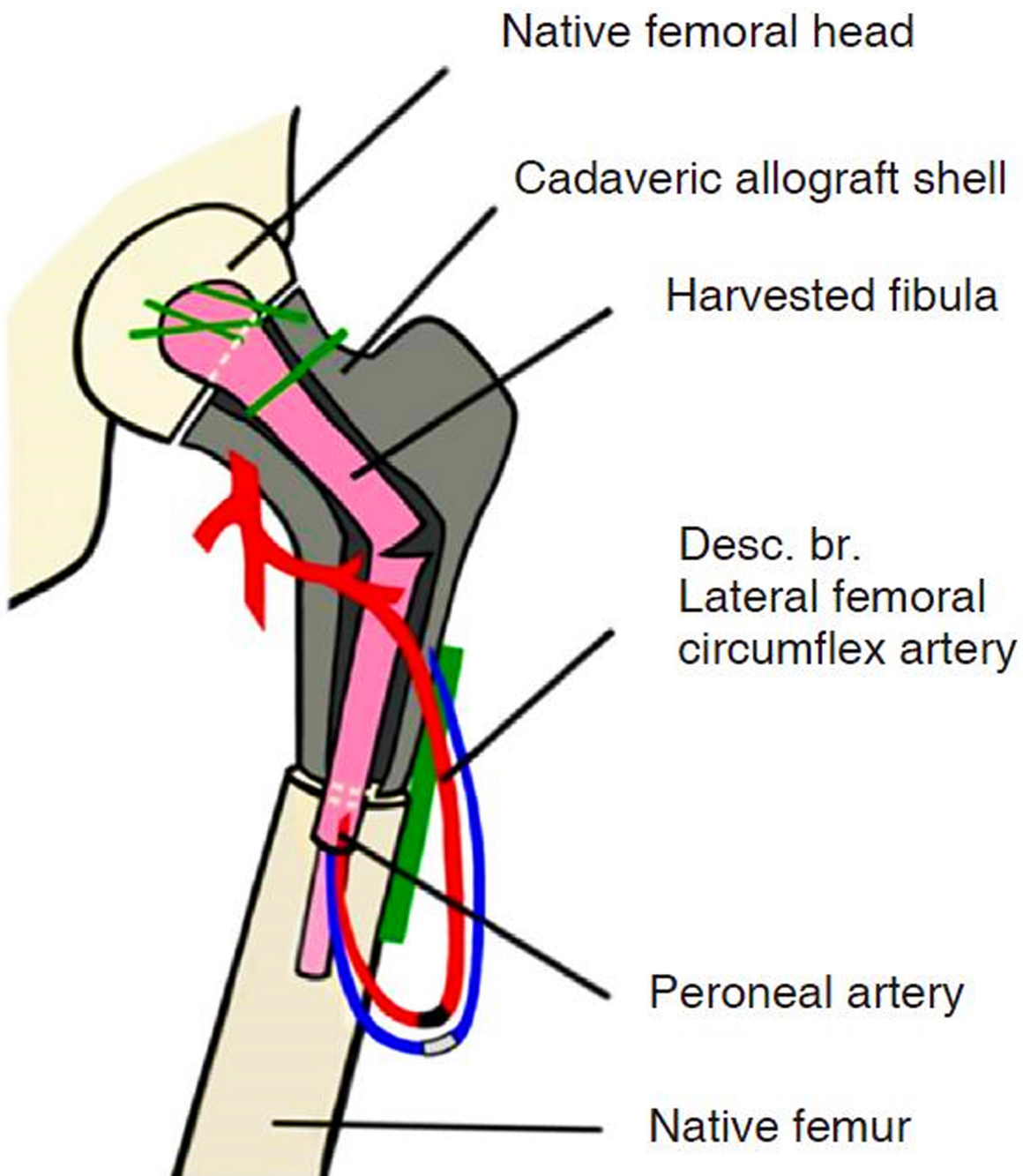


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Thermal distribution and response in Q-switched ruby laser treatment for oculodermal melanosis (Nevus of Ota)

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Dr. Cheng-Jen Chang is currently the vice Superintendent of Taipei Medical University Hospital, Taipei, China. He is also the Editor of *Laser Therapy and Aesthetic Surgery Journal*. Dr. Chang is an outstanding member of Fellow of American College of Surgeon (FACS) as well as Fellow of International College of Surgeon (FICS) and is honored to be the Fellow of American Society of Laser Medicine and Surgery (ASLMS). In addition, Dr. Chang has worked on publication review for the *Monthly Journal Archives of Dermatology* and for the *US Surgical Dermatology Magazine*.

ABSTRACT

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Aim: A clinically useful treatment laser must generate stable and precise energy of low diffusivity. This study assessed the photothermal response of a Q-switched ruby laser (QSRL) in the treatment of oculodermal melanosis (Nevus of Ota). **Methods:** A two-year retrospective review of 40 patients with oculodermal melanosis treated with a QSRL ($\lambda = 694$ nm, pulse duration = 25 ns, 3 mm spot size, energy density 6-10 J/cm²) was performed. Demographics included an age range of 18-54 years (mean 28) and a gender distribution of 25 females and 15 males. The values recorded from real-time infrared thermal imaging of the lasered skin were inserted into standard thermal wave equations. This permitted analysis of the resultant temperature distributions related to the energy change. **Results:** Skin temperature was unchanged during the initial heating stage. This was followed by a very rapid temperature rise. A thermal burn injury manifested by dermal-epidermal disruption, resulted when the energy density of the QSRL exceeded 8 J/cm² (> 44 °C). **Conclusion:** The use of infrared thermal imaging with a standard thermal wave equation allows prediction of skin temperature distribution when QSRL is used for the treatment of oculodermal melanosis. With the use of appropriate settings, complications may be minimized.



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INTRODUCTION

Treatment lasers generate a high influx of energy over a short period of time. As such, the energy generated must be of high stability and precision.^[1-3] Laser techniques have been successfully and broadly used in skin surgery. However, the various chromophores within the skin react differently, according to the absorption and scattering of the individual wavelengths of the lasers used. As such, lasers of different wavelengths can be used to treat various pathological skin conditions.

A nevus fusco-caeruleus ophthalmomaxillaris (oculodermal melanosis or Nevus of Ota) is a syndrome consisting of blue-black or gray-brown patchy pigmentation. It may be either unilateral or bilateral, and most commonly occurs in the trigeminal nerve dermatome. The lesions are present at birth in approximately 60% of cases and occur most commonly in patients that are of Asian descent or dark-skinned individuals.^[1] Histologically, the melanin pigment is seen contained within the dendritic dermal melanocytes, similar to that in Mongolian spots. Macular blue staining of the sclera on the affected side is seen frequently. When this occurs, melanocytic infiltration of the corneal, conjunctive, and intraocular structures may be observed.^[2-5] The effects of oculodermal melanosis transcend cosmesis as it may be associated with potentially devastating psychological complications. Personality development may be affected due to the adverse societal and cultural reactions to a "marked person".

Numerous treatment modalities have been described for oculodermal melanosis.^[6-9] The laser systems include the Argon (488 nm and 514 nm) and Q-switched ruby lasers (QSRL) (694 nm) [Figures 1 and 2].^[4,5,10-14] The Q-switched alexandrite laser (QSAlexL) (755 nm) and the Q-switched Neodymium:Yttrium-Aluminum-Garnet laser (QS Nd:YAGL) (1,064 nm) have taken preference for clinical treatment of benign epidermal pigmented lesions of the skin, such as oculodermal melanosis.^[15,16] However, if improper energy density is used, complications such as hypertrophic scarring and skin dyspigmentation may arise.^[12,13,17-21]

Selective photothermolysis is effective when the target tissue chromophore matches the wavelength of the laser used, with minimal collateral damage.^[22] Because the laser energy is packed into a very short delivery time period, the target tissues exhibit photothermal phenomena by absorbing the high energy of a laser beam nearly instantaneously, where surrounding tissue is narrowly affected. Therefore, the energy is capable of damaging target tissues and not injuring

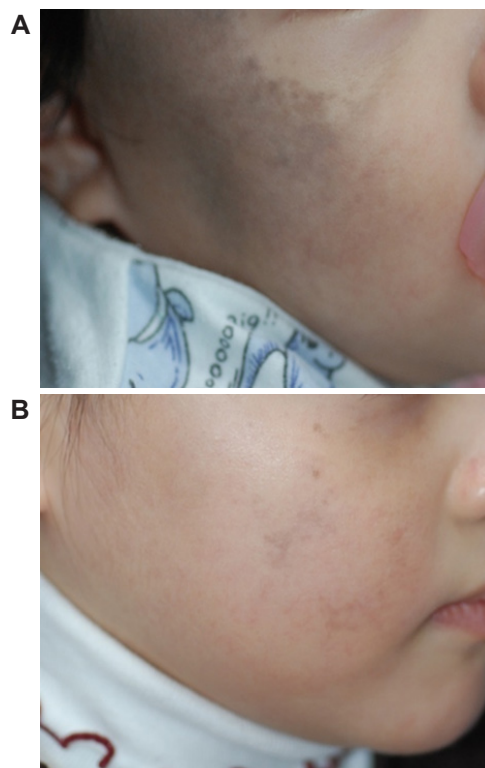


Figure 1: A 4-year-old Asian girl with Nevus of Ota of the right cheek: (A) prior to laser therapy; and (B) 2 years after two treatments with Q-switched ruby laser (694 nm) using an energy density of 8-9 J/cm². Result was evaluated as an excellent cleaning and fading response

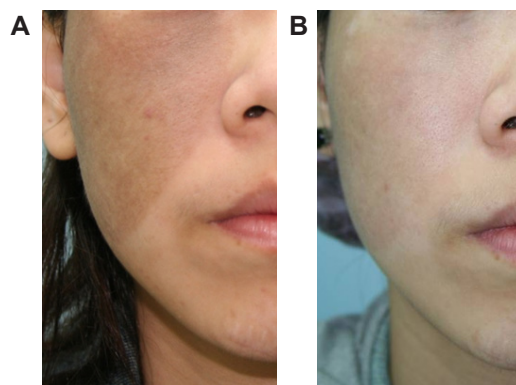


Figure 2: A 19-year-old Asian female with Nevus of Ota of the right cheek: (A) prior to laser therapy; and (B) 2 years after four treatments with Q-switched ruby laser (694 nm) using an energy density of 9-10 J/cm². Result was evaluated as an excellent cleaning and fading response

the surrounding skin -- a concept closely related to the knowledge of heat transfer. On the other hand, the photothermal phenomenon is due to the explosion of the pigment chromophore. This is because the energy that the pigment has absorbed has no time to dissipate and thus ruptures. It is the dissipation of heat energy that causes surrounding tissue damage. Such an understanding of the temperature distribution on the skin surface will contribute to effective laser surgery

and will result in the prediction of skin temperature distribution and the study of skin burn injury -- important issues in laser treatment.^[23] However, more information on the thermal response and temperature distribution during laser treatment is needed to avoid permanent complications.

Differential scanning calorimeters have been used to evaluate the surface heat flux, temperature, and heat absorption rate at the skin surface. An infrared thermal imaging device was used in this study to measure skin temperature in laser skin surgery. The main objectives of this study focus on the analysis and evaluation of skin temperature during laser application. This will in turn, assist medical practitioners in assessing and treating the reaction of skin to laser energy and avoiding complications.^[24] A heat transfer analysis using the thermal wave equation helps us to learn the importance of the thermal wave theory of photothermal effects. Using an infrared thermal image instrument and with the thermal changes obtained using a thermal wave equation, the reliability of the analytic solution will be ensured. Further discussion of the QSRL used in cutaneous laser surgery is presented to provide knowledge of the temperature changes of patients' skin during laser treatment. With this, more accurate predictions of skin surface temperature can be achieved which could serve as treatment references for researchers and clinicians.

METHODS

From January 2010 to June 2012, 40 patients with oculodermal melanosis treated with the 694 nm QSRL (Derma-Laser, Hopkinton, MA, USA) at the settings of 25 ns pulse duration, energy densities of 6-10 J/cm², with a spot size of 3 mm were observed in this retrospective study. The age range was 18 to 54 years, with a mean of 28 years. There were 25 females and 15 males. Based on pretreatment photographs, each oculodermal melanosis was assigned a severity grade using the Tanino classification system.^[25] Patients were grouped into four different clinical types: (1) mild; (2) moderate; (3) intensive; and (4) bilateral. Observation was analyzed based on the following variables: age, gender, severity, number of treatment(s), duration of treatment(s), and improvement following laser therapy. The study protocol was approved by the Institutional Review Board at Chang Gung Memorial Hospital. Inclusion criteria for the study was: (1) oculodermal melanosis suitable for comparison testing; (2) oculodermal melanosis greater than 20 cm²; and (3) apparent good health as documented by medical history. The following exclusion criteria was determined as: (1) inability to commit to a three month follow-up period; (2) pregnancy; (3) history

of photodermatoses or skin cancer; (4) concurrent use of known photosensitizing drugs; and (5) any therapy within the previous 2 months to the proposed oculodermal melanosis test sites.

For the infrared thermal imaging study, 5 QSRL test sites were prospectively identified on each patient for treatment assignment according to the following parameters: 6, 7, 8, 9, and 10 J/cm². Laser energy was delivered to the skin through an optical fiber and lens that focused the beam onto a 3 mm spot on the lesion. The untreated area was assigned as a control. Sites were assigned to one-treatment regimens by randomization. Every effort was made to place the test sites on optically uniform areas of the lesion to ensure that clinically relevant oculodermal melanosis characteristics and geometry (i.e. epidermal melanin concentration and depth) did not substantially vary between each of the test sites on an individual patient basis. Photographs were taken of the test sites after treatment regimen assignment and at follow-up visits.

The imaging and changes of skin temperature were measured in real time using an infrared thermal image instrument (ThermaCAM™ S60, FLIR System, Danderyd, Sweden). The results of temperature distributions related to the energy variance were analyzed. Data of the skin surface temperatures measured by the infrared thermal image instrument was put into the analytic solutions of the thermal wave equation with comparisons made between the results.^[26] The clearing and fading result of pigmentation was assessed by a DermoSpectrometer (Cortex Tech., Hadsund, Denmark) to calculate the melanin-index at follow-up visits for each of the test site treatment regimens.^[27-29]

The device emits light from diode sources at two defined wavelengths. The amount of light backscattered from the skin is then used to determine the indices for hemoglobin/melanin. Therefore, care was taken to make each measure with the device in contact with the skin, but without the application of pressure to the test site. The melanin index for pre-treated lesions, along with those of treated oculodermal melanosis, was also measured. The patients were observed after treatment(s), and those calculations were used to display a better correlation with how the oculodermal melanosis differed from the initial pre-treated lesion calculations. Differences between the responses of each site before and after QSRL treatment were then determined and analyzed. Patients were also closely monitored for any adverse effects. Each of the test sites was examined for unfavourable wound characteristics such as blistering, scabbing, erosion and scarring. The primary measure of efficacy was

Table 1: Skin surface temperatures for Q-switched ruby laser treatment for different energy density

Energy density (J/cm ²)	Skin surface temperature (°C)†	
	IR*	Thermal wave equation
6	40.8 ± 0.3	41.2 ± 0.2
7	41.9 ± 0.3	42.5 ± 0.4
8	44.1 ± 0.4	44.3 ± 0.3
9	46.9 ± 0.2	47.6 ± 0.2
10	50.8 ± 0.4	51.5 ± 0.4

†: baseline skin surface temperature 32.4 ± 0.2 °C ; IR*: temperatures measured by infrared thermal image instrument. $P = 2 \times 10^{-11}$

Table 2: Mean melanin index of clearing and fading response of Nevus of Ota after Q-switched ruby laser treatment for different energy density

Energy density (J/cm ²)	1 month	3 months	6 months
6	61.81 ± 1.42	55.77 ± 1.76	54.57 ± 1.75
7	55.13 ± 1.57	54.82 ± 1.63	53.68 ± 1.47
8	52.23 ± 1.08	47.85 ± 1.39	44.76 ± 1.11
9	51.46 ± 1.28	46.69 ± 1.07	40.47 ± 1.46
10	49.62 ± 1.54	45.78 ± 1.74	40.19 ± 1.53

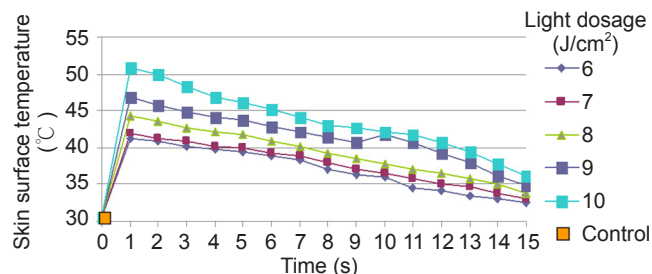
Mean-index of normal skin = 32.21 ± 2.75 ; mean-index of Nevus of Ota before Q-switched ruby laser treatment = 63.15 ± 1.44

quantitative assessment. Differences between the temperatures measured and clearing/depigmentation response indices for each test site were determined.

RESULTS

A one-dimensional equation was used with fixed surface illumination time and variable laser energy densities of 6, 7, 8, 9, and 10 J/cm². The initial body temperature was set at 37 °C [30]. An infrared thermal image instrument was used to measure the changes in surface skin temperature during QSRL treatment at the different energy densities. This showed the relationship between the energy densities and temperature changes of the QSRL illumination of the skin surface [Table 1]. Temperatures in the treated areas were observed to have risen significantly in response to laser exposure when the energy density of QSRL was higher than 8 J/cm² and thermal burn injury resulted (the temperature was higher than 44 °C). In other words, the energy density should be less than 8 J/cm² if the QSRL is to treat skin pathological changes. Using the Irving-Fisher statistical test, there were statistically significant differences ($P = 2 \times 10^{-11}$). These results indicate that the severity of the involved area was not directly related to the final outcome but to the energy density of treatments. Some patients needed more number of treatment to prevent complications and sustain excellent results.

An infrared thermal image instrument was used to measure the changes in superficial skin temperature during QSRL treatment. The baseline skin surface temperature was 32.4 ± 0.2 °C. Over the time span

**Figure 3: Temperature determination of superficial skin with infrared thermal image instrument for the Q-switched ruby laser treatment of the Nevus of Ota patients in different energy density**

of 15 s, the changes in temperature were recorded to assume proper care following treatment [Figure 3]. Based on what was observed in superficial skin regions, temperatures in those treated areas rose sharply within 5 s when there was a “T-jump” in response to laser exposure, and then immediately began to taper out and decrease gradually afterwards. The thermal wave equation showed that the baseline skin surface temperature (32.4 ± 0.2 °C) and the tissue temperature inside the body (37 °C) were undisturbed at the initial stage of heating and then took an instantaneous jump, which can be viewed as a wave front resulting from a step change in temperature at the skin surface [Table 1].^[31]

The infrared images and temperature plots of normal skin and oculodermal melanosis-affected skin represent a patient's reaction time post-treatment, with a QSRL energy density of 9 J/cm² and the resulting temperature [Figures 4 and 5]. Other images and graphs were also taken of patients to display the different reaction times of superficial skin after laser treatment, in which temperature averages are clear over the course of 10, 20, and 30 s. Injury due to laser illumination can be minimized while using optimum dosage to treat Nevus of Ota. A dermospectrometer was used to quantify the improvement in pigmentation at each of the follow-up visits at the following intervals of 1, 3, 6, and 12 months [Table 2]. Although thermal burns did occur when the energy density of QSRL was higher than 8 J/cm², permanent scarring was not observed on any of the treated sites. Hyperpigmentation was noted in 5% ($n = 2$) and delayed hypopigmentation was observed in 2.5% ($n = 1$) of patients but was transient and resolved spontaneously without medical intervention in all patients.

DISCUSSION

Cutaneous laser surgery can be modeled on the short-term heat transfer behavior of biological tissues, particularly in hyperpigmented lesions such as oculodermal melanosis. When the surface of biological tissues is heated causing a temperature change, a series of complex changes in its biophysics and

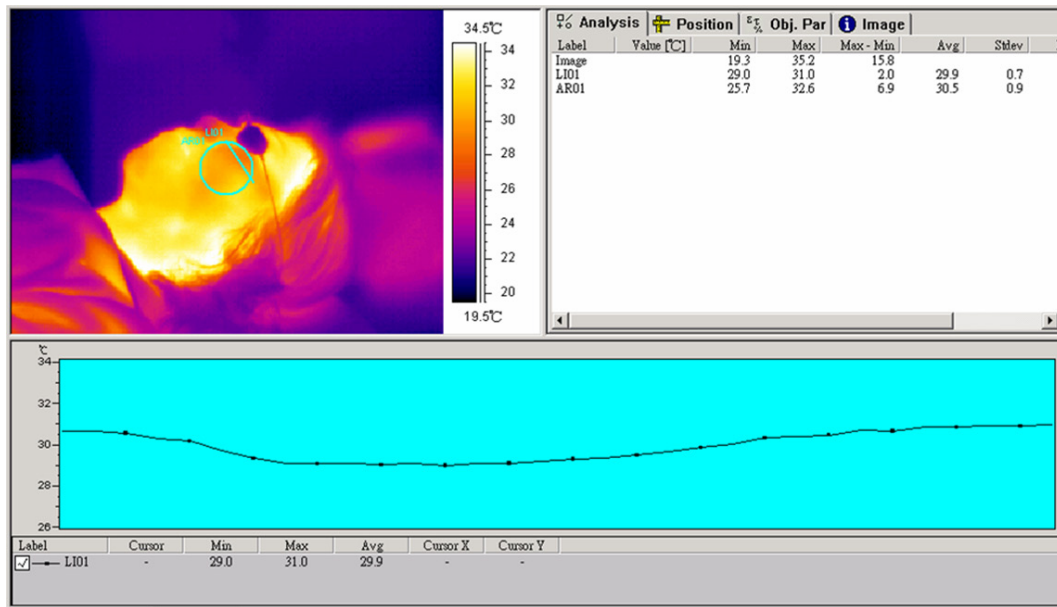


Figure 4: Plot of a patient's facial skin temperature before Q-switched ruby laser treatment for Nevus of Ota with infrared thermal image instrument

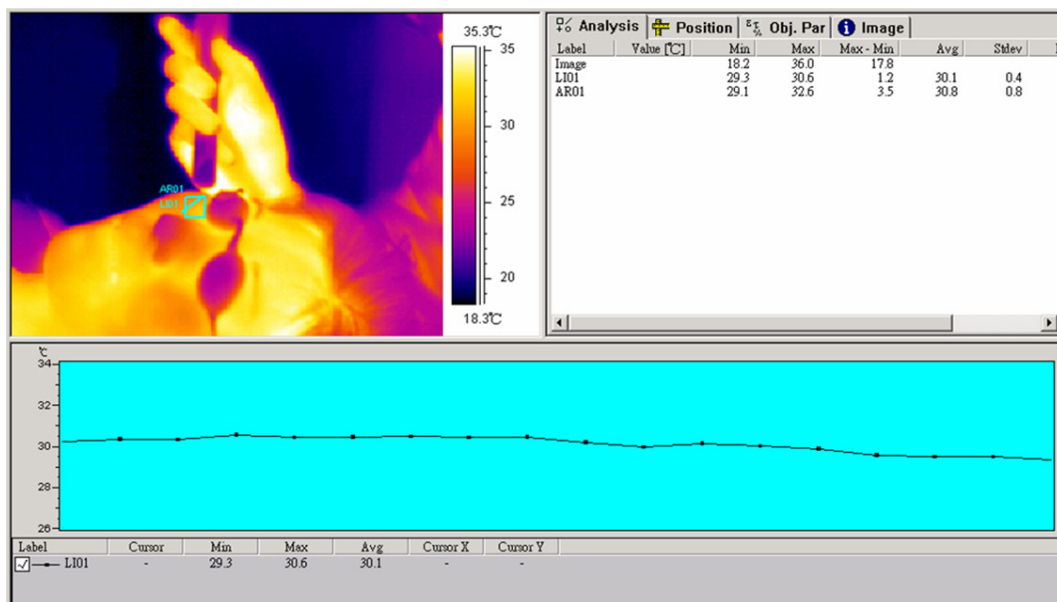


Figure 5: Plot of a patient's facial skin temperature 15 s after Q-switched ruby laser treatment with an energy density of 9 J/cm²

biochemistry occurs.^[30] As such, an perfect heat transfer analysis model is impossible obtain. It is common to use the Pennes equation to approximate the prediction of tissue temperature distribution in bioheat transfer studies. On the other hand, some researchers have discovered that the behavior of waves has to be taken into account in bioheat transfer studies when using fast heating systems.^[31,32] This has led to the proposal of the thermal wave theory and thermal wave equation. The thermal wave equation can be expressed as:

$$\partial^2 T / \partial x^2 - (\rho C \tau / K) (\partial^2 T / \partial t^2) - [(\rho C + \tau W_b C_b) / K] (\partial T / \partial t) +$$

$$W_b C_b (T_b - T) / K + Q / K = 0,$$

$$Q = Q_m + Q_r + \tau (\partial Q_m / \partial t + \partial Q_r / \partial t).$$

Here, K is presumed as a constant; Q represents the changes of tissues in terms of the heat source (including the metabolic rate of tissue); Q_m is the thermal energy transformed from chemical energy caused by partial metabolism; $[W_b C_b (T_b - T)]$ is the blood flow (the thermal energy transmitted from in/out controlled volume blood); Q_r shows the volumetric heating; K [W/(m²·k)] is the thermal conductivity; W_b [kg/(m³·s)] is the blood perfusion rate; C_b and C [J/(kg·k)] are the

specific blood and tissue, respectively; T_b and T ($^{\circ}\text{C}$) are temperatures of blood and tissue, respectively; Q_m (W/m^3) is the metabolic rate of tissue; Q_r (W/m^3) is the volumetric heating rate; and τ (kg/m^3) is the density of tissue.^[33]

Because the thermal wave equation is hyperbolic, it is common to use a numerical analysis instead of an analytic solution. Furthermore, due to the large temperature gradient observed in a thermal energy input spot on the skin surface when the laser is heating the tissue for a short time, we can neglect the temperature diffusion on the skin surface and focus primarily on heat transfer, which occurs in the same direction as the thermal energy input. The equation can be simplified as a one-dimensional equation for applying to the definite difference model to find the solution to the thermal wave equation.^[34-36]

At a high energy and a high heat flux of laser illumination, the heat convection effect is not apparent, and can be disregarded. The temperature of the surrounding environment was also not a significant factor. However, temperature decreases when the thickness of tissue increases. As human skin tissue contains three layers - epidermis (thickness is 0.00008 m), dermis (thickness is 0.002 m) and hypodermis (thickness is 0.01 m) - the thickness of human tissue would be 0.01208 m. When including laser illumination on the skin surface, the difference between Boundary Conditions and Initial Conditions should be considered. During laser application, it is necessary to consider burn injury when the skin temperature is 44°C .^[37] Second or third-degree burns on the skin will result if temperature increases and it is therefore necessary to carefully control skin surface temperature. Because of the close relationship between the temperature of the skin surface and the energy density of laser illumination, it is important to avoid burn injury when using lasers of different energy densities within certain times and areas.

Since the characteristic time of tissue (τ) has significant influence on temperature prediction, the result derived using the thermal wave equation with the thermal wave effect can be more accurate. For biological tissues, τ is defined as the characteristic time needed for accumulating the thermal energy required for propagative transfer to the nearest element within nonhomogeneous inner structures. That is, it is the time needed for the temperature of objects to drop by half from the warmest temperature after being illuminated with a laser.

For general homogeneous materials, τ is defined as the thermal relaxation time. The effect of the thermal

relaxation time (τ) should be taken into account when applying the thermal wave equation. This factor τ is neglected in the Pennes equation. Usually the thermal relaxation time τ for general homogeneous materials is very low, i.e. between 10^{-8} - 10^{-14} s.^[31] Thermal waves showed no clear effect during heat transfer except when there was a marked change in the heat flux rate. τ in biological systems has been predicted to be 20-30 s.^[31,32]

In 1995, researchers like Mitra *et al.*,^[37] conducted experiments on processed meat and obtained the following result: τ is 16 s. Currently most studies of biological tissues use a τ of 20 s.^[34,35] In this study τ is also set at 20 s. This concept is very important for laser surgeons to choose the correct τ for the treatment of hyperpigmented lesions such as Nevus of Ota.

Since laser illumination requires using an extremely short amount of time and its heat flux being tremendously high, the thermal wave effect is very clear during heat transfer, and therefore, our study conducted an analysis with the thermal wave equation to be able to observe and determines skin heat transfer. Currently the most common lasers used in cutaneous surgery for Nevus of Ota are the Q-switched ruby lasers. The wavelength of the QSRL is 694 nm, and the pulse duration is 25 ns. Regarding the input of laser energy, the use of a fixed illumination time on a surface as a boundary condition must also be considered. In order to obtain attainable results, the boundary condition was divided in terms of the energy density of input energy. As to the analytic solution, the separation variable method and superposition principle theory was used to obtain results. This made the discussion of skin heat transfer easier and more precise.

With an ambient skin temperature of 30°C and to ensure that the epidermal temperature does not exceed 70°C after pulsed laser exposure, the highest permissible "T-jump" (ΔT_{LASER}) is 40°C . If a preliminary sub-therapeutic diagnostic laser pulse, D_0 , produces a T-jump (because incident energy density is directly proportional to ΔT_{LASER}) then the threshold for epidermal damage (D_E) is $D_E = 40 D_0 / \Delta T_{\text{LASER}}$.

Consider a simple example to illustrate the principle in a patient with a normal skin surface temperature of 30°C : one joule of laser energy delivered to the skin produces a T-jump of 8°C . Therefore, in order to keep the T-jump after laser illumination at less than 40°C , such that the epidermal temperature does not exceed 70°C , the boundary condition should be divided in terms of the energy density of input energy. As to the analytic solution, the separation variable method and superposition principle theory can be used to obtain

results. This will make the delivery of skin heat transfer easier and more precise.

In our study, real-time monitoring with photothermal images and the prediction of temperature was reliable when using the thermal wave equation. We were able to clearly observe how the temperature distribution of heat transfer and the features of the thermal wave phenomenon were applicable in laser treatment. Our study also showed different predictions of QSRL illumination for different energy density. Results showed that the effective energy density of lasers should be lower than 8 J/cm² based on the thermal wave equation if the QSRL is applied to the treatment of skin pathological changes. This result is helpful for doctors in determining the optimum laser energy density while simultaneously minimizing damage to surrounding tissue. Nevertheless, when addressing Nevus of Ota patients with definitive treatment, exact thermal equations, proper procedural analysis of each patient and careful consideration of age, skin type, and area in-line for treatment all must be administered for a successful clinical application.

In conclusion, laser illumination requires an extremely short time and its heat flux is extremely high in cutaneous laser surgery. For prevention of complications, it is necessary to take the thermal wave effect into account. Real-time photothermal imaging and prediction of temperature response on the lesion site derived from this study is helpful for determining the energy density for laser treatment of Nevus of Ota patients. The effective energy density of lasers should be lower than 8 J/cm² to avoid complications. This study can serve as a precedent for increased and improved safety of laser surgery patients and lay groundwork for research of other laser treatments.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients gave informed consent.

Ethics approval

The study was approved by the Institutional Review

Board at Chang Gung Memorial Hospital.

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Case Report

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In vivo degradation of poly L-lactic D-lactic acid and tri-methylene carbonate sheets in orbital reconstruction

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ABSTRACT

This study was conducted to evaluate changes in the composition of a poly-L-lactic D-lactic acid and trimethylene carbonate (PLDLA-TMC) sheet after insertion into the human body. A 35-year-old woman had an orbital fracture that was reconstructed using a PLDLA-TMC sheet. During iliac bone grafting for enophthalmos 190 days after the insertion, the sheet was removed and analyzed using gel permeation chromatography and Fourier transform infrared spectroscopy. The weight average molecular weight decreased (from 151,000 Da to 10,000 Da), as did the number average molecular weight (from 15,600 Da to 255 Da). An amide functional group peaks at 1,655.43 cm⁻¹ (1,670-1,640 cm⁻¹) and its stretch band at 1,541.26 cm⁻¹ (1,640-1,550 cm⁻¹) newly appeared due to serum or tissue fluid incorporation. PLDLA-TMC is expected to exhibit favorable degradation properties.

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orbit,
orbital fractures



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INTRODUCTION

Absorbable sheets are used to treat orbital fractures. CPS sheets [poly L-lactic D-lactic acid and trimethylene carbonate (PLDLA-TMC)] absorbable sheets (Inion Co., Tampere, Finland) are commonly used to treat trauma and in reconstructive procedures of the orbital cavity. *In vivo* degradation of several absorbable materials has been documented.^[1-4] However, the compositional changes (appearance of radicals, etc.) of PLDLA-TMC after insertion into the human body have not yet been described.

The aim of this paper was to assess compositional changes in a PLDLA-TMC sheet, synthesized by a ring-opening polymerization process, 190 days after insertion into a human body.

CASE REPORT

Patient history and sample

A 35-year-old female patient had a pan-facial fracture due to a car accident. Upon examination, she did not show diplopia or hypoesthesia. A computed tomography scan showed a blow-out fracture of the right medial wall and floor with herniation of soft tissues [Figure 1].

Through a subciliary incision, the orbital floor and medial wall were exposed and the herniated soft tissues were

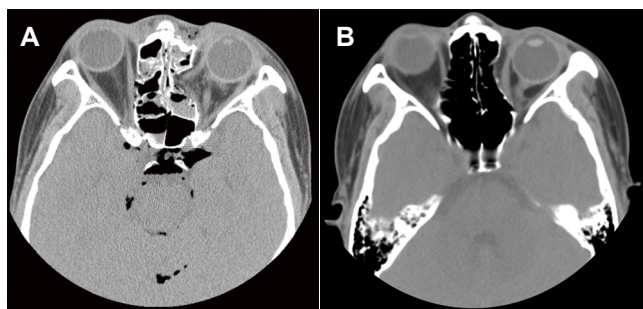


Figure 1: Axial computed tomography scans. (A) Fracture of the medial orbital wall and herniation of the soft tissue; (B) 190 days after CPS sheet insertion before secondary orbital floor reconstruction

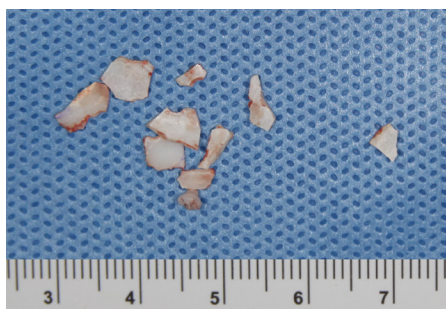


Figure 2: The removed fragile part of the sheet that had been inserted 190 days previously

reduced. The floor and medial wall were reconstructed with a trimmed (45 mm × 33 mm × 1.5 mm) CPS sheet made of PLDLA-TMC (Inion Co., Tampere, Finland) [Figure 2].

Exophthalmometry on postoperative day (POD) 9 revealed a 3-mm difference (right eye, 19 mm; left eye, 16 mm). The differences in exophthalmometry on POD 98 and POD 154 were 7 mm (right eye, 18 mm; left eye, 11 mm) and 8 mm (right eye, 19 mm; left eye, 11 mm), respectively. On POD 189 (1 day before the secondary operation), the difference was 5 mm (right eye, 18 mm; left eye, 13 mm).

Secondary reconstruction of the orbital floor was performed with an iliac bone graft 190 days after insertion. During the secondary operation, the fragile part of the CPS sheet that had been previously inserted was removed.

Analysis of molecular weight and components of the PLDLA-TMC sheet

The sample was analyzed using gel permeation chromatography (GPC) (Waters GPC system; Waters Co., Milford, MA, USA) to characterize changes in its molecular weight.

Fourier transform infrared spectroscopy (FT-IR) (JASCO FT-IR 4100; JASCO Co., Tokyo, Japan) was used to evaluate compositional changes that occurred due to being in the body.

The principles outlined in the Declaration of Helsinki were followed in this study.

Gel permeation chromatography

In the specimen from the operation, the weight average molecular weight (M_w) decreased from 151,000 Da to 10,000 Da, and the number average molecular weight (M_n) decreased from 15,600 Da to 255 Da. The polydispersity index (M_w/M_n) thus increased from 9.96 to 40.22 [Figure 3].

Fourier transform infrared spectroscopy

In the post-insertion spectrum, 1,655.43 cm^{-1} and 1,541.26 cm^{-1} peaks appeared, which are thought to be an amide peak (1,670–1,640 cm^{-1}) and its stretch bend (1,640–1,550 cm^{-1}), respectively [Figure 4].

DISCUSSION

Matsumura prepared poly(lactide-co-trimethylene carbonate) through the lipase-catalyzed ring-opening copolymerization of lactide and trimethylene carbonate, increasing the carbonate content from 0 to 100%.^[5]

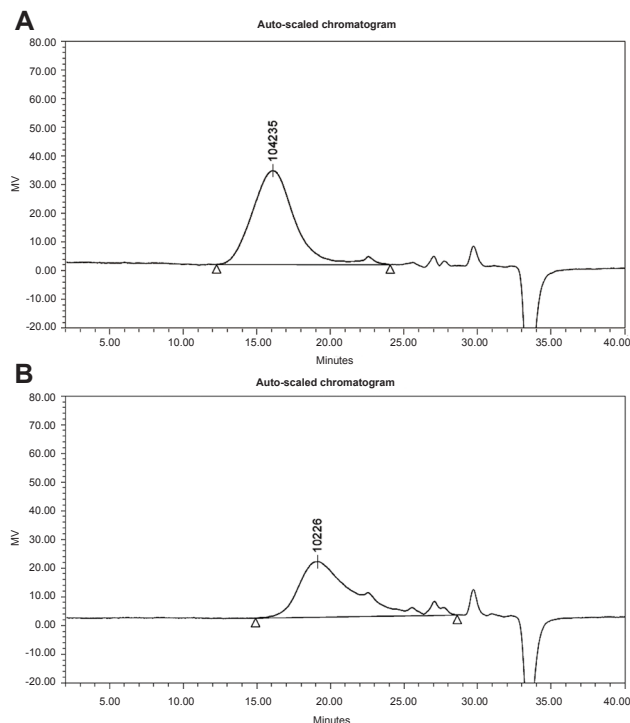


Figure 3: Gel permeation chromatograms. (A) Pre-insertion; (B) 190 days post-insertion

Yang *et al.*^[6] reported that hemolysis tests showed that all homopolymers and copolymers presented very low hemolytic ratios, indicating good hemolytic properties. Adhesion and activation of platelets were observed on the surface of polylactic acid, polycaprolactone (PCL), poly L-lactic acid (PLLA) and trimethylene carbonate (TMC) (PLLA-TMC), and poly-DL-lactide (PDLLA)-TMC films, while fewer platelets and less activation were found on poly(TMC). The most interesting results were obtained with PCL-TMC, which exhibited the lowest degree of activation, with few adhered platelets, in agreement with its outstanding anticoagulant properties.^[6]

Guo *et al.*^[7] in an experiment using 144 Wistar rats, stated that the molecular weight of PLLA decreased rapidly, from 72,000 to 68,000 kDa in the first 2 days and to 32,000 kDa 15 days later. Similar molecular weight decreases were obtained for PLLA-TMC and PDLLA-TMC copolymers, although PLLA-TMC appeared more resistant to hydrolytic degradation. Beyond 60 days, the molecular weight of PDLLA-TMC decreased below 10,000 kDa, in agreement with the rapid mass loss observed in this period.^[7] In our study, the weight average molecular weight (Mw) decreased from 151,000 to 10,000 Da.

Pêgo *et al.*^[8] in an *in vitro* study, reported that elastomeric (co)polymers of TMC and D,L-lactide

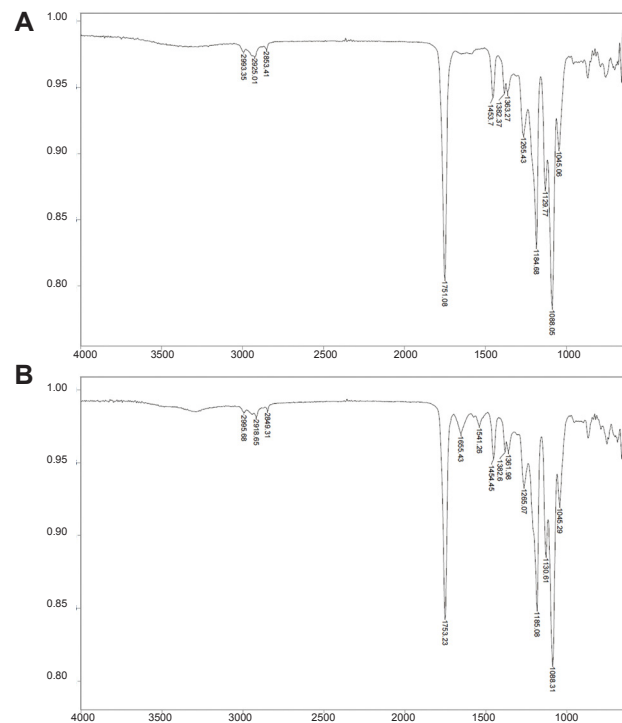


Figure 4: Fourier transform infrared spectra. (A) Pre-insertion; (B) 190 days post-insertion

(DLLA) scaffolds were dimensionally stable during incubation in phosphate-buffered saline at 37 °C. The number average molecular weight (Mn) of the polymer decreased gradually from 2.0×10^5 Da to 0.3×10^5 Da over a period of 4 months. Pêgo *et al.*^[8] added that the poly(TMC) specimens were extensively degraded after 3 weeks and, as confirmed by histology, totally resorbed in less than 1 year. He concluded that *in vivo*, poly(TMC) is degraded via surface erosion involving cellular-mediated processes. The degradation of the copolymers was slower than that of poly(TMC), taking place via autocatalyzed bulk hydrolysis, preferentially of ester bonds. The TMC-DLLA copolymer was degraded 20 times faster than the TMC-caprolactone copolymer. Significant mass loss was only observed for the TMC-DLLA copolymer, which underwent 96% mass loss in 1 year.^[9]

In our study, GPC was used to find that the Mw of PLDLA-TMC decreased from 151,000 Da to 10,000 Da 190 days after insertion. This suggests that that PLDLA-TMC has favorable degradation properties.

Originally, PDLLA-TMC did not have an amide peak ($1,670\text{--}1,640\text{ cm}^{-1}$) or its stretch bend ($1,640\text{--}1,550\text{ cm}^{-1}$). In our study, FT-IR of the post-insertion spectrum showed new $1,655.43\text{ cm}^{-1}$ and $1,541.26\text{ cm}^{-1}$ peaks, which are thought to be an amide peak ($1,670\text{--}1,640\text{ cm}^{-1}$) and its stretch bend ($1,640\text{--}1,550\text{ cm}^{-1}$), respectively.

Chapanian and Amsden^[10] investigated the potential of osmotic pressure-driven release of proteins from poly(TMC-co-DLLA) elastomers with varying amounts of DLLA, using bovine serum albumin (BSA) as a model protein. The BSA was co-lyophilized with either trehalose or trehalose combined with sodium chloride as osmotogens to produce particles with sufficient osmotic activity.

The reduced molecular weights in the post-insertion specimen suggest that PLDLA-TMC has favorable degradation properties. The newly appeared bands are thought to be an amide peak (1,670-1,640 cm^{-1}) and its stretch bend (1,640-1,550 cm^{-1}), resulting from serum or tissue fluid incorporation.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Obtained.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Five “Ds” of plastic surgery

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Although there are a variety of definitions that describe plastic surgery, confusion persists in the minds of both the lay public and doctors. A common lay misconception is that actual pieces of plastic are used to repair injured tissues or placed over defects to make them appear better. On the other hand, resident doctors from specialities such as ear-nose-throat and general surgery fail to appreciate the vast scope that plastic surgery specialty entails. In recognition of this, trainee plastic surgeons are often asked to briefly define our specialty in their final exams, so that subsequent misconceptions are minimized.

Plastic surgery is a specialised branch of surgery that is primarily concerned with deformities of the integument and underlying musculoskeletal system.^[1] It is a surgical specialty involving the restoration, reconstruction, or

alteration of the human body and includes cosmetic or aesthetic surgery, reconstructive surgery, craniofacial surgery, hand surgery, microsurgery, and the treatment of burns.^[2] The term “plastic” is derived from the Greek word *plasticos* that means “mouldable”.^[3]

From a practical perspective, it is imperative that every practising plastic surgeon has a clear reconstructive plan for every case that is salient and easily recalled. To this end, we have distilled this into five categories represented by the following five “Ds”:

1. Defect - Loss or breach in tissue continuity;
2. Deformity - Alteration in shape and contour;
3. Dysfunction - Abnormality and impairment of a bodily organ or system;
4. Disability - Impairment, limitation of activity and participation;



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5. Disfigurement - An aesthetically unacceptable surface abnormality that overlies normal contour.

Any plastic surgery condition can be placed into one of categories above and managed accordingly. This five “Ds” concept brings the key elements of the vast specialty of plastic surgery into focus. It is our hope that it will make it easier to understand the problems and their solutions more effectively.

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Patient consent

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Ethics approval

Not applicable.

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Portraits of two innovative plastic surgeons in the National Portrait Gallery

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It must at all times be kept in mind that the most important person is first, last, and all the time the patient.^[1] - Archibald McIndoe

As a medical doctor, when I visit a gallery or museum, I look for portraits of medical doctors. During my stay in London, I visited the National Portrait Gallery, where I happened to see the portraits of two famous plastic surgeons: Sir Harold Delf Gillies (1882-1960, [Figure 1](#)) and Sir Archibald Hector McIndoe (1900-1960, [Figure 2](#)). The name "Gillies" caught my eye because the approach named after him is one of the indirect approaches for the reduction of the zygomatic arch (Gillies: temporal; Keen: transoral; and Dingman: lateral brow). The name "McIndoe" was also familiar because of the "McIndoe operation" for reconstruction of the vagina in the congenital absence of the vagina, using an indwelling skin graft.^[2]

World War I (WWI, 1914-1918) was characterized by trench warfare, during which Combatant's head and neck were exposed to high-energy weapons, resulting in severe facial wounds.^[3]

Gillies was born in New Zealand and studied medicine at Cambridge University. When WWI began, he joined the Royal Army Medical Corps.

While working in France, Gillies met French-American dentist, Charles Valadier, and learned the basics of repairing jaw injuries, including how to do bone grafting. After his return to England, he worked at the Queen's Hospital, which was devoted to facial repairs. He developed many plastic surgery techniques. From 1917 to 1925, he performed more than 11,000 operations for 5,000 soldiers with facial injuries.^[4] His pre- and postoperative results were drawn by artist



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Figure 1: Sir Harold Delf Gillies (1882-1960), Plastic Surgeon



Figure 2: Sir Archibald Hector McIndoe (1900-1960), Plastic Surgeon

Henry Tonks with pastels, and by Daryl Lindsay with watercolors.

McIndoe was born in New Zealand and studied medicine at the University of Otago and moved to London at the age of thirty. When McIndoe arrived in United Kingdom, his cousin Gillies got McIndoe a temporary position at St Bartholomew's Hospital in London. McIndoe worked here for less than a year and obtained his British qualifications. Gillies put McIndoe forward for a lecturer position at the Hospital for Tropical Diseases. McIndoe was successful but he soon became bored of this position, so Gillies invited him to join his private practice. From 1931 to 1939, they performed hundreds of operations together and devised new techniques.

In World War II (1939-1945), the survival rates from the combat wounds increased due to the development of blood transfusion, endotracheal intubation, and rapid evacuation by aircraft.^[5] Severe burn cases appeared due to massive air strike from bombers. Thereafter, burn care significantly advanced during World War II.

Following the outbreak of World War II, McIndoe moved to the newly built Queen's Hospital and treated deep burn injuries and serious facial deformities, like the loss of eyelids.

At that time, the standard treatment for burns was coagulation with tannic acid, which is very painful. He observed different healing rates in extensively burned pilots who had come down on land and in the sea. From this, he discovered that immersion in saline promoted healing as well as improving survival rates, and thus began saline baths and early grafting instead of tannic acid. He recognized the importance of rehabilitation and social reintegration back into normal life.^[1] In fact, over eighty percent of his aircrew patients returned to duty.^[6]

On arriving home from the museum, I searched for the number of papers they wrote and their titles. Gillies and

McIndoe published 12 and 17 papers, respectively. Among them were 2 articles they co-authored.^[7,8]

Gillies wrote "A new principle in the surgical treatment of "congenital cleft palate" and its mechanical counterpart" (1921, cited 113 times)^[9] and "The design of direct pedicle flaps" (1932, cited 29 times),^[10] among others.

His technique for the treatment of cleft of hard and soft palate was based on a combined surgical and dental treatment. Soft palate was paired and lengthened surgically by separating the soft palate from the hard palate. A dental apparatus was applied on the hard palate, and skin graft was applied to the raw anterior edge of palate. After healing, Fry's apparatus was applied for stretching the soft palate.^[9]

McIndoe developed many new techniques, reflected in his publications which included "Total reconstruction of the burned face. The Bradshaw Lecture" (1958, cited 41 times),^[11] "Symposium: radiation necrosis" (1947, cited 32 times),^[12] "Operation for the cure of adult hypospadias" (1937, cited 23 times),^[13] "Surgical and dental treatment of fractures of the upper and lower jaws in war time" (1941, cited 15 times),^[14] "The burned hand" (1945, cited 12 times),^[15] and "Congenital absence of the vagina, treated by means of an indwelling skin-graft" (1938, cited 9 times).^[2]

His methods were very innovative and the first successful reconstruction for congenital absence of the vagina. A hollow vulcanite mold was used, which was completely closed at both ends, with the size and shape of a distended virgin vagina. A split thickness skin graft (9.5 inch long by 2.5 inch wide) was harvested from the inner thigh. An incision was made from a point half an inch posterior to the urethral meatus and carried vertically backwards to a point 3/4 inch in front of the anus. Blunt dissection was carried between the rectum and the bladder and a cavity was made for the mold. The mold was covered with the

Table 1: Brief summary of Dr. Gillies and Dr. McIndoe

	Gillies (1882-1960)	McIndoe (1900-1960)
Born	New Zealand	New Zealand
Medical School	Cambridge University	University of Ontario
Active in	WW I	WW II
Worked in	Queen's Hospital	Queen's Hospital
Operated mostly	Gunshot facial injury	Burns
Articles (co-work)	12 (2)	17 (2)
Cited (co-work)	162 (14)	127 (14)
Most cited papers		Reconstruction of burned face (41),
		Radiation necrosis (32),
	Congenital cleft palate (113),	Operation for adult hypospadias (23),
	Direct pedicle flap (29)	Treatment of fracture of jaw (15), Congenital absence of vagina by indwelling skin graft (9)

skin graft, raw surface outwards. The skin-covered mold was inserted into the cavity and the labia minora were sutured across its lower end leaving a small hole anteriorly just behind the meatus for drainage. The skin-covered mold was maintained for 5 months after operation.^[1]

It goes without saying that these two New Zealand born cousins were innovative plastic surgeons [Table 1]. Where did their innovative thinking come from? As in Gillies' case, innovation can come from being informed by other subjects of study or specialties. Innovation comes also from close observation, as in McIndoe's case. However, innovation mostly arises out of necessity, as when Gillies and McIndoe pursued their field practice.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

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Early muscle reinnervation by means of end-to-side neurorrhaphy in an experimental model

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ABSTRACT

Aim: The aim of the study was to provide early muscular reinnervation to avoid muscle atrophy and functional loss in an experimental model. **Methods:** Fifty rats were divided into five groups. In group 0 (control group) only nerve dissection was performed. Total peroneal nerve section was performed in the remaining groups. Immediate end-to-end neurorrhaphy (EEN) was made in group 1. In group 2, an end-to-side neurorrhaphy (ESN) was performed from the tibial nerve to the peroneal nerve. In group 3, a direct EEN, plus an ESN, were used as a nerve graft as a bridge from the donor nerve (tibial); all nerve coaptations were performed through an epineural window. In group 4, only a neurotomy was made without any type of reconstruction. **Results:** Neural diameters were similar in groups 0, 1, and 3 ($38 \pm 1 \mu\text{m}$, $31 \pm 6 \mu\text{m}$, $32 \pm 3 \mu\text{m}$). Neural fibers in group 3 had an 18% increase in the number of axons ($P < 0.001$) when compared to group 0. Group 2 ($28 \pm 1 \mu\text{m}$) and group 4 ($19 \pm 3 \mu\text{m}$) had diminished diameters with a lower index of muscle regeneration. Animals in group 4 presented with "clawed" lower extremities and had difficulty with ambulation. Neural graft diameters was similar in groups 2 and 3 ($33 \pm 4 \mu\text{m}$, $31 \pm 3 \mu\text{m}$), but axon density was significantly higher in group 3 ($53 \pm 6 \mu\text{m}$, $39 \pm 8 \mu\text{m}$) ($P < 0.001$). Axon density was 36% higher when the combination of EEN and ESN with a neural graft through an epineural window was performed. **Conclusion:** This study revealed that the combination of EEN and ESN repairs with the addition of a neural graft provides a lower index of muscle fiber destruction, and can be a reliable method for reconstruction in high neural injuries.

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Nerve transfer,
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INTRODUCTION

End-to-end neurorrhaphy (EEN) is the conventional reconstructive method for patients with peripheral nerve injuries. In some cases, as in patients with complex upper extremity trauma and/or extensive oncologic resections, an end-to-side neurorrhaphy (ESN) is considered to be a good alternative for neural reconstruction.^[1-3] However, this technique (ESN) has been abandoned by some surgeons secondary to discouraging functional outcomes.^[4-6] Viterbo *et al.*^[7,8] has stated that ESN from a “healthy” nerve can “bridge” a neurological deficit, and indeed the outcomes from this type of surgery are better than those obtained from end-to-end coaptation. End-to-side nerve coaptation has also been used for patients with unilateral facial paralysis with good results.^[9,10] There are experimental models in which the orbicularis oculi muscle has been re-innervated with this technique.^[11]

Patients with upper extremity proximal nerve injuries may require more than one year to achieve reinnervation in the distal extremity (during this time, axonal growth takes place). However, full reinnervation does not imply full recovery given the risk of often irreversible and uncorrectable muscle contracture and joint stiffness. In clinical studies, ESN has proven its usefulness by improving sensation alone.^[6]

The current study was conducted to evaluate the provision of early muscular reinnervation to avoid muscle atrophy and function loss.

METHODS

From January 2008 to November 2008, fifty male adult Wistar rats were used for study. Their weight ranged from 350 to 400 g and they were divided into 5 groups of 10 rats each. Before and after surgery, the animals were housed in plastic boxes, with a 12-h light/dark cycle, and were given free access to food and water.

The measured criteria included anatomic changes of the leg, difficulty with ambulation, and microscopic neural and muscle morphology of the implied nerves and muscles. All the study rats were analyzed 90 days after the procedure.

The rats were anesthetized with an intraperitoneal injection of a 1:10 pentobarbital solution (60 mg/mL) at a conventional dosage. During the procedure, a dose of 0.1-0.2 mL of the same solution was administered as needed. The procedure was performed on the peroneal and tibial nerves of the right lower extremity. In group 0, nerves were dissected and exposed without sectioning. In the remaining groups, a neurotomy of the peroneal nerve was made 20 mm proximal to its

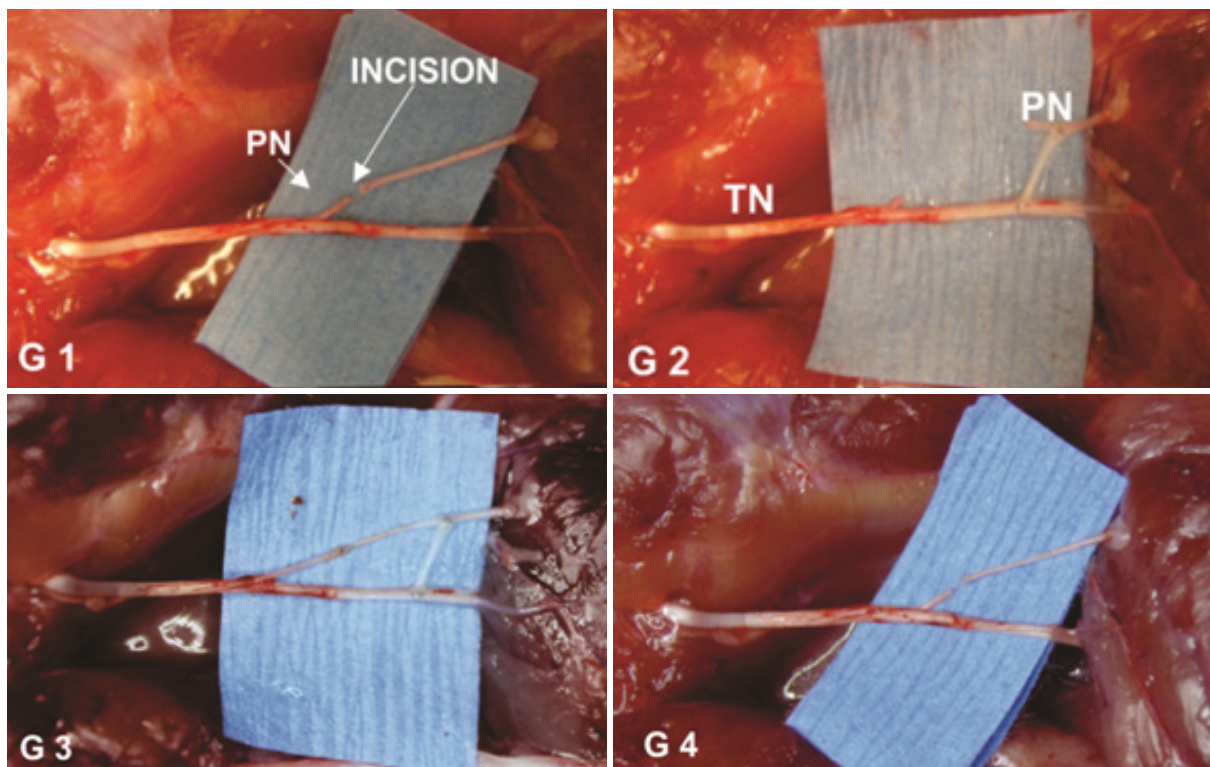


Figure 1: Surgical procedures. G1: Group 1 PN neurotomy and repair with EEN; G2: group 2, ESN without end-to-end repair; G3: group 3, both EEN and ESN using a nerve graft; G4: group 4, no repair done. EEN: end-to-end neurorrhaphy; ESN: end-to-side neurorrhaphy; PN: peroneal nerve; TN: tibial nerve. Optical lenses original magnification x400

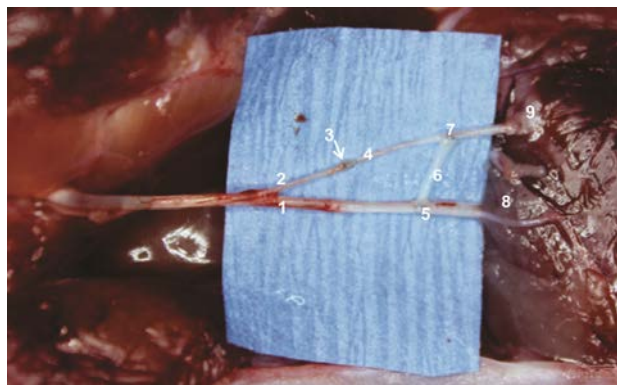


Figure 2: Zones used for microscopic analysis (tibial, peroneal and graft). Optical lenses original magnification $\times 400$

entrance to the muscle. The injury was repaired with an EEN in group 1. In group 2, an ESN was performed from the tibial to the peroneal nerve. In group 3, a direct EEN plus an ESN neurorrhaphy from the donor nerve (tibial) was used. In both groups 2 and 3, a nerve graft to bridge the gap between the tibial and peroneal nerves was used. In group 4, only a neurotomy was performed without reconstruction [Figure 1].

Morphological analysis

Ninety days after neurotomy and repair, the animals were sacrificed with an anesthetic overdose. Nerve fragments from several zones, as well as the corresponding muscles, were identified and marked (z1 to z9) [Figure 2]. These were fixed in a combination of 4% paraformaldehyde and 2.5% glutaraldehyde in a saline phosphate buffer solution (0.1 mol/L, pH 7.4). Following fixation they were treated with 2% OsO_4 , dehydrated with ethanol in increasing graduation, and finally placed in epoxic resin (Epon). Axonal diameter and myelin density were determined in 1- μm cross sections dyed with toluidine blue in zones 1 to 9. Axon and muscle ultrastructural analysis was also

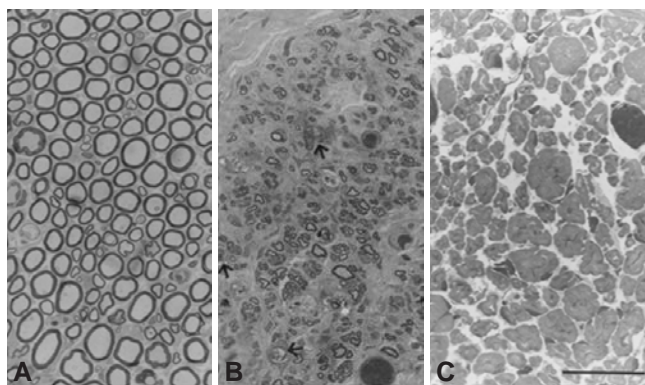


Figure 3: Peroneal nerve cross section in zone 9. A: Group 0, myelinated axons; B: group 3, axonal groups in regenerative process; their size and form are variable, with zones of disorganized myelin (arrows); C: axons in degenerative process were predominant in group 4. Bar = 25 μm

performed. Muscle cross sections were 60 nm thick, and viewed with uranyl acetate and lead citrate contrast (Reynolds, 1963) (EM 109 Carl Zeiss). Observations and diameter measurements were made with an Axioscop 2 plus microscope (Carl Zeiss) connected to a system of image analysis. Axiovision 4.0 software was used. All axons on the edges of the cut specimens were excluded from the count.

Statistical analysis was performed using analysis of variance (ANOVA), and an averages comparative analysis (Tukey's method) using Micro Cal Origin software.

RESULTS

Muscle/nerve morphology, and thickness of the myelin band

The morphology of nerves and muscles was different in all groups. Three morphological conditions were found: normal in group 0; regeneration in groups 1, 2, and 3; and degeneration in groups 1, 2, and 4.

The peripheral region of the nerve displayed large amounts of connective and fatty tissue. In group 0, the myelinated axons were situated in a semi-circular form, arranged one after another [Figure 3A]; myelin band thickness ranged from 80 to 470 nm, with the diameter of the fiber directly proportional to the thickness of the myelin band [Figure 4A]. In group 3, the main types of fibers were regenerative with a well-defined myelin band, with irregular and grouped dispositions [Figure 3B]. Abundant connective tissue was found among these groups. The thickness of the myelin band varied according to the diameter of the fiber and ranged from 40 to 280 nm [Figure 4B]. In groups 1 and 2, small regenerative axon fibers were found together with lost myelin architecture or only the

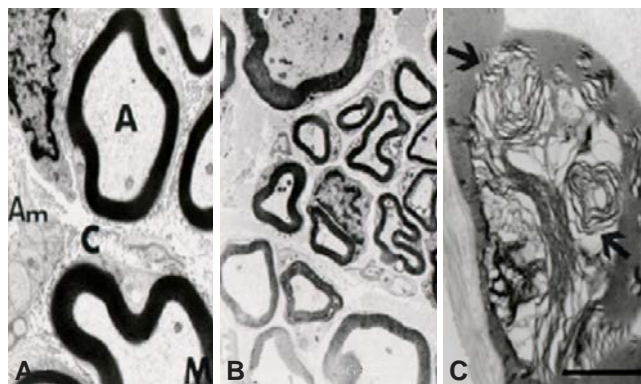


Figure 4: Micrography of myelinated axons. A: Group 0, axons with great diameter with a thick myelin band. A: normal muscle appearance; M: normal pattern; Am: interstium; C: disorganization level; B: group 3, axons organized in small groups showing regenerative process; C: group 4, disorganized myelin and some myelin remains. Arrows: striated pattern lost and myofibril remains. Bar = 1 μm

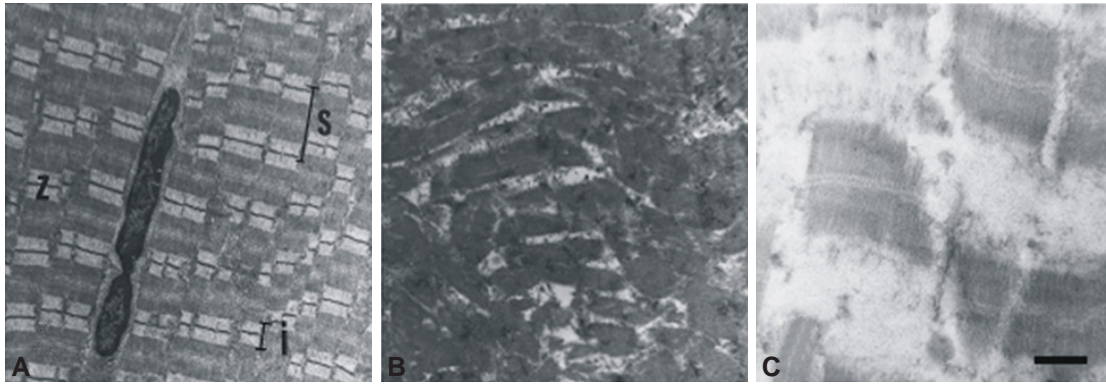


Figure 5: Muscle micrography. A: Represents findings in groups 0 and 3; normal muscle appearance, with normal-appearing transverse striation pattern. Z = Z line, S = sarcomere and I = band. Bar = 500 μ m; B: section showed in the image on the left, zoomed of this normally looking muscle; C: groups 1, 2, and 4 showed different levels of disorganization, striated pattern lost and myofibril remains. Bar = 200 μ m

myelin remains. Animals in group 4 developed a “claw leg” and difficulty with ambulation.

The peroneal nerve lost its form in group 4; through a light microscope, amorphous masses corresponding to be myelinated degenerating axons were observed [Figure 3C]. At an ultrastructural level, it was confirmed that these amorphous masses corresponded to myelin with lost architecture [Figure 4C]. The morphology of the gastrocnemius muscle was normal in all groups. In the tibialis anterior muscle from rats in groups 1 and 2, zones with muscular fiber disorganization were mixed with others of normal appearance. This muscle was normal in group 3; this group displayed fibers with peripheral nuclei, myofibrils with homologous bands, and fibers which differed from the normal striated pattern [Figure 5A]. In group 4, there was total atrophy of the muscular structure with retained myofibrils [Figure 5B and C].

Nerve diameter and axon density

A difference in the diameter of the peroneal nerve, zone 9, was detected. In addition, decreases in diameter were found in groups 2 ($28 \pm 1 \mu$ m) and 4 ($19 \pm 3 \mu$ m); in groups 0 ($38 \pm 1 \mu$ m), 1 ($31 \pm 6 \mu$ m), and 3 ($32 \pm 3 \mu$ m), the diameter was similar, as also found in the grafts in groups 2 and 3 ($33 \pm 4 \mu$ m and $31 \pm 3 \mu$ m, respectively).

Axonal fibers were found in the regenerating phase in zones 4, 5, 6, 7, 8, and 9. However, there was only a difference in zone 9 of the peroneal nerve in group 3 in which there was an 18% increase in comparison with group 0, $47 \pm 5 \mu$ m vs. $39 \pm 4 \mu$ m ($P < 0.001$). Nonetheless, a decrease was noted in the diameters of fibers in groups 2 and 4 ($28 \pm 4 \mu$ m and $13 \pm 4 \mu$ m, respectively), which was statistically significant ($P < 0.001$). The regenerated axon density in the nerve graft was 36% greater in group 3 than in group 2 ($53 \pm 6 \mu$ m

and $39 \pm 8 \mu$ m, respectively) ($P < 0.001$).

DISCUSSION

EEN is the most common method used for nerve injury repair, however, in recent years, ESN has become more established as an alternative method for repair of these injuries.^[12] According to Battal *et al.*,^[13] this is clinically useful when it is performed through an epineural window. It has been proposed that axons may grow through an epineural window in a damaged recipient nerve by means, for instance, of a reversed end-to-side neurorrhaphy.^[14,15] Other studies have demonstrated that operative injury to the donor nerve during ESN is the main prerequisite for motor reinnervation of the recipient nerve.^[16] A recent study revealed that performing end-to-side coaptation with a 40% neurectomy showed superior recovery both in axonal regeneration and electrophysiologic parameters.^[17] Results are optimized at the microscopic and histopathological levels when a “window” has been performed.^[18]

In the current study, EEN was combined as a primary method for nerve injury repair with a distal nerve graft used in an ESN manner. As Viterbo *et al.*^[8] has shown previously, the absence of an incision in the donor nerve was not a significant factor that altered the regenerative capacity, neural growth, or transmission of electrical stimuli through the nerve. As a result, animals in groups 1, 2, and 3 had a favorable clinical recovery because they did not show alterations during motion, whereas those in group 4 (neurotomy without repair) developed a “clawed” leg without signs of clinical recovery.

In studies performed by Cederna *et al.*,^[1] a decrease in metabolically active muscular cells was observed in the muscle innervated by the donor nerve after the epineural window had been made. In his experience,

this decrease was not significant. This was not observed in the current study. It is possible that neurotomy of the donor nerve, by itself may in fact enhance reinnervation of the recipient nerve, perhaps due to a normal inflammatory response with recruitment of neurotrophic factors.^[19]

After repair of the neurotomy of the peroneal nerve by means of EEN, and connection to the tibial nerve with an ESN using a neural graft with removal of an epineural window, an 18% extra-axonal density was obtained closer to the muscle in the group 0, partially avoiding muscular atrophy and therefore improving the motor and sensory functions.

A novel experimental model using the common peroneal nerve demonstrated that muscle mass preservation was better achieved with sensory reinnervation rather than with motor reinnervation. No differences were found in this model when comparison was made between surgical techniques, whether they were end-to-side or end-to-end.^[20]

When the group treated with Viterbo's principles (group 2) was compared with our study group (group 3), a similar nerve graft diameter was found, but with a 36% increase in axonal density in our proposed treatment group.

As a corrective procedure, EEN was combined with a nervous graft coapting the peroneal and tibial nerves through an epineural window by means of an ESN. The number of new neural fibers exceeded those present prior to section of the nerve, indicating a clearly beneficial sensory and motor effect. A significant decrease in axonal size, including the thickness of myelin bands, was accompanied by a regenerative process (sprouting); it is possible that when axons regain their normal size and myelin bands reaches their normal thickness, that the number of axons be equal to the number of axons in the group 0. Although the current study protocol required that study subjects be sacrificed to obtain muscle and nerve samples, it would be interesting to measure this parameter in a later study. It is now accepted that collateral sprouting is the main mechanism of nerve regeneration following end-to-side neurorrhaphies.^[17] Haninec *et al.*^[21] conducted a study to determine the utility of ESN from C5 to the ulnar nerve for motor and sensory reinnervation. More collateral branches were found in the group in which a perineural window had been performed. Although direct implantation of fibers into the target muscle has been recently performed, it can be avoided by performing an end-to-side procedure as proposed by Poppler *et al.*^[22]

The current study demonstrates the clinical importance of limiting muscular damage by using a "babysitter" to preserve motor function after proximal nerve injuries in the upper extremity before muscle atrophy is completely established. Several factors may alter the result. First, both the injury mechanism and the experimental model are crucial. Crush injury distal to the coaptation site has been found to increase the rate of myelin formation in regenerating axons.^[23] Further research is required to determine the role of pre-injury, as deliberate donor nerve axotomy is critical for optimization of motor neural regeneration as demonstrated in several studies.^[16-18] Recent research suggests that the number of axonal sprouts correlate with the degree of donor nerve manipulation secondary to liberation of neurotrophic factors, rather than the extent of the axotomy *per se*.^[24]

The results of the current study suggest that the same surgical principals can be applied to clinical practice with patients. Clinical recovery is potentially faster and more efficient as the distance for nerve growth is shortened with the nerve graft placed near to the muscle rather than waiting for normal axonal growth from the injury's site of origin. With the proposed treatment, irreversible muscular atrophy was avoided by supplying the target muscles with a constant neural impulse by means of this babysitter procedure.^[25] Several applications for the ESN are currently being studied.^[26-30] The authors of the current study intend to study the usefulness of this procedure in the scenario of acute trauma of the upper limb by creating nerve bridges at the wrist crease in order to ameliorate ulnar nerve injury, as it has been found that intrinsic muscle function tends to be compromised despite the efforts of a primary end-to-end repair.

In conclusion, this study revealed a lower index of muscle fiber destruction, and can be a reliable method for reconstruction in high neural injuries. These results may assist surgeons in the treatment of high neural injuries in humans by performing nerve bridges at the level of the wrist.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

There were no patients involved.

Ethics approval

The Ethics and Investigation Committees reviewed and approved the investigation protocol (Protocol no.

081/97). The animals were treated according to the Recommendations of Care and Use of Laboratory Animals (NIH publication no. 85-23, reviewed 1985, US Government Printing Office, Washington, DC) and according to the recommendations of source country (NOM-062-ZOO-1999).

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A study of correlation between prosthetic breast reconstruction, antibiotic prophylaxis and surgical wound drains

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ABSTRACT

Aim: The primary aim of this investigation into the correlation between prosthetic breast reconstruction, antibiotic prophylaxis and surgical drains was to determine whether the short-term prophylaxis recommended in the current guidelines is in fact able to sterilize the peri-prosthetic pocket in patients undergoing prosthetic breast reconstruction via tissue expansion, permanent implant placement, or Becker implants, as well as augmentation to correct symmetry. **Methods:** A total of 96 women who had undergone prosthetic breast reconstruction surgery were considered. Patients were recruited from the Plastic Surgery Clinic, Gemona, and the Surgery Clinic, Udine, both affiliated with the Udine "Santa Maria della Misericordia" University Hospital between May 2013 and May 2014. All patients were administered the recommended short-term antibiotic prophylaxis, i.e. 2 g cephazolin (plus 1 g eventually given after 3.5 h of surgery) 30 min before surgery. Records pertaining to each patient were kept in a specific study chart. **Results:** Samples of peri-prosthetic drainage fluid were taken from 92.5% of the recipients of breast reconstruction/implant surgery. Only 2.3% of the samples analyzed were found to be positive for microbial strains. **Conclusion:** The results of this preliminary study are encouraging, demonstrating that the guidelines regarding short-term antibiotic prophylaxis are indeed effective.

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INTRODUCTION

The guidelines in use at the Udine S. Maria della Misericordia University hospital, which conform to the recommendations published by the Italian National Guidelines System (SNLG) and adopted by the Friuli-Venezia-Giulia Regional Health Authority, recommend short-term pre-operative antibiotic prophylaxis via 2 g of cephazolin for breast implant patients, plus 1 g for operations scheduled to last more than 3.5 h. The guidelines specify that antibiotic prophylaxis must be administered immediately before (in this case 30 min) surgery, and be limited to the peri-operative period.

The literature indirectly confirms the efficacy of the short-term prophylaxis proposed in the guidelines, and published evidence supporting the superiority of prolonged prophylaxis is notably absent.^[1-3] Hence, based on the current evidence, extending prophylaxis to cover the first 24 h of the post-operative period can only be justified if there are major risk factors for post-surgical infection, and the reasons behind any decision to prolong prophylaxis beyond the recommended limit must be noted in the patient's medical records.^[4,5]

Although we can assume that most, if not all, specialists in the sector adhere to such guidelines, the duration of antibiotic prophylaxis is nonetheless often the object of much discussion. Aside from the fear of peri-prosthetic infections, major concerns are also raised by the sequelae of infections, in particular implant loss, delays in neo-adjuvant therapy administration, unsatisfactory aesthetic outcomes and the need for further corrective surgery, not to mention potential medico-legal issues.^[6,7]

Indeed, peri-prosthetic pocket infections tend to develop subclinically, leading to capsular contracture and other post-implant complications without overt signs or symptoms. However, peri-prosthetic discharge may represent an effective marker of even subclinical peri-prosthetic infection, and can be easily obtained from post-operative surgical drains.

Hence, in order to make a contribution, however minor, to this debate, the authors conducted a microbiological analysis of the peri-prosthetic discharge of breasts treated at Udine University Hospital. The aim was to establish objectively whether the short-term prophylaxis recommended in the guidelines is able to sterilize the peri-prosthetic pocket.

METHODS

Patients were recruited from the Plastic Surgery Clinic, Gemona, and the Surgery Clinic, Udine, both affiliated with the Udine "Santa Maria della Misericordia"

University Hospital between May 2013 and May 2014.

All study patients signed informed consent and gave their permission for publication of their pictures and samples analysis for research purpose; 86 patients (92.5%) of the 96 considered.

Inclusion criteria consisted of all women undergoing breast implant surgery, comprising: (1) post-mastectomy breast reconstruction via tissue expander/implant or Becker expander; (2) expander/implant replacement surgery; and (3) breast augmentation to correct asymmetry.

The patient sample also included 3 cases of corrective surgery secondary to complications arising in the post-operative period, in particular: (1) 1 implant replacement with contralateral mastopexy following Becker expander rupture; (2) 1 implant replacement with latissimus dorsi myocutaneous flap following implant exposure; and (3) 1 latissimus dorsi myocutaneous flap reconstruction implant with breast implant and contralateral mastopexy following breast cancer relapse.

A total of 96 women who had undergone prosthetic breast reconstruction surgery were considered. In 50 patients, reconstruction was performed immediately after mastectomy (modified radical, nipple-sparing or skin-sparing) following a diagnosis of breast cancer. Surgery was performed to fit either a tissue expander or a permanent implant, accompanied or not by contralateral mastopexy. In an additional 12 patients, deferred post-mastectomy reconstruction via expander or permanent implant positioning, with or without latissimus dorsi flap reconstruction and/or contralateral mastopexy, was performed. In another group of 31 patients, expanders were replaced with permanent implants, with or without contralateral mastopexy and/or lipofilling. The remaining three patients underwent corrective surgery secondary to post-implant complications, specifically implant rupture, implant exposure, and breast cancer relapse, respectively.

All patients received the recommended short-term antibiotic prophylaxis, i.e. 2 g cephazolin (plus 1 g eventually given after 3.5 h of surgery) 30 min before surgery.

Records pertaining to each patient were kept in a specific study chart, the first part comprising the patient's personal information, diagnosis, lesion site, and type of surgery received. The second part of the study chart was used to compile data pertaining to the patient's "unnecessary" habits (smoking, drinking,

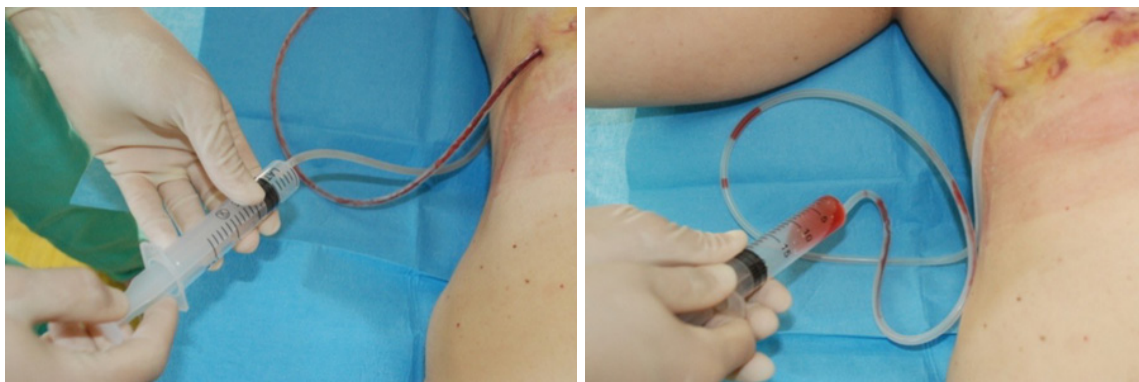


Figure 1: Aspirating fluid from the surgical drain

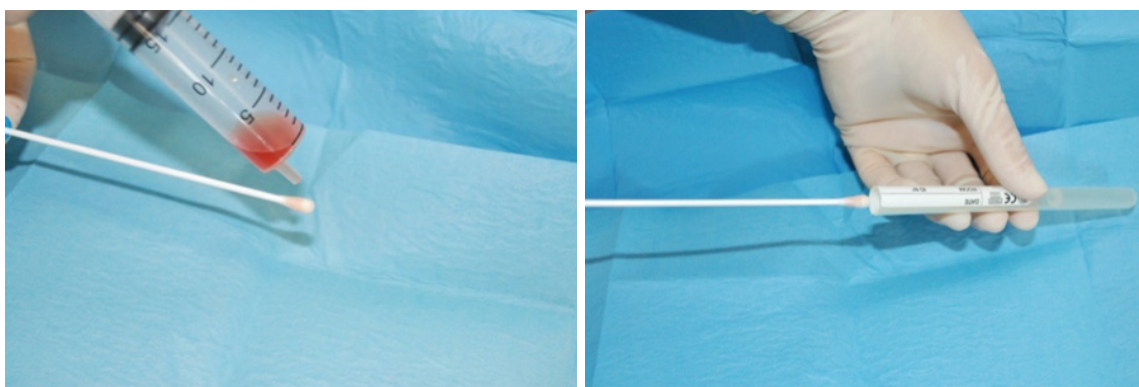


Figure 2: Preparing samples for microbiological testing



Figure 3: Evident signs of infection in the mastectomy/expander patient who tested positive for *Staphylococcus aureus*

not having a good diet, etc.), co-morbidities, and any medication or complementary treatment received or ongoing, while the third part was used to record the microbiological tests carried out, the results thereof, any microbial strain detected, and any signs of overt infection.

RESULTS

Samples of peri-prosthetic drainage fluid were taken from 86 (92.5%) of the 96 recipients of breast reconstruction/implant surgery; the remaining 7.5%

of patients did not adhere to the study. In this patient population the recommended short-term antibiotic prophylaxis was performed and the fluid collected was analyzed for microbiological contamination.

Samples were taken under sterile conditions by aspirating the peri-prosthetic fluid directly from the drain using a syringe, and transferring to sterile cotton swabs [Figures 1 and 2]. Samples were taken on the third day after surgery and upon drain removal (overall two times), and sent directly to the lab for testing.

Only 3 out of the 86 samples analyzed (2.3%) were found to be positive for microbial strains, specifically *Pseudomonas aeruginosa* [Figures 3-5] and *Propionibacterium acnes*, respectively. In 1 case, a peri-prosthetic accumulation formed in the post-operative period was found to be positive for *Staphylococcus aureus*, but the drainage fluid taken from the same patient tested negative. In regards to the clinical and therapeutic characteristics of the patients who tested positive, the 55-year-old *S. aureus* patient, after mastectomy and expander placement, developed a fever, increased breast volume, and collection of pus, and the expander was therefore removed. The 45-year-old patient whose drainage fluid tested positive for *Pseudomonas aeruginosa* experienced



Figure 4: Latissimus dorsi myocutaneous flap failure and implant exposure in a patient who tested positive for *Pseudomonas aeruginosa*



Figure 5: Patient positive for *Propionibacterium acnes* without clinical signs of infection

gradual loss of the apical portion of the skin paddle, originating at the medial apex, and consequent implant exposure following mastectomy and latissimus dorsi myocutaneous flap reconstruction. It is likely that the bacterial contamination of the peri-prosthetic environment was due to this exposure. Clinically, the patient demonstrated high inflammation indices and an accumulation of peri-prosthetic fluid, which was drained from the area of tissue loss.

In contrast, the 52-year-old mastectomy and implant reconstruction patient who tested positive for *Propionibacterium acnes* developed no clinical signs of infection, and completed the tissue expansion cycle with success. As no clinical signs of infection appeared during this cycle, the patient was not medicated, and the positive result was tentatively ascribed to contamination of the sample, pending further monitoring.

DISCUSSION

For each patient, including the three who tested positive for contamination, the variables associated in the literature with a greater risk of peri-prosthetic infection were analyzed. The first of these variables was age. The mean age of the 86 patients studied was

53 years. Forty-four out of 96 (45%), i.e. the majority, fell into the range of 45 to 55 years of age. Ten (20.8%) were in the age range 44 to 35 years, 18 (18.7%) were between 65 and 74 years of age, and the remaining 14 (14.5%) were aged between 55 and 64 years. There is no statistically significant correlation between advanced patient age and the risk of contracting a surgical site infection (SSI) in the literature, as the majority of studies show no statistically significant relationship between these 2 variables.^[2,8] In fact, rather than age, authors are more inclined to consider the presence of co-morbidities and the overall physical condition of the patient prior to surgery. Nevertheless, all three patients in the current study who had samples positive for microbial strains were of an intermediate age, with the patient infected by *Staphylococcus aureus* being 55 years old, the patient infected by *Pseudomonas aeruginosa* 45 years, and the patient infected by *Propionibacterium acnes* 52 years. The fact that these patients were not elderly confirms the widespread opinion in the literature that the risk of SSI onset is not conditioned by advanced age.

The second variable studied was smoking. Of the 86 patients, 14 (16.2%) were smokers, smoking a mean of 10 cigarettes a day, and had been smoking for an average of 15 years. The literature contains many studies that demonstrate a statistically significant correlation between smoking and SSI risk, and the majority of authors contend that there is a statistically significant relationship between these 2 variables.^[9,10] However, these studies do suffer from a common limitation, namely that it is difficult to define terms like "regular" and "active" smoking statistically. In order to obtain statistically valid data on this variable, it would be necessary to adopt standardized measures of smoking history and find suitable controls to eliminate any bias.

Wound healing is dependent on the local blood supply, and smoking induces a state of chronic

vasoconstriction, reducing blood vessel gauge and thereby reducing the flow of blood. Furthermore, the appearance of the scar is also adversely affected by smoking, and it is therefore strongly suggested that patients refrain from smoking in the 2-3 weeks before and after the operation. In the current study, however, none of the 3 women who tested positive admitted to smoking, and it is therefore impossible to confirm the literature findings in this sample.

The third variable considered in this study was the presence of co-morbidities. The majority of the 86 patients studied (70; 81.4%) were not found to be affected by other pathologies. Only 10 patients (11.6%) had metabolic issues or autoimmune disease; infectious diseases were not present. There was no comorbidity data available for 5 cases.

There are many studies in the literature that demonstrate a statistically significant correlation between the presence of co-morbidities in general and an increased risk of contracting an SSI.^[11-13] The National Nosocomial Infections Surveillance System considers three key variables to be independently associated with the risk of SSI, namely: (1) a wound infected or contaminated surgically; (2) the duration of the operation; and (3) an American Society of Anesthesiologists (ASA) Physical Status Classification score greater than 2. Olsen *et al.*^[14] also demonstrated that an ASA score of 2 or 3 is associated with a statistically significant risk of developing an SSI.

Regarding metabolic function disorders, many researchers have set out to find a possible link between diabetes mellitus, for example, and the risk of peri-prosthetic infection. However, secondary to contrasting findings reported in the literature, this topic remains controversial.^[8,14] As none of the three patients who tested positive in our study suffered from any metabolic diseases, the authors can add little to this debate.

There is no data in the literature suggesting that autoimmune diseases may represent a possible risk factor for SSIs. Nevertheless, the potential role of the drugs used to treat these conditions, e.g. steroids, cytostatics and immunosuppressors (azathioprine, cyclosporine), have been widely studied. The findings of several of these studies^[15-17] appear to suggest that patients treated pre-operatively with immunosuppressant drugs or steroids do in fact run a greater risk of SSIs. However, none of the three patients who tested positive in the current study had any concomitant diseases, and therefore no conclusions can be drawn in this regard.

The fourth variable analyzed was the presence of any complementary treatments administered prior to surgery, and their various combinations (chemotherapy, radiotherapy, hormone therapy). The majority (72; 83.7%) of the 86 patients in our sample had not received any complementary treatment, while the remaining 14 had a fairly uniform distribution in terms of the combination of possible treatment combinations.

Regarding radiotherapy (RT), the literature contains many studies which demonstrate a significant correlation between preoperative RT and the development of an SSI. Indeed, RT can provoke skin damage by the occlusion or damage of the microvascular system and chromosomal damage to the fibroblasts, inhibiting stem cell replication, angiogenesis, and collagen production. This manifests during the final phases of treatment as hyperemia and inflammation of the skin. Although this is a frequent occurrence, it is easily remedied via suitable topical treatment, and seldom necessitates the interruption of treatment. Nonetheless, connective tissue may also be damaged, and in the later stages of RT, areas of sclerosis, fibrosis, and hypertrophy of the pectoral muscle may occur. By provoking tissue fibrosis and microvascular damage, therefore, RT may delay wound healing, and can be associated with dehiscence, necrosis and infection. Moreover, when RT precedes reconstructive surgery, post-actinic damage may complicate the tissue expansion necessary to house the implant, as well as increase the risk of peri-prosthetic fibrosis and capsular contracture.^[8,14]

The role of preoperative chemotherapy (CT) as a potential peri-prosthetic infection risk factor has also been widely studied. Although contrasting results have been reported, CT is known to cause myelosuppression and neutropenia, and thereby potentially increase the risk of infection.^[8,16] In the current study, however, none of the 3 patients whose samples tested positive for microbial contamination had previously received CT. In fact, of these 3 cases, only 1 (infected by *Pseudomonas aeruginosa*) had undergone complementary treatment consisting of RT plus hormone therapy. Although the size of the sample does not enable meaningful statistical analysis, the influence of RT cannot be ruled out in this case.

The fifth variable considered was the use of post-surgical wound drains. Indeed, the drains themselves may represent a risk factor for infection by promoting biofilm formation on the surface of the device, which may in turn promote the transfer of bacteria into the wound. It is also possible to contaminate the lower end of the drain during disconnection and emptying, potentially causing intra-luminal infection and

contamination of the wound.^[15,18,19] Hence, although the drain performs an indispensable function, namely to eliminate accumulated serum from the wound site and thereby deprive endogenous pathogens of an excellent medium for proliferation, it can provide a route through which such pathogens can enter the body.^[20-24]

As mentioned previously, the regional guidelines for antibiotic prophylaxis (AP) dictate the use of 2 g cephazolin (plus 1 g in operations lasting longer than 3.5 h) solely before surgery. Cephazolin, the first choice antibiotic, is a cephalosporin that protects against a wide range of both gram-positive (staphylococcus strains, including aureus; coagulase-negative staphylococci, with the exception of methicillin-resistant strains; beta-haemolytic streptococcus groups A and B) and gram-negative (*E. coli* and *Klebsiella*) bacteria. Cephalosporins are generally well-tolerated and inexpensive drugs with time-dependent pharmacokinetics and a half-life of roughly 2 h. They are considered high protein bonding (85%), and provide excellent tissue distribution. Cephazolin, in particular, is one of the preferred options for clean surgery.

