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PLASTIC AND AESTHETIC RESEARCH

Peripheral Nerve Injuries in the Upper Extremity

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Topic: Peripheral Nerve Injuries in the Upper Extremity

Dr. Chim is an expert in upper and lower extremity limb salvage, brachial plexus and complex peripheral nerve reconstruction within the University of Florida Division of Plastic and Reconstructive Surgery. He is a board-certified plastic surgeon through the American Board of Plastic Surgery with a Certificate of Added Qualifications in Surgery of the Hand. In 2018, he received the Gelberman Scholar Award from the American Society for Surgery of the Hand (ASSH) and travelled around the world teaching and learning new surgical techniques as a representative of the ASSH and North American hand surgery. Recently, he served as a visiting professor for the ASSH, teaching peripheral nerve surgery to programs around the U.S. His aim is to continually push frontiers by developing new techniques and methods to treat our patients. He is engaged in research, and dedicated to developing new surgical techniques and assess outcomes.

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Topic: Peripheral Nerve Injuries in the Upper Extremity

As co-director of NYU Langone's Center for Amputation Reconstruction, Dr. Hacquebord provides specialized care using advanced surgical techniques and prosthetic technologies to people with limb loss. He also treats adults and children of all ages who have complex nerve, vascular, and bony and soft tissue injuries of the upper extremities, such as amputations, non-unions, severe wounds, and brachial plexus injuries. In addition, he treats children who have complex congenital hand conditions. Many of his patients come to me after consulting multiple surgeons, seeking solutions for their challenging problems. He strives to provide solutions where others are not able, helping people regain meaningful function.

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Plastic and Aesthetic Research

Review

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Distal median and radial nerve branch transfer techniques for upper extremity reanimation

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Abstract

Nerve transfers for peripheral nerve injuries have become increasingly popular over the past two decades. While techniques for ulnar nerve repair have been well-documented, more recent techniques for median and radial nerve branch reinnervation are still being explored. This review describes the outcomes of common and emerging techniques for reinnervation of the distal branches of the median and radial nerves.

Keywords: Anterior interosseous nerve, AIN, extensor carpi radialis brevis, ECRB, posterior interosseous nerve, PIN, nerve transfer, peripheral nerve reinnervation, upper extremity reanimation

INTRODUCTION

Nerve transfers provide additional options for restoring function through neurotizing recipient nerves with expendable donor nerves after severe injuries[1]. Extensive research into upper extremity shoulder, elbow, and distal ulnar nerve reanimation has been conducted, and new techniques for median and radial nerve

branch reinnervation have been described[2]. This review discusses common and emerging hand and wrist reanimation themes, specifically looking at more recent techniques for the neurotization of muscles innervated by the anterior interosseous nerve (AIN) and distal radial nerve branches.

OVERVIEW OF NERVE INJURIES AND REPAIR

A basic understanding of the physiology of nerve repair is required to understand the factors that contribute to the success of nerve transfers. After traumatic transection, the nerve fibers distal to the injury lose contact with the neuronal cell body. Axonal regeneration is the primary means of recovery for these injuries and involves Wallerian degeneration, axonal regeneration, and end-organ reinnervation. Any disruption of these 3 processes can affect functional outcomes[3]. Wallerian degeneration, or the clearing process of the distal stump, serves to create a microenvironment in which axonal regrowth and reinnervation can occur. This process generally occurs within the first week after the injury, after which a peripheral nerve will start to regenerate at a rate of approximately 1 to 3 millimeters (mm) per day toward a distal target. However, muscle fibrosis and atrophy begin as early as 3 weeks following denervation[3]. Given the distance needed to travel in a distal nerve injury, irreversible functional damage can occur within a few months[3]. Although the window for repair and functional recovery is generally accepted as within 12 to 15 months, it is ideal for motor nerve regeneration and target reinnervation to actively occur within 3 to 4 months. Some evidence suggests this is a critical time point, after which regeneration outcomes start to become poor[4]. Of note, timing is different with sensory nerves. Target muscles with pure sensory receptors are less time-sensitive to regeneration, but mixed motor nerves degrade even more rapidly, with repairs delayed more than one month demonstrating significant functional decline[5].

