letter

A cover letter is required to be submitted accompanying each manuscript. It should be concise and explain why the study is significant, why it fits the scope of the journal, and why it would be attractive to readers, etc.

Here is a guideline of a cover letter for authors' consideration:

In the first paragraph: include the title and type (e.g., Original Article, Review, Case Report, *etc.*) of the manuscript, a brief on the background of the study, the question the author sought out to answer and why;

In the second paragraph: concisely explain what was done, the main findings and why they are significant;

In the third paragraph: indicate why the manuscript fits the Aims and Scope of the journal, and why it would be attractive to readers;

In the fourth paragraph: confirm that the manuscript has not been published elsewhere and not under consideration of any other journal. All authors have approved the manuscript and agreed on its submission to the journal. Journal's specific requirements have been met if any.

If the manuscript is contributed to a special issue, please also mention it in the cover letter.

If the manuscript was presented partly or entirely in a conference, the author should clearly state the background information of the event, including the conference name, time and place in the cover letter.

2.2 Types of Manuscripts

There is no restriction on the length of manuscripts, number of figures, tables and references, provided that the manuscript is concise and comprehensive. The journal publishes Original Article, Review, Meta-analysis, Case Report, Commentary, *etc.* For more details about paper type, please refer to the following table.

Manuscript Type	Definition	Abstract	Keywords	Main Text Structure
-----------------	------------	----------	----------	---------------------

Original Article	An Original Article describes detailed results from novel research. All findings are extensively discussed.	Structured abstract including Aim, Methods, Results and Conclusion. No more than 250 words.	3-8 keywords	The main content should include four sections: Introduction, Methods, Results and Discussion.
Review	A Review paper summarizes the literature on previous studies. It usually does not present any new information on a subject.	Unstructured abstract. No more than 250 words.	3-8 keywords	The main text may consist of several sections with unfixed section titles. We suggest that the author include an "Introduction" section at the beginning, several sections with unfixed titles in the middle part, and a "Conclusion" section in the end.
Case Report	A Case Report details symptoms, signs, diagnosis, treatment, and follows up an individual patient. The goal of a Case Report is to make other researchers aware of the possibility that a specific phenomenon might occur.	Unstructured abstract. No more than 150 words.	3-8 keywords	The main text consists of three sections with fixed section titles: Introduction, Case Report, and Discussion.
Meta-Analysis	A Meta-Analysis is a statistical analysis combining the results of multiple scientific studies. It is often an overview of clinical trials.	Structured abstract including Aim, Methods, Results and Conclusion. No more than 250 words.	3-8 keywords	The main content should include four sections: Introduction, Methods, Results and Discussion.
Systematic Review	A Systematic Review collects and critically analyzes multiple research studies, using methods selected before one or more research questions are formulated, and then finding and analyzing related studies and answering those questions in a structured methodology.	Structured abstract including Aim, Methods, Results and Conclusion. No more than 250 words.	3-8 keywords	The main content should include four sections: Introduction, Methods, Results and Discussion.
Technical Note	A Technical Note is a short article giving a brief description of a specific development, technique or procedure, or it may describe a modification of an existing technique, procedure or device applied in research.	Unstructured abstract. No more than 250 words.	3-8 keywords	/
Commentary	A Commentary is to provide comments on a newly published article or an alternative viewpoint on a certain topic.	Unstructured abstract. No more than 250 words.	3-8 keywords	/
Editorial	An Editorial is a short article describing news about the journal or opinions of senior editors or the publisher.	None required	None required	/
Letter to Editor	A Letter to Editor is usually an open post-publication review of a paper from its readers, often critical of some aspect of a published paper. Controversial papers often attract numerous Letters to Editor.	Unstructured abstract (optional). No more than 250 words.	3-8 keywords (optional)	/
Opinion	An Opinion usually presents personal thoughts, beliefs, or feelings on a topic.	Unstructured abstract (optional). No more than 250 words.	3-8 keywords	/
Perspective	A Perspective provides personal points of view on the state-of-the-art of a specific area of knowledge and its future prospects. Links to areas of intense current research focus can also be made. The emphasis should be on a personal assessment rather than a comprehensive, critical review. However, comments should be put into the context of existing literature. Perspectives are usually invited by the Editors.	Unstructured abstract. No more than 150 words.	3-8 keywords	/

2.3 Manuscript Structure

2.3.1 Front Matter

2.3.1.1 Title

The title of the manuscript should be concise, specific and relevant, with no more than 16 words if possible. When gene or

protein names are included, the abbreviated name rather than full name should be used.