In cases of cephalosporin allergy, vancomycin or clindamycin are other viable options. Other drugs, such as ampicillin, amoxicillin, piperacillin, ampicillin/sulbactam, and amoxicillin/clavulanic acid, are also widely used for surgical applications, and are very efficacious against enterococcus strains, albeit no more so than the cephalosporins in AP.

The study charts showed that all 86 were administered 2 g of cephazolin intravenously, 30 min before skin incision, with an additional 1 g in cases lasting longer than 3.5 h. With this treatment, as already stated, 3 out of the 86 showed contaminated drainage secretion and 1 peri prosthetic infection but sterile drain.

The study charts confirmed adherence to the duration of AP suggested by both the literature and regional guidelines. Indeed, there is no statistical proof that long-term AP (for example until the time of drain removal) is any more efficacious at preventing SSIs.^[4] On the contrary, there are various reports that extending AP to cover tubes, drains and catheters is either useless^[1,2,8] or inadvisable.^[25,26]

Despite this evidence, it has been reported that many hospitals, both in Italy and abroad, routinely use long-term AP in surgical cases. Perrotti *et al.*,^[6] for example, state that over 50% of the plastic surgeons interviewed administer AP well beyond the operating time, and as

many as 61% until drain removal. Although this behavior is not very judicious, it is understandable. Indeed, should a surgery patient fall prey to an SSI, there are many legal questions to consider, not to mention the clinical and financial consequences of their sequelae, which may include implant loss, delay in neo-adjuvant therapy, unsatisfactory or unsightly outcomes, and, as a consequence, prolonged hospital stays and even revision surgery. This represents a strong incentive for surgeons to administer postoperative AP, especially in patients with drains, in the hope that prolonging the course of AP will reduce the risk of SSI. The practice is even more common in immediate prosthetic reconstruction patients, with the fear of infection-related implant loss being the driving concern.^[27,28]

However, the unrestrained use of antibiotics, perhaps fueled by the lack of prospective studies in the literature, has led to the development of methicillin-resistant colonies of *Staphylococcus epidermidis*, and to an increase in the incidence of colitis secondary to *Clostridium difficile*, in addition to side effects and secondary infections. Furthermore, antibiotics administered after wound closure seem to have no prophylactic effect on bacterial contamination during the surgery itself.^[29,30]

Having administered short-term AP as per the recommended guidelines, 2 (2.5%) out of the 80 patients drain secretion samples analyzed were found to be positive for microbial strains, specifically *Pseudomonas aeruginosa* in 1 case and *Propionibacterium acnes* in the other. The patient whose drain was found to be positive for *Pseudomonas aeruginosa* developed progressive loss of the apical portion of the skin paddle, originating at the medial apex, and consequent implant exposure in the postoperative period. This makes it likely that the route of the bacterial contamination was, in fact, the exposed implant. In contrast, the patient whose drainage secretion tested positive for *Propionibacterium acnes* developed no clinical signs of infection, and completed the weekly expansion cycle with no complications.

In a further patient, a positive result for *Staphylococcus aureus* was detected in a peri-prosthetic accumulation formed in the post-operative period, but the fluid taken from the drain of the same patient was found to be negative.

As contaminated drainage samples were found in only 2 out of the 86 patients, one conceivably attributable to implant exposure, this study appears to confirm the validity of the current guidelines regarding short-term AP. Nevertheless, there are certain limitations

to declare. First, as the operations were performed in more than one hospital, rigid standardization of the study protocol was not possible. Although the medical and nursing staff had been trained to adhere to the rules of the study, several (16) cases had to be excluded due to procedural inaccuracies. The major limitation of the study, however, was the small sample size, which prevents the conclusions from achieving statistical significance.

Nevertheless, patients have continued to be added to the study group, with a view to increasing the data available and addressing certain secondary objectives. Specifically, the authors wish to evaluate, via microbiological analysis of the peri-prosthetic pocket during revision surgery, whether subclinical colonization persists upon implant replacement, and whether or not bacterial colonization leads to a greater incidence of capsular contracture. It will also be interesting to follow the progress of the patient whose peri-prosthetic fluid tested positive for *Propionibacterium acnes* upon drain removal, despite an absence of signs of clinical infection. In particular, the patient will be monitored for any sign of capsular contracture, which would lend weight to the literature hypothesis that peri-prosthetic infection is an important risk factor for this event in the long term. Should contracture indeed occur, it will also be interesting to note whether the microbial species isolated from the capsule is the same as that present in the drain fluid.

Despite the above-mentioned limitations, the results of this preliminary study are encouraging, demonstrating that the guidelines regarding short-term AP are indeed effective. However, it remains to be demonstrated that not prolonging prophylaxis does not statistically increase the risk of surgical failure, and does not therefore expose either the patient or surgeon to the burden of complications, whether major or minor.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients signed informed consent.

Ethics approval

The Institutional Review Board approved this study.

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Review

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Multipotency and secretome: the mechanisms behind the regenerative potential of adipose-derived stem cells

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ABSTRACT

The use of stem cells for regenerating damaged organs and tissues which are unable to heal on their own is a widely studied field in plastic and reconstructive surgery as well as medicine in general. Among various stem cell types, adipose-derived stem cells (ASCs) are especially considered to be an ideal stem cell population for several clinical situations. These cells could be harvested from fat with relatively less invasive methods with high yield rates. ASCs have proved to be worthy of more research to understand the mechanisms behind their regenerative abilities. However, it remains uncertain if ASCs show their main effects by their multipotency, or by secreting abundant amounts of cytokines and growth factors. The authors have performed a review of the current publications and literature on the ASCs' immunophenotypical properties and isolation methods as well as basic and clinical science research about the mechanisms behind their regenerative effects. The purpose of this article is to synthesize information regarding ASCs' paracrine effects and their ability to differentiate into other cell lines, comparing these aspects in order to lead future research for a more effective cell therapy utilizing these cells.

INTRODUCTION

The concepts of creation and construction have always fascinated us human beings. With better understanding of human body, we also began to feel a powerful

and passionate desire to simulate and recreate the phenomenon of this very complex existence to satisfy our curiosity, and also as physicians to heal.

The innate regeneration capacity of various tissues led



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researchers to channel their effort to understand this phenomenon and the discovery of stem cells. After the discovery of mesenchymal stem cells (MSCs) in the bone marrow by Becker *et al.*^[1] in the 1960s, a new discipline called regenerative medicine has emerged. Many stem cell lines have been discovered since, but information about most of these is limited due to problems of availability, viability or potential risks. However, adipose tissue has proved to be an abundant and easily accessible source of multipotent stem cells. This cell population, named adipose-derived stem cells (ASCs) has been demonstrated to be widely available, viable and safe. The potential of ASCs administration has gained much interest for the conditions with limited or pathological repair of tissue damage caused by various insults.

Since the discovery of ASCs more than 10 years ago,^[2] their intrinsic properties suggesting similarity to other known MSCs such as bone marrow MSCs (BM-MSCs) were demonstrated, and currently ASCs are accepted to be MSCs. The abundance of these cells in fat tissue and the relative simplicity of harvesting fat from patients with procedures such as liposuction have made these cells a primary interest for plastic surgeons. There is a tremendous focus on using stromal vascular fraction (SVF) or isolated ASCs as a regenerative therapy method for chronic wounds or for the reconstruction of tissue defects after oncological tumor resection, as well as to achieve effective fat grafting or as a skin rejuvenating product in aesthetic surgical practice. There are active clinical trials investigating the effects of ASC or SVF administration on several pathological conditions.^[3,4] This clinical activity is predicted to expand in the future.

It is becoming more acknowledged that ASCs have a promising therapeutic potential for a broad spectrum of medical conditions. We have previously reviewed the literature on the properties of ASCs and their capacity as a tool of regenerative medicine.^[5-7] Recently, a new debate on the regenerative effects of these cells has been introduced. It is still not clear if ASCs show their main effects directly by differentiating into mature cells (e.g. osteocytes) at the site of implantation, or by their paracrine arsenal of many prominent growth factors to promote regeneration/remodeling and modulate inflammation in the tissue. We have performed a literature review of basic and clinical science regarding this subject using the PubMed and Cochrane databases using “ASCs” and “phenotype” or “isolation” or “angiogenesis” or “wound healing” or “radiation injury” or “immune regulation”. A total of 118 articles were reviewed regarding ASCs’ immunophenotypical properties and methods of isolation, as well as their

effects on vascular diseases, angiogenesis, radiation injury and chronic wounds including diabetic ulcers. Interaction of ASCs with cells of the immune system was also investigated. Articles with detailed information on ASCs’ molecular interactions with other cells were eligible for inclusion. Duplicate/similar studies and studies without information on ASCs’ effects at the molecular level were excluded.

THE IMMUNOPHENOTYPIC PROPERTIES OF ASCS

The immunophenotyping and isolation protocols for the ASCs are still not standardized. Without a universal protocol, comparison of experimental data and future advances are difficult. In order to achieve a consensus for isolating ASCs, International Federation for Adipose Therapeutics and Science and International Society for Cell Therapy have published a joint statement about the phenotypic properties of these cells as well as SVF cells.^[8]

SVF is a substance which consists not only of ASCs but also endothelial cells, erythrocytes, fibroblasts, lymphocytes, monocyte/macrophages and pericytes.^[9] The substance of cells in SVF is usually named as “SVF cells”. These SVF cells are identified as being negative for CD235a and sometimes CD31, yet positive for CD34 or CD45. Further passaging depletes most of the hematopoietic cells and alters the immunophenotype of the remaining cell population, which are mostly ASCs. These culture expanded ASCs are positive for CD34 (could be negative in further expansions), CD44, CD73, CD90 and CD105 like other MSCs and negative for CD31 and CD45 [Figure 1].^[10,11] ASCs are different from BM-MSCs since they are positive for CD36 (GPIIb) and negative for CD106 (vascular cell adhesion molecule-1).^[12,13]

It is also known that ASCs lose CD34 expression over time with consecutive passaging.^[14] Additionally, ASCs eventually senesce with consecutive passaging due to the low telomerase activity.^[15] This might lead the researcher to acquire inaccurate results if senescent cells of latter passages are used. For the reliability and standardization of the experiments, it is also advised that the ASCs’ multilineage (i.e. adipocytes, chondrocytes and osteoblasts) differentiation potential should be demonstrated, which is now a common practice.

ISOLATION OF ASCS

Since the application of ASCs/SVF is becoming increasingly common, there is focused interest on efficient isolation and preparation of ASCs from

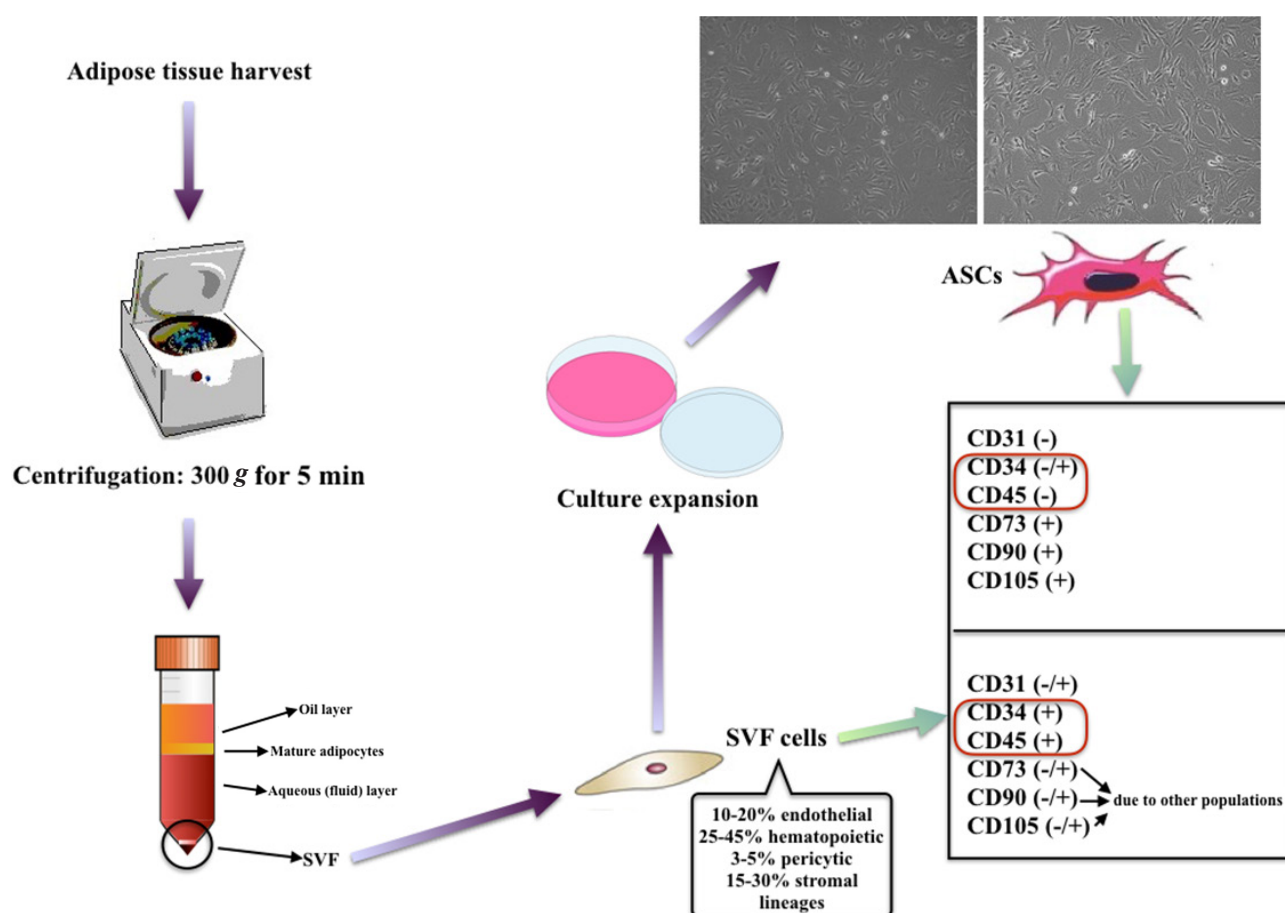


Figure 1: The phenotypic differences between SVF cells and culture expanded ASCs. ASCs: adipose-derived stem cells; SVF: stromal vascular fraction

adipose tissue. Liposuction is the most widely used method to harvest fat from humans. The liposuction aspirate is primarily composed of fragmented fat, blood and saline. ASCs are usually isolated from the fatty portion. A previous study showed that isolation of ASCs from the liposuction aspirate fluid (LAF) portion is also possible, but unfortunately this method yields less cells.^[14]

The investigation for new methods to increase efficiency of ASC isolation also needs to be mentioned. Conventional methods to acquire SVF or ASCs take a long time, making the process costly and increasing the risk of contamination. Sachs *et al.*^[15] and Francis *et al.*^[16] isolated viable ASCs from liposuction aspirate within thirty minutes without using collagenase digestion; however, the cell yield was much less compared to conventional isolation method. In another study, it is suggested that using fluorescent assisted cell sorting (FACS) for ASCs isolation is possible, however this method also yields less cells.^[17]

Schipper *et al.*^[18] investigated whether the region of harvest or the age of the donor had effects on ASCs'

function. Results of the study showed no statistically significant difference in terms of yield or function of ASCs harvested from different locations. Jurgens *et al.*^[19] compared ASCs harvested from abdomen versus hip/thigh region, and similarly no significant difference in the yield and function of ASCs was found. Gnanasegaran *et al.*^[20] has investigated whether the harvesting procedure affects isolated ASCs. They argued that cells harvested using liposuction had endodermal propensity while cells harvested by excision had meso/ectodermal propensity.

Preservation of human ASCs for further use is another subject which is being investigated. According to Shah *et al.*^[21] colony forming potential and cell marker expression of ASCs except CD34 and CD45 did not change with cryopreservation; however, their differentiation potential was significantly reduced. Further investigation on this subject is necessary.

THE EFFECTS OF ASCS ON ANGIOGENESIS

There is a considerable amount of research on the angiogenic effects of ASCs against ischemic diseases.

A fraction of these studies initiated by plastic surgeons attempt to utilize the angiogenic potential of ASCs primarily to introduce effective treatment modalities for debilitating chronic wounds. ASCs have shown to induce angiogenesis and increase the survival of ischemic tissues in these preclinical studies. The exact mechanisms for these phenomena are not well established, but it is suggested that the release of pro-angiogenic growth factors by ASCs could be mainly responsible.

There is also evidence that ASCs could integrate into tubular structures *in vivo* and express CD31, a marker for endothelial cells.^[22] However, there is no evidence that ASCs could directly differentiate into proper endothelium or fully functional blood vessels.

Suga *et al.*^[23] implanted green fluorescent protein (GFP) expressing ASCs into ischemic inguinal fat pads of mice in order to investigate their fate. They found out that although the transplanted ASCs gradually diminished after implantation, there was less tissue atrophy and higher vascular density in the ASC treated group compared with control. Tissue expression of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) were also found to be higher.

Several studies on cardiac regeneration also revealed the importance of paracrine secretions of ASCs. Sadat *et al.*^[13] documented that ASCs have cardioprotective effects via secretion of insulin like growth factor-I (IGF-I) and VEGF. Another study by Cai *et al.*^[24] suggests that the improvement seen with the administration of ASCs after myocardial infarction (MI) is not due to the cardiomyocyte differentiation of ASCs but due to their ability to augment angiogenesis by paracrine mechanisms. They showed that the density of newly formed vessels in the developing infarct was significantly higher in the group treated with ASCs. This is supported by the results of another study which demonstrated that the post-MI administration of ASCs augmented vessel density and prevented abnormal remodeling of the infarct area in pigs.^[25] Transplanted ASCs failed to stay engrafted in the myocardium, suggesting that their indirect paracrine effects could be responsible for the improved outcome.

Another study showed that ASCs implanted in ischemic hind limb of mice neither differentiate into endothelial cells nor integrate into the host capillary vasculature, however promote angiogenesis and formation of collateral vessels with amplified angiogenic signals (via VEGF/mTOR/Akt pathway). Similarly, these cells show low survival rates when implanted, which once again supports that the regenerative effects could be

due to their paracrine abilities.^[26]

There are also several studies which investigated the effects of ASCs administration on renovascular diseases. Administration of ASCs in pigs with renal artery stenosis restored renal hemodynamics and function. In addition, increased VEGF levels, angiogenesis promotion and normalized vessel diameters were observed in the renal tissue.^[27]

In our recent studies, we have also acquired results which convinced us that growth factor secretion by ASCs is quite important. Our group has demonstrated that the osteogenic regeneration potential of ASCs combined with platelet rich plasma (PRP) was greater than ASCs alone.^[28] *In vitro* studies showed that ASCs increased concentrations of transforming growth factor beta-1 (TGF- β 1), VEGF, IGF-1 and HGF when co-cultured with PRP. We concluded that improved osteogenesis could be related to increased growth factor secretion. Moreover, co-administration of ASCs with basic fibroblast growth factor (bFGF) on murine ischemic hindlimbs resulted in increased angiogenesis and the enhancement of blood flow to the ischemic limb. Secretion of several angiogenic growth factors was enhanced with bFGF, suggesting that a possible positive feedback mechanism might be responsible for the enhancement of blood flow to the ischemic limb in this study.^[29]

External changes in physiological factors also seem to be influencing the paracrine abilities of ASCs. Rehman *et al.*^[30] demonstrated that, when cultured in hypoxic conditions, VEGF secretion of ASCs increases by 5-fold. The conditioned media obtained from ASCs cultured in hypoxic conditions are found to be superior in enhancing endothelial cell growth compared with media obtained from ASCs cultured in normal conditions. This might be due to an increased secretion of growth factors by ASCs in hypoxic conditions.

The effects of ASCs transplantation on flap viability have also been investigated in detail.^[31] Suartz *et al.*^[32] has showed that ASCs injection increased the viability of random pattern dorsal skin flaps in rats. This application also seems to increase the viability of interpolation flaps and reduce the time until pedicle division, due to increased vascularity of the flap.^[33] Our group also demonstrated that ASCs treatment improves the survival of flaps with venous congestion or provides protection against ischemia-reperfusion injury.^[34] Moreover, when the ASCs were preconditioned in hypoxic conditions then implanted to skin flaps, they were shown to increase flap survival. This phenomenon is thought to be due to the increased release of VEGF

and hypoxia inducible factor-1 α (HIF-1 α) by the preconditioned ASCs.^[35]

There have been several clinical studies conducted on human patients as well. Lee *et al.*^[36] investigated the clinical safety of ASCs administration in patients with critical limb ischemia. Two thirds of the patients showed significant clinical improvement by complete wound healing and formation of collateral vessels in the affected area. There were no side effects or undesirable outcomes after treatment. The authors suggested that the improvement was due to the angiogenic paracrine properties of ASCs; however, the lack of histological and molecular evaluation of the results deems it impossible to offer a clear scientific explanation. Even though the beneficial effects of ASCs such as their differentiation capacity and secretion of pro-angiogenic factors are confirmed *in vitro*, the exact mechanisms for their *in vivo* activity are not well established. More clinical studies are needed to fully comprehend the therapeutic abilities of ASCs in wound healing in order to construct standardized treatment modalities in the future.

THE EFFECTS OF ASCs ON WOUND HEALING

Chronic wounds are a prominent health issue all around the world and the management of these wounds is challenging. Diabetic ulcers, venous ulcers and pressure ulcers represent 80-90% of all chronic wounds.^[37] Even with optimal conditions, the healing process mostly leads to scarring and fibrosis. Many cases fail to heal and lead to amputations of the lower extremity, which are very debilitating for the patient. In addition, these wounds usually have superposed infection, and if not treated correctly may lead to sepsis or even death.^[38] The importance and high prevalence of chronic wounds provoked numerous investigations in order to find a better treatment for these wounds. The positive effects of ASCs on wound healing in chronic and complex wounds (such as anorectal fistula due to Crohn disease) have been well demonstrated.^[39] It is critical to consider that the animal wound models used in these studies are different than human wounds in many aspects; however, the results are promising.

There is evidence that ASCs could be contributing to the healing of both mesodermal (i.e. dermis) and ectodermal (i.e. keratinocytes) derived tissues in the wound.^[40] The interaction between ASCs and keratinocytes has been a subject of interest and a fair amount of investigation has been done regarding this issue. Ozpur *et al.*^[41] has demonstrated that the administration of a fibrin matrix seeded with both

ASCs and keratinocytes led to epithelialization of full thickness wounds with minimal wound contracture. The authors claimed that this improvement in wound healing was due to the paracrine secretions of ASCs. Moreover, co-administration of acellular conditioned medium (CM) from ASCs cultures with PRP increased keratinocyte and fibroblast proliferation,^[42] as well as keratinocyte maturation.^[43]

There is also evidence that ASCs could differentiate into keratinocyte-like cells and express keratinocyte specific markers when co-cultured on a fibroblast layer.^[44,45]

Zografou *et al.*^[46,47] have investigated the effects of transplanted autologous ASCs on full thickness skin graft survival and wound healing in diabetic rats. Graft survival was improved compared with control. Curiously, ASCs showed arrangement in tubular structures which were positively stained with both VEGF and von Willebrand Factor (vWF) staining *in vivo*. Increased tissue expression of TGF- β 3 and VEGF were shown in skin grafts with transplanted ASCs by the same group in another study.

There is also evidence that ASCs have lifesaving effects on the residing cells of tissues after an ischemic insult. A study by Hao *et al.*^[48] showed that transplantation of ASCs inhibited myocyte apoptosis in the ischemic muscle.

Unfortunately, topical or injected ASCs usually tend to stay in the applied location and fail to effectively migrate. The delivery method of ASCs to wounds has been a thoroughly investigated topic of great importance. Delivery systems which supply a favorable microenvironment for the ASCs to survive are suggested to increase their regenerative effects. For example, administration of ASCs to open wounds on a silk fibroin-chitosan scaffold accelerated wound closure and new vessel formation. ASCs delivered by the scaffold infiltrated into the proliferating epithelium and vascular tissue and expressed smooth muscle actin, also differentiated into cells similar to of the epidermal epithelium.^[40] Currently, scaffolds are also being used to induce differentiation of ASCs into specific cell lines.^[49]

There is an increase of radiation injuries and wounds with the widespread use of radiotherapy, interventional radiological or cardiological procedures, and radioactive material intake for nuclear medicine related scans or treatments. Chronic radiation wounds usually cannot be treated with conventional methods such as flap surgery or skin grafting because of

tissue ischemia and fibrosis.^[50] The ischemia is due to inadequate vasculature and incompetent vessels in irradiated tissues. The radiated skin shows erythema, teleangiectasia, abnormal pigmentation and dermal atrophy. Once a radiation wound is developed, it becomes more and more complicated with necrosis, infection, and fibrosis.^[51] These chronic radiation injuries however could improve by sufficient blood supply to the tissues since it is a well known fact that the microvasculature is of utmost importance for proper wound healing.

ASCs therapy is promising for the treatment of such wounds. ASCs residing in the irradiated tissue are susceptible to radiation injury,^[52] but can survive in an irradiated tissue if implanted after the radioactive insult. ASCs administration leads to improved blood perfusion, capillary density and VEGF levels in irradiated wounds.^[22] Viability of irradiated skin flaps increased when treated with ASC injection in correlation with increased vascularity in the flaps injected with ASC.^[53] At cellular level, ASCs were shown to stimulate fibroblast proliferation and increase the expression of several cytokines such as interleukin-6 (IL-6), bFGF and VEGF secreted by fibroblasts after radioactive insult.^[54]

The literature is rich in terms of clinical applications of ASCs to cure radiation injury. Akita *et al.*^[55] injected ASCs to the chronic radiation wounds of 10 patients who received adjuvant radiotherapy after mastectomy. Autologous ASCs with human recombinant bFGF on an artificial dermis were applied on debrided radiation wounds of patients. It is known that MSCs are resistant to radiation. The angiogenic growth factor bFGF has proved to be very effective for patients with severe wounds. Human recombinant bFGF is clinically approved and widely used for the treatment of chronic wounds in Japan. Artificial skin substitutes provide a favorable environment for both internal and external cells and growth factors. This combination treatment led to complete healing of radiation wounds, lasting at least more than 1.5 years. In a similar study, Rigotti *et al.*^[56] investigated the effects of lipoaspirate administration into the radiation wounds of 20 patients who received adjuvant radiotherapy after mastectomy or quadrantectomy for breast cancer. Dramatic improvement of symptoms and complete healing of the wound was observed in all patients. This improvement is believed to be due to the proangiogenic paracrine effects of ASCs present in the lipoaspirate. Despite the encouraging clinical results, it should be noted that neither of these studies included a patient group without treatment for comparison. Future studies with randomized subjects are necessary for a higher level of evidence.

It is being more widely acknowledged that ASCs have revitalizing effects on stem-cell depleted tissues such as radiation wounds or ischemic fibrotic tissues.^[57,58] Administration of ASCs seems to improve vascularity and healing capacity for these morbid conditions. This matter is very promising since there are currently no effective treatments for these conditions.

THE SYNERGISM BETWEEN ASCS AND MACROPHAGES AND THE IMMUNE REGULATORY EFFECTS OF ASCS

Another recent focus of interest on ASCs research is the cells' relation to immunomodulation.^[59] Like any other cell, ASCs interact with other cells, and especially their relations with macrophages have recently become a topic of interest. It is known that there are two macrophage subsets; the M1 phenotype which has pro-inflammatory properties, and the M2 phenotype which has anti-inflammatory effects on tissue. ASCs are shown to interact especially with the M2 subset.^[60,61] M2 macrophage activation by the interaction with ASCs improves the volume retention of fat grafts by stimulating angiogenesis.^[62] As an explanation of this observation, gene expression of several angiogenic cytokines, such as VEGF, HGF, bFGF, and stromal cell-derived factor-1 were found to be increased in the macrophages cultured in ASCs conditioned media. Additional studies documented that the host macrophage depletion significantly impairs ASCs mediated angiogenesis and ASCs mediated angiogenesis can be prevented with monoclonal antibody mediated blocking of IL-10 (a cytokine product of macrophages).^[63] It was also suggested that M2 macrophages play an important role in the ASCs mediated lymphangiogenesis.^[47] Taken together, these findings support the hypothesis that an existing association with ASCs and might be an important regulator of angiogenesis [Figure 2].

In addition, it was demonstrated that ASCs inhibit and decrease inflammatory cytokines and increase IL-10 levels *in vivo* by acting on macrophages.^[64] This suggests that ASCs might have immunomodulatory effects by regulating pro-inflammatory cytokine concentrations in the inflamed tissue. It is most likely due to this effect that ASCs transplantation in dystrophic muscles of dystrophin-deficient mice improved muscle strength and resistance to fatigue.^[65] It was also documented that ASCs transplantation induces macrophage migration and the secretions of ASCs are dependent on inflammatory cells.^[66]

There are other studies regarding the interaction between ASCs and fibroblasts in the literature.

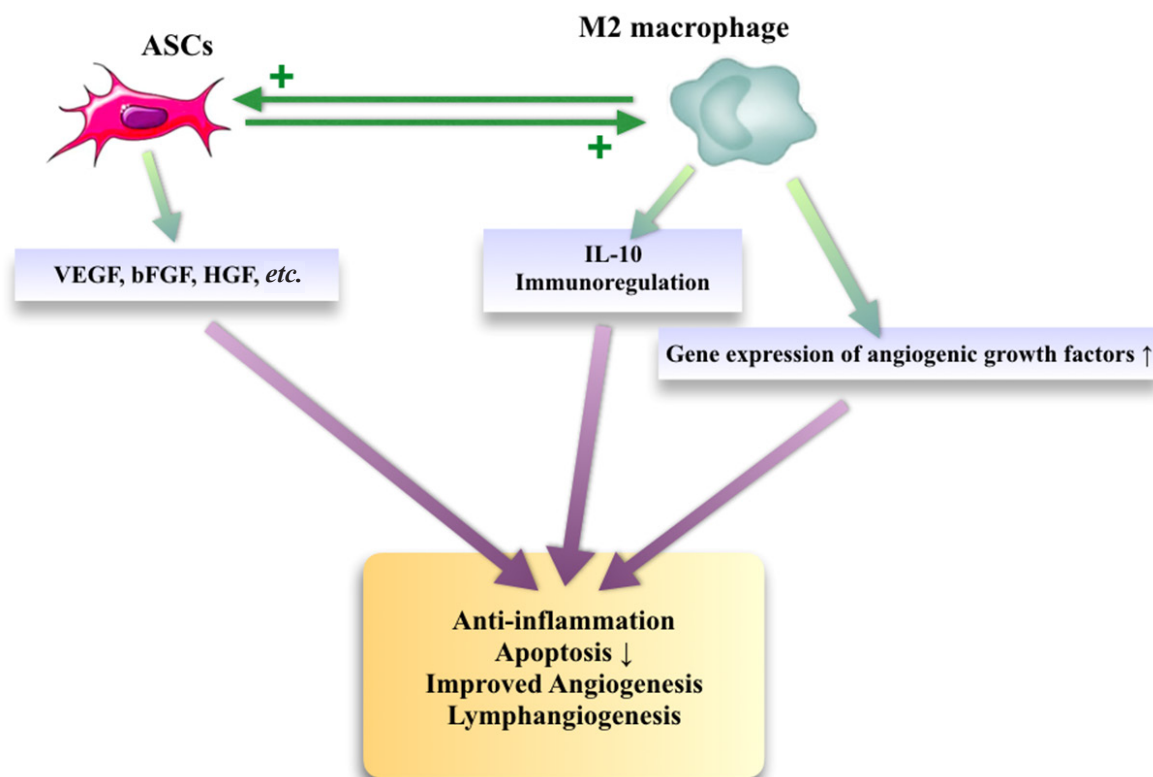


Figure 2: The interaction between ASCs and M2 macrophages. ASCs: adipose-derived stem cells; VEGF: vascular endothelial growth factor; bFGF: basic fibroblast growth factor; HGF: hepatocyte growth factor; IL-10: interleukin-10

Kim *et al.*^[67] showed that ASCs conditioned media promotes dermal fibroblast proliferation, suggesting the paracrine activation of fibroblasts by ASCs. The same fibroblasts cultured in ASCs conditioned media were found to secrete increased amounts of type I collagen, and their expression of ECM proteins were found to be augmented. These findings suggest that this interaction might be playing an important role in wound healing.

SUMMARY

Many tissues have “intrinsic” stem cells in a resting state, activated with injury in order to repair the damage. However, the number of these cells is usually very small for complete regeneration by differentiating into the harmed cell lines. Recent investigations suggest that most stem cell lines also secrete potent growth factors, and this indirect “paracrine” or “bystander” effect could be as important as their ability to differentiate in tissue regeneration.^[68] There is convincing evidence that the paracrine secretions by ASCs improve wound healing and angiogenesis. The data that we have obtained in our lab over the years in several experiments also suggest that the paracrine secretions of ASCs are extremely potent. We believe that an accurate knowledge of ASCs secretome and its effects will help us to establish ASCs as a more viable clinical therapy in the future.

Authors' contributions

Manuscript's preparation: D. Orgun

Manuscript's review: H. Mizuno

Concept and design: H. Mizuno

Literature search: D. Orgun

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration when reporting studies on human beings.

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Pressures secondary to circumferential digital dressings in clay models

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ABSTRACT

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Key words:

Pressure,
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Aim: With little manipulation, compression bandages placed circumferentially around the digit can be rolled up the digit, creating a tourniquet effect. The aim of this study was to elucidate the pressures induced by self-adherent bandages applied circumferentially around the fingers. **Methods:** After fabricating various clay finger models using the live finger as a model, the pressure of each self-adherent bandage was measured at the level of the proximal phalanx. Two different self-adherent bandages were applied with variables of different levels of tightness, number of wraps, and whether each was rolled up or not. Pressure was measured using a digital measuring device at a standardized location. **Results:** The measured pressure of 3 wraps along the adult finger model was higher than 1 wrap or 2 wraps, and untightened bandages had lower pressures than those of tightened bandages. The pressures of the unrolled bandages were lower than those of rolled up bandages, and pressures along the live finger of the rolled up group were higher than those in the adult finger model. Additionally, measured pressures from the child finger model were higher than those from the adult model. **Conclusion:** Precautions should be taken to prevent rolling up dressing materials, especially in children.

INTRODUCTION

The hands and fingers are common sites of injury, accounting for an estimated 4.8 million injured persons treated in US hospital emergency departments in 2001

alone. Three million of these injuries involved one or more fingers, of which 1.3 million (44%) were diagnosed as finger lacerations.^[1] To minimize the morbidity associated with these injuries, digital tourniquets are necessary to provide a bloodless environment to



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facilitate the identification of deep tissue injuries and foreign bodies.^[2] After the repair of hand lacerations, the wound dressing is usually covered with compression bandages that are applied circumferentially around the digit. Often, dependable tapes are used. However, with very little manipulation, these bandages can be lifted and rolled up the digit distally, creating a tourniquet effect. Vascular insufficiency from an occlusive dressing is an iatrogenic and avoidable complication, and therefore circumferential digital dressings should be applied correctly.^[3]

To prevent the dressing from rolling up and creating a tourniquet effect, Hart *et al.*^[4] suggested that the dressing should be brought down from the finger, to include the hand and wrist. Despite the importance of preventing finger necrosis,^[5,6] the pressures generated by circumferential dressings have not yet been studied. The aim of this study was to elucidate the pressures occurring secondary to self-adherent bandages applied circumferentially around the fingers.

METHODS

Making a clay finger model

With clay, finger models of 7 cm (adult) and 4 cm (child) in circumference at the level of the proximal phalanx level were made. Biscuit firing was performed. The pressure of each self-adherent bandage was measured using live adult finger models (7 cm circumference). A 6 cm width Peha-haft (Hartmann USA, Inc, Rock hill, SC) and a Coban (3M Co, St. Paul, MN) were used as self-adherent bandages. Experiments were performed with the following variable for each model: dressing materials, wraps, tightness and roll-up states.

Applying methods

According to the length

The pressures were measured according to the total length of the elastic dressings:

1C: elastic dressing was wound 1 lap around a finger model with the same length as its circumference (7 cm).
2C: elastic dressing was wound 2 laps around a finger model with 2 times the length of its circumference (14 cm).
3C: elastic dressing was wound 3 laps around a finger model with 3 times the length of its circumference (21 cm).

According to the tightness

The pressures were measured according to the tightness of the elastic dressings:

T0: 0% tightened.
T1: 9.4% tightened.
T2: 19.7% tightened.
T3: 33.3% tightened.
T4: 50.5% tightened.

Adult finger model

In the adult finger model, the pressures were measured according to the total length of the bandages without tightening, different tightness using 2 wraps, roll-up states and different dressing materials. According to the total length of the bandages without tightening, the self-adherent bandage was wound 1 (1C-T0), 2 (2C-T0), or 3 times (3C-T0) around the finger model with 1 (7 cm), 2 (14 cm), or 3 (21 cm) times the length of its circumference. For the different tightness, the self-adherent bandage was wound employing 2 wraps around the finger model with twice (14 cm, 0% tightened, 2C-T0) the length of its circumference, 91.4% (12.8 cm, 9.4% tightened, 2C-T1), 83.6% (11.7 cm, 19.7% tightened, 2C-T2), 75% (10.5 cm, 33.3% tightened, 2C-T3), or at 66.4% (9.3 cm, 50.5% tightened, 2C-T4) the length of its circumference [Figure 1]. The pressures were measured in both unrolled (NR) and rolled up (R) states. The width of the rolled up portion of the bandage was 6 cm. Pressures were also measured according to the dressing materials, Peha-haft (Ph) or Coban (Co).

Child finger model

In the child finger model, the same experiments as with adult finger model were done except the different tightness using two wraps. The width of the rolled up portion of the bandage was three cm.

Live adult finger

In the live adult finger, the same experiments as with child finger model were repeated. The width of the rolled up portion of the bandage was six cm.

Measurements using a pressure sensor

Pressures were measured using a FlexiForce B201-M pressure sensor, ELFTM system (Tekscan, Inc., South

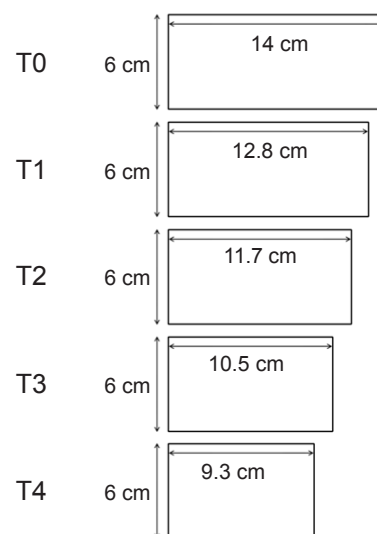


Figure 1: Size of the self-adherent bandages for different tightness

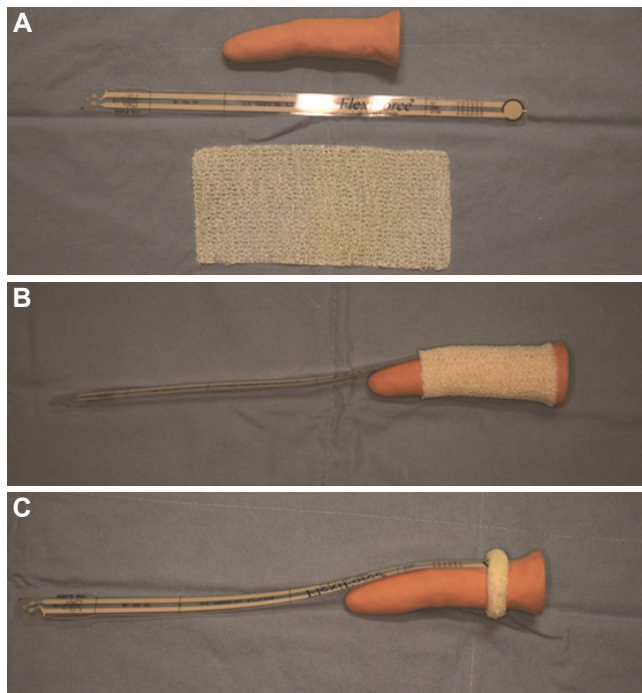


Figure 2: Making a finger tourniquet and pressure measurements. A: finger model, pressure sensor, and self-adherent bandage; B: the sensor was placed in a standardized location and the bandage was wound two wraps around the finger model; C: the bandage was rolled up along the finger model

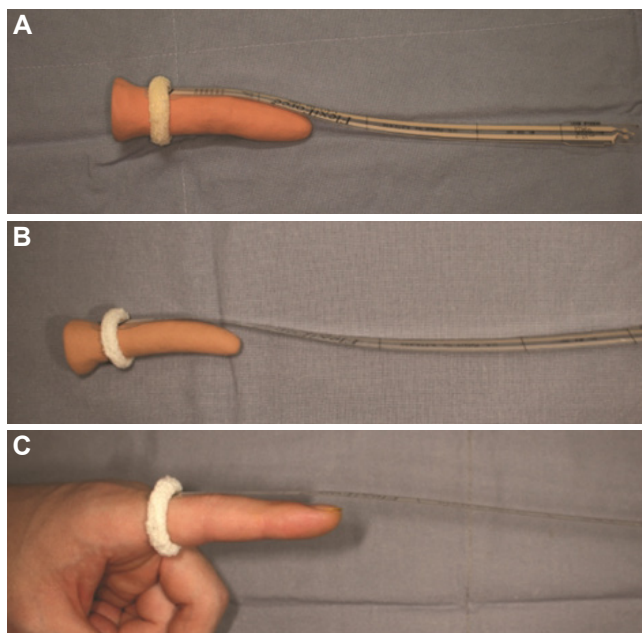


Figure 3: Finger models. A: adult finger model; B: child finger model; C: finger of a living body

Boston, MA), which is a flexible, wafer thin (0.005") 10 mm diameter disk-shaped sensor designed specifically to measure the force between 2 surfaces without disturbing the dynamics of the test.^[2] The sensor was placed in a standardized location on the dorsum of each digit equidistant from the

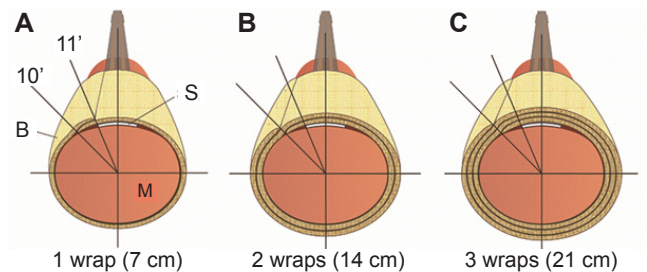


Figure 4: Schematic representation of the location of the pressure sensor (S) and wraps around the finger model (M); B: self-adherent bandage. A: 1 wrap with the same length of its circumference; B: 2 wraps with 2 times the length of its circumference; C: 3 wraps with 3 times the length of its circumference

metacarpophalangeal and proximal phalangeal joints with the reasoning that the pressures of the dorsal and volar surfaces are the same in a circumferential dressing, and pressure measurements of the dorsum are easier to take in living subjects [Figures 2-4]. The pressure sensor was calibrated to measure pressures in the range of 0 to 4,500 mm of mercury obtained by the Economical Load and Force software program at a refresh rate of 200 Hz. The pressure measurements were made by the same person to prevent bias.

Statistical analysis

The program SPSS 19.0 (IBM, Armonk, NY) was used for a statistical analysis. For comparison between 2 groups, the independent 2 samples *t*-test was used. For comparison among more than 3 groups, analysis of variance (ANOVA) was used. When the *P* value was less than 0.05, the data were interpreted as statistically significant.

RESULTS

Measured pressures were higher in tighter bandages, in rolled-up bandages, with the use of Co, in the live models, and in adults.

According to the length along the adult finger model (1C-T0, 2C-T0, 3C-T0): the measured pressure of 3 wraps (3C-T0, 384.9 ± 660.5 mmHg) was significantly higher than that for 1 wrap (1C-T0, 35.3 ± 37.5 mmHg, $P < 0.001$), or 2 wraps (2C-T0, 44.1 ± 47.7 mmHg, $P < 0.001$). However, there was no significant difference between 1 wrap and 2 wraps ($P = 0.994$) [Figure 5].

According to the tightness of 2 wraps along the adult finger model (2C-T0, 2C-T1, 2C-T2, 2C-T3, 2C-T4): the measured pressures of the untightened bandages (2C-T0, 44.1 ± 47.7 mmHg) were significantly lower than those of the tightened bandages (2C-T1~4, $680.2 \pm 1,274.1$ mmHg, $P < 0.001$). The measured pressures of the untightened bandages and each tightened

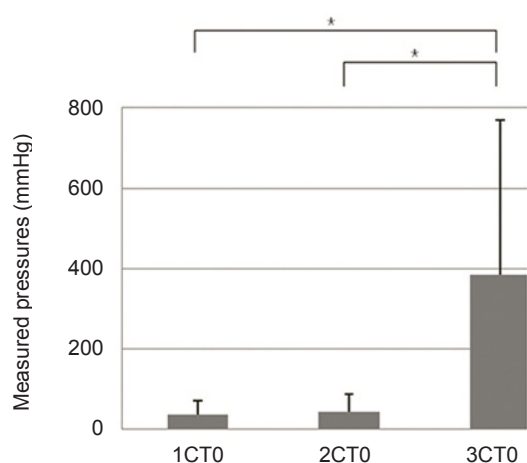


Figure 5: Measured pressures according to the length of the bandage without tightness along the adult finger model. 1CT0: 1 wrap with the same length of its circumference; 2CT0: 2 wraps with 2 times the length of its circumference; 3CT0: 3 wraps with 3 times the length of its circumference. * $P < 0.05$

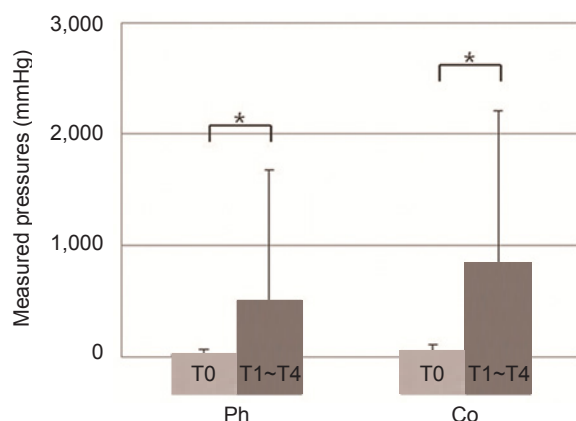


Figure 6: Measured pressures according to the tightness in different materials along the adult finger model. T0: untightened bandage; T1~T4: tightened bandages; Ph: Peha-haft; Co: Coban. * $P < 0.05$

bandage were 44.1 ± 47.7 mmHg (2C-T0, 0%), 61.2 ± 67.4 mmHg (2C-T1, 9.4%), 261.1 ± 409.5 mmHg (2C-T2, 19.7%), 471.2 ± 671.3 mmHg (2C-T3, 33.3%), and $1,945.0 \pm 1,945.0$ mmHg (2C-T4, 50.5%), respectively. The measured pressures of the 2C-T4 (50% tightened) were significantly higher ($P < 0.001$) than those in other groups. However, there was no significant difference between the 2C-T0, 2C-T1, 2C-T2, and 2C-T3 parameters ($P > 0.05$). For each material (Ph and Co), the measured pressures of the untightened bandage (T0-Ph, 34.8 ± 36.6 mmHg), (T0-Co, 53.5 ± 56.1 mmHg) was significantly lower than that of the tightened bandage (T1~T4-Ph, $511.9 \pm 1,166.1$ mmHg, $P < 0.001$), (T1~T4-Co, $848.4 \pm 1,360.2$ mmHg, $P < 0.001$) [Figure 6].

Regarding rolled bandages in the adult finger model (NR, R): the measured pressures of the unrolled bandages (NR, 14.2 ± 25.4 mmHg) were significantly

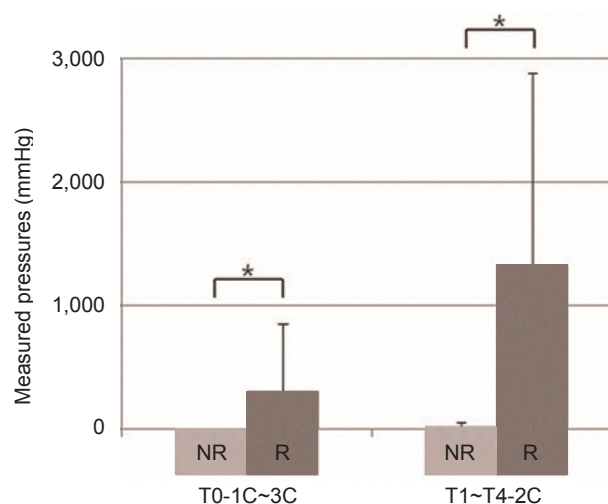


Figure 7: Measured pressures according to the rolling up of untightened dressings and tightened dressings along the adult finger model. NR: unrolled; R: rolled up; T0-1C~3C: untightened bandages; T1~T4-2C: tightened bandages. * $P < 0.05$

lower than those of the rolled bandages (R, $793.1 \pm 1,265.7$ mmHg, $P < 0.001$). In each untightened and tightened bandage (T0-1C~3C), (T1~T4-2C), the measured pressures of the unrolled bandages (T0-1C~3C-NR, 0 ± 0 mmHg), (T1~T4-2C-NR, 28.3 ± 29.9 mmHg), were significantly lower than those for the rolled bandages (T0-1C~3C-R, 309.6 ± 544.0 mmHg, $P < 0.001$), (T1~T4-2C-R, $1,332.0 \pm 1,551.1$ mmHg, $P < 0.001$) [Figure 7].

Regarding rolls of bandages at various lengths along the adult finger model (NR, R in 1C-T0, 2C-T0, 3C-T0): in each wrap (1C-T0, 2C-T0, 3C-T0), the measured pressures of the unrolled bandages (1C-T0-NR, 0 ± 0 mmHg), (2C-T0-NR, 0 ± 0 mmHg), (3C-T0-NR, 0 ± 0 mmHg) were significantly lower than those of the rolled bandages (1C-T0-R, 70.7 ± 15.9 mmHg, $P < 0.001$), (2C-T0-R, 88.2 ± 24.0 mmHg, $P < 0.001$), (3C-T0-R, 769.8 ± 764.0 mmHg, $P < 0.001$). In the above situations, the same results were yielded for each material (Ph, Co) [Table 1].

Regarding various levels of tightness along the adult finger model (NR, R in 2C-T0, 2C-T1, 2C-T2, 2C-T3, 2C-T4): at each tightness level, bandages of the 2 C group (2C-T0, 2C-T1, 2C-T2, 2C-T3, 2C-T4), measured pressures of the not-rolled up bandage (2C-T0-NR, 0 ± 0 mmHg), (2C-T1-NR, 0 ± 0 mmHg), (2C-T2-NR, 24.8 ± 25.4 mmHg), (2C-T3-NR, 24.76 ± 25.4 mmHg), (2C-T4-NR, 63.9 ± 14.7 mmHg) were significantly lower than those for the rolled up bandage (2C-T0-R, 88.2 ± 24.0 mmHg, $P < 0.001$), (2C-T1-R, 122.4 ± 37.9 mmHg, $P < 0.001$), (2C-T2-R, 497.5 ± 475.3 mmHg, $P < 0.001$), (2C-T3-R, 917.7 ± 710.4 mmHg, $P < 0.001$), (2C-T4-R, $3,790.4 \pm 675.2$ mmHg, $P < 0.001$). In the above situations, the same results were shown for each

Table 1: Measured pressures according to the length of different dressing materials and in a rolled up state in the adult finger model (mean \pm SD)

Group	NR	R	P value
1C-T0-Ph	0.0 \pm 0.0	57.9 \pm 7.2	< 0.001
2C-T0-Ph	0.0 \pm 0.0	69.5 \pm 12.1	< 0.001
3C-T0-Ph	0.0 \pm 0.0	114.1 \pm 34.0	< 0.001
1C-T0-Co	0.0 \pm 0.0	83.5 \pm 10.6	< 0.001
2C-T0-Co	0.0 \pm 0.0	107.0 \pm 17.0	< 0.001
3C-T0-Co	0.0 \pm 0.0	1,425.6 \pm 524.9	< 0.001

NR: unrolled; R: rolled up; 1C: elastic dressing was wound 1 lap around a finger model with the same length of its circumference (7 cm); 2C: elastic dressing was wound 2 laps around a finger model with 2 times the length of its circumference (14 cm); 3C: elastic dressing was wound 3 laps around a finger model with 3 times the length of its circumference (21 cm); T0: 0% tightened; Ph: Peha-haft; Co: Coban

material (Ph, Co) [Table 2].

Rolling up of different dressing materials along the adult finger model (NR, R in Ph, Co): for the Ph, the measured pressures of the unrolled elastic dressing (Ph-NR, 7.1 \pm 17.5 mmHg) were significantly lower than those for the rolled up elastic dressing (Ph-R, 612.5 \pm 1,217.8 mmHg, P < 0.001). For the Co, the measured pressures of the unrolled elastic dressing (Co-NR, 25.3 \pm 30.8 mmHg) were significantly lower than those for the rolled up elastic dressing (Co-R, 1,175.2 \pm 1,372.4 mmHg, P < 0.001) [Figure 8].

According to the dressing materials along the adult finger model (Ph, Co): the measured pressures of Ph (Ph, 309.8 \pm 910.3 mmHg) were significantly lower than those for Co (Co, 600.2 \pm 1,126.2 mmHg, P = 0.018). In the unrolled group (NR), the measured pressures of the Ph (UR-Ph, 7.1 \pm 17.5 mmHg) were significantly lower than those for Co (UR-Co, 25.3 \pm 30.8 mmHg, P < 0.001). In the rolled up group (R), the measured pressures of the Ph (R-Ph, 612.5 \pm 1,217.8 mmHg) were significantly lower than those for Co (R-Co,

Table 2: Measured pressures according to the tightness of different dressing materials and rolled up state in the adult finger model (mean \pm SD)

Group	NR	R	P value
2C-T0-Ph	0.0 \pm 0.0	69.5 \pm 12.1	< 0.001
2C-T1-Ph	0.0 \pm 0.0	87.9 \pm 17.3	< 0.001
2C-T2-Ph	0.0 \pm 0.0	112.5 \pm 13.7	< 0.001
2C-T3-Ph	0.0 \pm 0.0	370.6 \pm 156.7	< 0.001
2C-T4-Ph	49.5 \pm 0.0	3,475 \pm 803.3	< 0.001
2C-T0-Co	0.0 \pm 0.0	107 \pm 17.0	< 0.001
2C-T1-Co	0.0 \pm 0.0	156.9 \pm 9.4	< 0.001
2C-T2-Co	49.5 \pm 0.0	882.5 \pm 383.7	< 0.001
2C-T3-Co	49.5 \pm 0.0	1,464.8 \pm 613.0	< 0.001
2C-T4-Co	78.2 \pm 0.0	4,105.8 \pm 309.6	< 0.001

NR: unrolled; R: rolled up; 2C: elastic dressing was wound 2 laps around a finger model with the 2 times the length of its circumference (14 cm); T0: 0% tightened; T1: 9.4% tightened; T2: 19.7% tightened; T3: 33.3% tightened; T4: 50.5% tightened; Ph: Peha-haft; Co: Coban

1,175.2 \pm 1,372.4 mmHg, P = 0.011) [Figure 9]. In the untightened bandages (T0-1C~3C), the measured pressures of the Ph (T0-1C~3C-Ph, 40.2 \pm 46.4 mmHg) were significantly lower than those for Co (T0-1C~3C-Co, 269.3 \pm 562.0 mmHg, P = 0.002). In the tightened dressings (T1~T4-2C), the measured pressures of the Ph (T1~T4-2C-Ph, 511.9 \pm 1,166.1 mmHg) and Co (T1~T4-2C-Co, 848.4 \pm 1,360.2 mmHg) were not significantly different (P = 0.095). In 1 and 2 wraps (1C-T0, 2C-T0), the measured pressures of the Ph (1C-T0-Ph, 28.9 \pm 30.1 mmHg), (2C-T0-Ph, 34.8 \pm 36.6 mmHg) and Co (1C-T0-Co, 41.8 \pm 43.5 mmHg), (2C-T0-Co, 53.5 \pm 56.1 mmHg) were not significantly different (P = 0.285, P = 0.220). However, for 3 wraps (3C-T0), the measured pressures of the Ph (3C-T0-Ph, 57.0 \pm 63.0 mmHg) were significantly lower than those for Co (3C-T0-Co, 712.8 \pm 815.7 mmHg, P = 0.002). At each different tightness of the bandages of the 2C group, the measured pressures of the Ph and Co were not significantly different except at 19.7% and 33.5% of the

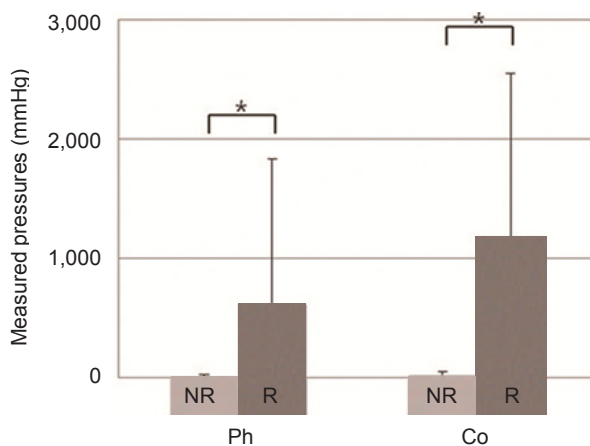
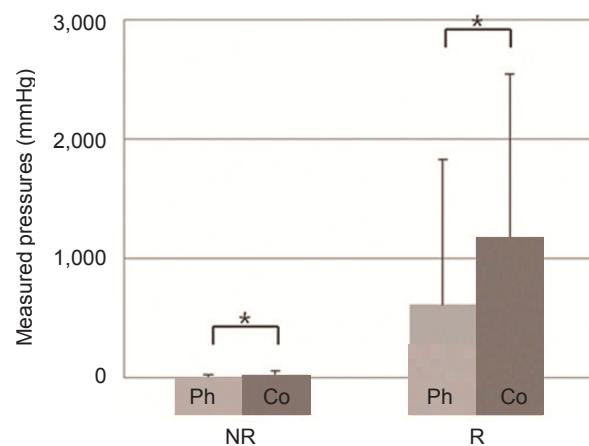
**Figure 8: Measured pressures according to the rolling up of the Peha-haft (Ph) and Coban (Co) along the adult finger model. NR: unrolled; R: rolled up. * P < 0.05****Figure 9: Measured pressures according to the bandage materials in the unrolled group (NR) and the rolled up group (R) along the adult finger model; Ph: Peha-Haft; Co: Coban. * P < 0.05**

Table 3: Statistical differences according to rolling up at different lengths in the child finger model (mean \pm SD)

Group	NR	R	P value
1C-T0-Ph	0.0 \pm 0.0	210.6 \pm 117.0	< 0.001
2C-T0-Ph	0.0 \pm 0.0	323.7 \pm 186.9	< 0.001
3C-T0-Ph	0.0 \pm 0.0	904.9 \pm 462.1	< 0.001

NR: unrolled; R: rolled up; 1C: elastic dressing was wound 1 lap around a finger model with the same length of its circumference (7 cm); 2C: elastic dressing was wound 2 laps around a finger model with 2 times the length of its circumference (14 cm); 3C: elastic dressing was wound 3 laps around a finger model with 3 times the length of its circumference (21 cm); T0: 0% tightened; Ph: Peha-haft

Table 4: Statistical differences according to rolling up at different lengths in the adult finger of a living body (mean \pm SD)

Group	NR	R	P value
1C-T0-Ph	0.0 \pm 0.0	277.5 \pm 227.5	0.004
2C-T0-Ph	0.0 \pm 0.0	636.2 \pm 558.0	0.006
3C-T0-Ph	0.0 \pm 0.0	1,005.6 \pm 644.5	0.001

NR: unrolled; R: rolled up; 1C: elastic dressing was wound 1 lap around a finger model with the same length as its circumference (7 cm); 2C: elastic dressing was wound 2 laps around a finger model with 2 times the length of its circumference (14 cm); 3C: elastic dressing was wound 3 laps around a finger model with 3 times the length of its circumference (21 cm); T0: 0% tightened; Ph: Peha-haft

tightened bandages of the 2C group. In the 19.7% and 33.5% tightened bandages of the 2C group (2C-T2, 2C-T3), the measured pressures of the Ph (2C-T2-Ph, 56.2 \pm 58.5 mmHg), (2C-T3-Ph, 185.3 \pm 218.6 mmHg) were significantly lower than those for Co (2C-T2-Co, 466.0 \pm 502.3 mmHg, P = 0.002), (2C-T3-Co, 757.2 \pm 839.7 mmHg, P = 0.008).

Rolling up at different lengths along the child finger model (NR, R in 1C-T0, 2C-T0, 3C-T0): in each wrap using the Ph (1C-T0-Ph, 2C-T0-Ph, 3C-T0-Ph), the measured pressures of the unrolled bandage (1C-T0-Ph-NR, 0 \pm 0 mmHg), (2C-T0-Ph-NR, 0 \pm 0 mmHg), (3C-T0-Ph-NR, 0 \pm 0 mmHg) were significantly lower than those for the rolled up bandage (1C-T0-Ph-R, 210.6 \pm 117.0 mmHg, P < 0.001), (2C-T0-Ph-R, 323.7 \pm 186.9 mmHg, P < 0.001), (3C-T0-Ph-R, 904.9 \pm 462.1 mmHg, P < 0.001) [Table 3].

Rolling up at different lengths along the live adult finger (NR, R in 1C-T0, 2C-T0, 3C-T0): in each wrap with the Ph (1C-T0-Ph, 2C-T0-Ph, 3C-T0-Ph), the measured pressures of the unrolled bandage (1C-T0-Ph-NR, 0 \pm 0 mmHg), (2C-T0-Ph-NR, 0 \pm 0 mmHg), (3C-T0-Ph-NR, 0 \pm 0 mmHg) were significantly lower than those for rolled up bandage (1C-T0-Ph-R, 277.5 \pm 227.5 mmHg, P = 0.004), (2C-T0-Ph-R, 636.2 \pm 558.0 mmHg, P = 0.006), (3C-T0-Ph-R, 1,005.6 \pm 644.5 mmHg, P = 0.001) [Table 4].

In the rolled up bandage of the untightened group (1C~3C-T0-R), the measured pressures along the adult

Table 5: Statistical differences according to rolling up of adult and child finger models (mean \pm SD)

Group	A	B	P value
1C-T0-Ph-R	57.9 \pm 7.2	210.6 \pm 117.0	0.003
2C-T0-Ph-R	69.5 \pm 12.1	323.7 \pm 186.9	0.002
3C-T0-Ph-R	114.1 \pm 34.0	904.9 \pm 462.1	0.000
(1C~3C)-T0-Ph-R	80.5 \pm 32.1	479.7 \pm 420.8	< 0.001

A: adult finger model; B: child finger model; R: rolled up; 1C: elastic dressing was wound 1 lap around a finger model with the same length as its circumference (7 cm); 2C: elastic dressing was wound 2 laps around a finger model with 2 times the length of its circumference (14 cm); 3C: elastic dressing was wound 3 laps around a finger model with 3 times the length of its circumference (21 cm); T0: 0% tightened; Ph: Peha-haft

Table 6: Statistical differences according to rolling up of the adult finger model and the live finger (mean \pm SD)

Group	A	C	P value
1C-T0-Ph-R	57.9 \pm 7.2	277.5 \pm 227.5	0.014
2C-T0-Ph-R	69.5 \pm 12.1	636.2 \pm 558.0	0.011
3C-T0-Ph-R	114.1 \pm 34.0	1,005.6 \pm 644.5	0.002
(1C~3C)-T0-Ph-R	80.5 \pm 32.1	639.7 \pm 577.1	< 0.001

A: adult finger model; C: finger in living body; R: rolled up; 1C: elastic dressing was wound 1 lap around a finger model with the same length as its circumference (7 cm); 2C: elastic dressing was wound 2 laps around a finger model with 2 times the length of its circumference (14 cm); 3C: elastic dressing was wound 3 laps around a finger model with 3 times the length of its circumference (21 cm); T0: 0% tightened; Ph: Peha-haft

finger model (1C~3C-T0-R, 80.5 \pm 32.1 mmHg) were significantly lower than those in the child finger model (1C~3C-T0-R, 479.7 \pm 420.8 mmHg, P < 0.001) and live adult finger (1C~3C-T0-R, 639.7 \pm 577.1 mmHg, P < 0.001). In the above situations, the same results were shown for each wrap [Tables 5 and 6].

DISCUSSION

As material is rolled around a digit, it becomes tighter, exsanguinating the fingertip and constricting the digit. This quickly becomes uncomfortable. If this happens to an adult, the patient will likely cut and remove the constricting device. However, children, especially those two years old and under, do not understand this and cannot remove the dressing quickly. A similar lack of understanding or action also may occur in elderly and mentally compromised patients. If the constriction tightens to the point that all vascular flow is impeded into the tip of the digit, hypoxia and eventually tissue necrosis will occur. Thus, a simple, soft tissue injury can become a more serious injury. Although no studies in the literature have reported the incidence of this condition, any physician who has applied a finger dressing knows how easily a circumferentially applied dressing, such as Co, can roll up when manipulated, as when a child plays with a dressing.^[4]

Lahham et al.^[2] noted that digital tourniquet methods

have complications associated with their use. Necrosis of a digit due to a forgotten tourniquet is an uncommon but catastrophic complication.^[7-11] Most complications occur with use of the least conspicuous dressings.^[12-16] While digital necrosis secondary to a forgotten tourniquet is the most severe complication related to digital tourniquet use, most complications are related to excessive tourniquet pressure.

Co (3 M Co, St. Paul, MN) is a self-adherent bandage made from a porous, non-woven polyester material, with strands of urethane coated with a cohesive substance. Co sticks only to itself and not to the skin, and provides sustained compression.^[17] In soft tissue injuries, it is recommended that 30 cm of the Co be unwound and allowed to relax because if applied directly from the roll, the tension will be too great. Mendlowitz^[18] reported the mean digital arterial systolic blood pressure in adults to be 100 mmHg, with a pressure range of 84 to 120 mmHg. Based on their experience using digital tourniquets on patients in a clinical setting, Shaw *et al.*^[19] reported pressures of 150 mmHg to be "very adequate" to maintain hemostasis.

Tuncali *et al.*^[20] reported a method for estimation of the arterial occlusion pressure; according to these principles the pressure necessary to prevent digital blood flow ranges from 110 to 140 mmHg. In this study, the average pressures in the rolled and untightened bandage group along the live finger were significantly higher than those for the adult finger model. Therefore, dressing materials are not intended to be rolled up on the finger in the clinical setting. Additionally, measured pressures in the child finger model (479.7 ± 420.8 mmHg, $P < 0.001$) were significantly higher than those for the adult finger model (80.5 ± 32.1 mmHg). These results support the need for great caution when using rolled bandages in children. The pressures with the use of Co were relatively higher than those for rolled Ph, which is thought to be due to the thickness of the dressing. The thickness of Co (2 mm) is thicker than that of Ph (1 mm) when unrolled, and therefore it becomes much thicker when rolled. Therefore, great caution is needed to prevent rolling of Co dressings.

In the current study, pressures were measured on a clay model as well as human model. In the human model, limb elevation is an important method used for the prevention of post-dressing limb edema. Limb elevation plays a role in the reduction of finger swelling and improving circulation. The same cannot be done in the clay model. Because all data was obtained based on the clay model instead of live fingers, it cannot be claimed that the data mimics the clinical situation perfectly. This is a limitation of this study.

This study was performed to prevent an over-tightening of bandages in fingers and to make the reader aware of the necessity to anchor the bandage above the wrist. In conclusion, when applying pressure dressings to fingers, great caution is needed to prevent rolling-up which can create a tourniquet effect.

Authors' contributions

Concept design: K. Hwang

Literature search: K. Hwang

Measurement of the pressure: H.J. Kim

Manuscript's preparation: H.J. Kim, K. Hwang

Manuscript's review: K. Hwang

This paper is made from the a thesis entitled "The Measurement of the Pressures Applied by Self-adherent Bandages to Prevent the Ischemic Damage of the Fingers" by Han Joon Kim, A THESIS Submitted to the faculty of INHA UNIVERSITY in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE, Aug, 2014.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration when reporting studies on human beings.

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Case Report

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Unilateral rhinophyma: report of a case and review

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ABSTRACT

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Rhinophyma is a less-common subtype of rosacea that presents as thickened skin with enlarged sebaceous glands that may progress to large bulbous growths with dilated pores on the nose. Rhinophyma can lead to morbidity aesthetically and sometimes functionally. The prevalence of rosacea ranges from 1% to 20%. The exact pathogenesis is not known, but potential factors include altered circulation, changes in microorganisms and/or alterations in immunity. Here the authors present a unique case where a patient presented with unilateral rhinophyma: a presentation warranting work up to rule out other more worrisome entities.

INTRODUCTION

Rhinophyma is the most prevalent presentation of the phymatous subtype of rosacea. Rosacea subtypes include erythematotelangiectatic type (type 1), papulopustular rosacea (type 2), phymatous rosacea (type 3) and ocular rosacea (type 4).^[1] Phymatous rosacea is characterized early by prominent follicular pores or patulous follicles with mild swelling while advanced disease reveals pronounced hyperemic skin thickening, irregular surface nodularities representing sebaceous gland hypertrophy and eventual distortion of the nasal surface architecture.^[2] It typically occurs on the nose as a bulbous irregular growth with dilated pores and background telangiectasia. Occasionally very advanced disease may lead to nasal obstruction and sleep apnea.^[3] While rhinophyma refers to when

this subtype occurs on the nose, phymatous rosacea can also occur more rarely on the chin (gnathophyma), ears (otophyma), forehead (mentophyma), or eyelids (blepharophyma). Rhinophyma can occur in isolation and its severity does not always correlate with duration of disease.^[4] It is no longer thought to be an end stage of rosacea.^[2]

Here we present a case of a patient with unilateral rhinophyma of the right nasal ala. This is an unusual presentation for which we believe this is the first report, as we cannot find any other reports in the literature.

CASE REPORT

A 77-year-old male with a medical history of hypertension and chronic kidney disease presented



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with a 1-year history of a growing mass on the right nasal ala. The patient reported it started as a small papule and spread over the ala over the course of a year; he noticed most of the growth during the last 4 months up to presentation. The patient denied any history of trauma to the area and denied manipulating the area. He denied using any topical medications or products on his nose. He did not have a history of similar lesions on the nose in the past. He denied any personal or family history of rosacea or of skin cancer. The patient was originally from El Salvador and then immigrated to the United States. He was retired from his work at the time of presentation. He previously worked outdoors in construction for many years and had a number of sunburns in the past.

Physical examination revealed a 2.5 cm × 2.0 cm soft lobulated skin colored nodule with overlying prominent dilated pores encompassing the entire right nasal ala [Figure 1]. The left nasal ala was not affected. On examination of the remainder of his face, his bilateral cheeks and nose showed sebaceous skin with multiple scattered dilated pores and open comedones and a few small telangiectasias. There were no facial pustules. There was not any palpable lymphadenopathy. The remainder of his skin on his body was normal. Because the differential diagnosis could include cutaneous sarcoidosis, we asked the patient and he did not have a cough or any shortness of breath. Review of systems was negative for any other symptoms or concerns. Given the growth and unilateral nature of the identified nodule, a shave biopsy was performed on the edge of the mass to evaluate the lesion. The pathology report from the biopsy was read as a fibrous papule. Clinically, however, the lesion was more consistent with rhinophyma. The patient underwent electrosurgical excision of the growth. The site healed successfully with secondary intention and a restored normal nasal alar contour [Figure 2]. Final excision pathology was consistent with rhinophyma [Figure 3]. The patient agreed with taking doxycycline 20 mg orally twice daily indefinitely as an anti-inflammatory treatment for rosacea and to attempt to prevent recurrence. He has maintained his results 1 year later.

DISCUSSION

While the prevalence of rosacea overall is estimated to be from 1% to 20%, the phymatous subtype is less common.^[5] In a population study of Estonian workers with Rosacea, only 1% was classified as having subtype 3. Rosacea overall has a slightly female predominance, but the incidence of rhinophyma is much higher in males and is seen most often after 40 years of age.^[3,5,6] Rosacea has been reported to be

more frequent in skin phototypes I and II, though it is increasingly being recognized as a condition seen in all skin types.^[2]

Although commonly diagnosed clinically, the differential diagnosis for rhinophyma should be considered, especially when appearing unilaterally as in our patient. Basal cell and squamous cell carcinomas can occur on phymatous skin, and should be considered when unilateral changes, rapid growth, ulceration or drainage occur.^[2,3] Other neoplasms including adnexal tumors would also be included and can be considered. Granulomatous processes such as sarcoidosis and infectious diseases such as rhinoscleroma (*Klebsiella*) or leishmania should also be considered in the appropriate clinical setting.

Histopathologically, rhinophyma classically shows findings compatible with rosacea (telangiectasia in the superficial dermis, dilated infundibula with occasional cysts and a lymphohistiocytic perifollicular infiltrate) with the addition of striking sebaceous hyperplasia.^[4-7] A severe form has also been described which shows marked dermal thickening with few infundibular cysts and reduction or absence of pilosebaceous structures.^[4]

The exact pathogenesis of rosacea and rhinophyma is not known but it is thought to be a combination of multiple factors leading to vascular changes and a trigger of the innate immune system. Numerous vascular growth factors and receptors have been shown to be increased in affected skin leading to an overall state of abnormal vascular reactivity. Specifically, vascular endothelial growth factor (VEGF), VEGF receptors, lymphatic endothelium marker D2-40 and CD 31 expressions are increased which provide stimulants for proliferation of vascular and lymphatic endothelial cells.^[8,9] This correlates with the grossly irregular and dilated vascular networks seen in affected skin histopathologically. Sun or ultraviolet exposure is also considered a contributing factor. In mice, it has been shown that UVB light induces dermal angiogenesis and also increases VEGF expression in keratinocytes.^[3]

Additionally, the innate immune response is triggered leading to an abnormal host response. Although the exact triggers are unknown, many environmental and genetic factors have been hypothesized to play a role. The cytokine cathelicidin has recently been found to be highly expressed in affected patients and thought to play a key role in the pathogenesis of rosacea. Triggered in response to innate antigens, this effector peptide has many functions including promoting angiogenic activity, modifying the local inflammatory response, regulating leukocyte chemotaxis and

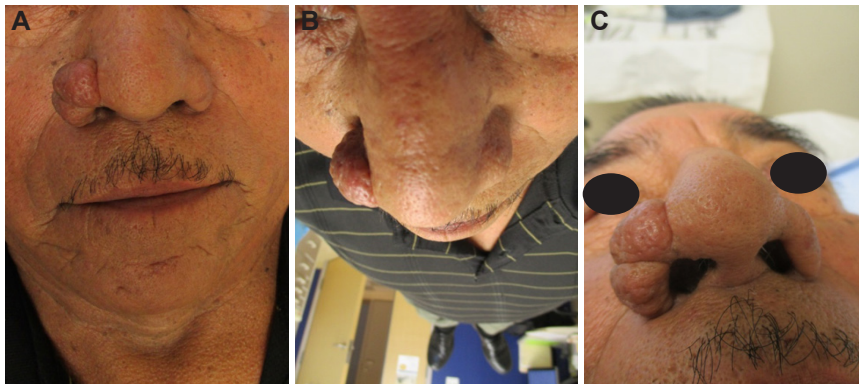


Figure 1: Unilateral rhinophyma (A: front view; B: superior view; C: inferior view)



Figure 2: Unilateral rhinophyma 2 weeks after electro-surgical excision (A: front view; B: lateral view)

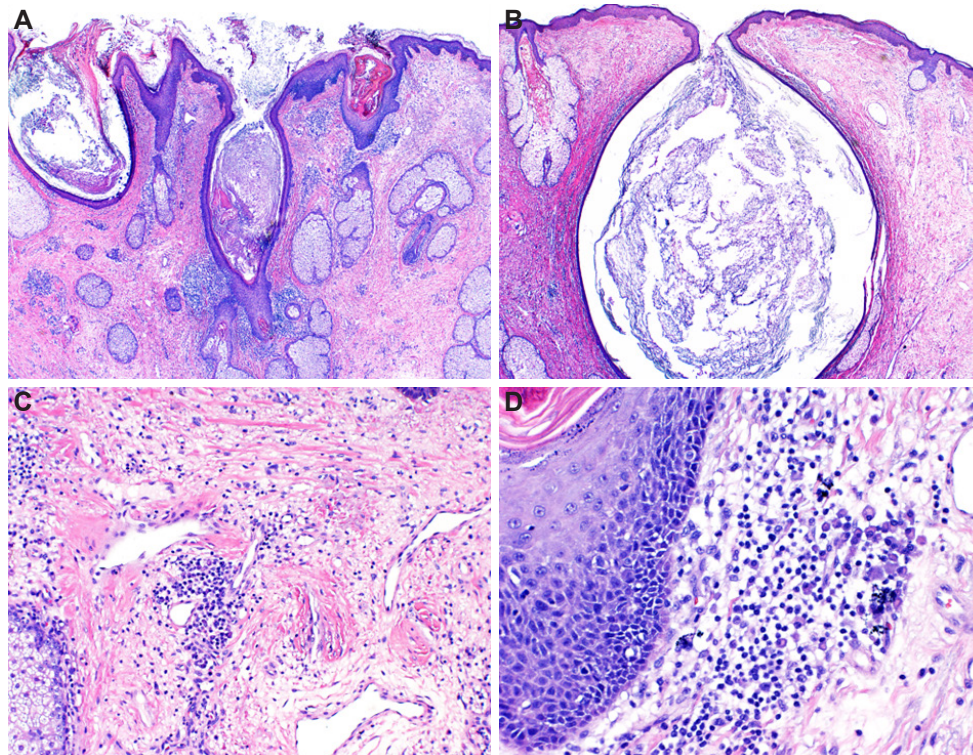


Figure 3: Histology of unilateral rhinophyma. Characteristic histopathologic features of advanced rhinophyma including comedonal (A) and cystic dilation (B) of follicular infundibulae, increased numbers of sebaceous glands (A), a perivascular lymphocytic infiltrate, marked dermal fibrosis and telangiectasia (C). A moderately dense perifollicular lymphocytic infiltrate with numerous plasma cells (D) typical of rosacea and its variants is also present. ($\times 20$ in A and B; $\times 100$ in C; $\times 200$ in D)

increasing vascular permeability.^[10,11]

What exactly triggers the innate immune response is not known but UV light, trauma and microorganisms such as Demodex mites are thought to play a role. Demodex mites, although common in the general population, are prevalent in up to 100% of rosacea patients.^[1] The mites are thought to trigger an immune response, act as a vector for other bacterial pathogens and block hair follicles.^[3] Additionally, smokers have been found to have a higher risk of developing rosacea.^[12]

The exact pathogenesis of the phymatous stage of rosacea is also not well understood. It is postulated to be a combination of the above factors in addition to alterations in blood flow via decreased dermal vasoactive intestinal peptide receptors.^[13] In the severe variant of rhinophyma described by Aloï et al.,^[4] they hypothesize that the pathogenesis is similar to that of lymphedema. They suggest that the severe fibroplasia seen in this form of rhinophyma impairs lymphatic drainage which leads to persistent edema and destruction of adnexal structures. Over time, this fluid collection stimulates further fibrosis via production of collagen and glycosaminoglycans.

The treatment for rhinophyma is approached in a different fashion compared to the other rosacea subtypes. Younger patients with early signs of rhinophyma may respond well to oral isotretinoin, but surgery remains the only definitive treatment for those with advanced disease.^[1,6,14,15] A surgical approach may include electrocautery, laser ablation, cryotherapy, dermabrasion, paring with a scalpel blade, or a combination of these techniques to achieve an optimal outcome.^[14,15] Use of electrosurgery to excise the rhinophyma can reduce bleeding.^[6] Preservation of the sebaceous glands allows for adequate re-epithelialization, and the excision should not extend deeply enough to expose cartilage.^[6,15] Skin grafts or local flaps can be used to cover the defect, or the wound can be allowed to re-epithelialize spontaneously within 2 weeks. Removing too much tissue can result in a smooth, shiny scar that does not match the rest of the nose.^[6,15] Laser ablation therapy is another option for treatment. One study evaluated 24 patients with rhinophyma who were treated with a 10,600-nm CO₂ pulsed laser. They found that 79.1% had high improvement, 16.7% had moderate improvement and 4.2% had low improvement, with minimal side effects.^[16]

Here we have presented what is, to our knowledge, the first reported case of unilateral rhinophyma.^[17] Why it appeared unilaterally is unclear. Interestingly, unilateral otophyma has been reported, and the authors

postulated that it may have occurred unilaterally due to localized factors such as sleeping on the affected ear, trauma or infection.^[17] The etiology of unilateral rhinophyma remains unknown, and possibilities include spontaneous or idiopathic asymmetric inflammation, or a localized lymphedematous or inflammatory process, such as might result from localized infection or trauma. Our patient has healed well after electrosurgical treatment and is pleased with his improvement.

Authors' contributions

Concept design: K.K. Reddy

Definition of intellectual content: K.K. Reddy, S. Walter
Literature search, data acquisition, data analysis: S. Walter, J. Ho

Manuscript preparation, editing, and review: S. Walter, J. Ho, S. Krueger, K.K. Reddy

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

The proper consent of the patient was taken for carrying out all the tests and treatment.

Ethics approval

The procedures followed were in accordance with ethical standards of the responsible committee on human experimentation. As an experiment was not performed, local institutional review board protocol was not required.

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Management of complications of Medpor® implants in rhinoplasty

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Dr. Raghav Shrotriya is a senior registrar in Plastic Surgery at Seth GS Medical College and KEM Hospital, Mumbai (India). His major interests are facial aesthetic surgery as well as reconstructive microsurgery. He has been associated with the senior author (KSA) in many surgical and literary endeavours and likes to pursue formal and informal writing while he is not operating, the notable amongst them being an account of his life as resident in the burn ward.

Sir,

Implants are widely used currently in aesthetic surgery to provide augmentation or support. To provide better stability, alloplastic materials such as porous high-density polyethylene (Medpor®) implants have been used in rhinoplasty and other procedures. Medpor® is manufactured from linear high-density polyethylene through the process of sintering in which small particles are fused together at high temperature and pressure, so that it is composed of 50% porous volume with pore

sizes ranging from 100 to 250 µm. This allows maximum fibrous tissue ingrowth and relative incorporation into host tissue.^[1] This property represents its primary strength but also its greatest weakness.

The authors' experience has been that the presence of the Medpor® implant causes thinning of the overlying skin envelope and although the implant becomes densely adherent to the surrounding soft tissue, it does not bond with the underlying bone or cartilage firmly enough and hence mild mobility is always a problem.



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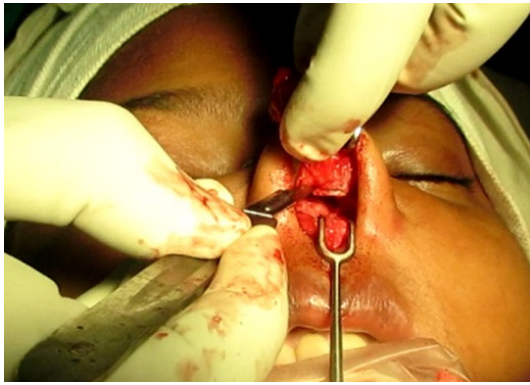


Figure 1: Incision taken over the fibrous covering of implant

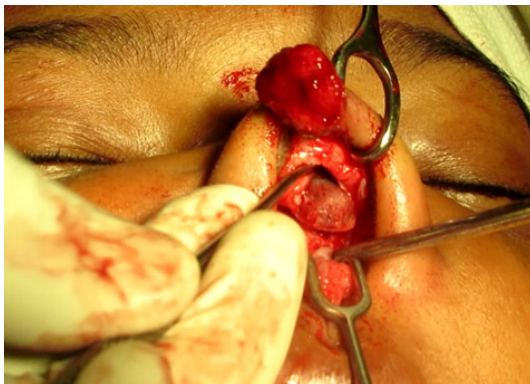


Figure 2: Implant separated on all sides by blunt dissection

This forces many surgeons to use a screw to fix it to the bone. Unfortunately, this combination of mobility and structural rigidity^[2] leads to displacement and high chances of extrusion.

These implants have high infection (3-4%)^[3] and extrusion rates, ranging from 3.1%^[4] to as high as 21%^[5] and often require removal, which can be extremely difficult because of tissue incorporation.^[5,6] Explantation surgery is treacherous as there is a high incidence of button holing, thinning, and irregularity of overlying skin and damage to surrounding structures.

To avoid this predicament, the authors propose a simple modification in dissection technique. Traditionally, the implants are removed by sharp dissection using a scalpel or scissors. The authors use a scalpel only to incise the fibrous covering of the indwelling implant at the tip [Figures 1 and 3A] and then go on to separate the implant from the incorporated fibrous cover using a Freer's elevator in the same manner in which they use it to raise the perichondrium off the costal cartilage [Figures 2 and 3B]. If the dissection is difficult, hydro-dissection by injecting saline in the plane between the implant and the fibrous covering can be helpful. The authors find it similar to peeling a banana, as you proceed by separating the capsule one side at a time and when you reach the most

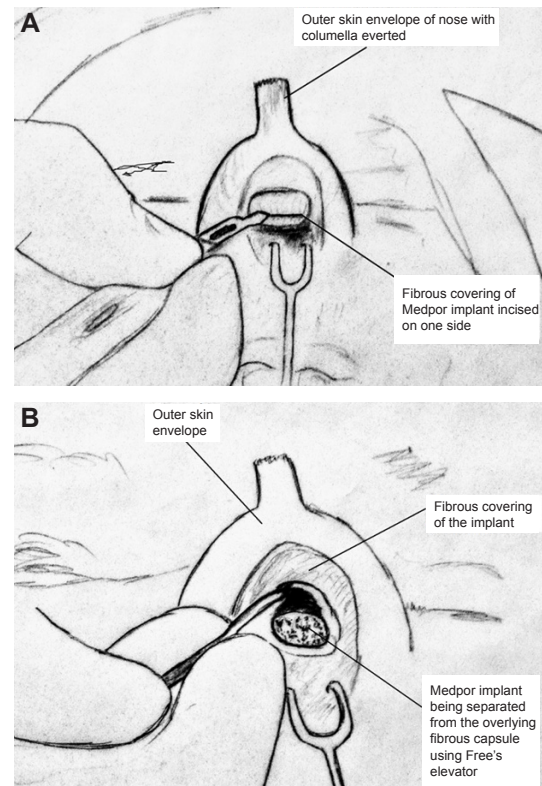


Figure 3: Schematic diagram showing (A) incision being taken over the fibrous covering of implant and (B) implant being separated on all sides by blunt dissection using Freer's elevator

proximal part, a few upward strokes bring the implant out along with the screw without the need to make a separate skin incision for this purpose [Video 1]. The trick is to avoid sharp dissection and leave behind sufficient connective tissue on the under surface of the skin so as to avoid damaging it. The advantages of this technique over the traditional methods are as follows: (1) the button holing of already thinned-out dorsal skin is avoided; (2) leaving the fibrous capsule under the dorsal skin provides additional soft tissue cushion; (3) the vascularity of the surrounding envelope is not disturbed; (4) irregularity of dorsal skin as well as cartilaginous dorsum is avoided (which is common with sharp dissection); (5) there is no need to take additional skin incisions to remove the screw if the implant is fixed with one; and (6) less bleeding occurs compared to sharp dissection.

Removal of implants is difficult in all cases but surgical site infections pose additional challenges. In such cases, the possibility of skin damage is higher and the management of the explanted depressed nose often remains a dilemma. If a secondary augmentation procedure is planned a few months later, it may be difficult to dissect thinned-out adherent dorsal nasal skin at that point without complications. In addition, simultaneous augmentation using cartilage or bone in the presence of infection is not desirable.

The authors prefer using a derma-fat graft as a filler and spacer until definitive augmentation surgery can be done after four to six months. The graft provides temporary support and avoids dorsal depression in the intervening period before the definitive surgery is performed. It also avoids adhesion of the thinned-out dorsal skin to the dorsum, and the dermis of the derma-fat graft provides good thickness to the dorsal skin. It allows the resolution of the infection and, during the later surgery, provides an easy dissecting plane between the dorsum and fat, thereby avoiding further complications.

Extensive online literature search on PubMed yielded no references on ways to remove Medpor® implants. Although the authors developed this technique for removal of nasal dorsal implants, it has also been found to be useful for removal of Medpor® implants in many other sites like malar and chin implants.

Thus, the technique of removal of Medpor® implants and using derma-fat graft as a filler before definitive autograft augmentation is a simple and safe solution to a common problem, and avoids associated complications by providing a cushion to the dorsal skin and a simple plane for future dissection. Some patients may not even need further augmentation.

Authors' contributions

Concept design: K. Agrawal
Literature search: R. Shrotriya

Manuscript's writing and editing: K. Agrawal, R. Shrotriya

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

Obtained.

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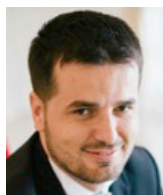
The experience performing extended abdominoplasty in massive weight loss patients

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ABSTRACT

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Key words:

Post-bariatric,
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tarsoplasty,
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body contouring,
body reshaping

Aim: The post-bariatric patients who undergo tarsoplasty often incur postoperative complications that dilate their recovery time. The authors propose the technique of extended abdominoplasty, described in 2012 for aesthetic torso remodeling, in post-bariatric patients in order to reduce complications and hospitalization time. **Methods:** The authors performed 21 extended abdominoplasties and compared them with 21 tarsoplasties in post-bariatric patients during a 1-year period. Data studied was age, gender, duration of the procedure, blood loss, complications and hospitalization duration. **Results:** Peri and postoperative bleeding led to 3 cases of anemia necessitating blood transfusions in 14.3% of the second group; no blood transfusion was needed in the first group. No other major complications occurred during the postoperative period in both groups. **Conclusion:** The authors believe that extended abdominoplasty is a viable alternative to the tarsoplasty in selected patients presenting a severe adipocutaneous circumferential laxity, as occurs in post-bariatric patients with a significant weight loss.