Not all nerve injuries require repair, as management depends on injury severity and resulting functional deficits. Nerve transfers and other surgical options such as nerve grafting and tendon transfers are generally reserved for Sunderland grades IV and V injuries, which involve complete loss of axonal, endoneurial, and perineural continuity; and spontaneous recovery is not expected[6,7]. This contrasts with Sunderland grades I-III, which involves damage of local myelin to axons and endoneurium with intact perineurium. Full recovery is expected in these cases and management is generally conservative[8]. Although nerve grafting was predominantly favored in the past for severe injuries, recent advances in nerve transfer techniques have led to faster, superior outcomes and created a paradigm shift in the treatment strategy for all peripheral nerve injuries[2]. This is especially true for nerve injuries in the upper extremity, with the most common indications for nerve transfers including restoration of shoulder abduction, elbow flexion, radial nerve function, and hand function[6].

ANATOMY, NERVE FUNCTION, AND INJURY CONSEQUENCE

To discuss the outcomes of high AIN and radial nerve transfer techniques, this review provides a general overview of the anatomy and function of particular nerves of interest: the AIN and radial nerve branches in the forearm, including the posterior interosseous nerve (PIN) and the nerve to the extensor carpi radialis brevis (ECRB).

Anterior interosseous nerve

The AIN is a motor branch of the median nerve (C8-T1) with some joint branches that provide proprioceptive and deep pain feedback. It innervates the deep muscles in the forearm that control finger flexion, specifically the flexor pollicis longus (FPL), the lateral portion of the flexor digitorum profundus (FDP), and the pronator quadratus (PQ)[9,10]. It can be found branching from the median nerve at the cubital fossa, usually on the distal border of the pronator teres muscle. However, the origin of the AIN and its relation to the pronator teres muscle can be variable[11].

AIN injuries can be traumatic or spontaneous, caused by penetrating stab wounds, supracondylar fractures, orthopedic surgery complications, compartment syndrome, neuritis, or entrapment under the pronator teres muscle[12]. Patients will often be unable to make an "OK" sign and will have a positive Pinch Grip Test, where a patient will be unable to pinch an object with normal strength[13].

Radial nerve branches

The radial nerve originates from the posterior cord (C5-T1) of the brachial plexus[14]. In the proximal forearm, it gives off branches to the brachioradialis, extensor carpi radialis longus (ECRL) and ECRB before dividing into a superficial branch and the PIN[15]. In most cases, these branches are found proximal to the supinator canal, although the location can be variable. Notably, the nerve to the ECRB is found in the proximal forearm and can have anatomical variation: originating from the radial nerve before it divides, the PIN before it pierces through the supinator, or the superficial branch of the radial nerve[16]. The ECRL and ECRB are responsible for wrist extension, while the PIN is responsible for finger extension, innervating the extensor digitorum communis (EDC), extensor digitorum minimi (EDM), extensor carpi ulnaris (ECU), abductor pollicis (AP), extensor pollicis brevis (EPB), extensor pollicis longus (EPL), and extensor indicis proprius (EIP).

Injury to the radial nerve causes weakness in extension, with an isolated PIN injury resulting in finger extension weakness. As stated previously, the branches to the ECRL and ECRB typically come off the radial nerve before it passes through the supinator muscle and branches to form the PIN, so wrist extension is spared in cases of PIN injury. Additionally, radial deviation is usually present due to the lack of motor input from the ECU with the preserved function of the ECRL and ECRB[17].

REINNERVATION TECHNIQUES

Median nerve: anterior interosseous nerve transfers

Brachialis to AIN

Technique: In this technique, the distal portion of the nerve to the brachialis, coming from the musculocutaneous nerve, is transferred to the AIN [Figure 1]. The patient is placed supine, and a sharp incision is made in the medial arm. Subcutaneous tissue is divided with sharp dissection and cautery, paying particular attention to the medial antebrachial cutaneous nerve. Once the median nerve and musculocutaneous nerve are exposed, the nerve to the brachialis can be identified, branching off the musculocutaneous nerve approximately 17 centimeters (cm) from the acromion. The brachialis branch is more distal than the biceps brachii nerve (13 cm from the acromion). The nerve branches are marked and protected, while the median nerve is inspected. The AIN fascicle is found within the median nerve proper, and intraoperative mapping is aided by a nerve stimulator to identify these fascicles. Once identified, the AIN is dissected proximally, and the remainder of the median nerve fascicles are identified. Following confirmation of the brachialis nerve with stimulation demonstrating brachialis muscle contraction, the brachialis nerve is dissected distally to decrease tension during the repair. The brachialis and AIN can then be coapted end-to-end using microsurgical techniques[18].