2.3.1.2 Authors and Affiliations

Authors' full names should be listed. The initials of middle names can be provided. Institutional addresses and email addresses for all authors should be listed. At least one author should be designated as corresponding author. In addition, corresponding authors are suggested to provide their Open Researcher and Contributor ID upon submission. Please note that any change to authorship is not allowed after manuscript acceptance.

2.3.1.3 Abstract

The abstract should be a single paragraph with word limitation and specific structure requirements (for more details please refer to Types of Manuscripts). It usually describes the main objective(s) of the study, explains how the study was done, including any model organisms used, without methodological detail, and summarizes the most important results and their significance. The abstract must be an objective representation of the study: it is not allowed to contain results which are not presented and substantiated in the manuscript, or exaggerate the main conclusions. Citations should not be included in the abstract.

2.3.1.4 Keywords

Three to eight keywords should be provided, which are specific to the article, yet reasonably common within the subject discipline.

2.3.2 Main Text

Manuscripts of different types are structured with different sections of content. Please refer to Types of Manuscripts to make sure which sections should be included in the manuscripts.

2.3.2.1 Introduction

The introduction should contain background that puts the manuscript into context, allow readers to understand why the study is important, include a brief review of key literature, and conclude with a brief statement of the overall aim of the work and a comment about whether that aim was achieved. Relevant controversies or disagreements in the field should be introduced as well.

2.3.2.2 Methods

Methods should contain sufficient details to allow others to fully replicate the study. New methods and protocols should be described in detail while well-established methods can be briefly described or appropriately cited. Experimental participants selected, the drugs and chemicals used, the statistical methods taken, and the computer software used should be identified precisely. Statistical terms, abbreviations, and all symbols used should be defined clearly. Protocol documents for clinical trials, observational studies, and other non-laboratory investigations may be uploaded as supplementary materials.

2.3.2.3 Results

This section contains the findings of the study. Results of statistical analysis should also be included either as text or as tables or figures if appropriate. Authors should emphasize and summarize only the most important observations. Data on all primary and secondary outcomes identified in the section Methods should also be provided. Extra or supplementary materials and technical details can be placed in supplementary documents.

2.3.2.4 Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study. Future research directions may also be mentioned.

2.3.2.5 Conclusion

It should state clearly the main conclusions and include the explanation of their relevance or importance to the field.

2.3.3 Back Matter

2.3.3.1 Acknowledgments

Anyone who contributed towards the article but does not meet the criteria for authorship, including those who provided professional writing services or materials, should be acknowledged. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgments section. This section is not added if the author does not have anyone to acknowledge.

2.3.3.2 Authors' Contributions

Each author is expected to have made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data, or the creation of new software used in the work, or have drafted the work or substantively revised it.

Please use Surname and Initial of Forename to refer to an author's contribution. For example: made substantial contributions

to conception and design of the study and performed data analysis and interpretation: Salas H, Castaneda WV; performed data acquisition, as well as provided administrative, technical, and material support: Castillo N, Young V. If an article is single-authored, please include “The author contributed solely to the article.” in this section.

2.3.3.3 Availability of Data and Materials

In order to maintain the integrity, transparency and reproducibility of research records, authors should include this section in their manuscripts, detailing where the data supporting their findings can be found. Data can be deposited into data repositories or published as supplementary information in the journal. Authors who cannot share their data should state that the data will not be shared and explain it. If a manuscript does not involve such issue, please state “Not applicable.” in this section.

2.3.3.4 Financial Support and Sponsorship

All sources of funding for the study reported should be declared. The role of the funding body in the experiment design, collection, analysis and interpretation of data, and writing of the manuscript should be declared. Any relevant grant numbers and the link of funder’s website should be provided if any. If the study is not involved with this issue, state “None.” in this section.

2.3.3.5 Conflicts of Interest

Authors must declare any potential conflicts of interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results. If there are no conflicts of interest, please state “All authors declared that there are no conflicts of interest.” in this section. Some authors may be bound by confidentiality agreements. In such cases, in place of itemized disclosures, we will require authors to state “All authors declare that they are bound by confidentiality agreements that prevent them from disclosing their conflicts of interest in this work.”. If authors are unsure whether conflicts of interest exist, please refer to the “Conflicts of Interest” of OAE Editorial Policies for a full explanation.