INTRODUCTION

In the last years, the prevalence of obesity has increased in most industrialized countries.^[1] The rise on obesity prevalence has taken a concomitant

increase in bariatric surgery procedures. Moreover, bariatric surgery has demonstrated to improve or even to eradicate significant obesity-related comorbidities including diabetes mellitus, hypertension, dyslipidemia, and obstructive sleepapnea.^[2-6]



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Despite the large number of benefits conferred by bariatric surgery, the massive weight loss causes a persistence of a large amount of inelastic skin and subcutaneous tissue, which can lead to skin irritations, mycotic infections and secondary self-imaging problems (potentially a worsened overall patient body-image). Skin redundancy following massive weight loss is both an aesthetic and functional problem.

The number of patients demanding plastic surgery correction of contour abnormalities has increased with the advancement in weight loss procedures. Massive weight-loss patients often present a circumferential truncal skin and subcutaneous tissue redundancy, which cannot be optimally corrected by common abdominoplasty techniques. The main issue is the remaining of skin bulges in the flanks and in the dorsal area. When gluteal ptosis is also present, a 360° contouring procedure is necessary: in these cases the most frequent operation is torsoplasty.^[7]

Nevertheless, both circumferential abdominoplasty and torsoplasty have intraoperative and postoperative high risk of complications such as bleeding, anemia, dorsal dehiscence of the surgical wound due to forced supine position, infection, seroma (often posterior ones).^[8-10]

As an alternative to circumferential abdominoplasty, we describe our experience with the extended abdominoplasty technique.^[11,12] This technique was first described by Mejia and Cárdenas Castellanos^[12] to treat aesthetic deformities of the abdomen in non-bariatric patients and it preserves the median dorsal area from surgical traumas. We extended the indication to the massive weight loss patients. The aim was to reduce postoperative complications and hospitalization time.

METHODS

Patients

Twenty-one consecutive patients underwent extended abdominoplasty after bariatric surgery [body mass index (BMI) ≥ 40] between September 2014 and November 2015. Data concerning age, gender, BMI at the time of plastic surgery, weight loss, duration of the procedure, resected tissue weight, perioperative blood loss, duration of hospitalization, follow-up, associated procedures and complications were collected and compared with those of 21 patients who had undergone a classical torsoplasty during the same period.

Patients were selected after passing the following inclusion criteria: severe abdominal and truncal skin

Table 1: Patients characteristics

Characteristics	Extended abdominoplasty		Torsoplasty	
	Range	Average	Range	Average
Age (years)	30-63	46.8	30-61	45.2
Bariatric BMI	41-61	51.6	42-56	47.5
Post-bariatric BMI	26-30	28.6	25-30	27.3
Weight loss (kg)	28-115	69.4	35-85	61.8

BMI: body mass index

redundancy, circumferential lipodystrophy type VI according to Mejia and Cárdenas Castellanos,^[12] unchanged weight during the last year, and age between 30 and 65 years.

Patients were excluded if affected by diabetes or coagulopathies, or if they had undergone prior trunk reshaping procedures were excluded.

Patients' characteristics are described in Table 1.

Planning and marking

We performed the body contouring procedures after twelve months of stable bodyweight. Liposuction wasn't performed in any case. Photographs were taken preoperatively and postoperatively.

Skin markings are placed preoperatively with the patient in standing position, the day before the procedure, using a method similar to that described by Mejia and Cárdenas Castellanos.^[12] The scars positioned low enough to be easily hidden by the underwear.

Anteriorly, a vertical supra-pubic midline is drawn. The lower point of the resection is 7-8 cm from the vulvar anterior commisure or from the base of the penis. Two lateral lines of 7 cm are drawn from the vertical line, and are then continued to the iliac crests.

Laterally the abdominoplasty line is stretched along the two sides keeping the iliac crest height without re-ascending [Figure 1A]. From this line, by pinching, the upper flap of adipocutaneous excess has to be marked along the lateral hip profile. The abdominoplasty superior line has to be stretched until the above-mentioned point [Figure 1B].

In the dorsal area, we draw a vertical line positioned in the interspinal line, and then the marking of the upper incision line is extended backwards, almost straight over the gluteal crease, not exceeding it [Figure 1C]. This line is then directed downwards and medially. And by pinching, the inferior line has to be marked in order to correct the gluteal ptosis [Figure 1D].

Lastly, vertical lines along the entire drawing have to

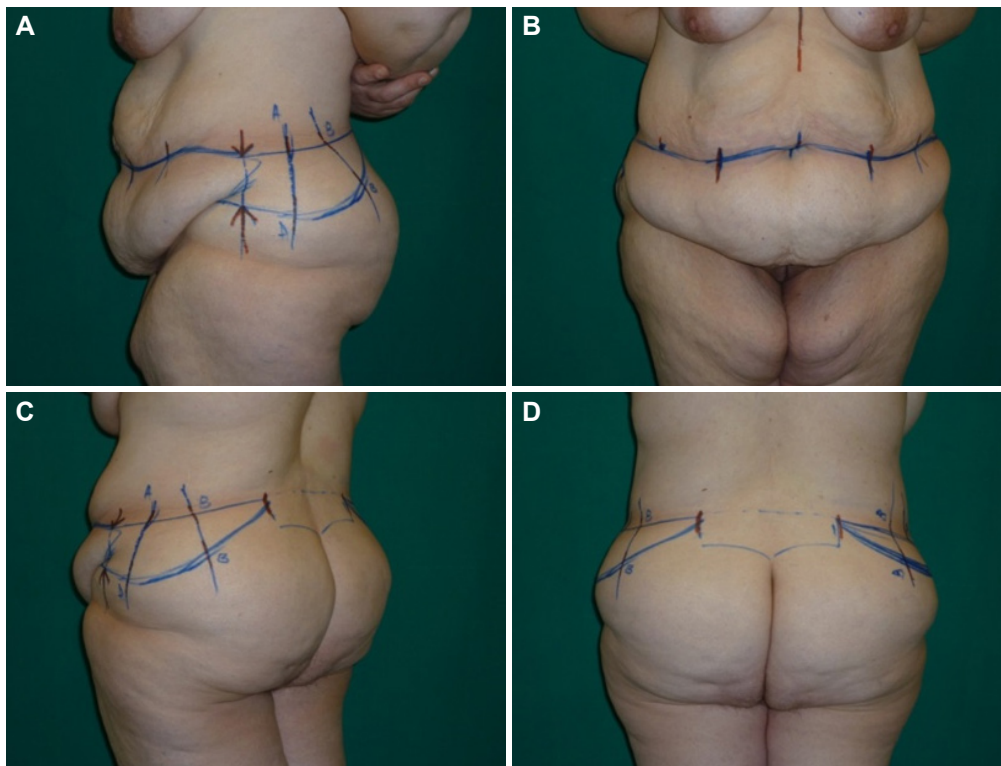


Figure 1: (A) Anterior pre-operative marking, arrows illustrate the border of the extension of abdominoplasty; (B) the upper flap of adipocutaneous excess marked; (C) extension of the incision line dorsally; (D) posterior pre-operative marking, in evidence the pre-sacral area non-interested by incision lines

be marked for the correct alignment of the upper and lower flaps during the suture.

Surgical technique

The patient is anaesthetised and then placed in prone position. Pressure sore protections are placed under shoulders, knees and ankles. The patient is prepared from scapula to buttocks with povidoneiodine. Skin and subcutaneous soft tissues are incised following the preoperative markings to the lumbar fascia without undermining of the non-resected tissues. Haemostasis is carefully performed by electrocautery. After the excision of the adipocutaneous tissue, two drains are placed. Three layer closure is performed: Vicryl 2/0 (Ethicon Inc, Somerville, New Jersey) for fascia superficialis, Monocryl 3/0 (Ethicon Inc, Somerville, New Jersey) for the deep dermis and Monocryl 4/0 for endodermic suture.

Then the patient is placed in the supine position; skin and subcutaneous tissues are incised down to the anterior abdominal wall fascia respecting the preoperative markings. Umbilicus is isolated and preserved and the flap is elevated to the chest and the xiphoid area. Adipocutaneous excess is removed by a flute mouthpiece incision from the subcutaneous tissue to the superficial fascia. Plication of the muscular fascia

is performed with a resorbable suture whenever is needed. The navel is externalized, and two additional drains are placed in the anterior trunk. The surgical wound is closed again in three levels, as in the dorsal incision.

Postoperative care

All patients received compression stockings and daily prophylactic low-molecular-weight heparin subcutaneously, until 1 week after discharge. The patients were mobilized from the first day after surgery. Antibiotics were administered intravenously during the surgery and continued orally until discharge. Drains were removed after 4-5 days.

Follow-up

The patients were discharged after a few days and followed up at 15 days, 1, 2, 3 and 6 months and 1 year, or more frequently in the presence of complications.

RESULTS

We performed the extended abdominoplasty technique on 21 post-bariatric patients from September 2014 to November 2015 and circumferential abdominoplasty or torsoplasty on 21 postbariatric patients during the same period.

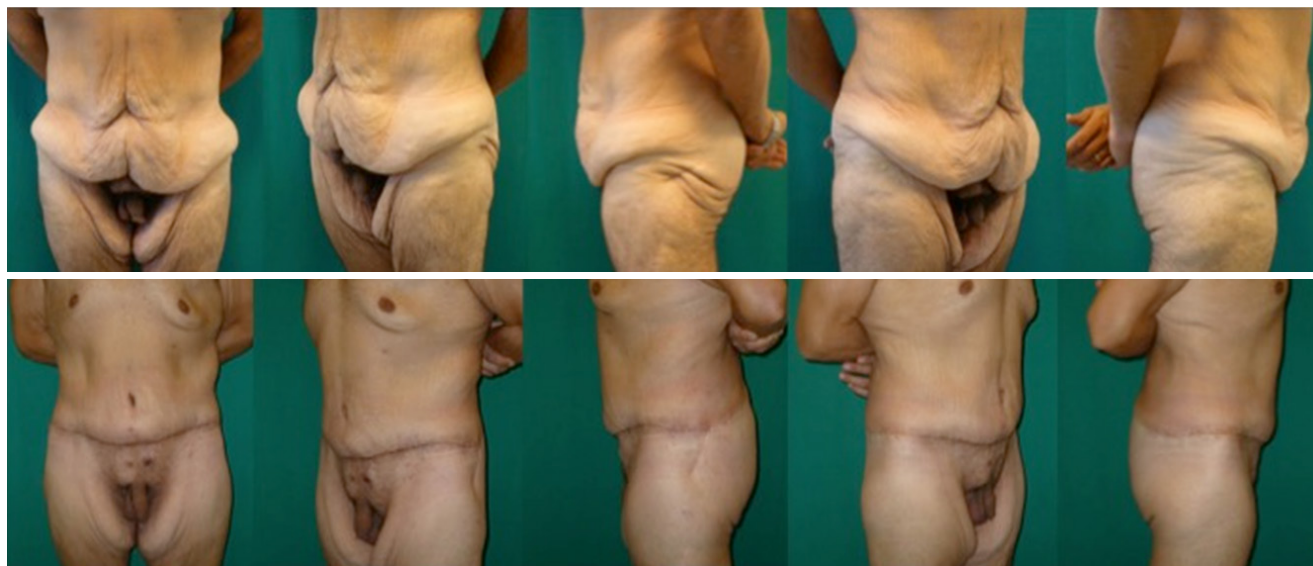


Figure 2: A male patient who underwent vertical banded gastroplasty. Weight loss: 115 kg, from 200 to 85 kg. Upper row, from left to right: pre-operative frontal view, left 2/3° view, left lateral view, right 2/3° view, right lateral view. Lower row, 8 months after surgery (extended abdominoplasty), from left to right: post-operative frontal view, left 2/3° view, left lateral view, right 2/3° view, right lateral view



Figure 3: A female patient who underwent vertical banded gastroplasty. Weight loss: 130 kg, from 198 to 68 kg. Upper row, from left to right: left lateral view, left 2/3° view, pre-operative frontal view, right 2/3° view, right lateral view, back view. Lower row, 8 months after surgery (extended abdominoplasty), from left to right: left lateral view, left 2/3° view, pre-operative frontal view, right 2/3° view, right lateral view, back view

Eight males [Figure 2] and 13 females [Figures 3 and 4] underwent extended abdominoplasty. The mean age was 46.8 years (30-63 years), and the average weight loss after bariatric surgery was 69.4 kg (28-115 kg). The average BMI at the time of surgery was 28.6 kg/m². Mean weight of skin and fat tissue removed was 3,430 g (1,750-8,960 g), mean operative time was 3 h and 30 min (2 h and 15 min-5 h) and the mean peri-operative blood loss was 628.6 mL. The patients remained hospitalized for 7.8 days, while the mean follow-up was 14 months.

Seven males and 14 females underwent torsoplasty. The mean age was 45.2 years (30-61 years), and the average weight loss after bariatric surgery was 61.8 kg

(26.5-108 kg). The average BMI at the time of surgery was 27.3 kg/m². Mean weight of skin and fat tissue removed was 3,460.9 g (1,780-8,930 g), mean operative time was 4 h and 30 min (2 h and 45 min-6 h and 20 min) and the mean peri-operative blood loss was 1,085.4 mL. The patients remained hospitalized for 12.5 days, while the mean follow-up was 14 months.

The comparison between extended abdominoplasty (ex) and torsoplasty (tp) gave the following results regarding blood loss (ex: 628.6 mL-tp: 1,085.4 mL, $P = 0.049$), transfusion rate (ex: 0%-tp: 27.3%), operation length (ex: 3 h 30 s-tp: 4 h 30 s, $P < 0.001$) and hospitalization days (ex: 7.8-tp: 12.5, $P = 0.002$) [Table 2].



Figure 4: Patient presented at Figure 3, 2 years after surgery. From left to right: pre-operative frontal view, back view, left lateral view, right lateral view

Table 2: Comparison between extended abdominoplasty technique and traditional torsioplasty

Characteristics	Extended abdominoplasty	Torsioplasty
Excised tissue, g	3,430	3,460.9
Blood loss, mL	628.6	1,085.4
Transfusion rate, %	0	27.3
Operation length	3 h 30 s	4 h 30 s
Hospitalization time, days	7.8	12.5

Peri and postoperative bleeding led to three cases of anaemia necessitating blood transfusions (14.3%) in the second group; no blood transfusion was needed in the first group.

No other major complications occurred during the postoperative period in both groups, there was no need to drain hematoma or seroma, patients were mobilized during the first postoperative day and were discharged without drains.

Only 5 cases of superficial cutaneous necrosis occurred on the bisiliac suture line, 2 in the first group and 3 in the second group, solved with local dressings in less than 3 weeks.

Patients were uniformly pleased with their results: 90% of them were very satisfied, whereas 10% graded their results as satisfactory.

DISCUSSION

The National Institutes of Health Consensus Conference stated in 1991 “only surgery has proven effective over the long term for most patients with clinically severe obesity”. This statement was confirmed and updated in 2004, by the American Society for Bariatric Surgery (recently renamed as the American Society for Metabolic and Bariatric Surgery).^[13] The number of bariatric surgery procedures has increased steadily since then and, as a result, the number of massive weight loss patients seeking body-contouring procedures has considerably grown. The redundant excess skin interferes with fitting clothing, physical and

sexual activity, hygiene, and it can frequently cause recurrent bouts of infection.

The post-bariatric patient represents a challenge for plastic surgeon. Although post-bariatric body-contouring procedures are generally associated with high rates of patient satisfaction, the surgeon has to face the negative impact of postoperative complications. The post-bariatric surgery population appears to be at higher risk compared to patients who are not obese.^[14]

Arthurs *et al.*^[15] found that pre-panniculectomy BMI was the most important factor that independently predicted postoperative complications after a panniculectomy; meaning that post-bariatric surgery population is at higher risk compared to non-obese patients. Patients with a BMI greater than 25 kg/m² are at nearly three times the risk of postoperative wound complications. Other important risk factors for complications are nutritional deficiencies, smoking, venous varicosities, and poor quality orinelastic tissues.

To obtain the best outcomes, a comprehensive perioperative approach is required. Proper patient selection, carefully considered surgical timing and the choice of the surgical technique are fundamental to avoid complications.

There are many anatomical regions that massive weight loss patients would like corrected: redundant flank and abdomen, hip rolls, breasts, arms, buttocks and thigh ptosis. For this reason body contouring is generally not considered as a single stage procedure.

Among all the body contouring procedures, abdominoplasty has a crucial role in body image recovery. But the results, even in the most extensive form of abdominoplasty are usually suboptimal because the back and lateral flank deformities are not considered.

To address the circumferential nature of the skin excess in these patients, various surgical techniques

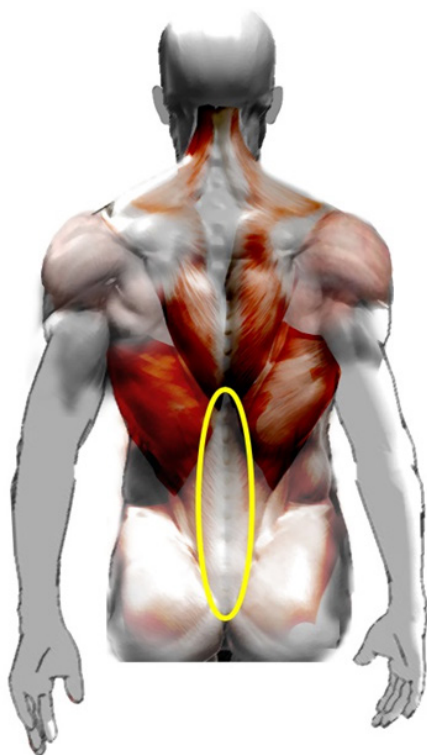


Figure 5: The median dorsal area. In this anatomical district, there is a fascial-aponeurotic tissue, rich in vessels, with skin and subcutaneous firmness

were developed. Circumferential torsioplasty was first described in 1960 as the “beltlipectomy” by Gonzalez-Ulloa.^[16] His technique involved anterior and posterior midline vertical wedge. Baroudi^[17] described a similar technique but without the wedge resection. In 1991 Lockwood^[18] described the superficial fascial system of the torso and extremities, and its use in high-tension-lateral closure in the transverse flank-thigh-buttock lift. In 1996 Hunstad^[19] described a combined technique of circumferential torsioplasty and liposuction.

In 2002, Pascal and Le Louarn^[20] proposed a new concept in the circumferential abdominoplasty: body lift with high lateral tension, creating a dermal flap for the suspension of the buttocks and trochanteric regions.

Belt lipectomy is also known as torsioplasty, circumferential torsioplasty, circumferential lipectomy and panniculectomy. This body contouring procedure is associated with a high rate of postoperative complications. The literature reports a rate of complications ranging from 17% to 50%.

Seroma is the most frequent complication. It commonly occurs in the posterior region, which is a well-known region for seromas after back surgery.

To minimize complications and hospitalization

time, we propose a modified approach to the traditional circumferential torsioplasty, described by Mejia and Cárdenas Castellanos^[12] as “extended abdominoplasty” in massive-weight-loss patients.

Compared to traditional torsioplasty the extended abdominoplasty technique preserves the median dorsal area from surgical trauma. This area contains a fascial-aponeurotic tissue, rich in vessels, with skin and subcutaneous firmness [Figure 5], which is at higher risk of bleeding and less involved in the ptosis processes. The advantage of avoiding this area is the reduction of intraoperative bleeding, operative time and hospitalization days.

Despite the limited number of cases, in our experience, the comparison between extended abdominoplasty and torsioplasty gives encouraging results regarding blood loss, transfusion rate, operation length and hospitalization days. We had no cases of seroma formation and no other major complication. We reported 5 cases of superficial cutaneous necrosis occurring on the bisiliac suture line, which was managed with local dressing changes for less than 3 weeks. As described in the result section, data analysis supports this hypothesis but the small number of patients limits its significance.

This procedure allows a better distribution of loose tissue after removal of the excess from the flanks. It permits narrowing of the waistline and suspending the skin of the gluteal area without stretching the buttock crease. Compared to the traditional torsioplasty, the aesthetic result is better considering the shorter size of the scars. Patients happily accept the perspective of a shorter scar.

In conclusion, this study presents the results of the use of the extended abdominoplasty in post-bariatric patients. According to the results, this technique allows a reduction in blood loss, operative time and hospitalization days, and consequently leading to less complications and costs.

We believe that extended abdominoplasty is a viable alternative to torsioplasty in selected patients presenting with a severe adipocutaneous circumferential laxity, as occurs in post-bariatric massive weight loss patients.

Authors' contributions

Manuscript's concept and design: M.A. Bocchiotti, S. Bruschi

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Data acquisition and analysis: L. Spaziante

Manuscript preparation, editing and review: E. Ruka

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

The study was approved by the ethics committee of our institution and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Hypospadias: an algorithm for repair with the aid of the microscope in 102 patients

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ABSTRACT

Aim: To demonstrate an algorithmic approach to hypospadias repair with the aid of the surgical microscope as a teaching aid, as well as an ergonomic tool. **Methods:** One hundred and two patients were operated on between 2009 and 2013, all by the senior surgeon (M Dalal). This is a retrospective review of results in the case series. The procedures used were one stage repair with no incision of the urethral plate, or the two stage Bracka repair. **Results:** Fifty-six patients underwent the one stage procedure and 46 patients underwent the two stage Bracka repair. Early complication rate was 4.9% ($n = 5$) and late complication rate was 10.7% ($n = 11$). The fistula rate specific to one stage and two stage procedures was 5.3% ($n = 3$) and 13% ($n = 6$) respectively. **Conclusion:** A structured approach to hypospadias surgery will aid the surgeon in choosing the appropriate procedure for the appropriate patient. The authors have chosen to use 2 types of repair for all hypospadias subsets based on the algorithm. They find the microscope an invaluable teaching aid, whilst at the same time providing an ergonomic benefit, and providing a wide range of surgical site magnification.

INTRODUCTION

Hypospadias surgery has been performed for decades and centuries. It has evolved quite rapidly and there have been many procedures described along with their modifications. It remains a relatively common condition, occurring in 1:300 live births.^[1] Hypospadias is characterised by the presence of an abnormally sited ventral urethral meatus, a dorsally hooded prepuce, and varying degree of penile ventral curvature "chordee". The main aspect in its diagnosis

is the abnormal position of the ventral urethral meatus, and to many, this position is related to complexity of the case and the type of repair chosen; when in fact there are other associated morphological aberrations that should be taken into consideration when considering repair. Common meatal positions are distal penile 70%, mid-penile 10%, and proximal types 20%.^[2] We follow an algorithm, which helps in choice of repair irrespective of the meatal site. The surgical procedure in itself requires magnification and a bloodless field to execute a successful repair.



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METHODS

One hundred and two patients were operated upon between 2009 and 2013; the senior author (M. Dalal) performed all patients. Inclusion criteria included primary hypospadias in the paediatric population irrespective of age at the time of initial presentation in clinic. Exclusion criteria, was 1 adult with delayed presentation of primary hypospadias, and 5 cases of phimosis, thought to have concealed hypospadias, treated with circumcision only. The following steps are common to both one stage and two stage procedures. All patients were subjected to a general anaesthetic augmented with a caudal block; for prolonged post-operative pain relief. After induction, co-amoxiclav antibiotic (Augmentin-GlaxoSmithKline) at a dose of 30 mg/kg is given intravenously over 3-4 min. Medical photography after obtaining the consent from the parents is a routine part of our practice. The photographs are taken in 2 views once the patient is covered in surgical drapes.

The foreskin is retracted and all the smegma removed with a swab soaked in aqueous chlorhexidine, after which the surgeon exchanges the gloves to commence surgery. A urethral dilator size 6/8-8/10 is passed after lubrication to ensure that there is an adequate urethral calibre. A polypropylene 5-0 suture (Prolene-Ethicon) is passed on the dorsal surface of the glans for retraction. An 8 French (Fr) urethral catheter is secured at the base of the penis with a haemostat as a tourniquet to facilitate a bloodless field. The microscope (Carl Zeiss Microscopy GmbH) microscope is brought into the field at this stage to aid in visualizing the anatomical landmarks as well as carrying out the procedure under $\times 3.5$ - $\times 6$ magnification [Figure 1]. A fine nib quill and ink are used to mark the incision lines, the markings for which differ between the one and two stage procedure. After the finishing the surgery, the suture line is covered soft non-adherent paraffin impregnated gauze (Jelonet-Smith & Nephew) and sandwiched on the child's abdomen between two layers of low-adhesive perforated plastic films (Melolin-Smith & Nephew). This is further secured with a broad sheet of adhesive tape (Mefix-Mölnlycke Healthcare). The same adhesive tape is then used to secure the catheter and the paediatric urine bag. This dressing is left undisturbed for 1 week.

Post-operatively patients are kept on oral co-amoxiclav (Augmentin-GlaxoSmithKline) 0.25 mL/kg of 125/31 suspension 3 times daily for ages up to 1 year of age and 5 mL of 125/31 suspension 3 times daily for children older than 1 year. Oxybutynin is administered to prevent bladder spasm, at a dose of 1.25-2.5 mg,

3 times a day. Both medications are continued until the catheter is removed at 1 week post-operatively. Analgesics are given as and when required. We aim to discharge patients on the second post-operative day. They are reviewed at 1 and 2 weeks postoperatively. They then are reviewed at 3 months, and from then on yearly till school age.

One stage repair (without urethral plate incision)

A subcoronal marking is made on the dorsal penile surface and is continued ventrally to the edge of the urethral plate. The ventral markings are made all around the edges of the urethral plate and around the anomalous urethral opening in a "U" shaped design. The ventral incision is made around the urethral plate, and care is taken when dissecting the ventral skin off the anomalous urethral opening, as the corpus spongiosum is deficient, and there is a chance of injury to the urethra. The use of a urethral dilator to guide this part of the dissection can be very helpful [Figure 2]. Ventral chordee encountered at this stage is corrected by degloving the penis. Glans flaps are dissected off the corpora cavernosa with a number fifteen Beaver blade (Beaver Visitec), to achieve a tension free ventral repair over the reconstructed neo-urethra. The dorsum of the penis is degloved in the sub-Dartos plane, and



Figure 1: Use of microscope during surgery with the background screen used for intraoperative teaching

a thin Dartos fascia flap is dissected starting at the distal end of the inner layer of preputal skin. Care is taken to carry the dissection proximally with adequate length in a manner that will allow tension free ventral transposition after neo-urethral reconstruction. This avoids rotation of the penis.

At this stage, a silastic size 6 Fr catheter is passed in the urethra and 1.5 mL of distilled water is used to inflate the balloon. The penis is retracted cephalad to allow for the reconstruction of the neourethra. The first step of the reconstruction is to form the distal most part of the neourethra with a single interrupted polyglactin 7-0 suture (Vicryl-Ethicon) around the inserted catheter. This produces a natural slit like urethral opening. The neourethra is then created starting at the edge of the anomalous ventral meatus and is carried distally with a running submucosal polyglactin 7-0 suture (Vicryl-Ethicon) using the native urethral plate. In contrast with the tabularized incised plate (TIP) procedure described by Snodgrass, the urethral plate was not incised in all of the patients but one. The width of the urethral plate is not routinely measured, but in general, it has to be

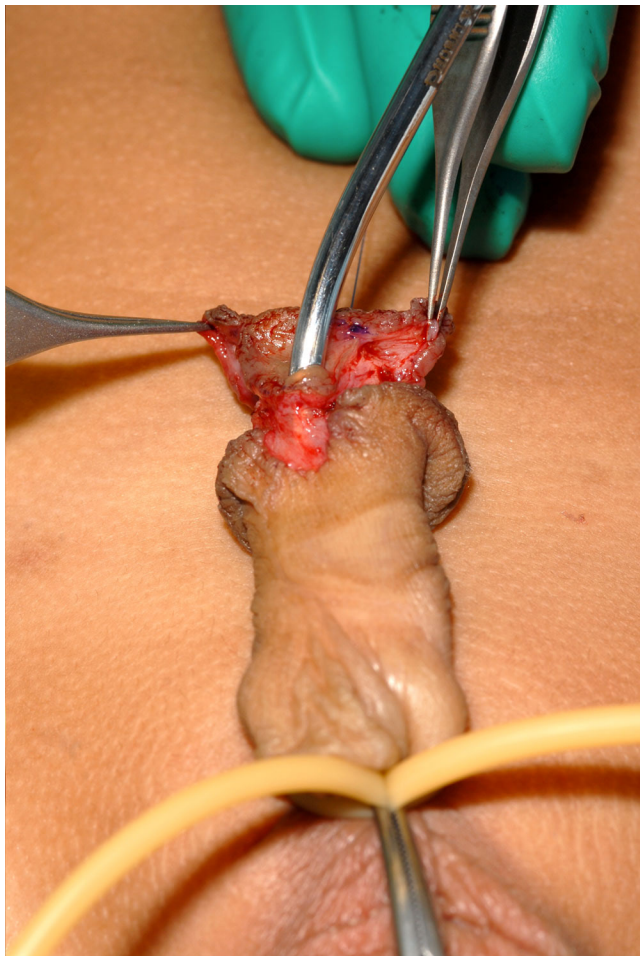


Figure 2: Utilization of a urethral dilator while degloving the ventral skin

sufficient to tubularise around the catheter chosen. This varies according to patient age, penis size, and the native urethral plate width; this is left to the clinical judgement of the senior author, hence the steep learning curve associated with hypospadias surgery.

A second layer from the soft tissue surrounding the neourethra is used to reinforce the reconstruction, and help create the deficient corpus spongiosum. It is repaired using the same suture material in a running fashion from proximal to distal. The competency of the neourethra reconstruction is tested with an intra-urethral injection of normal saline via a 22G intra-venous cannula (BD Venflon), to delineate possible leakage sites, which if found, are repaired using interrupted sutures. Care is taken to introduce the cannula dorsal to the urethral catheter to avoid injury of the neo-urethra. The previously dissected Dartos flap is transposed ventrally to create a waterproof layer with its distal extent at the level of the coronal sulcus. The Dartos flap is secured with interrupted polyglactin 7-0 sutures (Vicryl-Ethicon). The flap is not used in the distal (glandular and coronal) subset of metal openings, as it would create an unwanted and unnatural bulk under the glans flaps. The glans flaps are brought together with an undyed polyglactin 6-0 suture (Vicryl-Ethicon).

The tourniquet is released at this stage and bleeding vessels are cauterized with bipolar diathermy. After haemostasis is secured the tourniquet is reapplied. The ventral skin is closed in a "V-Y" manner starting distally, where the ventral skin is sutured to the glans flap with a four corner rapidly dissolving polyglactin 7-0 suture (Vicryl Rapide-Ethicon) at the frenulum. The remainder of the ventral vertical limb is closed with an interrupted suture using the same material. The excess preputal skin is marked for excision. A number 15 Beaver blade (Beaver-Visitec) is used to make the initial incision and the rest of the excision is carried out with the bipolar diathermy to facilitate a bloodless wound edge, which can be a source of postoperative bleeding in circumcision. Care is taken when closing the subcoronal incision to avoid a rotational deformity. The average time taken for the one stage is between 60-75 min.

Two stage Bracka repair

The penis is examined under magnification and the morphological findings are processed through the algorithm, at which stage it will indicate that a single stage repair is not suitable. With the two stage approach, there is generally a deficiency of tissues to form a neourethra and coverage.

The glans cleft in the centre of the narrow urethral

plate is incised vertically with horizontal extensions at the meatus; and glans flaps are raised. A full thickness skin graft is harvested from the inner surface of the dorsally hooded prepuce, its dimensions are not routinely measured, and however, the overall width of the urethral plate and skin graft should be at least 12 mm. The donor is closed primarily using rapidly dissolving polyglactin 7-0 suture (Vicryl Rapide-Ethicon). The skin graft is secured to the defect created using polyglactin 7-0 sutures (Vicryl-Ethicon). The same suture material is used to quilt the skin graft. Polypropylene 6-0 sutures (Prolene-Ethicon) are used to secure the non-adhesive bolster dressing applied to the skin graft. A size 6 Fr silicone Foley's catheter is inserted at this stage. The average time for the first stage is 45 min.

The second stage is performed for the patient 6 months after the first stage, where the graft has healed completely and the tissues have become soft and supple. The second stage is identical to the one stage repair, where by the lateral incisions are performed at the edge of the full thickness skin grafts. The average time taken is similar to the one stage repairs: 60-75 min.

RESULTS

A total of 102 patients were operated upon between 2009 and 2013. Inclusion criteria included primary hypospadias in the paediatric population. Exclusion criteria, was 1 adult with delayed presentation of primary hypospadias, and 5 cases of phimosis, thought to have concealed hypospadias, treated with circumcision only. Of the 102 patients, 56 underwent a one stage procedure while 46 underwent a two stage procedure. Mean age at presentation was 22 weeks \pm 29.75 (SD). The mean age at surgery was 25 months \pm 11.56 (SD).

Of the 102 cases, 41.2% ($n = 42$) were subcoronal, 20.6% ($n = 21$) coronal, 13.7% ($n = 14$) glandular, 1% ($n = 1$) terminal, 11.8% ($n = 12$) distal shaft, 2.9% ($n = 3$) mid-shaft, 3.9% ($n = 4$) proximal shaft, and 4.9% ($n = 5$) penoscrotal [Figure 3].

Early complications were those encountered within 6 weeks of the operative procedure, whilst any complication encountered after that period would be classed as a late complication. Early complication rate was 4.9% ($n = 5$) and they included dislodged/snapped catheters 1.9% ($n = 2$), wound dehiscence and infection 2.9% ($n = 3$). Overall late complication rate was 10.7% ($n = 11$). The most common complication was urethro-cutaneous fistula occurring in 8.8% ($n = 9$). The fistula

rate specific to one stage and two stage procedures was 5.3% ($n = 3$) and 13% ($n = 6$) respectively. Other late complications included, altered urine stream 0.9% ($n = 1$) and urethral stricture 0.9% ($n = 1$) [Figure 4]. No complications related to bleeding were encountered. Re-operation was required for 2 patients with wound dehiscence and 9 patients with fistula.

DISCUSSION

Many techniques and modifications have been described for the repair of hypospadias, yet there has been no general consensus on a specific procedure for a given subset of hypospadias meatal positions or morphology. Prat *et al.*^[3] published a series that covered three decades including 820 patients, highlighting different techniques and overall results. They performed meatal advancement and glanduloplasty (MAGPI), TIP, two stage procedures, onlay tabularised island flap, yet with a high incidence of complications. We employ the use of a simple double-armed algorithm ending in two procedures, which we feel are adequate to address treatment of hypospadias.

The algorithm [Figure 5] disregards the meatal position, and addresses other morphological findings; chordee, adequacy of the urethral plate, glans cleft, and presence of a urethral bar. A similar algorithm was utilised by Coleman *et al.*,^[4] whereby they used

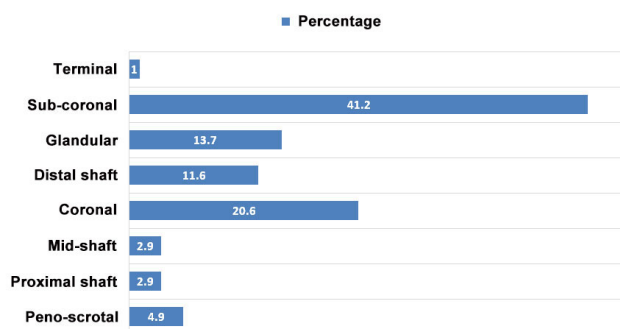


Figure 3: Hypospadias subtypes (%)

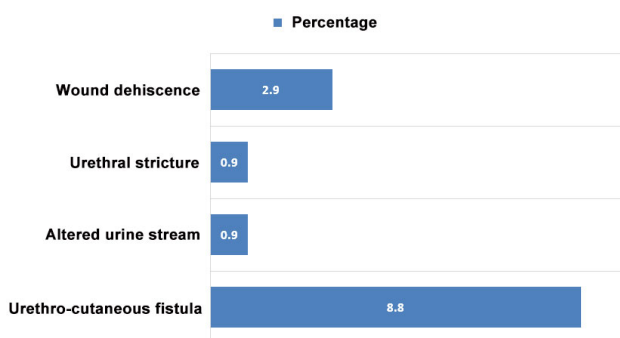


Figure 4: Complication rate (%)

their algorithm to arrive at a choice of a one or two stage repair.

Chordee was present in 94.1% ($n = 96$) of our patients with varying degrees; mild 81% ($n = 78$), moderate 7% ($n = 7$), severe 12% ($n = 11$). In the presence of mild to moderate chordee and adequate urethral plate, adequate glans cleft, and a thin or no horizontal bar within the urethral plate, a one stage repair (Snodgrass type without urethral plate incision) is used. This procedure was initially described as TIP.^[5] We found no need to incise the urethral plate in all but 1 patient.

Adequacy of the urethral plate is based on the fact that it will be tubularised around a 6 Fr urinary catheter, as is standard in our practice. A urethral plate of 8-10 mm or more is sufficient for tubularisation without the need for augmentation. If the findings are not in favour of a one stage procedure as per algorithm, then a two stage Bracka repair is used.

The microscope was used for all the hypospadias repairs in our series. We found that its use was quite ergonomic, when surgeons were sat in an upright posture with relaxed shoulders and elbows rested on the operative table; this is important for surgeons who will be doing hypospadias surgery regularly. The microscope used also had a separate video screen; this displayed a view of the operative field as seen by the surgeons. This is an invaluable teaching aid, as often there may be a second assistant that will not be able to see the field in the absence of this screen. Not only did the microscope serve an ergonomic and teaching purpose, but also provided magnification and

illumination required for surgery on delicate and small structures, where along with appropriate microsurgical instruments are hallmark to a meticulous repair. Wacksman reported that the use of the microscope has allowed for the use of small fine sutures with great accuracy translating into results.^[6] Wesson *et al.*^[7] found that it was a very useful teaching aid for residents. Unscrubbed junior colleagues observing will also be able to chronologically follow the surgical steps, to better understand this type of surgery, which does have a steep learning curve. It is also of note that other healthcare staffs in theatre are aware of the nature of the surgery that is being performed, and to be able to identify what stage of the surgery has been reached at any given time.

Gilbert *et al.*^[8] demonstrated that they experienced fewer complications when using the microscope. The non-microscope group had 17 complications, 12 of which required reoperation (24%), while the microscope group had 8 complications of which 4 required reoperation (6.5%). A head mounted microscope has been utilized in hypospadias surgery, again noticing a decrease in complications.^[9] Although this may provide magnification, there is no evidence to prove that it is more ergonomic than the surgical microscope.

In the 102 patients in our case series, 56 had one stage repairs while 46 had two stage Bracka repairs. Post-operative edema was not observed in any of our cases. Bhat and Mandal^[10] found that edema was the second most common early complication after hypospadias surgery. Urethro-cutaneous fistula remains the most common complication encountered by all. Snodgrass reported fistula rates at 13% in mid-shaft hypospadias and up to 37% in proximal shaft, depending on single or two layer closure and whether polyglactin or chromic was used.^[11] The two stage procedure was popularized by Bracka,^[12] and reports of a gross fistula rate of 5.7% and a stricture rate of 7%. It is worthwhile mentioning that there was no mention of magnification in the Snodgrass series, whereas Bracka does not rely on magnification at all.^[11,12] In our series we experienced one stricture and total fistula rate of 8.8%, 5.3% and 13% for one stage and two stage repairs respectively. The stricture was picked up by urethroscopy. Our postoperative follow-up regimen includes review at 1 and 2 weeks postoperatively. They then are reviewed at 3 months, and from then on yearly till 5-6 years of age before discharge. Khan *et al.*^[13] reported an increase in complications as a result of lack of magnification and microsurgical instruments. Hypospadias surgery has as steep learning curve, and it is more likely that more complications will be encountered earlier on in practice.^[14]

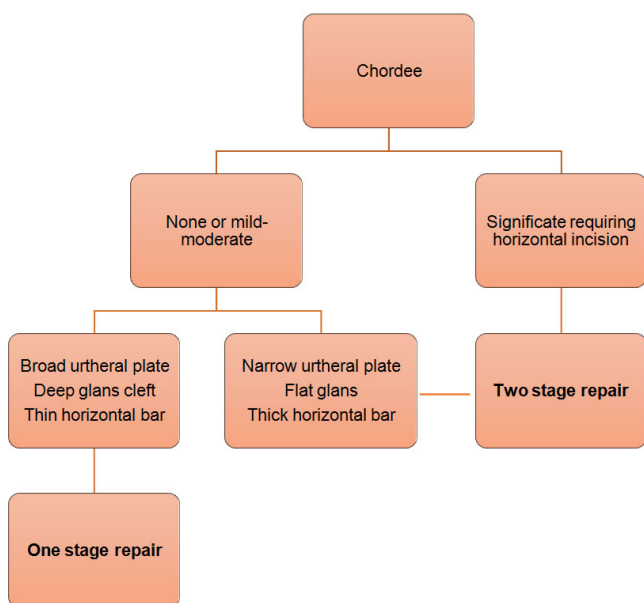


Figure 5: Algorithm for choice of repair

In conclusion, hypospadias surgery is practiced by a few surgical sub-specialties. It has been practiced for a long time and has evolved remarkably. There is a plethora of techniques and complication rates are still considered relatively high. Strategically approaching hypospadias with this simple algorithm and utilizing the microsurgical instruments with a surgical microscope will help in performing meticulous repairs. This approach will be much appreciated by those embarking in a career of hypospadiology.

Authors' contributions

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Concept design: M. Dalal

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All patients have signed a formal informed consent form for medical photography allowing publication.

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All procedures performed are in accordance with departmental ethics standards.

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Case Report

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Resolution of 2nd, 3rd or 4th interdigital space incomplete, simple syndactyly using a random vascularity flap

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ABSTRACT

Syndactyly consists of a variable fusion of soft tissue or of bone in adjacent fingers. This has important aesthetic and functional impacts on the development of the child due to the abnormal appearance of the hand. When the 1st web space is affected, it compromises grasp and development of the clamp function. Affliction of the 2nd, 3rd or 4th webspaces hinder the independent movement of the fingers adjacent to it. Current syndactyly release techniques have inherent disadvantages such as the use of skin from both the interdigital halves of the syndactylized fingers, the need to skin graft the donor site, postoperative flexion contracture, and need of 2 or more surgical procedures to obtain the desired result. The authors present 7 cases with incomplete simple 2nd, 3rd or 4th webspace syndactylies of multiple etiologies. All cases were treated at the unit of the corresponding author. The flap used in the treatment for all 7 cases did not require skin grafting of the flap donor site and used only skin from one of the fingers, while achieving a webspace dimension similar to normality, with a short recovery period. Furthermore, there were no postoperative finger contractures, diminishing the risk of future relapse.

INTRODUCTION

Syndactyly is one of the most common congenital anomalies, with an incidence of 1 in 2,000-2,500 live births.^[1-3] The etiology of syndactyly can be broadly divided into either congenital or acquired, with the latter predominantly secondary to burns. Its classification is based on the degree of soft tissue and bony involvement. Simple syndactyly affects

only skin and soft tissue between the affected fingers, whereas complex syndactyly has additional bony involvement. The distinction between a complete and incomplete syndactyly is determined by the extent of fusion in the proximal-distal axis. A complete syndactyly occurs when fusion involves the entire webspace from commissure up to and including the nail fold. The incomplete syndactyly in contrast, encompasses all fusions from the commissure that



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fall short of the nail fold.

The goal of treatment is to create a functional hand with minimal long-term morbidity. In order to achieve this, an aesthetically pleasing and functional interdigital space must be created preferably with as few procedures as possible.^[4] The current techniques available are based at the opening of the webspace with the purpose of obtaining a normal webspace while supplying adequate skin coverage for it.^[1,5-7] These surgical techniques can be classified into two types: those utilizing a local flaps alone and those that use skin grafting in addition to it. The latter technique is used especially in difficult cases of complete syndactyly to treat the fusion distal to distal interphalangeal joint. However in mild cases, such as incomplete syndactyly proximal to the proximal interphalangeal joint, various techniques for correcting the web only with local flaps from surrounding tissues have been reported.^[8] Some of the techniques used to recreate the webspaces include split and full-thickness skin grafts.^[9] Examples of local flaps used are such as the dorsal rectangular, palmar rectangular, interposed "V", dorsal metacarpal.^[10] The proximally-based dorsal rectangular flap is most commonly used.^[11] The main complications of corrective surgery are infection, delayed wound healing, graft loss, flap loss, syndactyly relapse and contracture of adjacent fingers.^[12]

CASE REPORT

Surgical technique

Marking

The depth of a normal adjacent webspace is measured and compared to the affected interdigital space. This is done to obtain the intended target webspace depth for the procedure [Figure 1]. The target depth is marked in the affected web using methylene blue dye. The marking can be made either on the dorsal or palmar side of web, depending on the quality of the skin or presence of scars. After due consideration for the required flap size, and the quality and quantity of the skin available in both adjacent fingers, one of the fingers is selected to design the flap on. The presence of adequate tissue laxity is verified to ensure a primary closure of the donor site. A proximally-based flap with a length matching the target webspace depth is then outlined. A length to base-width ratio of 3:1 for the flap is respected. The most-distal portion of the flap donor site must not surpass the proximal interphalangeal joint, so as to reduce the risk of subsequent contracture [Figure 2].

Anesthesia

The procedure can be performed under either general

or local anesthesia. Pre-operative exsanguination of the hand is used in all cases and can be achieved with an Esmarch bandage or pneumatic device (Kidde).

Creation of the new webspace opening

Under $\times 3.5$ surgical loupe magnification, the syndactylized soft tissue is incised with a 15 blade along the previous markings to achieve the desired webspace depth [Figure 3]. Blunt dissection of the interdigital space is performed with special consideration taken to release the natatory ligament and to preserve the digital neurovascular bundles [Figure 4].

Flap dissection

The skin and subcutaneous tissue of the flap is dissected along the pre-marked limits. Distal to proximal dissection is performed with thin curved scissors, achieving adequate flap thickness without damaging the main vascular pedicle of the finger. Only the skin and the subcutaneous tissue should be raised with the flap and must not include the main vascular pedicle of the finger. Thus, the flap is of a vascular random pattern variety and must not exceed the length to base width ratio of 3:1 to ensure its vascular viability [Figure 5].

Flap rotation

The dissected flap must be able to freely rotate to

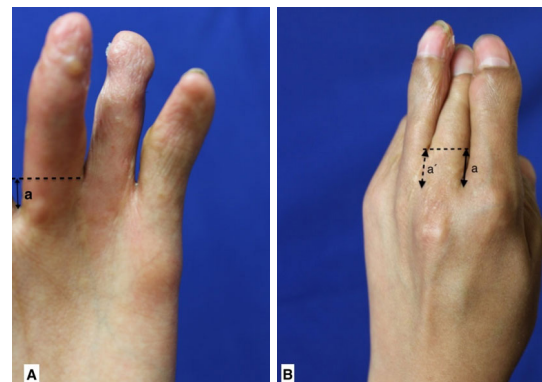


Figure 1: (A) Palmar view; (B) dorsal view. a: normal interdigital space depth; a': desired interdigital space depth



Figure 2: Flap design and marking

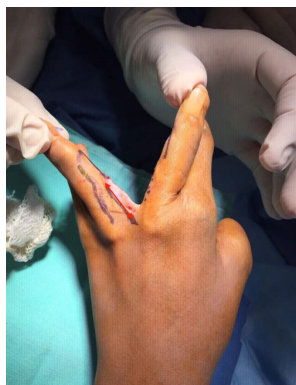


Figure 3: Surgical incision according to the desired web space depth



Figure 4: Interdigital space dissection



Figure 5: 3:1 (length:base) relationship to ensure vascularity



Figure 6: Flap rotation



Figure 7: Flap fixation and donor site primary closure

achieve full coverage of the newly created webspace. Then the flap can be tailored away to remove redundant skin [Figure 6].

Flap fixation and closure

Single sutures of 5-0 Vicryl are placed to secure the flap in the desired position. The donor site is closed primarily with simple interrupted 5-0 absorbable sutures [Figure 7]. Care must be taken to avoid any kind of tension on the donor finger that may modify the shape of the finger, cause deformity, limit finger movement or cause ischemia. The hand is splinted in a neutral position for the first post-operative week.

Postoperative care

Post-operative analgesia and prophylactic antibiotics are recommended. Patients are discharged from hospital the next day. Moisture at the surgical site can modify the results of the procedure and may cause wound dehiscence or infection and must be carefully managed. Suture removal is unnecessary as absorbable sutures are used. Scar moisturization can commence at the 2-week point. Patients are reviewed at the hand surgery clinic weekly during the first month, monthly for the next 2 months and every 2 months subsequently until final clinic discharge.

Outcome

We present 7 cases with incomplete simple syndactyly of the 2nd, 3rd or 4th webspace of multiple etiologies, presenting to the hand surgery service of the corresponding author and operating between February 2015 and May 2016. Cases include both unilateral and bilateral presentations of syndactyly [Table 1].

A proximally-based vascular random pattern flap was used to provide skin coverage to the webspace in all cases.

The demographics comprised 4 males and 3 females of an average age of 10.14 years (range 1-18 years).

Table 1: Details of patients

Case No.	Age (year)	Gender	Disease	Affected area	Affected web space	Treated web space	Complication	Operating time (h:min)	Hospital stay (day)	Result	Follow up (month)
1	1	M	SIS	Right hand	2nd	2nd	None	00:32	1	Good	2
2	18	M	BS	Both hands	2nd, 3rd both hands	2nd, 3rd both hands	None	01:25	1	Good	4
3	16	F	SIS	Left hand	3rd	3rd	None	00:42	1	Good	1
4	2	F	SIS	Left hand	4th	4th	Wound dehiscence	00:35	1	Good	2
5	14	M	ABS	Right hand	2nd	2nd	None	00:40	1	Good	2
6	7	F	BS	Both hands	2nd, 4th right, 4th left	2nd, 4th right, 4th left	None	01:35	1	Good	2
7	13	M	AS	Both hands	2nd, 4th right, 2nd, 3rd, 4th left	3rd left	None	00:47	1	Good	1

M: male; F: female; SIS: simple incomplete syndactyly; ABS: amniotic band syndrome; BS: burn sequels; AS: apert syndrome

Two patients had Apert syndrome and amniotic bands. Two further patients had syndactylies from burns and the remaining 3 as isolated non-syndromic congenital syndactylies. Two patients each had either the left and right hand involved. The remaining 3 had bilateral involvement. Three patients were recurrent syndactylies from previous syndactyly surgeries.

Complications included a case of partial dehiscence of the surgical wound on the third post-operative day. This was subsequently healed by secondary intention without affecting the functional outcome of the procedure.

All flaps were viable and continue to be monitored at the clinic to assess hand function.

DISCUSSION

The vascular random pattern flap has some inherent advantages such as a short surgical time. Neither dissection of the vascular pedicle with a microscope nor skin grafts were necessary. It is also a technically simple operation to perform and does not have a steep learning curve. In addition, this can be a day surgery procedure or at most an overnight stay, making it convenient for patients. There is also reduced morbidity by using only 1 finger as a donor site for the flap and having the donor site closed primarily. The latter eliminates the lengthy healing process for a skin graft and shortens the healing period to 5-10 days, the time taken for a primarily closed wound to heal. Aesthetic modification of the donor finger can already be seen after primary closure, and this continues to improve with time.

Techniques using skin grafts may result in higher rates of early postoperative complications (infection, flap necrosis, graft failure), web creep, contracture,

hypertrophic scarring and revisional surgery when compared with advancement flaps.^[13] Previous studies have shown that skin grafts increase the risk of web creep by exerting tension across the web space, particularly when the graft abuts either the dorsal commissure flap or palmar scar junction.^[12]

Of the surgical techniques reviewed, those described by Matsumine *et al.*^[11] in 2011, Hsu *et al.*^[14] in 2010 and Yamashita *et al.*^[8] in 2016 do not require the use of a skin graft for the flap donor site. However, these techniques require using tissue from both adjacent fingers to recreate the desired space.

Our series has a zero flap failure rate. We propose that the use of a vascular random pattern flap instead of an axial pattern flap reduces the risk of pedicle-related complications such as bending, injury or thrombosis of the same. There has been no flexion contractures at the four-month follow-up and can be explained by the fact that the skin used to cover the created interdigital space grows in the same direction and speed at which the finger grows. The flap length that does not surpass the level of the proximal inter-phalangeal joint may also contribute to the favorable lack of flexion contracture seen in our case series. This flap is versatile and can be altered to utilize either the dorsal or palmar skin to reopen the affected space. This is useful when there may be unfavorable features such as scars or other characteristics that diminish the quality of the skin on either surface. As skin from only one finger is used, there is a choice to either use the radial side of one finger or ulnar side of the other, depending on the skin quality on the finger.

This flap can also be used to tackle cases of relapse where other options may already have been exhausted previously. This technique is also a good option for the management of burn syndactyly as the scar tissue can

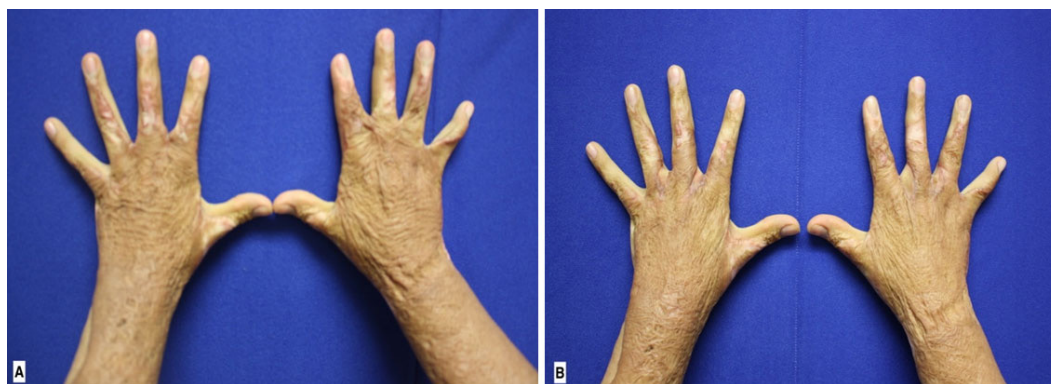


Figure 8: Dorsal view. Preoperative and 4 months postoperative comparison of a 18-year-old patient with burn sequelae in both hands. The 2nd and 3rd interdigital spaces were opened using the proposed technique. (A) Preoperative view; (B) 4 months postoperative view

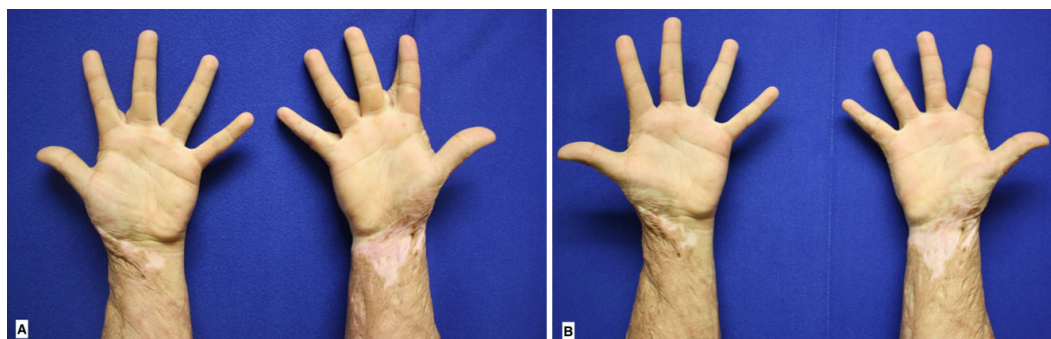


Figure 9: Palmar view. Preoperative and 4 months postoperative comparison of a 18-year-old patient with burn sequelae in both hands. The 2nd and 3rd interdigital spaces were opened using the proposed technique. (A) Preoperative view; (B) 4 months postoperative view

be included in the rotation flap for webspace coverage [Figures 8 and 9].

The possible disadvantages of this flap include the risk of vascular insufficiency of the flap if an insufficiently broad base (at least a 3:1 length-base relationship) is not adhered to. There is also a risk of vascular compromise if a wide donor area is taken and primary closure is performed under tension. Flexion contracture of the proximal inter-phalangeal joint of the donor finger can occur if the length of the flap surpasses the level of this joint and if sufficient dissection is not performed adequately. Another disadvantage of the proposed flap is that both sides of a finger cannot be used simultaneously as flap donors. This is due to the risk of vascular compromise for the donor finger as well as the functional (flexion contraction) and aesthetic (deformity of the finger) complications that may arise.

The proposed flap only improves soft tissue and as such its use is limited to simple syndactyly cases. As the flap cannot surpass the proximal interphalangeal joint, its use is limited to cases of incomplete syndactyly.

Because of the large quantity of soft tissue needed to

resurface the first webspace, we do not consider this flap a good option for these cases. The amount of soft tissue that can be taken from the donor finger while allowing primary donor site closure is exceeded in most of these cases.

Possible complications of this flap include wound dehiscence, infection, flap necrosis, flexion contracture of the donor finger, and syndactyly relapse. In our experience, this flap did not present any of the aforementioned complications with the exception of one case of surgical wound dehiscence that was resolved. No other complications were seen in our case series.

Authors' contributions

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Patient consent

All operations and photographs were performed after the patients' written consent.

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Reverse latissimus dorsi muscle flap for complex back defects: our experience

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ABSTRACT

Aim: The aim was to study the effectiveness of the reverse latissimus dorsi muscle flap in reconstruction of complex defects of the back. **Methods:** This is a retrospective study of patients who underwent reverse latissimus dorsi flap for reconstruction of the back, in a tertiary care hospital. The patient demographics, etiology, surgery indications and complications were studied. **Results:** The study had five patients between 2012 and 2016 who underwent reverse latissimus dorsi flap for reconstruction. The flaps survived in all the patients. Two patients had complications, unrelated to the latissimus dorsi muscle flap. **Conclusion:** The vascularity of the flap is reliable can be used to obliterate the dead space, can be used to control the infection, in complex cases of the back.

INTRODUCTION

The back has the vertebrae in the middle and exposure of the bone gives us a complex defect. The etiology includes myelomeningocele defects, post excision defects of the back, and pressure sores. The various options for coverage of myelomeningocele defects include local skin flaps, skin graft, latissimus dorsi muscle flap and other variations.^[1] The latissimus dorsi flap is a

versatile flap based on the thoracodorsal vessels and the perforators from the posterior intercostal and lumbar perforators. It is a type V muscle flap based on the Mathes and Nahai classification.^[2] The latissimus dorsi muscle is frequently used based on the thoracodorsal pedicle. The reverse latissimus dorsi flap is based on the secondary pedicles which are the perforators from the posterior intercostal and lumbar vessels.^[2] The reverse latissimus dorsi flap is used for coverage of the midline



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Figure 1: Latissimus dorsi muscle flap raised based on the secondary pedicle

and contralateral back, lumbar and sacral midline. This muscle flap can also be used for the reconstruction of the diaphragm.^[3] Simple midline defects can be covered by various fasciocutaneous flaps like rhomboid, transposition, rotation, advancement, Z flaps, S flaps, lumbar perforator based flaps, etc.^[2] Complex defects in the lower back over the lumbar and sacral region are a difficult problem for plastic surgeons. In complicated cases, we cannot rely on these fasciocutaneous flaps alone, we need to combine muscle flaps with either fasciocutaneous flaps or skin grafts. Muscle flaps have many advantages: they are sturdy, more vascular, have a large surface area that can be used to obliterate dead space. For coverage of complex posterior defects, we can use gluteus maxims, latissimus dorsi muscle flaps alone or with other variations.

The gluteus maximus muscle can be used to cover sacral defects. However, lumbar defects are not as easy covered. The ipsilateral latissimus dorsi flap based on the thoracodorsal vessels can be moved medially to cover the lumbar region. The turnover of the latissimus dorsi flap from lateral to medial side can be used to cover the midline thoracic defects. These flaps are based on the thoracodorsal vessels. Latissimus dorsi musculocutaneous flaps with the skin extending to the posterior axillary line would cover the lower lumbar and sacral defects.

METHODS

A retrospective study was conducted in a tertiary care hospital of patients who underwent reverse latissimus dorsi flaps between February 2012 and December 2016.

There are 5 cases in this study. The patient records were analyzed for the age, gender, indications, surgical procedure, defect size, complications. The neurosurgeons released the tethered spinal cords in case of myelomeningocele in first 3 cases, excised the

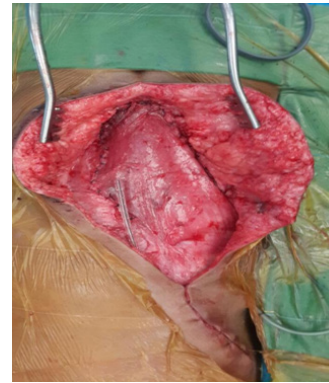


Figure 2: Latissimus dorsi muscle inset given, donor site closed. Viability confirmed before closing the wound

recurrent sacral cordoma in the fourth case, while the onco surgeons excised the sarcoma of the chest wall in the fourth case. After the primary surgeries as mentioned above, the cases were presented for reconstruction. The dura was reinforced with sutures and fibrin in cases with myelomeningocele. An oblique incision from the edge of the defect to the ipsilateral axilla was used to expose the latissimus dorsi muscle. The skin flaps were raised. The muscle was cut at 10 cm from the insertion. The thoracodorsal vessels and nerve were identified, ligated and divided. The muscle was raised from the undersurface until the secondary pedicles were identified [Figure 1]. The muscle was turned over to the defect in such a way that superficial surface of the muscle covered the defect. After turnover, the flap was inset with absorbable sutures. Flap vascularity was confirmed by color and distal tip bleeding [Figure 2]. Over this muscle flap, adjacent fasciocutaneous flaps were advanced. The donor site was closed in layers and a drain was placed. Post operatively patients were nursed in either prone or lateral position. Sutures were removed by 15 days and the drain by 10 days.

Case 1

This patient had a myelomeningocele with raised intracranial pressure and a ventriculoperitoneal shunt. We had high suspicion that there might be a cerebrospinal fluid leak (CSF leak) [Figure 3]. Hence, a muscle flap was planned to cover the defect including any minor leaks and to provide a vascular cover over the dura. A reverse latissimus dorsi muscle flap was used to cover the defect and a fasciocutaneous flap was advanced over the muscle [Figure 2]. The postoperative course was complicated by 1 cm skin necrosis, which was dressed regularly and allowed to heal by secondary intention.

Case 3

This patient was operated for amyelomeningocele of the lumbosacral region. The tethered cords were released and dura was repaired by the neurosurgeons.



Figure 3: Case 1. Myelomeningocele defect, after release of teethered cords

The skin adjacent to the defect was advanced to close the defect. She developed CSF leak manifesting as swelling in the operated site and also excess drainage collection. She was reexplored to correct the CSF leak. The dura was reinforced with sutures and glue. The reverse latissimus dorsi turnover flaps were used to cover this complicated myelomeningocele defect. Here, the distal end of the latissimus dorsi flap was not showing adequate vascularity and was debrided. This flap was able to cover only the upper two thirds of the defect. A contralateral gluteus maximus muscle flap was advanced to the lower part of the defect [Figure 4]. The skin was advanced to cover the defect. The wound healed well with no complications.

RESULTS

A total of 5 patients [Table 1] were treated with a reverse latissimus dorsi flap for various defects of the back. Among these 5 patients, 2 were male and 3 were female. Three patients aged below 2 years and 2 patients aged 55 years and 60 years. Two patients had

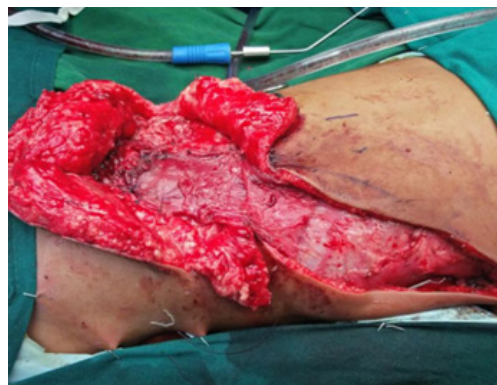


Figure 4: Case 3. Reverse latissimus dorsi muscle flap and gluteus muscle flap to cover the myelomeningocele defect

cancer excision and 3 patients had myelomeningocele correction. Four patients underwent turnover of the reverse latissimus dorsi flap and 1 patient had transposition of the reverse latissimus dorsi flap. All 4 reverse latissimus dorsi turnover muscle flap were done by a single surgeon and the reverse latissimus dorsi muscle transposition flap was done by another surgeon. Four patients had advancement of fasciocutaneous flaps over the muscle flap; 1 patient had a split thickness skin graft over the muscle.

The indications for the use of a muscle flap in these cases were CSF leak, sinus, wound dehiscence, need for vascular cover over the implants, obliteration of the dead space, and to reconstruct the chest wall defect.

Two patients had prior surgery within a week before the reverse latissimus dorsi flap was used to cover the defect. Three patients had not undergone prior surgery.

In case 3, the distal muscle did not look healthy; hence the contralateral gluteus maximus flap was raised

Table 1: All the cases included in the study

No.	Age/gender	Diagnosis	Indication	Defect size	Muscle flap used and movement of flap	Complications after the surgery
1	9 days/male	Lumbosacral myelomeningocele	Associated with hydrocephalus, had a ventriculo-peritoneal shunt, high suspicion of chance of CSF leak from the dural patch	10 cm × 8 cm lumbosacral defect	RLDMF turnover	Skin edge necrosis of 1 cm, was allowed to heal by secondary intention
2	14 months/male	Lumbosacral myelomeningocele	Operated 4 days before, developed CSF leak	12 cm × 5 cm lumbosacral defect	RLDMF turnover	Nil
3	12 months/female	Lumbosacral myelomeningocele	Operated 1 week before and developed CSF leak	14 cm × 6 cm lumbosacral defect	RLDMF turnover and GMMF	Nil
4	55 years/female	Recurrent sacral chordoma of sacral and lumbar vertebrae	Cross linking of left and right iliac bones with the lumbar bones using pedicle screws after sacrectomy	15 cm × 20 cm lumbosacral defect	RLDMF turnover and FCRF	Nil
5	61 years/female	Spindle cell tumor of lung and lower posterior chest wall	Excision included posterior chest wall and lower lobe of lung	12 cm × 10 cm thoracic defect	RLDMF transposition	Excision margins were positive for malignancy and patient declined further intervention

CSF: cerebrospinal fluid; RLDMF: reverse latissimus dorsi muscle flap; GMMF: gluteus maximus muscle flap; FCRF: fasciocutaneous rotation flap

and advanced to cover the lower defect. At the end of surgery, both muscles were healthy. We identified three big lower perforators, but even then the vascularity of the muscle tip was inadequate.

In case 5 the flap dehiscd, there were increased secretions from the wound, empyema due to incomplete excision of the tumor and patient was unwilling to undergo further procedures. The flap in case 5 looked healthy and the skin graft take was more than 90%.

Otherwise, the other 4 cases had no postoperative fevers, increase in discharge or particulate matter in the drain, which suggested a healthy muscle flap.

There were no donor site complications in any of the above cases. All these patients, except for case 5, followed up for six months and had no problems recorded with regards to shoulder movement.

DISCUSSION

The most common indication for the use of the reverse latissimus dorsi muscle flap has been a complex defect or a complicated defect, like infected ulcer, post radiotherapy ulcer, CSF leaks.^[4-8] In the present study we have used it for complex wounds with CSF leak, prosthesis *in situ*. The reverse latissimus dorsi is considered only as an alternative for meningocele closure. Ayad *et al.*^[4] used the reverse latissimus dorsi flap as a primary reconstruction for large defects.

The reverse latissimus dorsi muscle flaps are based on the perforators from the posterior intercostal vessels and the lumbar vessels. The turnover of the reverse latissimus dorsi muscle flap from upper back to the lower back can cover midline lumbar and sacral defects. The reverse latissimus dorsi muscle flap can be transposed to cover the lumbar orthoracic defects and can be used inside the chest. The superior perforators can be divided for adequate reach of the flap, but the inferior pedicles need to be preserved for the survival of the flap. In case 3 the distal part of the latissimus dorsi flap was not healthy and thus we had to debride part of the flap. We felt the secondary pedicles were not sufficient to vascularise the distal end. Studies have found that the vascularity of the reverse latissimusdorsi flap is reliable.^[4,5]

There is thinning of the skin over the myelomeningocele. There is decreased soft tissue support in the midline if the skin over the defect is thinned by expansion. The use of a muscle cover in addition to the fasciocutaneous flap, over the repaired dura will give additional support as well as act as a vascularized cover over the dura.

The layered closure had helped Söyüncü *et al.*^[9] to decrease the CSF leakage by using omentum and latissimus dorsi flap.

A reverse latissimus dorsi flap can also be used for 3D coverage and to control bacterial contamination.^[5,6,10] In our experience, complicated acquired defects (like in the fourth case) require muscle to fill the dead space around the fixators as a first layer to cover the implants. Dead space is a potential space for seroma collection and infection. So, with a muscle flap we were able to successfully prevent the formation of seroma and infection.

Large meningocele defects have also been reconstructed with reverse latissimus dorsi flap and skin graft.^[7] In one case we decided to leave the wound to heal by secondary intention as the skin necrosis defect was 1 cm in size. We had a healthy muscle covering the dura and hence, we were able to allow for secondary intention without the risk of dura break down and infection.

Latissimus dorsi muscle is a type V muscle flap based on thoracodorsal artery and perforators from the lumbar and posterior intercostal vessels. These perforators are usually present 5 cm from the midline.^[11] The perforators were present within 5 cm of the midline in our series. All the flaps except 1 survived without any distal necrosis, even though the distal perforators were intact. The distal 2 perforators are enough for the survival of the muscle for the lower part of the muscle.^[12] Hayashida *et al.*^[13] have published a case report on reverse latissimus dorsi flap based on the tenth perforator. In the above case the reach of the flap was up to the anterior superior iliac spine. In our cases the flaps reached the lower sacrum without tension or compromise on the muscle vascularity in all cases except 1 case. Though, many authors have described that the flap can survive with the lower 9th and 10th perforators^[13] we feel distal flap necrosis may be encountered. We do not have a large series as proof, hence further studies would be needed.

The flap reaches down to the lower sacrum, however, one might have difficulty covering the lower part of the sacrum. As an option, the gluteus maximus muscle flap can also be used as described in one of our cases. The most frequent complication of the latissimus dorsi muscle flap is seroma.^[14] However, in our series we did not encounter it.

The reverse latissimus dorsi flap is robust with a reliable vascularity. The chances of failure are small. Alternatives include the use of local flaps, which do

not have the mopping qualities of the muscle. We can deepithelialise the skin flaps and use it to obliterate the dead space. This may lead to the development of epithelial cysts. Söyüncü *et al.*^[9] have used latissimus dorsi muscle flap along with omentum with a view that layered closure would decrease chances of CSF leak in recurrent cases of CSF leak.

Free flaps are an option, however the recipient vessels are deep and hard to find. The vessels which could be harvested as recipient are the superior gluteal vessels, inferior gluteal vessels, and intercostal vessels, perforators from the deep femoral system,^[15] superficial femoral trunk, and thoracodorsal vessels. The other possible methods of obtaining a recipient are using an interposition vein graft between the distant vessels to the donor vessels,^[16] or a carrier vessel may be used and flap transferred in stages. Reverse latissimus dorsi flap has been transferred to the defect and supercharged the flap by anastomosing the thoracodorsal vessels with the inferior gluteal vessels.^[17]

We have followed up the patients for 6 months; the functional deficit of the shoulder could not be assessed in children. However there was no appreciable difference in movement of the shoulder when compared to the opposite shoulder. In case 4, we did not find any restriction when compared to the opposite shoulder. Case 5 was lost in follow up. Other studies regarding functional assessment have also found no significant shoulder function disability.^[18,19]

Our study had 5 cases; it is not a comparative study. Further studies may be required to compare other flaps with the reverse latissimus dorsi flap to establish that it is a better choice in complex defects of the back. However, most of the authors in the literature have agreed that reverse latissimus dorsi flap is a choice for reconstruction of the back with CSF leaks, difficult wounds with infection, radiation, *etc.*

In conclusion, we feel that reverse latissimus dorsi muscle flap is a robust flap with reach up to the lower part of sacrum. We recommend it as a definite choice for big complicated meningocele defect or any posterior defect in the lumbar and sacral region. We feel that this flap may be considered as a primary choice for big meningocele defect. This needs further studies.

Authors' contributions

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Manuscript's review: K.M. Kumar, V.P. Waiker, U.S. Odeyar

Concept design: K.M. Kumar

Literature search: K.M. Kumar

Case material's provide: K.M. Kumar, S.K. Shivalingappa

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There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

Obtained.

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Case Report

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Double-paddled pectoralis major myocutaneous flap as an alternative to microvascularized free flaps in complex orocervical defects

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ABSTRACT

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microvascularized free flap failure

The authors present the double-paddled pectoralis major myocutaneous flap as a successful alternative for the reconstruction of complex orocervical defects following failure of prior microvascularized free flaps or free flap harvest is not feasible. This method was used for the reconstruction of post-ablative defect in a 36-year-old male with a T4 squamous cell carcinoma of the base of tongue with laryngeal involvement. The distal paddle was adapted to reconstruct a defect of the floor of the mouth and further sutured in two layers (muscle-basal mandible and skin paddle-oral mucosa) while the proximal skin paddle was used to close the cervical skin and the peri-tracheostomy defect.



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INTRODUCTION

Reconstruction of large oral cavity defects following resection for advanced cancer is a challenge for reconstructive surgeons. In the microsurgical era, microvascular free flaps constitute the main reconstructive option for achieving excellent aesthetic and functional results. However, in cases of flap failure or inability to harvest a free flap, pedicled flaps provide a reliable alternative with predictable results. The pectoralis major myocutaneous flap (PMMF), considered the workhorse in head and neck surgery, represents one such pedicled flap. In the event of major defects requiring a large area volume for cutaneous coverage and mucosal lining, a modification of the standard technique is required.^[1-3]

CASE REPORT

The authors describe a surgical technique for repair of a complex orocervical defect following failure of microsurgical reconstruction with use of a double-paddle PMMF. A 36-year-old man was diagnosed with T4 squamous cell carcinoma of the base of tongue with laryngeal involvement. Under general anaesthesia,

a tracheostomy was performed. A total laryngectomy and partial glossectomy extending to the right base of the tongue were performed by a “pull-through” approach exposing the entire tongue, oropharynx and suprahyoid space. A bilateral modified type III radical neck dissection was performed. The intraoral and primary cervical defects were reconstructed with a microsurgical anterolateral thigh flap. In the postoperative period, the remainder of the tongue underwent total necrosis with subsequent distal flap dehiscence, cervical fistulae and a large defect in the floor of the mouth [Figure 1]. In an attempt to solve these complications by providing sufficient tissue for reconstruction of the floor of the mouth while closing the orocervical fistulae, a PMMF with two skin islands was designed. This flap consisted of two vertically separated skin islands over the area of the pectoralis major myocutaneous vascular territory: one skin island was medial to the nipple-areolar complex and the other was lateral. The skin paddles were designed horizontally. The skin and the subcutaneous fat were closed using vicryl sutures to avoid shearing of perforator vessels vascularizing the skin. The flap was raised using standard surgical technique leaving its proximal paddle pedicled to the arterial plane [Figure 2]. The proximal skin paddle was used to close the cervical skin and the peri-tracheostomy defect [Figure 3A]. The distal paddle was adapted to floor of the mouth and sutured

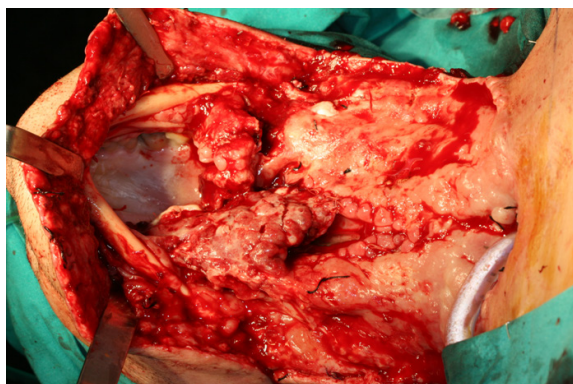


Figure 1: Distal flap dehiscence, cervical fistulae and large defect in the floor of the mouth following failure of a microsurgical anterolateral thigh flap

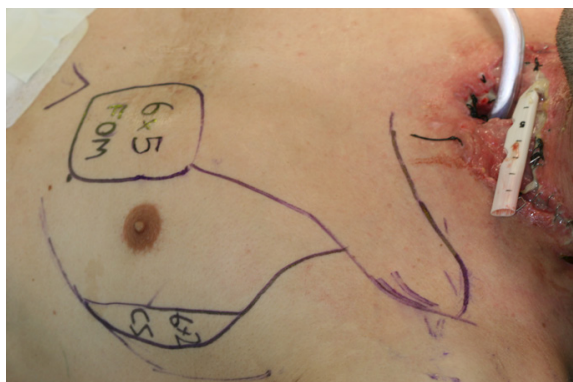


Figure 2: A pectoralis major myocutaneous flap design with two skin islands: one skin island was designed for the floor of the mouth defect with the other skin island for the cervical skin defect

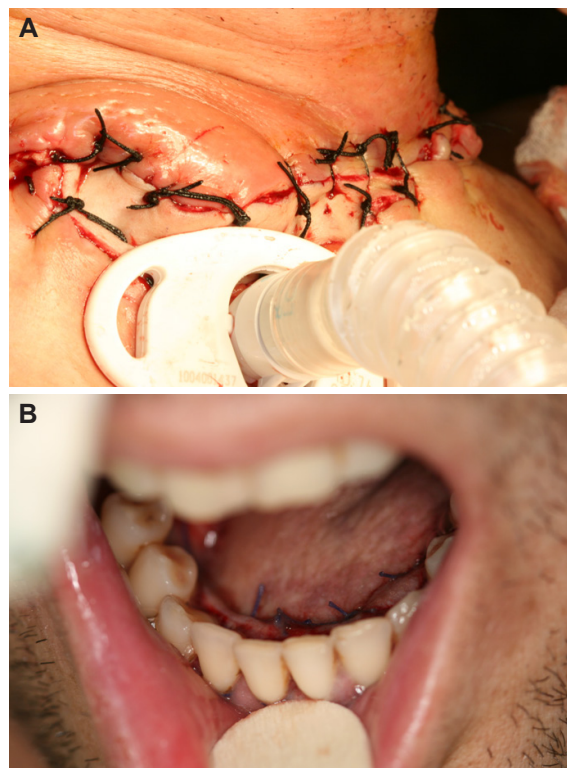


Figure 3: (A) The first skin paddle was used to close the cervical skin and the peri-tracheostomy defect; (B) the second skin paddle was adapted to floor of the mouth



Figure 4: The donor site was closed primarily and remained intact throughout the post-operative period

in two layers (muscle-basal mandible and skin paddle-oral mucosa) [Figure 3B]. The donor site was closed primarily and there were no dehiscence defects during the post-operative period [Figure 4]. Both skin islands remain viable to date [Figure 5].

DISCUSSION

Reconstruction of complex oral cavity defects following oral cancer surgery is a great challenge for the head and neck surgeon. The evolution of myocutaneous and free flaps has achieved good results in the reconstruction of large oncological defects. Currently, microvascular free flaps are considered to be the first option in the reconstruction of head and neck defects. However, in cases of free flap failure or when a free flap is simply not feasible, pedicled flaps provide a reliable alternative with predictable results. The bilobular or double-paddled PMMF simplifies the closure of large surgical defects of both the mucosa and skin which cannot be successfully closed in a primary approach. The closure of defects using a PMMF was first reported in 1979 by Ariyan.^[4] This author also described the division of the skin into two parts. Ord and Avery^[5] later suggested that placing the skin paddles side-by-side horizontally was less risky than placing them vertically one above the other. The two lobes of the pectoralis major myocutaneous flap evolved from a desire to simplify the closure of large surgical defects of both the mucosa and skin that could not be satisfactorily closed primarily. The mucosal and skin defects are closed by two skin paddles supported by a single muscular vascular pedicle.

In the current case, the double-paddled PMMF was used to reconstruct both intraoral and cervical defects. The distal paddle was adapted to the floor of the mouth and the proximal skin paddle was used to close the cervical skin and the peri-tracheostomy defect. The main advantages^[6] of the double-paddle PMMF include: (1) easy access within the same surgical field;

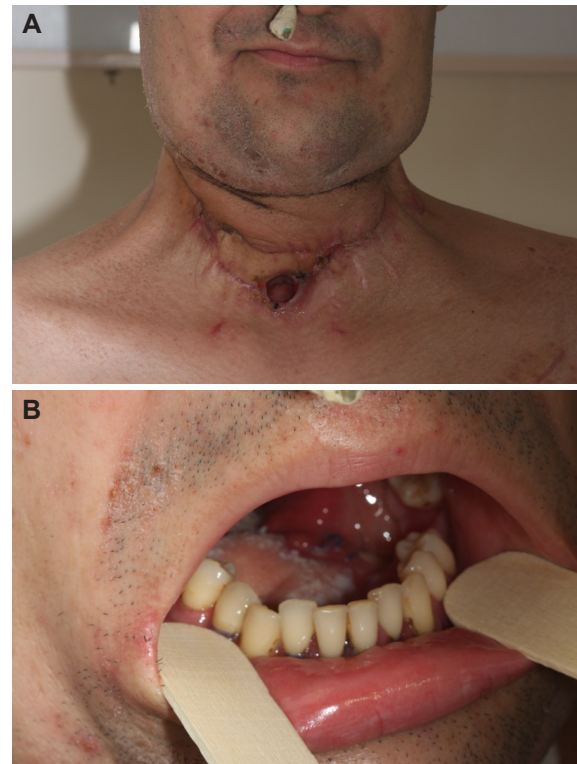


Figure 5: (A and B) Both skin islands remain viable to date

(2) shorter operating time; (3) elimination of the need for two separate flaps and a second surgical procedure; (4) technical simplicity with a short learning curve; (5) a reliable vascular framework; and (6) adequate muscle coverage of major cervical vessels, which provides greater protection during radiotherapy. Nonetheless, the success of this flap depends on the arch of rotation and anatomic limitations such as obesity, or the combination of a long neck with a short thorax.

In summary, the double-paddled PMMF can be successfully used for reconstruction of complex head and neck cancer defects following failure of microvascularized free flaps or when free flap harvest is not possible.

Authors' contributions

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Manuscript's review: R. González-García, C. Moreno-García

Concept design: R. González-García

Literature review: M. Moreno-Sánchez

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Ethics approval

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Reconstruction of a large defect of the female chest following keloid excision with use of the rectus abdominis myocutaneous flap

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Dr. You-Bin Wang is an outstanding Professor in the Department of Plastic Surgery at Peking Union Medical College Hospital. He is famous in keloid treatment and study. He has invented many new surgical methods in keloid treatment and has published many articles in this field. He is also good at cleft lip surgery, nose reconstructive surgery and breast reconstruction.

ABSTRACT

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Keloid,
rectus abdominis myocutaneous flap,
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Aim: This study aimed to investigate the efficacy of the myocutaneous flap of the rectus abdominis in the surgical treatment of a large defect on the female chest following keloid excision. **Methods:** According to the location and size of the keloid on the chest, a myocutaneous flap based on the left or right rectus abdominis muscle was designed and transferred for repair of a chest defect following keloid resection. Radiotherapy was performed in the surgical area on the first and seventh postoperative days. **Results:** From January 2015 to March 2016, rectus abdominis myocutaneous flap coverage and early radiotherapy were used to treat 7 cases of keloids on the female chest. A postoperative follow-up of 10-14 months (average 12 months) was conducted. All the flaps survived well without evidence of keloid recurrence, and all patients achieved an improved chest shape. **Conclusion:** The rectus abdominis myocutaneous flap is a viable method for wound closure following resection of large keloids on the female chest.

INTRODUCTION

Keloids formation occurs secondary to excessive local fibroblast proliferation and synthesis of collagen

fibers;^[1] this process frequently occurs in the chest wall, shoulder, upper arm and other locations. The disease course of a keloid on the chest wall is longer, and these areas tend to be wider, particularly in



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females^[2] in whom the lesions frequently involve the breast and other peripheral organs. Many treatment methods have been reported including triple therapy in which surgery is combined with steroid injections and silicone sheet application.^[3] While surgery combined with radiotherapy is effective in the treatment of keloids,^[4] the wound cannot be directly closed following resection of keloids greater than 10 cm × 10 cm in width and length on the chest wall. In women, given the presence of breast tissue, it can be even more difficult to employ primary closure. Skin grafting would delay radiotherapy.^[5] Therefore, for large defects following keloid excision in females a rectus abdominis myocutaneous flap was used to repair the wound, and achieving a better therapeutic efficacy than a skin graft.

METHODS

Clinical data: 7 female patients, aged between 25 and 46 years, with an average age of 33.40 ± 8.32 years presented with keloids of the chest. Five patients had keloid formation following hyperplasia of chest acne infections, and 2 patients developed keloids after the resection of a skin mass. None of the patients had a history of upper abdominal surgery.

Preoperative preparation

Large keloids frequently have surface irregularities and crevices which can permit the accumulation of contaminating substances and put the patient at risk for postoperative infection. In cases in which an infection is already present, debridement, drainage and dressings should be performed until the infection has been brought under control. Three days prior to surgery, daily povidone-iodine disinfection was performed for patients who have recently recovered from an infection or in whom sinuses have formed beneath the keloid mass. All other patients were required to shower daily beginning three days prior to surgery. With instructions to thoroughly clean the keloid and any depressed region or gaps. Cotton swabs were used during each cleanse and running water was used to rinse the gaps.

The skin surrounding the keloid mass was also determined to be healthy and clean prior to surgery. In cases in which infective acne was present in the surrounding skin, daily 75% alcohol local disinfection was performed until the infection was controlled. For cases in which the acne was in its recovery stage with resolution of erythema and pain, the remaining pustules were cleaned and the wounds were covered with sterile gauze. Patients were healthy and received medical clearance prior to surgery. Blood glucose levels were controlled in diabetic patients. Prior to beginning surgery, an abdominal flap was designed based on



Figure 1: Keloid on the chest and flap design

the size of the keloid. A Doppler stethoscope was first used to determine the site of perforation of the superior epigastric artery into the upper abdominal skin, and then, according to the perforation point, the rotation point of the flap pedicle, the size of the flap, and the location of the flap were determined and marked [Figure 1].

Surgical methods

The operation was performed under general anesthesia. The patient was placed in the supine position, and the chest and abdomen were disinfected and covered with sterile drapes. Local infiltration anesthesia was performed using a 0.06% lidocaine (1:20,000 adrenaline) solution in the area surrounding the planned incisions. An incision extending to the deep fascia was first created around the keloid on the chest. The keloid tissue was then removed at the level of the deep fascia. Complete hemostasis was performed. For those patients in whom a preoperative local infection and sinus had been present, the wound was rinsed with hydrogen peroxide solution followed by saline. For patients without a pre-existing infection, saline solution alone was used for irrigation. After re-confirming the size and shape of the wound as well as the design of the abdominal flap, an incision was made within the markings of the designed flap and extended to the deep fascia. The anterior sheath of the rectus abdominis was separated and opened. The rectus abdominis muscle was exposed and separated from its posterior sheath. The rectus abdominis was divided distally with vessel ligation. The flap was elevated proximally to the level of the xiphoid until the flap could freely rotate to the chest using the superior epigastric artery as the pedicle [Figures 2 and 3]. Following complete hemostasis, the flap was transferred to cover the chest wound and the abdominal donor site wound was closed [Figure 4]. As much of the anterior rectus sheath was preserved as possible in order to maintain the integrity of the abdominal wall.

Postoperative treatment

Radiotherapy was administered to the chest and

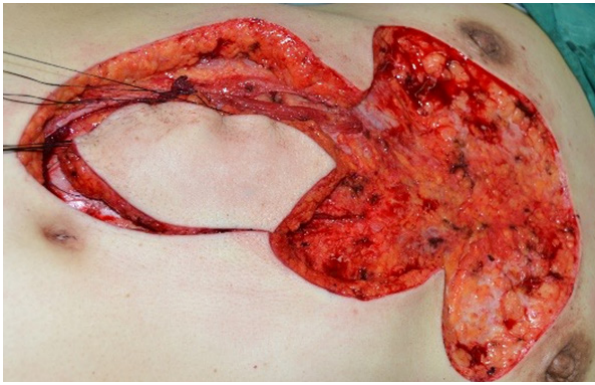


Figure 2: After the formation of the myocutaneous flap of the rectus abdominis

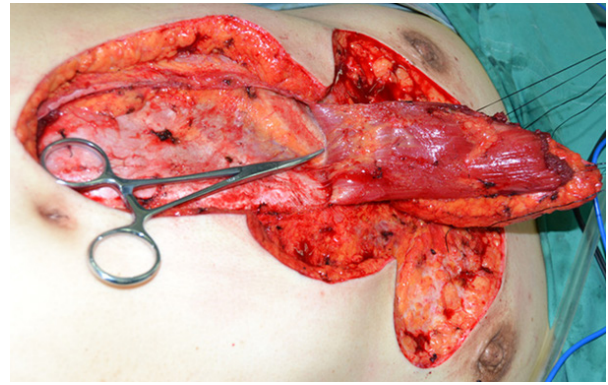


Figure 3: The pedicle with the perforating vessels of the superior epigastric artery



Figure 4: Closed chest wound 2 weeks after flap transfer

abdominal donor site on the first and seventh postoperative days; each dose was 900 cGy for a total dose of 1,800 cGy. The wound was checked and cleaned every three days following surgery and sutures were removed 14 days postoperatively. A compression garment was used 1 month after suture removing until the wound scar become pale and flat.

RESULTS

From January 2015 to March 2016, the rectus abdominis myocutaneous flap was used combined

with early radiotherapy to treat 7 cases of large keloids on the female chest. All flaps survived, and the incisions healed during the primary stage without any cases of infection, dehiscence or other complications. All patients completed their courses of thoracic and abdominal radiotherapy. Follow-up was conducted for 10-14 months (average of 12 months) and demonstrated that all incisions healed well without any cases of keloid recurrence. Furthermore, the patients were satisfied with the shape of the chest and abdomen [Figures 5 and 6].