Outcomes: The nerve to brachialis to AIN transfer is widely reported in the literature, and many reports have demonstrated favorable results. When assessing outcomes and clinical function, the Medical Research Council (MRC) scale for muscle strength can be utilized, with a grade 3 sufficient for object release and hand opening following AIN reinnervation[19]. Mackinnon *et al.* reported the first case of thumb and finger reinnervation after a spinal cord injury with brachialis to AIN transfer 23 months after injury[20]. Fifteen months postoperatively, the patient regained MRC grade 3 strength of the FPL and FDP[20]. In a case series of 4 patients written by Ray *et al.*, all patients with brachial plexus injuries who received brachialis to AIN

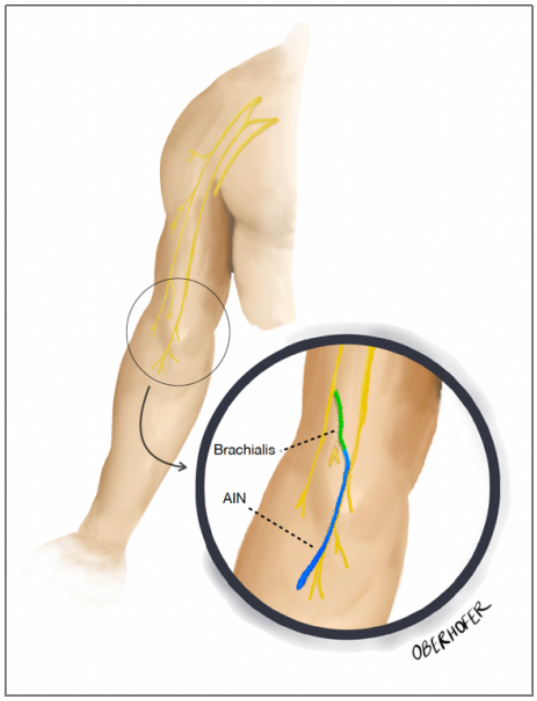

Figure 1. Illustration of relevant anatomy for nerve to brachialis to AIN transfer technique. The donor nerve to the brachialis is transferred to the recipient AIN. AIN: Anterior interosseous nerve.

transfers regained grip strength, and 3/4 regained at least partial pinch strength[21]. All patients met at least MRC grade 3, with 3/4 patients recovering MRC grade 4 function of the FPL and FDP[21]. Hawasli *et al.* reported a detailed case of a patient who received a brachialis to AIN transfer after a complete C7 spinal cord injury[18]. At 3 months postoperatively, the patient demonstrated early reinnervation, regaining MRC grade 3 strength in the FDP and FPL of the left hand[18]. One of the most recent case series for this technique was described by Souza *et al.* in 2020, where 11 patients had lower brachial plexus injuries and received brachialis to AIN transfers in addition to supinator to PIN transfers[22]. Regarding the brachialis to AIN transfers, 8/11 recovered MRC grade 3 or higher on finger flexion[22].

Summary: Although this is an older reported technique, brachialis to AIN has shown relatively good outcomes, with 14/17 cases regaining at least MRC grade 3 flexion strength within two years of follow-up.

ECRB to AIN

Technique: This technique transfers the nerve to the ECRB to the AIN [Figures 2 and 3]. An oblique incision in the proximal forearm is made, following the line of the pronator teres muscle. The median nerve is then exposed through medial retraction of the pronator teres. On the anterior or lateral aspect of the median nerve, the AIN can be identified as it passes under the pronator teres muscle, while the superficial branch of the radial nerve can be identified adjacent to the radial artery. The ECRB motor nerve branch can be identified most commonly as a trifurcation with the superficial radial nerve and PIN. It is confirmed with nerve stimulation demonstrating wrist extension. The ECRB is then dissected distally, and the AIN is cut proximally and the transfer is performed with tension-free coaptation[23].