2.3.3.6 Ethical Approval and Consent to Participate

Research involving human subjects, human material or human data must be performed in accordance with the Declaration of Helsinki and approved by an appropriate ethics committee. An informed consent to participate in the study should also be obtained from participants, or their parents or legal guardians for children under 16. A statement detailing the name of the ethics committee (including the reference number where appropriate) and the informed consent obtained must appear in the manuscripts reporting such research.

Studies involving animals and cell lines must include a statement on ethical approval. More information is available at Editorial Policies.

If the manuscript does not involve such issue, please state “Not applicable.” in this section.

2.3.3.7 Consent for Publication

Manuscripts containing individual details, images or videos, must obtain consent for publication from that person, or in the case of children, their parents or legal guardians. If the person has died, consent for publication must be obtained from the next of kin of the participant. Manuscripts must include a statement that a written informed consent for publication was obtained. Authors do not have to submit such content accompanying the manuscript. However, these documents must be available if requested. If the manuscript does not involve this issue, state “Not applicable.” in this section.

2.3.3.8 Copyright

Authors retain copyright of their works through a Creative Commons Attribution 4.0 International License that clearly states how readers can copy, distribute, and use their attributed research, free of charge. A declaration “© The Author(s) 2015.” will be added to each article. Authors are required to sign License to Publish before formal publication.

2.3.3.9 References

References should be numbered in order of appearance at the end of manuscripts. In the text, reference numbers should be placed in square brackets and the corresponding references are cited thereafter. Only the first five authors’ names are required to be listed in the references, other authors’ names should be omitted and replaced with “et al.”. Abbreviations of the journals should be provided on the basis of Index Medicus. Information from manuscripts accepted but not published should be cited in the text as “Unpublished material” with written permission from the source.

References should be described as follows, depending on the types of works:

Types	Examples
Journal articles by individual authors	Weaver DL, Ashikaga T, Krag DN, Skelly JM, Anderson SJ, et al. Effect of occult metastases on survival in node-negative breast cancer. <i>N Engl J Med</i> 2011;364:412-21. [PMID: 21247310 DOI: 10.1056/NEJMoa1008108]
Organization as author	Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. <i>Hypertension</i> 2002;40:679-86. [PMID: 12411462]

Both personal authors and organization as author	Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. <i>J Urol</i> 2003;169:2257-61. [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]
Journal articles not in English	Zhang X, Xiong H, Ji TY, Zhang YH, Wang Y. Case report of anti-N-methyl-D-aspartate receptor encephalitis in child. <i>J Appl Clin Pediatr</i> 2012;27:1903-7. (in Chinese)
Journal articles ahead of print	Odibo AO. Falling stillbirth and neonatal mortality rates in twin gestation: not a reason for complacency. <i>BJOG</i> 2018; Epub ahead of print [PMID: 30461178 DOI: 10.1111/1471-0528.15541]
Books	Sherlock S, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub; 1993. pp. 258-96.
Book chapters	Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. pp. 93-113.
Online resource	FDA News Release. FDA approval brings first gene therapy to the United States. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm . [Last accessed on 30 Oct 2017]
Conference proceedings	Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.
Conference paper	Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. pp. 182-91.
Unpublished material	Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. <i>Proc Natl Acad Sci U S A</i> . Forthcoming 2002.

For other types of references, please refer to U.S. National Library of Medicine.

The journal also recommends that authors prepare references with a bibliography software package, such as EndNote to avoid typing mistakes and duplicated references.

2.3.3.10 Supplementary Materials

Additional data and information can be uploaded as Supplementary Materials to accompany the manuscripts. The supplementary materials will also be available to the referees as part of the peer-review process. Any file format is acceptable, such as data sheet (word, excel, csv, cdx, fasta, pdf or zip files), presentation (powerpoint, pdf or zip files), image (cdx, eps, jpeg, pdf, png or tiff), table (word, excel, csv or pdf), audio (mp3, wav or wma) or video (avi, divx, flv, mov, mp4, mpeg, mpg or wmv). All information should be clearly presented. Supplementary materials should be cited in the main text in numeric order (e.g., Supplementary Figure 1, Supplementary Figure 2, Supplementary Table 1, Supplementary Table 2, etc.). The style of supplementary figures or tables complies with the same requirements on figures or tables in main text. Videos and audios should be prepared in English, and limited to a size of 500 MB or a duration of 3 minutes.