DISCUSSION

Keloids occur in the skin and can expand rapidly towards surrounding normal tissue. Keloids are pathologically composed of collagen fibers and often protrude clinically from the skin. They often occur epidemiologically in young people, especially in females.^[6,7] Keloids frequently form on the chest, shoulder, and lower mandible of the face secondary to acne.

Various therapeutic management techniques have been reported in literature including conventional surgery, cryosurgery, medical therapy including steroid and

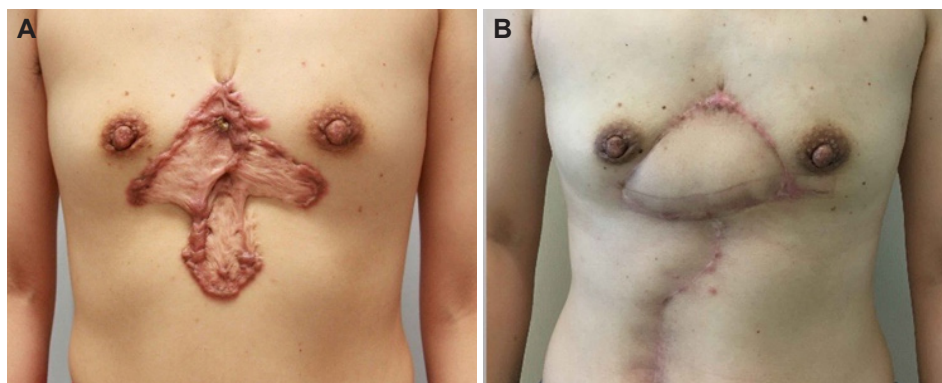


Figure 5: Case 1. (A) Preoperative chest keloid and (B) 8 months after the keloid resection and the repair with the rectus abdominis myocutaneous flap

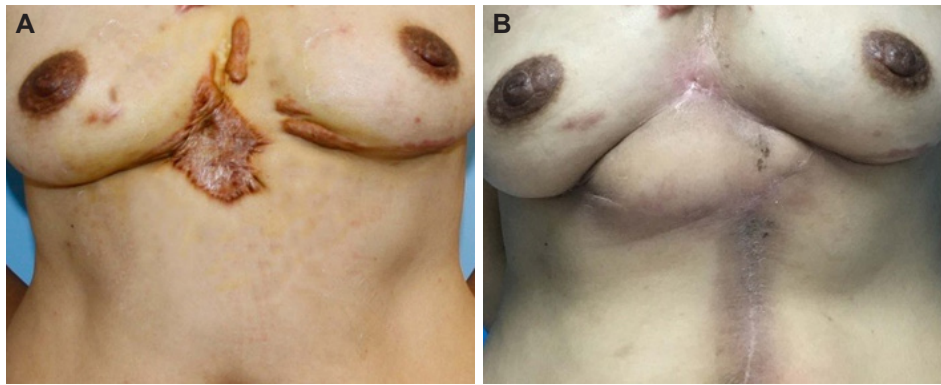


Figure 6: Case 2. (A) Preoperative chest keloid and (B) 1 year after the keloid resection and the repair with the rectus abdominis myocutaneous flap

5-fluorouracil injections, and physical modalities such as radiation and laser treatment. Combination usage of these techniques has also been widely reported. 5-fluorouracil combined with steroid injections is often used with clinical results better than with 5-fluorouracil alone.^[8] Laser treatments in conjunction with steroid injections has also been reported.^[9] Careta *et al.*^[10] reported encouraging results following the use of cryosurgery with intralesional steroid injections in the treatment of earlobe keloids. However, the combination of surgery with other techniques is more widely used, particularly the combination of surgery and radiotherapy. Mankowski *et al.*^[11] suggested that surgery and postoperative radiotherapy was the most effective method out of all keloid treatment modalities.

The surgical resection of scar tissue combined with postoperative radiotherapy can inhibit the proliferation of fibroblasts and the synthesis of collagen proteins during early wound healing. Postoperative radiotherapy is a reliable method for the treatment of keloids. The primary requirement for early postoperative radiotherapy is wound closure following resection of the keloid; otherwise, radiotherapy cannot be applied. Primary closure is strongly recommended in this method.^[12]

Methods for wound closure include direct closure, local flap transfer, internal mammary artery (IMA) perforator flap transfer, and skin grafting.^[13-16] Different methods can be selected based on the width of the keloid on the anterior chest wall. For single or multiple isolated lesions with a diameter within 1-3 cm, keloid resection and direct closure can be performed. If direct closure cannot be readily achieved, skin flaps or skin grafts should be performed to decrease the wound tension. For chest wall lesions with a diameter greater than 3 cm, a local flap or IMA perforator flap can be performed to cover the defect and avoid wound dehiscence. For lesions less than 5 cm × 5 cm, randomized local flaps are possible with primary closure of the donor site. IMA

perforator flaps are a better option for keloids larger than 5-10 cm in diameter. For very large keloids larger than 10 cm × 10 cm, skin grafts are the best option following resection.^[5]

Although both primary closure and local flap transfer are suitable for the surgical treatment of small keloids, free flaps can more adequately cover larger wounds. There are particular challenges associated with wound coverage of large chest keloids in female patients secondary to aesthetic considerations of the breasts. The wound can be covered with a skin graft, but layers of gauze covering the skin graft region often affect the performance and efficacy of radiotherapy. Conversely, radiotherapy may also cause a failure of the skin graft. In addition, for female patients, the breasts limit the effective use of a chest flap. Therefore, choosing an appropriate wound repair method is both challenging and important in the treatment of large thoracic keloids in females. The blood supply to the rectus abdominis myocutaneous flap is reliable with minimal injury to the donor site.^[17] For wounds following resection of a keloid on the chest wall, and especially on the distal aspect, the rectus abdominis muscle flap not only is easy to transfer but provides a good tissue match to the recipient site in color, texture and thickness.^[18]

The rectus abdominis muscle is located on both sides of the median line of the anterior abdominal wall of the human body, and has a relatively constant blood supply from the superior and inferior epigastric arteries. The superior epigastric artery generates a thick perforating artery at the proximal aspect of the rectus abdominis muscle. The external diameter of this perforating vessel is often larger than 1 mm. The perforating branches are primarily distributed within a range of one tendinous inset above the umbilicus and 8.0 cm below the umbilicus. The medial perforating vessels are often the dominant blood vessels among the perforating vessels of the inferior epigastric artery.^[19] Because the superior and inferior epigastric arteries have a relatively wide

range of distribution of perforating vessels to the abdominal skin, specific perforating vessels can be selected according to the size of the chest wound and its distance from the abdomen.

The rectus abdominis muscle is important in maintaining abdominal wall strength. Partial preservation of this muscle therefore essential when designing the rectus abdominis myocutaneous flap. In a report by Chen *et al.*,^[20] 8 patients underwent breast reconstruction with the muscle-sparing TRAM flap. Of these 8 patients, 2 experienced borderline necrosis and subcutaneous fat liquefaction within zone IV of the flap, with healing following debridement. Although partial skin flap necrosis is well-tolerated in breast reconstruction patients, it is problematic in keloid treatment as it delays the initiation of postoperative radiotherapy. This scenario also increases the risk for keloid recurrence secondary to chronic inflammation.^[21] Abdominal wall strength is preserved and herniation is prevented by saving the anterior sheath of the rectus abdominis muscle.

The IMA perforator flap is another option for patients with keloids of the chest wall. Trauma to the abdominal wall is minimized with this method as compared to the rectus abdominis myocutaneous flap. Ogawa *et al.*^[22] have reported use of this skin flap design in chest wall keloid wound coverage. In their report, a skin flap measuring 14 cm × 5 cm was designed based on the dominant perforators of the IMA in the 6th, 7th, 8th and 9th intercostal spaces. In the current study, however, the borders of the keloids extended more distally. The perforators were difficult to identify by Doppler ultrasound secondary to the overlying keloid mass. These perforators would also have been damaged following resection of the, and therefore would have been unsuitable for use as a flap pedicle. The rectus abdominis myocutaneous flap is a more appropriate choice in this situation for very large keloids which cover the inferior chest and upper abdominal wall.

Although use of the rectus abdominis myocutaneous flap from the abdominal wall for wound repair following keloid resection can provide a reliable blood supply and good soft tissue match, the extent of surgical trauma and the patients' medical status demands that one consider the following points when selecting this surgical method:

(1) This surgical approach is appropriate for women and patients engaged in light physical labor because of the effect of muscle harvest on abdominal wall strength. For men and patients engaged in moderate to heavy physical labor, the method should be selected only after careful consideration. During surgery, the

integrity of one side of the rectus abdominis muscle is compromised, which to a certain degree damages the strength and integrity of the abdominal wall. Therefore, for young male keloid patients, this surgical method is not recommended, and is why all patients in this series were women.

(2) The rectus abdominis muscle flap is more suitable for wound recovery following resection of a keloid located in the middle or distal aspect of the chest. Secondary to limitations of the length of the pedicle, it would be difficult to repair a keloid located in the middle or proximal chest. Moreover, the subcutaneous tissue of the flap is quite thick which provides a poor match to tissue of the upper chest. In addition, the longer the pedicle required, the wider the dissection must be, increasing the size of the donor site defect. For patients who have demonstrated a propensity towards keloid formation, the risk of postoperative scar hyperplasia or additional keloid formation is even greater. When a keloid in the middle or lower part of the chest wall has been repaired with a myocutaneous flap from the rectus abdominis muscle in the middle or upper abdomen, the postoperative incision will be located within the radiotherapy range, which is both convenient for performing radiotherapy and reduces the extent of radiation damage to the normal tissue. Therefore, it is recommended that a myocutaneous flap of the rectus abdominis from the middle or upper abdomen be used to repair the wound following keloid resection from the middle or lower chest.

(3) Although a rectus abdominis myocutaneous flap can provide a large portion of tissue for wound repair, the amount of tissue that this approach can provide is nevertheless limited. When the wound following resection exceeds the amount of tissue that can be provided by the flap, one must additionally consider other methods or the use of multiple flaps in combination for repair.

Authors' contributions

Manuscript's preparation: Q.C. Men, S. Liu
Manuscript's review: Y.B. Wang, Z. Lin, L. Xiao
Concept design: Y.B. Wang
Literature search: K.X. Song, L. Hao, X.H. Dong

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Informed consent was obtained from the patients.

Ethics approval

All treatment procedures were provided in accordance with the ethics approval of Peking Union Medical College Hospital.

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Inflatable pressure garment device for pressure therapy after chest wall keloid operation and radiotherapy

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Dr. You-Bin Wang is an outstanding Professor in the Department of Plastic Surgery at Peking Union Medical College Hospital. He is famous in keloid treatment and study. He has invented many new surgical methods in keloid treatment and has published many articles in this field. He is also good at cleft lip surgery, nose reconstructive surgery and breast reconstruction.

ABSTRACT

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Chest wall keloid,
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Aim: Keloids often occur on the chest wall, with high recurrence rates despite surgery and radiotherapy. Garment pressure therapy is commonly used to treat hypertrophic scars and keloids. Irregularity of the chest wall surface can inhibit the effects of the garment pressure therapy. This clinical study is to determine the effect of inflatable pressure garment in preventing keloid recurrence after keloid operation and radiotherapy. **Methods:** Chest wall keloid was removed and radiotherapy was administered at the surgical sites on the 1st and 7th postoperative days in 61 patients. An inflatable pressure garment device was designed and its pressure effect was confirmed by comparing it with the general pressure garment at the sites of the right and left infraclavicular area, manubrium and sternal area between breasts. The keloid patients were treated with inflatable pressure garment device 1 month after the operation. The clinical results were observed. **Results:** The detected pressures were 0.26 ± 0.21 , 0.49 ± 0.16 , 0.53 ± 0.10 and 0.91 ± 0.17 kPa at the sites of the right infraclavicular area, the manubrium area, the left infraclavicular area and sternal area between breasts with the general pressure garment. These were obvious lower ($P < 0.05$) than that generated with the inflatable pressure garment device of which the average pressures were 7.26 ± 0.41 , 7.6 ± 0.32 , 9.02 ± 0.54 and 10.31 ± 0.14 kPa at the corresponding sites. Sixty-one patients were treated with this device after keloid surgical excision and radiotherapy. Satisfactory results were observed. **Conclusion:** Appropriate and effective pressure can be generated with inflatable pressure garment on the chest wall. This device may be useful in preventing chest wall keloid recurrence after keloid operation and radiotherapy.



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INTRODUCTION

Keloids may be induced by many causes, such as acne, folliculitis, insect bites or surgery.^[1] Keloids often occur on the chest wall. Many therapeutic approaches for keloids have been reported in the literature. The most commonly accepted treatments include excision, irradiation, steroid injections, and pressure therapy with silicone gel sheets or bandages.^[2]

Keloids are likely to recur, which complicates their treatment. The reported keloid recurrence rate varies depending on the treatment method.^[3] In the chest wall, the reported keloid recurrence rate ranges from 9.7% to 43.1% for patients treated with surgical excision and postoperative radiation.^[4,5] Recurrent keloids often spread faster and become larger; it is therefore necessary to identify a method to prevent keloid recurrence.

Pressure therapy is effective in treating hypertrophic scars, especially scars on the ear^[6] or body.^[7] Pressure garments are often used in body scar pressure therapy. During treatment, a pressure garment is placed over the scar and is effective when appropriate pressure is applied to the scar surface. However, the pressures that can be generated at different anatomical sites differ significantly, and lower pressures generally are less effective. Due to the larger radius of the chest, pressure garments usually generate low pressures in this area, and pressures are even lower in concave areas, such as the mid-sternum.^[8] To solve this problem, we designed an inflatable pressure garment device.

METHODS

Surgical methods

The edge of the keloid was marked with gentian violet; then, 0.5% lidocaine was infiltrated to provide local anesthesia in the skin around the keloid. A full-thickness incision was made along the mark, and the keloid was removed. After achieving hemostasis, the skin around the incisional border was undermined at the deep layer of the superficial fascia for 3-5 cm, and the incision was closed. A skin graft was used if the wound was too wide to be closed primarily. The wound was then covered with sterile gauze. Radiation therapy was administered. The sutures were removed 14 to 21 days after the operation.

Radiotherapy methods

Radiotherapy was administered at the surgical sites (closed primarily) on the 1st and 7th postoperative days. Every surgical site was treated with 900 cGy of

electron beam irradiation at each session. A second radiotherapy session was administered on the 14th postoperative day if skin graft was used, when survival of the skin graft had been established and the sutures had been removed.

Comparative study of inflatable pressure garment device and general pressure garment

In order to confirm the pressure effect of the inflatable pressure garment device, a comparative study was conducted between the device and the regular pressure garment. The device consisted of 3 parts: a regular pressure garment, an inflatable silicon expander and an inflation device. Ten volunteer young patients (5 male and 5 female, age range between 21 and 30 years) wore the regular pressure garment (WSY003 Short Sleeve Garment, Beijing Medical Elastic Sleeve) first. Pressure was detected and recorded using a manometer (COMARK C9553, England) at the sites of the right and left infraclavicular area, manubrium and mid-sternum area between breasts. Then the inflatable silicon expander was inserted under the garment at the same area and was inflated until the patients felt slight pain at the sites. The pressure was then detected and recorded. The data was analyzed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA) using the *t*-test. All data are reported as the mean \pm standard error of the mean. The level of the test was considered statistically significant if less than 0.05.

Pressure therapy with an inflatable pressure garment device

The inflatable pressure garment device was used 1 month after the operation to allow for appropriate wound healing. First, the wound site was cleaned with warm water. A piece of silicon gel was applied to the wound after the site was dry. Then, the patient was asked to wear a regular pressure garment [Figure 1A]. Afterwards, the silicon expander, which was wrapped with soft cloth, was inserted under the garment. The expander was carefully adjusted to ensure that it covered the entire area of the scar. The inflation device

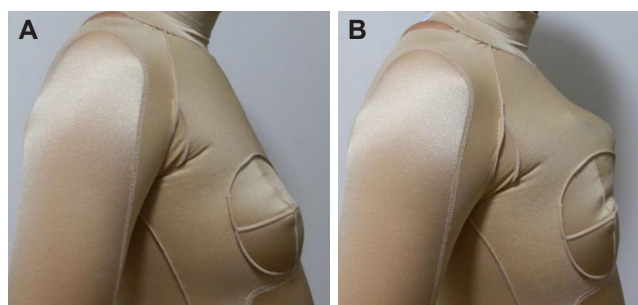


Figure 1: The concave site became convex after the expander was inflated. (A) The conventional pressure garment; (B) the inflatable pressure garment

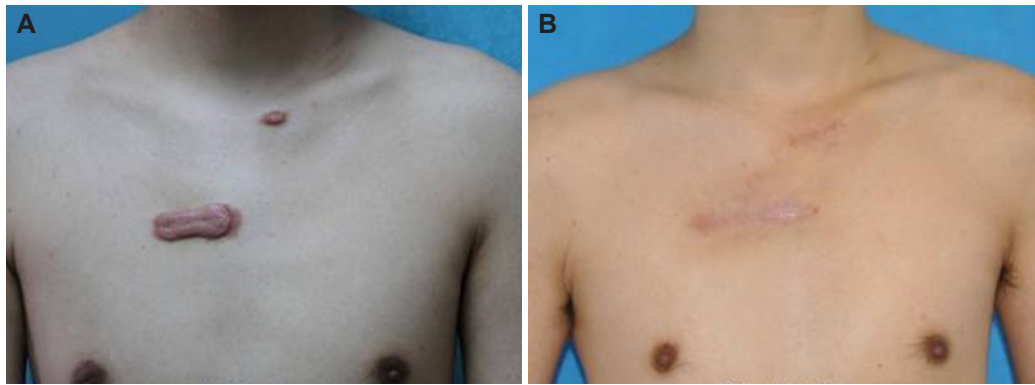


Figure 2: A male patient with a chest wall keloid that was treated with surgical excision, radiotherapy and inflatable garment pressure therapy. (A) Preoperative view; (B) 8 months after the operation, the incision scar was flat, pale, smooth and almost invisible

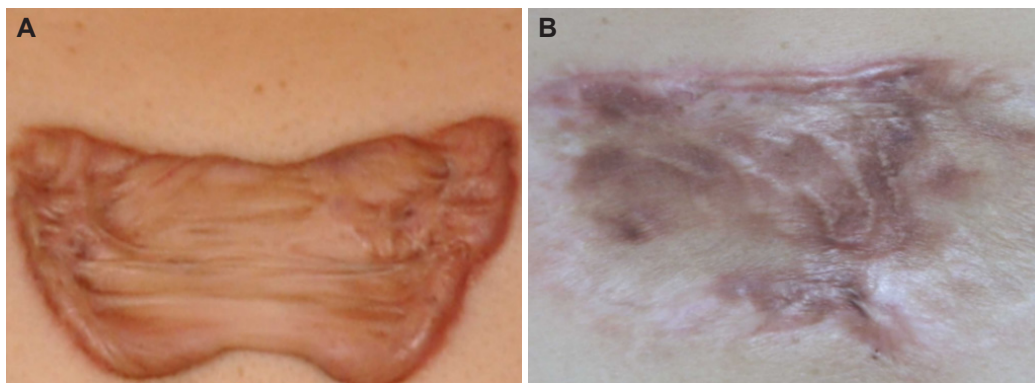


Figure 3: A female patient with chest wall keloid that were treated with surgical excision, skin graft, radiotherapy and the inflatable garment pressure device therapy. (A) Preoperative view; (B) almost all of the incision was flat and pale 18 months after surgery

was used to inflate the expander, generating pressure [Figure 1B]. As more air was added to the expander, the pressure increased. The appropriate pressure range was from 4.5 to 10 kPa. Higher pressure may cause pain at the involved site, whereas lower pressure may be less effective. None of the patients reported breathlessness. The patient was able to adjust the pressure by controlling the inflation device; the expander size was chosen based on the size of the scar. Patients were asked to use the inflatable pressure garment device daily for at least 12 h during the therapy period. Pressure therapy could be stopped after 6 to 12 months of therapy, once the scar had become pale, flat and smooth.

RESULTS

Pressure generated with the inflatable pressure garment device and the regular pressure garment

The detected pressures using regular pressure garment were 0.26 ± 0.21 , 0.49 ± 0.16 , 0.53 ± 0.10 , and 0.91 ± 0.17 kPa, at the site of the right infraclavicular area, manubrium area, left infraclavicular area and mid-sternum area between breasts respectively. Higher

pressure was generated after the silicon expander was inserted and inflated. The average pressures were 7.26 ± 0.41 , 7.6 ± 0.32 , 9.02 ± 0.54 , and 10.31 ± 0.14 kPa at the site of the right infraclavicular area, the manubrium area, the left infraclavicular area and mid-sternum area between breasts respectively. The difference of the recorded pressure effect was obvious at each site between the inflatable pressure garment device and the regular pressure garment ($P < 0.05$).

Clinical effects of the inflatable pressure garment device

Effective pressure was obtained on the chest wall of the patients. Satisfactory results were observed in patients treated with keloid excision, radiotherapy and inflatable garment device-based pressure therapy. Sixty-one patients were treated with this method between May and October of 2013. The follow-up time was between 6 and 18 months. No recurrences were observed in these patients. The incision scars were flat, pale, smooth and almost invisible at the operation sites in patients without skin graft. The patients were satisfied with the results [Figures 2 and 3]. Some recurrences were observed in patients treated with the regular pressure garment before [Figures 4 and 5].

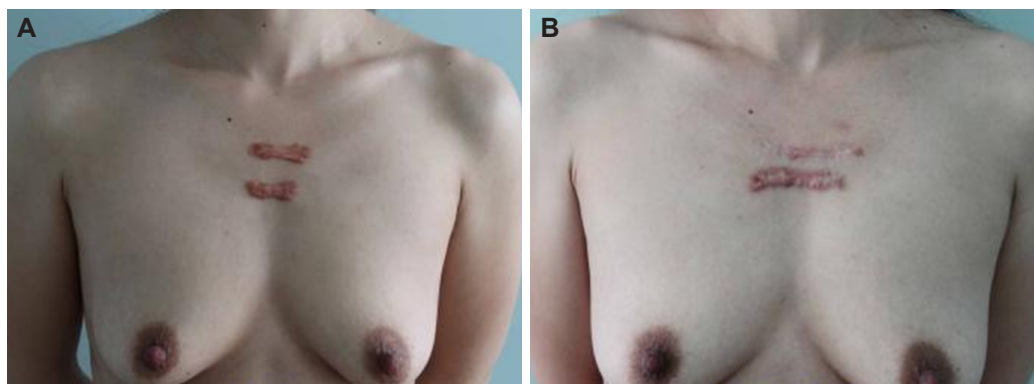


Figure 4: A female patient with chest wall keloids that were treated with surgical excision, radiotherapy and conventional garment pressure therapy. (A) Preoperative view; (B) 21 months after the operation, keloid recurrence was observed

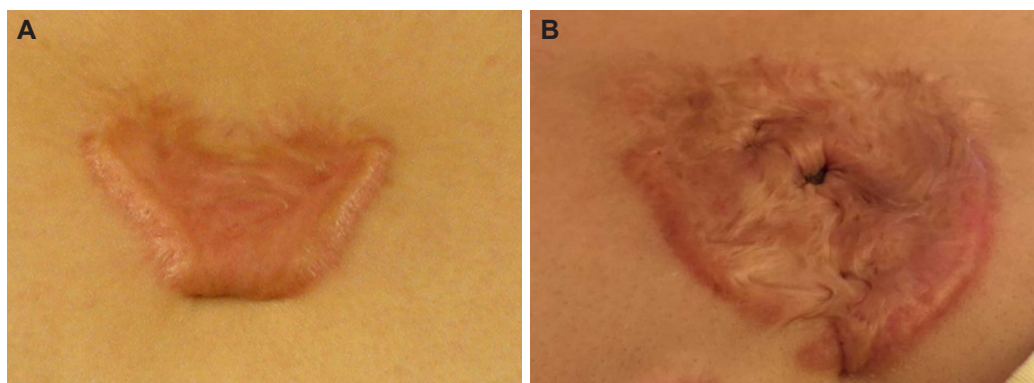


Figure 5: A female patient with chest wall keloid that were treated with surgical excision, skin graft, radiotherapy and conventional garment pressure therapy. (A) Preoperative view; (B) keloid recurrence was observed 3 years after operation

DISCUSSION

Pressure has been known to be a useful treatment method for scars since the 16th century.^[9] Garment pressure therapy is now widely used in the treatment of hypertrophic scars and keloids. Possible mechanisms of its effect include hypoxia, biochemical changes and cellular or collagenous influences.^[8] The effects of pressure have also been reported on the growth of human scar fibroblasts and on cellular proliferation and apoptosis.^[10,11] Pressure inhibits the proliferation of cells, especially fibroblasts; it also suppresses collagen production and accelerates apoptosis, inhibiting the growth of hypertrophic scars and keloids.

Appropriate pressure levels are required for garment pressure treatment. Van den Kerckhove *et al.*^[7] compared the effects of 10 and 15 mmHg pressure garments. They observed that 15 mmHg of pressure tends to accelerate scar maturation. Some authors have recommended the use of pressures between 20 and 40 mmHg, based on the theoretical 25 mmHg arterial capillary pressure level.^[8] Although no standard pressure values have been established, some common practices are accepted. One study recommended a pressure above 15 mmHg.^[8]

Rose and Deitch^[12] reported that the most important factor in determining the effectiveness of pressure therapy is the anatomical area treated. In general, the clinical response is positively correlated with higher pressure generated.^[8] However, different pressures are generated by conventional pressure garments at different anatomical sites. Therefore, to achieve better pressure effectiveness, pressure garments, or the other pressure methods used, should be improved.

Anatomical concavity is the most important factor in the reduction of the pressure applied by garments. Therefore, conventional garment pressure therapy is seldom effective in the treatment of chest wall keloids, and its usage is limited. We have previously observed many recurrences in patients with chest wall keloids that were treated with conventional pressure therapy [Figures 4 and 5]. Anatomical convexity increases the garment pressure; therefore, methods that can convert an anatomical concavity to an anatomical convexity will also theoretically change the garment pressure. Our inflatable pressure garment device was designed according to this hypothesis. The concave site on the chest wall was converted into a convex shape by inserting the expander under the garment and inflating it. The convexity and pressure increase can

be controlled by an inflation device, which permits the generation of a range of pressures from 4.5 to 10 kPa (approximately 40 to 77 mmHg). These pressures are higher than the 20 to 40 mmHg pressure range that other authors have recommended.

Compared to hypertrophic or normal scars, keloid scars have a higher recurrence potential. A pressure range under 40 mmHg may be effective in treating hypertrophic or normal scars. However, this is not the case in the treatment of keloids, where higher treatment pressures may be necessary. The generated pressure range is limited for conventional pressure garments, which cannot generate suitable pressure levels in specific areas, especially concave sites. The inflatable pressure garment that we designed can generate any anticipated pressure at any specific site. Pressures higher than 40 mmHg at a keloid site can be generated with this device. The pressure generated with this device may be more effective in treating keloids, preventing recurrence and achieving satisfactory clinical results.

Although pressure therapy is effective in scar treatment and prevention, inflatable pressure device can generate more effective therapy pressure, surgical intervention should also be emphasized in keloid treatment especially chest wall keloid treatment. Effective wound tension release should be achieved. Normal wound healing process should be guaranteed. To achieve this, some operation method such as "Z-plasty" and tension line redirection can be used. More satisfactory results would be reached if combined application of the inflatable pressure device with other clever surgical methods.

In conclusion, an inflatable pressure garment can generate appropriate and effective pressure on the chest wall by changing its shape from concave to convex and may be a useful device for preventing keloid recurrence involving the chest wall.

Authors' contributions

Manuscript's preparation: S. Liu, K.X. Song

Manuscript's review: Y.B. Wang

Concept design: Y.B. Wang

Literature search: S. Liu

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

The informed consent have been obtained from the patients.

Ethics approval

All the treatment procedures are in accordance with the ethics approval of Peking Union Medical College Hospital.

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A new tool to assess human fat grafts transplanted into nude mice using a nuclear magnetic resonance device

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ABSTRACT

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Aim: Over the past two decades, there has been a dramatic increase in the research of the use of autologous fat grafting in clinical practice. Despite the many advantages this method possesses, the unpredictable fat resorption rates limit its use. The primary aim of this study was to develop an accurate, quick, non-invasive assessment tool, using the nuclear magnetic resonance (NMR) technique, which allows the injection of fat in small droplets rather than in large aliquots (the main drawback of our formerly described method) which allows assessment of fat retention in a more clinically relevant way. **Methods:** A total of 7 nude mice were transplanted with human fat using the Coleman technique. Pre- and post-transplantation and then once weekly, mice were analyzed using an NMR scanner. At the end of the 7-week experimental period the mice were sacrificed. **Results:** Seven weeks following transplantation 7 mice demonstrated a decrease of 40% of their average fat content compared to immediately post transplantation (standard deviation of 18%). All mice followed the same trend, and the low standard deviation throughout emphasizes the accuracy of NMR as a reliable assessment tool. **Conclusion:** This preliminary study demonstrates that NMR is a reliable and accurate tool to assess fat content, and has allowed development of a clinically relevant animal model for human fat transplantation.



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INTRODUCTION

Autologous fat transplantation for soft-tissue augmentation has become increasingly popular in recent years. For more than a century fat grafting has been used for facial contouring, breast augmentation, breast reconstruction after mastectomies, post-traumatic deformities, congenital anomalies and burn injuries.^[1-3]

Fat tissue is abundant, readily available, inexpensive, host compatible, associated with low morbidity and can be harvested easily and repeatedly. However, according to the literature, there is a varied overall survival rate of the fat graft in the range of 20-70%.^[4-6]

Aspirated fat tissue used for autologous fat transplantation is devoid of blood microvessels which have been destroyed during aspiration and removed during processing prior to injection. Therefore, the fat tissue that is injected into a recipient is considered to be an ischemic fat cell mass. During the early period following transplantation, the fat transplant exists under hypoxic and hypo-nutritional conditions. Revascularization fail to be initiated in this early period, apoptosis ensues and results in late fat cell degeneration, low viability and ultimately fat resorption.^[7]

In order to maximize the surface area and hence exposure to blood supply of the graft, surgeons now inject very small aliquots of fat grafts into multiple subcutaneous tunnels (Coleman's technique).^[8]

We previously developed a novel animal model in which human fat was grafted into the scalp area of nude mice.^[9-13] This model allowed investigation of the mechanisms of fat absorption and exploration of the efficacy of new compounds, with potential to increase the vasculature and viability of fat grafts.^[14-18] In this previous model, fat was grafted as a bolus to allow ease of collection and analysis.

However, a bolus has a relatively small surface area in contact with vascularized tissue, and therefore the center of the graft suffers from higher rates of ischemia, necrosis and resorption. Therefore, a new and more clinically relevant animal model needed to be developed.

In this manuscript, a new animal model is presented which is consistent with the clinically relevant Coleman fat grafting technique in which small droplets are transplanted, and a new assessment tool (NMR) is used [Figure 1]. Using this technique allowed measurement of the small fat droplet content *in vivo*,

without the difficulties of manual collection of the dispersed small fat droplets at the end of the study.

METHODS

Isolation and preparation of human fat tissue

Fat was harvested from the thigh of a 50-year-old woman undergoing suction-assisted lipectomy under general anesthesia. Prior to commencement of the procedure, the areas of aspiration were injected with a local anesthesia solution containing lidocaine (0.5%) and adrenaline in order to decrease bleeding during fat aspiration and relieve pain after the procedure. The fat was aspirated using a 14-gauge 3-hole blunt cannula, and then processed under sterile conditions for subsequent grafting into nude mice within 2 h of collection. Following aspiration, the fat-containing syringe underwent 2 rounds of centrifugation (1,200 rpm, 10 min at room temperature) and then was placed vertically for 10 min.^[14-18]

Between centrifugations, the three different layers (oil, adipose and fluid) were separated. After the last centrifugation, the adipose layer was collected and loaded into 2 mL syringes. All procedures were performed under sterile conditions.^[19]

The participant gave her written informed consent, and the study was reviewed and approved by the Helsinki committee of the Rambam Health Care Campus and the institutional review board of the Technion Animal Care and Use Committee.

Animals and study design

The study was composed of nine 7-week-old female CD-1 nude mice (Envigo, Jerusalem, Israel). Seven mice received transplants of human fat, while two mice served as controls without human fat transplantation.

The animals were housed in a specific pathogen-free room, with 1 animal per cage in a room with an artificial 12 h light/dark cycle at a constant temperature range ($24 \pm 2^\circ\text{C}$) and relative humidity ($55 \pm 10\%$). The mice

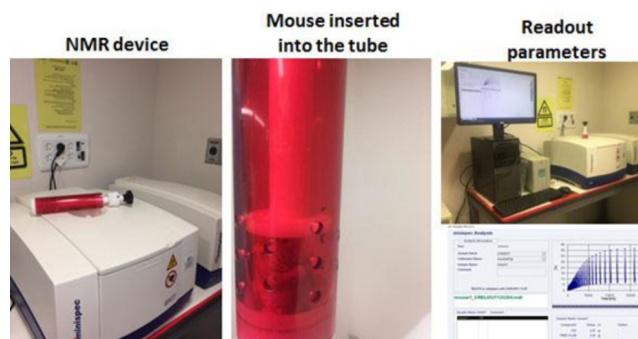


Figure 1: Nuclear magnetic resonance device

were acclimatized for 5 days prior to the study, and fed standard chow and water *ad libitum*.

The recipient area of the mouse was disinfected with 70% ethanol. Fat was subsequently slowly injected as small droplets into multiple tunnels in the two lateral sides of 7 nude mice at 1 mL volume per side (for a total of 2 mL per mouse) [Figure 2].

Follow-up and data collection

The duration of the study was 7 weeks starting from the day of human fat transplantation. Before and immediately post-transplantation, and then once weekly following transplantation, the mice were weighed using a standard digital weighing machine and were analyzed using the minispec live mice analyzer (minispec, LF90. Bruker, USA). Seven weeks following human fat transplantation the mice were photo-documented [Figure 2B] and were sacrificed.

NMR analysis

The time-domain NMR (TD-NMR) provides a precise method for *in vivo* measurements of lean tissue, body fat and body fluid in live mice and rats.

The advantages of the TD-NMR make it an ideal device to measure fat and lean content in the following industries: food, textile, polymer, pharmaceutical and healthcare.

NMR uses a permanent magnetic field and radio frequency energy to examine sensitive nuclei, such as hydrogen and fluorine. The radio frequency signals generated by the nuclei are detected by the device. Each sample's properties are translated by the minispec as different amplitudes and signal durations.^[20] The use of the device is simple and not time consuming [Figure 1]. The miniaturization of the device makes it more accessible and cost-effective when compared to the NMR device used in the clinic.

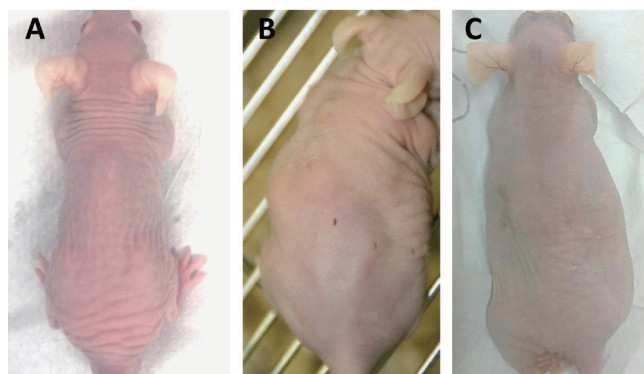


Figure 2: Representative photographs of nude mice before fat transplantation (A), 1 h following fat transplantation (B), and (C) 7 weeks following transplantation

Statistical analysis

Means and standard deviation were calculated. Differences between means were analyzed for statistical significance using one-way analysis of variance with the Tukey-Kramer multiple comparisons post test (SPSS version 17.0). *P* values ≤ 0.05 were considered significant.

RESULTS

All 9 mice completed the 7-week study period. They appeared to be healthy and there was no evidence of cachexia during the entire study period. The photographs of the mice before and at the study endpoint clearly demonstrated the resorption of the fat droplets over the 7-week period [Figure 2].

Seven mice were transplanted with human fat. Before fat transplantation, the average fat content, as analyzed by the NMR device, was 3.8 ± 0.8 gr per mouse. One day following transplantation, the fat content increased to 6.0 ± 0.7 gr [Figure 3A].

Seven weeks following transplantation, the average fat content had decreased by 0.9 ± 0.3 gr per mouse to 5.1 ± 0.6 gr ($P < 0.04$) [Figure 3A], representing $40 \pm 18\%$ percent fat resorption as compared to day 1 following transplantation [Figure 3B].

In the control group, 2 mice, not injected with human fat, were measured by the NMR device and demonstrated consistent fat content throughout the study period (2.5 ± 0.9 at day 1, and 2.6 ± 1.0 , not significant) [Figure 3A].

The NMR device calculates both lean body mass and fat content. During the 7 weeks following fat transplantation, a decrease was also observed in the fat to lean ratio, as compared to the ratio 1 day following transplantation (0.29 ± 0.02 and 0.31 ± 0.03 , respectively, $P < 0.05$) [Figure 3C]. The decrease of calculated fat content and fat/lean ratio represents an increase of the calculated lean content. Indeed, lean content increased from 15.0 ± 3.0 gr before transplantation to 17.6 ± 1.8 gr following the 7-week experimental period.

The total weight of the mice (as analyzed by a standard digital weighing scale), increased throughout the study from 28.8 ± 1.6 gr before fat transplantation, to 31.3 ± 1.9 gr 1 day following fat transplantation, to 32.4 ± 2.3 gr at the end of the study [Figure 3D]. This elevation was a result of fluid intake and increased lean body mass. The standard digital weighing scale measures total body weight which includes water content, lean body mass, and

fat mass. The advantage of the NMR analyzer is in its ability to characterize the water content, lean body mass, and fat mass into separate measurements.

The distribution of the human fat within the tested mice is demonstrated in Figure 4. Although prior to transplantation all mice demonstrated variable fat content with the most lean mouse having 2.2 gr of fat and the most obese mouse having 4.6 gr of fat content (average of 3.7 gr with standard deviation of 0.8), 1 day following fat transplantation the average transplanted fat content (calculated as fat content 1 day post transplantation minus fat content 1 day before transplantation) was much less variable (2.2 gr with standard deviation of 0.2).

Figure 5 demonstrates a 40% decrease in fat graft weight with an average weight of 2.2 ± 0.3 gr following transplantation and 1.3 ± 0.1 gr 7 weeks following transplantation, as was observed by the

NMR analysis. Most mice demonstrated a consistent decrease in fat graft weight ($34 \pm 7\%$) with only 1 mouse demonstrating an 80% decrease in fat weight 7 weeks following transplantation.

DISCUSSION

Autologous fat transplantation was first described a century ago, but only in the past decade has it gained attention as an ideal filler for soft tissue reconstruction.^[21] Because of the unpredictable outcomes associated with autologous fat transplantation, clinical scientists and physicians have experimented with various methods to find ways to increase the viability of injected fat while reducing its rate of reabsorption.^[22] Researchers have evaluated how the fat is harvested, prepared, and injected, and if the fat can be treated with different compounds in order to improve survival. This includes compounds to increase angiogenesis

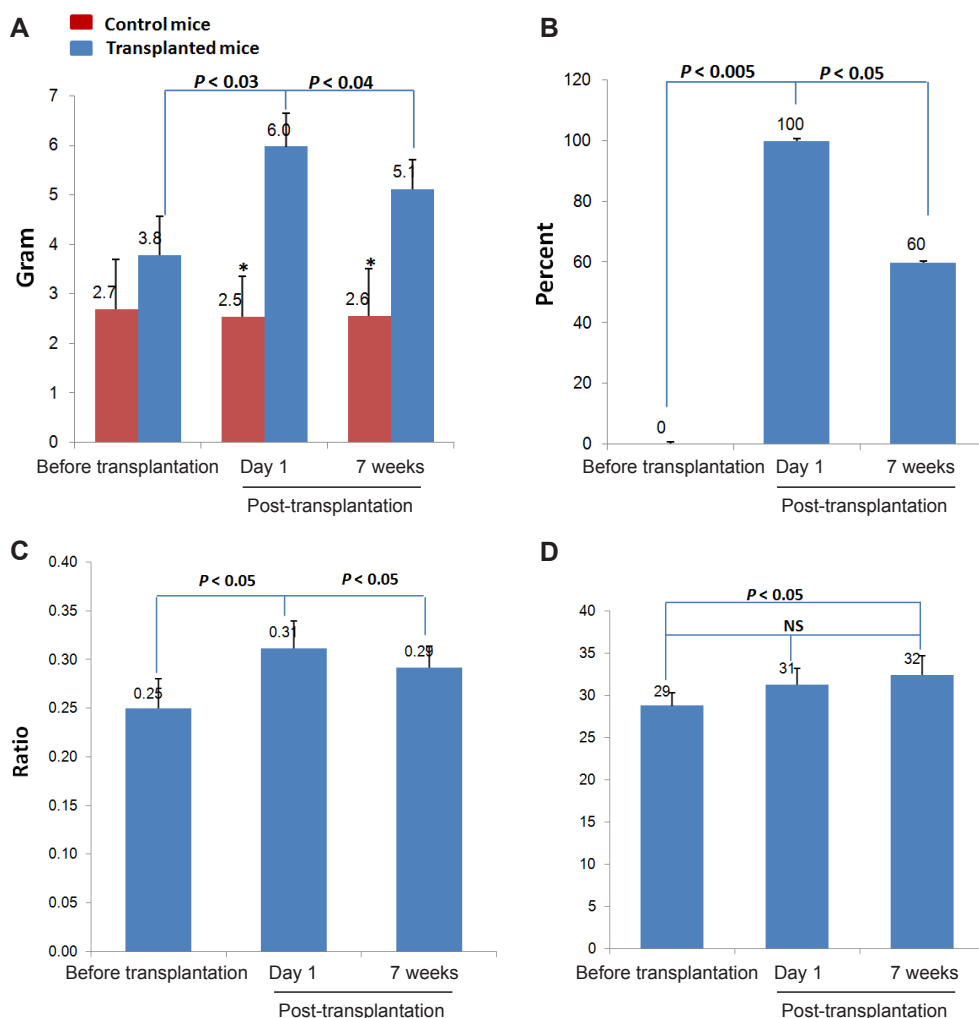


Figure 3: (A) Fat content as determined by nuclear magnetic resonance (NMR) analysis; (B) percent of fat absorption at the study end point; (C) fat/lean ratio (NMR analysis); (D) standard digital weight assessment of mice at different time points. NS: not significant (as compared to control mice before transplantation)

such as erythropoietin, and growth factors including insulin growth factor, fibroblast growth factor, platelet derived growth factor and vascular derived growth factor.^[23,24] Other relatively new methods include cell-assisted lipotransfer with adipose-derived stromal cells,^[25] and the use of an enriched, serum free cell culture medium (Cariel) as a supplement to the injected fat.^[18] Although most of these new methods have slightly improved the take of the transplanted fat, none have shown truly satisfactory and cost-effective results.

The majority of published results on long-term fat survival following transplantation and outcomes are based on subjective analysis of photographs or anecdotal reports.^[26,27] In human studies, there is a relative lack of evidence with only a small number of objective studies using three-dimensional imaging, ultrasonography, computed tomography (CT), and magnetic resonance imaging.^[28-30]

Small animal models have facilitated more accurate evaluations of fat graft survival and “take”. However, histologic assessment of fat grafts in animals is expensive, time consuming and not amenable to the examination of large volumes of tissue and accurate assessment of fat grafted by use of the Coleman technique. Further, it requires sacrifice of the animal in order for tissues to be harvested for processing, embedding, sectioning, and staining with subsequent analytical evaluation. Traditional CT or micro CT examination is expensive, time consuming (30+ min per animal), requires anaesthetic, and radiates the animal with roughly 30 Gy. Its use is limited as early fat necrosis cannot be easily distinguished from viable fat.

Currently, there are two types of instruments available

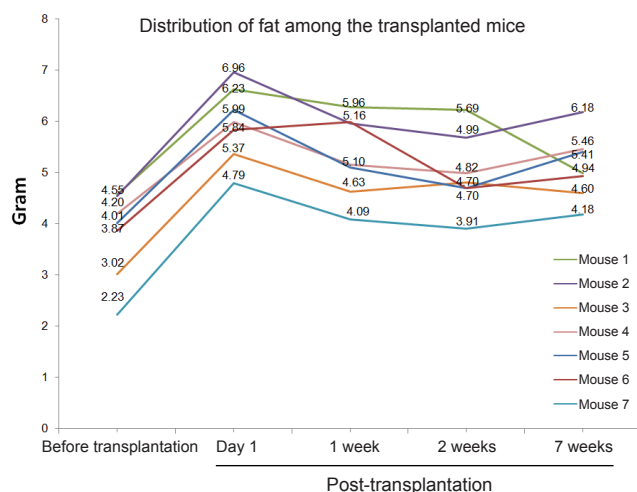


Figure 4: A graph demonstrating the change of fat composition at different time points as analyzed by nuclear magnetic resonance technology

for non-invasive and sequential *ex vivo* analysis of small animals: dual energy X ray absorptiometry (DXA) and small animal NMR. The NMR has several advantages over the DXA including the speed and cost of measurements (< 2 min) and the ability to ethically study non-anesthetized animals.^[31,32]

NMR is a physical phenomenon which exploits the magnetic properties of certain nuclei to provide detailed structural, dynamic and energetic information of molecular compounds.^[33] Although NMR spectroscopy is a powerful technique, application has been limited due to the high cost and complexity of the device. Recently, miniaturized low-field benchtop TD-NMR instruments have been developed. While the newly developed device lacks some degree of sensitivity and resolution, it is capable of powerful relaxation time analysis and has gained popularity due to its simplicity and cost-effectiveness.

However, validation studies of NMR instruments are currently limited and have not been used in fat graft assessment. Taicher *et al.*^[34] examined the precision and accuracy of the NMR (EchoMRI) compared to DXA and chemical carcass analysis. They found higher precision of NMR (vs. DXA) for measurements of fat content in lean and obese mice. In diet-induced obese mice, the coefficient of variation for fat mass by NMR and DXA were 0.34% and 9.59%, respectively.

In order to overcome the inaccuracy of small droplet fat grafting collection and analysis, the use of a whole body composition analyzer based on NMR technology was studied (Brukerminispec, BCA-Analyzer). It is a precise method for measurement of lean tissue, fat and fluid in living mice.

A useful animal model should resemble the human disease, condition or technique, with as much

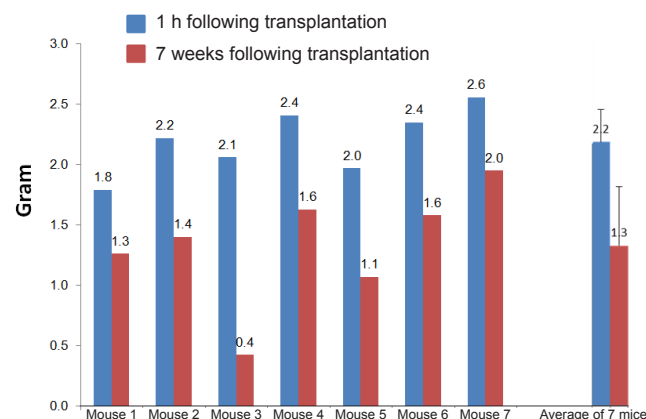


Figure 5: The difference between fat graft subsequently and 7 weeks following transplantation as analyzed by nuclear magnetic resonance technology

accuracy as possible, yet be readily available and provide reproducible results. A number of such models have been developed primarily with immune deficient rodents.

During the last twenty years our lab has used the nude mouse model for human fat transplantation.^[14-18] The athymic nude mouse model was selected because of its limited ability to reject xenografts. This model, which has been previously used for studying fat injection, enables the observation of the take of human fat in an animal model without a confounding immune response leading to graft rejection.

In our prior work human fat was injected as a bolus with a volume of 1 mL and a diameter of approximately 1 cm × 1 cm. The disadvantage of this relatively large fat bolus is necrosis of the adipocytes in the center of the bolus as a result of poor revascularization. Clinicians now inject human fat as small droplets < 0.1 mL, to maximize surface area and thus vascularization.

Indeed, many studies using the Coleman technique have confirmed that small droplets of fat provide better “take” than larger ones, secondary to improved vascularization, nutrient diffusion and less ultimate resorption.^[35-37]

The main disadvantage of our previous model was the inability to inject small droplets of human fat due to the difficulty of assessing the fat graft “take” using traditional methods.

Use of the NMR device demonstrated a 53% fat resorption following the seventh week experimental period. This data is in accordance with the clinical and pre-clinical data demonstrating a rate of 20-70% of fat resorption following transplantation.

The accuracy of the NMR device and its suitability for our purposes has been emphasized by the measurements of 2 control mice without human fat transplantation, demonstrating a small and non-significant increase in fat content during the 7 weeks follow-up. In addition, the average delta of 2.2 gr of fat content before and 1 day following fat transplantation demonstrates the accuracy of the NMR device and its relevance to our model.

The conclusion from this study is that the NMR device may serve as a tool for the assessment of the Coleman small droplet fat grafting technique. Until now it was technically impossible to collect small droplets of transplanted fat for volume/weight analysis at the end of the study. Therefore, the fat

graft was previously injected as a bolus, which was not clinically applicable. Another advantage of the NMR device is its ability to measure grafted fat without the need to sacrifice the animal, allowing the researcher to measure the fat at different time points during the study.

The advantages of this new model are the ability to analyze small fat droplets *in vivo* without the necessity for manual excision of the fat. This enables use of the more clinically relevant small fat droplet transplantation technique. This newly improved mouse model will allow researchers and clinicians to test new compounds for minimizing fat resorption.

Authors' contributions

Data analysis and interpretation: A. Keren

Manuscript preparation: S. Filson

Technical assistance: N. Smirnov-Shalom

Manuscript's review: A. Gilhar

Concept design, manuscript preparation and data interpretation: Y. Ullmann

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

The participant gave her written informed consent.

Ethics approval

The study was reviewed and approved by the Helsinki committee of the Rambam Health Care Campus and the institutional review board of the Technion Animal Care and Use Committee.

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Commentary

Open Access

Comment on “Multipotency and secretome: the mechanisms behind the regenerative potential of adipose-derived stem cells”

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"Orgun D, Mizuno H. Multipotency and secretome: the mechanisms behind the regenerative potential of adipose-derived stem cells. Plast Aesthet Res 2017;4:32-40."

The application of stem cells technology to the intractable disease has emerged in the 21st century. It has been applied to almost all areas of medicine, including cardiovascular, neurologic, hematologic, genetic, liver, endocrine and musculoskeletal diseases. In particular, stem cell mediated tissue regeneration has opened treatment options for previously-considered intractable diseases, with no other treatment alternatives.

Stem cells have the ability of self-replicating and differentiate into cells that make up various post-

embryonic organ systems. They play an important role in regeneration of organs and tissues throughout life. There are two basic types of stem cells: embryonic stem cells derived from blastocysts, and adult stem cells obtained from fully developed adult tissue or placenta. Embryonic stem cells proliferate with ease due to great self-replicating ability of their undifferentiated state. However, applying this knowledge raises ethical problems. Therefore, studies on adult stem cells are in progress.

Bone marrow-derived stem cells are one of better-characterized adult stem cells.^[1,2] However, harvesting these bone marrow remains a challenge, and their isolation and yield ability is relatively low. For sufficient amounts of clinical use, multiple samples are required. Therefore, researchers have begun to explore new alternative sources of stem cells. Zuk *et al.*^[3] reported



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multi-lineage cells isolated from adipose tissues called stromal vascular fractions, which are assumed to be stem cells and named the cells “processed lipoaspirate.” Lately, these “processed lipoaspirate” cells have come to be called adipose tissue-derived stromal cells, or adipose tissue-derived stem cells (ASCs).^[4,5] These cells, after being extracted and separated from adipose tissue, show stable growth and proliferation in culture environments, and have the capability of differentiating into various cell types, just like marrow stem cells.^[6]

The authors reviewed 118 articles regarding ASCs using PubMed and Cochrane databases. They summarized: (1) immunophenotypic properties; (2) cell yield; (3) angiogenic effect; (4) effects on wound healing; and (5) immune modulation effect of ASCs. They raised a question of whether stem cell function alone or via a paracrine effect. Jun *et al.*^[6] reported that the effects of ASCs on neuronal regeneration might be caused by both the stem-cell itself, and a paracrine effect. The ability of mesenchymal stem cells to differentiate has been also reported to vary according to the tissue of origin, or the donor's age.^[7] However, the theory that the origin of the fat extract, gender, or age of the donor may affect the characteristic of differentiation is not yet supported by sufficient data.

In the authors' paper, ASCs have the ability to differentiate into several cell lineages, improve wound healing, and promote angiogenesis. I believe this study will be used to establish better applications of ASC therapy in the future.

Authors' contributions

Y.J. Jun contributed solely to the paper.

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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Keloid treatment: what will be the right choice?

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Dr. You-Bin Wang is an outstanding Professor in the Department of Plastic Surgery at Peking Union Medical College Hospital. He is famous in keloid treatment and study. He has invented many new surgical methods in keloid treatment and has published many articles in this field. He is also good at cleft lip surgery, nose reconstructive surgery and breast reconstruction.

I do not know the meaning of “disease without satisfactory treatment method”, but I know the principle the doctor should obey when he faces such patients. That is he should choose the most effective method for the patients, considering not the interest of himself, but the benefit of the patients, not the treatment method he can offer, but the method the patients need. Unfortunately, such principles are not followed sometimes. Patients in plight are often manipulated by evil hand and then drop into despair circumstance. They become suspicious of every doctor in this field in the end. The development in this field is then blocked forever.

Keloid is one of such disease. The dilemma of its treatment fosters many treatment methods such as surgical therapy, cryosurgery, steroid injection, 5-fluorouracil injection, radiation therapy, laser therapy, and so on, even plaster made of herbs and

combination usage of them. Which method is the most effective? Which method should we choose? These questions have been partially answered in literatures. One can find some of these answers with just one browse. Articles in this keloid treatment series add more tips to the answer database. They covered wide knowledge range of keloid treatment from surgical method to adjunctive radiotherapy and post surgery scar rehabilitation. I hope that these tips can bring the patient some delightful tip. I also hope more tips will be added in this database in the future.

It is not very easy to make a decision for keloid patient, especially when one faces a patient with suspicion. It is also easy to make a decision for keloid patient, especially when one make the decision in favor of the patient. Maybe you can not confirm the choice is right or not in the long ran at first, but the patient will tell you the answer in the future. More patients will come for



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your help if your choice is right. They will never come back otherwise. You choose for the patient, the patient will choose you in the future. No absolute truth is there in the field of keloid treatment, but there is absolute truth in keloid patient treatment. Try to find a right method from the literature database and make the right choice for keloid patient. Summarize the results and add more tips for the literature database. The patient will benefit from what you have done.

Authors' contributions

Y.B. Wang contributed solely to the paper.

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Ethics approval

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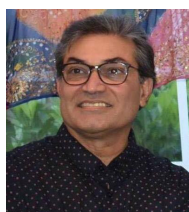
Preoperative planning and breast implant selection for volume difference management in asymmetrical breasts

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Dr. Umar Daraz Khan is working as an aesthetic plastic surgeon. He went to Dow University of Health Sciences in Pakistan for his medical degree and obtained post graduate degree from Royal College of Surgeons in Ireland. After getting training in plastic surgery in Ireland and UK, he started working in private setup and founded his own clinic in Kent, UK. In this private setup, called Reshape, he has performed over 6,000 procedures. His special interest and pioneered techniques involves abdomino plasties and breast aesthetic surgeries. He has published well over 60 articles in peer-reviewed journals, contributed his work on aesthetic breast surgery in books and has given well over 250 presentations in international conferences and congresses.

ABSTRACT

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Key words:

Breast ptosis,
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muscle splitting biplane breast
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muscle splitting mastopexy,
multiplane internal mastopexy

Aim: To assess volume management in patients presenting with breast asymmetry and ptosis. **Methods:** Retrospectively collected data was analysed. The patients were divided into 3 groups. Group A included patients who had volumetric difference alone and had different size implants alone. Group B included patients who had volumetric difference with breast ptosis requiring mastopexy with different size implants. Group C included patients who presented with breast asymmetry with ptosis and had same size implants on both sides with different volume breast reduction. **Results:** Subgroup A1 included 145 patients who had larger implants placed on right side. Subgroup A2 included 95 patients who had larger implants on the left side. Subgroup B1 included 7 patients who had larger implants on the right. Subgroup B2 included 13 patients who had larger implant on the left side. Subgroup C1 included 7 patients who had larger reduction on right side. Subgroup C2 included 11 patients who had larger reduction on left. **Conclusion:** When different volume implants are used, the vast majority of the patients do not require a volume difference of more than 60 mL. When the breast is larger on the right then larger mean volumes are used on left side to offset the larger right breast.



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INTRODUCTION

Breast and chest asymmetries are common and have been documented in aesthetically perfect models as well as randomly selected females through public advertisement.^[1,2]

Randomly selected patients presenting for augmentation mammoplasty had their preoperative pictures retrospectively analysed by independent observers.^[3] Breast and chest asymmetries also were prospectively recorded using detailed physical examination and measurements. Data was analysed and reported along with the relative prevalence and distribution of the larger side involved in these asymmetrical cases.^[4] All published articles in last 6 decades may have reflected from different angle highlighting various aspect and asymmetries of chest and breasts but one thing was commonly shared by all these authors was that breast and chest asymmetries are very common. However there is a lack of information on different volume implants used or different volume reductions performed for the management of these asymmetries when these patients presents for augmentation mammoplasty or one stage augmentation mammoplasty with mastopexy. The current article highlights volume management in 278 such patients who had different size implants or different weight tissue resection for asymmetry correction.

METHODS

In current study for breast volume difference management, retrospectively collected data was analysed. All patients had round cohesive gel textured implants placed in muscle splitting biplaner pocket and single surgeon consecutively performed all surgeries. Patients presenting with breast asymmetry requiring different size implants alone, mastopexy with different size implants and same size implants with different breast volume reduction for mastopexy were selected.

The patients were divided into 3 groups. Group A included patients who had volumetric difference without ptosis and were treated with different size implants alone. Group A was further divided into A1 receiving larger of the 2 implants on the right side and A2 receiving larger of the 2 implants on the left side. Group B patients included who had volumetric difference along with breast ptosis or nipple level difference. The group was treated using different size implants for volume correction with similar size tissue resection for mastopexy. This group was further divided into B1 and B2. B1 included patients who had larger size implants on the right hand side and B2 included patients with larger implants placed on the left

hand side. Group C included patients who presented with breast asymmetry with ptosis and had same size implants on both sides with different volume breast reduction on one side to correct asymmetry. Group C was further divided into C1 and C2. C1 included patients who had more tissue removed from right side than the left and C2 included patients who had more tissue removed from the left side.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 19.0. The results are presented in the text as frequency, percentage for qualitative/categorical variable (smoking, difference in implant size) and mean \pm SD for quantitative/continuous variables (age, implant size, and tissue removed, etc.). The statistical analysis was performed using the Chi-square test of proportion for the comparison of qualitative/categorical variables and the *t*-test for the comparison of quantitative/continuous variables. A *P*-value < 0.05 was assumed to be statistically significant.

RESULTS

Since 2005, 1,450 patients had augmentation mammoplasty and 150 patients had augmentation mammoplasty with mastopexy in muscle splitting biplane pocket. Of these 1,600 patients, 278 patients presented with significantly noticeable asymmetry and were operated for augmentation mammoplasty alone or augmentation mammoplasty with mastopexy.

Group A

Of 1,450 patients who had augmentation mammoplasty alone, 240 patients presented with significantly noticeable breast volume asymmetries without noticeable nipple level asymmetries or ptosis. Mean age of patients was 29.3 ± 7.9 years (range 18-53 years). Mean size of the implant on the right side was 343.4 ± 66.2 mL (range 200-605 mL) and the mean size of implants on the left side was 352.9 ± 86.5 mL (range 170-655 mL). There was no statistical difference when mean implant size of symmetrical augmentation mammoplasty was compared with mean implant size used on right or left side in patients with asymmetrical breasts (*P* = 0.650 and 0.052 respectively) [Tables 1 and 2].

This group was further divided into A1 and A2. Subgroup A1 included 145 patients who had larger implants placed on right side. In this group of patients, mean implant size used on the right was 358.6 ± 63.3 mL as compared to 317.0 ± 62.5 mL on the left side. Subgroup A2 included 95 patients who had larger

Table 1: Average distribution of age and size of the implants used in 240 patients who presented with asymmetrical breasts and compared with the mean age and size of implants used in 1,210 symmetrical breasts

	Same size implants (n = 1,210)	Different size implants (n = 240)
Age (years)		
Range	18-67	18-53
Mean \pm SD	29.7 \pm 8.71	29.3 \pm 7.94
Implant size (mL)		Right Left
Range	170-700	200-605 170-655
Mean \pm SD	341.5 \pm 57.96	343.4 \pm 66.24 352.9 \pm 86.56

Table 3: Relative distribution and comparative analysis of implants used in asymmetrical breasts

	Implants on right side (mL)	Implants on left side (mL)	P value
Group A1 (n = 145)	358.6 \pm 63.37	317.0 \pm 62.51	0.001
Group A2 (n = 95)	329.3 \pm 64.09	407.8 \pm 89.53	0.001

implants on the left side. In this group, mean size of the implants on the left was 407.8 \pm 89.5 mL as compared to 329.3 \pm 64.1 mL on the right side. There was a significant statistical difference between the sizes of the implants used on the two sides in both subgroups ($P = 0.001$ and 0.001 respectively) [Table 3 and Figures 1 and 2].

Group B

Of 137 augmentation mammoplasty with mastopexy, 20 patients presented with significant asymmetry of breasts and treated with different size implants with same size breast tissue reduction. The group had a mean age of 31.6 \pm 10.1 years (range 18-51 years).

Table 2: Comparative analysis of implants sizes used in patients with symmetrical and asymmetrical breasts who were treated with mammoplasty alone

	Symmetrical breasts (n = 1,210)	Asymmetrical breasts	P value
		Average size of implants used on right (n = 240)	
Range (mL)	170-700	200-605	
Mean \pm SD	341.5 \pm 57.96	343.4 \pm 66.24	0.650
		Average size of implants used on left (n = 240)	
Range (mL)	170-700	170-655	
Mean \pm SD	341.5 \pm 57.96	352.9 \pm 86.56	0.052

Mean size implants used was 314.0 \pm 75.1 mL (range 200-495 mL) on right and 339.0 \pm 99.7 mL on left.

This group was further divided into B1 and B2. Subgroup B1 included 7 patients who had larger implants on the right. In this subgroup, mean size of the implant on the right side was 334.0 \pm 52.2 mL as compared to 270.0 \pm 42.7 mL on the left side. There was a statistical difference between the implant sizes used on two sides ($P = 0.027$). Subgroup B2 included 13 patients who had larger implant on the left side and mean size in this subgroup was 377.0 \pm 102.4 mL on left as compared to 297.0 \pm 82.1 mL on the right. There was a statistical difference on the two sides ($P = 0.037$) [Tables 4 and 5].

Group C

Of the 150 augmentation mastopexy, 18 patients presented with significant asymmetry with ptosis and had same size implants with more tissue removed

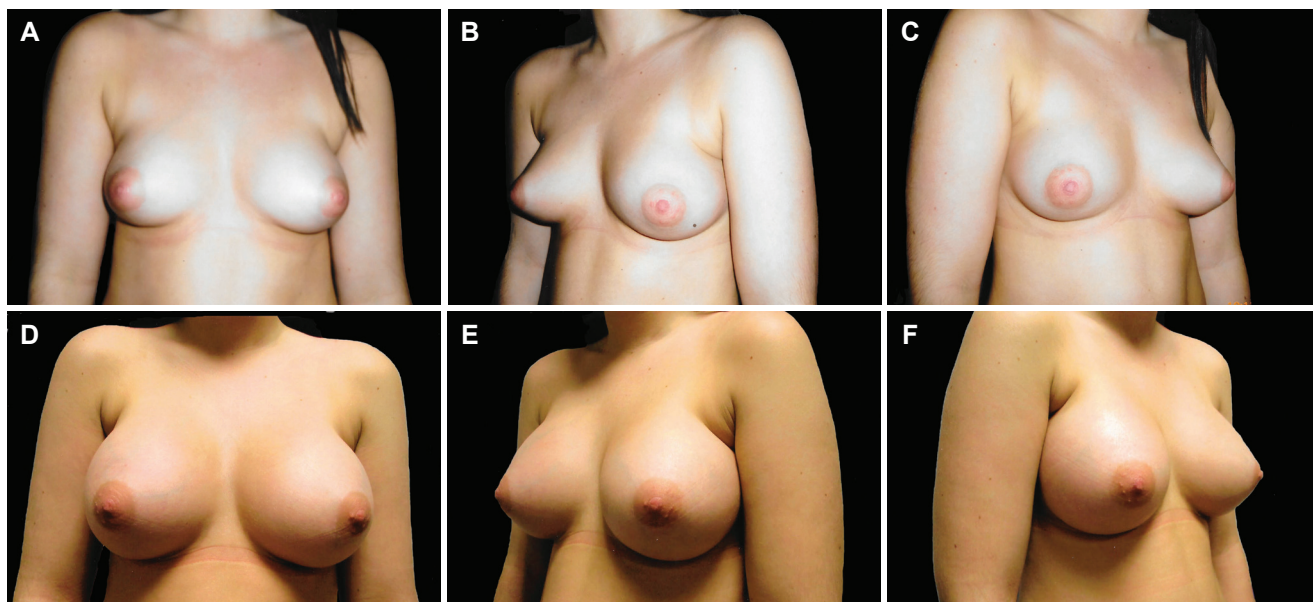


Figure 1: (A-C) A 23-year-old patient with moderate asymmetry of breast with no nipple level asymmetry. Her left breast is moderately larger than right; **(D-F)** 6 months postoperative views showing results following 330 mL and 360 mL high profile round textured cohesive gel silicone implants on her left and right side respectively

Table 4: Comparison of average size implants used in symmetrical breasts with ptosis and that of average size implants used in asymmetrical breasts requiring mastopexy with different size implants with same volume tissue reduction (group B)

	Symmetrical breasts with ptosis (n = 117)	Asymmetrical breasts with ptosis	P value
		Average size of implants used on right (n = 20)	
Range (mL)	170-800	200-495	
Mean \pm SD	302 \pm 87.1	314 \pm 75.1	0.563
	Same size implants (n = 117)	Average size of implants used on left (n = 20)	
Range (mL)	170-800	200-615	
Mean \pm SD	302 \pm 87.1	339 \pm 99.7	0.088

from one of the two sides for breast volume asymmetry correction (> 20 g). Mean tissue excised from right side was 114.0 ± 172.1 g as compared to 124.0 ± 107.8 g on the left. There was no statistical difference between the tissues removed from two sides ($P = 0.835$) [Figures 3 and 4].

The group was further subdivided in C1 and C2. Subgroup C1 included 7 patients who had larger breasts on right side and had more tissue removed from their right side (> 20 g). Mean weight of tissue excised from the right side was 276.0 ± 265.9 g as compared to 181.0 ± 185.8 g on left side. There was no statistical difference on the breast tissue removed from two sides in this group ($P = 0.530$). Subgroup C2 included 11 patients who had larger breast on left and more tissue excised from left side. In this group mean weight of the tissue removed from left side was 105.0 ± 44.6 g as compared to 49.0 ± 24.5 g on right.

Table 5: Comparative analysis and relative distribution of different size implants used in asymmetrical breasts with ptosis (group B1 and B2)

	Larger implant used on		P value
	Right (mL)	Left (mL)	
Group B1 (n = 7)	334 \pm 52.2	270 \pm 42.7	0.027
Group B2 (n = 13)	297 \pm 82.1	377 \pm 102.4	0.037

Statistical analysis was significant on two sides ($P = 0.001$) [Table 6].

DISCUSSION

Chest and breast asymmetries are very common and its prevalence has been reported in retrospective and prospective studies.^[1-4] The reported incidence of prospective clinical examination showed volume and nipple areolar level difference of 46.6% and 32.6% respectively and were significantly noticeable on left.^[4] Chest and breast asymmetries were also noted in 88% of patients^[3] and a combination of manual and 3D photography showed 81.7% soft tissue volumetric differences and when these soft differences were combined with chest bony asymmetries, incidences of asymmetry rose to 100%.^[5] Another commonly overlooked asymmetry is asymmetrically placed nipple areolar complex in horizontal axis.^[6] However none of the above studies gave details of volume difference management.^[3-6]

Augmentation mammoplasty when performed alone or as a single stage breast augmentation with mastopexy has shown an acceptable results.^[7-9] However,

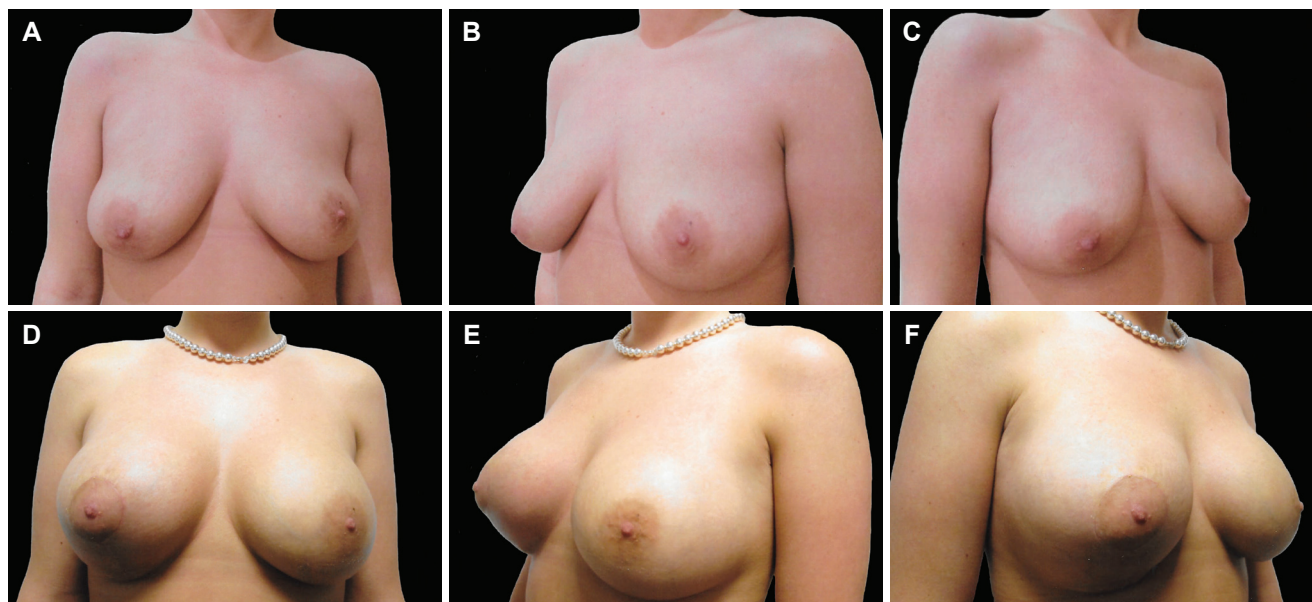


Figure 2: (A-C) A 25-year-old patient with class B and A ptosis on her right and left side respectively along with breast asymmetry; **(D-F)** 8 months following single stage right vertical scar mastopexy with 35 g tissue resection from her right side. She had 260 mL round textured moderate profile implants bilaterally

Table 6: Over all mean tissue resection from each side in group C, as well as respective mean tissue resection from each breast when breast were larger on either right (C1) or left side (C2)

	Right breast	Left breast	P value
Average tissue resection from asymmetrical breasts (n = 18)	114 ± 172.1	124 ± 107.8	0.835
More tissue resected from right bigger breast (group C1, n = 7)	276 ± 265.9	181 ± 185.8	0.530
More tissue resected from left bigger breasts (group C2, n = 11)	49 ± 24.5	105 ± 44.6	0.001

studies did not include details for volume difference management in asymmetrical breasts even though the most common reason for implant related revision noted was change of size of implant.^[9,10] A good interactive process of preoperative sizing for implants is effective and can avoid revisional surgery.^[11,12] A more rigid high five or more scientific and accurate way is to use 3-D photography combined with measurements of patients.^[5,13] However a rigid five point system or 3-D photography without patient's participation can leave the subject unhappy. In author's practice, a trial of fixed volume implants in a desired size brassiere is practical and effective and revision rates of less than 1% was reported.^[14] After carrying out a careful examination of chest, breast and tissue characteristics, different size and profile implants are placed in a desired size bra until surgeon and patients agree on the size and symmetry of breasts. Those who presents with breast asymmetry with ptosis, patients are given the choice to have either similar size implants with more tissue

resection from larger breast or having same amount of tissue reduced from both sides with different size implants. There is an advantage of asymmetrical breast tissue reduction and use of same size implants. In case, a patient gains or loses weight in future, breast volume is likely to go up or down in similar proportions without reintroducing asymmetry. However when two different size implants are used leaving original breast asymmetry unaddressed, patient's weight changes may accentuate original breast volumetric differences. The use of fixed-volume implants for asymmetry correction has shown low revision rate.^[14-17] Other commonly used options are adjustable breast implants or intraoperative sizers.^[18,19] In more complex deformities, more complex surgical procedures are required.^[20]

Analysis of the current study has shown some interesting results. In group A that required asymmetry correction using different size implants only, out of 240 patients, 145 (60%) breasts were larger on the left showing a relative predisposition of left side to be larger as reported in earlier studies.^[4,14] When different sizes implants were used on two sides in group A (A1 and A2) and compared with the size of the implants used in symmetrical breasts, there was no statistical difference between the sizes of implants used in each group [Table 2]. However when the implants sizes were compared on two sides in patients with asymmetry, the difference in breast implant sizes was significant [Table 3]. Also, when the right breast is larger, the difference is likely to be more noticeable requiring larger average volume for correction on

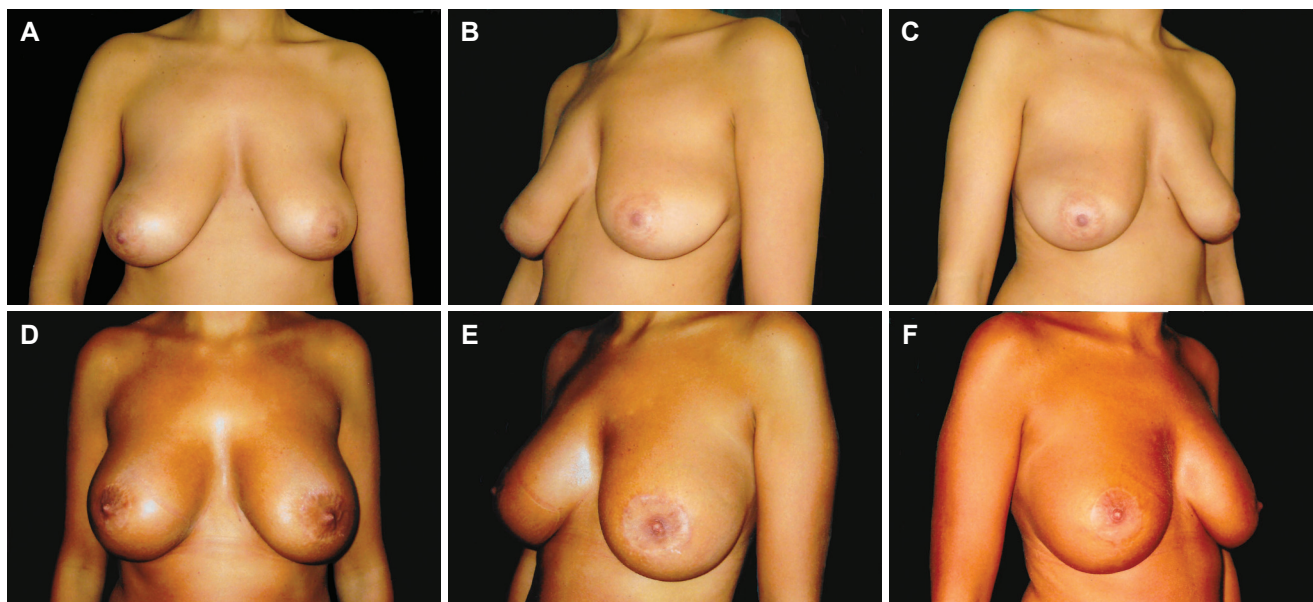


Figure 3: (A-C) A 29-year-old patient who presented with bilateral breast asymmetry with associated class C ptosis on her right and class B ptosis on her left side; (D-F) 8 months following right vertical scar and left periareolar mastopexy. She had 255 mL moderate profile round textured cohesive gel silicone implants. She had 55 g tissue removed from right side as compared to 12 g from her left side

Table 7: Relative incidence of larger volume implant used on respective sides based on the volume of the prosthesis used in asymmetrical breasts

Difference (mL)	Implant bigger right A1 (n = 145)	Implant bigger left A2 (n = 95)	P value
< 30	31 (21.4%)	20 (21.1%)	0.951
30-60	96 (66.2%)	38 (40.0%)	0.001
> 60	18 (12.4%)	37 (38.9%)	0.001

smaller left breast (mean volume 407.8 mL) as compared to the volume of implant used on the right side to correct asymmetry when left breast is larger (mean volume 317.0 mL) [Table 3]. Similarly when left breast is larger, only 12.4% patients had larger than 60 mL implants on the right breast as compared to 38.9% requiring more than 60 mL difference implant on the opposite side when right breast was larger. The results again concurred with the previously published work [Table 7].^[14]

As one would expect, patient requiring mastopexy with augmentation mammoplasty have in general or present with larger breasts than patients who require augmentation mammoplasty alone. The latter group is generally hypoplastic as compared to those patients requesting for augmentation mammoplasty and mastopexy due to excess breast skin and excess breast tissue accompanied with ptosis. It was expected that relatively higher prevalence of larger breast be on right than on left side. When the sizes of the implants in this group was analysed, it was noted that slightly larger mean size implant (339 mL) was needed on left breast to compensate right larger side breast (B2)

when compared with the mean size implant (314 mL) used on the right side to compensate left larger breast (B1). This also was noted that mastopexy requiring augmentation mammoplasty, larger mean size implants in group B2 were used on the left side in 13 patients with a larger difference (80 mL) as compared to 7 patients in group B1, where larger implant was used on the right with smaller difference (64 mL) to compensate larger breasts on the left side.

The weight of tissue resection was also analysed in 18 patients (group C) presenting with noticeable breast asymmetry requiring mastopexy with augmentation mammoplasty. These patients had same size implants with more tissue removed from the larger side (> 20 g). This was noted that when the breast was larger on the right side, the mean weight of the tissue removed was 95 g more as compared to 56 g, when left breast needed reduction for symmetry. The result emphasize that when the breast is larger on the right, it tends to be relatively larger than patients presenting with larger breast on the left side [Table 6].

Volume difference in asymmetrical breasts can be assessed preoperatively using 3D photography^[5] or retrospectively by analyzing the volume difference of the implants used on two sides in patients who presented with asymmetrical breasts and had augmentation mammoplasty without mastopexy. The volume difference can also be analysed in patients who needed augmentation mammoplasty with mastopexy. In the latter group, volume difference of the implants can be analysed when two different size

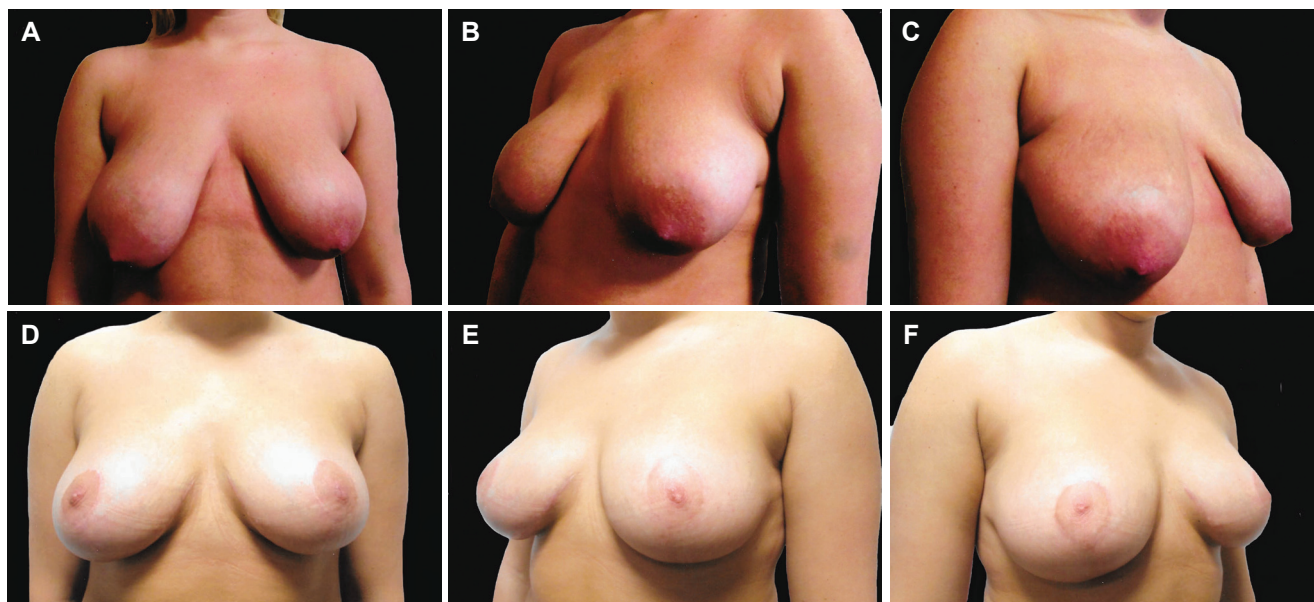


Figure 4: (A-C) A 19-year-old patient presenting with breast hypertrophy, asymmetry and bilateral class C ptosis. Her right breast was markedly larger than the left; (D-F) postoperative results 10 months following Wise pattern mastopexy with 230 mL round low profile textured cohesive gel silicone implants. She had 173 g tissue removed from her right and 147 g tissue removed from her left breast

implants were used with similar breast tissue reduction or where two different weight tissue reductions were performed with same size implants. In author's opinion 3D photography is a more scientific and accurate tool to evaluate the difference as it measures the difference of chest wall asymmetry as well as breast volume asymmetry. Use of 3D photography has shown an incidence of 100% asymmetries and comprised of soft tissue, chest wall and combined soft tissue and chest wall asymmetries. The breakdown of volumetric differences was also reported in the study. The article noted a difference of 0-10 mL in 2.2%, 11-25 mL in 21.9%, 26-50 mL in 28.9%, 51-100 mL in 29.3% and > 101 mL in 17.7% of the females. However revision rate for the size or shape of the implants was not reported in the study neither the relative distribution of larger size breast, chest or combined asymmetries of the two.^[5] In a previously published author's article, a retrospective analysis of the volume differences in 146 augmentations mammoplasties showed twice as many patients needing larger implants on the right side to compensate larger breast on the left. Less mean volume was needed on the right side to compensate left larger breasts than the mean volume used on the left side to offset larger breast on the right. In the same study 0-30 mL volume difference was needed in 35.6%, 31-60 mL difference was used in 48.6%, 60-90 mL difference was used in 7.5% and > 90 mL difference was used in 8.2% of the patients. There was only one patient who required revision surgery for size change on one side.^[14] Sample included patients who had augmentation mammoplasties alone, all patients were operated by the same surgeon using muscle splitting technique for implant pocket. In current study, asymmetries of breasts requiring augmentation and mastopexy were added to augmentation mammoplasty group. It was again noted that when asymmetries are present, left breast was larger in majority of the patients. In subgroup A1 with larger left breasts, 87.6% needed implants with a difference of less than 60 mL as compared to 61.1% in subgroup A2 with larger right breasts. Similarly, when a volume greater than 60 mL was needed to compensate for size difference, it was mostly needed on left side for the right larger breasts [Table 7].^[14]

There are many approaches to assess and manage breast and chest asymmetries. The options include preoperative planning using 3D photography or simple examination and measurements of breasts. Intra operative management includes use of sizers and adjustable implants. Despite of the various measures taken to achieve symmetry in breast asymmetries, it is not guaranteed that a perfect result can be achieved in all cases. Some degree or level of differences are likely to persist and that a patients should be warned

of this residual asymmetry. In the author's opinion and practice, careful examination and measurements are the most time efficient, cost effective and reproducible method. In this series of 278, only one patient was unhappy with the postoperative results requiring revision surgery for implant volume difference readjustment. High profile implants of different sizes are the choice for patients requiring volume adjustment alone. Those patients who present with asymmetry of skin excess, breast volume and ptosis requiring one stage mastopexy and augmentation, moderate profile implants is the choice of author. Combination of different profiles implants is seldom required and limited to patient who present with hemithoracic disjunction or noticeable anteroposterior chest dimension asymmetry with or without breast volume asymmetry.^[4,14]

In conclusion, breast and chest asymmetries are very common. The left breast or chest or both are likely to be larger than the right chest, breast or both. Not all patients request or require different size implants. When different volume implants are used, the vast majority the patients do not require a volume difference of more than 60 mL. When the breast is larger on the right then larger mean volumes are used on left side to offset the larger right breast.

Authors' contributions

U.D. Khan contributed solely to this paper.

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Conflicts of interest

Author declares no potential conflict of interest with respect to the research, authorship and publication of the article.

Patient consent

All patients signed an informed consent form.

Ethics approval

This is a retrospective data analysis of procedures performed in a private centre therefore international review board approval was not required. All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

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The radiation therapy in keloids treatment: a comprehensive review of pathomechanism, damage mechanisms and cellular response

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ABSTRACT

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Keloid management has always been frustrating and challenging. The combination therapy of surgical excision and radiation therapy was deemed as the last resort for decades. The authors performed a thorough and comprehensive review over the mechanisms on how radiation therapy damages the keloid cells. The keloid cells' cellular response towards damage induced by irradiation was also studied based on original and current literatures. Mechanisms of damage generated by radiation therapy on keloid cells remained partially understood. However, direct damage was identified playing dominant role, in contrast to damage involved cancer cell apoptosis. Moreover, the p53 pathway and some inflammatory factors like interleukin-6 were believed to function in cellular response to irradiation. However, the transforming growth factor beta, which was the major dysregulated pathway involved in pathogenesis of keloid formation showed no apparent correlation with cellular response to irradiation damage. These pathways could partially explain radiation resistance in some refractory keloid lesions. The scientific basis and experimental proof in this field was still inadequate, which drove us to find more evidence to identify the key regulator response to damage engendered by radiation therapy. Further pathway identification may benefit the drug development to prevent keloid recurrence.



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INTRODUCTION

Keloids have been considered frustrating issues for many decades since surgeries evolved. The keloids were firstly considered as pathological wound healing process. Deemed as benign tumors, keloids were uncontrolled and unconfined sharply bounded hyperplasia of dermal connective tissues arising from an abnormal wound healing process. This benign lesion often follows dermal injury, burn injury, tattooing and even simple acnes. However, the cause of keloid formation remained a mystery. Familial tendency and darker skin races preference were observed in prevalence of this benign disease.^[1] The keloid is gradually considered as a genetic disease with genetic predisposition that demonstrates an autosomal dominant or X-linked inheritance pattern. Even though there was no specific genes identified directly related to keloid formation, several susceptibility loci were reported before. In one study utilizing genome-wide sequencing technology to discover susceptible loci, 4 potential single-nucleotide polymorphisms in 3 chromosomal regions in Japanese patients were identified.^[2] Two rare syndromes were historically named due to its familial tendency, the Rubinstein-Taybi syndrome and Goemrine syndrome.

Black people are more likely to have this benign lesion, while the Caucasians are least likely. In African populations, the incidence is 6-16%, which is 15 times higher than whites.^[3] The more piercing happened among women might bring the confounding bias which leads to female predominance.^[4]

Moreover, keloid growths are more likely seen on the chest, shoulders, upper back, back of the neck and earlobes, where larger skin tension should be noted. Notably, the earlobe is exceptional, which indicate lower recurrence rate under similar treatment. Therefore, this site-specific characteristic provides us the site-specific treatment algorithms, for example, to decide whether or not the lesion requires radiation therapy. There were several characteristics of keloids, several morphological and histological differences. It is also noted that, the hypertrophic scarring and keloids often confuse dermatologists and surgeons when it comes to diagnosis due to their similar appearances.

Clinically, keloids are firm nodules, which can be skin colored, dispigmented, or erythematous secondary to telangiectasias. The keloid scars in Caucasian people, are more likely to be erythematous and telangiectatic. Comparatively, hyperpigmentation is more popular in Blacks.^[5] The lesion always extends beyond the border of demarcated primary lesion, and often with irregular shape, just like how the word “keloid” originated from

the Latin word “crab”. However, the hypertrophic scars are apparently more linear, nodular, or papular with more regular borders and are always within the original wound borders.

The hypertrophic scars usually occur 4 to 8 weeks postoperatively or after the injury, compared to high variability of keloids formation time. The time of keloid formation can be quite volatile, from generally within 3 months to many years after the dermal injury. Unlike the hypertrophic scars, which often gradually regress after years, keloids persist for longer period of time and do not regress spontaneously. Moreover, even both lesions are pruritic, the keloids are more likely to cause significant pain and hyperesthesia.