Outcomes: This technique has shown very favorable outcomes. Bertelli *et al.* reported 4 patients with high median or ulnar palsy or C7-T1 brachial plexus root avulsions who received nerve to ECRB to AIN transfers

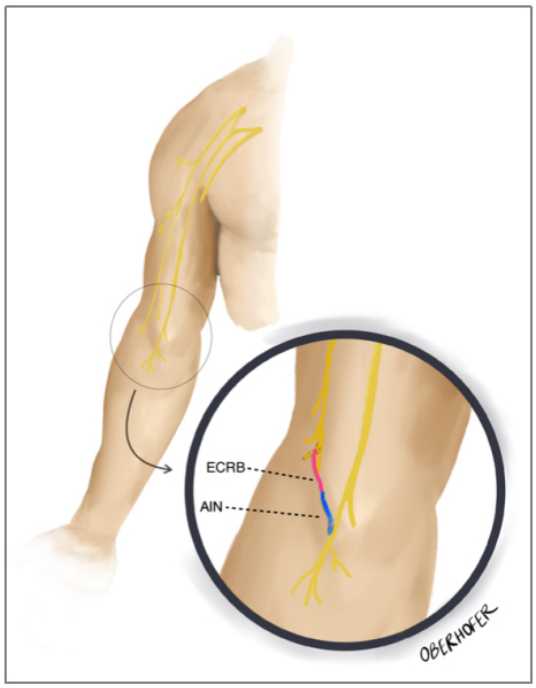

Figure 2. Illustration of relevant anatomy for nerve to the ECRB to AIN nerve transfer technique. The donor nerve to the ECRB is transferred to the recipient AIN. AIN: Anterior interosseous nerve; ECRB: extensor carpi radialis brevis.

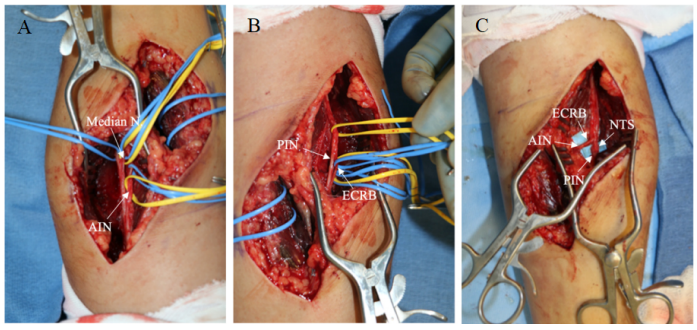

Figure 3. (A) Identification of the AIN branching from the median nerve. (B) Identification of the PIN and nerve to ECRB. (C) The donor nerve to the ECRB is transferred to the recipient AIN. The nerve to the supinator (NTS) is also transferred to the PIN. AIN: Anterior interosseous nerve; ECRB: extensor carpi radialis brevis; PIN: posterior interosseous nerve.

within 8 months of injury[23]. At 13 months postoperatively, all patients regained full finger and thumb flexion with grade MRC grade 4 strength[23]. Another study by Bertelli *et al.* compared surgical outcomes of 9 patients and 17 limbs after cervical spinal cord injury[24]. Nerve to the brachialis to AIN transfer was performed in 3 limbs, brachialis to other median nerve motor fascicles in 5 limbs, brachioradialis to AIN in 4 limbs, and nerve to the ECRB to AIN in 5 limbs. Finger flexion restoration was only observed in 4/8 limbs with brachialis transfer, with 3 limbs achieving MRC grade 3 flexion and one limb achieving MRC grade 4 flexion. Similarly, brachioradialis to AIN transfer showed incomplete flexion with MRC grade 4 strength. Meanwhile, ECRB to AIN had the best reported outcomes, with MRC grade 4 strength and full finger flexion in all 5 limbs and no downgrading of wrist extension or elbow flexion[24]. Salomão *et al.* most recently reported a single case report of a 29-year-old male who sustained a gunshot wound and received ECRB to AIN transfer 16 months after injury[25]. At a 2-year follow-up, the patient regained full flexion with

MRC grade 4 strength and no donor site morbidity[25].

Summary: This technique shows great results with 10/10 cases of nerve to ECRB to AIN regaining MRC grade 4 finger flexion strength. This contrasts with brachialis to AIN, in which the majority of patients only regained MRC grade 3 strength. In addition to good reported outcomes, there were no cases of donor site morbidity.

Supinator to AIN

Technique: This technique utilizes an expendable branch of the radial nerve, the nerve to the supinator, to reinnervate the AIN. First, an incision is made below the antecubital fossa. To visualize the median nerve and branches, the superficial head of the pronator teres is retracted medially. Next, the AIN is identified and dissected from the median nerve. The radial nerve can be identified by locating the superficial radial nerve and following it proximally. There are typically 1 to 3 small nerve branches to the supinator, which can be confirmed with nerve stimulation. The nerve(s) to the supinator is then divided distally, and the AIN is divided proximally to allow for tension-free end-to-end coaptation.