2.4 Manuscript Format

2.4.1 File Format

Manuscript files can be in DOC and DOCX formats and should not be locked or protected.

2.4.2 Length

There are no restrictions on paper length, number of figures, or number of supporting documents. Authors are encouraged to present and discuss their findings concisely.

2.4.3 Language

Manuscripts must be written in English.

2.4.4 Multimedia Files

The journal supports manuscripts with multimedia files. The requirements are listed as follows:

- Video or audio files are only acceptable in English. The presentation and introduction should be easy to understand. The frames should be clear, and the speech speed should be moderate.
- A brief overview of the video or audio files should be given in the manuscript text.
- The video or audio files should be limited to a duration of 3 min and a size of up to 500 MB.
- Please use professional software to produce high-quality video files, to facilitate acceptance and publication along with the submitted article. Upload the videos in mp4, wmv, or rm format (preferably mp4) and audio files in mp3 or wav format.

2.4.5 Figures

- Figures should be cited in numeric order (e.g., Figure 1, Figure 2) and placed after the paragraph where it is first cited;
- Figures can be submitted in format of tiff, psd, AI or jpeg, with resolution of 300-600 dpi;
- Figure caption is placed under the Figure;

- Diagrams with describing words (including, flow chart, coordinate diagram, bar chart, line chart, and scatter diagram, *etc.*) should be editable in word, excel or powerpoint format. Non-English information should be avoided;
- Labels, numbers, letters, arrows, and symbols in figure should be clear, of uniform size, and contrast with the background;
- Symbols, arrows, numbers, or letters used to identify parts of the illustrations must be identified and explained in the legend;
- Internal scale (magnification) should be explained and the staining method in photomicrographs should be identified;
- All non-standard abbreviations should be explained in the legend;
- Permission for use of copyrighted materials from other sources, including re-published, adapted, modified, or partial figures and images from the internet, must be obtained. It is authors' responsibility to acquire the licenses, to follow any citation instruction requested by third-party rights holders, and cover any supplementary charges.

2.4.6 Tables

- Tables should be cited in numeric order and placed after the paragraph where it is first cited;
- The table caption should be placed above the table and labeled sequentially (e.g., Table 1, Table 2);
- Tables should be provided in editable form like DOC or DOCX format (picture is not allowed);
- Abbreviations and symbols used in table should be explained in footnote;
- Explanatory matter should also be placed in footnotes;
- Permission for use of copyrighted materials from other sources, including re-published, adapted, modified, or partial tables from the internet, must be obtained. It is authors' responsibility to acquire the licenses, to follow any citation instruction requested by third-party rights holders, and cover any supplementary charges.

2.4.7 Abbreviations

Abbreviations should be defined upon first appearance in the abstract, main text, and in figure or table captions and used consistently thereafter. Non-standard abbreviations are not allowed unless they appear at least three times in the text. Commonly-used abbreviations, such as DNA, RNA, ATP, *etc.*, can be used directly without definition. Abbreviations in titles and keywords should be avoided, except for the ones which are widely used.

2.4.8 Italics

General italic words like *vs.*, *et al.*, *etc.*, *in vivo*, *in vitro*; *t* test, *F* test, *U* test; related coefficient as *r*, sample number as *n*, and probability as *P*; names of genes; names of bacteria and biology species in Latin.

2.4.9 Units

SI Units should be used. Imperial, US customary and other units should be converted to SI units whenever possible. There is a space between the number and the unit (i.e., 23 mL). Hour, minute, second should be written as h, min, s.

2.4.10 Numbers

Numbers appearing at the beginning of sentences should be expressed in English. When there are two or more numbers in a paragraph, they should be expressed as Arabic numerals; when there is only one number in a paragraph, number < 10 should be expressed in English and number > 10 should be expressed as Arabic numerals. 12345678 should be written as 12,345,678.

2.4.11 Equations

Equations should be editable and not appear in a picture format. Authors are advised to use either the Microsoft Equation Editor or the MathType for display and inline equations.

2.5 Submission Link

Submit an article via <https://oaemesas.com/par/>.



OAE Publishing Inc.

www.oaepublish.com

**Plastic and Aesthetic Research
(PAR)**

Los Angeles Office

245 E Main Street ste122, Alhambra,
CA 91801, USA

Tel: +1 323 9987086

E-mail: par_editor001@parjournal.net

Website: www.parjournal.net