PATHOPHYSIOLOGICAL BASIS OF KELOIDS FORMATION

Keloids can derive from any form of dermal injury. However, the pathological process of its formation is still poorly understood. Both environmental and genetic factors contribute to this pathological process. Apparently, a universally accepted theory is that both keloids and hypertrophic scars are considered results of persistent chronic inflammation. In histological view, continuous local inflammation was observed along with keloid progression.^[6] Inflammatory cells, increased numbers of fibroblasts, angiogenesis, and new collagen deposition were all observed. Besides, inflammatory cytokines or mediators were also overproduced in keloids or hypertrophic scar tissues, including interleukin (IL)-1 α , IL-1 β , IL-6, and tumor necrosis factor (TNF)- α . These pro-inflammatory genes or products are believed to be sensitive to trauma, induce continuous inflammation and collagen deposition. Moreover, persistent chronic inflammation could potentially explain the relative higher invasiveness of keloid scars. The major occasion where inflammation happened, reticular dermis is believed to function primarily in keloid formation. This theory is partly supported by the valid therapeutic value of corticosteroids injection/tape/ointment in keloid treatment. Besides, one of the many widely accepted theories is that more injury and inflammation will more likely generate excessive scar tissue. A multitude of cells were involved in wound healing process, as well as keloid scarring. One of the very important cells, fibroblast produce collagen show sustained activity.^[7] Aberrantly excessive growth factor and overproduction of its receptors were both observed in growth pattern of keloid-derived fibroblasts. Overexpression of vascular endothelial growth factor (VEGF), transforming growth factor (TGF)- β 1, TGF- β 2, connective tissue growth factor, insulin-like growth factor (IGF)-1, as well as the

platelet-derived growth factor (PDGF)- α receptor were all reported in previous studies.^[8] Alterations of these growth factors secretion were believed to be pivotal for scarring process. Keloid-derived fibroblasts were reported more sensitive to several key growth factors like TGF- β 1, PDGF and IGF-1 compared to normal fibroblasts, which might explain the overproduction of collagen by keloid-derived fibroblasts.^[9] Moreover, other than the collagen-producing cells fibroblasts, keratinocytes isolated from keloid formation also were shown to have an aberrant behavior, especially co-cultured with fibroblasts. Two vital cytokines were believed secreted from keloid-derived keratinocytes, the hypoxia-inducible factor-1 α (HIF-1 α) and release of IL-1.^[10] Some paracrine secretion by keloids were also deemed as contributor to fibroblasts overgrowth and collagen overproduction.^[11] What's more, melanocytes, mast cells and myofibroblasts were also all considered playing important roles in keloid scarring.^[12,13]

As pathomechanism parallel to skin fibrosis, TGF- β was currently considered as one of the key regulators in keloid formation. TGF- β is the cytokine with a wide variety of biological function implicated in other fibrotic disorders. Stimulation of cell proliferation and cellular differentiation made TGF- β family a very important mediator in wound repair process, especially functioning in extracellular matrix production. In normal wound healing process or hypertrophic scarring, TGF- β 's activity will finally regress accompanied with wound sites to be mature. However, in pathological process, like keloid formation, TGF- β 's expression level and activity remain sustainably upregulated.^[14] SMAD signal-transduction pathway, as the major downstream mediator of TGF- β , is believed to be dominant in keloid scarring process. Upregulated TGF- β diminishes the SMAD3 expression, which subsequently increase procollagen gene expression and enhance ECM deposition.^[15] Except for TGF-SMAD pathway, other pathways involved in other fibrotic disorder or solid tumors were also reported playing roles in keloid formation at different levels, like p53 and mTOR.^[16] These pathways also provide us with substantial background when studying keloid's response to radiation.

MANAGEMENT OF KELOIDS

Management of keloids was considered a conundrum without definitive optimal treatment strategies. A well-established treatment strategy was reported before, mentioning a new emerging treatment strategy comprised of surgical excision, radiation, corticosteroid injection, laser and conservative multimodal therapy. The current mainstream of current definitive treatment

strategies emphasized on 5 major treatment modality, including intralesional corticosteroid injection, cryotherapy, surgical manipulation, radiotherapy and laser therapy. Intralesional injections started since 1960s, but demonstrating various but limited clinical outcome. The suppression effect of topical inflammation is considered the basis of intralesional corticosteroid injection.^[17] Diminished collagen or extracellular matrix and inhibition of fibroblasts migration were both reported. However, the response rate was quite uncertain, varying from 50% to 100%.^[18,19] The control of recurrence rate was also fluctuating, ranging from less than 10% to over 50%.^[20,21] The most common adverse effects included dermal atrophy, telangiectasia and local pain at the injection site. Another monotherapy utilized accompanied with less trauma is cryotherapy, which is believed to function through vascular damage, then anoxia and tissue necrosis.^[22] The success rate ranges from 32% to 74% when utilized for at least two sessions. The adverse effects were quite similar to intralesional corticosteroid injection. Botulinum toxin A injected intralesionally was considered as another critical way to treat keloids, effective but better tolerated than intralesional steroid.^[23] Besides, both intralesional corticosteroid injection and botulinum toxin A injection are combined with other therapies, especially radiation therapy. Furthermore, laser treatment is another modality proved to be effective in controlling keloid formation. Since the 1980s, multiple laser treatment modalities were introduced for keloids and hypertrophic scars, such as carbon dioxide laser and 585-nm pulsed-dyelaser (PDL) laser. Notably, PDL laser is nowadays considered the most effective among all laser treatment utilized, especially initial hypertrophic scars or primary keloids.^[24] Laser treatment can control keloid growth through generating ischemic microenvironment. Besides, more and more treatment modalities were utilized, generating different clinical outcome. The major adjuvant preventative therapy includes pressure, silicone gel sheeting, flavonoids. Some other drugs, especially chemotherapeutic or immune suppressive drugs, such as 5-fluorouracil (5-FU), Bleomycin, mitomycin C, botulinum toxin were also applied to treat keloids.

Surgery and radiation therapy

Lastly, as one of the traditional treatment for keloids and hypertrophic scars, surgical treated lesions alone have a recurrence rate ranging from 45% to 100%. The surgery is believed to be another skin trauma which potentially causes more damage than before. Then the combination therapy of surgery and other post-operative treatment became popular around the world. Among these treatment modalities, combination therapy of surgical excision and radiation therapy was

considered as the last resort which can significantly reduce recurrence rate.^[25] Notably, the definition of recurrence is controversial which might cause bias in clinical studies. The universally accepted definition was an elevation of the scar, extending beyond the original surgical field.^[26] Early in 1970s, several negative results drew the determined conclusion that simply surgical excision was accompanied with high rate of recurrence, ranging from 40% to 100%.^[27] The possible explanation was surgery itself was considered as the stimulation of additional collagen synthesis. Therefore, the surgical excision was no longer used alone. The combination therapy of surgical excision and radiation therapy gradually replace the traditional surgical excision. Starting from superficial X-ray irradiation, the radiation therapy effectiveness was gradually proven. Radiation therapy has a long history being applied in treating keloids. The inhibition of scar growth and postoperative keloids formation was found back to early in the 20th century. DeBeurman and Gougerot first described X-ray treatment of keloids in 1906 and serial positive reports followed.^[28] First recommended in keloids prevention and then escalated to keloids treatment.^[29] Meanwhile, the rapid technology development also contributed to extension of radiation therapy application in treating keloids. From kilovoltage irradiation to electron beam irradiation, from outside of the body to inside of the body, the transition of technology brought improvement recurrence rate reduction and better normal tissue sparing. As one of the experienced radiation therapy center, our team is quite familiar with this combination therapy. Actually, different radiation therapy facility, technology, different treatment modality combined and different treatment protocol will cause variable clinical outcome. For example, due to the radiation therapy center of our hospital, we here gave our recommendation of our treatment modality. The first radiation therapy should be performed within 48 h postoperatively or after other procedures. The radiation therapy was performed 1st day postoperatively and on the 8th day of hypofractions as reported by Shen *et al.*^[30] previously. The external beam was administered using 6 or 7 MeV electrons. Flat lesion surface was largely achieved by patient position change confirmed by radiation therapists. The field of irradiation field covered the entire lesion site with 1 cm margin to ensure the enclosure the margin. Normal tissue shielding was implemented by appliance of a 0.8 cm customized lead sheet. Additionally, 0.5 cm of wax was utilized to broaden the radiation field. For every single lesion, a total dose of 18 Gy in 2 fractions with interval of 1 week was well established. In a brief summary, the relative low $\bar{\alpha}/\beta$ ratio of lower fractions and higher doses were presumed as the choice of treatment. Ranging from superficial X-rays, to electron-

beam irradiation and to low dose rate or high dose rate brachytherapy, radiation therapy technology treatment has provided us with several options on different lesions and different sites. However, we still believe that the damage mechanism and the mechanism behind resistance generation are largely similar among all radiation therapy types. Moreover, the cellular response to radiation therapy was rendered as a possible explanation accounting for local recurrence. Indeed, what role did irradiation played remained unclear. We now present a comprehensive review over this issue, trying to identify the most valuable pathway involved in cellular response to irradiation.

POTENTIAL MOLECULAR PATHWAYS AND CELLULAR RESPONSE

Unfortunately, no present literatures could perform a thorough review on the ways which irradiation played. It might be attributed to the diversity of irradiation source and particles or uncertainty of molecular pathways dominance in keloid formation. A fraction dose of 5 Gy was considered effective in eliminating aberrantly activated fibroblasts and promoting the rest of normal fibroblasts.^[31] Similarities of direct damage and cellular response to ionizing irradiation could bring us some potential inspirations. Genetic susceptibility, radiosensitivity and complications were taken into our consideration. As known to us, the biological effectiveness of radiation was quite dependable owing to different sites, linear energy transfer (LET), total dose, fractionation rate and radio-sensitivity. Various mechanisms were reportedly involved in killing cancer cells or benign tumor cells. Early explanation was built on the hypothesis that local fibroblasts which were destroyed by irradiation cannot be replaced by distant fibroblasts.^[32] Under light microscope, programmed cell death or apoptosis dominated in post-irradiated targeted tissues. Apoptotic numbers and ratio in postoperative keloid tissues were considered as very important index evaluating the radio-sensitivity and direct DNA damage. Correspondingly, necrosis, mitotic cell death or mitotic catastrophe, senescence, autophagy were also observed and partially proved in some *in vitro* studies.^[33] The intracellular target was apparently the DNA, whose damage can cause irreversible cell injury or triggering the programmed cell death. The most effortless classification of these damages was naturally dividing them into two parts, direct damage and indirect damage. Direct damage essentially referred to the interaction between radiation and DNA, while indirect damage referred to the damage from radiation-derived free radicals. Direct actions dominate in high-LET ionizing irradiation technology (neutrons and other heavier ions), generating high-

density energy deposition.^[34] On the contrary, low-LET ionizing irradiation technology (X-rays, gamma-rays and electrons) addresses the indirect actions, accomplishing a ratio between indirect and direct actions. Both of these actions achieve lethal DNA damage, comprising single strand DNA breaks, double strand DNA breaks and DNA cross-linking. Even though most of these damages can be repaired by efficient base repair excision system. A small fraction of complex DSB, however, was the exception, which leads to ultimate cell death. As for cancer cells, complexity of mechanisms induced a variety of cell death mentioned above, having many pathways assumed. One previous study made use of cancer patients' microarray data prior- or post-irradiative to obtain differentially expressed genes, protein domain enrichment analysis also help to highlight some related pathways.^[35] Notably, deemed as the aberrant wound healing process, collagen synthesis related genes were also unearthed. The collagen triple helix repeat family members collagen type (COL) 5A2, COL9A3, COL6A3, COL21A1, COL5A3, COL11A1, COL7A1 was significantly identified by protein-protein interaction. Notably, there was no clear evidence explaining the exact mechanisms other than direct damage towards DNA. We not only want to extract the molecular pathways from closely related research but also provide insights from keloid formation process and cancer cell response towards radiation therapy.

P53 and apoptosis

Even the pathways were not fully elucidated, direct and indirect DNA damage will be largely repaired by the cell DNA repair system, generating G1/G2/M block. However, the cellular response and characteristics of targeted tissue cells are quite complicated. Genomic instability and chromosome aberrations were observed *in vitro* studies by radiation induction apoptosis. Being the principle guardian of DNA damage response, p53 accordingly maintains the genetic stability through phosphorylated ATM or phosphorylated ATR proteins.^[36] ATM-p53-Bax-cytochrome C was reportedly associated with apoptosis, while the p53-Caspases-cytochrome c pathway mitotic catastrophe-related.^[37,38] What's more, p53 also enabled extrinsic CD95-FADD-caspases apoptotic pathway, which is considered to be enhanced by CD-95 mediated pathway.^[34] Senescence was also believed to have p53 regulation involved.^[39] Dysregulated p53 expression and function plays a critical role in tumorigenesis of diversified malignant tumors. Abnormal expression of p53 in non-neoplastic lesions and benign neoplasmas of soft tissue including keloids was also brought to light early in 1993, positivity in 9 of 9 keloids tissues baffling researchers whether it indicated malignancy.^[40-42] Further genetic studies

ensued to elucidate the biological significance of the aberrant expression of p53 benign soft tissue lesions. As keloids gradually being considered as dysregulated wound healing process, a study randomly selected 20 archival-paraffin-embedded keloid samples for an immunoperoxidase assay with antibodies against fas, p53, bcl-2, and bcl-x using target antigen-retrieval technique.^[43] Among them, 18 of 20 keloids expressed p53 protein, while bcl-2 was expressed in 19 of 20 fibroblasts, which indicated that focal dysregulation of p53 combined with upregulation bcl-2 might help produce a combination of increased cell proliferation and decreased cell death in keloids. Prominent Fas expression was detected in all 20 specimens, limited to the central area, favoring the potential hypothesis that p53-induced Fas apoptotic process dysregulated in keloid hyper-proliferative area. Another study in exploration differences in different regions in entire keloid tissue, the "older parts of the keloid", the central parts of keloids are shrunken and soft in texture compared with peripheral keloids tissue parts, showing much less proliferative and invasive characteristics.^[44] With majority of fibroblasts derived from keloid centers staying in G0 or G1 phase, Fas and Bcl-2 expression did not differ significantly between the two regions, but p53 expression was much higher in fibroblasts derived from central parts than from peripheral parts.^[45] Based on these molecular explanations for cells' overgrowth in keloid tissues, experimental 5-FU modality induced p53 and p21 accumulation together with a decrease in cyclin B1 and Bcl-2 levels in treated keloid fibroblasts.^[46,47] Further evidence uncovered several possible explanations for how p53 played in keloid scarring. As a sequence-specific transcription repressor of p53, overexpression of $\Delta N63$ isoform showed essential dominance in suppressing p53 protein in keloid tissues compared to normal skin, with the similar nuclear localization like p53 protein.^[48,49] Dysregulated p53 function, altered expression and asymmetric protein deposition observed in keloid tissues all enables its potential as the main target. Both contribution to intrinsic and extrinsic apoptotic pathway, reactivation, upregulation and accumulation of p53 in response to ionizing irradiation initiated the caspase lethal pathway, achieving programmed cell death.

TGF- β and response to irradiation

TGF- β was considered as the major altered pathway explained in keloids' pathogenesis, especially at early stages.^[50] More than 90% immunostaining in keloids was significantly higher than the 60% found in normal scars. Significant elevation of TGF- β expression was observed in keloid tissue compared to normal tissue, which may be explained by alteration expression of SMAD3, SMAD6 and SMAD7.^[51] Specifically,

downregulation of Dickkopf-3 (DKK3) in keloids fibroblasts disinhibited cell proliferation in TGF- β 1-induced keloid fibroblasts transfected with pcDNA3 through downregulated Bax and caspase-3 expression and increase expression of Bcl-2.^[52] Additionally, dramatic overproduction of collagen proteins and mRNAs was also contributed to DKK3 overexpression, which made DKK3 a potential mediator functioning in TGF- β /SMAD signaling pathway. Overexpression of TGF- β can explain overproduction of collagen and extracellular matrix,^[53] outweighing other postulated pathways explaining the pathogenesis.^[54] Immune system including T-cell function and keloid fibroblasts proliferation were included in this process.^[55] Radiation therapy can induce and enhance TGF- β signaling in radiation oncology, which means this process was much less important in keloid treatment.^[56] Several literatures reported that radiation could potentially induce persistent TGF- β overproduction in animal models.^[57-59] In radiation induced fibrosis, high doses of radiation can be delivered to the skin and the underlying subcutaneous tissues, and severe skin burns can be observed, resulting in extensive fibronectin tissues.^[60] TGF- β 1 was observed sustainably overexpressed in all phases of skin fibrosis, especially in late phase of fibrosis at a level of 10 folds more than underlying tissue. In human patients, similar long-term activation of TGF- β expression pattern was found in mammary skin biopsies from breast cancer patients who had received radiation therapy up to 10 years before. Considering the parallel relation between keloid scarring and skin fibrosis, TGF- β pathway is less likely to be target of radiation therapy in treating keloid lesions. However, TGF- β overexpression could potentially provide plausible explanation of some radiation-refractory patients, explaining their higher rates of recurrence. Therefore, direct and indirect DNA damage and p53-induced apoptosis possibly outweigh TGF- β signaling activation in keloid radiation therapy treatment.

Other potential responses

TNF receptor superfamily not only coordinates with p53 in canonical extrinsic apoptotic pathway, but also induces necrosis by TNF (alpha)-PARP-jnk-Caspases pathway.^[61] The signaling cascade ULK-1 initiated the process of autophagy, upregulating Hif1a and blocking Bcl-2 and, finally releasing Beclin1.^[62] Beclin1 was deemed as the initiator of autophagy. Anti-inflammation effect was considered playing the minor role in treating keloids and other proliferative benign disease.^[63] Moreover, PI3K/Akt/mTOR pathway can potentially enhance the tissue sensitivity towards the radiation damage through inducing apoptosis, reducing autophagy, suppressing NHEJ and HR repair pathways.^[64] Inhibition of mTOR pathway

could potentially enhance damage towards lesion vasculature and obviously decrease inflammation.^[65] However, we believe that mTOR pathway is central to some solid tumor formation, which is not the case in keloid formation. Besides, inflammation is initial phase of wound healing process and also keloid formation process, IL-6 is one of key cytokines mediating inflammation. Overexpression of IL-6 first reported in 1990s, both in keloid fibroblasts culture and collagen synthesis.^[66] IL-6 is not only accumulated in collagen, but also related to JAK/STAT3 and ERK/MAP kinase. In an epidemiological study in China, a marked increase in serum IL-6 levels in KS patients with GG genotypes when compared to keloids patients harboring the CC genotype indicating IL-6 polymorphisms is partially related to keloid susceptibility.^[67] Recently, a case report demonstrated a Castleman's disease (a rare lymphoproliferative disorder) patient developed bilateral auricular keloids, which is believed due to overproduction of IL-6 in Castleman's disease patients.^[68] Moreover, antibody towards IL-6 resulted in reduced collagen accumulation which made IL-6 a target for pharmacologic intervention. However, no post-radiation therapy can potentially support this assumption. From genetics to epigenetics is another very important issue in the past few years. The fact that the proportion of apoptotic cells in keloid fibroblasts can be modulated by methylation inhibitors indicated that methylation also plays an important role in keloid formation.^[69] DNMT1, DNA methyltransferase 1, a well-known DNA methyltransferase, expressed 100% in keloid tissue compared to 8% in normal skin tissue.^[70] In one study working on relevance between methylation levels and radiation therapy, clear difference induced by radiation therapy is observed.^[71] Moreover, histone deacetylase 2 (HDAC2) upregulated in keloid tissue *in vivo*, was also observed in scar tissue mice model of wound repair.^[72] Notably, the capacity of the HDAC inhibitor suberoylanilide hydroxamic acid to modulate radiation response in human tumor cell lines is verified in another study, demonstrating a dose-dependent inhibition effect. The radiation-induced apoptosis was significantly enhanced.^[73] Acetylation level of histone is also altered after radiation therapy in lymphoblastoid cell lines.^[74] Therefore, even though valid evidence is absent, we can still predict that the methylation and histone post-translational modification levels will change in response to radiation therapy. Besides, a recent new perspective of keloid and hypertrophic scars renders these two disorders as vascular disease.^[75] All so-called effective treatments of keloids including radiotherapy, compression therapy, steroid administration, and long-pulsed Nd:YAG laser therapy all directly or indirectly damage blood vessels or suppress new blood vessel growth. The

new assumption is that primary scars are always due to congenital endothelial dysfunction, while secondary scars is always caused by aging. Therefore, keloids and hypertrophic scars tend to appear on younger patients, while normal scars are not. These new evidence and assumptions might indicate the damage towards endothelial cells or preceding blood vessels can partly explain the damage induced by radiation therapy.

Long non-coding RNA and microRNA

Long non-coding RNA (lncRNA) and microRNA are both hot issues in the past decades, especially in oncology. The lncRNAs and microRNAs were both unearthed being involved in pathological process of keloid formation, which is assumed to have potential to partially explain the cellular response to radiation therapy. The microarray technology was first applied in study of keloids in our hospital.^[76] Our published data demonstrated that 1,731 lncRNAs constantly upregulated and 782 downregulated, 1,079 mRNAs upregulated and 3,282 downregulated in keloid respectively (fold change ≥ 2.0 , $P < 0.05$). Some selected 3 upregulated and 1 downregulated lncRNA were re-confirmed by performing quantitative real time polymerase chain reaction (qRT-PCR). We had 55 pathways highlighted in total, 11 pathways related with upregulated transcripts and 44 with downregulated in keloid. What's more, the CACNA1G-AS1, one of the selected lncRNA potentially functions vitally in keloid formation. In another study working on ear-lobe keloids also by microarray, a total of 2,068 lncRNAs and 1,511 mRNAs differentially expressed between earlobe keloid and normal tissues were identified.^[76] Similarly, more than 1,000 lncRNAs and mRNAs were upregulated, with another several hundreds of lncRNAs and mRNAs downregulated. In this study, 35 pathways were also highlighted. However, the lncRNAs regulating encoding transcripts/genes involved in Wnt signaling pathway in keloids is previously reported.^[35] Eleven top co-expressed lncRNAs characterized with the highest co-expression coefficients to the 17 identified skin-related keloid-aberrant Wnt-genes. After PCR confirmation, 4 lncRNAs including CACNA1G-AS1, HOXA11-AS, LINC00312 and RP11-91111.1 with their 6 paired Wnt-genes were believed to function in keloid formation. These lncRNAs responded to the pre-designed array and qPCR test simultaneously. However, unluckily, no updating data generated from post-irradiation keloid tissue or even cancer tissue supporting this assumption. But lncRNA is now believed to be excellent biomarker for predicting breast cancer and prostate cancer survival, which will lead us to keep our eyes closed on this area. MicroRNAs are 21-23 nucleotide molecule, which

are not participated in protein synthesis but targeting the 3'UTR of mRNA.^[77] MicroRNAs were considered playing roles in multiple stages of cancer development, including cell proliferation, apoptosis and migration. Reasonably, microRNA deregulation was believed to indicate clinical intervention. A number of microRNAs have been identified due to differentially expression in keloid tissues and keloid fibroblasts. In the study published in 2012, a total of 32 differentially expressed in keloid tissues comparatively.^[78] Among them, 23 miRNAs (e.g. miR-21, miR-4269, miR-382) were upregulated and 9 miRNAs were downregulated (e.g. miR-203, miR-205, miR-200b/c), which participated in some important signaling pathways functioning in wound healing process or scar formation, specifically mitogen-activated protein kinase, focal adhesion and biosynthesis of collagen protein.^[79] Furthermore, these differential-expressed microRNAs were observed as major function in keloid fibroblasts. The altered microRNA profiling narrowed down to 6 upregulated and 3 downregulated microRNA genes. Meanwhile, microRNAs were considered playing important regulatory roles in various pathways, at least in cancer treatment.^[80] These microRNAs were functioning in different aspects, including DNA damage response, the microenvironment and survival pathways and other radioresistance-related pathways. Some microRNAs were reported in both the function of keloid formation process and the response to radiation therapy process. For example, miR-21 is believed to promote phosphatidylinositol 3 kinase-AKT-pathway-mediated survivals by suppressing its direct and indirect negative regulators PTEN, deemed as one of vital survival pathways. Therefore, miR21 was regarded as one of the most promising targets for RNA-based therapy in treatment of breast cancer. Triggered by diverse stimuli including ionizing radiation, autophagy is considered as a self-degrading process.^[81] MiR-199-5p is also considered as an autophagy suppressor in MCF7 cells. MiR-199-5p also delivers radiosensitive potential to breast cancer cell lines.^[82,83] MiR-199a-5p overexpression inhibits DRAM1 and Beclin1 expression in MCF7 cells and also sensitizes MDA-MB-231 cells to irradiation. This novel microRNA is now considered as one of the therapeutic target.^[84] In another study, miR-199a-5p is believed to have an influence on the proliferation of keloid fibroblasts. Transfection of different overly expressed miRNAs into a keloid fibroblast with EdU assay showed a significant downregulated cell proliferation rate and altered cell cycles.^[85] Moreover, miR200b and miR200c, both belonging to miR200 family, were associated to aberrant proliferation of fibroblasts and radiation-induced apoptosis, respectively.^[86-88] MiR-200b was downregulated by more than 2-fold in hypertrophic scars, regulating the

cell proliferation and apoptosis of human hypertrophic scar fibroblasts through affecting collagen I and III, fibronectin expression and TGF- β 1/ α -SMA signaling.^[88] On the contrary, miR-200c overexpression could sensitize human breast cancer cells through escalation of apoptosis and DNA double-strand breaks. Another phenomenon is that overexpression of TBK1 can partially rescue apoptosis induced by miR200c. We predict that miR-200b could demonstrate similar effect on keloid tissue radiosensitization. Along by more and more microRNAs identified being related to keloid formation or cellular response to radiation therapy, these microRNAs will be candidates for therapeutic targets in radio-sensitization.^[89]

Similarity and distinction to cancer cell, and its response to radiation

Regarded as a benign tumor, keloids demonstrate some similarities of malignant tumors. Aberrant cell growth pattern, indefinite proliferation, increased proliferation rate and familial tendency enabled the application of radiation therapy in disposing this frustrating clinical problem. Compared to cancer cells, benign growth pattern of keloids do not exhibit the strong invasiveness and strong capacity of distant metastasis. And molecular mechanisms varied largely between keloid and malignant tumors. Specifically narrowing down to keloid fibroblast response to ionizing irradiation, multiple genetic interrelated pathways were identified from different resources, like whole-genome sequence or some inherited familial pattern discovered.^[90] Apoptotic and senescent cells were identified from X-ray irradiation keloid tissues based on extended G0/G1 phase and overexpression of p16, p21 and p27, which were all senescence-related genes.^[91] IL-6, as one of interleukins functioning in induced inflammations, was firstly identified based on bioinformatics analysis of post-irradiation keloid fibroblasts global gene expression,^[92] which seldom reports in other malignant tumors response towards irradiation. Further evidence supporting this hypothesis ensued. IL-6 was then reported playing a critical role in benign tumor-like stem cell similar to keloid derived precursor cells, suggesting inducing stem cell associated gene overexpression, then indirectly uncontrolled self-renewal and increased proliferation.^[93] The updating concept of keloid progenitor cells, exhibit clonogenicity, self-renewal, distinct embryonic and mesenchymal stem cell surface markers, and multipotent differentiation, indicating similar resistance derived from cancer stem cells.^[94] Furthermore, in contrast to cancer cells, keloid cells displayed enhanced apoptosis ratio in response to hypoxia, which was thought as the key initiator enabling radio-resistance through HIF-1 and VEGF dysregulation,^[95]

while cancer cells radiation therapy resistance is largely thought dependent on hypoxia.^[96-98]

CONCLUSION

We are still far away from generating a comprehensive understanding of the underlying mechanisms in radiation therapy for keloid. Lack of detailed fundamental studies also prevented us from uncovering the precise differences between radiation therapy treating keloids or cancer cells. However, relatively lower genome instability and lower growth rate possibly indicate that the direct effect might outweigh the indirect effect in killing keloid fibroblasts. Cellular response to irradiation also varies between keloids fibroblasts and cancer cells, ascribing to comparatively intact DNA repair system. Some genes which were thought to have the potential to drive keloid formation and differentially expressed prior or post irradiation should be regarded as therapeutic targets. Furthermore, updating study of pathogenesis of keloids including microRNA dysregulation and epigenetics might provide us with more potential in exploring the keloids cells' targets of radiation therapy.^[99] Currently, there are biological and antineoplastic agents that can potentially treat and prevent excessive scar formation.^[100] However, prevention is the best way to avoid the development of cosmetically unacceptable scars. Clinically, although numerous treatments exist, no single modality has been proven superior over others.^[101] Evidence in pediatric patients indicates that Asian patients have a three-fold increased rate of hypertrophic scarring relative to Caucasians.^[102] According to the guideline update on scar management for treating Asian patients, it is recommended that all Asian patients should initiate scar prevention following surgery.^[103] Figuring out the molecular mechanism of keloid could eventually help the clinicians to better treat their patients, especially among the Asian population. Understanding the molecular pathway in how to decrease profibrotic isoform could be crucial in accomplishing control of the fibrotic process underlying keloids. Comprehension of the molecular mechanisms could lead to the development of new promising therapies for keloids.

Authors' contributions

Conception and design of the study: X. Long
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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

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Original Article

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Anatomical features associated with venous congestion in DIEP flap using CT angiography with three-dimensional reconstruction

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ABSTRACT

Aim: Computed tomography angiography (CTA) using three-dimensional (3D) virtual reconstruction has been increasingly used in planning deep inferior epigastric artery perforator (DIEP) breast reconstruction. Although the most common complication associated with this surgery is diffuse venous congestion, its origin remains unclear. The aim of this study was to assess the anatomical characteristics of the anterior abdominal wall vessels that could predict venous congestion, using CTA with 3D virtual reconstruction. **Methods:** A retrospective case-control study was conducted and a total of 169 DIEP flaps were reviewed. An abdominal CTA with 3D virtual reconstruction was analyzed with regard to anatomical features of the abdominal wall vessels. Seven venous congestive cases were identified. For each case, 3 controls that had not exhibited any vascular complications were randomly selected. **Results:** The global venous congestion rate was 4.14%. No statistically significant differences were found between the groups' superficial inferior epigastric vein (SIEV) diameter ($P = 0.915$), number of branches of SIEV ($P = 0.371$), number of perforators per flap ($P = 0.255$), flap subcutaneous tissue thickness ($P = 0.652$), direct communications between SIEV-perforators ($P = 0.418$), and communications of both SIEVs across the abdominal midline ($P = 0.371$). **Conclusion:** The present study provided



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new information concerning the identification of the controversial anatomical features associated with venous congestion in DIEP flaps. CTA and 3D virtual reconstruction were useful tools for evaluating the abdominal wall anatomy and for planning DIEP breast surgery, but neither for predicting nor preventing the diffuse congestive phenomenon.

INTRODUCTION

Since the deep inferior epigastric artery perforator (DIEP) flap was used for the first time for breast reconstruction by Allen and Treece,^[1] it has been adopted as the gold standard for autologous breast reconstruction, overtaking other popular autologous methods such as the latissimus dorsi flap and the transverse rectus abdominis myocutaneous flap. The amount of available tissue, the low abdominal morbidity, the ability of replacing like-for-like, and the good aesthetic results, are the most notable advantages of this technique that have contributed to its widespread use.^[2] The success rate is high, with a flap loss rate under 3% according to the review by Lie *et al.*^[3] on more than 17,000 DIEP flaps.

The main arterial inflow is provided by the deep inferior epigastric artery (DIEA), while the main venous drainage is provided by the superficial inferior epigastric vein (SIEV). Although the arterial component of the flap has been widely documented,^[4,5] the venous system has not been as thoroughly studied. When a DIEP flap is dissected, a redirection of the venous outflow occurs from the dominant superficial system to the deep system. This redistribution could favor venous congestion in some of the flaps, leading to the most common vascular complication, the diffuse venous congestion of the DIEP flap, neither caused by pedicle-related issues (such as venous thrombosis or kinking) nor by technical errors (for example, deficient suture or avulsion of the pedicle).^[6,7] This phenomenon is observed in 2-10.9% of cases^[7-9] and it may cause partial or total flap loss if unsolved. In fact, up to 40% of total DIEP flap necrosis are associated with venous problems.^[3] Paradoxically, the mechanisms behind this complication remain unclear and have not been clarified yet.

Several strategies exist to overcome such complication of DIEP flap diffuse venous congestion.^[10-12] However, the origin remains to be elucidated. Some triggering factors have been proposed: diameter of the SIEV larger than 1.5 mm,^[6,13] absence of communications of both SIEVs crossing the abdominal midline,^[6,13] absence of direct communications by perforators between the SIEV and the deep inferior epigastric vein (DIEV),^[6] number of perforators of the flap,^[5] and subcutaneous tissue thickness.^[14] Nevertheless, scarce evidence has been reported to date as only one study was able to refuse the correlation with the

diameter of the SIEV,^[8] and another one indicated a higher chance of congestion in DIEP flaps based on just one perforator without direct communication with the SIEV.^[7]

The routine use of preoperative imaging to assess the microvascular anatomy of the anterior abdominal wall helps to achieve optimal outcomes.^[15] Preoperative planning of DIEP flaps with computed tomographic angiography (CTA) followed by three-dimensional (3D) reconstruction has proved to be an effective technique to map the abdominal vascular anatomy, allowing a better tracking of the perforators, including their size, location and course, so as to shorten the operative time and number of complications.^[16,17] On the other hand, little is known about the anatomical features related with the postoperative diffuse venous congestion and how new imaging technologies are able to identify aspects that can threaten the perfusion of the DIEP flap.

This study aimed to evaluate the anatomical features that could preoperatively predict the potential venous congestion of DIEP flaps, using 3D virtual reconstructions from CTA.

METHODS

This retrospective case-control study included 210 consecutive DIEP breast reconstructions in which a CTA was performed prior to surgery. These flaps were carried out consecutively by the same surgeon (D. Sicilia-Castro) in the Department of Plastic and Reconstructive Surgery of the Virgen del Rocío University Hospital in Seville, Spain, between January 2004 and January 2016. All patients were prophylactically administered low molecular weight heparin every 24 h postoperatively, in a dose of 40 mg of enoxaparin, and flaps were assessed clinically and with a hand-held Doppler probe hourly during the first 48 h, and every 2 h during the next 48 h. All patients signed informed consent to be included in the study.

Cases were defined as DIEP flaps preoperatively planned with CTA and 3D virtual reconstruction, which exhibited diffuse venous congestion intraoperatively after ligating the SIEV, not due to pedicle-related issues (venous thrombosis, twisting or kinking) or to technical failures (deficient suture or venous avulsion during manipulation). Controls were defined as DIEP flaps preoperatively planned with CTA and 3D virtual

reconstruction, that did not exhibit previous nor other vascular complication, such as arteriovenous thrombosis or necrosis.

Thirty-seven reconstructions were excluded as the preoperative perforator mapping was performed with a hand-held Doppler probe. Four flaps that had exhibited vascular complications different to diffuse venous congestion (2 cases of intraoperative partial venous congestion related to abdominal midline scars, 1 case of intraoperative venous thrombosis, and 1 case of late venous thrombosis 6 days following the surgery) were discarded as well. The final sample group included data from 169 DIEP flaps. According to the inclusion criteria, 7 cases were identified as diffuse congestive flaps [Figure 1]. Due to the limited number of cases, 3 controls per case (21 controls) were selected by computer randomization, in an attempt to control the power of the study and to avoid selection bias.

Imaging procedures

The studies of CTA were carried out by a 16-detector-row computed tomography scanner (General Electric Light-Speed 16; General Electric Company, Fairfield, Conn.). The parameters followed by the CT scans were: 0.37 s rotational speed of the gantry, 0.63 mm collimator width slice thickness, and 1.37 helical detector pitch. The voltage of the X-ray tube was 120 kV and tube current was 250 to 300 mA. Prior to scanning, all patients received an intravenous administration of 100 mL of nonionic iodinated contrast medium at a concentration of 350 mg/mL (Omnipaque 350; GE Healthcare, Barcelona, Spain) into an antecubital vein.

Sections of 0.63 in width were obtained at an 0.5-mm interval from 4 cm above the umbilicus to the minor trochanter of the hip. The resulting set of images was automatically transferred to a computer workstation, which generated multiplanar reformatted images and 3D volume-rendered images. Data were stored as

a Digital Imaging and Communications in Medicine (DICOM) compatible file on a CD-ROM to be uploaded to a personal computer with the AYRA® software (formerly known as VirSSPA®; Andalusian Health Department, Seville, Spain). The 3D reconstructions of the abdominal wall were generated using the DICOM files by means of the virtual reality AYRA® software. All the variables were assessed in these 3D virtual models.

Evaluation of the images

The preoperative 3D reconstruction of each case was retrieved by the same observer (A. Ruiz-Moya). The following anatomical variables were retrospectively analyzed in both groups: the existence of direct communications between the SIEV and the perforators of the flap [Figure 2], the existence of communications of both SIEVs across the abdominal midline [Figure 3], the 8-cm-diameter SIEV caudal to the most superior aspect of the iliac crests [Figure 4], the number of branches of the SIEV, the number of perforators included in each flap [Figure 5], and the flap subcutaneous tissue thickness at a point located

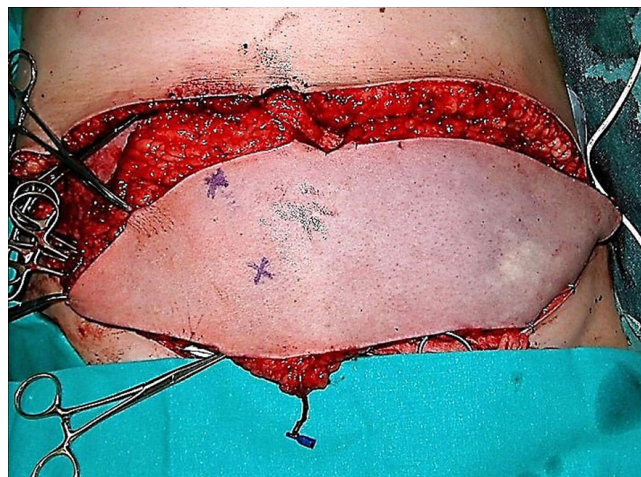


Figure 1: Deep inferior epigastric artery perforator flap exhibiting diffuse venous congestion

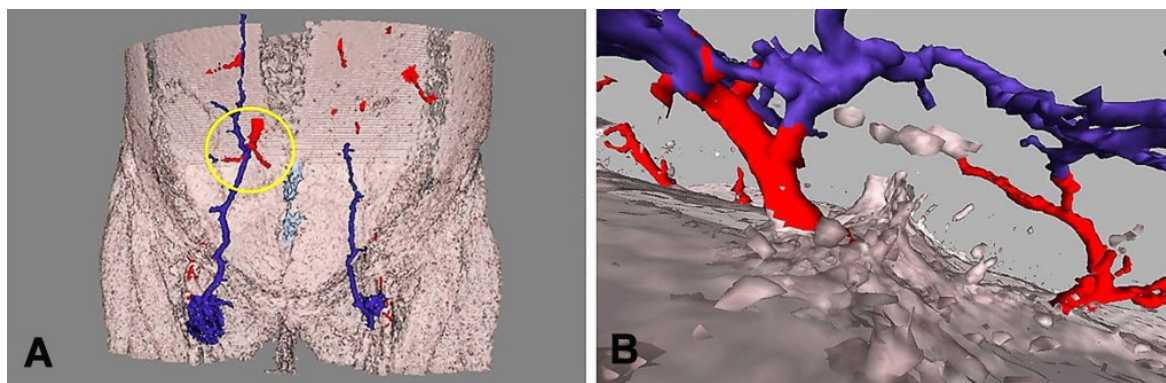


Figure 2: Three-dimensional abdominal wall reconstruction with AYRA software from computed tomography angiography images. (A) Point of assessment (circle) of direct communications between perforators (red) and superficial venous system (blue); (B) direct communications viewed from the abdominal wall

at the level of the most superior aspect of the iliac crests and at the midpoint of the rectus abdominis muscle width [Figure 6].

Statistical analysis

According to the small sample size, the quantitative variables were evaluated with the *U*-Mann-Whitney non-parametric test, and the qualitative variables with the Fisher exact test. For the statistical analysis, the IBM SPSS Statistics 19 package® (SPSS Inc. Chicago, IL) was used, considering significant differences when $P < 0.05$.

RESULTS

The global venous congestion rate was 4.14% (7 flaps). The mean age of case and control subjects was 50.1 years (range 38-58 years) and 49.1 years (range 35-64 years), respectively.

In the case group, direct communications between the DIEA and the SIEV through perforators were found in 57.14% of flaps (4 cases), direct communications

of both SIEVs across the abdominal midline were found in 42.86% of flaps (3 cases), with a mean diameter of the SIEV of 3.04 mm (± 0.60 mm), a mean of 1.43 branches per SIEV, a mean of 1.86 (± 0.69) perforators nourishing each flap, and with an average flap subcutaneous tissue thickness of 3.56 cm (± 0.90 cm) [Table 1]. In every congestive flap, an additional venous anastomosis was performed, either to the second concomitant vein of the DIEA (5 cases) or to the cephalic vein (2 cases). After this salvage procedure, all of the 7 flaps overcame congestion and survived without necrosis. In the control group, direct communications between the DIEA and the SIEV through perforators were found in 38.10% of flaps (8 controls), direct communications of both SIEVs across the abdominal midline were found in 23.81% of flaps (5 controls), with a mean diameter of the SIEV of 3.08 mm (± 1.20 mm), a mean of 1.24 branches per SIEV, a mean of 2.24 (± 0.77) perforators nourishing each flap, and with a mean flap subcutaneous tissue thickness of 3.72 cm (± 0.83 cm) [Table 2]. No statistically significant differences were found between the two groups for any of the variables ($P > 0.05$) [Table 3].

DISCUSSION

The present study was not able to confirm any of the studied anatomical variables as predictive factors of venous congestion, despite being suggested in the literature.^[5,6,13,14] The abdominal superficial venous dominance is one of the most extended and accepted (but not proved) hypothesis for explaining the diffuse congestion as a large diameter SIEV may denote dominance over the deep venous system.^[6] Blondeel *et al.*^[13] suggested that when this diameter is > 1.5 mm, the SIEV should be preserved for venous supercharging in case of congestion. However, in a study with CT angiography, Sadik *et al.*^[8] did not find a correlation between the SIEV diameter and the venous dominance of the flap, concluding that the SIEV

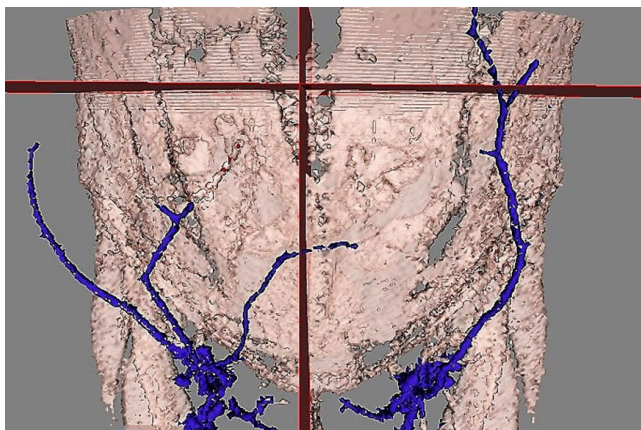


Figure 3: Three-dimensional abdominal wall reconstruction with AYRA software from computed tomography angiography images showing direct venous communication of the superficial inferior epigastric vein across the abdominal midline

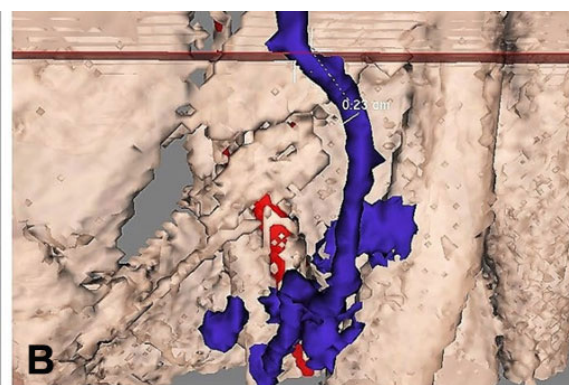
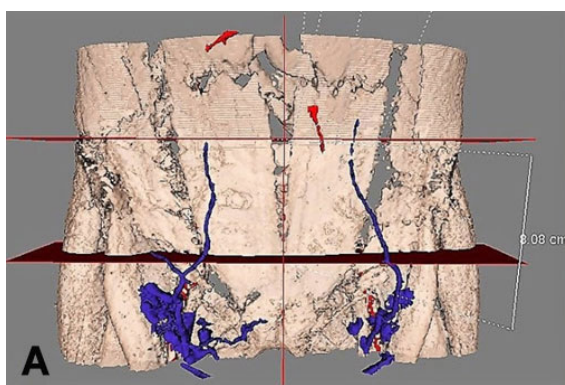


Figure 4: Three-dimensional abdominal wall reconstruction with AYRA software from computed tomography angiography images. (A) Horizontal plane 8 cm inferior to the horizontal plane connecting the iliac crests, marking level of measurement of the SIEV diameter; (B) measurement of the SIEV diameter. SIEV: superficial inferior epigastric vein

Table 1: Variables studied in case group

Case No.	Communication SIEV DIEA	Communication SIEV	Diameter of SIEV (mm)	Branches of SIEV	Perforators	Subcutaneous thickness (cm)	Age (years)
1	No	No	2.7	2	3	2.38	51
2	Yes	Yes	3.6	2	2	3.19	48
3	Yes	Yes	2.4	1	2	2.91	49
4	No	No	2.9	1	2	4.49	38
5	Yes	No	3.9	1	2	2.98	54
6	Yes	Yes	3.5	2	1	4.35	53
7	No	No	2.3	1	1	4.64	58

SIEV: superficial inferior epigastric vein; DIEA: deep inferior epigastric artery

Table 2: Variables studied in control group

Case No.	Communication SIEV DIEA	Communication SIEV	Diameter of SIEV (mm)	Branches of SIEV	Perforators	Subcutaneous thickness (cm)	Age (years)
1	Yes	No	3.4	1	3	3.98	58
2	No	No	3.0	1	3	2.72	54
3	No	No	3.7	2	2	5.00	39
4	Yes	No	2.7	1	2	4.14	57
5	No	No	4.5	1	3	4.66	41
6	No	No	1.7	1	2	3.70	64
7	Yes	No	2.6	1	3	2.69	51
8	No	No	3.1	1	2	4.50	35
9	No	No	2.1	1	3	3.27	40
10	No	Yes	2.4	2	2	3.50	50
11	Yes	Yes	3.5	1	2	3.70	51
12	Yes	No	3.6	2	2	4.42	47
13	No	No	3.1	1	2	3.70	57
14	Yes	No	3.3	2	1	4.27	50
15	No	No	2.7	1	4	2.20	60
16	Yes	Yes	3.9	1	2	3.57	37
17	No	No	5.2	1	2	3.40	52
18	No	No	2.1	1	1	5.49	36
19	Yes	Yes	6.2	1	2	2.99	59
20	No	Yes	3.0	2	1	3.57	50
21	No	No	2.5	1	3	2.64	44

SIEV: superficial inferior epigastric vein; DIEA: deep inferior epigastric artery

Table 3: Statistical analysis of variables between groups

Variables	Cases (n = 7)	Controls (n = 21)	Significance (P)	Difference and 95% CI
Diameter of SIEV (mm), mean \pm SE	3.04 \pm 0.63	3.08 \pm 1.22	0.915	-0.04 (-1.04, 0.95)
Branches of SIEV (2 branches), n (%)	3 (42.86)	5 (23.81)	0.371	19.05 (21.90, 60.00)
Perforators per flap, mean \pm SE	1.86 \pm 0.69	2.24 \pm 0.77	0.255	-0.38 (-1.05, 0.29)
Subcutaneous thickness (cm), mean \pm SE	3.56 \pm 0.90	3.72 \pm 0.83	0.652	-0.16 (-0.92, -0.60)
Communication SIEV-perforators, n (%)	4 (57.14)	8 (38.10)	0.418	19.05 (-23.10, 61.20)
Communication SIEVs midline, n (%)	3 (42.86)	5 (23.81)	0.371	19.05 (-21.90, 60.00)

SIEV: superficial inferior epigastric vein; CI: confidence interval; SE: standard error

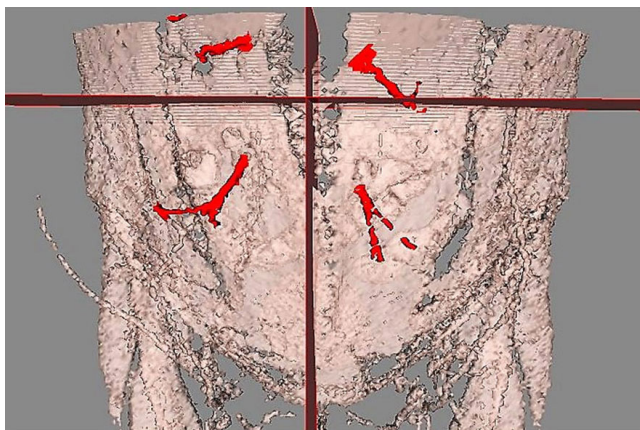


Figure 5: Three-dimensional abdominal wall reconstruction with AYRA software from computed tomography angiography images showing abdominal wall perforators

diameter was not useful for predicting congestion. This finding is consistent with the present study, as no statistically significant evidence ($P = 0.91$) was found when evaluating the SIEV diameter.

Another proposed feature in studies by Schaverien *et al.*,^[4] Rozen *et al.*,^[6] and Blondeel *et al.*^[13] was the absence of direct venous communications of both SIEVs across the abdominal midline, that could favor congestion further this line. This hypothesis was not consistent with the results of our study, as no statistically significant evidence ($P = 0.37$) was found for this variable, being these communications more numerous in the case group than in the control group (48.86% vs. 23.81%).

Taking into account the redirection of the venous

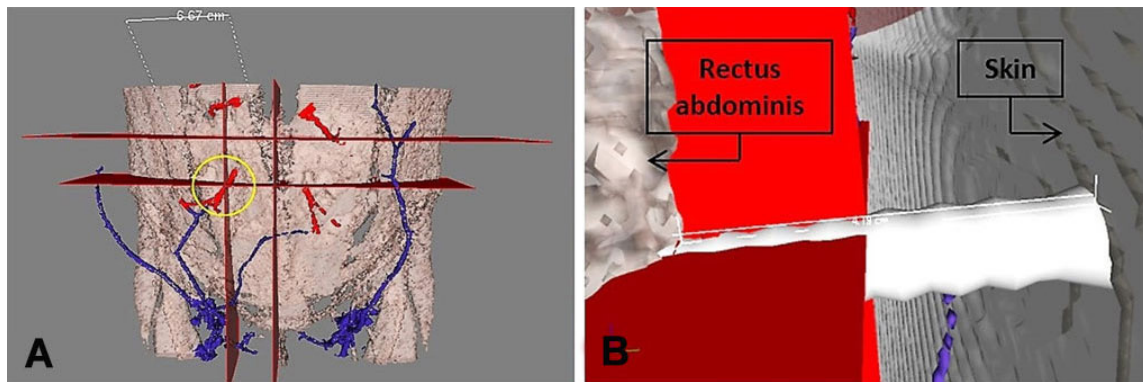


Figure 6: Three-dimensional abdominal wall reconstruction with AYRA software from computed tomography angiography images. (A) Point of measurement (circle) of flap subcutaneous tissue thickness, at the level of the iliac crests horizontally and at the midpoint of rectus abdominis width vertically; (B) measurement of flap subcutaneous tissue thickness

outflow from the superficial towards the deep system, several studies^[6,7,11] have suggested that the absence of direct communications between the SIEV and the DIEV through venous perforators could favor congestion. However, statistically significant evidence was only reported by Schaverien *et al.*^[7] using magnetic angioresonance, and only when a DIEP flap was dissected based on just one perforator without direct SIEV-DIEV communication. In fact, a larger proportion of these communications was found in the case group than in the control group (57.14% vs. 38.10%) in the present study, although statistically not significant ($P = 0.42$).

The number of perforators per flap is another controversial topic. Previous research has revealed that one medial row periumbilical perforator of appropriate caliber provides the best perfusion to the DIEP flap including Hartrampf's zone IV.^[4,5] Nevertheless, from the point of view of venous perfusion, DIEP flaps sometimes exhibit a diminished drainage with an increased venous pressure. Douglas *et al.*^[5] suggested that just one arterial perforator could provide the optimal perfusion, stating that with two arterial perforators the filling pressure could drop, decreasing the gradient and favoring congestion. For their part, Mohan *et al.*^[18] found a non-significant four-fold congestion rate in DIEP flaps based on a single perforator compared to those based on multiple perforators. In the present study, no statistically significant evidence was found for the number of perforators per flap ($P = 0.25$).

The flap subcutaneous tissue thickness was another anatomical feature analyzed. Rubino *et al.*^[19] demonstrated that bigger flaps intrinsically develop greater flow rates, and consequently, demand a higher drainage. Bast *et al.*^[14] found a correlation between the suprascapular fat pad thickness and the SIEV caliber, suggesting that thicker pads may

show superficial drainage dominance. However, no evidence was reported supporting this hypothesis. Statistically significant evidence was neither found in the present study.

The number of branches of the SIEV was the last anatomical feature evaluated, with a mean of 1.43 for the case group and 1.24 for the control group. Unfortunately, no statistically significant evidence was found.

DIEP breast autologous reconstruction is recognized as a reliable procedure with excellent outcomes and low donor site morbidity.^[3] Whereas success rates of over 95% have generally been reported, some flaps exhibit vascular complications and eventually fail.^[3] The major complication that may arise is the diffuse venous congestion due to drainage insufficiency,^[6,7] neither originated by venous thrombosis nor by technical failures. Finding predictive factors of congestion preoperatively would be extremely helpful for the surgeon. Using duplex ultrasonography, Figus *et al.*^[20] reported that the identification of the dominant venous perforator of the flap entailed high possibilities of finding an arterial perforator of adequate caliber (93.5%), higher than the possibilities of finding a venous perforator of good caliber after the identification of the dominant arterial perforator (69.8%). Gravvanis *et al.*^[21] compared two subgroups of breast reconstructions regarding vascular dissection: dominant arterial perforator-dissected versus dominant venous perforator-dissected DIEPs. A significant higher rate of venous congestion was found in the arterial perforator group. Laporta *et al.*^[22] and Santanelli *et al.*^[23] selected the type of perforators and their number for each flap depending on the diameter of the vein, and found that medial row perforators were a negative predictor for flap complications.

As previously stated, CTA is the gold standard

technique for planning DIEP flap surgery. To our knowledge, the present study is the first to attempt to link the morphological characteristics of the abdominal wall vessels with DIEP venous congestion by CTA and 3D virtual reconstruction. Unfortunately, according to the results obtained, this method has not demonstrated clinical utility to predict venous congestion. We hypothesize that further than a single anatomical feature, a multifactorial origin leads to venous congestion. During the dissection of a DIEP flap, physiological adaptive changes can take place. The diversion of flow through different pathways or vasodilatation are among them.^[15] Therefore, the pressure gradient between arterial perfusion and venous drainage is modified, resulting in an imbalance that may lead to venous congestion.

When a DIEP flap becomes congested, the main effective strategy for enhancing drainage outflow is the pressure relief by venous supercharging of the SIEV, whereas supercharging the second DIEV is less commonly performed.^[24,25] This salvage procedure decreases venous pressure, increases pressure gradient and overcomes the venous congestion. Adding large caliber venous anastomosis in parallel decrease the risk of venous congestion, because of the ability to provide a superior drainage. One of the most popular modalities of venous supercharging is the anastomosis of the superficial epigastric vein to the cephalic vein. Other common strategies include the anastomosis of the SIEV to a second internal mammary vein, to an internal mammary perforator, or end-to-side to one of the DIEVs of the flap.^[10,25,26] Less popular options include the anastomosis of the SIEV to the thoracoacromial vein, to the contralateral intermammary vein (which may need a vein graft), or to the toracodorsal vein (which may prevent the use of a latissimus dorsi as a rescue surgery in case the DIEP flap fails), among others. Notwithstanding, carrying out a second venous anastomosis is time-consuming, which represents the main drawback of this procedure, taking between 30 to 90 min.^[26] The experience of the surgeon and the use of coupler devices may help to reduce this lapse of time. There is another potential drawback, specifically associated with the use of the cephalic vein, which is the possibility of triggering lymphedema in the upper extremity due to the impairment of the lymphatic drainage. Women who have received radiotherapy seem to be more likely to develop this phenomenon. However, the overall risk appears to be reasonably low, being able to consider the harvest of the cephalic vein a safe option.^[25]

The systematic venous supercharging has been advocated to prevent the potential drainage

insufficiency, after significant results experiencing less congestion.^[26] However, a recent meta-analysis has failed to demonstrate the efficacy of the SIEV supercharging to reduce the flap-related complication rate.^[9] Whereas venous supercharging has proved its capacity to rescue DIEP flaps that exhibit congestion and would eventually experience partial or total necrosis, the debate still continues about the convenience of supercharging every flap as a preventive strategy for minimizing perfusion-related complications.^[9]

The present study has some limitations that should be considered. The low incidence of this phenomenon hinders prospective randomized controlled or prospective nonrandomized trials. Although the sample size is relatively small, this is one of the largest series specifically focused on congestive DIEP flaps reported to date. Further studies are needed to clarify the congestive phenomenon. Pressure gradient is of paramount importance, and its assessment along the flap could shed light on the subject. Larger sample sizes may also led to statistically significant differences when evaluating anatomical features.

In conclusion, this study provided new information to the literature concerning the identification of the anatomical features associated with venous congestion in DIEP flaps. No statistically significant differences were found between venous congestion of the flap and the suggested and accepted predisposing anatomical features. The congestive phenomenon is probably multifactorial, not being able to aim at any of them as the single cause. CTA was a useful tool for identifying the abdominal wall anatomy and planning DIEP breast surgery, but not for preventing the possible diffuse venous congestive phenomenon of this flap preoperatively.

DECLARATIONS

Authors' contributions

Concept design, manuscript preparation, data analysis and interpretation: A. Ruiz-Moya
Data analysis and interpretation: R.A. Lopez-Garcia
Case material's provide: D. Sicilia-Castro, T. Gomez-Cia
Manuscript preparation and review: P. Infante-Cossio

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients signed informed consent to be included in the study.

Ethics approval

The study was reviewed and approved by the Virgen del Rocio University Hospital Ethics Committee.

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Tips and tricks for getting more out of your delayed primary repair of ruptured flexor pollicis longus tendon

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Sir,

Primary tendon repairs are often difficult in patients with delayed presentation. Tendons are contracted and shortened with extensive scarring occurring along the path of the tendon. Pulleys and the wound bed can be filled with granulation tissue which obstructs the passage of the tendon. Many of such patients would then be treated with a two stage tendon reconstruction, which involves the insertion of a silicone rod for pseudosheath formation^[1] before tendon grafting at a second stage. This however, would set the patient back for roughly six months, especially involving multiple visits to physiotherapy and being off work. We would like to describe several tips and tricks in our armamentarium and illustrate these using a case we recently encountered [Figure 1].

A 40-year-old mechanic presented with a 5-week-old rupture of the flexor pollicis longus (FPL) at the interphalangeal joint (IPJ) of the left thumb. A plan for a two-stage reconstruction of the tendon was discussed with him and was scheduled for a silicone rod insertion. Bruner incisions to zone 3 were made and the distal end of FPL was seen but the proximal

end had retracted to the wrist.

Our tips and tricks used were as follows:

1. Use of a size 6 feeding catheter attached to a saline-filled syringe for hydrodissection of the path. Palpation of the catheter through the skin can be performed to allow localisation of path.
2. Adequate debridement of granulation and scar tissue was performed along the path of the tendon, especially under the pulleys of the thumb. Pulleys were also stretched using a fine tooth artery clip for several seconds, which avoided any venting.
3. The FPL tendon found at the wrist level was delivered through a wrist incision and stretched under tension for 2 min using an artery clip. Le Viet's releasing incisions can be performed at the tendon-muscle belly junction for added length if required.^[2]
4. When attaching the FPL tendon to the feeding catheter, a gap is left when suturing the two together. Careful retraction of the feeding catheter with the tendon is then performed.
5. A combination of a two strand modified Kessler core suture and a mattress suture was used with a 3/0



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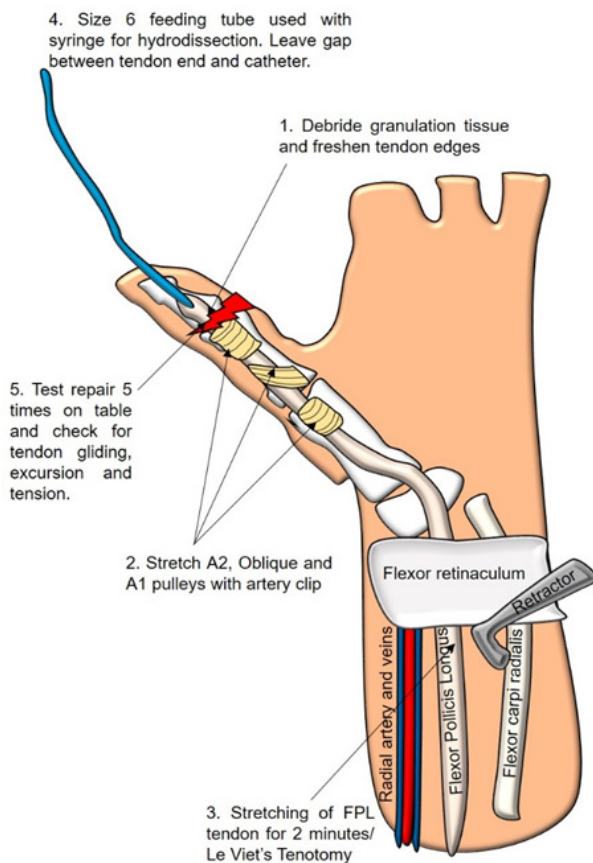


Figure 1: Schematic diagram illustrating the tips and tricks used for getting more out of a primary FPL tendon repair. FPL: flexor pollicis longus

prolene suture. A running epitendinous repair with 4/0 prolene was performed.

We tested our repair on table by flexing and extending the thumb IPJ five times, and ensured tendon gliding and excursion was not compromised. The thumb was splinted with a dorsal blocking splint in slight IPJ flexion. If on table tendon rupture or inadequate tendon excursion and gliding occurs despite the techniques performed above, a two-stage tendon reconstruction is then indicated.

DECLARATIONS

Authors' contributions

Manuscript preparation: C.Y.Y. Loh, A. Tan

Manuscript review: M. Tare

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There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

Not required.

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Immediate iliac bone graft reconstruction of post ablative defect of benign mandibular pathology - a systematic review

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ABSTRACT

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Key words:

Benign pathology,
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bone graft,
iliac crest,
non-vascularized,
immediate reconstruction

Aim: Autogenous iliac crest bone graft is frequently used in immediate reconstruction of post ablation defect of benign mandibular pathologies. The aim of this study was to conduct a systematic literature review on the complication and failure rates with this technique and factors associated with failure. **Methods:** The initial literature search in PubMed and Cochrane databases identified 915 articles. **Result:** Of these, 7 were included in the final review. The majority of the studies were retrospective in nature. These articles encompassed 127 procedures with non-vascularized iliac crest bone graft; with complication rate of 13.3% and failure rate of 3.1%, most complications did not result in failure. All failures were due to infection with no main factor associated with failure. **Conclusion:** Use of non-vascularized iliac crest bone graft for immediate mandibular reconstruction appears to be associated with low complication and failure rates in carefully selected cases.



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INTRODUCTION

Mandibular defects resulting from tumor ablation often result in considerable challenges to the patient and the surgeon.^[1,2] On the part of the patient there is varying degree of functional, aesthetic and psycho-social challenges which may severely affect the quality of life of the patient. On the part of the surgeon the challenge is that of reconstruction to restore the normal anatomic form and function of the mandible.^[3,4] Various reconstructive options that have been documented in published literature include autograft, xenograft and alloplast.^[4-6] Newer options like genetically engineered bone and distraction osteogenesis are also getting more attention among surgeons as novel options for mandibular reconstruction.^[7-10]

Use of alloplast as bridging plates may have the advantage of ease of placement, maintenance of shape over time, lack of donor site morbidity, satisfactory aesthetic outcome in the immediate post operative period but the draw back is in the long term performance due to the risk of hardware rejection, fracture, plate extrusion and limitation in use of dental implants. A failure rate of 60-80% for alloplastic material has been documented in the literature.^[3]

Newer options like genetically engineered bone are still in the early stage of development, needs expensive equipment, expertise and are not widely available yet.^[9]

At present, autogenous graft (vascularized or non vascularized) remains the most popular means of reconstructing continuity mandibular defect having the best chance of take as they provide viable and immune compatible osteogenic cells.^[11,12]

The main aim of mandibular reconstruction following ablative surgery is the restoration of form and function usually achieved by autogenous bone grafts (ABG).^[13,14] Different sites of the body are available for harvesting the graft, however, the choice of a particular donor site depends on factors such as the type and extent of tissue defect, rehabilitation expectation of the patient, condition of the recipient bed, availability of necessary equipment and expertise of the surgeon.^[2,13-15] ABG options include vascularized and non vascularized grafts. The major limitation of non-vascularized bone graft (NVBG) lies in the fact that it is avascular making it susceptible to infection thereby increasing the chances of failure with increasing length of the defect. Also defective intra-oral soft tissue cover for the graft following tumor ablation exposes the NVBG to the risk of failure from saliva microbial contamination and subsequent infection. Vascularized bone graft

(VBG) overcomes these shortcomings by virtue of its inherent own vascularity and can also be harvested with soft tissue for cover and lining in situations where there is defective soft tissue at the recipient site. This explains the increased popularity of vascularized bone graft which is fast becoming the standard of care in reconstruction of mandibular continuity defect among many surgeons in developed nations. However it also has a number of disadvantages like longer length of surgery, expensive equipment and expertise.^[2,13-15]

NVBG still remains an attractive and viable option in mandibular reconstruction in many parts of the world especially in developing countries where there is no facility or expertise for microvascular anastomosis. This traditional technique for the reconstruction of the mandible is indicated mainly to bridge segmental defects of the mandible where adjuvant radiotherapy is not indicated after ablative surgery.^[16] Possible donor sites for NVBG include the calvarium, ilium, rib, scapula, clavicle and fibula.^[3,17] However the ilium remains the workhorse with most authors due to its relative advantages like ease of harvest, good osseous bulk, contour, favorable bio-mechanics and sufficient width for implant placement.^[17,18] Despite its relative advantages, varied complication/failure rate have been reported with non-vascularized iliac crest bone graft (NVICBG) while controversies remain about the ideal timing for the reconstruction.^[3,18,19] Immediate reconstruction is highly desirable and could potentially eliminate the shortcomings of delayed procedure such as functional and aesthetic limitation leading to reduced quality of life. Furthermore, the high failure rate previously cited^[20,21] with immediate NVICBG has been countered by other authors who opined that failure may be connected with inappropriate patient selection and sub-optimal method of treatment.^[22,23] The aim of this review was to conduct a systematic literature review on the complication and failure rates of use of NVICBG and factors associated with failure.

METHODS

Literature search

We searched the PubMed, Medline and Cochrane databases using the terms "mandibular reconstruction" AND "autogenous bone graft" to retrieve all relevant articles. The search was restricted to human studies published in English. In addition, the "related articles" options in PubMed Medline and manual search of bibliographies of identified articles were used to retrieve additional studies.

Criteria for eligibility

Studies were included if they reported on success/

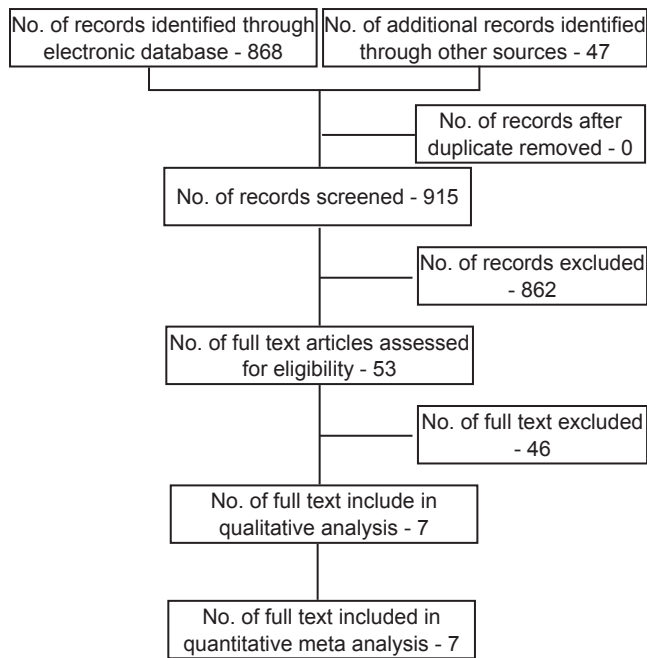


Figure 1: Flow chart

failure of immediate mandibular reconstruction of post ablative continuity defect of benign pathology using NVICBG.

Articles that referred to infants or patients treated with radiation, had a diagnosis of malignancy, were being grafted for reasons other than benign pathology and those that did not report a follow up of at least six months were excluded. Reviews and case reports of a single case were not included. The title and abstract of the identified articles were screened based on these criteria after which the full text of all eligible articles were retrieved for further analysis.

Extraction of data

A proforma was used to extract data from the eligible articles. Information extracted included primary author, year of publication, study type, age and number of patients, method of fixation, follow up, and documented complication and failure. Extent of defect was classified as segmental and hemi-mandibulectomy defect.

For this review, recipient site complication was counted as per patient irrespective of the number. Failure is defined as inability to control infection necessitating graft loss or removal. Whenever possible, factors associated with failure were identified.

Statistical analysis

Descriptive statistics was used for analysis. The characteristics of the included publications were summarized and presented in tables.

RESULTS

Initial electronic searches of MEDLINE and Cochrane retrieved 868 articles as potentially eligible, 47 publications were identified from other sources. After initial review of the titles and abstracts, 53 articles were accepted for further consideration, and 862 were rejected [Figure 1]. Of the 53 articles accepted for further consideration, 46 were excluded because they did not meet the inclusion criteria which left 7 full-text articles for further consideration and analysis. Of the 7 included articles reviewed, all were retrospective cohort studies except 2 which were prospective longitudinal studies.

A total of 127 patients treated with NVBG were included in this review. Gender characteristics were reported in all the articles with slight female preponderance (female 65/127, 51.2%; male 62/127, 48.8%). Age was reported as mean in all publications ranging 24.6-31.6 years. Table 1 shows the study characteristics of the publications. All the articles reviewed except one reported the histologic diagnosis of the lesions for which mandibular resection was carried out. Majority of the lesions were ameloblastoma - 80 (74.8%), followed by ossifying fibroma - 9 (8.4%) [Table 2]. Segmental mandibulectomy was done in 100 patients (78.7%) while the remaining 27 (21.3%) had hemi-mandibulectomy. Both intra and extra oral incisions were utilized in 100 patients (78.7%) with the remaining 27 (21.3%) receiving only intra oral incision. Reconstruction plate was the method of fixation in the majority 87/127 (68.5%) while stainless steel wire/intermaxillary fixation was used in the remaining 40/127 (31.5%). Autologous platelet rich plasma was used as graft enhancement in 32/127 patients. The follow up period was presented as means, of which the highest was 7 years and lowest was 6 months.

Recipient site complications such as infection, wound dehiscence, etc. were reported in 16/120 [Table 3] patients giving a complication rate of 13.3%. The case series did not clearly report complication in the 7 cases presented however none of the cases failed as at last review. Overall failure rate was 4/127 or 3.1%. Of the 4 cases that failed, 2 were reported by 1 publication while 1 each was reported by other 2. All failures were due to uncontrollable infection, 2 occurred in hemi-mandibulectomy defect while the remaining 2 occurred in segmental defect. One of the failed reconstruction had been enhanced with platelet rich plasma (PRP). Age, gender, type of incision and method of fixation did not appear to affect failure rate.

Only 22 patients (10 implants and 12 acrylic partial dentures) received prosthesis following reconstruction.

Table 1: Study characteristics of publications reviewed

Author/ year	Journal name	Type of study	No. of patient	M/F	Mean age (years)	Incision	Type of defect, segmental/ hemimandible	Method of fixation	Graft enhancement, yes/no	Mean follow-up (months)	Complication	Failure	Prosthesis
Obiechina <i>et al.</i> ^[25] /2003	<i>West Afr J Med</i>	Retrospective cohort	20	14/6	25.5	Intra oral/ extra oral	15/5	SS wire/ IMF	No	13 (2-25)	1	1	None
Shirani <i>et al.</i> ^[30] /2007	<i>J Craniofac Surg</i>	Retrospective case series	7	4/3	24.6	Intra oral	7/0	Recons plate	No	24.4 (7-60)	Not stated	0	None
Agrawal <i>et al.</i> ^[3] /2012	<i>J Oral Biology Craniofac Res</i>	Prospective	10	3/7	26.9	Intra oral/ extra oral	7/3	Recons plate	No	6 (0-6)	3	0	None
Simon <i>et al.</i> ^[29] /2013	<i>Int J Oral Maxillofac Surg</i>	Retrospective cohort	32	11/21	27.7	Intra oral/ extra oral	32/0	Recons plate	Yes (prp)	27.9 (6-84)	3	1	Acrylic PD/12
Olusanya <i>et al.</i> ^[19] /2014	<i>Nig Med J</i>	Prospective	20	8/12	31.6	Intra oral/ extra oral	11/9	SS wire/ IMF	No	24 (0-24)	4	0	None
Schlieve <i>et al.</i> ^[23] /2015	<i>J Oral Maxillofac Surg</i>	Retrospective cohort	20	11/9	28.3	Intra oral	20/0	Recons plate	No	22 (6-61)	2	0	Implant/10
Okoturo ^[28] /2016	<i>Oral Maxillofac Surg</i>	Retrospective cohort	18	11/7	29.4	Intra oral/ extra oral	8/10	Recons plate	No	13.5 (5-22)	3	2	None

Table 2: Histologic diagnoses per author

Histologic diagnosis	No. of cases per author	n (%)
Ameloblastoma	Simon <i>et al.</i> ^[29] - (32), Okoturo ^[28] - (10), Schlieve <i>et al.</i> ^[23] - (13), Shirani <i>et al.</i> ^[30] - (4), Obiechina <i>et al.</i> ^[25] - (13), Agrawal <i>et al.</i> ^[3] - (8)	80 (74.8)
Ossifying fibroma	Okoturo ^[28] - (4), Schlieve <i>et al.</i> ^[23] - (2), Obiechina <i>et al.</i> ^[25] - (3)	9 (8.4)
Odontogenic myxoma/fibromyxoma	Schlieve <i>et al.</i> ^[23] - (2), Okoturo ^[28] - (2), Obiechina <i>et al.</i> ^[25] - (2), Shirani <i>et al.</i> ^[30] - (1)	7 (6.5)
Odontogenic keratocyst	Shirani <i>et al.</i> ^[30] - (1), Agrawal <i>et al.</i> ^[3] - (1)	2 (1.9)
Ameloblastic fibroma	Obiechina <i>et al.</i> ^[25] - (2)	2 (1.9)
Cementoblastoma	Schlieve <i>et al.</i> ^[23] - (1)	1 (0.9)
Odontogenic cyst	Okoturo ^[28] - (1)	1 (0.9)
Central giant cell granuloma	Okoturo ^[28] - (1)	1 (0.9)
Spindle cell tumor	Shirani <i>et al.</i> ^[30] - (1)	1 (0.9)
Arteriovenous malformation	Schlieve <i>et al.</i> ^[23] - (1)	1 (0.9)
Osteoblastoma	Schlieve <i>et al.</i> ^[23] - (1)	1 (0.9)
Osteomyelitis	Agrawal <i>et al.</i> ^[3] - (1)	1 (0.9)
Total		107 (100)

Table 3: Types of recipient site complication

Type of complication	n (%)	Complication per author
Wound infection	10 (62.5)	Schlieve <i>et al.</i> ^[23] - (2), Obiechina <i>et al.</i> ^[25] - (1), Agrawal <i>et al.</i> ^[3] - (3), Simon <i>et al.</i> ^[29] - (2), Olusanya <i>et al.</i> ^[19] - (2)
Wound dehiscence	5 (31.3)	Okoturo ^[28] - (2), Agrawal <i>et al.</i> ^[3] - (1), Olusanya <i>et al.</i> ^[19] - (2)
Orocutaneous fistulation	1 (6.2)	Okoturo ^[28] - (1)
Total	16 (100)	

DISCUSSION

The present review provides the largest data yet on the outcome of NVICBG in immediate mandibular reconstruction. The review was limited to post ablative defect of benign mandibular pathologies to rule out inappropriate patient selection as a cause of failure.

Notwithstanding the retrospective nature of majority of the publications reviewed, strict inclusion and exclusion criteria used enabled us to identify only studies able to answer the research question. However, recall bias associated with retrospective reports have to be borne in mind although the authors made every effort to deduce the most appropriate information.

There is no consensus from this review on the definition of success as various authors used different criteria. Schlieve *et al.*^[23] defined success as provision of enough bulk to support implant placement. It should however be remembered that not all patients will prefer this additional treatment and definition of success should align with the aim of restoration which is to restore form and function.

Some authors believe that the method of immobilization has a big role to play in the success of the graft,^[23-25]

citing the risk of micro-movement in non rigid immobilization jeopardizing the viability of the graft,^[25] Although a number of the studies in this review employed rigid fixation of the graft with the use of plates and the authors claiming it as one of the main factors for graft success. Few of the studies due to non-affordability of plates by patients employed the use of stainless steel wires for immobilization with good outcomes even in long defect spans.^[26] However Olusanya *et al.*^[19] employing use of wires for immobilization reported progressive and significant deviation and resorption in the central region with alteration in the initial aesthetic contour obtained during a one year review period. This complication was absent in their patients that had reconstruction of lateral defect.^[19] On the contrary, Agrawal *et al.*^[3] and Futran *et al.*^[27] employing rigid plate fixation reported progressive improvement in aesthetics with no report of gross resorption noted. Okoturo^[28] did not employ NVIBG for central defect (defect spanning between 33 and 43 i.e. C classification), the only two graft failure were; one that had anterior component with the lateral component (excluding the condyle) (LC) and another one that had anterior component with hemi-mandibulectomy component (HC) claiming that non vascular grafts do not perform well in this region and should be reconstructed with a flap.

Compressive, tensile and torsional forces are present in the symphyseal part of the mandible which places significant stress on any construct placed in this region. These forces may exert excessive pressure on the graft which may lead to rapid resorption and even loss of the graft. Rigid reconstruction plate may help to shield the graft from these forces and may explain the progressive significant resorption noted in patients where wire was used for graft immobilization as against those with plate immobilization in the central mandibular region.

A number of authors favor extra oral approach during the procedure of reconstruction with non vascularized graft predicated their decision on avoidance of contamination of graft site with saliva leading to infection and high failure rate.

Majority of the authors in this review employed a combined intra and extra-oral approach.^[6,19,26,28,29] However, Schlieve *et al.*^[23] and Shirani *et al.*^[30] employed transoral approach with no record of graft loss among all their study population. Adequate (water tight, tension free) wound closure as well as method of fixation was cited as important factors that contributed to the success. They claimed that despite the potential risk of contamination of the graft

by saliva, grafts are still able to perform well and survive in contaminated environments if rigid fixation is achieved. The high failure rate encountered by earlier authors was largely blamed on contamination with saliva and subsequently led to the popularity of delayed reconstruction to allow for use of extra-oral route. This view is now being challenged by recent research and factors other than saliva contamination including research design of those earlier work are being suggested to be responsible for the high failure rate noted in earlier works.^[23] Other works in the literature have also reported good outcome of grafts in contaminated environment when good immobilization was ensured.^[29] This view is supported by the results in the present review in which majority of the procedures that initially presented with signs of infection eventually survived, with only few resulting in graft loss from the uncontrolled infection. It has also been argued that several intra-oral bone grafting procedures are carried out with saliva contamination and most times without water tight closure including bone grafting procedures in implantology and periodontology with low failure rates recorded.^[23] As opined by Schlieve *et al.*,^[23] bone grafting in the presence of contamination is possible and this brings to question the fear of oral contamination during grafting procedures.

Several published literature have reported significant association between length of defect and graft failure.^[24] Different authors have cited different lengths at which use of non vascularized bone is significantly associated with complication. Pogrel *et al.*^[14] cited a graft length of 9 cm, more recent work have cited even shorter lengths of between 5-6 cm suggesting that NVBG should only be employed in defect size less than this cut-off.^[25,31,32] In the present review, Agrawal *et al.*^[3] also noted significant association between length of defect and complication. They reported a mean defect length of 9.0 in those with complication compared with 7.0 in those without complication.^[3] On the contrary, another study in the present review found no significant association between defect size and complication.^[23] Although the defect size in their series ranged between 3-10 cm which is much outside the cut off of 5-6 cm suggested by earlier authors, no complication was associated with length of defect.^[23] Obiechina *et al.*^[26] also reported no significant association between graft length and graft failure. Part of their series involved grafting the hemi-mandible spanning the symphysis to the ramus, only one graft failure lost to infection was recorded although it was not stated whether it was one of the long span grafts.^[26] Some authors have suggested that intra-oral approach alone resulted in better outcome of grafting because there was less disruption of soft tissue/periosteal envelope as well as less disruption of

vascular supply to the host tissue from multiple incisions required for the combined approach.^[23,32]

PRP was used in one of the studies in this review and the authors claimed that it was one of the possible factors responsible for the high success rate obtained in their study.^[32] Previous studies have also claimed the enhancement of PRP on bone healing although animal studies have failed to demonstrate unequivocally the beneficial effect of PRP on bone healing.^[33-37] On the other hand, other studies in the review got comparable or even better result despite not utilizing PRP.^[23,26] Therefore it may be difficult to ascribe the outcome to any beneficial effect of PRP as claimed by the authors. A well-designed randomized control trial may be needed to clarify any possible effect of PRP on graft success.

Factors previously identified as determinant of outcome such as age, gender, histologic type, type of incision and method of fixation did not appear to be associated with failure or success of bone grafting in this review.

The complication rate and failure rate are low suggesting that in selected cases with appropriate surgical resection margins, NVICBG done as a primary procedure is an attractive option especially in resource scarce nations. It saves the patients the cost of a second surgery and as the ablation and graft harvesting can be done simultaneously, duration of procedure does not have to be extended. Immediate reconstruction also has the advantage of better chance of achieving the desired restoration of form and function following reconstruction. Maintenance of normal spatial relationship of soft and hard tissue is key in achieving the normal form and function following reconstruction.^[22] Fibrosis following healing of initial surgery could make any desired surgical alteration in tissue positioning at subsequent surgery quite difficult if not impossible once the tissues have been fixed in a less optimal position. Subsequent dental rehabilitation and aesthetic outcome may then be severely hampered.^[22] The four cases that failed were due to infection, perhaps good infection control practices may further improve outcome. Interestingly, two case of failure each occurred in segmental and hemi-mandibulectomy defect respectively. Much has been documented on the role of defect size on outcome but the present review does not support this. Of note also is the fact that use of platelet rich plasma did not appear to improve success rate. This is despite the many documentation supporting its use as a bone graft enhancement.

In conclusion, use of NVICBG for immediate mandibular reconstruction appears to be associated

with low complication and failure rates. Careful selection of patient, availability of adequate soft tissue cover, rigid fixation with the use of plates, tension free water tight soft tissue closure are factors that seem to contribute significantly to the success of grafting in use of NVICBG for mandibular reconstruction following ablative surgery for benign mandibular lesions.

DECLARATIONS

Authors' contributions

Concept and design, analysis and interpretation, writing and revision of manuscript and approved final draft: O.K. Ogundipe

Design, analysis and interpretation, writing and revision of manuscript and approved final draft: O.O. Gbolahan

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The authors declare that there are no conflicts of interest regarding the publication of this article.

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A novel skeletal anchorage for rigid external distractor

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ABSTRACT

Aim: Maxillofacial surgery has always aimed to find alternative therapies to treat severe maxillary hypoplasia. Distraction osteogenesis of the midface has become the technique with the best functional and aesthetic results. Nevertheless, anchoring a distractor to the middle third of the face continues to involve complex planning. Plus, achieving the desired force vector can sometimes be cumbersome and uncomfortable. The aim of this study is to propose a novel skeletal anchorage technique for the rigid external distractor. **Methods:** Non-controlled, prospective study of 9 patients with severe midface hypoplasia who were treated with distraction osteogenesis using a rigid external distractor anchored to the infraorbital rims and the bilateral pyriform apertures. The activation phase started the first postoperative day at a rate of 1 mm per day. The consolidation period lasted 6 to 8 weeks. **Results:** Eight patients achieved the desired distraction objective (24.5 mm on average), with only 1 suffering a 5-mm relapse. None of the patients reported complications. **Conclusion:** Distraction osteogenesis of the midface by skeletal anchorage is an alternative method when treating patients with severe maxillary hypoplasia. It has significant advantages compared to traditional anchoring because it simplifies the procedure, diminishes the costs and complications.

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INTRODUCTION

Solving cases of severe maxillary hypoplasia has always been a challenge for oral and maxillofacial surgeons.^[1,2] Molina and Ortiz-Monasterio^[3] proposed a gradual advancement of the maxilla using a facemask for elastic orthodontic traction or distraction. However, an adequate maxillary advancement in cases of severe hypoplasia was not achieved. Besides, the forces applied could not be controlled and ulcers in the chin and forehead were created.^[4] Polley and Figueroa^[1,5] also used elastic distraction with facemask and had similar findings, reporting insufficient maxillary advancement (4 to 6 mm on average) with under-corrected residual inverted anterior bite.

In 1997, some authors proposed the use of the rigid external distraction device I (RED I)^[4-6] in order to overcome these shortcomings. The device was anchored to the skull and the denture in order to distract facial bones.^[7] The use of the RED I became an excellent treatment strategy, because it allowed precise and controlled distraction osteogenesis of the maxilla.^[8,9] Additionally, results were stable and predictable.^[10] Later, the RED II was introduced to improve the vector control by means of an additional anchorage to the zygomatic bone plate. All of these attributes make the use of RED I and II an excellent treatment alternative for patients with severe maxillary hypoplasia.

RED I and II use a custom-made intraoral orthodontic splint^[11] anchored to the first permanent molars or second temporary molars to generate the maxilla pulling force. The splint is made using cast models and 0.050 or 0.045 mm stainless steel wires. A wire emerges from the splint up to the height of the nostril floor, which generally coincides with the maxilla's centre of rotation.

Despite the many advantages offered by the RED I and II, both devices have some disadvantages. The need for teeth to anchor the device is one of them.^[11] Dental anchoring results in patient discomfort and interferes with the normal functions of the oral cavity, i.e. eating, speaking and performing proper oral hygiene.^[12] On the other hand, teeth act as an intermediary between the RED and the bone to be distracted, impeding direct force to be applied to the bone.^[11]

The aim of this article is to propose an alternative to the dental anchorage used when distracting with RED I and II. We suggest the use of a skeletal anchorage with a gauge of 0.4 or 0.5 mm of stainless steel wire, that we called skeletal anchorage for the rigid external device (SARED).

METHODS

The study was a non-controlled, prospective study involving 9 patients, 3 female and 6 male (9 to 24 years old; mean age 17.5 ± 5.4 years), selected from the Department of Oral and Maxillofacial Surgery at Hospital del Salvador between April 2007 and January 2015. Inclusion criteria were patients diagnosed with severe midface hypoplasia aged 5 years or older (to allow proper post distraction occlusal stability and an adequate teeth interdigitation shown in the hand-articulated models).

Preoperative assessment included clinical digital photography, articulated models and three-dimensional studies to plan a surgical treatment objective (STO).

Distraction osteogenesis of the midface was performed using SARED by means of the rigid external distraction device (RED, Cibeil Medical Treatment Appliance Co. Ltd., Ningbo, China). Depending on the STO a Le Fort I or III osteotomy was done. When a Le Fort III osteotomy ($n = 6$) was performed, the RED was anchored bilaterally with percutaneous wires to the infraorbital rims and the pyriform apertures (gauge of 0.4 or 0.5 mm of stainless steel wire). When a Le Fort I osteotomy ($n = 3$) was performed, the RED was anchored bilaterally with percutaneous wires to the pyriform apertures only. In both cases the use of plates or screws were unnecessary, as the percutaneous wire osteosynthesis was fixed directly to the bone.

All patients were operated on by one surgeon.

Surgical procedure

All surgeries were performed in an operating room, under general anaesthesia, using orotracheal intubation. Through a maxillary vestibular approach, a Le Fort I ($n = 3$) or III ($n = 6$) osteotomy was performed using a reciprocating or piezoelectric saw. In patients who underwent a Le Fort III osteotomy a transconjunctival approach was also utilised. A nasal septum osteotomy and pterygomaxillary disjunction were performed subsequently.

A cylindrical burr was used to perforate below the pyriform apertures. A 0.40-mm stainless steel wire was passed through the apertures to the floor of the nasal cavity. A 14-G cannula was used to move the wire percutaneously towards the skin along the nasolabial fold.

Patients who underwent a Le Fort III osteotomy also underwent upper skeletal anchorage. An aperture was opened with a cylindrical burr alongside the mid lateral

Table 1: Patient distribution according to age, gender, diagnosis, type of osteotomy, amount of distraction, relapse, and follow-up

Patients No.	Age (years)	Gender	Diagnosis	Overjet before surgery	Type of osteotomy	Days of activation (mm)	Overjet a year after distraction (mm)	Relapse (mm)	Follow-up (months)
1	9	M	Crouzon Sd	-20	Le Fort III	30	+3	0	15
2	15	F	Severe class III malocclusion	-16	Le Fort III	25	+2	0	55
3	17	M	Crouzon Sd	-13	Le Fort III	24	+3	0	24
4	25	M	Crouzon Sd	-16	Le Fort III	22	+3	0	36
5	9	M	CLP	-15	Le Fort III	25	-5	5	60
6	20	F	CLP	-12	Le Fort I	20	+2	0	30
7	18	M	Crouzon Sd	-25	Le Fort III	30	+2	0	36
8	21	F	CLP	-14	Le Fort I	25	+3	0	36
9	24	M	CLP	-12	Le Fort I	20	+2	0	30
Average	17.5			-15.8		24.5	1.6	0.55	35.7

CLP: cleft lip and palate; Sd: syndrome



Figure 1: Wires skeletally fixed to the infra orbital rim

area of the infraorbital rims over the anterior wall of the maxilla. Through this aperture a 0.40-mm stainless steel wire was passed through and returned through the osteotomy on the orbit's floors. A 14-G cannula was used as a guide to move the wires towards the skin, allowing a percutaneous exit [Figure 1].