This technique is advantageous because it does not preclude future tendon transfer to muscles innervated by the AIN if the resulting motor function is not adequate after the transfer. Furthermore, as forearm supination is primarily powered by the biceps, there is minimal donor site deficiency after transfer[26].

Outcomes: There are fewer reports on this technique in the literature than on transferring the nerve to the brachialis or nerve to the supinator to the AIN. Notably, Hsiao *et al.* described a case report of a patient with median nerve palsy following a proximal humerus fracture who received nerve transfers of supinator to AIN and ECRB to the pronator teres branch of the median nerve[26]. At 1-year follow-up, grip strength and pinch strength were regained at MRC grade 4+ for FPL and 4- for FDP. Although strength was adequate, the patient underwent tenodesis at 18 months to improve index finger flexion strength[26]. Murphy *et al.* also described a unique case of a 56-year-old woman with median nerve loss who underwent transfer of a branch of the nerve to the ECRB to the pronator nerve and nerve to the ECRB and supinator to AIN[27]. The patient regained MRC grade 3 thumb and index finger flexion after one year and almost complete function and MRC grade 4 FPL strength by 4 years[27].

Summary: Although there are not many cases reported in the literature, this technique is promising, with 2/2 cases of supinator to AIN regaining MRC grade 4 FPL and FDP flexion strength. Although this has shown equal MRC grade 4 strength compared to ECRB to AIN, the latter technique has been more widely reported.

Distal radial nerve transfers

FDS to ECRB

Technique: This technique transfers the branch of the median nerve innervating the flexor digitorum superficialis (FDS) muscle to the branch of the radial nerve innervating the ECRB muscle. An incision is made below the antecubital crease in the proximal forearm. An intraoperative nerve stimulator is then used to identify the median nerve and its branches. The FDS branch can be identified by visualizing finger flexion at the proximal interphalangeal joints after stimulation. Of note, there can be significant anatomical variation in the location of the FDS branch. Once the median nerve and its branches are protected, the radial sensory nerve is identified and followed proximally to find the PIN and the branch to the ECRB. Following the identification of all nerves, the ECRB is divided proximally, and the FDS is divided distally to allow minimal tension and is repaired end-to-end with microsurgical techniques[28].

Outcomes: Although outcomes for this seem promising, there are few reports in the literature. Good outcomes for radial nerve branch transfers are defined by achieving at least grade MRC grade 3 on extension[29]. In 2007, Mackinnon *et al.* described a case report of a 32-year-old woman with radial nerve palsy after intramedullary humerus rod placement who received a transfer of FDS and FCR to ECRB and PIN, respectively[28]. At 18 months postoperatively, she regained MRC grade 4 finger and wrist extension strength[28]. Similarly, Ukrit *et al.* described two case reports of patients with C5, C6, and C7 avulsion injuries who received FDS to ECRB[30]. Both patients recovered MRC grade 4 wrist extension strength at the 2-year follow-up visits[30].

Summary: There are not many reports of this technique in the literature, but this technique is very promising, with 3/3 cases of FDS to ECRB regaining MRC grade 4 extension strength.

Distal AIN (PQ) to ECRB

Technique: The nerve to the pronator quadratus is transferred to the nerve to the ECRB in this technique. An oblique incision is made in the proximal forearm, a few centimeters below the antecubital fossa. The nerve to the ECRB can be identified by tracing the superficial branch of the radial nerve proximally. Following identification of the ECRB branch, the incision is extended distally and the distal AIN can be identified through a trans-FCR approach to expose the proximal aspect of the pronator quadratus. The AIN can then be seen entering the pronator quadratus. Contraction of the pronator quadratus with nerve stimulation confirms the correct identification of the AIN. The AIN is traced proximally, and care is taken to preserve the branch to the FPL. The ECRB is cut proximally at its origin, and the AIN is cut distally and, if necessary, further dissected within the substance of the pronator quadratus muscle for additional length. Following division, the AIN is turned proximally and passed radially to allow for coaptation to the ECRB motor branch.