A halo frame was fixed to the skull using three percutaneous screws on each side, secured to the scalp. The screws were parallel to Frankfort's horizontal plane.

The distraction vector was calculated according to the patients' needs. The latency period was one day. Active distraction started on the first postoperative day at a rate of 1.0 mm per day divided in 0.5 mm in the morning and 0.5 mm in the evening. In every case desired advancement was achieved without overcorrection. The distraction device was removed after a consolidation period of 6 to 8 weeks, followed by intermaxillary elastics to improve the occlusal relationship.

The RED was removed in an outpatient care room without the need for local anaesthetic. The skeletal anchor wires were cut and removed. The halo frame's



Figure 2: Wires emerging percutaneously. They are fixed to the infraorbital rim and the piriform aperture

pins were unscrewed and removed.

RESULTS

On average, a 24.0 ± 3.6 mm (range 20-30 mm) midface distraction was obtained. The overjet before surgery was on average -15.8 ± 4.2 mm, and a year after distraction was 1.6 ± 2.5 mm [Table 1]. None of the patients reported complications during the course of the treatment. There were incidents of the wires breaking, skin infection or bone fractures associated with the skeletal anchors.

The distraction objective was achieved in all but one patient, who suffered a relapse of 5 mm. The deformity was secondary to a cleft lip and palate, and the patient did not have ideal dental overjet or overbite in hand-articulated models before the treatment. The patient subsequently underwent a conventional Le Fort I osteotomy to achieve ideal results.

Patient follow-up lasted 35.7 months on average, ranging between 15 and 60 months. It is vital to highlight that follow-up continues [Figures 2-4].

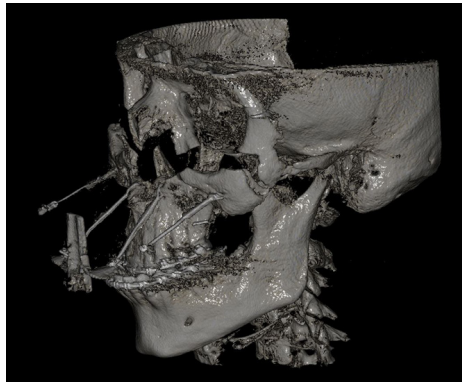


Figure 3: Cone beam computed tomography showing the wires anchored directly to the bone

DISCUSSION

Distraction osteogenesis was introduced in the craniofacial field in 1992 by McCarthy *et al.*^[13] to correct mandibular hypoplasia.^[14] The procedure has since been widely used in the field of craniofacial surgery, and is considered today as an alternative method to treating craniofacial dysplasia.^[5,15] Intra and extraoral distraction devices can be used. Extraoral devices are easier to handle, allow for more force to be applied and for greater advancement to be achieved. They also allow modification and better control of the distraction vector.^[6,15,16] When an extraoral device is used, further surgery is not needed to remove the distractor.^[6,17]

This study aimed to overcome some of these limitations by modifying the method by which facial bones are anchored to an extraoral distraction device, specifically RED II. Several authors^[1,5,10,11] describe one of the limitations being the need for teeth to be used as anchorage. Regardless of the dentition phase, they need to be in good and healthy condition. In the proposed technique, the pyriform apertures and infraorbital rims are used as anchorage points and teeth are only necessary to stabilize the distracted segments once they have achieved the desired occlusion.

Nevertheless, as Nishimoto *et al.*^[18] emphasised, the presence of teeth is ideal because it diminishes the chance of relapse, since occlusion holds skeletal bases in position. Furthermore, they state that when teeth are missing, consolidation time should be longer.

In the publication by Nout *et al.*^[10] an alternative is mentioned for distraction with RED without dental anchoring in a patient diagnosed with Pfeiffer's syndrome. They suggested using bilateral anchorage to the pyriform aperture only, fixed with screws. SARED does not require the use of osteosynthesis (plates nor screws) nor a custom-made intraoral orthodontic splint, reducing the cost of treatment and diminishing the risk of damage of dental follicles and roots.

Since teeth anchoring is unnecessary in SARED, the force can be applied directly to the bone. This in turn



Figure 4: Patient 4. (A) Frontal view before surgery. Crouzon syndrome patient with severe midface hypoplasia; (B) frontal view after surgery. Note the reduction in exophthalmos; (C) lateral view before surgery. Hypoplastic maxilla, exophthalmos due to shallow eye sockets, relative mandibular prognathism; (D) lateral view after surgery. Adequate advancement of the maxilla, reduced exophthalmos; (E) axial view before surgery. Note exophthalmos due to shallow eye sockets and the asymmetric nostrils; (F) axial view after surgery. The advancement of the maxilla with an adequate cheekbone and infraorbital rim projection; (G) occlusal view before surgery. Negative overjet showing the discrepancy between the maxilla and the mandible teeth; (H) occlusal view after surgery. Adequate occlusion achieved with midface distraction osteogenesis

means that the line of action of the force vector is direct as there is no intermediary device to reduce the force. As Figueroa and Polley^[5] discuss, the wire splint of RED I, which has an extraoral wire and traction hooks, has some flexibility, which allows the distraction wire force to accumulate and then be liberated gradually. In other words, once the screw is activated, the distraction effect is not immediate, but as the wire recovers its shape it becomes a continuous tension.^[3,11,19] We believe the mechanism described by the authors^[5] is not ideal because the wire undergoes elastic deformity that prevents the applied force from being transferred in its entirety to the bone being distracted.^[11,12]

SARED is more comfortable than the intraoral splint anchorage, because it does not interfere with the functions of the oral cavity. It allows uninterrupted eating because there is no device, wires or splints inside the mouth. Patients can, therefore, brush their teeth even when they have braces. In addition, patients with SARED can continue their orthodontic treatment during the whole distraction and consolidation period.

The percutaneous exits of the wires from the nasolabial folds do not compromise aesthetics because the scars are hidden in face wrinkles. Other authors have previously suggested the use of percutaneous wires emerging from the zygomatic bone to distract with RED II and have reported no major complications.^[18]

Finally, SARED does not require further surgery to be removed, as do osteosynthesis anchored devices.^[11] The halo and wires can be pulled out without local anaesthetic on an outpatient basis. The use of SARED simplifies a process that is highly complex itself and delivers better conditions for the patient and surgeon.

Using SARED is a convenient method to distract the midface. Advantages include better control of the distraction vector and force when compared to the use of a dental anchorage (RED I) or a dental anchorage with an osteosynthesis plate anchorage (RED II). SARED improves patient comfort levels, oral hygiene and overall oral health. The method proposed is simple, reduces costs and complications.

DECLARATIONS

Authors' contributions

Concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review: R. Fariña, F. Salinas

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None.

Conflicts of interest

The authors have no commercial or financial associations that might create a conflict of interest with the information presented in this manuscript.

Patient consent

All patients signed an informed consent letter before participating in the study.

Ethics approval

This study was approved by ethical board of Hospital del Salvador.

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The distribution of hair in Han Chinese

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Dr. Zhi-Qi Hu, MD, chairman of plastic surgery of Nanfang Hospital. He have engaged in plastic and cosmetic surgery for more than 20 years. His research interest is advanced basic and clinical facial paralysis, basic and clinical study of hair transplantation. He is experienced in clinical curing for AGA, scar after trauma, and congenital facial deformity. Now he is devoting himself to curing alopecia, including the medicine cure, and the surgical operation - follicle unit extraction (FUE). At present, his research of hair transplantation gets ahead in China and the research of hair follicle regeneration is in the domestic first-class and international advanced level.

ABSTRACT

Article history:

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Hair,
follicular units,
distribution

Aim: To explore the characteristics of normal hair distribution in Han Chinese. **Methods:** A total of 146 healthy Han Chinese and 41 patients with androgenetic alopecia (AGA) were selected as research subjects. Digital photographs of the vertex, temporal, and occipital regions were taken after their hair was trimmed. An image analysis software was used to compute the number of follicular units (FUs) and hairs. **Results:** The mean FU density of the 146 healthy Han Chinese was 74.36 ± 13.33 units/cm² and their mean hair density was 143.33 ± 28.08 hairs/cm². There was no significant difference between males and females ($P > 0.05$). The mean FU density in the occipital region of AGA patients was 77.78 ± 2.99 units/cm² and their mean hair count was 148.12 ± 6.98 hairs/cm². Both were lower than those of healthy Han Chinese, and the differences were statistically significant ($P < 0.001$). Two-hair FUs (52.62%) were the predominant type found in Han Chinese. **Conclusion:** The FU and hair densities of healthy Han Chinese are lower than those of whites and Africans. The study provides hair transplantation surgeons with information on hair distribution in Han Chinese. It also provides a quantitative basis for the area of donor site and transplantation density necessary for hair transplantation surgeries. The research findings provide some theoretical data for the hair distribution characteristics of Han Chinese. These data can contribute to the preoperative assessment, surgery planning, and postoperative outcome evaluation by hair transplantation surgeons.



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INTRODUCTION

Follicular unit transplantation (FUT) and follicular unit extraction (FUE) have become two preferred methods in hair transplantation surgery due to their aesthetic and natural postoperative appearance, and high survival rate. FUT and FUE achieve their cosmetic and modification effects by the redistribution of existing hair rather than by increasing the absolute number of hairs. Thus, no matter which surgery method to choose, patients will require detailed evaluation in multiple aspects, including the area of donor site to excise or extract^[1,2]. Western scholars have conducted detailed research on the hair distribution of whites and Africans^[3-5]. These studies have shown that the hair density of Asians is lower than that of whites and Africans. However, due to geographical and ethnic differences leading to disparities in hair distribution among Asians, it is necessary to investigate the hair distribution in Han Chinese. This paper aims to explore the normal hair distribution characteristics of Han Chinese, in order to facilitate clinical practice.

METHODS

Research subjects

A total of 146 healthy volunteers were Han Chinese residents aged 20-70 years. None had ever received hair coloring, perming, or other treatments. The volunteers and their relatives had no hair diseases, such as androgenetic alopecia, alopecia areata, or hirsutism. Another 41 patients with androgenetic alopecia (AGA) were selected for comparative analysis. All volunteers were informed of the objectives and specific methods of the study, and all gave informed consent.

Experimental method

The vertex region (the intersection between the preauricular line connecting the left and right ears, and the line connecting the glabella and external occipital protuberance), temporal region (2 cm above the preauricular line for both ears), and occipital region (centered on the external occipital protuberance) in the volunteers were selected as the observation sites. Close-up photographs were taken of 2.5 cm × 1.5 cm areas within the observation regions after the hair within the area was trimmed. Photoshop CS5 was used to read the images and count the number of follicular unit (FU) types (n_1 , n_2 , n_3 , n_4 , and n_5) comprising of 1, 2, 3, 4 and 5 hairs, respectively, within 1 cm² of the photographed region [Figure 1]. The following two formulas were used to calculate FU density and hair density: FU density (hairs/cm²) = $n_1 + n_2 + n_3 + n_4 + n_5$; Hair density (hairs/cm²) = $n_1 + 2 \times n_2 +$

$$3 \times n_3 + 4 \times n_4 + 5 \times n_5.$$

As the vertex and temporal regions of most AGA patients had no hair, these regions had no statistical meaning. Thus, the photography and statistical methods were only applied to the occipital region in this group [Figure 2]. The statistical data were processed in the same way as in the healthy group.

Statistical analysis

SPSS 13.0 software was used for statistical analysis of the data. The measurement data were expressed as mean ± standard deviation. Comparisons between two groups were performed using independent-samples *t*-tests. Comparisons among multiple groups, such as homogeneity of variance, were performed using one-way analysis of variance (ANOVA) and Bonferroni pairwise comparison. Welch's approximate

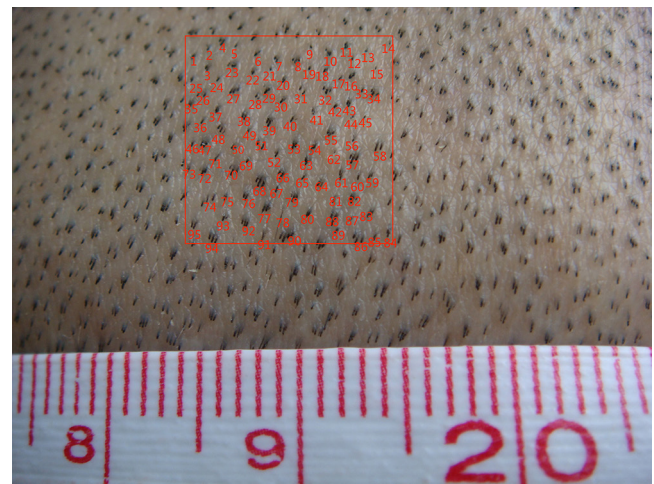


Figure 1: Area measured at 1 cm². The FU density in the occipital region of healthy patient was 95 units/cm². FU: follicular unit

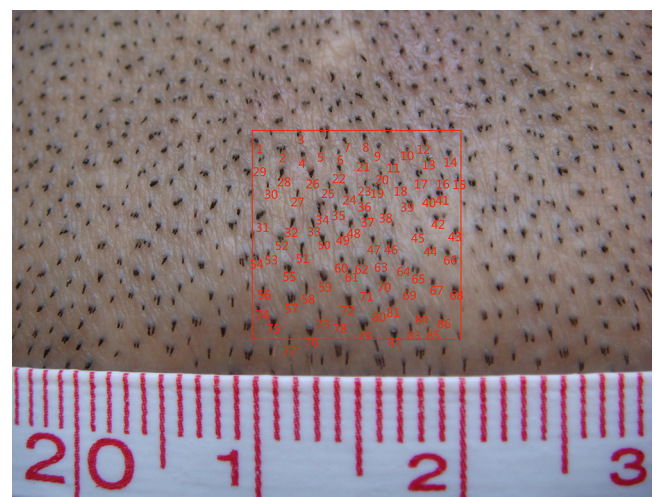


Figure 2: Area measured at 1 cm². The FU density in the occipital region of AGA patient was 86 units/cm². AGA: androgenetic alopecia; FU: follicular unit

ANOVA and Dunnett's T3 pairwise comparison were used for data with heterogeneity of variance. Correlation analysis was performed using Spearman correlation analysis. $P < 0.05$ indicated that a difference was statistically significant.

RESULTS

Demographic characteristics

The selected 146 healthy Han Chinese included 80 males and 66 females and had a mean age of 44.47 ± 14.53 years. The 41 alopecia patients included 36 males and 5 females, and had a mean age of 41.24 ± 10.71 years.

Comparisons of FU density and hair density in healthy Han Chinese

Results are shown in Table 1. The overall FU density of the population was 74.36 ± 13.33 units/cm² and hair density was 143.33 ± 28.08 hairs/cm². The differences between males and females ($P > 0.05$) were not statistically significant. FU density and hair density were high in the vertex and occipital regions but low in the temporal region. The difference was statistically significant ($P < 0.001$).

Comparisons of FU density and hair density in the occipital region of AGA patients

Results are shown in Table 2. The FU density was 77.78 ± 2.99 units/cm² and hair density was 148.12 ± 6.98 hairs/cm², which were lower than the values in the occipital region of healthy Han Chinese. The differences were statistically significant ($P < 0.001$).

Types of follicular units

Results are shown in Table 3. One-hair FUs accounted for 28.38%, 2-hair FUs accounted for 52.62%, 3-hair FUs accounted for 17.48%, 4-hair FUs accounted for 1.30%, and 5-hair FUs accounted for 0.21%. No FUs comprising 6 hairs and above were found in our sample.

Correlation analysis between FU density and age

To analyze the relationship between FU density at various sites and age, we conducted correlation analyses on the FU density at three sites according to age. The results are shown in Table 4. The FU density at the three sites exhibited negative correlations with age.

DISCUSSION

Headington found that hairs are not uniformly distributed singly, but instead grow as a unit of 1-5 hairs. Each unit has a relatively independent sebaceous gland, erector pili muscles, and perifollicular vascular plexus and nerve fibers, which form a FU^[6]. FUT and FUE has been two primary surgical methods for hair transplantation due to their high postoperative hair survival rate and natural postoperative appearance^[7]. However, patients detailed evaluation before hair transplantation surgery, including determination of the amount of donor site to excise or extract. Thus, the theoretical support of data on hair distribution density is needed. There are differences in hair among various races. Previous research has indicated that there are substantial differences in hair density among whites, blacks, and Asians^[5]. Thus, the populations of various races usually require different areas of donor sites.

Table 1: Distribution of follicular unit and hair counts in Han Chinese (mean \pm SD)

	Density of follicular units (units/cm ²)			Hair density (hairs/cm ²)		
	Total	Males (n = 80)	Females (n = 66)	Total	Males (n = 80)	Females (n = 66)
Vertex	83.32 ± 7.75	83.56 ± 7.88	$83.02 \pm 7.64^*$	160.95 ± 20.66	161.33 ± 21.00	$160.50 \pm 20.40^*$
Occipital	82.66 ± 4.12	83.05 ± 4.16	$82.20 \pm 4.05^*$	158.90 ± 13.41	160.15 ± 13.26	$157.39 \pm 13.54^*$
Temporal	57.10 ± 2.97	57.50 ± 2.88	$56.62 \pm 3.02^*$	110.14 ± 10.17	111.20 ± 9.57	$108.85 \pm 10.79^*$
Overall	74.36 ± 13.33	74.70 ± 13.33	$73.94 \pm 13.36^*$	143.33 ± 28.08	144.23 ± 27.96	$142.25 \pm 28.26^*$
P_1	0.751	0.940	0.828	0.680	0.965	0.828
P_2	0.000	0.000	0.000	0.000	0.000	0.000
P_3	0.000	0.000	0.000	0.000	0.000	0.000

P_1 : vertex vs. occipital; P_2 : vertex vs. temporal; P_3 : occipital vs. temporal. Based on a comparison with males, $^*P > 0.05$, $^*P > 0.05$

Table 2: Distribution of occipital follicular unit and hair counts of AGA patients and healthy Han Chinese (mean \pm SD)

	Density of follicular units (units/cm ²)			Hair density (hairs/cm ²)		
	Total	Males	Females	Total	Males	Females
AGA group	77.78 ± 2.99	77.42 ± 2.89	80.40 ± 2.51	148.12 ± 6.98	147.11 ± 6.59	155.40 ± 5.68
Healthy group	82.66 ± 4.12	83.05 ± 4.16	82.20 ± 4.05	158.90 ± 13.41	160.15 ± 13.26	157.39 ± 13.54
P	0.000	0.000	0.008	0.000	0.000	0.007

AGA: androgenetic alopecia

Table 3: Percentages of different types of FU (%)

	1-hair FUs	2-hair FUs	3-hair FUs	4-hair FUs	5-hair FUs
Vertex	27.65	53.72	17.23	1.23	0.17
Occipital	29.24	51.31	17.96	1.25	0.24
Temporal	28.26	52.84	17.25	1.43	0.22
Overall	28.38	52.62	17.48	1.30	0.21

FU: follicular unit

Table 4: Correlation analysis between density of follicular units and age

	<i>r</i>	<i>P</i>
Vertex	-0.897	0.000
Occipital	-0.876	0.000
Temporal	-0.788	0.000

r: Spearman correlation coefficient

As the Chinese population is predominantly Han, it is necessary to investigate and study FU and hair density in Han Chinese.

Our study found that the mean FU density in 146 healthy Han Chinese was 74.36 ± 13.33 units/cm². This is lower than the results obtained by Bernstein and Rassman^[3] and similar to the result by Tsai *et al.*^[8] (71.78 units/cm²). There were no statistical differences between males and females ($P = 0.553$). The mean hair density in healthy Han Chinese was 143.33 ± 28.08 hairs/cm², which is lower than that in whites and Africans^[7]. There were no statistical differences between males and females ($P = 0.464$). The mean FU densities of the vertex, occipital, and temporal regions were 83.32 ± 7.75 units/cm², 82.66 ± 4.12 units/cm², and 57.10 ± 2.97 units/cm², respectively. The mean hair densities were 160.95 ± 20.66 units/cm², 158.90 ± 13.41 units/cm², and 110.14 ± 10.17 units/cm², respectively. These results indicate that there are differences in the FU density and hair density among the different scalp sites of Han Chinese. There was no statistical difference between the vertex and occipital regions, but both had significantly higher values than in the temporal region^[7-9]. This provides us with strong data for the theoretical support of temporal hair transplantation.

The results on the 41 AGA patients indicate that the mean FU density of the occipital region was 77.78 ± 2.99 units/cm² and the mean hair count was 148.12 ± 6.98 hairs/cm². Both results were lower than those in the occipital regions of healthy Han Chinese, and the differences were statistically significant ($P < 0.001$). Orentreich^[10] successfully transplanted non-hormone sensitive hair follicles from the occipital region into the bald area and proposed the donor dominance theory, which has become the theoretical basis of hair transplantation surgery for patients with alopecia. Our research data provide a reference to evaluate the area of donor site that should be transplanted in Han

Chinese AGA patients.

Our research on the distribution of FU types in healthy Han Chinese found that 1-hair FUs accounted for 28.38%, 2-hair FUs accounted for 52.62%, 3-hair FUs accounted for 17.48%, 4-hair FUs accounted for 1.30%, and 5-hair FUs accounted for 0.21%. No FUs comprising more than 5 hairs were observed in our study. The proportions of FU types are different for different races^[3]. Our research indicates that the FU types found in healthy Han Chinese are dominated by 2-hair FUs. The result is consistent with the FU types of whites, whereas the FU types of Africans are dominated by 3-hair FUs.

The result of correlation analysis indicated that FU density decreased with an increase in age; therefore, the FU density at the vertex can be used as an indicator to evaluate the degree of aging in healthy Han Chinese.

Our research findings have provided some theoretical data on the hair distribution characteristics of Han Chinese. These data can contribute to preoperative evaluation, surgery planning, and postoperative outcome evaluation performed by hair transplantation surgeons. The required amount of hair transplantation, area of donor site excision or extraction, postoperative density, and cost may be estimated, depending on the area of recipient site during the preoperative consultation^[11,12]. For example in a male patient with vertex hair loss with a recipient site measuring 2 cm × 2 cm, assuming that all the transplanted FUs survive, the transplantation of 200 FUs can achieve 60% of the normal density of vertex hair. By mean of FUT, this requires a scalp area of about 2.4 cm² to be excised from the occipital region. By mean of FUE, according the theory that it will be not significantly affect the occipital region appearance after the extraction of 40% the occipital hair follicles^[13], this requires a scalp area of about 6 cm² to be extracted from the occipital region. The transplantation of 300 FUs can achieve 90% of the normal density of vertex hair. This requires a scalp area of about 3.6 or 9 cm² to be excised or extracted from the occipital region.

We hope that our results can serve as a reference for clinical practice. In addition, we will continue to collect clinical cases to establish a database for hair distribution of Han Chinese for further research.

DECLARATIONS

Authors' contributions

Images' analysis and wrote the article: Z.H. Guo
Collected hair photoes of clinical patients: G. Wang

Analyzed data and made statistical charts: Y. Miao, Z.X. Fan

Communicated with patients and selected the right patients: X.M. Liu, Q. Qu

Searched some related literature: K. Ye, D.C. Zhu

Offered advice and corrected the article: Z.Q. Hu

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Conflicts of interest

There are no conflicts of interest.

Patient consent

All volunteers were informed of the objectives and specific methods of the study, and all gave informed consent.

Ethics approval

The experiment was performed under the approval of the Southern Medical University Ethics Committee.

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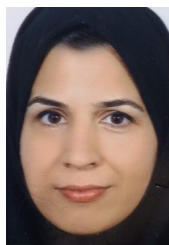
Comparison of breast reconstruction using ipsilateral and contralateral pedicle transverse rectus abdominis musculocutaneous flaps

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Dr. Ramesh Omranipour is a cancer surgeon presently working as full professor at Cancer Institute of Tehran University of Medical Sciences (TUMS) in Iran. She is the first and the sole lady who has reached full professor degree in general surgery in academic medical schools of her country. Dr. Omranipour is the head of Breast Cancer Research Center of TUMS and the vice chancellor of education at Cancer Institute. She is the author or co-author of more than 90 published papers. She was the invited speaker as an oncologist, especially a breast cancer surgeon in more than 200 national conferences.

ABSTRACT

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Breast reconstruction,
transvers rectus abdominis
musculocutaneous flap,
unilateral pedicle TRAM flap,
ipsilateral pedicle TRAM flap

Aim: Breast reconstruction has several beneficial effects on psychosocial well-being and quality of life. The ultimate goal has always been to create the most natural breast mound. Thus in many centers, the unilateral pedicled transverse rectus abdominis myocutaneous (TRAM) flap remains the most common technique for breast reconstruction. Our objective was to retrospectively compare the outcomes of ipsilateral and contralateral pedicle TRAM flaps. **Methods:** The total of 110 patients underwent unilateral breast reconstruction with pedicle TRAM flap at Cancer Institute of Tehran University of Medical Science from January 1996 to June 2011. Premorbid risk factors, postoperative outcomes and demographic data were assessed. The analysis of the recordings was done by SPSS 20. **Results:** Out of 110 patients who were included in the study, 87 had ipsilateral and 23 contralateral pedicle TRAM flaps. The incidence of flap complications that did not require surgical intervention was 19.7% in ipsilateral and 30.4% in contralateral pedicle TRAM flap. The incidence of flap loss requiring revision was significantly higher in contralateral group ($P = 0.001$). Major complications were noted in 11.5% of the ipsilateral pedicle TRAM patients and 26.1% of the contralateral group ($P < 0.001$). Minor complications were noted in 17.2% of the ipsilateral



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pedicle TRAM patients and in 34.8% of the contralateral group ($P < 0.001$). Total early hospital stay was longer in contralateral pedicle TRAM flaps (7.66 days vs. 10.68 days, $P = 0.83$). Higher complications were encountered in contralateral pedicle TRAM flaps compared to ipsilateral pedicle TRAM patients (39.1% vs. 19.5%, $P = 0.001$). The type of pedicled TRAM flap (ipsilateral vs. contralateral), had significant effect on complications (odds ratio = 0.007, $P = 0.002$) while other variables had no significant effect on the incidence of complications. **Conclusion:** This study indicates that the overall outcome and mid-term morbidity-free survivals of ipsilateral pedicle TRAM flap breast reconstruction are statistically superior to contralateral pedicle TRAM flap breast reconstruction. Both of these procedures are reasonably feasible and safe. These findings lead us to discourage the use of contralateral pedicle TRAM flap when an ipsilateral option is feasible.

INTRODUCTION

Breast reconstruction has several beneficial effects on the psychosocial well-being and quality of life. Different studies have shown that breast reconstruction improves self-image, sexuality, and decreased rates of depression in women who have had mastectomy^[1]. Additionally, patients who undergone reconstruction with autologous tissue, in comparison with those who have undergone reconstruction with tissue expanders/implants, have better long-term quality of life^[2].

Transverse rectus abdominis myocutaneous (TRAM) techniques have long been applied but selecting a superior technique is controversial. The selection of the best procedure significantly affects the outcome of flap viability, patients' satisfaction, and quality of life^[3]. The pedicle TRAM flap is still one of the most common procedure performed in many centers. Our study demonstrates that it is associated with a low complication rate and a high level of patient satisfaction in our center^[4].

Morbidity and adverse events following different reconstructive breast surgeries are reported to be widely varied. In general, patients selected for pedicle TRAM flap reconstruction must have adequate abdominal soft tissue for the procedure to be successful. There are several identified risk factors contributing to the post operative complications of pedicle TRAM flap reconstruction. These factors are cigarette smoking, obesity, prior radiation therapy, abdominal surgery, and significant medical comorbidities^[5].

As the experience and comfort with micro-surgical techniques and instrumentation and post-op monitoring facilities are not available in all centers. Surgeons perform the pedicle TRAM flap because it demands less technical and facility requirements and has fewer complete flap loss in comparison with free flap techniques^[6].

Rotation of pedicle TRAM flap can be ipsilateral or contralateral. Some surgeons believe that the ipsilateral procedure might result in more tension on the vascular pedicle and folding of the pedicle could

reduce the blood supply of the flap^[7,8]. In order to avoid the folding and the vascular flow surgeons have preferred to use the contralateral pedicle TRAM flap. The contralateral pedicle TRAM flap also seemed to have some aesthetic limitations due to ablation of the xiphoid subunits and the medial infra-mammary fold. There are also some limitations from the shorter pedicle length^[7]. There are reports indicating differences in early and long-term outcome of these two techniques^[9]. Some authors reported similar safety of both techniques^[10] while others favored one pedicle TRAM technique over the other one^[8,9].

Our objective was to retrospectively compare outcomes of ipsilateral and contralateral pedicle TRAM flaps in a retrospective cohort study. In our center free flaps for breast reconstruction are not routinely performed. Therefore we performed this study to analyze the outcomes and complications of TRAM flaps performed in our center. We were able to assess the risk factors which could cause more post-operative complications and compare the results of ipsilateral and contralateral TRAM flaps retrospectively. We are aware that free flaps will substitute TRAM flaps inevitably, so in this study we measured the results of TRAM flaps in our center. The study primary endpoints were postoperative morbidity (defined as occurrence of at least one of the postoperative complications within the follow-up period), need for re-hospitalization and need for re-operation.

METHODS

In total of 110 patients who underwent unilateral breast reconstruction with pedicle TRAM flap at the Cancer Institute of Tehran University of Medical sciences from January 1996 to June 2011, were included in this study. The ethics committee accepted this study and the patients were informed about it during their follow-up exams. Patients with micro-vascular supercharging of the flap or those who received a bi-pedicle or bilateral TRAM flap were excluded. Patients' age, height, weight, history of smoking, and associated comorbidities (diabetes mellitus, dyslipidemia and hypertension), steroid use, history of liposuction, tumor staging (based on TNM criteria), presence of tumor markers (estrogen receptor status, progesterone

receptor, P53, Her2Neu), history of post-mastectomy radiotherapy or chemotherapy and finally the time length between mastectomy and reconstruction were abstracted from the medical records. Type of pedicle TRAM (ipsilateral vs. contralateral), timing of the procedure (immediate vs. delayed), and usage of mesh for the abdominal wall closure were also recorded.

All patients had follow-up examinations every week for the first month and monthly thereafter for 6 months. Postoperative outcomes were assessed using clinical data records if available, otherwise we communicated with the patients' physicians. The mean follow-up duration was 2.69 years for ipsilateral group and 3.21 years for contralateral group.

Immediate post-reconstructive complications were recorded. Postoperative complications were then categorized into major or minor events. Complications which required re-admission or re-hospitalization such as total flap loss were defined as complete necrosis of the skin and fat; partial flap loss, was defined as ischemic tissue loss exceeding 25% of the flap. Wound infection was defined as redness, swelling, and exudate and requiring antibiotics. Seroma formation was defined as palpable fluctuation of subcutaneous tissues requiring suction or drainage. Hematoma, requiring evacuation, pulmonary embolism, sepsis, hernia, ileus and acute renal failure were categorized as major complications. All the other complications were categorized as minor.

SPSS 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, with comparison of discrete variables by Pearson chi-square or Fisher's exact test, and comparison of means by *t*-test. A value of $P < 0.05$ was considered significant. Predictors exhibiting a statistically significant relation with postoperative morbidity were taken for multivariate logistic

regression analysis to evaluate their independence as predictors. Odds ratio (OR) and 95% confidence intervals were calculated.

RESULTS

Table 1 presents the baseline characteristics of the study population and the type of procedures. Out of 110 patients who were included in the study, 87 had ipsilateral and 23 contralateral pedicle TRAM flaps. There were no significant differences in demographic characteristics between ipsilateral and contralateral pedicle TRAM flap groups. Tumor size and the number of lymph node involvement were higher in contralateral pedicle TRAM flap group. Immediate reconstruction was more commonly performed in contralateral pedicle TRAM flap group, (34.8% vs. 10.3%, respectively).

Co-morbidities included hypertension, diabetes mellitus, hyperlipidemia, presence of abdominal scar, and smoking. The two procedures had similar clinical and demographic characteristics. Co-morbidities were more common in ipsilateral pedicle TRAM group.

Table 2 summarizes the categories of complications during follow-up period. Comparing the ipsilateral with the contralateral TRAM groups, the incidence of flap complications that did not require surgical intervention was 19.7% in ipsilateral and 30.4% in contralateral pedicle TRAM flap, respectively. The incidence of flap loss requiring revision was significantly higher in contralateral group ($P = 0.001$). Major complications (any complication that required hospital admission or operative procedure) were noted in 11.5% of the ipsilateral pedicle TRAM patients and 26.1% of the contralateral group ($P < 0.001$). Minor complications were noted in 17.2% of the ipsilateral pedicle TRAM patients and in 34.8% of the contralateral group, respectively ($P < 0.001$). When individual complications

Table 1: Baseline characteristics of the study population and the type of procedures for breast reconstruction, *n* (%)

Characteristics	Ipsilateral pedicled TRAM (<i>n</i> = 87)	Contralateral pedicled TRAM (<i>n</i> = 23)	<i>P</i>
Age (years), mean \pm SD	42.58 \pm 9.15	39.22 \pm 6.6	0.99
Body mass index (kg/m ²), mean \pm SD	27.43 \pm 4.28	24.54 \pm 3.47	0.64
Diabetes mellitus	9 (10.1)	1 (4.3)	0.003
Hypertension	6 (6.9)	1 (4.3)	0.002
Hyperlipidemia	1 (1.1)	0 (0.0)	0.011
Tobacco use	7 (8)	1 (4.3)	0.005
Abdominal scar	22 (25.3)	11 (47.8)	0.004
History of radiotherapy	65 (74.7)	12 (52.2)	0.025
History of chemotherapy	61 (70.9)	19 (82.6)	0.67
Immediate reconstruction	9 (10.3)	8 (34.8)	0.001
Time between mastectomy and reconstruction	50.39 \pm 42.14	36.51 \pm 30.65	0.071

TRAM: transverse rectus abdominis myocutaneous

Table 2: Postoperative complications of ipsilateral and contralateral pedicle TRAM flap, n (%)

Characteristics	Ipsilateral pedicled TRAM (n = 87)	Contralateral pedicled TRAM (n = 23)	P
Length of stay in hospital (days), mean ± SD	7.66 ± 7.27	10.68 ± 7.25	0.83
Total morbidity	17 (19.5)	9 (39.1)	0.001
Flap ischemia	1 (1.1)	0 (0)	0.23
Flap necrosis	7 (8)	4 (17.4)	< 0.001
Sub-flap hematoma	0 (0.0)	2 (8.7)	0.040
Sub-flap seroma	4 (4.6)	5 (21.7)	0.059
Flap wound infection	2 (3.3)	4 (17.45)	0.004
Deep vein thrombosis	1 (1.1)	1 (4.3)	0.74
Re-hospitalization	7 (8)	5 (21.75)	0.20
Re-operation	6 (6.9)	4 (17.4)	0.35

TRAM: transverse rectus abdominis myocutaneous

were compared by procedure group, sub-flap hematoma, sub-flap seroma, flap necrosis, and flap wound infection were significantly higher in contralateral pedicle TRAM patients.

As summarized in Table 2, the total early hospital stay was longer in contralateral pedicle TRAM flaps. (7.66 days vs. 10.68 days, $P = 0.83$). There were higher complications in contralateral pedicle TRAM flaps (39.1% vs. 19.5%, $P = 0.001$). Flap necrosis and sub-flap seroma were two most common early post-operative complications in both groups.

Logistic regression was used to assess the effect of procedure technique (ipsilateral vs. contralateral) on major, minor and ischemic flap complications while controlling for patient age, body mass index (BMI), radiation therapy, procedure timing, surgical delay of the flap, comorbidities, smoking and abdominal scar [Tables 3 and 4].

The type of pedicle TRAM flap (ipsilateral vs. contralateral), had significant effect on complications (OR = 0.007, $P = 0.002$). Other variables had no significant effect on the incidence of complications.

DISCUSSION

Although the pedicle TRAM flap provided a foundation for the burgeoning field of breast reconstruction, the overall contemporary trend has focused on approaches which provide improved aesthetic outcomes while minimizing complications and donor site morbidity. The most advantageous benefit of pedicle TRAM flaps as a method of autogenous reconstruction is to employ removed excess lower abdominal tissue thorough a cosmetic abdominoplasty and achieve a long lasting satisfactory outcome. To do this, careful selection of patients and the best procedural technique in addition to pre-operative risk profile management can effectively reduce post-operative adverse events.

A history of mastectomy, chest wall radiation, advanced age, tobacco use, and some other underlying medical conditions are identified as predisposing factors to postoperative complications^[5]. In our study, based on conclusions from the multivariable regression model, none of the study variables other than the laterality of the flap could predict morbidity.

The overall rate of morbidity observed in our study regardless of the type of technique was 27.4%. This

Table 3: Multivariate analysis of correlation of overall complication with pedicle TRAM breast reconstruction

Independent variable	OR (95% CI)	P
Type of technique (ipsilateral vs. contralateral)	0.007 (0.005-0.443)	0.002
Age	0.98	0.49
Body mass index	0.47	0.94
Surgical delay of flap	0.98	0.49
Presence of at least one co-morbidity	0.38 (0.54-4.92)	0.38
Abdominal scar	0.74 (0.127-18.32)	1.644
Smoking	0.45 (0.03-4.55)	0.57
History of radiotherapy	0.12 (0.17-1.23)	0.27
Timing (immediate vs. delayed)	0.23 (0.68-4.99)	0.24

TRAM: transverse rectus abdominis myocutaneous; CI: confidence interval; OR: odds ratio

Table 4: Multivariate analysis of correlation of minor complication with pedicle TRAM breast reconstruction

Independent variable	OR (95% CI)	P
Ipsilateral vs. contralateral	0.001 (0.005-0.38)	0.005
Age	0.49	0.99
Body mass index	0.39	0.8
Surgical delay of flap	0.42	0.85
Presence of at least one co-morbidity	0.11 (0.87-14.32)	0.1
History of radiation therapy	0.98 (0.28-4.59)	0.87
Timing (immediate vs. delayed)	0.24 (0.58-9.37)	0.23

TRAM: transverse rectus abdominis myocutaneous; CI: confidence interval; OR: odds ratio

seemed to be lower than the previously reported 31.82% by Fathi *et al.*^[11] The difference might be explained by the differences in the definition of postoperative morbidity and the time of follow-up period in our study in comparison with theirs. We did not encounter any total flap loss which is the most serious complication of microsurgical breast reconstruction.

Unlike some other previous reports we did not find any correlation between age or BMI and morbidity in this study. The only comorbidity which could increase the rate of post-operative complications was smoking.

In this study we aimed to determine the superiority of ipsilateral or contralateral pedicle TRAM flap based on postoperative complications and morbidity. There were differences in total morbidity, flap ischemia, flap necrosis, sub-flap hematoma, sub-flap seroma, and flap infection, between the two pedicle TRAM flap groups. The rate of complications in contralateral pedicle TRAM flaps (39.1%) was significantly higher than ipsilateral pedicle TRAM flaps (19.5%), ($P = 0.001$). The type of pedicle TRAM flap did affect the total postoperative morbidity, even in the absence of other base line risk factors and co-morbidities. Our results were contrary to some previous reports which indicated that the type of pedicle TRAM flap does not increase postoperative complications. In Clugston *et al.*^[8] study of ipsilateral pedicle TRAMs, the authors reported a moderately high minor complication rate but a relatively low major complication rate^[12].

The rate of complications of pedicle TRAM flap in our study (27.4%) is similar to other studies (16-41%)^[13-16]. Partial flap necrosis in our study was 13.7% which is less than previous reports by Janiga *et al.*^[9] (16-41%).

We found that the rate of major complications (needing re-hospitalization or re-operation) following pedicle TRAM flap was 17.9%, while the rate of a minor complication was 24.8%. Minor complications included wound infection, seroma or hematoma not requiring operation, and flap ischemia. Major complications, were significantly higher in our contralateral group. This finding can be explained by limitations of contralateral technique. Contralateral pedicle TRAM flap seems to have some aesthetic limitations due to ablation of the xiphoid subunits and the medial infra-mammary fold. There are also some limitations from the shorter pedicle length.

In a previously irradiated breast, because of the ischemia due to damage to the internal mammary vessels, some surgeons prefer not to use ipsilateral pedicle

TRAM flap for breast reconstruction. We could not find any correlation between previous radiotherapy and morbidities after contralateral or ipsilateral pedicle TRAM flap. This result is similar to the study of Janiga *et al.*^[9]

The experience gained in these procedures during the last two decades has enabled surgeons to identify certain risk factors such as obesity, previous abdominal surgery, advanced age, and tobacco use that can increase complication rates. Some researchers suggest considering those factors as contra-indications for a pedicle TRAM flap^[15,16]. We did not find in our study a higher morbidity rates associated with these risk factors except for smoking. The outcome of pedicle TRAM flap reconstruction in obese patient was similar to non-obese patients in our previous report^[17].

The most important finding in this study is that it is not necessary to use contralateral TRAM flap to overcome the limitations of ipsilateral TRAM flap. Moreover, we found out more complications in contralateral TRAM flaps.

The present study had some limitations. It is a retrospective study, inevitably it could have confounding biases due to lack of information on some factors not available in the medical records. Patients in this study were operated on by different surgeons and this could affect the outcome of procedures. However, we were successful in comparing the outcomes and morbidity-free survival rates of the two commonly performed pedicle TRAM flaps (ipsilateral vs. contralateral).

This study indicates that the overall outcome and mid-term morbidity-free survivals of ipsilateral pedicle TRAM flap breast reconstruction are statistically superior to contralateral pedicle TRAM flap breast reconstruction. Both of these procedures are reasonably feasible and safe. According to our findings we recommend against the use of contralateral pedicle TRAM flap to overcome limitations of ipsilateral pedicle TRAM flap. Larger prospective studies are required to address this conclusion. We believe that the ipsilateral compared to the contralateral pedicle TRAM flap has noticeable advantages including total flap vascularity, seroma formation, and partial flap necrosis. In the end, a surgeon's familiarity and experience with either procedure, is likely the most important predictor of a good outcome.

DECLARATIONS

Authors' contributions

Concept and design: R. Omranipour

Literature research and manuscript preparation:

S. Mashayekhi, H. Mahmoodzadeh

Data acquisition: S. Alipour

Data analysis and statistical analysis and manuscript editing: M. Vasigh

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Approved by the ethics committee and the patients were informed about this study during their follow-up period.

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Controlled clinical trial for evaluation of hair growth with low dose cyclical nutrition therapy in men and women without the use of finasteride

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Dr. Rajendrasingh Jalamsingh Rajput, fondly known as Dr. Rajesh Rajput, is a plastic surgeon from Mumbai, India. international certified trichologist, (International Association of Trichology – Australia). Has dedicated hair restoration practice for past 25 years. Follows micro FUE with “Stick & Place” technique for implantation. He was the founder member and past president Association Hair Restoration Surgery-India. First Indian, honored to be fellow of the International Society of Hair Restoration Surgery (ISHRS), Fellow International Society of Hair Restoration Surgery-USA, tutor for trichology course by IAT, tutor for basic surgical skills. He presented and published his works at national and international meetings. Pioneering program on vitamin therapy for hair growth has been published by the ISHRS forum in 2008 and translated into Chinese, Italian & Japanese. He recently completed work on herbal hair growth program. Authored a chapter on hair transplant and a chapter on nutritional correction of hair loss is under publication. He conducts hands-on training programs, has observers from all over India, Taiwan, Iran, Iraq, UAE, USA, Canada, Spain & UK.

ABSTRACT

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Key words:

Androgenic alopecia,
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Aim: To evaluate possible results with the stimulation use of minoxidil and the strengthening of hair roots with nutritional cyclical supplements, resulting in increased hair regrowth, without the use of anti androgens and enzyme blockers. **Methods:** This prospective controlled clinical trial compares the current acknowledged form of treatment for hair loss within two controlled groups for both men and women against the use of cyclical nutritional therapy and minoxidil 2%. One hundred patients in each of the 4 groups, a total of 400 patients, were followed for 1 year. The progress was evaluated every 2 months with computerised measurements of hair density, hair calibre, global photography and uniquely designed self-assessment scores. **Results:** The use of nutritional supplements showed consistent improvements in both treatment groups of men and women against the controlled groups with a correction of hair fall and minimum 18% increased density within 2 months with further improvement to a maximum of



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trichoscopy,
hair growth,
hair loss,
side effects,
cyclical therapy

156% over 1 year. **Conclusion:** Hair loss occurs when weak, sensitive, follicles are affected by multiple causes. Hair regrowth can be achieved consistently and safely by strengthening the hair roots and promoting hair growth without necessarily depending on the use of anti androgens.

INTRODUCTION

Today, with the understanding of teloptosis and kenogen by Guarrera *et al.*^[1-3], patients develop baldness, not due to hair loss but due to the empty follicle stage. Patients gradually develop empty bald areas as a result of the falling telogen hair no longer being replaced with new anagen hair. The physiological balance of the hair growth cycle is disrupted^[3-6] leading to loss of density, gradually manifesting into baldness. However, patients assume they are balding due to the visual hair loss and pursue multiple remedies for control. The loss of 100-150 hair follicles a day is normal^[7,8] in Caucasians. Caucasians have over a 100,000 hair follicles on the head and losing 150 follicles a day, or 4,500 in a month, is a loss of less than 5%. We would draw attention to the fact that, even after considering individual variation in the total number of follicles lost, there would remain 85% to 95% of follicles which are not in the active fall phase - these follicles are available and willing to grow. How can we make these follicles grow better and healthier? Let us look at the available knowledge in a new perspective to promote hair growth and achieve better density instead of fighting hair fall.

Various factors affecting hair loss, weaken the hair roots and make them sensitive to normal levels of androgens in the body^[9-12]. Pattern hair loss can occur with normal androgen levels^[12,13], pattern hair loss can occur before puberty^[13-15], it has been reported in hypogonadism^[16] and also in a case of complete androgen insensitivity syndrome^[17]. Instead of insisting on anti-androgens in management of hair loss patients, we should focus on strengthening the hair follicle and promoting better hair growth to ensure more hair on the head. Eminent research workers Trueb^[3], Klingman^[4], Rook and Dawber^[5] in their studies of the dynamics of hair growth, have highlighted the fact that hair loss is a result of dysregulation of the hair growth cycles or imbalance between factors regulating, hair loss and hair growth or to say the factors known to be, favourable and unfavourable for hair growth. The same is also emphasised by the studies of Headington^[6], Paus and Cotsarelis^[7], Liyanage and Sinclair^[8]. The role of dihydrotestosterone (DHT) levels in hair loss is being questioned^[18]. Research and understanding today suggest that hair loss can be genetic, hormonal, nutritional, inflammatory or due to

altered immunity^[11,19-22].

Research workers have attributed the thinning and miniaturization of the hair as the hallmark of androgenic alopecia (AGA). Now numerous other types of thinning and hair loss have been identified as mimicing AGA^[22-25]. Therefore we found the need to develop a new category of description and classification defined as diffuse unpatterned hair loss (DUPA)^[8,26]. We now clinically face hair loss that displays all the characteristics of AGA but does not confirm to genetic predisposition and has no family history^[27]. AGA can skip siblings and skip generations. Though siblings carry the genes, there are more collaborators than just the presence of DHT to manifest miniaturization and present the clinical characteristics of AGA. Works of Headington, Philpott, Farjo N, Farjo B and Bahta have indicated that the multiple pathways of hair loss are in fact, interlinked, overlapping and in over 33% of the cases there may not be any identifiable cause^[6,28].

DHT has been considered to be a cause for hair loss but it is uncommon to find raised DHT levels in patients and there is no correlation between DHT levels and the grade of hair loss manifested in the patients^[18]. Under the influence of other known and unknown factors, even normal androgen levels can lead to hair loss. DHT's presence is what causes the genes to express the balding gene and the blood levels alone do not relate directly to the extent of hair loss. Thus we say, not a raised DHT but a higher sensitivity of the hair roots is responsible for hair loss^[11,29-31]. Studies by Sawaya and Price^[32], on the 5-alpha reductase type 1, type 2, aromatase and androgen receptors, along with the cutaneous androgen metabolism studies by Chen *et al.*^[33] and Hoffman and Happle^[34] current understanding of androgenic alopecia, all support the conclusion that sensitivity of the follicles is of greater concern than raised levels of androgens. We have discovered a limited correction of one of the mechanisms for hair loss by blocking conversion of testosterone to DHT but are attempting to treat all the various types of hair loss with the same approach. Minoxidil and finasteride, which to date are the only two FDA approved and commonly accepted treatments for hair loss, were both discovered by serendipity and not by studying the hair loss cycles. Patients treated with minoxidil do not always show a predictable standard

response. Similarly patients treated with finasteride do not always show the same predictable responses^[35-36], some patients do not respond definitively. Reports by Kaufman *et al.*^[37] in their long term finasteride study have reported that 17% patients have deteriorated during their treatment with finasteride.

Hypothesis and the proposed perspective

There are numerous causes for hair loss - these cannot be isolated as singularly responsible, but most of the times are working in tandem. We propose that the approach of cause based on treatment planning does not work for hair loss. The causes are vague, not quantifiable; are not measurable by any yardstick; and they cannot be confirmed to have a direct cause and effect relationship with hair loss. A group of people exposed to the same cause do not suffer the same kind of hair loss, if you try to treat one cause, hair roots being sensitive may fall prey to hair loss from another cause. We should consider the fact that the androgens or DHT levels in most hair loss patients are normal and not raised^[18,23,24]. There are several persons with similar androgen levels who do not have any hair loss at all. As well as there are other persons who carry the genes, passing them off to the next generation, who do not themselves, manifest any hair loss symptoms. There are several persons losing hundreds of hair per day but not going bald because their fallen hair is regularly replaced with new hair, as the hair cycle continues^[1-3]. Focus should be on the promotion of hair growth cycles and not on fighting the androgens. The anti-androgenic treatments are required to be used for a long periods of time, possibly even lifelong. Recent studies by Irwig^[38] and Traish *et al.*^[39] highlight the point that long term use of anti-androgens increases the possibility of negative side effects that may also be irreversible. Therefore, it is more scientifically beneficial to strengthen the hair roots, provide a toxin free environment for the cells and promote hair growth rather than trying to treat a suspected causes that cannot be confirmed. Strengthening the hair and promoting growth can be achieved with vitamins, minerals and nutritional supplements which will deliver wellness, good health as well as hair growth. The falling hair originates from the gradual weakening of the natural available stock hair roots on the scalp, if these are made strong, the basic source from which falling hair is generated will be blocked preventing further hair loss. In a sense it would reduce the number of hair falling in every cycle.

DHT can be blocked by antioxidants

An initial experimental study by Eun^[40] discovered that DHT does not directly cause inhibition of hair growth but it induces the release of transforming growth factor

beta 1 (TGFβ1) which results in the miniaturization and hair loss. Shin *et al.*^[41] followed this research further with cultured androgen sensitive dermal papilla cells and the addition of DHT to this androgen sensitive cell caused an accumulation of free radicals ROS within the cultured cells, which in turn induced the release of TGFβ1. The next step of the study was the addition of free radical scavenger N-Acetyl cysteine to the cell culture, that successfully blocked the accumulation of free radicals resulting in successful blockage of DHT induced secretion of TGFβ1^[41]. Therefore, we can consider now that antioxidants can prevent accumulation of free radicals or reactive oxygen species which in turn can neutralize the mechanism of the action of DHT. Vitamin D has direct action on induction of hair growth from the dermal papilla. The role of oxidative stress^[42], nutrients, vitamins^[43], minerals^[44,45], amino acids in maintaining immunity, preventing micro inflammation^[46,47], and promoting hair growth has been discussed by several research scientists. The details of the role of non-androgenic factors have previously been published^[48].

Due to the long term practical use of a hair care program, a more natural alternative solution is desirable. Cellular turnover and metabolic activity in the hair follicles is equivalent to bone marrow and intestinal epithelium therefore, hair growth requires multiple nutrients: antioxidants, amino acids, vitamins, minerals and fatty acids^[49]. While studying the nutrients it was highlighted that use of too many supplements at a time, can interfere with the absorption and efficiency of one another. Iron and calcium, given together can chelate each other and reduce the absorption^[50]. Regular intake of iron can create mucosal blocks to iron absorption^[51], while excess iron can become pro oxidant through Fenton reaction^[52,53]. Excess cellular calcium can induce apoptosis of the cells^[54]. High intake of vitamin C does not ensure higher levels in circulation^[55]. High intake of antioxidants reverses the benefit and makes them behave as pro oxidants^[56]. Details of such interaction have been discussed in our previous published study^[49].

High protein consumed in diet is ultimately digested to amino acids that enter the circulation, creating a surge that makes the blood pH acidic. The high acidity requires to be buffered immediately to maintain homeostasis. Physiologically, calcium is the best buffer system in the body. High blood acidity, causes reabsorption of calcium to buffer the acidic blood, leading to high calcium levels in the circulation. Kidneys recognise the excess calcium and begin excreting the calcium leading to a loss of calcium^[57-60] - ultimately causing weakening of hair and bone resulting in hair loss instead of hair growth. We found hair is an

unusual organ that grows when cells in the body are allowed to die. Hair is created when the piling up of dead keratinized cells are serially pushed upwards while new dead cells are generated from below. Keratin deposition in the cells gradually increases as the cells are pushed towards the outer layers of the skin, finally the cells become non-viable, dead cells pile up over one another and are pushed out of the body in the form of hair and nails. Saturation of the body with vitamins, especially vitamin A^[61,62], vitamin E^[63-65], Omega three fatty acids^[66] become pro oxidant, interfere with keratinisation leading to non-creation of hair keratinized cells ultimately manifesting as hair loss instead of hair growth.

It should be highlighted that the recommended daily allowance (RDA) of various nutrients was decided by a discussion and consensus between random selected committees to meet requirement of the rations supplied to soldiers and industrial workers rather than by following experimental analysis of the metabolic requirements within the human body^[67]. Nutrients and vitamins have two kinds of doses. A therapeutic dose given to patients suffering disease due to deficiency of the selected nutrient - which does is very high. A prophylactic or preventive dose to promote good health that can be as low as possible^[68]. Part of the nutrients could come through diet while part via a low dose supplement.

Aims and objectives

To test the hypothesis that stimulation of hair growth and supporting cell division with nutritional supplements can result in hair growth, without the need to use antiandrogens or enzyme blockers in both men and women.

METHODS

Patient selection

Male and female patients between the ages of 25 to 50 years, requiring treatment for hair loss, were explained the nature of the study. Patients made their choice to have treatment with finasteride and minoxidil or follow minoxidil with the low dose once in 3 days supplement program. A total 400 patients (200 men and 200 women) agreed to choose the standard therapy or accept the nutritional therapy for a commitment of 1 year, were selected to form the control group and the treatment group with a total of 100 patients per group. The age distribution of male and female patients in the study is displayed in Table 1. We have attempted to have patients with comparable age and comparable grades of hair loss in the control groups and treatment groups as displayed in Tables 1-3.

Exclusion criteria: (1) patients who had previously tried any kind of hair loss treatment within the last 6 months, were excluded; (2) patients who were on any kind of supplements, protein shakes, medical treatment for any condition were excluded; (3) patients with regular alcohol intake and smokers were excluded; (4) male patients with Norwood Hamilton grade I and grade II hair loss and female patients with Ludwig grade I hair loss were excluded.

Control group for men (CM) and control group for women (CW): CM consisted of 100 volunteer male patients who were between 25 to 50 years of age and had hair loss between Norwood Hamilton grade III to grade V. The male control group received 1 mg finasteride every day and application of 2% minoxidil lotion 2 times a day, 1 mL in the morning after bath and 1 mL in the evening before sleep every day.

Control group for women consisted of 100 volunteer female patients who were between 25 to 50 years of age and had hair loss Ludwig grade II and III. The female control group did not receive finasteride, but were prescribed the application of 2% minoxidil lotion 1 mL, 2 times a day, morning after bath and evening before sleep.

Treatment group for men (TM) and treatment group for women (TW): Treatment groups for both men and women followed the same protocol. Patients in both the groups did not receive finasteride. Both men and women treatment group applied 2% minoxidil lotion 1 mL, 2 times a day, morning after their shower/bath and again in the evening prior to sleep. In addition, they received nutritional supplements which included antioxidants, vitamins, minerals, omega 3, amino acids and biotin. In order to avoid inter nutrient interactions, improve absorption and have better efficiency we planned to have these supplements in synergistic combinations over a 3 day cycle [Table 3].

Method of hair care and use of nutritional supplements

Table 1: Age distribution of the patients in the study, (%)

Age (years)	Male	Female
25-30	32	36
30-40	47	40
40-50	21	24

Table 2: Grade of hair loss in male patients, (%)

	Control group	Treatment group
Grade III	30	32
Grade IV	50	48
Grade V	20	20
Ludwig II	48	46
Ludwig III	52	54

We developed a 3 day cycle to utilize 6 supplement formulations, in combinations that do not interfere with the efficiency of one another and could be synergistic in action. The patients also felt that they were not taking too many medicines at one time - a simple 2 per day. Patients who had a light or no breakfast were permitted to have the supplements after lunch. Patients who felt heaviness in the stomach could take 1 supplement after lunch and one after dinner. All patients applied minoxidil 2% 1 mL in the morning and 1 mL in the evening every day.

Scalp hygiene

All patients in all groups were advised regular shampoo 3 times a week. Removing dirt, grime, scalp secretions were considered important in facilitating better hair growth.

Evaluation of hair regrowth by global photography

All patients had standard photographic views with a 12 megapixel digital camera in a fixed, designated place with identical settings, the same light, same flash, same distance and same camera. Photographs were taken at day 1, then every 2 months to record the progress for 1 year. Before and after photographs taken, in 5 standard views as front hairline, vertex with head bent forward, right side, left side and occipital whorl area. Analysis of the photographs were done by 4 different evaluators who were blind to the patient profile and patient group. The criteria selected in order to evaluate in the photographs, were hair quality, hair density or fullness, reduction of bald area and new hair growth. The improvement was graded from grade I to grade V as I - no change, II - marginal change or barely noticeable change, III - noticeable improvement, IV - good improvement and V - very good improvement.

Evaluation of hair density and calibre by computerized analysis

All patients had computerized folliscope analysis for measurement of hair density and calibre at micro pigment tattooed, fixed test spots over their perceived area of thinning which was their selected area of most

concern. With the computerized folliscope analysis we measured hair growth in terms of density per square centimetre and hair calibre in microns. The counts and calibre were recorded on day one and repeated every 2 months for the 1 year period of study.

Villus hair count

Villus hair counts were recorded initially and compared over 2-month intervals for 1 year. The attempt was to correlate if such a method allows to determine the conversion of villus hair to terminal hair during the treatment period.

Self-evaluation

Patients also had a self-evaluation score at the end of 1 year. Self-assessment score were designed to record the personal response of the patients within the study. Scores were allotted to control of hair loss, appearance of new hair growth, change in the size of the bald spot and difference noticed by friends and family. Zero score was allotted for no change and negative score for deterioration of the area. An assessment score of 4 was satisfactory and 5 was considered good. A score of 3 was average and below 3 was considered poor [Table 4].

Patients were inquired about sexual side effects, loss of libido, decreased volume of semen, softer erections, gloomy feeling and difficulty to focus on the task or the feeling of disinterest. Patients were requested to report any other concerns, as number of hair falling per day, dandruff or itching.

RESULTS

Reduction of hair fall

In both the treatment groups TM and TW 68% patients reported reduction in hair fall per day within 1 month of commencing the therapy. By the end of 4 months 85% patients reported reduced hair loss. The average improvement did not improve further than 85% till the end of the study period of 1 year. Result being statistically significant with *P*-value 0.019. The remaining 15% patients said the hair loss continued to be the same, though it has not increased. In both the control groups CM and CW, hair fall continued

Table 3: Cyclical vitamin therapy low dose once in three days, have one each after breakfast odds ratio, one each after lunch odds ratio, one after lunch and one after dinner

Days of the week	Supplement combinations
Monday & Thursday	Antioxidant, calcium, vitamin D3, magnesium
Tuesday & Friday	Iron, folic acid, vitamin C & omega 3
Wednesday & Saturday (Sunday - no medicines)	Essential aminoacids, B - complex & biotin
2% Ketoconazole & zinc pyrithione shampoo	
Wet your hair, massage the shampoo into the scalp, keep for 3 min & wash, once in 3 - days	
Minoxidil 2% solution - 1mL morning & 1mL evening - everyday	

Table 4: Patient's self-assessment scores, min 0 to max 5

Criteria	Score
Area has become worse than before	-1
Area looks the same	0
Hair loss is under control	1
Area looks better than before	1
Area is showing new hair growth	1
Area of hair loss has become smaller than before	1
Friends and others are noticing the difference	1

unabated all through the study period in 41% patients having no relief. At the end of 4 months 22% patients reported that they had some relief from hair fall, while 37% patients insisted their hair fall had increased despite being on treatment.

Density and calibre

Group TM showed 18% average improvement in density at 2 months and 30% and at 4 months. All patients responded with variable improvement in density and calibre. The average improvement in calibre in 2 months was 9% and at 4 months was 21% [Figure 1]. As the follow-up continued beyond the first 4 months cycle, the patients in the treatment group TM had 51% improvement in hair density at 6 months and 76% improvement at the end of 1 year [Figure 2]. The results were statistically significant with P-value 0.00057. One patient showed a maximum of 156% further improvement in hair density by 1 year

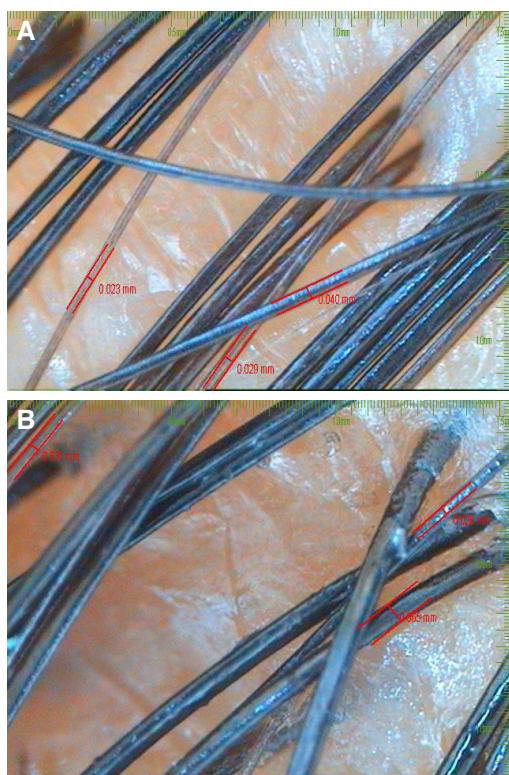


Figure 1: A: hair calibre folliscope measurement before; B: computerized folliscope measurement of hair calibre after 4 months

[Figure 3]. Patients with thinning in the crown area also responded well to cyclical medicine [Figure 4]. The additional improvement in hair calibre was 24% at 6 months which raised to 63% by the end of 1 year.

Group TW, female patients on cyclical medicine showed an average 20% improvement in density at 2 months and 36% at 4 months [Figure 5]. All patients responded with variable improvement in density and calibre. The improvement in calibre was on average 10% in 2 months and 25% in 4 months. As the follow-up continued beyond the first 4 months cycle, the patients in the treatment group TW had 41% improvement in hair density at 6 months and 70% at 1 year [Figures 5B and 6A]. The results were statistically



Figure 2: A: grade V baldness day one before starting treatment; B: improvement after 2 months of nutritional correction and 2% minoxidil; C: regrowth in grade V baldness in 6 months without finasteride

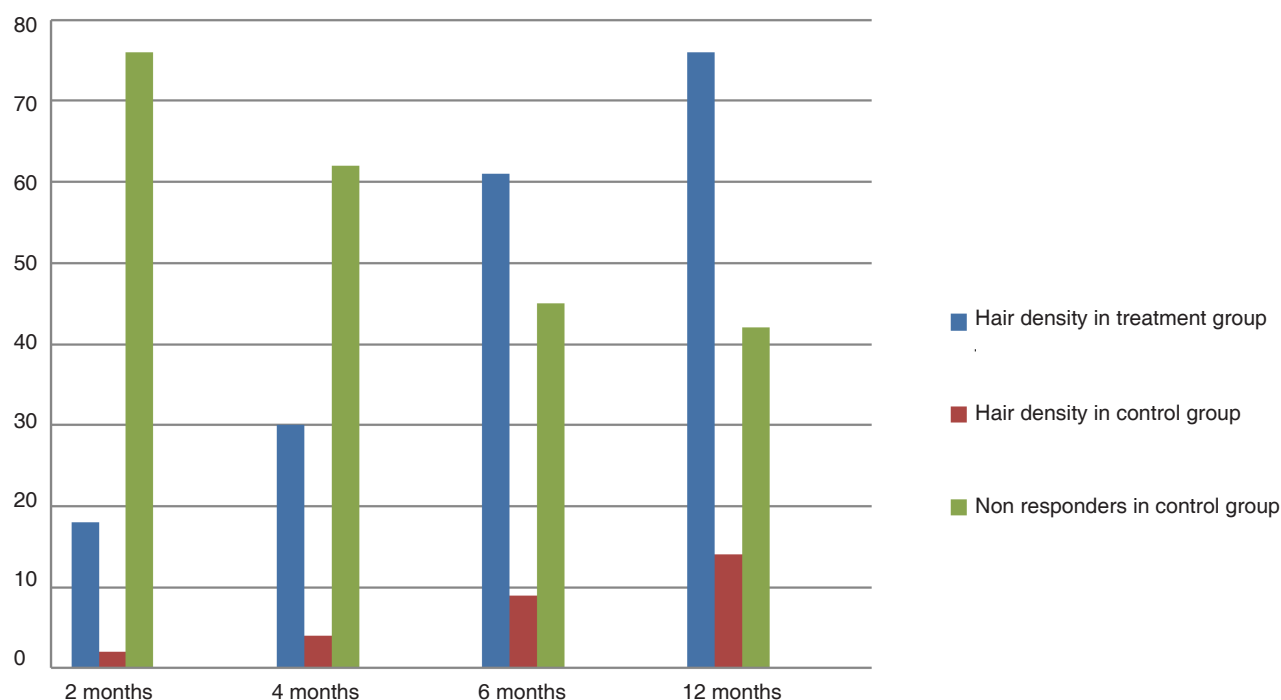


Figure 3: Hair density in men

significant with P -value 0.00038. Patients with temporal angle receding and thinning also responded well to cyclical medicine [Figure 7]. Maximum improvement in hair density in 1 of the women was 112%. Improvement in hair calibre was 33% at 6 months and 58% by the end of 1 year [Figure 8].

In the control group CM for men, 76% patients had no response in the initial 2 months and 62% had no response even at 4 months with 2% minoxidil and 1 mg finasteride every day. The density improved by an average 2% at 2 months and 4% at 4 months. Hair calibre measured on folliscope, was 2% better at 2 months and 3% at 4 months. There were 48% patients having no improvement at all in either density or calibre at the end of 4 months. At 6 months the

average improvement in density was 9% and the average calibre improved by 7%. At 1 year, the hair calibre had improved 11% while at the end of 1 year the maximum density had improved 14%. There were 45% patients with no change in density or calibre at 6 months - this number was reduced to 42% non-responders at the end of 1 year.

In the control group CW for women, density improved by 3% in 2 months and 4% in 4 months, 56% females had no improvement at all at 2 months. Density improved by an average of 1.5% in 2 months and 3.5% in 4 months. Calibre was unchanged in 60% patients, it was 2% better at 2 months and 3% at 4 months, with 38% patients still having no improvement at all in density or calibre. At 6 months, the average



Figure 4: A: crown area grade V baldness day one before starting treatment; B: improvement over crown area after 2 months of nutritional correction and 2% minoxidil; C: regrowth in grade V baldness over crown area in 6 months without finasteride

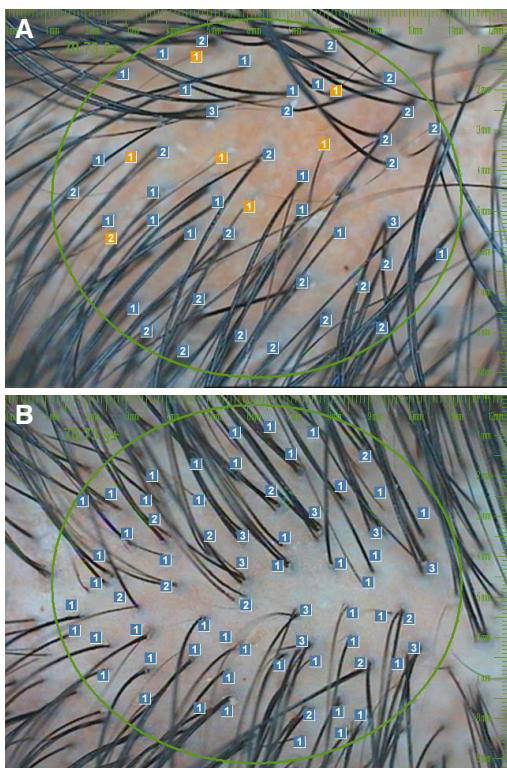


Figure 5: A: folliscope measurement of hair density before starting treatment; B: folliscope measurement of hair density after 4 months of nutritional correction and 2% minoxidil



Figure 7: A: temporal receding and thinning in female patient day one before starting the treatment; B: hair regrowth over temporal area after 4 months of 2% minoxidil and nutritional treatment



Figure 6: A: female pattern frontal hair loss day one before starting the treatment; B: hair regrowth over frontal area after 6 months of 2% minoxidil and nutritional correction

improvement in density was 10% and the average calibre improved by 8%. At the end of 1 year follow-up, the density had improved 16% and calibre had improved 12%. There were 31% patients with no change in density or calibre at 6 months. This number reduced to 26% non-responders at the end of 1 year follow-up in women.

Villus hair count

Villus hair counts were recorded initially and compared over 2-month intervals for 1 year. The minimum and maximum villus hair counts for both the treatment groups initially were between 12-35%, these reduced to between 5-24% at 4 months. The average counts again raised to 15-28% at 8 months and remained 10-21% at the end of 1 year. Villus hair counts in control groups initially were between 14-38% and changed marginally at 11-40% at the end of 8 months and were between 16-34% at the end of one year.

Global photography

The overall rating in the control groups for both men and women were similar. The grading in the control group which started as no change at 2-4 months, improved to a noticeable change in 56% patients by the end of 1 year but none could be rated as good improvement. While the rating in the treatment groups

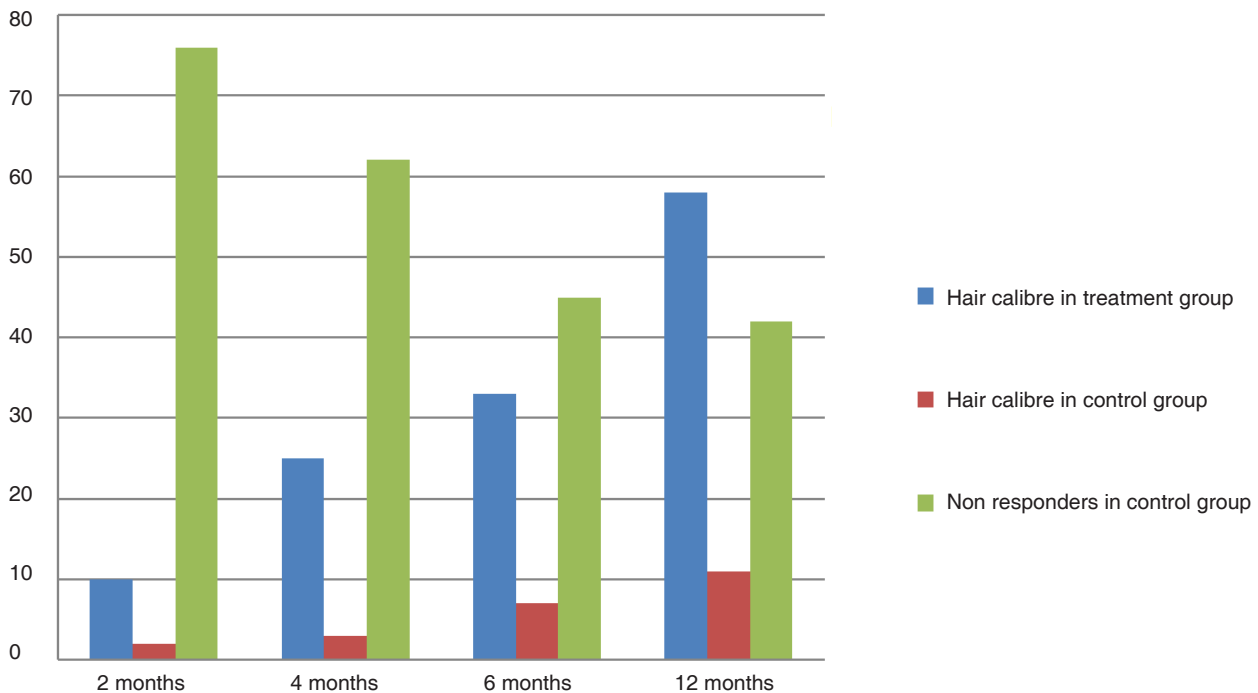


Figure 8: Hair calibre in women

for both men and women were similar, the improvement started as a noticeable change in 2 months for over 70% patients and progressed to good in all the patients by the end of 6 months, becoming very good by end of 1 year.

Self-assessment scores

Self-assessment in treatment groups TM and TW had scores of 4 seen in 70% men and 62% women noticing good hair growth within 4 months of commencing the therapy. Whereas 49% men and 74% women had a score of 5, reporting that their hair stylist, their family and friends noticed the changes in their hair growth, thickness and quality at the end of one year.

Self-assessment in the control groups CM and CW for all patients were poor, below 3. At the end of 1 year had 64% men and 71% women said that they looked the same, had continued hair loss and could not appreciate any improvement. There were 23% men and 14% women who noticed improvement in some areas and a few patients, 13% men and 15% women rated that they were worse than before.

DISCUSSION

Similar benefit as 68% reduction of hair fall in 1 month and 85% in 4 months were seen in the present study was reported by Beer *et al.*^[69] who studied the benefits from a keratin supplement with minerals and vitamins, which showed 12.5% reduction in hair loss over

placebo at 1 month, 34.5% at 2 months and 34.4% reduction in hair loss at 3 months^[69]. Rizer *et al.*^[70] who studied the benefit of marine protein supplement reported 20% reduced hair shedding within 4 months, while the placebo group had increased shedding by 50%. Hair loss in control group continued the same in 41% and increased in 37% patients at the end of 4 months. Some relief from hair shedding seen in the control group may be due to the benefit of 2% minoxidil. A certain basic amount of steady hair fall did continue even in treatment group which can be expected to happen as per the natural hair cycle.

The improvement in density and calibre in both the male and female treatment groups were similar to improvement recorded by Beer *et al.*^[69] as per their criteria for evaluation of hair quality. Beer *et al.*^[69] studied the benefits from a supplement of keratin with minerals and vitamins which showed an improvement of 17.6% at 1 month, 35.3% at 2 months, and 47.1% at the end of 3 months^[69]. Another study by Nicholas *et al.*^[71] comparing a supplement of green tea extract, omega 3 and 6 fatty acids, melatonin, cholecalciferol, betasitosterol, and soy isoflavones, over a period of 24 weeks (6 months), showed 4.9% improvement in terminal hair counts. Rizer *et al.*^[70] studied the benefit of marine protein supplement to find an overall 8% improvement in diameter for villus hair after 6 months. Rizer *et al.*^[70] did not compare terminal hair counts and hair calibre but suggested that further improvement could be possible if the supplements were continued for 1 year,

as was observed to happen in the present study at the end of 1 year.

Improvement in hair density and calibre were found to begin early within 2 months in men and women in the treatment groups having nutritional supplements. Minoxidil stimulates hair growth and the addition of nutrients provides building blocks to ensure the sudden rapid cell division required at the initiation of anagen. Antioxidants provide a toxin free cellular environment which favours hair growth^[24,25,72-74]. Use of different nutrients on different days prevents inter nutrient interactions and improves efficiency^[75,76]. It also allows the use of wide variety of nutrients without the possibility of over dose or hyper vitaminosis^[24,25,49,71,73] as the hair care is required to continue for a long time to sustain good results.

In the control groups the hair growth started after 4-6 months which is the standard time frame required for the effect of finasteride and minoxidil^[37-39,75]. The benefit with finasteride and minoxidil alone was slow and the maximum growth achieved in the control groups was below 50% of the improvement achieved in the treatment group. The results are similar to long term studies on the use of finasteride which have reported 48-59% improvement with 41-52% non-responders^[35,37] at the end of 1 year and 17% patients having deteriorated with hair loss more than the initial status after one year^[35].

Villus hair counts in our study initially reduced but were later found to rise. The initial reduction was because the villus hair had converted to terminal hair while the later rise was due to new hair growth induced with the treatment cycle and the counts finally stabilize as per the individual hair cycle and the individual turnover of hair fall and hair growth. Rizer *et al.*^[70] reported improvement in thickness of villus hair in 60% patients in their marine protein supplement study. Nicholas *et al.*^[71] reported 5.9% improvement of villus hair to terminal hair in 6 months of their study. The initial conversion of villus hair to terminal hair in our study was found to be higher, however, more villus hair were generated as new hair growth was induced. We could not establish a direct predictable correlation between reduction of villus hair counts and a proportionate improvement in hair growth.

Our study has noted early improvement in global photography evaluation within 2 months and reached higher grades of improvement over the period of completing the study. Similar evaluation was reported by Nicholas *et al.*^[71] with overall improvement of 80% on global photography out of which 40% were regarded as moderate and 10% excellent improvement in a period of 6 months. Our study being for 1 year,

had the time for all the treated patients to achieve very good improvements.

Having self-assessment scores was a unique feature of our study. Patients appreciated the fact that they were allowed to express their concern and rate their results in the form of a score. The system also encouraged interaction of the patients with their friend, family and hair stylist who approved and agreed of noticeable changes in the hair. Thus the improvement was not only subjective.

Side effects

Irritation from minoxidil 2% solution causing burning, redness or itching after application was seen in 8% patients. This is mainly due to the propylene glycol and not due to minoxidil. Dryness of scalp after minoxidil 2% application was seen in 26% patients^[76]. Use of moisturizers on the scalp helped in these cases. Sexual side effects were reported by 4% of patients in the control group after the initial 2 months of therapy and 9% patients after 4 months of the therapy. These men had a loss of libido, decreased seminal volume and softer erections. Feeling gloomy, lack of enthusiasm, taking longer to complete the work at hand and being disinterested in meeting friends was reported by 7% patients. All these were patients having 1mg finasteride every day. Similar side effects which can be persistent, were reported by Irwig^[38] and by Traish *et al.*^[39]

The nutritional supplements caused gastric irritation, constipation, feeling of heaviness in the stomach, nausea or feeling of acidity in 7% women and 3% men. Though supplements were in low dose and spread over a 3 day cycle, 2 women doubted they had marginal weight gain due to the program. Rizer *et al.*^[70] in their study of marine protein supplement reported 3 patients in treatment group and three patients in the placebo group complaining of bloating and stomach discomfort. Lengg *et al.*^[15] in their study on nutritional therapy in telogen effluvium, reported gastric discomfort and weight gain. Sarris *et al.*^[77] in an individual study of multivitamins also reported of gastric discomfort in their study group. In the present study, it was noted that, the days when calcium and iron were included caused the most gastric problems. Avoiding supplements on empty stomach, dividing the supplements into 2 separate doses 1 supplement after breakfast or lunch and second supplement after dinner helped to ease the gastric symptoms.

Beneficial effects

Patients reported improved wellness on the low dose vitamin therapy. A female patient who preferred

having regular blood test on her own, initially had a haemoglobin never above 9.6 gm for past 10 years, reported a level of 11 gm in 2 months and 14 gm in 4 months. Patients had better energy levels, better stamina at work, improvement of small aches and pains, better skin, better nail growth, feeling of wellness, better grasping of studies in college, good sleep and waking up fresh, with the vitamin therapy. Similar benefits were also reported by Sarris *et al.*^[77] in their study of multivitamins.

In conclusion, finasteride was introduced for hair loss management by serendipity. The benefit from finasteride is seen clinically only after 6 to 9 months and long term studies have shown that it is effective only in 50-60% cases. DHT is not always raised in hair loss patients. Not high DHT but increased sensitivity of the hair follicles is the cause for miniaturization and hair loss. Instead of long term use of DHT blockers with the fear of side effects, we have studied a better option of strengthening the hair roots and promoting hair growth with nutritional supplements. The prospective controlled clinical trial shows that a low dose cyclical nutritional program planned to avoid nutrient interactions and improve synergy can be used to achieve consistent hair regrowth in men and women beginning within 2-4 months and continuing to benefit for 1 year. We can regrow hair safely, without our patients having to depend on finasteride which has been recently recognized to have persistent side effects.

DECLARATIONS

Authors' contributions

The author contributed solely to the paper.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients volunteered to give consent and made a choice to be enrolled in the conventional therapy group or the nutritional therapy group. All patients also agreed to complete the study for a period of one year.

Ethics approval

Not applicable.

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Degree and location of metacarpal angulations

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ABSTRACT

Aim: Fractures of metacarpals are commonly encountered in hand surgery. For adequate fixation, a thorough knowledge about the anatomy is essential. While fixing the metacarpals with plates and screws, plates are bent to contour the dorsal surface. However, there are no reference values in literature for the location and degree of angulation. The authors studied the dorsal surface of metacarpals in cadavers to gather data regarding the location and degree of angulation of the dorsal cortex. **Methods:** Cadaveric dissections of 118 metacarpals from 30 hands were performed. A true lateral view of each metacarpal was taken using fluoroscopy. These pictures were analyzed using Image J software. The dorsal cortex angle was measured in each image, and the center of rotation of angulation (CORA) was identified. The distance from the CORA to the base of metacarpal was measured and calculated as a percentage of the metacarpal length. **Results:** The average dorsal angle of the metacarpals was 11.5°. The average angles for each metacarpal were as follows: 2nd metacarpal = 13° (range, 6-26°; SD, 4.73), 3rd = 10° (range, 1-25°; SD, 5.28), 4th = 11° (range, 1-20°; SD, 4.45), 5th = 12° (range, 2-24°; SD, 5.11). The average location of the CORA from the base of the metacarpal as a percentage of the metacarpal length was identified as follows: 53.5% for the index finger, 52.1% for the long finger, 48.3% for the ring finger and 50.3% for the small finger. **Conclusion:** These measurements are able to serve as reference values for plate bending while operating on a metacarpal fracture or metacarpal corrective osteotomy.

INTRODUCTION

Metacarpal fractures are a common injury of the hand, with an incidence of 13.6/100,000 in the United States each year^[1]. The angulation and displacement are crucial factors in determining operative management. There are various options for fixation of metacarpal fractures which include K wires, intramedullary nails, plates and screws, and external fixators. Plate and screw fixation is commonly employed for complex injuries^[2].

During plate fixation, it is a common practice to bend the plates^[3]. If the plate is not adequately bent, tightening the screws will result in a gap in the opposite cortex [Figure 1]. The location and degree of plate bending can be challenging to predict, especially in cases of a comminuted fracture, or fracture with bone loss. Therefore, a thorough knowledge of the anatomy of the dorsal surface is important. However, literature is scarce with this regard. The various metacarpal parameters described in literature include capital and subcapital angulations, proximal articular inclination,



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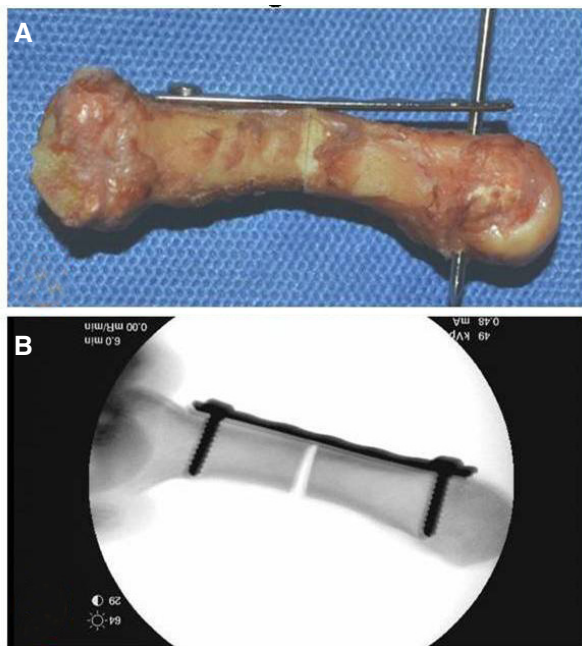


Figure 1: A: metacarpal with a plate placed across a transverse fracture; B: tightening the screws without bending the plate results in gap formation

and the shaft bending angles^[4,5]. These measurements do not aid in plate bending.

It is technically difficult to obtain the dorsal angulations on a conventional lateral radiograph in a living patient due to overlap of metacarpals. Thus anatomical study is necessary.

METHODS

The study was performed in cadaveric metacarpal models. Statistical power studies demonstrated that 100 specimens were required to obtain statistical significance. After obtaining approval from the Human Tissue Committee, thirty cadaveric hands were

dissected to harvest 118 metacarpal bones. Two hands had one digit missing. The bones were dissected free from the surrounding soft tissue.

After harvesting the metacarpal, a true lateral view of each metacarpal was taken using fluoroscopy. The pictures were analysed by Image J software (National Institute of Health, Bethesda, Maryland, USA).

Dorsal cortex angle and centre of rotation of angulation

Using the Image J software on the lateral view, two lines were drawn. The first line was drawn from the base of the metacarpal, along the dorsal surface distally. A second line was drawn from the neck of the metacarpal, along the dorsal surface proximally. The point where these two lines meet was identified as the center of rotation of angulation (CORA). The angle between the two lines was recorded as the dorsal cortex angle [Figure 2].

Location of CORA-CORA ratio

The location of the CORA was calculated as a ratio as follows: the distance from the CORA to the metacarpal base was measured against the total length of the metacarpal to get the CORA ratio [Figure 2].

The metacarpals were assigned numbers, and measurements were taken by blinding the observer to avoid observer expectancy bias.

RESULTS

Dorsal cortical angle

Table 1 demonstrates the mean dorsal cortical angles and standard deviations in the 30 cadaveric hands. The average angles were as follows: 2nd metacarpal = 13° (range, 6-26°; SD, 4.73), 3rd = 10° (range, 1-25°; SD 5.28), 4th = 11° (range, 1-20°; SD, 4.45), 5th = 12°

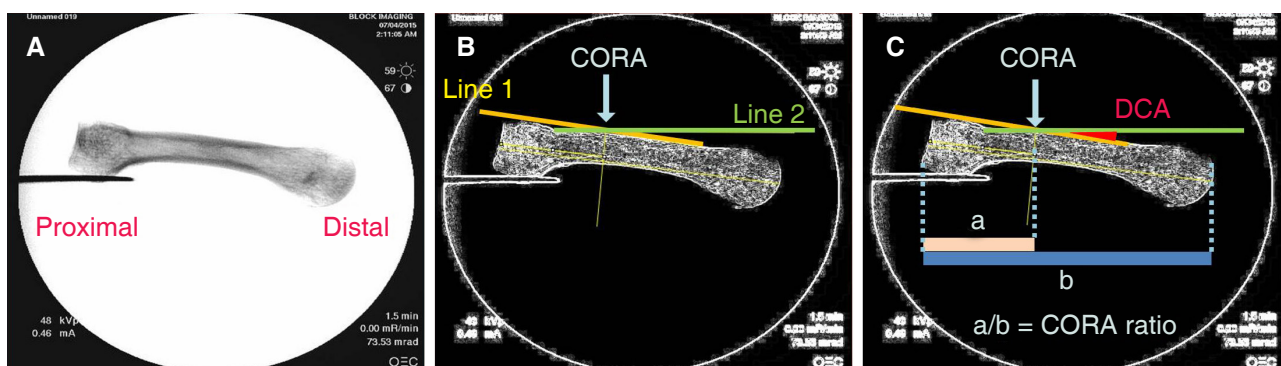


Figure 2: Showing the calculation of DCA and location of CORA. A: lateral fluoroscopy view of metacarpal; B: two lines were drawn. The first line was drawn from the base of the metacarpal, along the dorsal surface distally. The second line was drawn from the neck of the metacarpal, along the dorsal surface proximally. The point where these two lines meet was identified as the CORA. The angle between the two lines was taken as the DCA; C: the distance from the CORA to the metacarpal base was measured against the total length of the metacarpal to get the CORA ratio; DCA: dorsal cortical angle; CORA: center of rotation of angulation

Table 1: Dorsal cortical angle

	Mean (°)	Range (°)	Standard deviations
2nd	13	6-26	4.73
3rd	10	1-25	5.28
4th	11	1-20	4.45
5th	12	2-24	5.11

(range, 2-24°; SD, 5.11). There was no progressive difference as we moved from the II digit to the V digit.

CORA ratio

The following CORA ratios were obtained: 53.5% for the index finger (range, 42-85%; SD, 12.5), 52.1% for the long finger (range, 32-100%; SD, 17.8), 48.3 for the ring finger (range, 34-86%; SD, 11.5) and 50.3% for the small finger (range, 27-86%; SD, 12.4) [Table 2]. The location of CORA was found to be consistent across the four digits [Figure 3].

DISCUSSION

The knowledge of anatomical characteristics of metacarpals is crucial in diagnosis of metacarpal fractures and planning treatment. Assessment of the metacarpals is routinely done by radiographs. Braakman^[4] defined various radio graphical parameters of metacarpals of the ring and small fingers. The purpose was to gain consistency in reporting and to reduce inter-observer variations. These parameters include 4 axes and 4 angles. The axes were: (1) full-shaft axis: line through the centers of the shaft, measured at 1/3 and 2/3 of the bone length; (2) capital axis: line drawn perpendicular to a line through the widest part of the caput, indicating the end of the cartilage cap; (3) sub capital axis: the “logic” axis through the middle of the subcapital neck; and (4) proximal articular line: the tangent to the 2

Table 2: Center of rotation of angulation

	Mean (%)	Range (%)	Standard deviations
2nd	53.5	42-85	12.5
3rd	52.1	32-100	17.8
4th	48.3	34-86	11.5
5th	50.3	27-86	12.4

bony eminences in case of a concave bony ending, as a line through the points indicating the widest osseous space in case of a convex cortex ending, and in case of a flat bony ending as a line parallel to this surface. The angles were: (1) capital axis angle (CAA): angle between the capital-axis and the full-shaft axis; (2) sub CAA: this is formed by the angle between the subcapital axis and the full-shaft axis; (3) shaft bending axis (SBA): this lies between the proximal and distal shaft-axis. The proximal and distal shaft-axis are defined by the 2 lines connecting the centers of the proximal shaft (measured as 1/3 and 1/2 of the metacarpal length) and the distal shaft (measured as 1/2 and 2/3); and (4) the proximal articular angle: this lies between the full-shaft axis and the proximal articular line.

In their study, Braakman^[4] reported CAA of 22° and 27° on the postero-anterior view and 19° and 24° on the oblique views for the ring and small metacarpals, respectively. They found that the SBA was 2° in all tested digits in both projections. Rivlin *et al.*^[5] analysed the CAA and SBA using computer tomography with three dimensional reconstruction. They showed that CAA averaged 14° and 12° in the ring and small metacarpals, respectively. Apex dorsal SBA averaged 12° and 10° in the ring and small metacarpals, respectively. Although these studies describe important anatomical landmarks which aid in repairing the fracture, they do not provide any detail regarding the “surgically important” dorsal surface.

In our study, we specifically measured the dorsal surface angulations. Since plate fixation involves the dorsal surface, the knowledge of its anatomy is imperative for successful plating. It has been traditionally considered that the dorsal surface is convex^[6]. However, our results suggest that it is more angular than it is curved. In our study we obtained the average CORA ratio and dorsal cortex angle, which answers “where” and “how much” the angulation is. The numbers that we developed can serve as reference values for future metacarpal fixation procedures.

Knowledge of these angulations would be even more important in surgical correction of malunions. Bimdorf *et al.*^[7] studied the effect of angulation on metacarpal fractures and found that with progressive increase in metacarpal

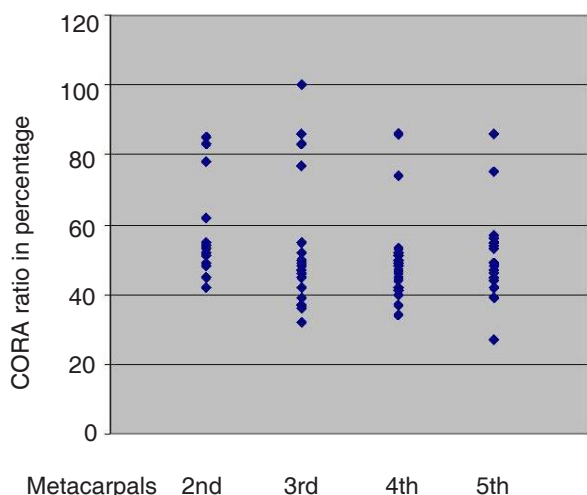


Figure 3: Scatter diagram showing distribution of CORA ratio. CORA: center of rotation of angulation

angulation, there was an increase in tendon excursion, tendon load, and work required for flexion. Thus, returning the metacarpal to normal alignment is imperative.

In any curved long bone, the concave surface bears the compressive force. When such bones are fractured, the load bearing osteosynthesis should ideally tackle this concave surface. In the context of metacarpals, the volar surface would be the compression cortex. However, the easily accessible dorsal surface is preferred for plating, even though it is not the compression cortex. Metacarpals have attachments of A1 pulleys, and the flexor tendons, passing under these A1 pulleys, exert a flexion force on the distal part of the metacarpal. In setting metacarpal fractures, the flexor tendons can lead to volar angulation of the distal fragment. This may also account for increased incidence of screw loosening seen in the distal fragment^[8]. Since the angle of the metacarpals is in the same direction as the flexion force, it may contribute to volar displacement as well as screw loosening.

In conclusion, the dorsal surface of metacarpals has an angulation rather than a curvature. The location of the angulation is somewhat consistent at the middle of the metacarpal. The degree of angulation is variable.

DECLARATIONS

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Authors' contributions

Analysis and interpretation of data, drafting of manuscript and critical revision: L. Bhandari

Study conception and design; acquisition, analysis and interpretation of data: C. Sathega, F. Aguilar, L. Vicentela, E. Galvis
Drafting of manuscript and critical revision: E. Galvis

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

This study obtains approval from the Human Tissue Committee.

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Case Report

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Teen aesthetic surgery may eliminate bullying

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ABSTRACT

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The media has a large influence on what constitutes modern day beauty, as it suggests to susceptible young girls and boys what makes someone beautiful. The term “beautiful” is portrayed as curvy, thin, tall, with voluptuous hair, big eyes, large breasts, round buttocks, and full lips. Very few people in society naturally appear like this, and thus many people undergo cosmetic surgery for this desired look. This article will examine the difference of opinions regarding the exact age to consider aesthetic plastic surgery. Adolescence is frequently bullied about any defect. The authors discuss some of these opinions and present three very unusual cases where early surgery has been beneficial.

INTRODUCTION

Anyone with a real or imagined physical defect such as a crooked nose, asymmetrical face, small or large breasts, or being “overweight” can be very sensitive to comments made by others. This is profoundly important to teenagers as their body changes and everyone compares each other to everyone else. The media, movies, magazines and peers, add fuel to the fire of desire for acceptance.

The development and ubiquity of “social media”, has made ridicule and bullying, fast, easy and public beyond a few peers. The effects can be devastating

for adolescences. Bullying may be the single most common cause for teen suicide.

Aesthetic or cosmetic surgery was a natural outgrowth of plastic reconstructive surgery that occurred following World War I and II, when medical advances such as antibiotics and sterilization made it possible for people with severe injuries to survive. They often required reconstructive surgery to create a more normal appearing face, hands, and other body parts. Due to the imbalance that was caused when only one side of their body was reconstructed, it became aesthetically necessary to operate on both sides in order to obtain a balance. It is also noted that patients looked younger



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through a variety of techniques such as brow lifts, face lifts, rhinoplasty, and other procedures developed to completely change the body from subnormal to a more aesthetic appearance.

Aesthetic surgery is a growing popularity fueled by a culture that idolizes a youthful appearance^[1]. Popular operations include breast augmentations, tummy tucks, and liposuction. More than 4,000 teenagers, ages 18-year-old and younger have had breast implants and over 6,000 have undergone liposuction. Over the years, the number of plastic surgery procedures in teens has increased from 59,890 in 1997 to more than 205,119 in 2007, nearly 4 times as many, according to Conwell^[2]. Many experts claim that this increase is most likely fueled by the media through Internet and television.

Recently, there has been more of a debate over the controversy as to whether or not teens should undergo cosmetic surgery. Some argue that teenagers are simply concerned with their appearance and how their peers may view them. Undergoing plastic surgery would only suggest that happiness is “a nip and a tuck away”, argues Arthur Caplan in Friedman’s^[3] article. Moreover, many adolescents are not completely developed yet and have not had ample time to become accustomed to their own bodies, and thus should not be going under the knife to fix their changing insecurities. Other experts such as Schneweis^[4] claim that surgeries only offer temporary fixes and that despite a “new physical image, a fragile self-esteem may still exist”. Furthermore, plastic surgery is the reconstruction of a new image, which is what those like Gilbert^[5] claim to be “against nature”.

Cutis laxa refers to a rare condition that can be acquired or congenital, in which skin becomes hypoelastic causing loose, redundant skin^[6-7]. The effect of this condition causes the patient to appear decades older than their actual age^[8-12]. For children suffering from this rare condition, aesthetic surgery has shown to provide a dramatic improvement in skin laxity. Aesthetic surgery to enhance the appearance of cutis laxa patients dates back to the late 1960s, where patients as young as 13-month-old benefited from such surgeries. In 1969, Dingman *et al.*^[9] reported a case in which a 13-month-old patient underwent the excision of large amounts of redundant skin of the neck. At just 16 months, the same patient underwent a rhytidoplasty with excision of redundant skin from the scalp, face, and neck on her right side. *The British Journal of Plastic Surgery* advocates for early surgical intervention in these patients, who benefit psychologically and emotionally from aesthetic surgery^[7].

In 2013, approximately 30% of American adolescents were overweight or obese. This corresponds to the 47% increase in global obesity since 1980^[13]. With the rise of childhood obesity, more and more teens are undergoing weight loss surgeries such as bariatric surgery and liposuction. The controversy that surrounds childhood obesity is often fueled by critic’s belief that surgery is not a necessary means for weight loss and that diet and exercise are sufficient to achieve desired results^[14-16]. However, many experts argue that there is no effect of diet in the treatment of pediatric obesity and studies would suggest that dietary restriction alone is ineffective in adolescents^[17-19]. Overweight and obese children lack the self-worth and social support associated with psychosocial adjustment^[20]. Further research expresses the psychological effects of childhood obesity that equate to “depression, low self-esteem, and social marginalization and have decreased physical activity and lower academic scores”^[17]. The Wall Street Journal (14 Sep 2017) showed that suicide is the most common death for Americans between the ages of 15 to 34. Obstructive sleep apnea (OSA) has also been associated with obesity in adolescents. The International Journal of Pediatric Otorhinolaryngology suggests that weight loss in adolescents significantly improves the effects of OSA^[21]. One study consisting of patients ages 13-21 years old undergoing bariatric surgery showed a long term decrease in the prevalence of type II diabetes from 16% to only 2% after 5 plus years post-op^[22].

Psycho-cybernetics

Maltz^[23] defines self-image as the “foundation upon which your entire personality, your behavior, and even your circumstance are built”. He goes on to say that one is “never too young or too old to change his self-image and thereby start to live a new life”. In recent years, this aspect of being “too young” has gained much media attention and controversy as more and more teens undergo aesthetic surgery in an effort to change their self-image. Self-image refers to the manner in which one views themselves, and is directly correlated to one’s self-esteem. Maltz^[23] goes so far as to say “self-esteem is as necessary to the spirit as food is to the body”. When individuals, especially teenagers and young adults, lack a level of self-confidence, they become inherently vulnerable to rejection and psychological damage. The effect of this psychological damage can be detrimental to a teenager and their ability to function at their optimum. “When your self-image is adequate and one that you can be wholesomely proud of, you feel self-confident. You feel free to “be yourself” and to express yourself. You function at your optimum”^[23].

Beauty pays

Hamermesh^[24] argues that those who are considered less attractive will suffer economically as compared to their colleagues who are equally as qualified, trained, and intelligent, but are considered more attractive by social means. This disadvantage equates to a loss of “\$140,000 over a lifetime compared to the earnings of an average-looking worker”. In his concept referred to as “protecting the ugly”, Hamermesh^[24] compares the level of disadvantages that a less attractive person experiences to that of an individual subject to discrimination based on gender, race, or disability status. Thus, he argues that the government should protect “ugly” individuals in the same ways as it has historically protected other disadvantaged groups. This protection would be for the benefit of both the “ugly”, as well as the economy as a whole. He suggests correcting this net worth disparity by cash compensation from the government. He fails to mention, that cash contribution could be used to correct the very defaults that qualify for the beauty impaired (see three cases below).

The American college of obstetricians and gynecologists recently published a committee opinion based on the increasing interest of adolescents in breast and labial surgery. The committee emphasizes the necessity of physical maturity and emotional readiness when dealing with adolescent patients, as well as “education and reassurance regarding normal variation in anatomy, growth, and development”^[25]. The necessity of these procedures is often questioned and highly controversial, as nonsurgical alternatives appear to be much more practical and less invasive for adolescents. Dr. Abbey B. Berenson believes that most women will likely never notice the variance in appearance of external genitals, and those that do feel insecure about their genitalia should be well informed and counseled on this natural variance^[26]. This normal variation among women includes size, shape, and appearance of external genitalia including the labia minora. The committee argues that asymmetry is seen as a “normal variant” and “despite increased awareness and focus on the appearance of the external genitalia, no consensus on the definition of labial hypertrophy or criteria for surgical intervention has been established”^[25]. In another opinion published by The American College of Obstetricians and Gynecologists, the committee argues that patients who are already anxious and insecure regarding their genital appearance or sexual function may actually be “further traumatized” by such procedures that lack supporting data on safety and efficacy. The committee states it is “deceptive” of physicians to give the impression that such procedures are accepted and

routine surgical practices^[27]. They seem to be unaware of the extensive literature that discusses standards of normality^[28-31] and other opinions based on actual clinical experience with patients and their families.

Countless evidence provided by Michael Olding in Friedman's^[3] article seems to show that plastic surgery can actually limit psychological consequences and physiological consequences. For example, otoplasty helps remove what others coin “dumbo ears”, which in effect removes the bullying stimulus. Other operations, such as breast reduction, gynecomastia and macromastia, can actually help with physiological consequences as extremely large breasts can cause back and shoulder pain. Through undergoing cosmetic surgery, procedures can alleviate significant psychological strain and improve self-esteem. Moreover, it is unfair that teenagers should be excluded from plastic surgery simply due to their age, especially when some parts of the body such as the nose, reach complete maturation in the teenage years. Furthermore, plastic surgery is not harming anyone else and only helps boost self-confidence of the patient, and thus should be allowed for anyone, no matter what age, seeking out aesthetic surgery.

CASE REPORT

All of our patients have been operated in our outpatient surgery facility where they were discharged to go home or to a hotel that night. All of our previous patients have been treated with valium and ketamine sedation exclusively. We have performed more than 30,000 aesthetic operations since 1978 to the present day; all have been performed with valium and ketamine sedation, discharged same day. In 40 years, there have been about 100 patients under 18 years of age none experienced complications, deep vein thrombosis or mortality ever. We present 3 cases in detail of teenage cosmetic surgery to illustrate that earlier is better.

Patient 1

Our first patient was a 15-year-old girl who had a peculiar habitus, perhaps Ehlers-Danlos syndrome where she had very lax skin, a hypoplastic chin and a large nose. She was depressed because she looked far older than her older sister and even her mother. They were unable to find anyone in her native England homeland to consider doing aesthetic surgery for a 15-year-old girl. Thus, she was an outcast at school, was ridiculed and had a terrible self-image. The patient had even contemplated suicide.

As seen in the **Figure 1**, we did a face-lift, brow-lift, rhinoplasty, and chin augmentation for this girl as an

outpatient. She is now back in school, has been living a normal life, is engaged, and will soon be married. She and her family were delighted with the results and she is now a normal, happy person.

Patient 2

Our second patient [Figure 2] was a 12-year-old grossly overweight girl, at an astonishing 230 pounds. She had tried every method of dieting possible, but nothing had worked^[32]. Her father called in asking if we would consider doing liposuction for a 12-year-old girl. Our initial impulse was to decline, but we decided

to meet with her family. In the process of discussing different liposuction methods, the family explained that their daughter was unable to exercise because after an attempt to run or do strenuous calisthenics, she would become plethoric and dyspnic. She confided that she had no friends and was bullied for being overweight.

She mentioned how she had gone to a birthday party in which the whole class was invited. Later that night, the parents of the birthday child called for her mother to come take her home, but she had noticed that all the other girls had sleeping bags hidden. She felt that they sent her home because they did not like her



Figure 1: A: Patient 1 at age 15 holding her birth certificate; B: patient 1 at 6 months later, post brow lift, face lift, rhinoplasty, autologous fat transplantation to lips (3 mL upper lip, 1 mL lower lip) and cheeks (3 mL each), and chin augmentation; C: side view of patient 1 prior to surgical procedures; D: side view of patient 1 at 6 months post-op; E: profile view of patient 1 prior to any procedures; F: profile view of patient 1 at 6 months post all procedures

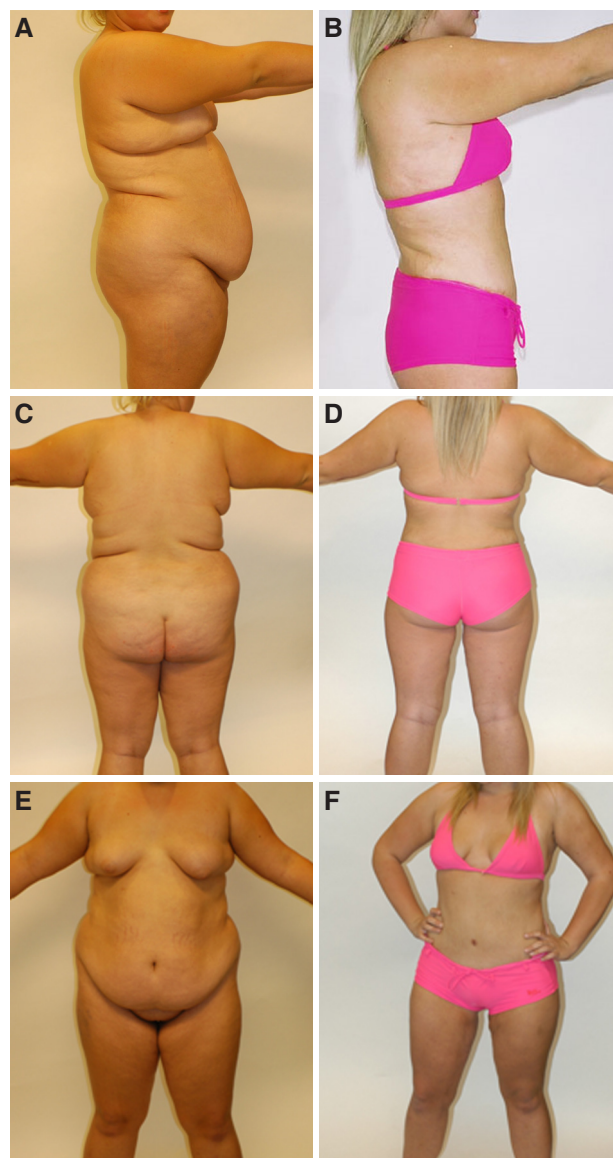


Figure 2: A: Patient 2 at 12-year-old and 230 pounds; B: patient 2 at 5 months post liposuction (3 times), abdominalplasty, brachioplasty, and medial thigh lift. Total weight loss of 58 pounds and weight of 185 pounds; C: rear view of patient 2 at 219 pounds, prior to all surgical procedures; D: rear view of patient 2 at 5 months post-op at a weight of 160 pounds; E: front view of patient 2 prior to any surgical intervention; F: front view of patient 2 at 5 months post-op

in company. As a result, she was quite desperate to have something done and had even mentioned the thought of suicide. The patient discussed her hope of her father seeing her in a nice dress before he died of bladder cancer.

To help her achieve her dreams and eliminate humiliation, we did liposuction with 2 units of autologous blood and removed 15 L (about 38 pounds) of subcutaneous fat (including 8 L of infiltration), followed by 2 other liposuction procedures after waiting for complete healing in 6 weeks. Additionally, we did a breast augmentation, abdominoplasty, brachioplasty, and a thigh lift on the patient.

Figure 2A shows the patient at just 12-year-old and 230 pounds, prior to any surgical intervention. Her menarche had begun at age ten so physiologically, she was mature.

Figure 2B was taken just 5 months after all procedures and an astonishing 58-pound weight loss. Since then, the patient continued her weight loss journey and weighed in at 152 pounds after a year. Her life has become normalized, as she is enrolling in college as a nursing student and has recently gotten married.

Patient 3

Case 3 [**Figure 3**] is a 14-year-old boy who was overweight. He had very few friends and was an

introvert because of low self-esteem, especially pertaining to his big legs, gynecomastia, and overweight body habitus. His father brought him in to evaluate his lower extremities, as he was concerned the legs may become a chronic lymph edema or permanent deformity.

Under valium and ketamine sedation, we performed liposuction to his legs, pelvis, abdomen, and chest. After returning back to school, he obtained more friends, became athletic, a straight A student, and took extra elective courses so he could graduate from high school with a grade point average above a 4.0. He has recently been accepted to a top university of his choice.

DISCUSSION

It is often stated by people like caplain in Friedman's^[3] article that teenagers are too young to make a decision about their appearance permanently. It perhaps would be better to wait until they are fully mature, at ages 21 through 25. Moreover, some believe that surgery is risky for young people. However, there is no evidence for that rumor, as we do not hesitate to operate on infants with cleft lips at merely 10 weeks of age, 10 pounds of weight, and hemoglobin of 10 grams. Otoplasties are usually performed before children go to school to prevent them from being ridiculed for their entire life^[3].

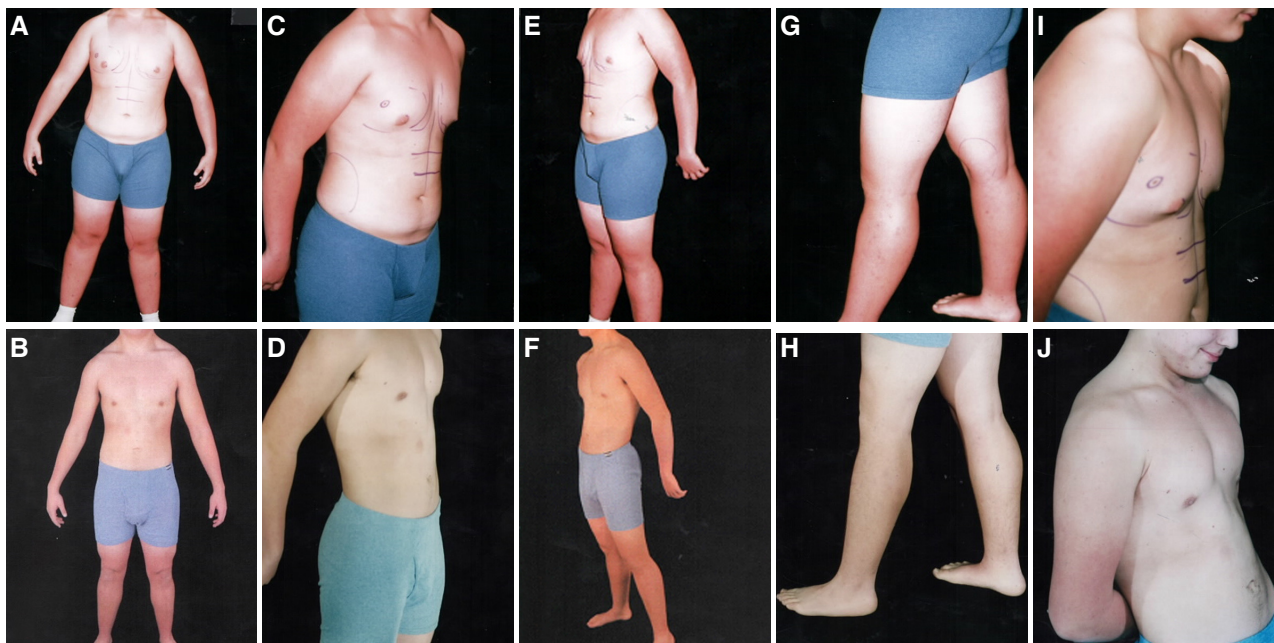


Figure 3: A: Patient 3 at 14-year-old and 220 pounds; B: patient 3 one year later, post liposuction to his chest, abdomen, flanks, knees, calves, and thighs; C: patient 3 prior to any surgical intervention; D: patient 3 one year post-op; E: side view of patient 3 prior to surgical procedures; F: side view of patient 3 one year post-op; G: legs and calves of patient 3 prior to any surgical procedures; H: legs and calves of patient 3 one year post-op; I: side view of chest and abdomen of patient 3 prior to all surgical procedures; J: side view of chest and abdomen of patient 3 one year post-op

Lee et al.^[33] studied 3,534 adolescents. Their findings were that, "Adolescents involved in bullying, in any role, were significantly more interested in cosmetic surgery than uninvolved adolescents." Desire for cosmetic surgery was highest in girls. Being victimized by peers resulted in poor psychological function.

In a review of the literature, they found that 50% of adults seeking cosmetic surgery report a history of teasing or bullying mostly during adolescence^[34-37]. There is now ample evidence that peer victimization is a childhood trauma that negatively affects psychological function both concurrently and longitudinally^[38-42].

There is no reason why these children should be condemned to suffer for so many years as they are often socially rejected and are treated negatively by their peers. These children undergo psychological damage through being bullied or teased about their appearance. Furthermore, the younger the individual is, the healthier they generally are, and the more likely they are able to respond favorably to a surgical procedure^[3-5,23,24,32]. The safety of procedures like sequential (serial) liposuction has been extensively studied and there is much literature that supports this method of large-scale liposuction^[43-46]. As seen in patient number 2, the safest method of removing large amounts of fat is to remove the fat in serial subsequent episodes^[26]. The effect of this level of weight loss on a young person is not only psychologically and emotionally beneficial, but also a key step into a healthier lifestyle, a lifestyle that is not subject to health factors like Type II diabetes, hypertension, etc.^[26]

The protocol of using ketamine and valium sedation is "found to be effective, reliable, and reproducible, and the experiences of the patient and plastic surgeon has been overwhelmingly favorable^[47]". The surgery should be performed after complete consultation with their parents at any age^[48-50]. The guidelines are: (1) objective evidence of a correctible defect by the surgeon and staff; (2) the patient actively seeks correction; (3) both parents agree. Thus aesthetic plastic surgery may make a substantial difference in a child's life.

DECLARATIONS

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Authors' contributions

Chief Surgeon for each case, collected photos, wrote

the case report: R.A. Ersek
Editorial review and offered clinical advice pertaining to literature: D. Derrick, L. Crawford, J. Sheridan, R. Buckspan
Researched related literature and corrected article grammar: A. Delgado, S. Gualy, D. Vo, M. Salisbury

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Conflicts of interest

There are no conflicts of interest.

Patient consent

In this study, all patients give their consent.

Ethics approval

Not applicable.

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Towards the future of plastic surgery: from flaps to microsurgery and regenerative medicine and biofabrication?

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Plastic surgery is a specialty that is now worldwide recognized as its own academic discipline within the surgical community. The roots however are as old as 600 BC when in the Sushruta Ayurveda the reconstruction of a nose with a flap from the forehead was described. Plastic surgery is a problem solving discipline that meanwhile is an integral part within modern surgical concepts. A number of groundbreaking inventions and developments from plastic surgery had led to relevant innovations and these influenced the whole field of surgical specialties, including the nobel prize for the first successful renal transplantation, performed by the plastic surgeon John Murray. Although principal details of operation techniques that had been described as early as 600 BC are still part of the surgical armamentarium, many innovative methods have enriched the current spectrum of possibilities. Whereas over many centuries techniques of reconstruction utilized delayed pedicled random pattern flaps and needed multi stage

procedures (even before the advent of anaesthesia) today axially vascularized and perforator based flaps have replaced these often tedious and painful techniques. It was the publication of the Indian method of nose reconstruction in the Gentlemen's magazine in England that replaced the random pattern flap based method that was described in Tagliacozzi's two volume book *De Curtorum Chirurgia per Insitionem* (1597), where he detailed the different surgical steps with graphic illustrations that became a hallmark of surgical textbooks ever since.

When within the last decades the rapid development of microsurgery allowed for transplantation of vascularized tissue to almost any part of the body this spread as a fascinating extension of older surgical methods to many other surgical specialties as well. Modern reconstructive and oncological concepts rely on the interdisciplinary character of plastic surgery making our specialty an essential part of any reconstructive



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concept and rendering plastic surgery as a problem solving discipline within the concert of all medical specialities. It has been shown that such modern interdisciplinary concepts contribute significantly to improving the patient's quality of life.

As an example one can look at the salvage of hypovascularized wounds in the lower extremity, that is made possible by transferring well vascularized tissue utilizing microsurgery. This concept utilizes the surgical induction of angiogenesis for the treatment of chronic, poorly vascularized wounds, such as in diabetic ulcers and ulcers following arteriosclerotic disease^[1-5]. Autologous venous bypass grafts can be used as a prolongation or as arterio-venous loops to allow for a distal free flap connection even in the absence of appropriate local vessels, before amputation is necessitated. We have been using this concept for more than 20 years now and have investigated a larger cohort of such selected patients who needed bypasses and microsurgical free flaps. We have therefore assessed and advocated an algorithm based on our results and from current literature data^[6-11].

Perforator flaps have significantly contributed to a further reduction in donor site morbidity when compared to myocutaneous or muscle flaps. Perforator flaps have been advocated to be another soft tissue choice for all zones of the lower extremity, recognizing that donor site function preservation is their major asset because in such perforator flaps no muscle needs to be included [Figures 1 and 2]. When patients do not have relevant microperfusion problems in the recipient area and when arterial inflow is not compromised, peninsular, propellor, or advancement perforator flaps can be regarded as valuable local non-microsurgical flap alternatives in appropriate cases^[12]. However, the indication to decide whether a local flap or a free tissue transfer is necessary depends on the localization



Figure 1: A 58-year-old male patient with pretibial defect following radical resection of malignant melanoma with exposed tibial bone and immediate aspect at the end of free microvascular anterolateral thigh flap transfer

and the size of the defect as well as on the vascular situation of the recipient site^[13]. In diabetic foot ulcers for instance the indications for local flaps are rather limited. It also has to be taken into account that any local flap does not only cause a donor site defect but also may further deteriorate the vascular supply of the distal extremity. In experimental studies the potential role of neo-angiogenesis at the non-ischemic/ischemic interfaces are key to the biological healing process. Such interfaces occur after transfer of free vascularized flaps into ischemic wounds^[14,15]. Due to the standardization of microsurgery the age of patients seems to be no hindrance to become eligible for free flap transfers to the lower extremity. A correlation between flap loss and increased risk factors and age was not found in the elderly population so far^[16-18].

We have gained experience with more than 100 patients who received a bypass or an av-loop (primarily or staged) along with a free flap and we could show that weighed against the gain in quality of life the donor site morbidity is comparatively low and acceptable. Nevertheless a consequent patient selection and a thorough planning can help to keep the rate of complications low.

It is the daily routine of plastic surgeons to deal with



Figure 2: Three months postoperative aspect of defect reconstruction with free microvascular anterolateral thigh fasciocutaneous flap transfer to pretibial defect

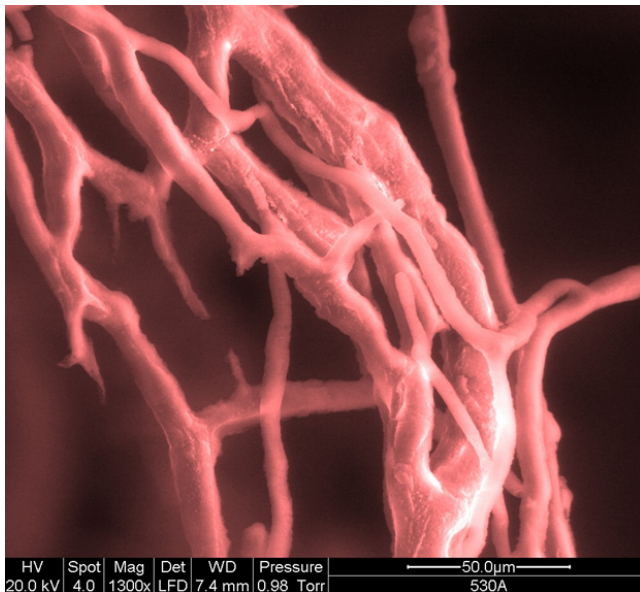


Figure 3: 3D negative imprint of angio- and vasculogenesis network sprouting out from arterio-venous loop in an isolated chamber after 6 weeks

tissue loss and tissue replacement. Therefore it is of no wonder that plastic surgeons who were engaged in replacing lost tissue were amongst the initial founders of what has then be termed tissue engineering (TE) and hence have been involved into all kinds of research in TE and regenerative medicine. Basically the initial idea of TE was to build appropriate scaffolds and then seed cells on such matrices to transplant them into the recipient area. In the laboratory considerable results have been obtained in generating replacement tissue but have not found their way into daily clinical practice yet. The main obstacle has turned out to be the lack of initial vascularization especially in large constructs^[19]. These suffer from sufficient initial blood supply after transplantation to nourish inherent or adherent cells right from the beginning of their inset. One possible way to overcome this problem is the prevascularization of such scaffolds utilizing microsurgically created arterio-venous (av-) loops to three-dimensionally vascularize large constructs before the designated cells are inoculated [Figure 3]. These prevascularized constructs can then be successfully transplanted^[20-23]. Methods derived from such approaches have been successfully implemented into the clinical scenario^[24-27]. For the first time in the literature we were able to successfully apply av-loops in two patients, fill in the patient's own bone marrow stem cells, along with a hydroxyl-apatite powder and fibrin sealant and we then have seen a permanent replacement and restoration of large human bone defects^[28]. This is a very promising approach that offers a way from bench to bedside already in selected cases. Latest advances now include the integration of 3D bioprinting of cells

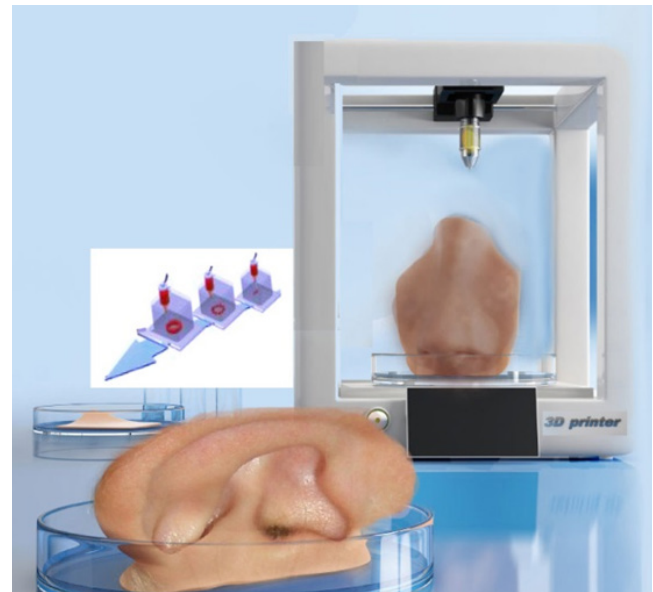


Figure 4: Future applications of 3D bioprinting envision a precise specialdeposition of cells and molecules into 3D scaffolds to mimick natural tissue conditions and to facilitate artificial tissue replacement, such as in this artistic rendering of an ear or a nose for example, using tools of biofabrication

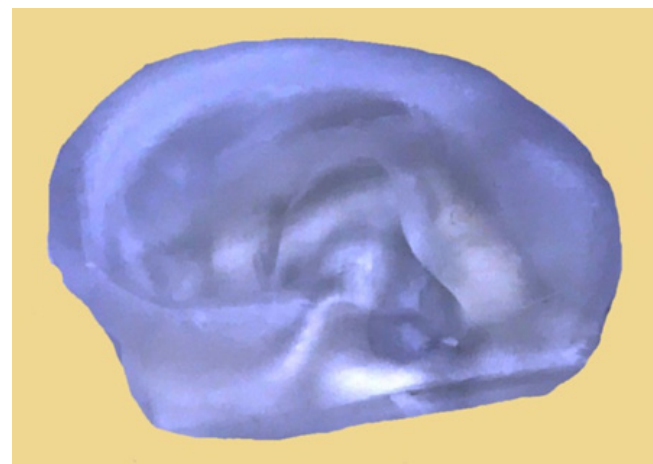


Figure 5: 3D bioprinted ear frame work with bioink that can contain living cells to be positioned into the printed construct

and proteins together with biodegradable matrices [Figures 4 and 5], generally now perceived as the new field of “biofabrication”^[29]. It has been postulated by researchers that bioprinting would now be on the cusp of entering the translational phase where laboratory research practices can be scaled up into manufacturing products specifically designed for individual patients^[30]. In addition to tissue replacement such modalities could help to also fight systemic conditions, such as diabetes mellitus or malignant diseases. With the help of biofabricated protein synthesizing producer cells in a 3D microvascularily connected defined container it can become possible to treat systemic or local diseases. The advantage of such containers with 3D

hierarchically printed reporter/producer cells would be that it could potentially produce antibodies in a clinically relevant amount and could be removed when no longer needed. Ravnic *et al.*^[31] reported on recent successful attempts to generate beta-cells and how this can be coupled with bioprinting technologies in order to fabricate pancreas tissues, which holds great potential for type 1 diabetes. They postulated that it would be possible to integrate vascularization and encapsulation in bioprinted tissues. This would lend other future prospects, such as pancreas-on-a-chip or organoids on a chip^[31]. Our own group is actively investigating the value of bioprinting to generate such arterialized 3D prevascularized containers which can then be loaded with protein producing cells. These cells are supposed to continuously express functional substances and address specific functions in the recipient organism. This interdisciplinary approach is a fine example of how we can combine the knowledge, skills and expertise of plastic surgical microvascular techniques with the science of bioengineering and biology. Therefore, it seems promising to help our patients better than today with customized solutions to overcome morbidities that are rarely curable today. In summary, all the findings from regenerative medicine and tissue engineering are now more and more merging into the new field of biofabrication. This might well enrich our daily clinical practice of to the benefit of our patients by combining the art of plastic surgery with basic science^[32,33].

DECLARATIONS

Authors' contributions

Designed and wrote the manuscript, performed literature research, produced the figures and finalized the manuscript: R. E. Horch

Discussed the content, read and corrected and proofread the final manuscript: A. Weigand, H. Wajant, R. An, J.M. Sun, A. Arkudas

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There are no conflicts of interest.

Patient consent

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Ethics approval

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Case Report

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Complex reconstructive surgery for a recurrent ischial pressure ulcer with contralateral muscle

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contralateral

ABSTRACT

The management of recurrent pressure ulcers is a frequent problem in patients with spinal cord injuries. Many local muscle and fasciocutaneous flaps can be used to cover ulcers of all sizes. However, when a recurrent pressure ulcer has been repeatedly addressed, the number of available flaps becomes quite limited. Contralateral muscles, such as the gracilis, can be used to cover recurrent ischioperineal ulcers and should be employed before last resort surgeries, such as hip disarticulation and the total thigh flap.

INTRODUCTION

Spinal cord injury predisposes patients to additional medical complications. Pressure ulcers are the second most common cause of rehospitalization within the first two decades after injury^[1]. The prevalence of pressure ulcers in patients with spinal cord injury is 25-66% and 95% of all patients with spinal cord injuries will develop a pressure ulcer at some point during their lifetime^[2,3]. The presence of a pressure ulcer limits patient participation in rehabilitation and daily activities, requires meticulous wound care, and increases the

risk of serious infection or sepsis. Therefore, pressure ulcers, and the constant attention required to prevent them, represent a significant lifetime burden for patients with spinal cord injuries.

The basic tenets of pressure ulcer repair include adequate debridement and durable wound coverage with muscle, myocutaneous or fasciocutaneous flaps. The gluteus maximus, gracilis, and biceps femoris muscles are routinely used for the obliteration of ulcer dead space while posterior thigh, tensor fascia lata, and gluteal fasciocutaneous flaps provide durable skin coverage.



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Unfortunately, despite adequate flap coverage, nearly one-third of patients will develop a recurrent pressure ulcer^[4,5]. A history of previous pressure ulcer increases the risk of developing a second pressure ulcer, particularly in the ischial region^[1,6]. Fortunately, many of the flaps commonly used for pressure ulcer treatment can be readvanced or reused under certain conditions. However, difficulty arises when the patient requires repeated coverage of large ulcers in the same location and has exhausted the available local muscle options. Here, we present a case of recurrent ischioperineal ulcer in which the contralateral gracilis muscle was used for wound coverage.

CASE REPORT

Our patient is a 49-year-old Hispanic male with T3 incomplete paraplegia due to a motorcycle accident in 1984. His comorbidities include neurogenic bowel and bladder, lower extremity spasms, gallstones, chronic anemia, and depression. Past surgical history includes exploratory laparotomy, orchiopexy, colostomy, and left hip incision and drainage with partial osteotomy and antibiotic cement spacer. He has had multiple pressure ulcers, requiring flap surgery, in the past, including: (1) bilateral gluteus maximus sliding island advancement flaps for a stage IV sacral ulcer in 2010; (2) a right gracilis myocutaneous flap for a stage IV right ischial ulcer in 2014; (3) a right biceps femoris muscle flap and tensor fascia lata rotation flap for a stage IV right posterior trochanter ulcer in 2016; and (4) a right Girdlestone procedure, femoral shortening osteotomy, right vastus lateralis muscle flap, and right posterior thigh fasciocutaneous rotation flap for stage IV right posterior trochanter and ischioperineal ulcers in 2017.

Three months following the most recent right posterior trochanteric and ischioperineal ulcer repair, the patient presented with sepsis due to a recurrent and extensive right ischioperineal stage IV pressure ulcer, which developed from an injury sustained while transferring from wheelchair to shower [Figure 1]. A plain radiograph of the patient's pelvic anatomy is shown in Figure 2. Based on the location of the wound, there was concern for urethral involvement, however, urethrogram did not demonstrate a leak. Ulcer debridement and closure with the left gracilis muscle and a right V-Y hamstring advancement flap was planned.

The patient was placed in the prone position and the right ischioperineal ulcer was excised down to healthy, bleeding tissue, taking care to protect the rectum and urethra, both of which were in close proximity to the ulcer [Figure 3]. The prominence of the right ischium



Figure 1: A view of the right ischioperineal ulcer with the patient in the prone position. Note the multiple previous incisions. The planned left gracilis muscle flap and right V-Y hamstring myocutaneous advancement flap were marked preoperatively



Figure 2: Antro posterior (AP) radiograph of the patient's pelvis demonstrates rotation, bony resorption, and heterotopic ossification of the pelvis. History of a right Girdlestone procedure and shortening of the right femur is evident. The left femoral head has been resected and antibiotic cement spacer was placed in the left acetabulum for treatment of a prior infection



Figure 3: The right ischioperineal ulcer was debrided down to healthy bleeding tissue and the prominence of the ischial bone was reduced. Note the proximity of the ulcer to the anus and extension into the perineal region

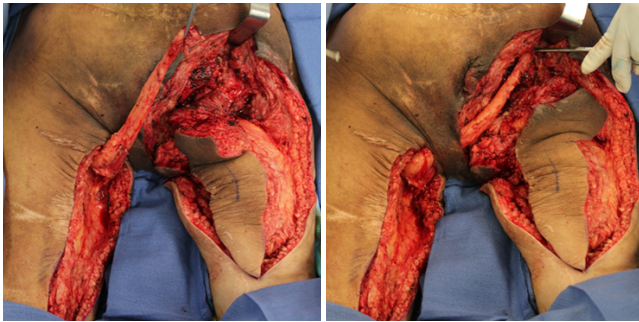


Figure 4: The left gracilis muscle was harvested, tunneled through the perineum, and used to cover the right ischial bone

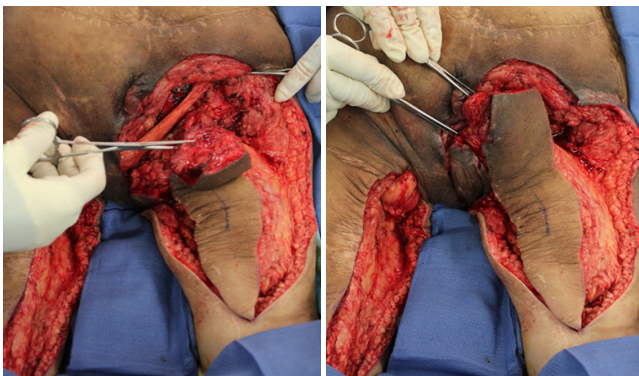


Figure 5: The right biceps femoris muscle was re-elevated and re-advanced proximally to cover the ischial bone. Perineal and proximal thigh tissue was rotated superiorly to close the medial perineal wound

was reduced using an osteotome and then rasped until smooth. The left gracilis muscle was harvested through a longitudinal left posteromedial thigh incision and tunneled subcutaneously across the perineum to cover the exposed right ischial bone [Figure 4].

A V-Y hamstring myocutaneous advancement flap was outlined, with sufficient width to cover the wound. The biceps femoris muscle, which had been advanced previously to cover a prior ulcer, was re-elevated proximally and released distally to provide maximal advancement to fill the dead space in conjunction with the left gracilis muscle [Figure 5]. After advancement of the V-Y hamstring myocutaneous flap, the perineal skin was advanced superiorly to cover the remaining medial aspect of the wound [Figure 5]. All muscle flaps were secured in place with interrupted 0-vicryl sutures. Three drains were placed to drain bilateral posterior thigh donor sites as well as the right ischial surgical site. All skin incisions were closed in layers, using 0-vicryl for the fascial and deep dermal layers, followed by a 2-0 monocril running continuous stitch and a 0-prolene running continuous stitch [Figure 6]. All incisions were dressed with copious bactroban, xeroform gauze, dry 4 × 4 gauze, and ABD pads and



Figure 6: The postoperative appearance after drain placement and closure of all incisions



Figure 7: At 4 weeks postoperatively, all incisions are closed and well-healed

taped in place. A hip abduction pillow was placed to limit undue movement and tension at the surgical site when the patient is repositioned or turned in bed.

The patient followed our standard postoperative protocol, involving 4 weeks of bedrest on an air-fluidized bed, with the first dressing change performed on postoperative day 5 and twice weekly thereafter. At 4 weeks postoperatively, all external sutures were removed [Figure 7]. The patient remained on bedrest but was transitioned to a low air loss mattress. He began a progressive sitting program at 6 weeks, starting with 1 h and increasing in 30 min increments

every other day. The flap was monitored closely for any signs of breakdown. He was discharged home when the 6 h maximum sitting time was reached without complication.

DISCUSSION

Successful surgical treatment of stage IV pressure ulcers requires the appropriate choice of a local tissue flap or combination of flaps which provide muscle, subcutaneous tissue, and skin, as well as adherence to a strict and lengthy postoperative protocol^[7,8]. Despite this, many patients with spinal cord injury will develop recurrent pressure ulcers. While there are multiple gluteal and lower extremity muscle and fasciocutaneous flaps which can be utilized for pressure ulcer wound coverage, the challenge arises when all local muscles have been previously used.

Durable, stage IV pressure ulcer coverage requires not only soft tissue and skin but also muscle to fill the dead space. Closure of a stage IV ulcer with a skin or a fasciocutaneous flap alone often results in poor apposition of the flap to the deepest portion of the ulcer. This inhibits optimal wound healing and can lead to seroma or bursa formation and an increased risk of recurrent ulceration. Therefore, adequate closure of a stage IV ulcer typically requires both a muscle flap to obliterate the cavity and a fasciocutaneous flap for replacement of soft tissue. In cases involving an ulcer of small diameter, advancement of a myocutaneous flap, such as the gluteus maximus or biceps femoris may be sufficient and, in cases of shallow ulcers, fasciocutaneous flaps or skin grafting alone may be adequate. However, in our spinal cord injury population, the presence of small or shallow ulcers is rare.

The patient presented here had had four prior surgeries to close right-sided stage IV pressure ulcers. The ipsilateral gracilis, gluteus maximus, biceps femoris, vastus lateralis, and tensor fascia lata had already been harvested and rotated to fill prior ulcers, leaving very few options for coverage of a large ulcer. Hip disarticulation and a total thigh flap are often the last resort for recurrent pressure ulcers^[9,10]. While some suggest that hip disarticulation improves patient quality of life and function, our patients are reluctant to accept lower extremity amputation and feel that the positive benefits of ulcer coverage do not necessarily outweigh the social and psychological effects of limb amputation^[11]. Additionally, hip disarticulation, while providing necessary tissue for wound coverage, significantly alters pelvic mechanics when seated and patients must learn new techniques for positioning and self-care to prevent future ulceration, a scenario which

could be very devastating. Therefore, we often employ contralateral musculature to delay hip disarticulation while continuing to provide durable wound coverage. Even in paraplegic patients with muscle atrophy, the gracilis muscle provides sufficient bulk to fill the deepest portions of wound cavities. The anatomy of the gracilis is well-suited for the coverage of posterior trochanteric, sacral, and ischial ulcers. The location of the vascular pedicle, which enters the deep surface of the muscle proximally, allows rotation in all directions without sacrificing length and the gracilis can easily reach the contralateral ischium.

Aside from total thigh flaps and the gracilis muscle, other flap options for coverage of recalcitrant or recurrent pressure ulcers have been described. The posterior thigh fasciocutaneous flap is based off of the descending branch of the inferior gluteal artery. By dissecting a long fascial pedicle with the skin paddle at the distal thigh, this flap can be taken from the contralateral leg and used to cover ischial pressure ulcers^[12]. Alternatively, an inferiorly-based rectus abdominis myocutaneous flap can be rotated inferiorly through the pelvis to treat recalcitrant or recurrent ischial and perineal ulcers. The flap can be harvested from ipsilateral or contralateral sides, depending on the location of the colostomy, and did not affect the ability of spinal cord injury patients to sit upright^[13]. In the closure of all pressure ulcers, both initial and recurrent, it is important to remember that adequate closure may also require the rotation or re-advancement of multiple muscle, myocutaneous, or fasciocutaneous flaps in combination to achieve sufficient bulk and area of coverage^[13,14].

Once a patient develops the first pressure ulcer, multiple recurrences are common. One reason for this is that, while flap surgery covers the wound with additional soft tissue, the inciting event or events for pressure ulceration are not altered. In our practice, we see a high degree of ischial and posterior trochanter ulcer recurrence. We believe this is due, in part, to altered spinal and pelvic anatomy as a result of chronic spinal cord injury. Many of our patients develop scoliosis and increased anterior pelvic tilt, causing increased pressure in the ischio perineum and other non-anatomical regions. Similarly, over time, the femurs rotate posteriorly such that the greater trochanter becomes a weight-bearing pressure point when sitting. The Girdlestone procedure removes the proximal femur and is useful for the treatment of recurrent trochanteric ulcers^[15,16]. For ischioperineal ulcers, postoperative physical therapy and careful adjustment of pressure-relieving devices are paramount to minimizing the recurrence rate.

In summary, recurrent pressure ulceration is a

significant challenge for spinal injury patients. Care must be taken to design muscle, myocutaneous, and fasciocutaneous flaps wisely, to plan for the possibility of additional flap coverage in the future. Before committing to a hip disarticulation and total thigh flap when all local tissue has been used for prior ulcer coverage, consider flaps from the contralateral lower extremity, including the gracilis muscle, which can be combined with re-advancement or re-rotation of local flaps.

DECLARATIONS

Authors' contributions

Editorial review and offered clinical advice pertaining to literature: S. Rubayi
 Researched related literature and corrected article grammar: E. Weber

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Patient signed consent for photography during surgery and after surgery.

Ethics approval

Ethical committee approved the case study.

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Microsurgical restoration of failed or unsatisfactory breast reconstruction: a systematic review and pooled-analysis of outcomes

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tertiary,
breast reconstruction

ABSTRACT

Aim: Autologous tissue transfer to salvage breast reconstruction following a previously failed or unsatisfactory reconstruction has been described by previous studies to be an effective strategy to optimize outcomes. The purpose of this systematic review is to assimilate the relevant literature to evaluate surgical and aesthetic outcomes following autologous breast reconstruction in the setting of a prior unsuccessful reconstruction. **Methods:** A systematic review of the English literature was performed on Pubmed/MEDLINE to identify all manuscripts reporting surgical outcomes, aesthetic outcomes, or patient satisfaction of autologous breast reconstruction in the setting of a previously failed or unsatisfactory breast reconstruction. **Results:** Nineteen studies met the criteria for inclusion. Of these, 15 studies reported outcomes following autologous conversion of unsuccessful prosthetic reconstruction (778 breasts). Pooled-analysis of these studies demonstrated total flap loss in 1.6%, microsurgical revision in 3.2%, total complications in 21.7%, and revision surgery in 26.5%. Review of these studies demonstrated high rates of positive aesthetic outcomes and patient satisfaction. Five studies (54 patients) evaluated outcomes following autologous salvage of prior unsuccessful autologous breast reconstruction. Pooled-analysis of these studies demonstrated no instances of microsurgical revision, total complications in 42.2%, and revision surgery in 70.0%. Total flap failure following tertiary reconstruction utilizing microsurgical free flaps occurred in 9.5%. Data describing aesthetic outcomes or patient satisfaction was lacking in these studies. **Conclusion:** Autologous conversion in the setting of unsuccessful prosthetic breast reconstruction appears to be a valuable option to improve outcomes. There is little evidence to suggest that prior prosthetic reconstruction negatively impacts outcomes of autologous breast reconstruction. Data describing autologous breast reconstruction following prior flap loss is limited but suggests it is a viable method to salvage breast reconstruction in appropriate patients.



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INTRODUCTION

Breast reconstruction has consistently been shown to enhance body image and quality of life in breast cancer patients undergoing mastectomy^[1-4]. Despite this, patients suffering reconstructive failures or unsatisfactory outcomes are not negligible^[5,6]. Previously failed breast reconstruction provides multifaceted and unique challenges for plastic surgeons. Following evaluation of the causes of failure and reassessment of patient goals, autologous tissue transfer to salvage breast reconstruction has been shown to be an effective strategy to optimize outcomes^[6-8]. Also termed tertiary reconstruction by previous studies, autologous salvage has been reported as a means of breast restoration following both failed prosthetic breast reconstruction and previously failed autologous reconstruction^[7,8].

The majority of the literature pertaining to tertiary reconstruction describes autologous conversion following complications with prosthetic reconstruction^[7,9-11]. Prosthetic reconstruction is the most common method of breast reconstruction and has increased at a rate of 5% a year^[12]. Despite its increasing popularity, complications leading to poor aesthetics, persistent pain, and implant loss are not uncommon, particularly in the setting of adjuvant radiotherapy^[13,14]. In addition to alleviating implant-related complications, autologous conversion may provide a more natural appearance and improve longevity of the reconstructed breast. However, the impact of a prior complicated prosthetic reconstruction on outcomes of autologous conversion remains unclear. A recent study has suggested that patients with unsatisfactory prior prosthetic reconstruction have increased recipient vessel scarring and major complications with autologous conversion as compared to patients that undergo *de novo* autologous reconstruction^[10].

Tertiary reconstruction following failed autologous reconstruction by utilization of a second flap has also been described^[8]. Although uncommon, flap failure in autologous breast reconstruction is a stressful and demanding situation for the patient and the surgeon^[15]. Use of an additional flap to salvage breast reconstruction may provide a means to still obtain an acceptable reconstructive result and mitigate patient distress associated with flap failure. Despite demonstrating success in previous reports, questions concerning the risk of reattempting autologous reconstruction with a different flap exist as risk factors that contributed to the initial flap failure and sequelae of the previous surgery may compromise its survival^[8,16]. In addition, data evaluating aesthetic outcome and quality of life following tertiary reconstruction of failed

autologous breast reconstruction are lacking and further add to the confusion regarding its potential benefit.

Due to the infrequency of failed or unsatisfactory breast reconstruction, management of this group of patients in the literature is primarily limited to several small case series from a few centers^[7,8,16]. As a result, the indications, methods, and expected outcomes of tertiary reconstruction are poorly defined. The purpose of this systematic review is to assimilate the relevant literature to evaluate surgical and aesthetic outcomes following tertiary reconstruction. The goal is to provide surgeons with a foundation of knowledge to assess the risks and benefits associated with autologous salvage of a previously unsuccessful breast reconstruction.

METHODS

A systematic search of the literature published from January 1, 1980 to December 29, 2016 was performed using search terms “salvage”, “tertiary”, “restoration” and “breast reconstruction” to identify all relevant articles on Pubmed/MEDLINE. Inclusion criteria included studies that reported surgical outcomes, aesthetic outcomes, or patient satisfaction of autologous breast reconstruction following failed or unsatisfactory breast reconstruction. The reference lists of all included studies were reviewed to identify relevant articles that may have not been captured in the search. Exclusion criteria included studies that reported relevant outcomes of less than 5 patients, non-English language articles, reviews, and studies reporting previously published data. Studies reporting management of patients with complicated or failed reconstruction that did not adequately describe outcomes of the autologous salvage procedure were excluded. One reviewer performed the search protocol and article selection (B.E.), and two reviewers (K.M.P. and A.C.H.) reconciled any discrepancies.

Adherence to the standardized methodologic principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses for reporting of systematic reviews guided the analysis^[17]. Study characteristics, patient demographics and comorbidities, oncologic treatment characteristics, and details regarding the initial failed breast reconstruction were extracted. Primary outcomes included flap choice for autologous salvage, total complications, microsurgical revisions, total flap loss, and revision procedures associated with tertiary reconstruction. Secondary outcomes of tertiary reconstruction included hematoma, seroma, infection, fat necrosis, partial flap loss/skin necrosis, and measures of aesthetic outcome or patient satisfaction.

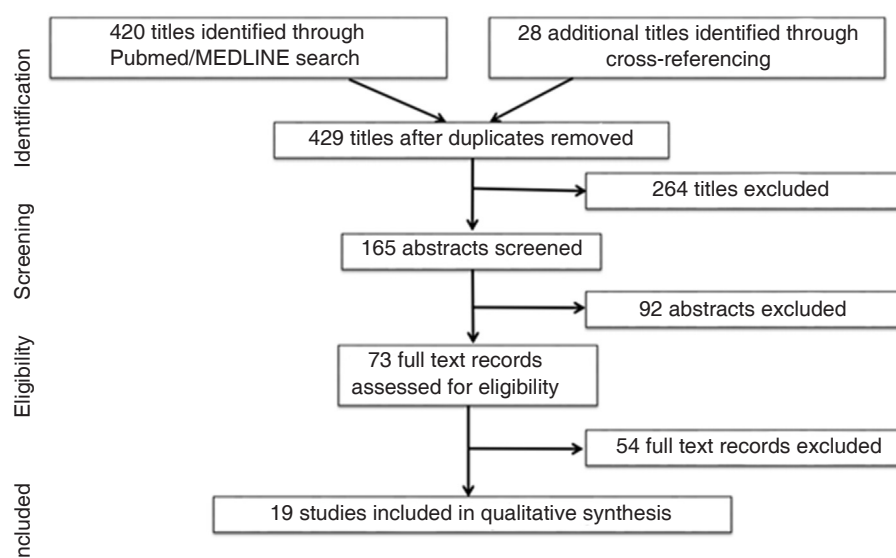


Figure 1: Flowchart of article selection process

Data analysis was completed using simple means allocating weight to each study by sample size. If only the median was reported, then a Gaussian distribution was assumed and the medians were equated to means. Outcomes were stratified by method of failed/unsatisfactory initial breast reconstruction. Qualitative analysis of aesthetic outcome/patient satisfaction is described due to the heterogeneity of included studies. Statistical significance was defined as $P < 0.05$.

RESULTS

Results from the initial search yielded 420 titles. Screening yielded 165 studies for abstract review, of which 73 were selected for full text review. Ultimately, 19 studies met inclusion criteria and were included in this review [Figure 1]. There were no randomized clinical trials, 17 studies (89.5%) were retrospective, and 2 studies (10.5%) were prospective. Study characteristics and patient demographics and comorbidities within included studies are described in Table 1.

Autologous salvage of unsuccessful prosthetic breast reconstruction

Fifteen studies evaluated outcomes following autologous conversion of failed or unsatisfactory prosthetic reconstruction including a total of 564 patients (778 breasts)^[6,7,9-11,18-27]. Study size weighted mean age was 49.3 years and mean body mass index (BMI) was 26.6 kg/m². Mean follow-up was 23.5 months. Thirteen of these studies (719 breasts) reported implant related complications occurring prior to autologous conversion^[6,7,9-11,18,19,21-24,26,27]. Capsular

contracture was the most commonly cited implant related complication with modified Baker grade III-IV contracture occurring in 168 breasts (23.4%), modified Baker grade I-II contracture in 137 breasts (19.1%), and uncharacterized capsular contracture reported in 144 breasts (20.0%). Other commonly reported indications for autologous conversion were poor cosmesis or asymmetry in 102 breasts (14.1%), pain/discomfort in 72 breasts (10.0%), infection/exposure in 71 breasts (9.9%), implant rupture in 25 breasts (3.5%), or recurrence in 12 breasts (1.6%). Neoadjuvant or adjuvant radiotherapy prior to autologous conversion was reported in 231 patients (48.8%). The deep inferior epigastric perforator (DIEP) flap was the most commonly utilized flap for autologous conversion and was reported in 398 breasts (51.1%). Other common flaps choices included a free transverse abdominis myocutaneous (fTRAM) flap in 89 breasts (11.4%), superior gluteal artery perforator (SGAP) flap in 67 breasts (8.6%), transverse upper gracilis flap or transverse myocutaneous gracilis (TMG) flap in 65 breasts (8.4%), superficial inferior epigastric artery (SIEA) flap in 53 breasts (6.8%), inferior gluteal artery perforator flap in 35 breasts (4.5%), latissimus dorsi (LD) flap with or without implant in 27 breasts (3.5%), or other or undescribed flaps in the remaining 29 breasts (3.7%).

Thirteen studies ($n = 748$ flaps) reported complications following autologous salvage of complicated prosthetic reconstruction [Table 2]^[6,7,9-11,18,20-24,26,27]. A total of 12 total flap losses (1.6%; range 0-6.9%) were reported, including 3 DIEP flap loss, 3 SGAP flap loss, 2 fTRAM flap loss, and flap loss in 4 breasts that were not described. Microsurgical revisions were reported in 20

Table 1: Study characteristics and patient demographics of included studies

Authors	Study type	Patients (n)	Years of patient inclusion	Mean age (year)	Mean BMI (kg/m ²)	Smoking (%)	Prior chemotherapy (%)	Prior radiation (%)	Follow-up (month)
Munhoz <i>et al.</i> ^[16] 2016	Retrospective	12	1999-2013	47.3	-	-	66.6	66.6	42.5
Roostaeian <i>et al.</i> ^[10] 2016	Retrospective	89	2005-2014	51.3	26.5	5	-	48.7	10.2
Püzl <i>et al.</i> ^[18] 2015	Retrospective	33	2006-2011	46*	-	-	-	-	51.6
Mioton <i>et al.</i> ^[19] 2014	Retrospective	18	2004-2010	50.5	29.4	0	58.8	41.4	-
Mohan <i>et al.</i> ^[20] 2013	Retrospective	29	2004-2010	50.5	26.1	16.1	-	52.3	20
Rabey <i>et al.</i> ^[21] 2013	Retrospective	14	2000-2012	50*	-	7.1	50.0	85.7	21
Spear <i>et al.</i> ^[6] 2013	Retrospective	7	2005-2010	-	28.5	-	-	43.3	-
Peled <i>et al.</i> ^[22] 2012	Prospective	5	2005-2007	45.4	25.9	3.5	52.0	51.8	52.5
Levine <i>et al.</i> ^[9] 2011	Prospective	191	1998-2008	49*	-	-	-	20.0	-
Hamdi <i>et al.</i> ^[7] 2010	Retrospective	54	2002-2009	46.8	-	7.4	72.2	74.0	31
Hamdi <i>et al.</i> ^[8] 2010	Retrospective	8	2002-2009	46.7	24	21.4	86.0	35.7	37
Visser <i>et al.</i> ^[11] 2010	Retrospective	42	2001-2007	53*	26*	-	-	27.9	24*
Hammond <i>et al.</i> ^[28] 2007	Retrospective	14	1992-2002	48	-	14.3	-	35.7	-
Gurunluoglu <i>et al.</i> ^[23] 2005	Retrospective	7	1994-2001	45.7	-	-	-	-	57.6
Mosahebi <i>et al.</i> ^[24] 2005	Retrospective	5	-	55	-	-	-	0	15
Karanas <i>et al.</i> ^[29] 2002	Retrospective	7	-	54	-	-	-	14.3	-
Spear and Onyewu ^[25] 1999	Retrospective	19	1990-1997	-	-	-	-	100	-
Weiss and Ship ^[26] 1995	Retrospective	26	-	47.4	-	-	-	-	-
Feng <i>et al.</i> ^[27] 1994	Retrospective	33	1988-1993	47	-	33	-	-	-

*median. BMI: body mass index

flaps (3.2%; range 0-3.7%). Complications requiring surgery were reported in 10.0% (range 0-17.4%) of flaps and total complications were reported in 21.7% (range 10.0-34.4%) of flaps. Of these complications, hematoma was reported in 18 flaps (2.7%; range 0-7.7%), seroma in 9 flaps (1.9%; range 0-2.5%), infection in 10 flaps (3.5%; range 0-11.1%), wound healing problems in 9 flaps (3.7%; range 0-7.1%), and fat necrosis 18 in flaps (3.5%; range 0-4.8%). Breast related revisional surgery to improve aesthetic outcome was reported in 84 patients (26.5%; range 4.6-80%). A single study compared outcomes of patients with free flap breast reconstruction following complicated prosthetic reconstruction to those with *de novo* autologous reconstruction ($n = 178$)^[10]. No difference was observed in flap loss (2.5% vs. 2.4%, $P = 1.00$) or total complications (27.2% vs. 26.0%, $P = 0.89$) between the two cohorts.

Measures of aesthetic outcome or patient satisfaction were reported by 5 studies including 147 patients^[11,19,20,25,27]. Review of these studies demonstrated significant heterogeneity in methods of evaluation, rating scales, and reporting of aesthetic outcomes. Aesthetic means based on numerical rating scales were reported in 3 studies^[11,19,25]. Utilizing a 5-point Likert scale (5, very satisfied; 1, very dissatisfied), one study reported numerical means of self-reported assessments in 29 patients with scores of 4.24 for breast volume, 4.16 for breast shape, 3.83 for symmetry, 3.92 for breast scars, and 3.42 for nipple/

NAC complex^[11]. Another study utilized a 4-point scale (4, excellent; 1, poor) to evaluate 14 irradiated implant reconstructions with later addition of a TRAM or LD flap^[25]. They reported a mean overall aesthetic score of 3.25, which was similar to the mean score of 3.28 in patients with non-irradiated implant reconstruction. A validated 3-point scale (0-2) of 5 distinct aesthetic domains was used by another study, which reported mean scores of 1.6 for volume, 1.6 for contour, 1.75 for placement, 1.80 for inframammary fold, and 1.35 for scarring in 18 patients who had autologous conversion after experiencing complication with initial expanderimplant reconstruction^[19]. They reported superior scores across 4 of these domains (volume, contour, placement, and inframammary fold) as compared to patients completed expander implant reconstruction without complication. Two of the studies (71 patients) reported proportions of patients satisfied with the aesthetic result following tertiary reconstruction, with satisfaction rates ranging 84-89%^[11,20]. Lastly, one study noted that 92% of their sample of 25 patients reported improved cosmesis with autologous conversion than with prior implant reconstruction^[27].

Autologous salvage of prior unsuccessful autologous breast reconstruction

Five studies (54 patients) evaluated outcomes following autologous salvage of prior unsuccessful autologous breast reconstruction [Table 3]^[8,16,20,28,29]. All of these studies were small retrospective case series. Study size weighted mean age was 48.6 and mean

Table 2: Studies reporting surgical outcomes of autologous conversion following failed or unsatisfactory prosthetic-based reconstruction

Authors	Breasts (n)	Indications for autologous conversion	Flap choice	Surgical outcomes			
				Microsurgical revisions, n (%)	Total flap loss, n (%)	Total complications*, n (%)	Revisional surgery#, n (%)
Roostaeian <i>et al.</i> ^[10] 2016	121	62 % CC; 13% rupture; 7% mastectomy; infection 4%; 13% other	60% DIEP; 26% fTRAM; SIEA 7%; SGAP 5%; Other 2%	2 (1.7)	4 (2.5)	33 (27.2)	-
Püzl <i>et al.</i> ^[18] 2015	52	61% Grade I-II CC; 39% grade III-IV CC; 85% pain; 73% foreign body sensation; 52% asymmetry	Depithelialized free TMG	0	0	-	13 (81.3) ^c
Mohan <i>et al.</i> ^[20] 2013	29	Grade III-IV CC, asymmetry, extrusion, exposure, or poor cosmesis	76% DIEP; 14% LD +/- implant; 10% fTRAM	-	2 (6.9)	-	-
Rabey <i>et al.</i> ^[21] 2013	14	100% poor cosmesis; 86% pain; 64% CC; 43% tightness	64% DIEP; 36% msTRAM	-	0	2 (14.2)	1 (7.1)
Spear <i>et al.</i> ^[6] 2013	7	66% infection; 24% exposure; 10% infection and exposure	43% DIEP; 29% LD + implant; 14% msTRAM; 14% LD DIEP or TRAM	-	0	-	-
Peled <i>et al.</i> ^[22] 2012	5	100% infection		-	0	-	-
Levine <i>et al.</i> ^[9] 2011	284	46% grade III-IV CC; 41% grade I-II CC; 8% infection; 5% other	58% DIEP; 18% SGAP; 12% IGAP; 11% SIEA; 2% TUG	11 (3.7)	3 (1.1)	57 (20.1)	13 (4.6)
Hamdi <i>et al.</i> ^[7] 2010	81	46% poor cosmesis; 24% infection/exposure; 24% CC; 4% recurrence	81% DIEP; 14% SIEA; 5% TMG	4 (4.9)	1 (1.2)	-	29 (53)
Visser <i>et al.</i> ^[11] 2010	61	68% pain/tightness; 64% poor cosmesis; 14% infection	77% DIEP; 16% mini-TRAM; 7% TMG	2 (3.3)	0	21 (34.4)	19 (45)
Gurunloughu <i>et al.</i> ^[23] 2005	14	100% grade III-IV CC	43% msTRAM; 36% DIEP; 21% SIEA	-	0	1 (7.1)	-
Mosahebi <i>et al.</i> ^[24] 2005	10	100% grade III-IV CC, pain; and poor cosmesis	DIEP	0	0	1 (10.0)	-
Weiss and Ship ^[26] 1995	18	89% CC; 22% implant failure; 11% pain	61% DMP; 39% pTRAM	-	0	4 (22.2)	-
Feng <i>et al.</i> ^[27] 1994	52	82% CC; 29% rupture; 6% infection	62% fTRAM; 21% SGAP; 17% LD	1 (1.9)	3 (5.8)	6 (11.6)	-

*Complication rate reported as a percentage of the total number of flaps; #includes breast related operations performed to improve aesthetic outcome or symmetry, not including nipple reconstruction; °reported revisions required in patients with unilateral reconstructions only (n = 16). CC: capsular contracture; DIEP: deep inferior epigastric perforator flap; fTRAM: free transverse rectus abdominis myocutaneous flap; msTRAM, muscle sparing TRAM; SIEA: superficial inferior epigastric artery flap; IGAP: inferior gluteal artery perforator flap; SGAP: superior gluteal artery perforator flap; TMG: transverse myocutaneous gracilis flap; LD: latissimus dorsi flap; TUG: transverse upper gracilis flap; DPM: dual pedicle dermoparenchymalmastopexy

BMI was 24.7 kg/m². Prior to autologous salvage, 23 (42.6%) patients received neoadjuvant or adjuvant radiotherapy. Initial autologous reconstructions consisted of 18 (33.3%) pedicle TRAM flaps, 14 (25.9%) DIEP flaps, 12 LD flaps (22.2%), 4 (7.4%) free TRAM flaps, 3 (5.6%) SGAP flaps, 2 (3.7%) SIEA flaps, and 1 (1.9%) TMG flap. The most common indications for autologous salvage included total flap loss in 30 (55.6%) breasts, partial flap loss in 16 (29.6%) breasts, and fat necrosis in 4 (7.4%) breasts. The most common flap utilized for tertiary reconstruction was the LD flap which was used in 31 breasts (57.4%). Other flaps reported include the contralateral free LD flap in 12 (22.2%) breasts, SGAP in 5 (9.3%) breasts, TMG in 3 (5.6%) breasts, thoracodorsal artery perforator flap (TDAP) in 2 (3.7%) breasts, and DIEP flap in 1 (1.9%) breast.

Four studies included outcomes following tertiary reconstruction using pedicle flaps (33 patients)^[8,20,28,29] and 2 studies included microsurgical free flaps (21 patients)^[8,16]. Of the studies utilizing free flaps, total flap loss was reported in 2 breasts (9.5%; range 0-22.2%), one occurring with a SGAP flap and the other with a TMG flap. One partial flap loss (4.8%; range 0-8.3%) occurred following reconstruction with a contralateral free LD flap. No total or partial flap loss was reported with pedicle LD flap reconstruction. Revisional surgery to improve aesthetic outcome occurred in 23 breasts (70.0%; range 42.8-92.9%). Total complications were reported in 19 breasts (42.2%; range 14.2-64.3%). Complications besides total/partial flap failure included one hematoma (2.1%; range 0-7.1%), one infection (2.1%; range 0-8.3%), 11 seroma (23.4%; range 7.1-57.1%), and 2 wound healing problems (6.5%; range

Table 3: Studies reporting surgical outcomes following restoration of previously failed or unsatisfactory autologous reconstruction

Authors	Breasts (n)	Initial reconstruction	Indication for salvage	Flap choice	Surgical outcomes			
					Anastomotic revisions, n (%)	Total flap loss, n (%)	Total complications, n (%)	Revisional surgery [#] , n (%)
Munhoz <i>et al.</i> ^[16] 2016	12	Pedicle LD	Total flap loss	Contralateral free LD	0	0	5 (41.7)	7 (58.3)
Mohan <i>et al.</i> ^[20] 2013	7	86% DIEP; 14% TMG	Total flap loss	LD +/- implant	-	0	-	-
Hamdi <i>et al.</i> ^[8] 2010	14	57% DIEP; 21% SGAP; 14% SIEA; 7% msTRAM	79% total flap loss; 14% partial flap loss; 7% recurrence	36% SGAP; 21% TMG; 21% LD; 14% TDAP; 9% DIEP	-	2 (14.2)	4 (28.6)	13 (92.9)
Hammond <i>et al.</i> ^[28] 2007	14	pTRAM	Partial flap loss	LD	-	0	9 (64.2)	-
Karanas <i>et al.</i> ^[29] 2002	7	56% fTRAM; 44% pTRAM	57% fat necrosis; 14% radiation; 14% insufficient volume; 14% chest wall depression	LD	-	0	1 (14.3)	3 (42.9)

*Complication rate reported as a percentage of the total number of flaps; [#]includes breast related operations performed to improve aesthetic outcome or symmetry, not including nipple reconstruction. LD: latissimus dorsi flap; DIEP: deep inferior epigastric perforator flap; TMG: transverse myocutaneous gracilis flap; SGAP: superior gluteal artery perforator flap; SIEA: superficial inferior epigastric artery flap; msTRAM: muscle sparing transverse rectus abdominis myocutaneous flap; pTRAM: pedicle transverse rectus abdominis myocutaneous flap; fTRAM: free transverse rectus abdominis myocutaneous flap; TDAP: thoracodorsal artery perforator flap

0-7.1%). No instances of microsurgical revisions or fat necrosis were reported.

Two studies evaluated patient satisfaction (17 patients) and no studies directly evaluated aesthetic outcomes in patients with restoration of previously failed autologous reconstruction^[28,29]. Of these, one study determined patient satisfaction following LD salvage of partial TRAM loss via telephone interview and stated that all 10 patients interviewed “found the procedure worthwhile”^[28]. The other study also evaluated satisfaction after LD salvage of partial TRAM loss and reported a 100% patient satisfaction rate ($n = 7$)^[29].

DISCUSSION

Failure of post-mastectomy breast reconstruction can be a devastating experience for patients^[15]. Evaluating outcomes of techniques to salvage reconstruction is crucial to optimizing their management and enhancing quality of life. Tertiary reconstruction via use of autogenous tissue has been suggested to provide improved outcomes in these patients by several studies^[6-8]. However, as demonstrated in this review, much of the data pertaining to tertiary reconstruction is limited to case series that suffer from their retrospective nature, limitations in sample size, and institutional variability. The purpose of this systematic review was

to consolidate surgical outcomes, aesthetic outcomes, and patient satisfaction of tertiary reconstruction in order to better characterize its benefits and pitfalls.

Tertiary reconstruction is best described following failed or unsatisfactory prosthetic breast reconstruction. In this review, 79% (15/19) of included studies evaluated outcomes of tertiary reconstruction in this setting. Since 2002, prosthetic reconstruction has surpassed autologous tissue as the leading reconstructive modality and its use has continued to grow in recent years^[12]. The reason for this is multifactorial but likely related to its technical feasibility, lack of donor site morbidity, and changes in mastectomy patterns, such as increased bilateral mastectomies. Despite these advantages, risk of potential complications and unsatisfactory long term aesthetic outcomes are significantly increased as compared to autologous reconstruction^[13,30]. In this review, capsular contracture, poor cosmesis, persistent pain, and infection were the most commonly cited reasons for patients choosing to undergo tertiary reconstruction. History of neoadjuvant or adjuvant radiotherapy has been shown to significantly increase the risk of these adverse outcomes and was present in nearly half of patients who underwent autologous conversion in this review.

Prior implant placement and resulting capsule formation

may increase the complexity of autologous breast reconstruction. It has previously been reported that recipient vessel scarring was 5.23 times more likely in patients with prior prosthetic reconstruction at the time of autologous conversion as compared to those with *de novo* autologous reconstruction^[10]. However, the impact of prior implant reconstruction on outcomes of autologous conversion remains unclear. Planned autologous conversion after immediate tissue expander reconstruction and adjuvant radiotherapy, termed delayed-immediate reconstruction, has been described by several studies as a method of preserving the tissue envelope while avoiding deleterious effects of radiation on the flap^[31-33]. In a series of 16 delayed-immediate reconstructions, Kronowitz *et al.*^[31] reported intra-arterial thrombosis in 12.5% of breasts following autologous conversion, however, no patients suffered a flap loss. In a larger study, Patel *et al.*^[33] compared outcomes of autologous conversion as a part of the delayed-immediate protocol in 74 reconstructions to 118 delayed autologous reconstructions after radiation with no prior prosthesis insertion. They reported no difference in anastomotic revisions (6.8% vs. 5.9%; $P = 1.0$) or rate of flap failure (4.1% vs. 2.5%; $P = 0.68$). The literature pertaining to unplanned autologous conversion secondary to implant-related complications has suggested similar success but is limited. Only one study included in this review provided a head-to-head comparison between autologous conversion after unsuccessful prosthetic reconstruction to patients with *de novo* autologous reconstruction^[10]. Roostaeian *et al.*^[10] reported no difference in rates of flap loss or operative take back between the two groups, but did note an increase in major complications in the group with a prior prosthesis (17.4% vs. 8.1%; $P = 0.035$). Consistent with these studies, pooled-analysis in this review demonstrated a low incidence of total flap loss or microsurgical revisions in 1.6% and 3.2%, respectively. Overall, there is little evidence to suggest that prior prosthetic reconstruction negatively impacts later autologous reconstruction in the setting of tertiary reconstruction or the delayed-immediate protocol. However, future prospective studies are required with larger sample sizes to fully understand the impact of unsuccessful prosthetic reconstruction on autologous conversion.

In addition to salvaging breast reconstruction, autologous conversion in the setting of tertiary reconstruction may provide an improved long-term aesthetic result and satisfaction^[30]. In this review, 2 studies compared aesthetic outcomes of patients with autologous conversion to patients that completed prosthetic reconstruction^[19,25]. Mioton *et al.*^[19] reported superior scores across 4 out of 5 domains evaluated

(volume, contour, placement, and inframammary fold) in 18 patients with autologous conversion after complicated implant reconstruction as compared to 136 patients with uncomplicated prosthetic reconstruction. Spear and Onyewu^[25] compared aesthetic scores of patients with autologous conversion after irradiated prosthetic reconstruction to patients with non-irradiated prosthetic reconstruction and reported similar aesthetic means of 3.25 and 3.28 (4-point scale), respectively. In this review, all 5 included studies demonstrated acceptable rates of positive aesthetic results and patient satisfaction following tertiary reconstruction in the setting of unsuccessful prosthetic reconstruction^[11,19,20,25,27]. This suggests that improved aesthetic result associated with autologous breast reconstruction may be attained even in patients with prior unsuccessful prosthetic reconstruction.

Studies reporting outcomes following restoration of a previously failed autologous breast reconstruction utilizing a second flap are limited and make it difficult to draw any definitive conclusions. In this review, all 5 studies that met inclusion criteria retrospectively assessed outcomes of less than 15 patients^[8,16,20,28,29]. Of these, 4 studies reported outcomes of unsuccessful autologous reconstruction by utilizing a pedicle LD flap^[8,20,28,29]. Overall, no partial or total flap loss was observed in these patients. Only 2 included studies evaluated the utility of microsurgical free flap reconstruction in the setting of previous total flap loss. Hamdi *et al.*^[8] assessed outcomes following second free flap reconstruction after prior flap loss and noted total flap loss in 2 of 9 patients (22.5%). In another series, Munhoz *et al.*^[16] evaluated outcomes following the use of a contralateral free LD flap to salvage breast reconstruction after previous LD breast reconstruction failure. They reported 1 partial flap loss (8.3%) but no total flap loss. Overall, the available data suggests that a second free flap after prior free flap failure is a feasible technique to salvage breast reconstruction in select patients. However, future studies with significantly increased sample sizes are required in order to better define outcomes and determine the optimal approach to managing patients with unsuccessful autologous breast reconstruction. In addition, data evaluating aesthetic outcomes, patient satisfaction, or quality of life are lacking and is necessary to evaluate the potential benefits that tertiary reconstruction may provide.

Tertiary reconstruction in the setting of prior failed autologous breast reconstruction brings several challenges that need to be addressed to ensure its success. The previous failure must be analyzed in order to adjust strategy and eliminate potential

causes of failure for the new flap. Previously cited considerations for attempting microsurgical free flap reconstruction in the setting of prior free flap failure include reassessment of the preoperative preparations, flap choice, the recipient vessels and anastomotic technique, the patient's coagulability and potential for thrombosis, the appropriateness of intraoperative positioning, the postoperative care, and the surgeon's own level of experience^[34]. Full blood and coagulation tests with consultation of hematologist may also be required, particularly in those patients without evidence of obvious technical problem as the cause of flap failure. Hamdi *et al.*^[8] reported underlying hematologic disorders in 3 out of 14 patients who underwent tertiary breast reconstruction after failed free flap reconstruction. Two of these patients went on to have successful breast restoration with the use of a second free flap and the other patient underwent successful implant reconstruction. This suggests that with proper medical management, successful microsurgical restoration in these patients may be attained.

This is the first systematic review to evaluate the literature and consolidate the available data concerning autogenous tissue transfer to salvage unsuccessful breast reconstruction. However, there are several inherent limitations in this systematic review, including retrospective study design and the biases within each of the studies included. Inconsistently reported data and scarce reporting of patient comorbidities also limited the findings of this review. The majority of current studies report outcomes from a single institution, many of which significantly differ in their approach of managing patients with unsuccessful breast reconstruction. Outcomes are often heterogeneously reported precluding a true meta-analysis. A benefit of this manuscript is that it gives a general perspective of the surgical success and aesthetic result that may be obtained with tertiary breast reconstruction. The authors acknowledge that there are many factors that contribute to a patient's decision when assessing whether to reattempt breast reconstruction after experiencing an adverse outcome with a past attempt. Based on this data, autologous conversion in the setting of unsuccessful prosthetic breast reconstruction appears to be a valuable option to improving outcomes in these patients. In addition, data describing autologous breast reconstruction in the setting of a previous unsuccessful attempt is extremely limited but suggests it is a viable method to salvage breast reconstruction in appropriate patients. This systematic review identifies the risk of complications and reconstructive failure associated with tertiary reconstruction, stressing the importance of proper patient selection when contemplating breast reconstruction in the setting of past unsuccessful breast reconstruction.

DECLARATIONS

Authors' contributions

Conception and design of review, performed literature search protocol, data collection, drafting of manuscript, final revisions, and final approval of manuscript: B. EL-Sabawi

Design of search protocol, study selection, review of data, data analysis and interpretation, drafting of manuscript, final revisions and final approval of manuscript: A.C. Howell

Design of review, study selection, data interpretation, drafting of manuscript, final revisions, and final approval of manuscript: K.M. Patel

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

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Current applications of propeller flaps in reconstruction of trunk wounds

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ABSTRACT

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Aim: Propeller flaps provide excellent reconstructive options for defects of many etiologies. Trunk wounds are a commonly encountered issue for the plastic surgeon and multiple techniques to address them should be prepared for implementation. Propeller flaps are a subject rarely brought up as an option to address these wounds. The authors sought to elucidate this topic in the current plastic surgery literature available. **Methods:** A PubMed search was conducted based upon the defined inclusion and exclusion criteria and publications reviewed in detail. Search terms included "trunk wound propeller flap", "trunk propeller flap", and "freestyle trunk wound flap". Duplicate studies were excluded. Data was extracted from each study pertaining to trunk wounds and reconstructions with propeller flaps. **Results:** The electronic search yielded 49 results with 21 studies ultimately meeting inclusion criteria. A total of 365 flaps were described collectively amongst the included studies. Among them, 190 propeller flaps addressing trunk defects were performed across all studies reviewed to address a total of 165 defects of the trunk: 14 abdomen, 101 back, 50 chest defects and adjacent respective flaps were utilized for surgical reconstruction. Overall, cancer excision wounds were by far the most prevalent with 105 cases (59.0%). Defect sizes of those specified in the articles ranged from 2 cm × 5 cm to 30 cm × 24 cm. Of the 190 propeller flaps identified, 63 total complications were identified. The most common complication was 48 total cases of transient venous congestion (25.3%). The second most common complication was partial flap necrosis (6.3%). No total flap loss was noted. There were 2 cases of seroma (1.1%) and 1 case of wound breakdown (0.5%). **Conclusion:** Propeller flaps are a viable reconstructive option for trunk wounds and should be in the armamentarium of plastic and reconstructive surgeons. Few studies are available in the literature regarding propeller flap reconstruction in trunk wounds. More aggregate data is needed in order to further review, evaluate, and refine propeller flap techniques and results.

INTRODUCTION

The concept of the perforator flap was first introduced in 1988 by Kroll and Rosenfield^[1] as

well as independent work introduced in 1989 by Koshima and Soeda^[2]. Since then, the concept of perforator flaps and propeller flaps has flourished both in theory, innovation, and clinical application.



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As is true of most plastic surgery, the propeller flap can be utilized in essentially any part of the body so long as plastic surgical principles are adhered to and meticulous surgical attention is directed toward flap design, dissection, and ultimately to reconstruction. While clinical application is broad, the focus of this article is in review of propeller flaps for trunk wound reconstruction.

METHODS

A PubMed Boolean search was conducted searching for the terms “trunk wound propeller flap”, “trunk propeller flap”, and “freestyle trunk wound flap”. The results of this search were compiled and duplicates excluded. The remaining publications were vetted based on the inclusion and exclusion criteria noted below. The publications were then reviewed in detail.

Inclusion criteria for this study were that the studies be a case study, case report, case series, clinical trial, reply to another study with new patient data, cohort analysis, or other retrospective or prospective studies identifying trunk wounds as the reconstructive defect. Additionally, a propeller flap had to be utilized for surgical reconstruction. Exclusion criteria for the study were that the publication was not entirely in the English language, publication not reproducibly accessed, paper did not provide enough detail regarding surgical intervention to determine if propeller flap technique was utilized, pedicled perforator flaps were not utilized in propeller fashion, or that the paper was primarily a review of the literature.

RESULTS

The results of the PubMed online search yielded 49 publications. After excluding duplicates, 35 publications remained. These 35 were reviewed in detail and the publications vetted based on the inclusion and exclusion criteria noted above. Twenty-one articles remained for further in-depth review.

Of these 21 articles, 13 articles were case series, 8 articles were case studies/reports, and no clinical trials or cohort studies were identified. The oldest article found in the search dated back to August 2009.

A total of 365 flaps were described collectively amongst the included studies. Among them, 190 propeller flaps addressing trunk defects were performed across all studies reviewed to address a total of 165 defects of the trunk: 14 abdomen, 101 back, 50 chest defects and adjacent respective flaps were utilized for surgical reconstruction. The

discrepancy between the total number of flaps utilized and the total number of defects was that in some cases more than one propeller flap was utilized for reconstruction of a site.

Etiologies of the defects addressed resulted from burns, wounds, pressure sores, hidradenitis suppurativa, hardware exposures, keloids and/or scars, myelomeningoceles, pseudomeningoceles, pilonidal disease, radiation wounds, and cancers of various types. One case had an unspecified cause of the defect. Overall, cancer excision wounds were by far the most prevalent with 105 cases (59.0%). Defect sizes of those specified in the articles ranged from 2 cm × 5 cm to 30 cm × 24 cm. Please see [Table 1^{\[3-23\]}](#) for the breakdown of each etiology related to each defect for each included study in the review.

Perforators for the flaps were identified most commonly by handheld Doppler ultrasound. Other methods of perforator identification included color Doppler ultrasonography (CDU), combined laser Doppler spectrophotometry, computed tomography angiography (CTA), and dissection with visual identification and palpation. Some studies did not specify the method of perforator identification. Of the studies that specified flap dimensions, the propeller flaps ranged from 4 cm × 6 cm to 30 cm × 17 cm.

Of the 190 propeller flaps identified, 63 total complications were identified. The most common complication was 48 total cases of transient venous congestion (25.3%). The second most common complication was partial flap necrosis (6.3%). No total flap loss was noted. There were 2 cases of seroma (1.1%) and 1 case of wound breakdown (0.5%).

DISCUSSION

The propeller flap concept and technique has continued to evolve in idea and application. The benefits of utilizing a propeller flap include locoregional reconstruction, reliable anatomy based upon the angiosome and perforasome concepts^[24], minimization of donor site morbidity, and design that is largely limited only by ability to close primarily.

The evolution of the propeller flap has included multiple modifications both in application and technique. Papers indicating flap degrees of rotation less than 180 degrees were described and utilized successfully. Some series utilized this as a workhorse in propeller flap reconstruction for trunk wounds.

Reviewing the data from the series, it is interesting

Table 1: Aggregate results of all papers included in study

	Total No. of flaps of meeting study criteria	No. of flaps of meeting study criteria	Location of defect	Defect dimensions	Etiology of defect	Method of perforator identification	Flap dimensions	Donor site closure	Patient risk factors	Flap complications
Brunetti <i>et al.</i> ^[3]	40	20	9 back, 11 chest	5 cm × 4 cm to 13 cm × 9 cm	15 cancer, 2 HS, 3 PS	Doppler	10 cm × 4 cm to 21 cm × 10 cm	20 (100%) primary closure	10 smokers, 3 RT	3 (15%) partial flap necrosis
Zang <i>et al.</i> ^[4]	1	1	1 chest	13 cm × 6 cm	1 RT	Doppler	15 cm × 6 cm	Skin graft	1 RT	None
Moon <i>et al.</i> ^[5]	13	13	13 back	2 cm × 5 cm and 8 cm × 8 cm, 11 cases unspecified	2 HE, 2 PM, 9 PS	CTA	5 cm × 11 cm to 10 cm × 28 cm	13 (100%) primary closure	Unspecified	1 (7.7%) total flap loss, 1 (7.7%) seroma
Cheng and Saint-Cyr ^[6]	1	1	1 abdomen	30 cm × 24 cm	1 burn	Doppler and CTA	30 cm × 17 cm	Primary closure	None	None
D'Arpa <i>et al.</i> ^[7]	85	13	3 back, 10 chest	Unspecified	8 cancer, 4 HE, 1 PS	Unspecified	8 cm × 3 cm to 23 cm × 12.5 cm	13 (100%) primary closure	Unspecified	None
Go <i>et al.</i> ^[8]	1	1	1 chest	5 cm × 4 cm	1 cancer	Doppler	Unspecified	Primary closure	1 RT	Seroma
Ono <i>et al.</i> ^[9]	16	9	1 back, 8 chest	Unspecified	1 burn, 7 K/S, 1 pilonidal	CTA	8 cm × 3 cm to 18 cm × 5 cm	9 (100%) primary closure	Unspecified	None
Ang <i>et al.</i> ^[10]	1	1	1 abdomen	Unspecified	1 cancer	CTA	Unspecified	Primary closure	Unspecified	None
Xu <i>et al.</i> ^[11]	7	7	6 back	Unspecified	1 cancer, 5 PS	Doppler	12 cm × 16 cm to 25 cm × 30 cm	7 (100%) primary closure	Unspecified	1 (14.3%) wound breakdown
Zang <i>et al.</i> ^[12]	9	9	1 abdomen, 4 back, 2 chest	6 cm × 6 cm to 30 cm × 20 cm	7 cancer	Doppler	13 cm × 6.5 cm to 28 cm × 10 cm	9 (100%) primary closure	Unspecified	3 (33.3%) partial flap necrosis
Oh <i>et al.</i> ^[13]	11	11	11 back	Unspecified	10 cancer, 1 PS	Doppler	Unspecified	11 (100%) primary closure	4 smokers	5 (45.5%) TVC
Yu <i>et al.</i> ^[14]	33	18	3 abdomen, 6 back, 2 chest	6 cm × 6 cm to 30 cm × 20 cm	11 cancer	Doppler	13 cm × 6.5 cm to 28 cm × 11 cm	17 (94.4%) primary closure, 1 skin grafted	Unspecified	4 (22.2%) partial flap necrosis
Yuste <i>et al.</i> ^[15]	2	2	1 back	Unspecified	1 MM	Unspecified	Unspecified	Local tissue rearrangement	Unspecified	TVC
Schmidt <i>et al.</i> ^[16]	1	1	1 back	Unspecified	1 MM	Unspecified	Unspecified	Primary closure	Unspecified	None
Kim <i>et al.</i> ^[17]	1	1	1 chest	10 cm × 7 cm	1 RT	CTA	16 cm × 7 cm	Primary closure	1 RT	None
Brunetti <i>et al.</i> ^[18]	20	9	9 back	4 cm × 4 cm to 6 cm × 8 cm	9 cancer	Doppler	4 cm × 6 cm to 6 cm × 14 cm	9 (100%) primary closure	Unspecified	None
Ioannidis <i>et al.</i> ^[19]	14	9	6 back, 3 chest	Unspecified	9 cancer	Doppler	11 cm × 5 cm to 25 cm × 15 cm	9 (100%) primary closure	Unspecified	1 (7.1%) TVC
Kneser <i>et al.</i> ^[20]	10	2	2 back	Unspecified	1 cancer	CLDS	14 cm × 6 cm to 17 cm × 8 cm	2 (100%) primary closure	Unspecified	None
Iida <i>et al.</i> ^[21]	13	3	3 back	Unspecified	1 PS, 2 wounds, 1 unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified
Gunnarsson <i>et al.</i> ^[22]	34	10	10 back	Unspecified	8 cancer, 1 K/S, 1 wound	CDU and dissection	6 cm × 7 cm to 8 cm × 21 cm	10 (100%) primary closure	Unspecified	None
Baghaki <i>et al.</i> ^[23]	52	49	8 abdomen, 16 back, 12 chest	Unspecified	1 burn, 24 cancer, 2 HS, 4 K/S, 5 wounds	Doppler	6 cm × 9 cm to 14 cm × 35 cm	49 (100%) primary closure	Unspecified	40 (81.6%) TVC, 1 (2.0%) partial flap necrosis
Total	365	190	14 abdomen, 101 back, 50 chest	2 cm × 5 cm to 30 cm × 24 cm, rest unspecified	105 cancer, 4 HS, 6 HE, 12 K/S, 2 MM, 1 pilonidal, 2 PM, 20 PS, 2 RT, 8 wound	Doppler, CDU, CLDS, CTA, dissection, unspecified	4 cm × 6 cm to 30 cm × 17 cm, rest unspecified	183 (96.3%) primary closure, 2 skin grafted, 2 local tissue rearrangements, 3 unspecified	14 smokers, 6 RT, rest unspecified	12 (6.3%) partial flap necrosis, 2 (1.1%) seroma, 1 (0.5%) wound breakdown, 48 (25.3%) TVC

CDU: color Doppler ultrasonography; CLDS: combined laser Doppler spectrophotometry; CTA: computed tomography angiography; HE: hardware exposure; HS: hidradenitis suppurativa; K/S: keloid/scar; MM: myelomeningocele; PM: pseudomeningocele; PS: pressure sore; TVC: transient venous congestion; RT: radiotherapy

to find that the highest rate of complication was with venous congestion but that no permanent flap loss was noted in any case. All cases of venous congestion identified were transient, whether they were managed expectantly or with some intervention (i.e. leeches, derotation of flap, *etc.*). The other complications were with much less frequency and reviewing the patient's risk factors, they did not seem to adversely affect the outcomes. Unfortunately, many series did not identify preoperative risk factors in patients and so drawing conclusions from this are limited in this review. In addition, of those that did specify the risks factors, the patient-specific data was often combined with flaps of other areas of the body and/or there was not enough detailed information provided to determine if the complications occurred in those with risks factors (i.e. transient venous congestion occurrence in relation to patients that smoked).

Interestingly, none of the etiologies for the defects mentioned in any of the studies were traumatic. This may be that trunk wounds are generally not as likely to be traumatic compared to lower extremity wounds. Anecdotally, traumatic wounds do raise some concern in the reconstruction of a wound using a propeller flap as the perforator may be captured in the zone of injury.

One of limitations of this study is that the search terms and search database is limited. One of the challenges of broadening this search would be to search for each propeller flap by a described name or technique (i.e. LICAP flap) as it relates to the trunk, which would be much more extensive of a search. However, this provides an opportunity for further delving into the literature and providing a larger review that may be more inclusive than the broader search terms listed as part of our study. Another notable limitation is that publication bias of positive findings with relation to propeller flap outcomes of the studies currently available.

Variability in design of propeller flaps of course depends upon the shape, size, depth, and location of the defect. In general, axes of the flaps designed should be based perpendicular or oblique on the trunk and in parallel in extremities^[7,24].

When identifying perforators for dissection, it is the authors' preferred method to do so via handheld Doppler ultrasound as well as visual inspection upon dissection. Ono *et al.*^[25] provided a recent publication in 2017 with an excellent overview with preoperative modalities to identify perforators. While CTA, MRA, and CDU have grown tremendously as modalities in

addition to multi-detector row computed tomography, the authors find these modalities time consuming and costly in a climate of American healthcare costs that continue to rise. However, there is significant value in these modalities in the authors' opinions with respect to complex reconstruction or those of reoperative reconstructive fields. Some colleagues at our institution utilize these modalities routinely and so there remains no consensus nor compelling data in the literature to support use of these methods over handheld Doppler ultrasound or even dissection with direct visualization. Indeed, a palpable pulse of the perforator in question is always a reassuring finding and indicator of flap viability. In keeping dissection principles in mind, we try to adhere in line with the findings of Wong *et al.*^[26] in that a 3-cm pedicle length dissection is attempted to be obtained when safe. This is particularly prudent when utilizing degrees of rotation beyond 90 degrees in propeller fashion, but is only done when skeletonization is deemed appropriate and safe.

As discussed in the Tokyo criteria of 2011, the perforator-based propeller flap can be rotated a maximum of 180 degrees for wound reconstruction^[27]. This has to do with torsion and kinking of the pedicle, ultimately which can lead to flap compromise and loss. If flap compromise in the form of venous congestion develops, return to the operating room and releasing the flap from its inset position is of the first consideration. Following this, if the compromise is not addressed then the flap should be rotated back to the donor site and observed for improvement. Still if minimal or no improvement is noted, dissection of the flap to its pedicle should occur to ensure the vascular leash is not the complicating factor.

With respect to management of the donor site, the authors agree with the conclusion of D'Arpa *et al.*^[7] in the decision tree of when a perforator-based propeller flap is utilized for reconstruction. Specifically, if the donor site cannot be closed primarily, then a free flap reconstructive option is sought first that would lead to less to donor site morbidity and improved cosmesis. In other words, a perforator-based propeller flap may be designed as large as the defect dictates so long as the donor site may be closed primarily. As with all reconstructions in plastic surgery, each defect poses its own challenges and nuance that the plastic and reconstructive surgeon must take into consideration prior to surgical intervention.

In conclusion, propeller flaps are a viable reconstructive option for trunk wounds and should be in the armamentarium of plastic and reconstructive

surgeons. Despite its broad applicability and use, little is published regarding propeller flap reconstruction in trunk wounds. More aggregate data is needed in order to further review, evaluate, and refine propeller flap techniques and results.

DECLARATIONS

Authors' contributions

Inception of the study, study design, and written manuscript: S. Moshrefi, G.K. Lee

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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Topic: Complex Reconstruction of the Face, Breast and Wounds with Microvascular Free Flaps **Open Access**

Proximal femur reconstruction using a vascularized fibular epiphysis within a cadaveric femoral allograft in a child with Ewing sarcoma: a case report

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ABSTRACT

Periarticular reconstruction of appendicular bones in skeletally immature patients after tumor resection is a surgical challenge that requires a multidisciplinary approach. The authors present a case of Ewing sarcoma of the proximal femur in an 8-year old girl treated with wide resection of the primary tumor and reconstruction using a vascularized fibula epiphyseal autograft within a cadaveric femoral allograft. The native femoral head was preserved to restore articular anatomy. Postoperative course was without complications. This report demonstrates the use of a vascularized fibula autograft within a cadaveric femoral allograft to optimize growth potential and joint durability in a pediatric patient.

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INTRODUCTION

Reconstruction of bones of the appendicular skeleton in pediatric patients poses a difficult challenge for reconstructive surgeons^[1]. Treatment for Ewing sarcoma (ES), a common bone malignancy in individuals under the age of thirty years, often requires a complex, multi-disciplinary approach^[1]. The current

standard of care for localized ES combines surgical resection of the primary tumor with neoadjuvant and adjuvant chemotherapy to eliminate micrometastases and minimize the risk for recurrence^[2].

Complete surgical resection of the primary tumor and reconstruction using traditional prostheses often has good outcomes for adult patients^[3,4]. However,



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Figure 1: Magnetic resonance imaging of primary Ewing sarcoma tumor in patient's left hip

prostheses and non-vascularized allografts are insufficient for pediatric patients due to the need to both restore joint function and preserve growth potential^[5]. Vascularized fibular head autografts have been previously used successfully in mandibular and radial reconstructions^[6]. The proximal femur and acetabulofemoral joint has a unique structure that allows wide range of motion and weight-bearing properties. Reconstruction using a vascularized fibular autograft alone is insufficient to restore the native anatomy of the proximal femur. However, its structure can be augmented using an acellular cadaveric femoral allograft, which acts as a scaffold on which the autograft can grow^[6]. Utilizing this method preserves the epiphyseal plate in a child, restoring both function and growth potential. Previous studies have combined acellular allografts with vascularized fibular autografts to reconstruct intercalary bony defects post-tumor resection^[7-10]. However, there is a paucity of research on the reconstruction involving epiphyseal portions of long bones and articulations with this method^[6].

We present a case of an 8-year-old female with ES of the left proximal femur who underwent wide resection of the primary tumor followed by reconstruction of the acetabulofemoral joint using a vascularized fibular head free flap with a cadaveric femoral head allograft shell. The patient had no complications at 6-month follow-up. This case report demonstrates the novel use of an acellular cadaveric femoral allograft with a free fibula autograft including the articular head of the fibula for complex proximal femoral reconstruction of the femur and hip joint.

CASE REPORT

An otherwise healthy 8-year-old girl initially presented with left hip pain and was treated for presumed osteomyelitis; however, upon open biopsy of the left femoral neck, she was found to have ES extending from the femoral neck into the proximal diaphysis. The patient began a neoadjuvant chemotherapy regimen as specified by her local hospital protocol. Past medical history and family history are unremarkable.

Eight months after initial onset of symptoms, the patient and her family met with her treatment team at Johns Hopkins, which included pediatric orthopedic oncology and plastic and reconstructive surgery [Figure 1]. She and her family decided to pursue single staged resection of the primary tumor and reconstruction of the left proximal femur using an ipsilateral vascularized fibula autograft and cadaveric femoral allograft shell with articular restoration through preservation of the native femoral head.

The patient was taken to the operating room and placed on her right side. The left proximal femur was accessed via a lateral approach, starting proximal to the joint and extending distally approximately halfway down the thigh. The muscular attachments were dissected off the femur and the tumor was excised *en bloc*, revealing negative margins. An anterior capsulectomy was performed. The femur was dislocated from the acetabulum and a circumferential capsulotomy was performed in order to save the femoral head cap and preserve the native articular anatomy. After tumor excision, the defect extended from immediately below the femoral head cap to the proximal portion of the diaphysis.

The fibular harvest was initiated with a lateral incision on the ipsilateral leg. The musculature was elevated off the fibula and the anterior crural septum was transected. A distal osteotomy was performed 6 cm below the lateral malleolus using an oscillating saw. The deep peroneal artery and vein were ligated distally to be used as the vascular pedicle. The fibula and vascular pedicle were elevated completely out of the leg.

Within the left hip, the descending branch of the lateral femoral circumflex artery and vein were dissected out to their origin, prepared by microscope, and clamped. Meanwhile, the cadaveric femoral allograft shell was prepared *ex-vivo* by cutting the allograft length-wise and reaming out the core to create a trough for the fibular autograft. The fibular autograft was fractured to

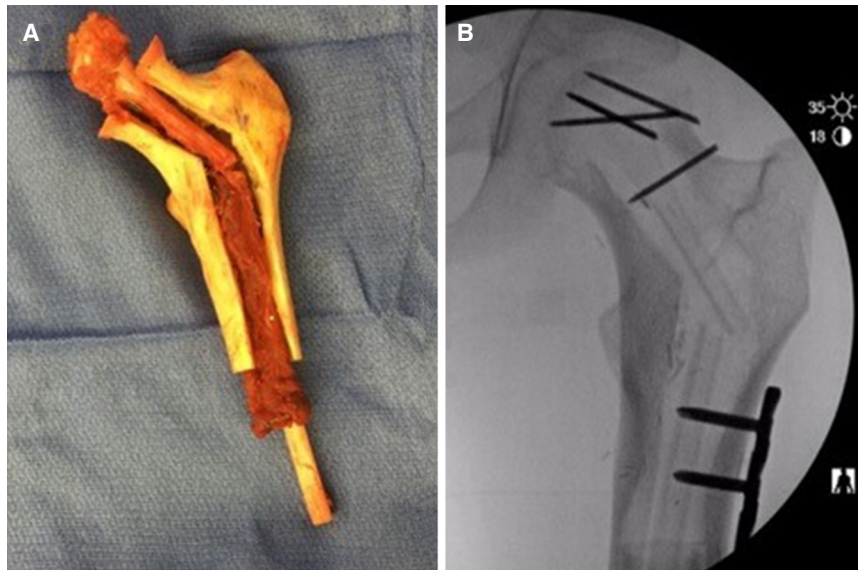


Figure 2: (A) Vascularized fibular autograft within cadaveric femoral allograft; (B) radiograph of final construct inset within patient's hip

recreate the angle of the femoral neck, then secured within the trough of the cadaveric femoral allograft shell. The fibula extended out of the distal portion of the allograft shell to ensure intussusception, or bony overlap within bone, into the native femoral diaphysis. The femoral allograft was reamed out to allow 1.5 cm of intussusception and the distal aspect of the autograft-allograft construct was malleted into the native femoral shaft. The native femoral head was modified to form a well-aligned cap to the proximal portion of the autograft-allograft complex. Terminally threaded Steinmann pins were used to hold the native femoral head cap and autograft-allograft complex together [Figure 2]. C-arm fluoroscopy was utilized to ensure that the pins did not protrude outside the bone. The left hip was reduced into the acetabulum and a 7-hole Synthes plate was placed to secure the autograft-allograft complex with the native femoral shaft. C-arm fluoroscopy was used again to ensure proper positioning of hardware in the construct.

The deep peroneal artery and vein were anastomosed in a retrograde fashion to the descending branch of the lateral femoral circumflex artery and vein [Figure 3]. A 2.5-mm coupler was used for venous anastomosis and 9-0 nylon suture was used to anastomose the arteries end-to-end. The patient was secured in a posterior splint and an epidural was placed in the operating room for postoperative pain management.

The patient tolerated the procedure well without perioperative surgical or anesthetic complications. She resumed her chemotherapy regimen immediately after surgery and returned to the operating room on postoperative day (POD) 7 for placement of a

double leg spica cast for hip joint immobilization. Her postoperative stay was uneventful and she was transferred to her local hospital on POD 18 for continued care and management. She has had no complications at 6 months follow-up. Surveillance imaging has demonstrated good healing, maintenance of the hip joint, and absence of local recurrence. She remains non-weight bearing and will begin physical therapy after the completion of her chemotherapy regimen. At 9 months follow-up, the patient presented with no pain. X-rays demonstrated that the leg was healing well and that she could potentially advance her weight bearing status [Figure 4].

DISCUSSION

Advancements in skeletal reconstruction have improved options for limb salvage, but reconstruction remains challenging when tumors occur in the joints or epiphysis of children due to the need to preserve both growth and durability^[7]. Most bone sarcomas are localized to the metaphysis of the bone. In adults, the entire proximal or distal portion of the bone is resected and reconstructed with prostheses^[8]. Diaphyseal bone defects can be reconstructed using megaprotheses and intercalary allografts, both of which have high rates of postoperative complications such as nonunion, fracture, and infection^[8-10]. However, the Capanna technique can also be considered as a method to reconstruct bony defects through the use of a vascularized autograft set within a decellularized allograft, and has demonstrated positive outcomes in variety of cases^[11]. Though prostheses and allografts can successfully reconstruct joints in adults, special

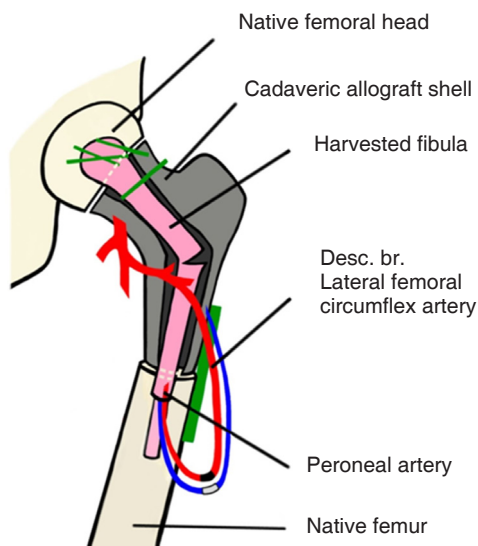


Figure 3: Schematic depicting final inset. Note intussusception of the distal portion of the fibula autograft into the femoral diaphysis

measures should be taken in pediatric patients to preserve growth potential, as well as restoration of a durable, functional joint that mimics native form.

Reports of using the Capanna technique in pediatric patients are limited^[12], however the decision to utilize this technique was pursued because it offered the patient the best prospective outcome in preservation of growth potential and durable joint function. The use of the decellularized cadaveric allograft in particular was opted because of its increased strength when compared to the fibula autograft alone^[13]. Because the defect was extensive and required a long vascular pedicle, a larger portion of the autologous fibula than previously described by Capanna *et al.*^[11] was needed. The peroneal vessels provided the pedicle length necessary for anastomosis to the descending branch of the lateral femoral circumflex vessels. The epiphysis of the fibula was utilized to give the patient the best chance at continued growth, as previously described in similar procedures^[14]. Because the peroneal artery is subject to atherosclerosis in adults, the anterior tibial artery is most often used as the vascular pedicle^[15,16]. However, in children, atherosclerosis has typically not yet developed; thus, the peroneal artery is a good option in cases where increased pedicle length is needed.

This patient underwent neoadjuvant chemotherapy, which has been shown to be effective in shrinking tumor size and allowing a closer margin than would be considered safe in a tumor without this treatment^[17,18]. It is known that vascularized fibular autografts are a preferred reconstruction material



Figure 4: X-ray at 9 months postoperation indicating bony integration

due to their osteogenic capacity and resistance to infection, chemotherapy, and radiotherapy^[5,19,20]. However, a fibular autograft alone would not provide the structural integrity needed to reconstruct the proximal femur and stabilize the hip joint^[21]. The vascularized fibula within an allograft shell capitalizes on the immediate tensile strength of the allograft with the advantage of a biological autograft that can remodel and revascularize with the patient^[8,11,15]. The patient's postoperative radiographs demonstrated bone healing and alignment and are likely to achieve complete union in the future.

The key to the success for this patient's reconstruction was the participation and cooperation of a multi-disciplinary team in preoperative planning and throughout the surgery itself. Perspectives and techniques specific to orthopedic oncology, such as the design and inset of the final construct, as well as plastic and reconstructive surgery, including knowledge of lower extremity vasculature and technical skill in microsurgical anastomoses, were critical to providing the patient with the most appropriate treatment plan. Patients requiring complex skeletal reconstruction would benefit from seeking treatment at tertiary care centers where they have access to specialized surgical teams that can ensure that the patient is receiving personalized care.

The major contraindication for this technique is the inherently variant nature of vascular anatomy in the leg. Even in remarkably similar cases, surgeons should proceed with caution prior to surgery, making sure to utilize preoperative angiography in determining

epiphyseal vascular supply^[15].

From this case report, we learned that single staged joint reconstruction is an option in joint reconstruction given comprehensive coordination between plastic surgery and orthopedic surgery teams. Though this is a rare case, it is a justifiable option in reconstruction of other joints, such as the shoulder and knee, where structure and function must be maintained. Discussion of the patient and their family's goals, such as preservation of the weight bearing nature growth potential of the limb, is crucial to patient selection. This is a long and technically complex procedure, and the ideal patient for this reconstruction is an otherwise healthy child with an extensive support network at a tertiary care center where collaboration between departments is possible.

In conclusion, this case report demonstrates the use of a vascularized fibula autograft within an acellular cadaveric allograft shell for complex reconstruction of the proximal femur and hip joint. The vascularized fibula autograft included the epiphyseal plate, allowing the reconstruction to grow with the patient. The cadaveric allograft shell serves as a biologic scaffold to allow the patient's vascularized free fibula with the fibular head to grow and expand into the construct through osteoconduction, providing increased stability to the reconstruction. This construct provides the potential for continued growth and weight bearing of the lower extremity. Patients requiring complex skeletal reconstructions should be treated at tertiary care centers where a multi-disciplinary team of orthopedic, oncologic, and reconstructive surgeons can be utilized.

DECLARATIONS

Authors' contributions

Concept and design: C.D. Morris, J.M. Sacks
Definition of intellectual content: B.H. Cho, A. Hassanein, A.L. Wong, C.D. Morris, J.M. Sacks
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Manuscript editing: B.H. Cho, H.M. Carl, T.J. Bos, A.L. Wong
Manuscript review: A. Hassanein, C.D. Morris, J.M. Sacks

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

The patient's guardian provided us with consent to publish this case report.

Ethics approval

Obtaining ethical clearance was not necessary for the publication of this case report.

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Larger breast implants warranted for post-mastectomy reconstruction

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ABSTRACT

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implant

Aim: Our goal was to ascertain if there was a role for larger breast implants in breast reconstruction. **Methods:** Patients that underwent mastectomy and implant-based breast reconstruction were identified and reviewed. **Results:** Of the total specimens, 92 (14.7%) weighed more than 800 g with a mean weight of 1140 g (range 803 to 2177 g). Of the patients with these larger specimens, 45 (48.9%) selected the largest available implants (800 mL implants) for their reconstruction. **Conclusion:** There are patients undergoing mastectomy and implant-based breast reconstruction who are unable to have reconstruction to their native breast volume because of the current implant-volume restrictions.

INTRODUCTION

The mastectomy rate in the United States has been steadily increasing, including the rate for contralateral prophylactic mastectomy and elective mastectomy^[1-5]. Mastectomies permanently alter a patient's body image and thereby impact self-esteem^[6]. Patients who undergo breast reconstruction after mastectomy are more satisfied than those who undergo mastectomy without reconstruction^[7-9]. However, the reconstructed breast can leave a patient feeling incompletely restored when the native breast size was larger than reconstructed breast volume^[10]. Limited data

exists that links patient satisfaction to the size of a reconstructed breast^[10], especially for patients who have native breast volumes larger than 800 mL. These women are not able to match their native breast size with implant alone based reconstruction with the current implant-size limitations imposed by the US Food and Drug Administration (FDA) (maximum volume, 800 mL, Table 1). Of note, the FDA has recently approved human trials of larger breast implants (volumes to 1445 mL)^[11,12]. We designed a retrospective study to determine how native breast volumes related to reconstructive implant volumes for patients who underwent mastectomy followed by



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Table 1: FDA-approved breast implants (January 1, 2016)

Breast implants	Volume range (mL)
Saline-filled	
Ideal Implant Saline-Filled Breast Implant (Ideal Implant Inc.)	210-755
Allergan Medical RTV Saline-Filled Breast Implant (Allergan, Inc.)	120-800
Mentor and Spectrum (Mentor Worldwide)	125-700
Silicone Gel-filled	
Allergan Natrelle (Allergan, Inc.)	80-800
Allergan Natrelle 410 (Allergan, Inc.)	140-740
Mentor MemoryGel (Mentor Worldwide)	100-800
Mentor MemoryShape (Mentor Worldwide)	120-775
Sientra (Silimed Indústria de Implantes Ltda)	80-700

FDA: US Food and Drug Administration. Data from FDA. Silicone gel-filled breast implants [Internet]. 20 Sep 2013 [cited 24 Mar 2016]. Available from: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants>

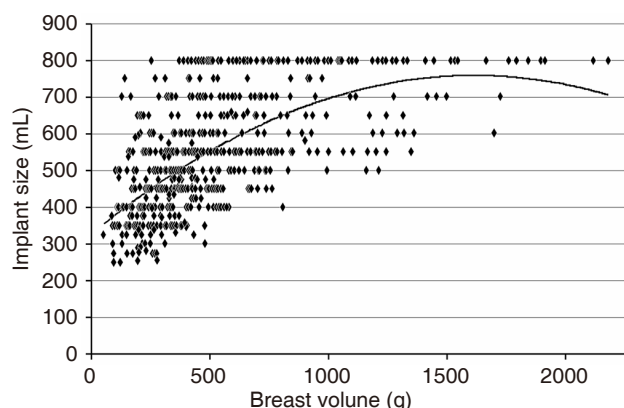


Figure 1: Relationship of breast volume to implant size, with curve of best fit showing a high positive correlation between native breast volume and the implant size used for reconstruction

reconstruction with a silicone gel-filled implant.

METHODS

This retrospective study was conducted at 2 tertiary care centers after institutional review board approval at both locations. We reviewed electronic health records of patients who underwent mastectomy followed by reconstruction with silicone-gel breast implants during a 5-year period from January 2009 to December 2014. All patients included in the study underwent mastectomy either for a diagnosis of breast cancer or a desire for prophylactic mastectomy. All patients had reconstruction with breast implants either at the time of mastectomy or by tissue expansion and subsequent implant reconstruction. Each patient had only one implant per reconstructed breast, no implant stacking was utilized. We collected data regarding mastectomy specimen weights and final implant volumes used in the breast reconstructions. The patients' native breast volume was extrapolated from the recorded mastectomy specimen mass. Each breast was considered separately (a patient with a bilateral mastectomy and bilateral implant reconstruction

was entered in the data twice, with unique data for each breast). Patients who underwent any form of autologous tissue reconstruction or had saline implants were excluded.

RESULTS

Weights were available for 627 mastectomy specimens for patients who underwent mastectomy and implant-based reconstruction during the 5-year period. The mean gross mastectomy specimen weight was 501.2 g (range 51 to 2177 g). The mean implant size used in the reconstructions was 533.9 mL. The mean patient body mass index (BMI) was 26.9 (range 16.6 to 52). Of the total specimens, 92 (14.7%) weighed more than 800 g (mean 1140 g and range 803 to 2177 g) and these patients had a mean BMI of 34.0 (21.3 to 52). Forty-five (48.9%) of the patients with these larger specimens selected 800 mL implants for their reconstructions. From our total patient population, 80 patients (12.7%) chose 800 mL implants for their reconstructions. The mean specimen weight for this group was 933 g (252 to 2177 g) and the mean BMI was 34.6 (20.3 to 49.5). The Figure 1 shows the trend for native breast mass (as a proxy for volume) vs. reconstruction implant size.

DISCUSSION

Patients' desires ultimately determine the goal of post-mastectomy breast reconstruction. Not all patients with large native breasts (mastectomy specimens > 800 g) selected 800 mL implants for their reconstruction. Alternatively, some women with smaller breasts (mastectomy specimens < 800 g) chose to increase the size of their breasts at the time of implant-based reconstruction by selecting 800 mL implants. Thus, at the time of breast reconstruction, some patients with large breasts wanted to have smaller reconstructed breasts, some with smaller breasts wanted larger

reconstructed breasts, and many elected to maintain a similar breast volume following their mastectomy. Other factors to be considered in the decision regarding the size of implant used in reconstruction may include history of radiation or other comorbid conditions such as current smoking status and diabetes. Native breast shape and degree of ptosis must also be considered. These are especially important when trying to achieve symmetry in unilateral breast reconstruction. There are many reconstructive options available to patients, thus surgeons must aid patients in this decision making process.

A study by Huber *et al.*^[10] reported that women who augmented their native breast volume at the time of reconstruction were more satisfied with their overall reconstructive outcome than those who did not, and no increase in complication rate occurred in those who augmented their breast volume. For woman with large breasts, low patient satisfaction may be related to the inability to match native breast volume with a similarly sized implant at reconstruction because of current implant-volume restrictions. Patient-reported outcomes would provide more insight as to what influences patients' initial decisions, if they remain satisfied long-term with their choice, and if they would have chosen differently had a larger implant been available at the time of their reconstruction.

Women may have asymmetry between native breast volumes. Those who underwent unilateral mastectomy with implant based reconstruction likely desired their reconstructed breast to appear similar in size and volume to their native breast. This would affect their choice in implant size.

Our study is limited by the lack of patient-satisfaction data for our patient population. However, it was not designed to evaluate this aspect of breast reconstruction. To investigate this further, we would use an outcome measurement tool, such as the BREAST-Q questionnaire (Memorial Sloan Kettering Cancer Center). Future studies could investigate the relationship between patients' preoperative decisions and postoperative satisfaction scores. For example, how many patients would have selected an implant with a volume > 800 mL if they had that option available to them at the time of their reconstruction? This will be especially informative when patients have the option to match their native breast volume to breast implant volumes as large as 1445 mL.

In addition to satisfaction data, future studies will investigate complication rates to ensure that larger implants are as safe and effective as those currently

approved for use in reconstruction. Larger implants will have their own unique risks. Known complications that may be associated with breast implants include, but are not limited to, asymmetry, tissue atrophy/skin necrosis, extrusion, infection, hematoma, ptosis, and pain. The specific incidence of these, and other, complications associated with large volume implant use will need to be determined.

Furthermore, patients with class II or III obesity have an increased risk of surgical morbidity following breast reconstruction of any modality^[13]. The risks of larger implant use in this population should be carefully considered. In our study, women with breast volumes greater than 800 g had a mean BMI of 34.0. BMIs of 30-34.99 are classified by the World Health Organization as obesity class I^[14]. This patient cohort is not at increased risk of surgical morbidity following breast reconstruction^[13].

There may be a role for implants larger than 800 mL for patients undergoing post-mastectomy breast reconstruction in the United States. The FDA has recently approved ATHENA, a clinical trial that will allow patients to select breast implants with larger volumes ranging from 800 to 1445 mL for breast reconstruction. Patient preferences and outcome goals will continue to guide reconstructive efforts. Future studies on satisfaction and complication rates will allow us to better counsel our patients and assist them in their decision making.

DECLARATIONS

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Authors' contributions

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Substantial data collection, manuscript review: A.M. Rodriguez
Abstract writing and data collection, manuscript review: V. Gargya
Substantial data collection, manuscript review: H.D. Lucas
Primary investigator, original idea, manuscript review: R.C. Mahabir

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Conflicts of interest

Dr. Mahabir serves on the Mentor Advisory Board.

Patient consent

Institutional review board approval was obtained at both locations of data collection prior to beginning this retrospective study.

Ethics approval

Institutional review board approval was obtained at both locations of data collection prior to beginning this study.

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Hyaluronic acid: a versatile biomaterial in tissue engineering

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ABSTRACT

The design and application of hyaluronic acid (HA)-based scaffolds to control cell response and construct ideal tissue engineering products have been of great interest in the past few decades. This review provides an overview of the biological properties of HA to better understand how to engineer a cell-scaffold composite that is qualified in tissue engineering; important tissue engineering applications of HA including cartilage tissue engineering; and lastly, the problems of the current research on HA. All the data described above were collected and analyzed from PubMed, EMBASE and Medline.

INTRODUCTION

Hyaluronic acid or hyaluronan (HA) was the first isolated from bovine vitreous humor by Meyer and Palmer^[1] in 1934. It was named because of its transparent appearance in water and the probable presence of hexuronic acid as one of the components. HA is a linear polysaccharide without branches and is one of the most important components of extracellular matrix. Researches demonstrated that HA plays an important role in regulating cell differentiation, migration, angiogenesis and inflammation responses^[2-5]. HA has

become a hotspot in the fields of scaffold materials in tissue engineering because of its ubiquitously distribution in vertebrate tissues, good biocompatibility and non-toxic degradation products. The versatility of HA is closely related to its unique properties, and HA with its different states or molecular weights can exhibit diverse features. Therefore, to understand the application of HA, the basic physical, chemical and biological properties of HA must first be understood.

A review of the literature was performed by searching the keywords "hyaluronic acid" AND "tissue



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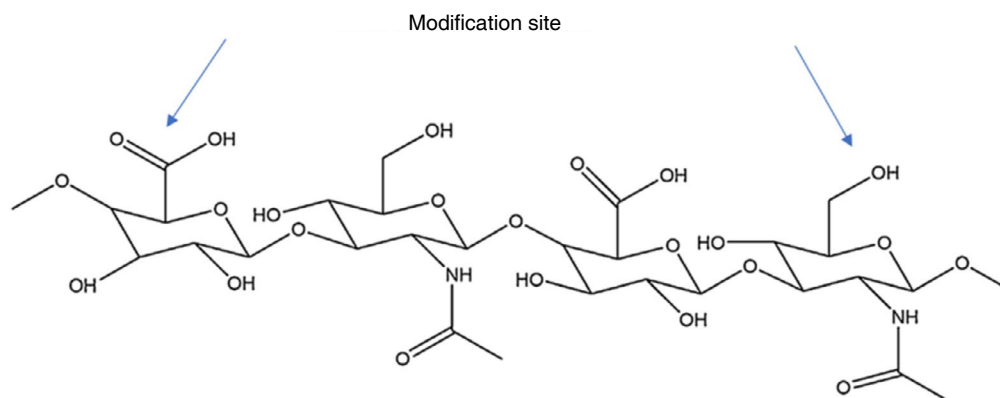


Figure 1: Molecular formula of hyaluronic acid disaccharide unit

engineering” OR “tissue regeneration” OR “stem cells” in PubMed, EMBASE and Medline. The most important or typical papers discussing cartilage and bone tissue engineering using HA-based scaffolds were viewed and selectively cited. Skin and soft tissue engineering with HA-based scaffold were reviewed as well.

THE PHYSICAL, CHEMICAL AND BIOLOGICAL PROPERTIES OF HA

HA is an unbranched non-sulfated glycosaminoglycan composed of repeating disaccharides [β -1,4-D-glucuronic acid (known as uronic acid) and β -1,3-N-acetyl-D-glucosamide] [Figure 1]^[6]. Since HA is rich in carboxyl and hydroxyl groups, it can form a hydrogel under mild conditions like chemical modification, crosslinking or photo-crosslinking. The mechanical strength, physical and chemical properties of the materials depend on the degree of the modification and crosslinking^[1,7]. The physical properties of HA include its compressive stress, compressive modulus, storage and loss modulus, porosity, swelling rate, degradation rate and density^[8].

The physical property of HA

HA has a molecular weight between 10^3 and 10^4 kDa, which can reach a length of 25 μm when fully extended^[9,10]. The high hydrophilicity of HA is the physical basis for its wide presence in the human body. The molecular chains of HA are intertwined in solution and it occurs even when the concentration is very low. This phenomenon can be observed in HA solution as low as 1 mg/mL, which is one of the reasons to the unique rheological characteristics of HA [Figure 2]^[11]. In human bodies, especially soft tissues, HA often exists in the form of high molecular weights which is the essential reason for its high viscosity even in diluted solutions. Moreover,

the mutual macromolecular crowding in human body contributes to the higher viscosity^[12]. With macromereconcentrations from 2 to 20 wt%, networks exhibited volumetric swelling ratios ranging from ~42 to 8, compressive moduli ranging from ~2 to over 100 kPa, and degradation times ranging from less than 1 day up to almost 38 days in the presence of 100 U/mL of hyaluronidase. Although higher molecular weight or crosslinking degree can result in improved compressive modulus that is essential in the tissue engineering of cartilage or bone, the viability of seed cells would be compromised^[13]. In most instances, HA exhibited a highly porous morphology so that cells can permeate into the scaffold easily. Under most circumstances, the HA macromere is degraded by hyaluronidase. However, it can also be degraded by reducing substances or at acidic pH values after modification^[14].

The chemical property of HA

The characteristics of HA including its consistency, biocompatibility, hydrophilicity, limited immunogenicity and unique viscoelasticity have made it an excellent moisturizer in cosmetic dermatology and skin-care products as well as a potential biomaterial in tissue engineering. However, HA without modification tends to be absorbed rapidly in human body, which makes it unqualified in tissue engineering. To overcome this defect, chemical modification is indispensable. Many biomaterials do not have a lot of chemically modified sites, while HA can be chemically modified with its hydroxyl, carboxyl and N-acetylaminoends^[15]. The chemical modification of HA can be roughly divided into two types: esterification and crosslinking. The purpose of esterification is to link HA with certain hydrophobic groups, reducing the poly anion properties of HA. Under certain conditions, the carboxyl group of HA can undergo esterification reaction to produce HYAFF, an esterified derivative of HA^[16]. In this reaction, many different alcohols, such as fatty

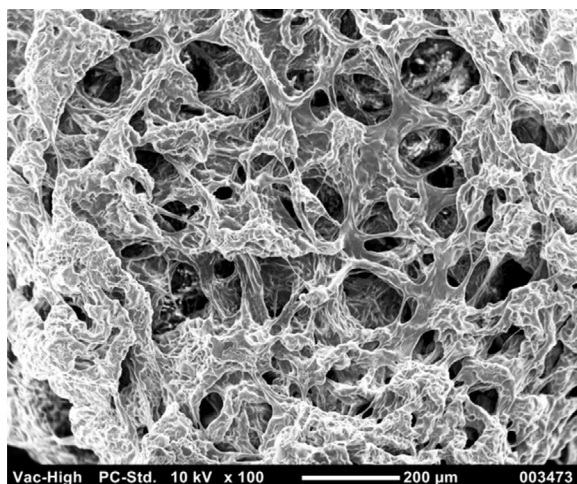


Figure 2: The morphology of hyaluronic acid (RESTYLANE®) using scanning electron microscopy

alcohols and aryl fatty alcohols can be bound to HA molecules in order to improve the chemical properties of HA and its stability as a tissue engineering scaffold, as well as to extend its maintenance in the human body. The purpose of HA cross-linking is to convert it from solid state to hydrogel state under mild conditions and to prolong its maintaining time in the human body^[17]. Besides, the mechanical strength of crosslinked HA can be remarkably improved compared to the non-crosslinked one, which makes it more suitable for tissue engineering applications.

The cross-linking reaction of HA can be divided into complete or incomplete one. The complete cross-linking reaction causes the HA molecules to be covalently attached to the continuous polymer network so that HA is no longer soluble in the water. While the incomplete reaction prompts part of the covalent binding reactions of HA molecules, resulting in partial solubility after the reaction. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, divinyl sulfone, glutaraldehyde, butanediol-diglycidyl ether are the most common crosslinking agents [Figure 3]^[18].

The biological property of HA

HA is synthesized by HA synthesis (HAS) on the cell membrane. And it is the only glycosaminoglycan that is not synthesized in the Golgiosome. There are three different HAS in mammals, HAS1, HAS2 and HAS3. The three enzymes are located on different chromosomes, producing HA with different molecular weights^[11]. The expression of HAS isoenzymes varies under different status of morphogenesis and pathology. For example, HA in infants is of abundant quantity, however, in the process of growing up it is gradually replaced by collagen fibers and proteoglycans which accounts for the fact that mature tissue can



Figure 3: The gross view of cross-linked hyaluronic acid using BDDE at the concentration of 0.8%

withstand greater mechanical force^[19].

It is almost certain that most kinds of vertebrate cells synthesize HA at some point in their natural history. When fibroblasts, mesothelial or certain other kinds of cell are plated out in tissue culture, they surround themselves in a few hours with a transparent gel-like HA which can protect themselves against damage by immune cells, impedes virus infection and may be important in mitosis^[19].

CELL-MATRIX INTERACTIONS IN HA HYDROGEL SCAFFOLDS

At present, different origins derived stem cells are the most universally used seed cells in tissue engineering. HA can interact with many stem cell surface receptors, inducing intracellular signal transduction through the connection with these receptors and activating corresponding proteins in a direct or indirect pattern^[20].

Through signal transduction receptors, HA can affect the most essential cell activities including proliferation, survival, movement and differentiation. One of the most important receptors is CD44, which provides an agent for maintaining and anchoring the proteoglycan polymer to the cytoplasmic membrane. CD44 plays an important role in tissue formation by mediating the remodeling of extracellular matrix, intercellular interactions, and cell-matrix interactions^[21]. In addition, the close connection with the cytoskeleton allows CD44 to induce intracellular signal transduction, thereby experiencing changes in the extracellular matrix environment and triggering cellular responses^[22]. Besides, CD44 receptors are of widespread concern because they are essential to

maintain cartilage phenotype and HA catabolism^[5]. HA-containing materials can also interact with proteins or cells through the receptor for hyaluron-mediated motility or intercellular adhesion molecule-1.

There are also some reports that HA-based scaffolds can directly induce or promote stem cell differentiation^[22]. *In vitro* experiments conducted by Meng *et al.*^[23] demonstrated that HA-based scaffold can induce stem cells into cartilage in basal medium without the addition of growth factors. The increased expression of an important HA receptor like CD44, also suggested the interaction of cells with HA^[24]. In addition, Choi *et al.*^[25] reported that HA oligomers in the skin substitute models could promote the survival of basal stem cells. Their experiments demonstrated that a recognized skin stem cell marker p63 expression was elevated in the skin substitute model added HA oligomer (400-2000 Da), therefore, HA may also help to maintain stemness^[25]. Huang *et al.*^[26] also reported that mesenchymal stem cells grown on chitosan-HA membranes performed better in maintaining stemness markers (Oct4, Sox2 and Nanog) than cells cultured on common dishes. On the contrary, if CD44 was blocked by the antibody, then the cells would lose their ability to maintain the spherical form while the stemness gene expression would also decline. It indicated that HA may assist in maintaining stemness through CD44^[26].

HA IN TISSUE ENGINEERING

Tissue transplantation is one of the most frequent and most important treatments in plastic and reconstructive surgery. However, autologous transplantation is often limited by the insufficiency and trauma of donor site, while allogeneic transplantation is faced with immune rejection, donor scarcity, transplant infection and other risks. The emergence of tissue engineering is a promising technique to overcome these problems above.

Tissues or even organs can be regenerated by the coordination of seed cells, scaffold and growth factors. The histocompatibility, chemical modification and biodegradability of HA make it an ideal scaffold for tissue engineering. The properties of hydrogel can mimic the water content of human tissue and contribute to the exchange of oxygen, nutrition and metabolic waste^[27,28]. In addition, the fluid morphology makes it possible to inject the scaffold through a tiny needle hole, which can greatly reduce the trauma and infection rate of the operation. Therefore, it has been one of the hotspots in tissue engineering materials and

used in a variety of fields. The ideal tissue engineering scaffold should have good cell adhesion to support the growth of seed cells, however, HA tends to have weak cell adhesion. Therefore, modifications like heparin decorated, Arg-Gly-Asp (RGD) sequence linking are indispensable^[29-31].

HA in vascular tissue engineering

In tissue engineering construction, a scaffold has to maintain its structure for several months or longer before extracellular matrix is deposited. Since the diffusion of nutrients and essential gases to cells is typically limited to a depth of 150-250 µm from a capillary (3-10 cells thick)^[32], tissue constructs must permit in-growth of a blood capillary network to nourish and sustain the viability of cells within^[4]. HA can be chemically modified to promote angiogenesis without changing its original biocompatibility or weak immunogenicity^[33]. HA can be degraded into oligomers (HA oligomers, HAO) (4-25 dose units) by hyaluronidase *in vivo*. These HAOs have a high biological activity and are capable of affecting cell behavior including angiogenesis through monovalent bond to the host cells^[3,34]. Silva *et al.*^[2] demonstrated that gellan gum-HA hydrogel can be degraded by hyaluronidase and release various amounts and sizes of HA oligomers that are capable of promoting the proliferation of human umbilical vein endothelial cells. Besides, in the mice hind limb ischemia model, HA-cell composite can significantly promote angiogenesis. A series of *in vitro* and *in vivo* experiments have shown that long-chain (native high molecular weight) HA at physiological concentrations has the ability to resist inflammation and inhibit angiogenesis. Long-chain HA can bind to CD44, and inhibit cell proliferation, cell cycle in the key signal transduction, thereby inhibiting angiogenesis. While HAO will compete with long-chain HA for binding to CD44 and prompt mitosis and angiogenesis^[35]. The CD44-HA oligosaccharide interactions that primarily cause these pro-mitotic effects have also been shown to stimulate matrix metalloproteinase-2 and -9 production and thereby increase cell invasion through extracellular matrix barriers to facilitate vessel sprouting and outgrowth^[36]. Since the pro-angiogenic HA oligomers cannot by themselves be crosslinked to yield solid biomaterials, and can also potentially incite inflammatory/activated cell responses, they must be presented on other scaffolding biomaterials, either synthetic or natural^[37,38]. Another method is to mix with the more bioinert long-chain HA in such a manner as to fulfill the physical and mechanical requirements of the biomaterial, elicit the desired biologic responses, and yet deter excessive and long-term inflammation^[4].

HA in cartilage tissue engineering

In the application of HA-based materials, cartilage tissue engineering is the most extensive due to the fact that HA is quite a suitable scaffold for the growth of chondrocyte. The extracellular matrix of chondrocytes is rich in glucosamine and HA while the latter one plays an important role in regulating the function of chondrocyte^[39]. Moreover, since HA can also be used as a scaffold in bone regeneration^[40], it is a suitable material for osteochondral tissue engineering^[41,42]. HA, as a scaffold, has several possible mechanisms to promote cartilage formation. First, HA can induce stem cells, cartilage progenitor cells to differentiate into chondrocytes. Some papers indicate that HA involves in the maintenance of chondrocyte phenotype, which is utmost important for the reason that chondrocyte can lose its phenotype during *in vitro* culture^[43]. Furthermore, HA is favorable to the deposition of extracellular matrix which is essential in cartilage tissue engineering^[44-48]. Besides, HA-containing hydrogel material has a lower oxygen concentration, while the hypoxic environment is conducive to the growth of chondrocytes^[48]. Another possible mechanism is that HA interacts with cells through the cell surface of the CD44 receptor, regulating cell migration, proliferation, differentiation, and other close contact with the cytoskeleton to CD44-activated cells within the signal transduction^[49]. HA binds to proteoglycans by the aid of core proteins. These proteoglycan monomers can connect with CD44 receptors on chondrocytes, while the released ones in the extracellular matrix can enhance matrix permeability, therefore improve the stress resistances^[39]. Lammi et al.^[50] reported that HA deposition would occur in the areas of cartilage injury and it would attract exogenous mesenchymal stem cells to the injured area. HA can also act as a cell carrier, wrapping stem cells and chondrocytes in the injected area so that the cells can proliferate and differentiate *in situ*^[45,51]. Chung and Burdick^[52] demonstrated in both *in vivo* and *in vitro* experiments that methacrylated HA is capable of providing a microenvironment that facilitates differentiation of mesenchymal stem cells into cartilage, and the effect can be enhanced in the presence of certain cytokines such as transforming growth factor- β 3.

Methacrylated HA is gaining increasingly attention because it can gelatinize through an easy photo-crosslinking, moreover, seed cells can be encapsulated into HA in this way which enables the cell to live in a 3D environment^[52,53]. Conventional cartilage tissue engineering materials require a much larger incision than injectable ones, and photo-crosslinking HA can transform from liquid to hydrogel

through ultraviolet irradiation after injected into the ideal site and fill the defect space with various shapes. Chung and Burdick^[52] used methacrylated HA with human multipotent stromal cells (MSCs) to regenerate cartilage, and they demonstrated that both *in vitro* and *in vivo* cultures of MSC-laden HA hydrogels permitted chondrogenesis, measured by the early gene expression and production of cartilage specific matrix proteins. This kind of *in situ* cross-linking ways including photo-crosslinking and thermosensitive crosslinking will be a possible future trend.

Besides served as a scaffold, HA can also be used as a biologically active molecule to modify bio-inert artificial materials such as polyethylene glycol (PEG), small intestinal submucosa, etc.^[54]. The HA-based cell-scaffold composite can provide a framework for the regenerated matrix. Skaalure et al.^[51] demonstrated that biodegradable PEG hydrogel modified by high concentration of HA can evidently improve the deposition of extracellular matrix and proliferation of chondrocytes.

HA is most generally used in the cross-linked, modified form or as composite with other materials such as platelet-rich plasma^[55], fibrin^[46], chitosan^[45], tricalcium phosphate, collagen^[48], alginate, etc. This is because the cross-linked HA has better mechanical properties than the linear one, while the composite material can combine the advantages of different materials, corresponding with the requirements of tissue engineering scaffold materials^[22]. Chen et al.^[55] demonstrated that HA and platelet-rich plasma can restore the down-regulation of cartilage gene expression induced by interleukin-1 β and tumor necrosis factor- α , including SOX-9, collagen type II and aggrecan.

In addition, there have been reports of using HA as scaffold in the engineering of intervertebral disk^[56], vocal cords^[57], nucleus pulposus^[58], etc.

HA in bone tissue engineering

HA also has a wide range of research and application in bone tissue engineering, it can be used as a scaffold or molecular carrier to promote bone tissue regeneration^[40,59]. The existing papers show that its application has been explored in the field of skull^[60], alveolar^[61] and so on. As in cartilage tissue engineering, HA is also usually required for modification in bone tissue engineering. Since the mechanical properties of HA are weaker than that of human natural bones, the use of HA alone as a scaffold material is not sufficient to support the cell-scaffold composite and requires other materials to

be compounded. For example, Subramaniam *et al.*^[61] demonstrated that HA can be compounded with hydroxyapatite (one of the components of the bone matrix) and modified with calcium sulfate, which encapsulates collagenase. The composite above can serve as a substitute for alveolar bone to produce satisfactory outcomes.

HA can regulate cell differentiation and bone formation by binding to CD44, CD168 on seed cells, such as mesenchymal cells^[62]. Zhu *et al.*^[63] demonstrated that N-cadherin modified HA can promote the differentiation of human mesenchymal cells into bone, leading to more bone matrix deposition. N-cadherin is an important factor in mediating cell-cell interactions during the cluster of mesenchymal cells in bone formation^[64]. In the experiment, they also modified HA with RGD peptide because only the calcium cadherin was sufficient to provide sufficient cell adhesion.

As a molecular carrier, HA has a wide range of applications on the *in vivo* experiments. Of all the researches, carrying bone morphogenetic protein 2 (BMP-2) to promote bone formation, fracture healing is the most commonly used method. BMP-2 is a potent bone-forming molecule that has been approved by the Food and Drug Administration for intervertebral fusion, open tibial fractures, and alveolar bone expansion^[65]. Bhakta *et al.*^[66] confirmed that the thiolated-HA exhibited a low burst followed by a sustained release of BMP-2 while collagen sponge rapidly released BMP-2 with a high burst phase that was followed by a low sustained phase. Analysis of bone formation by micro-computed tomography revealed that low burst followed by sustained release of BMP-2 from a HA hydrogel induced up to 456% more bone compared to a BMP-2 dose-matched collagen sponge that has a high burst and sustained release. Bhakta *et al.*^[67] also reported that heparin-modified HA also had a similar controlled release effect.

HA in skin and soft tissue engineering

Tissue engineering skin equivalents (substitutes) is one of the most successful and most widely used products in tissue engineering so far. It is usually manufactured by seeding keratinocytes and fibroblasts into non-human (e.g. type I bovine collagen) matrix^[68]. However, this tissue engineering skin can only last for approximate 8 weeks due to its high shrinkage of the extracellular matrix, which is not sufficient to form a normal human extracellular matrix consisting of fat, fibrin, glycosaminoglycans and polysaccharides^[68]. Stark *et al.*^[69] seeded keratinocytes on esterified HA fibers, producing the dermal equivalents that could last for a longer period and was more similar to normal

skin tissue.

In addition to tissue engineering of skin substitute, HA has also been used to increase the retention rate of fat grafts. Alghoul *et al.*^[70] used HA as a cell carrier, mixing with autologous fat of the same volume and transplanted into the back of a nude mouse. They found that HA can improve the survival rate of early fat transplantation and prolong the fat maintenance time.

DISCUSSION

Tissue engineering is one of the most promising methods in wound healing, while HA is one of the most suitable natural materials in hydrogel scaffolds. HA has similar water content as human tissue, has good tissue compatibility, and it plays an important role in promoting the proliferation and differentiation of seed cells. In addition, high molecular weight HA has a certain anti-inflammatory effect, and low molecular weight HA oligomers have been shown to promote angiogenesis. At present, HA as a scaffold material, connecting molecules, carrier of drugs and other small molecules has been widely used in tissue engineering. Since the microenvironment formed by HA is particularly suitable for the growth of chondrocytes, the application of HA in cartilage tissue engineering is the most popular. Researchers have also devoted themselves to the regeneration of bone tissues, myocardial tissues, skin and soft tissues with the utilization of HA. Natural HA has a short reservation time *in vivo* due to the rapid degradation by hyaluronidase, therefore appropriate cross-linking and modification of the active group is essential. HA after cross-linking and modification has been widely used alone or compounded with other materials in the tissue engineering. Since HA itself doesn't have a satisfying cell adhesion, modification with RGD sequence or heparin can be considered as a necessary improvement.

The current problem is that there are a variety of cross-linking and modification methods of HA. Moreover, the raw materials from different origins owning divergent molecular weight (ranging from hundreds to millions), thus exhibiting different biological properties, which brings about quite a lot of difficulties to the research and application of HA. Since the high cross-linking (high molecular weight) and low cross-linking (low molecular weight) HA make such a great difference in the biological properties that how to combine the anti-enzymatic ability of high molecular weight HA with the high biological activity of low molecular weight HA remains to be explored.

DECLARATIONS

Authors' contributions

Data collection and analysis: Z. Zhu, Y.M. Wang

Manuscript preparation: Z. Zhu, X.S. Luo

Manuscript's review: J. Yang

Concept design, manuscript preparation and data interpretation: X.S. Luo

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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Modified lower eyelid blepharoplasty improves aesthetic outcomes in patients with hypoplastic malar prominences

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ABSTRACT

Aim: Aging affects the appearance of the eyelids and the surrounding malar region. Blepharoplasty improves the aesthetic appearance of this region, and multiple variants of the procedure have been reported. We here report our technique for modified lower lid blepharoplasty and cheek lift for patients with hypoplastic malar regions, which was introduced after observing prominent lower orbital rims in patients with flat malar prominences after blepharoplasty. **Methods:** This technique combines standard canthopexy and cheek-lift for rejuvenation of the mid-face with redraping of orbital fat and concurrent sub orbicularis oculi fat pad (SOOF) lift to “double-breast” the lower orbital margin. Data on 33 patients who had undergone this modified lower lid blepharoplasty was collected retrospectively. **Results:** Thirty-three patients underwent the modified lower lid blepharoplasty resulting in smooth and youthful appearance of the malar region that was consistent and sustained. No recurrence of V-deformity was observed on a median follow-up of 14 months. Twenty-two (66.6%) and 11 (33.3%) patients were pleased and satisfied with postoperative outcomes respectively. Three (9.1%) patients experienced minor postoperative complications and no major complication was observed. **Conclusion:** The proposed modified lower lid blepharoplasty is a safe and effective alternative to the existing technique with improved aesthetic outcomes and therefore is recommended in patients with flat malar prominences.

INTRODUCTION

Aging is an inevitable natural process of life that affects all parts of the human body. Multiple age-related changes are observed in the anatomy of the

eyelids and the surrounding structures including the malar region. The malar prominence lies just inferior to the eyelid and is an important aesthetic component of the eyelid-cheek junction. The concomitant loss of the elasticity of the musculature (leading to laxity) and



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the overlying skin (resulting in a saggy appearance) of the inferior eyelids, contribute significantly to the elongation of the vertical aperture resulting in an increased visibility of the sclera^[1-3]. Concurrently, pseudo-herniation of the post-septal fat leads to the formation of irregular contours of the lower eyelids. These irregularities along with fat and osseous atrophy lead to the displacement of the eyelid-cheek junction inferiorly and development of the tear trough deformity. Other associated changes include the prominent appearance of the malar bags and skeletonization of the inferior orbital margin^[4-7].

Blepharoplasty remains an important modality in lower eyelid rejuvenation leading to a youthful and aesthetically pleasing appearance of the eyes and the malar region. The ideal technique of blepharoplasty still remains debateable, and therefore different variations in the surgical approach have been described^[6,8-12]. These are aimed at improving aesthetic outcomes and reducing postoperative complications associated with the procedure. Early reports described a sub-ciliary approach which was adopted by Miller^[13] to remove excess skin on the eyelids. Successively, a trans-conjunctival approach was described by Bourguet^[14] that involved removal of herniated periorbital fat. Traditional blepharoplasty evolved on the basis of these two techniques and involved excision of skin, fat, and muscle with septal plication^[6,15]. Substantial removal and sculpting of the orbital fat were involved in these techniques, which was aimed at achieving aesthetically acceptable results. However, soon it became evident that this excessive removal resulted in skeletonization of the orbit with resulting hollowed appearance of the eyes^[16]. This led to further evolution of the techniques by integration of fat preservation. In early 1980's Loeb^[17] described a technique that involved sliding of a vascularized fat pad into the cheek, by means of a sub-ciliary approach, to correct the naso-jugal depression (tear trough). Loeb's technique was then further modified by Hamra^[18] in 1995 and 2004^[16] and described as the "septal reset" technique; a sub-ciliary technique that was aimed at overcoming the shortcomings of the earlier techniques. Hester *et al.*^[19], later described an approach assisted by an endoscope consisting of subperiosteal dissection of the midface and elevation of the orbicularis muscle based on "passive septal tightening". A transconjunctival technique was then described by Goldberg^[20] involving positioning of orbital fat pedicles into a subperiosteal pocket created after incision of the arcus marginalis. Another transconjunctival approach that has been described the repositioning of fat in an intrasuborbicularis oculi fat plane^[21].

Table 1: Garcia-McCollough scale for lower eyelid appearance

Overall appearance
1 = Worsened eyelid contour
2 = No improvement in eyelid contour
3 = Minimal improvement in eyelid contour
4 = Moderate improvement in eyelid contour
5 = Significant improvement in eyelid contour
Visibility of scar
1 = Elevated, hypertrophic scar
2 = Flat but widened scar
3 = Flat but thin scar
4 = Barely perceptible scar
5 = Imperceptible scar
Eyelid position
1 = Frank ectropion
2 = Canthal rounding with significant scleral show
3 = Mild eyelid retraction with scleral show
4 = Unchanged scleral show
5 = Improved scleral show

There has always been a room for improvement in the surgical techniques available for lower eyelid rejuvenation^[22]. Here we present our technique of a modified lower lid blepharoplasty which is a modification of the earlier mentioned techniques tailored to address patients with hypoplastic malar prominences. In our experience, the use of this technique results in improved aesthetic outcomes and is therefore recommended for this select patient population.

METHODS

Methodology

Data on all patients who had undergone this modified lower lid blepharoplasty was retrospectively collected from both private and National Health Service records. The aesthetic appearance was assessed using the Garcia-McCollough scale for Lower Eyelid Appearance [Table 1]^[23]. Patient satisfaction with the outcomes of the procedure was evaluated using an existing validated questionnaire.

The technique

The lateral skin incision is marked [Figure 1A]. It starts 2-3 mm inferolateral to the lateral canthus and tapers infero-laterally along the natural skin crease for 8-10 mm. Blunt dissection is then employed to make a small subcutaneous pocket under the incision [Figure 1B]. The skin of the lower eyelid is incised horizontally 2-3 mm inferior to the lower lid margin, using tenotomy scissors to prevent any damage to the hair follicles [Figure 1C]. The medial margin of the skin incision lies just short of the inferior punctum.

A pre-orbicularis cutaneous flap is then raised to expose the underlying musculature, and the extent of cutaneous undermining depends on the level

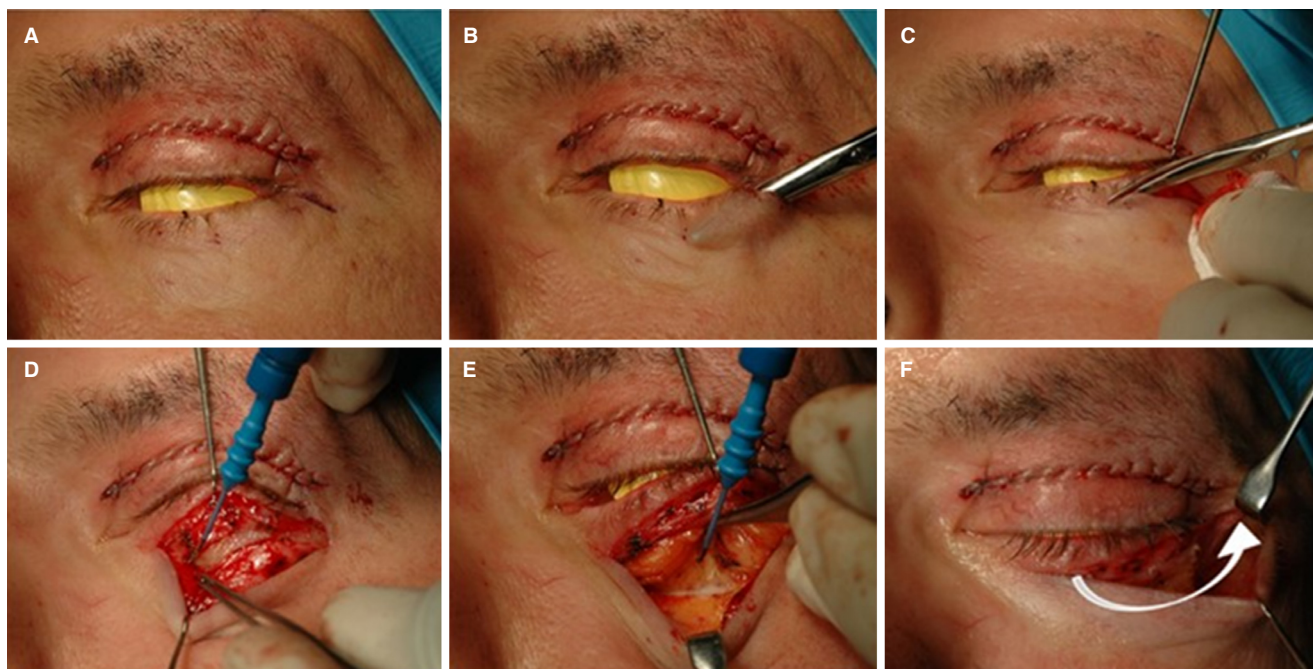


Figure 1: Incision and initial dissection. (A) The lateral skin incision marking; (B) subcutaneous undermining; (C) sub-ciliary incision; (D) incision of the orbicularis oculi muscle; (E) dissection in the sub-muscular plane releasing the fascia over the sub orbicularis oculi fat pad; (F) orbito-malar ligament release and lateral pocket dissection

of skin excision that is clinically required which is generally titrated to each case. A fine tipped cutting diathermy is used to incise the underlying orbicularis oculi muscle preserving 1.5 cm of the vertical muscle height from the ciliary margin superiorly [Figure 1D]. Further dissection is undertaken infero-laterally in the submuscular plane towards the infraorbital margin and zygoma and the orbito-malar ligament over the sub orbicularis oculi fat pad (SOOF) is released [Figure 1E]. Generous use of cold normal saline is employed after the use of cutting diathermy to cool tissue and reduce the risk of chemosis. The pocket is further extended supero-laterally under the orbicularis oculi till the temporalis fascia to prepare for the lateral canthoplasty and orbicularis suspension sutures [Figure 1F]. No subperiosteal dissection is performed.

The post-septal fat, in its pseudo-herniated state, has an irregular gross appearance. The fat is teased into a uniform apron [Figure 2A] to give it a smooth appearance and is redraped over the inferior orbital margin to augment the volume of this skeletonized anatomical landmark. A 5/0 vicryl suture is used to secure a bite through the septum at 2.5 cm from the lower lid margin, followed by a bite of the free edge of the post septal fat apron edge and then a bite through the periosteum of the inferior orbital margin and then through the free edge of the post septal fat apron again. Securing this suture simultaneously plicates the septum and secures the re-draped post septal fat to

the inferior orbital margin [Figure 2B]. The suture is not cut and a bite of the SOOF is taken, lifting it superiorly and securing it on top of the redraped fat over the inferior orbital margin. This SOOF lifting suture also lifts the malar soft tissue by 2-3 mm, augmenting the volume over the inferior orbital margin and also smoothens the contours of the re-draped post septal fat by “double breasting” it [Figure 2C]. Three-four similar sutures are then used in a medial to lateral manner [Figure 2D] and this two-layered volume augmentation over the skeletonized inferior orbital margin results in an improved aesthetic outcome in patients with hypoplastic malar prominences. The excess muscle is then excised using unipolar diathermy [Figure 2E]. The width of this excised muscle depends on its laxity and can vary between 5-12 mm.

This is followed by the placement of a lateral canthopexy suture using a double needled suture (4/0 surgidac-synthetic, non-absorbable). A generous subcutaneous bite of the lateral canthus and adjacent soft tissue is taken and secured to the periosteum that lines the inner surface of the lateral orbital margin at the margin or 2-3 mm superior to an imaginary line passing through the pupil as dependent on the patient's anatomy [Figure 2F]. This is followed by a cheek/midface lift suture (4/0 surgidac-synthetic, non-absorbable) which includes a bite of the fat pad released from the anterior surface of the zygoma and

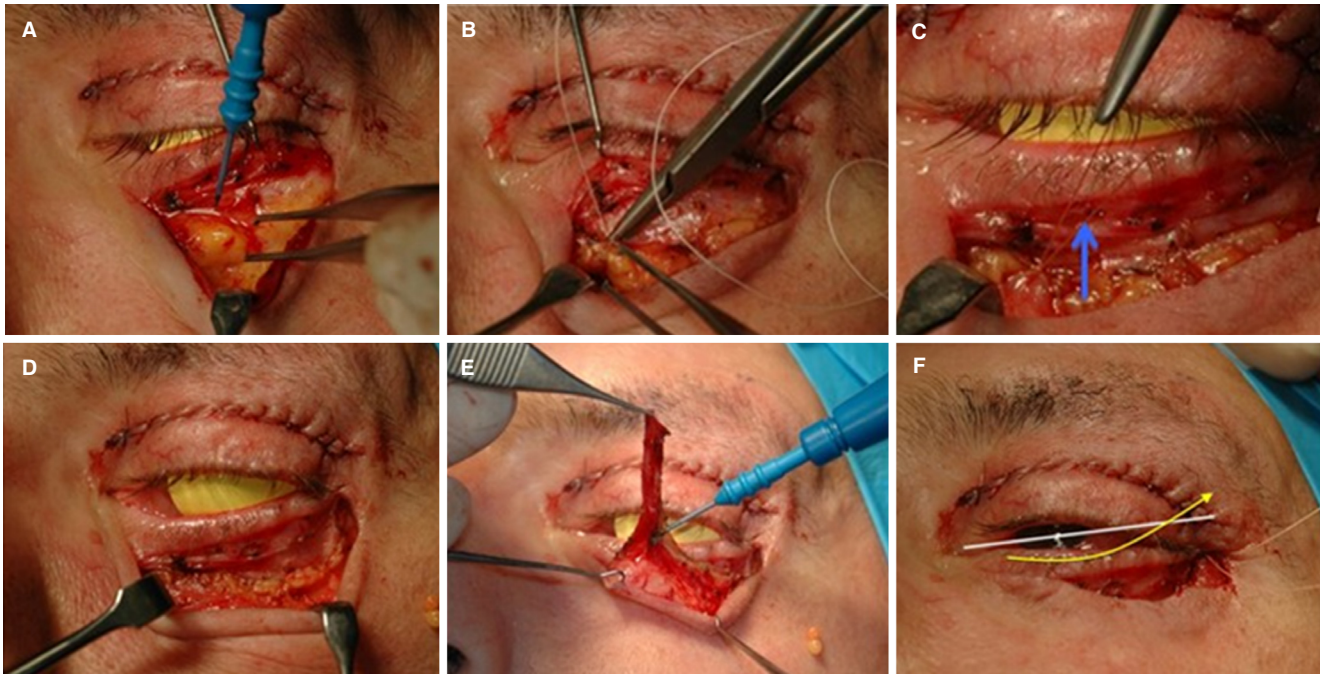


Figure 2: Volume augmentation over the inferior orbital rim and malar tissue lift and lateral canthopexy. (A) The post septal fat in all three compartments is teased into a uniform apron; (B) plication of the inferior orbital septum and redraping of post septal fat over the infraorbital margin (first layer of volume augmentation); (C) sub orbicularis oculi fat pad double-breasting over the post septal fat on the infraorbital margin (second layer of volume augmentation while simultaneously lifting malar tissues) see arrow; (D) three to four similar sutures are used from medial to lateral; (E) excision of excess muscle; (F) lateral canthopexy suture

the under surface of the soft tissue of the cheek in the line of the lateral orbital margin and is secured to a fixed point i.e. the periosteum of the lateral orbital margin. By securing this suture, the bulk of cheek/midface soft tissue is seen to move upwards and over the inferior orbital margin and zygoma to enhance the fullness of the cheek and provide a youthful appearance.

Later two orbicularis suspension (orbicularis hitch) sutures (4/0 surgidac-synthetic, non-absorbable) are placed that secure the incised inferior edge of the orbicularis oculi muscle to the temporalis fascia above the zygomatic arch [Figure 3A] lateral to the lateral canthus. This further elevates the cheek securing it in this position and eliminating downward pull on the lower eyelid margin. A third orbicularis suspension suture is placed which opposes the superior and inferior incised margins of the orbicularis muscle and secures the complex to the periosteum of the lateral orbital margin [Figure 3B]. The extra lower eyelid skin is excised leaving enough skin to prevent postoperative ectropion [Figure 3C].

A lateral contouring suture is then placed using 5/0 prolene, through the skin edges just lateral to the lateral canthus to secure them to the periosteum of the lateral orbital margin. This “quilting” facilitates the creation of a smooth trough which is the

natural depression seen lateral to the lateral canthus [Figure 3D]. This suture is left loose and tied at the end of the procedure after placement of the other sutures both medial and lateral to it. The skin of the lateral incision is closed with 6/0 prolene interrupted sutures and the edges are secured medially with 3-4 vicryl rapide (6/0) interrupted sutures as shown in the immediately postoperative images [Figure 3E and F].

Postoperatively the patients are nursed in a head up position with cooling goggles placed above the surgical site.

RESULTS

We employed the above mentioned technique to perform blepharoplasty in 33 patients between December 2009 and December 2013. The majority of patients (60.6%) were female, the mean age was 49.1 (39-72) years, and the mean BMI was 26.2 (19-33) kg/m².

The mean time taken to perform a unilateral procedure was 23 min while the mean weight of the excised soft tissue was 12 (8-25) g. A standard postoperative protocol of an overnight hospital stay was followed for all patients. The mean follow-up time was 14 (12.5-19) months. The outcomes of interest

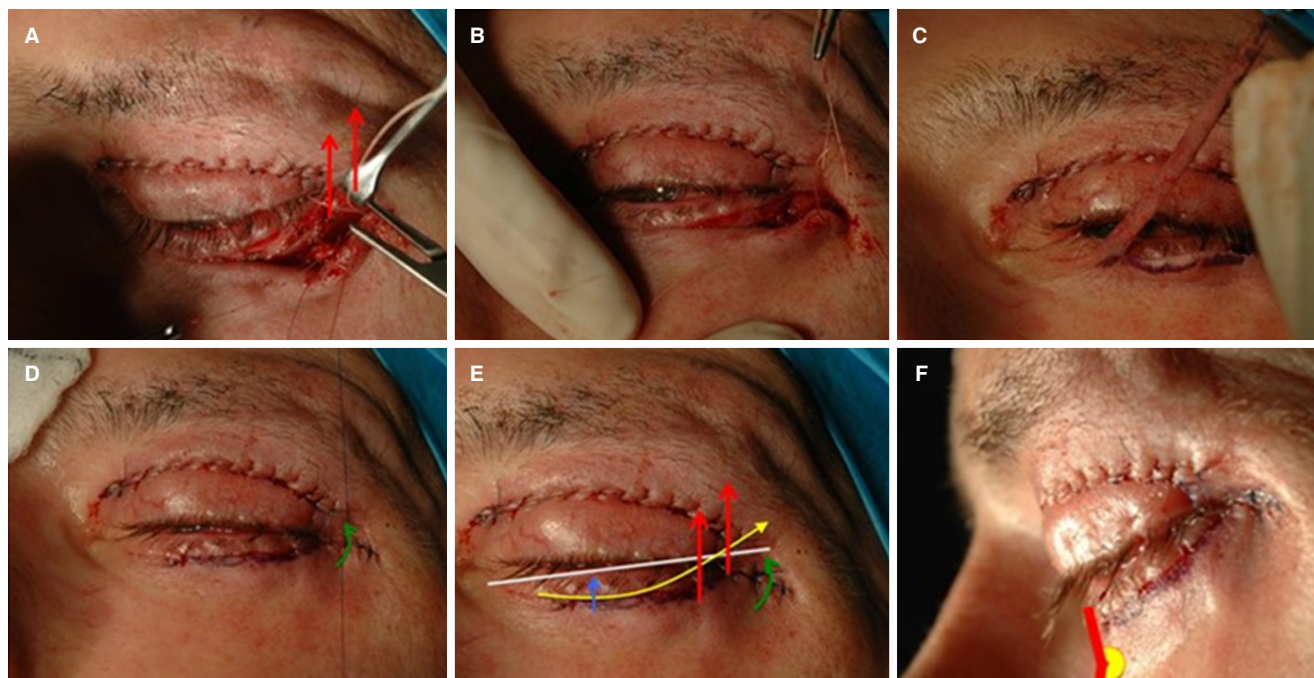


Figure 3: Orbicularis suspension and opposition, reconstruction and immediate postoperative results. (A) Two orbicularis suspension sutures; (B) third orbicularis suture; (C) excess skin excision; (D) lateral contouring suture; (E) immediate postoperative result (antero-posterior view); (F) immediate postoperative result (lateral view)

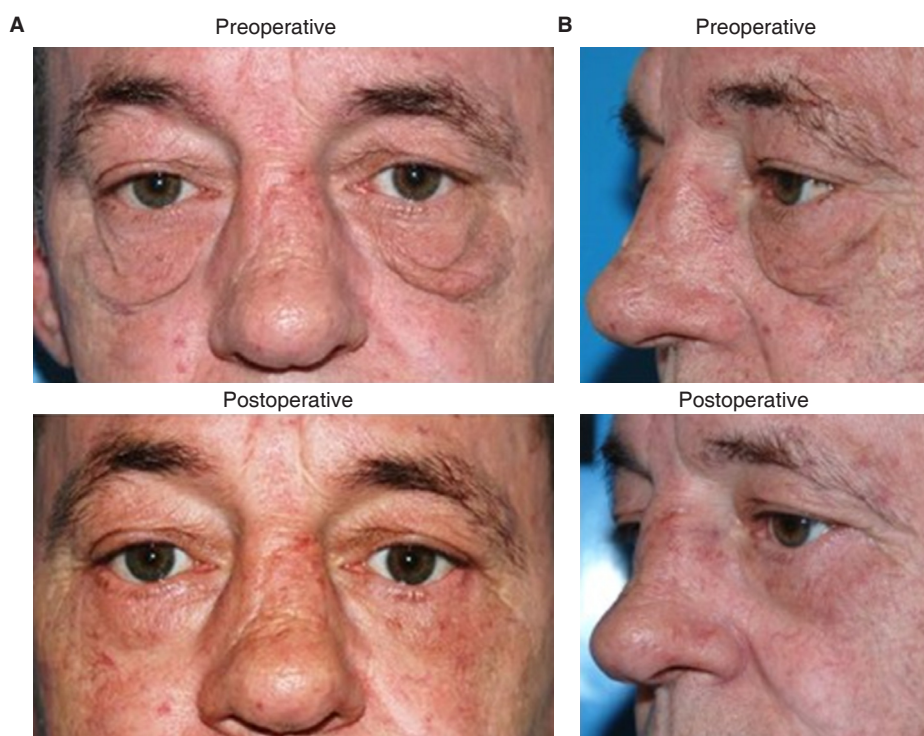


Figure 4: Postoperative outcomes. (A) Pre- and postoperative appearance (antero-posterior view); (B) pre- and postoperative appearance (lateral view)

were the postoperative aesthetic appearance, patient satisfaction, and complications.

The aesthetic appearance was assessed using

the Garcia-McCollough scale for Lower Eyelid Appearance. Postoperative photos at long-term follow up (1 year) are shown in **Figures 4-7**. All patients demonstrated a satisfactory aesthetic appearance.

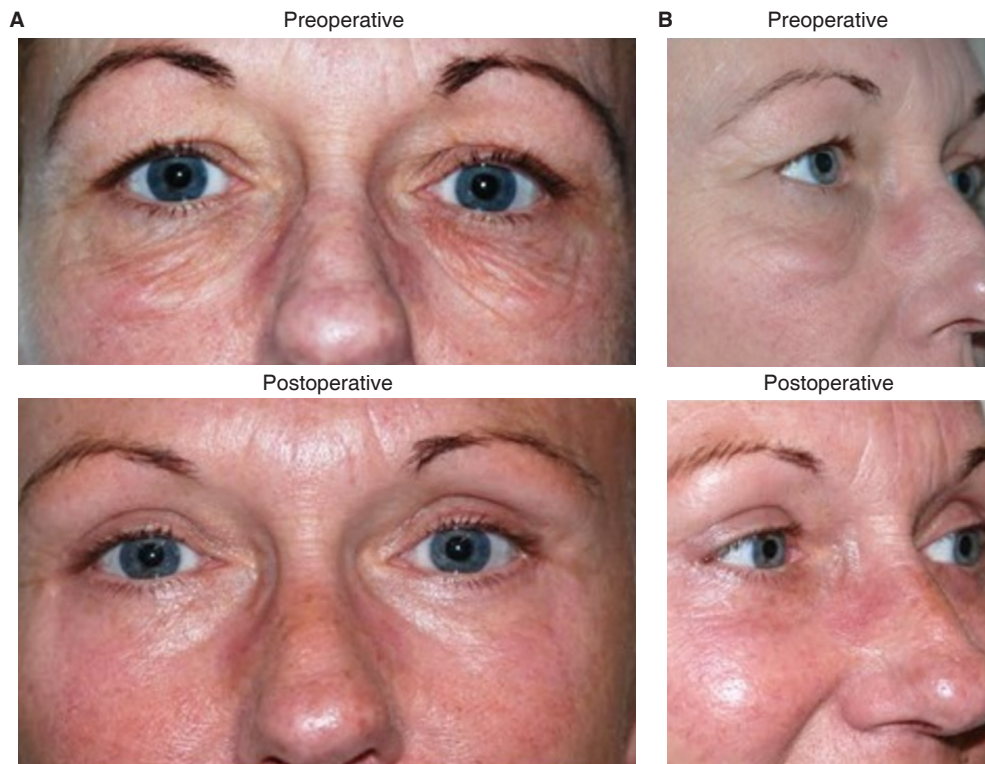


Figure 5: Postoperative outcomes. (A) Pre- and postoperative appearance (antero-posterior view); (B) pre- and postoperative appearance (lateral view)

To assess patient satisfaction a validated satisfaction questionnaire was used. Twenty-two (66.6%) patients were pleased by the postoperative aesthetic outcome while 11 (33.3%) patients were satisfied. There were no major postoperative complications. Minor complications were observed in 3 (9.1%) patients. These included 1 case each of hypertrophic scarring in the segment of the scar lateral to the lateral canthus, stitch sinus and chemosis. All 3 patients were managed conservatively and showed improvement. No patient developed a postoperative infection, ectropion or scleral show.

DISCUSSION

Our proposed technique has several features that differentiate it from the traditional blepharoplasty techniques and aims at achieving a better aesthetic outcome in patients with hypoplastic malar eminences.

Firstly, the location of our trans-muscular incision is significantly lower than the cutaneous incision which ensures that both incisions are not at the same level in different planes. This reduces scarring at the same level thus decreasing the chances of development of postoperative ectropion. Our technique is based on fat preservation and the pseudo-herniated post-septal fat pad is used “ecologically” to augment volume over the

skeletonized inferior orbital margin. In addition “double breasting” of the SOOF over the stabilized “lobular” post-septal fat smoothens it, lifts malar tissues and further augments volume over the inferior orbital rim and imparts a fuller appearance to both the infraorbital and malar regions.

Secondly, the placement of the canthopexy sutures raises the lateral canthus superolaterally avoiding a droopy look that is commonly associated with aging. Securing the canthopexy suture to the inner periosteum of the lateral orbital wall allows the lower eyelid to conform better to the contours of the globe. This prevents the formation of an ectropion and ensures proximity of the lower eyelid to the globe to provide protection.

Thirdly, the placement of the two orbicularis suspension (orbicularis hitch) sutures (4/0 surgidac-synthetic, non-absorbable) secure the incised inferior edge of the orbicularis oculi muscle to the temporalis fascia above the zygomatic arch [Figure 2C] lateral to the lateral canthus. This results in a 2-3 mm elevation of the lid-cheek junction further improving the volume deficit in patients with hypoplastic malar prominences. The third orbicularis suspension suture opposes the superior and inferior incised margins of the orbicularis muscle and secures the complex to the periosteum of

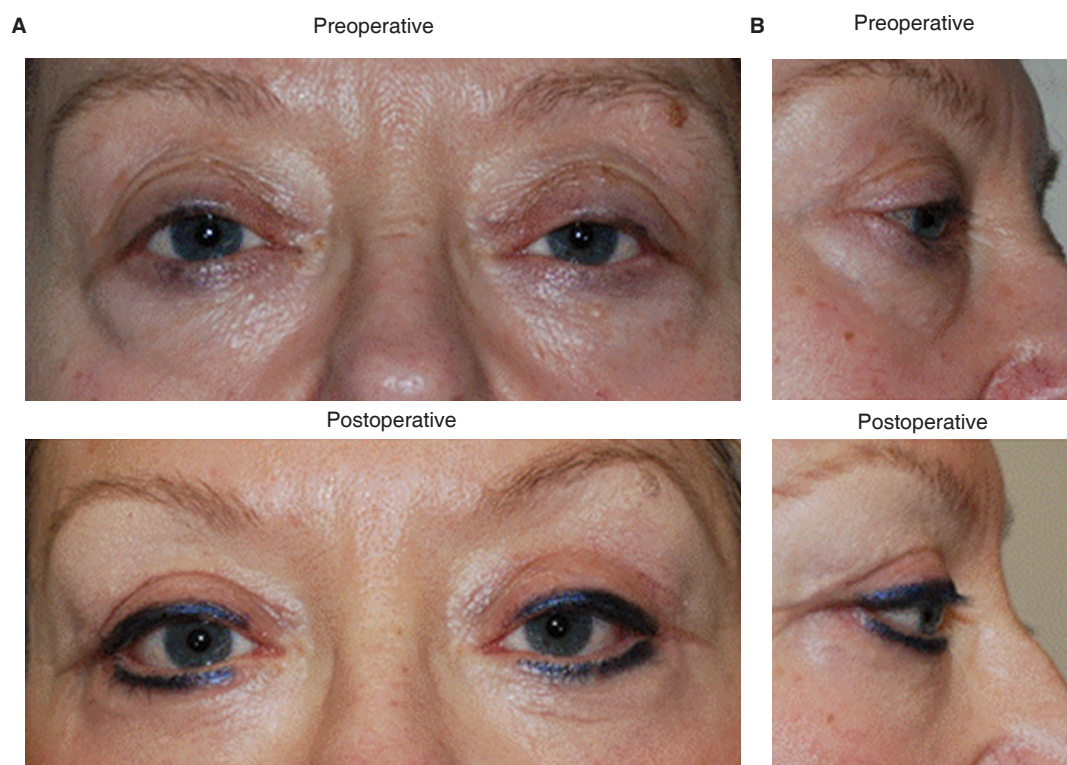


Figure 6: Postoperative outcomes. (A) Pre- and postoperative appearance (antero-posterior view); (B) pre- and postoperative appearance (lateral view)

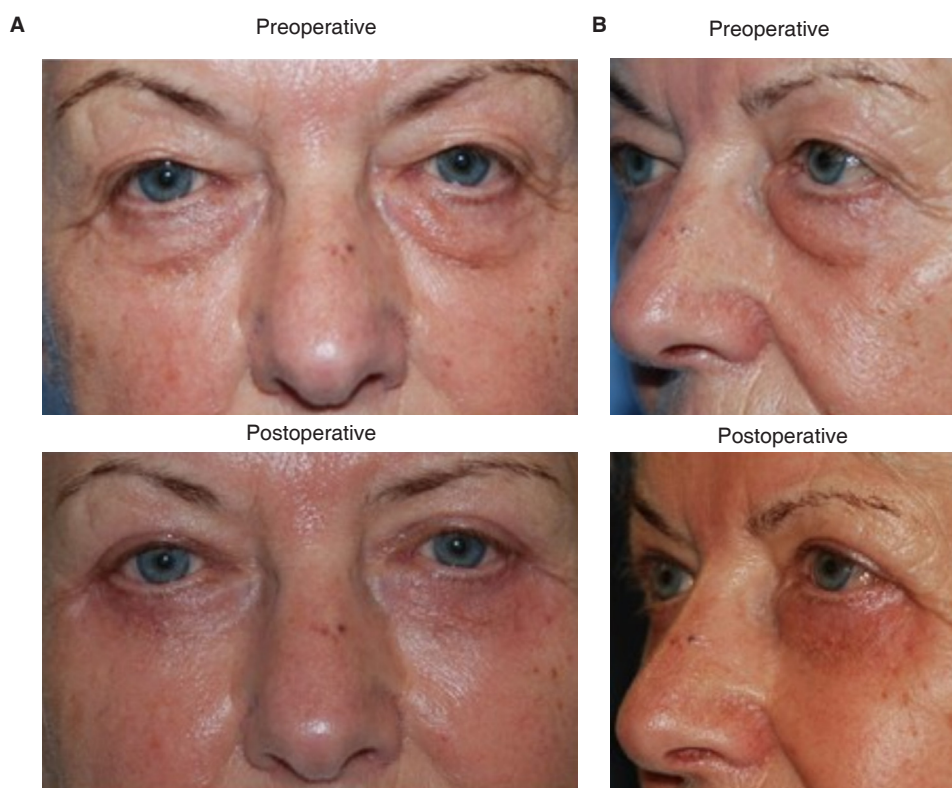


Figure 7: Postoperative outcomes. (A) Pre- and postoperative appearance (antero-posterior view); (B) pre- and postoperative appearance (lateral view)

the lateral orbital margin. Leaving 1-2 mm of excess skin while excising the extra lower eyelid skin prevents postoperative ectropion.

The cheek lift and initial two orbicularis suspension sutures raise the malar soft tissues whereas the third orbicularis suture helps avoid overlapping of the muscles and prevents postoperative contour irregularities. The contouring suture lateral to the lateral canthus ensures a smooth trough appearance which is a part of the normal anatomy of the eye thus further enhancing the aesthetic outcomes.

In conclusion, lower eyelid blepharoplasty is a complex procedure and the malar complex must be considered as a part of the lower eyelid when performing this procedure to obtain improved results. Our proposed technique of a modified lower lid blepharoplasty is a safe and effective alternative to the existing technique which improves the aesthetic outcomes.

This technique is valuable in a patient with a flat malar prominence and therefore its use is recommended in the management of this patient cohort.

DECLARATIONS

Authors' contributions

Concept and design: M.A.A. Khan, A.A. Javed, M. Gorman, D. Othman, M. Riaz

Data collection and analysis: M.A.A. Khan, K. Aziz, A.A. Javed, D. Othman

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Review and final approval: M.A.A. Khan, K. Aziz, A.A. Javed, M. Gorman, D. Othman, M. Riaz

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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AUTHOR INSTRUCTIONS

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2. Submission Preparation

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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;

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Manuscript Type	Definition	Abstract	Keywords	Main Text Structure
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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.
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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

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2.3.1.1 Title

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protein names are included, the abbreviated name rather than full name should be used.

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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.

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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.

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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

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Books	Sherlock S, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub; 1993. pp. 258-96.
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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.
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