Outcomes: In 2012, Bertelli *et al.* described the technique for transferring the distal AIN branch to pronator quadratus to the ECRB motor branch and reported 4 patients with brachial plexus injuries who underwent surgery within 10 months of injury[31]. At 12 months postoperatively, all patients gained MRC grade 4 wrist extension without loss or downgrading of pronation or strength in FPL or FDP flexion[31]. In another case series by Bertelli *et al.*, 28 patients with C5-8 root injuries had this operation within 7 months after injury[32]. At approximately 22 months postoperatively, 25/28 patients scored MRC grade 4 extension, 2/28 scored MRC grade 3, and one scored MRC grade 2. Furthermore, there was no loss of function or downgrading of the FPL or FDP flexion strength[32]. Similarly, Bhatia *et al.* reported results of 20 patients with C5-8 root injuries who underwent operations within 9 months of injury[33]. In this series, 17/20 patients gained MRC grade 4 wrist extension, with the remaining 3 gaining MRC grade 3 extension. However, the authors reported that the 3 patients with lower scores had MRC grade 3 recordings of the DIP and thumb flexion before the transfer, indicating weakness of the donor nerve. Additionally, there was no loss in pronation in 14/20 patients, while 4/20 were downgraded to MRC grade 3 and one patient had complete loss of pronation. There were no cases of thumb and DIP flexion strength loss or downgrading[33]. Bertelli recently reported a larger case series of 14 patients with radial nerve lesions who received AIN to ECRB and FCR to PIN in 2020. 13/14 recovered M4 and 1/14 recovered M3 wrist extension strength[34].

Summary: Distal AIN (PQ) to ECRB is a reliable technique with very good reported outcomes, as 59/66 cases of PQ to ECRB regained MRC grade 4 wrist extension strength. This technique is much more widely reported compared to FDS to ECRB, although outcomes with FDS to ECRB are similar.

FCR to PIN

Technique: This technique utilizes a branch of the median nerve, the nerve to Flexor Carpi Radialis (FCR), for reinnervation of the PIN. A proximal, volar forearm incision is made below the antecubital fossa. The FCR branch of the median nerve is identified with nerve stimulation, with stimulation causing wrist flexion. The PIN can then be found by following the radial sensory nerve proximally. Following identification, the PIN is divided proximally, and the FCR is divided distally to allow tension-free coaptation[28].

Outcomes: Previous reports demonstrated good wrist and finger extension results. As described earlier, Mackinnon *et al.* reported a transfer of FDS to ECRB and FCR to PIN[28]. At 18 months postoperatively, the patient gained MRC grade 4 finger and wrist extension strength[28]. Additionally, García-López *et al.* reported 6 cases of nerve to the pronator teres (PT) to nerve to ECRL and nerve to FCR to PIN in patients with radial nerve palsy or posterior cord injuries[35]. After 20 months, all patients recovered MRC grade 4 ECRL strength with PT to ECRL transfer. With FCR to PIN transfer, 2/6 recovered MRC grade 3 and 4/6 recovered MRC grade 4 metacarpophalangeal extension and ECU strength. All patients recovered MRC grade 4 thumb extension strength[35]. As previously described, in Bertelli's case series of 14 patients who received AIN to ECRB and FCR to PIN, 8/14 recovered M4 and 4/14 recovered M3 finger extension, and 13/14 recovered M4 wrist extension. 11/14 recovered full thumb extension[34].

Summary: FCR to PIN has shown good results with 18/21 cases of FCR to PIN recovering MRC grade 4 and 3/21 recovering MRC grade 3 wrist extension strength. In addition to wrist extension, 13/21 recovered MRC grade 4, and 6/21 recovered MRC grade 3 finger extension strength. Finally, 18/21 recovered full thumb extension.

Supinator to PIN

Technique: This technique transfers the nerve to the supinator to the PIN [Figure 4]. On the dorsal side of the arm, an incision is made at the level of the lateral epicondyle between the ECRL and brachioradialis. Careful dissection is essential to preserve branches of the posterior antebrachial cutaneous nerve, which provides sensation to the posterior portion of the forearm[19]. Once the brachioradialis and ECRL are identified, dissection in this interval allows exposure of the superficial branch of the radial nerve, PIN and supinator branches. Alternatively, the supinator can also be exposed by dissecting in the interval between the ECRB and EDC[36]. Finally, a volar approach can also be used, dissecting radially deep to the brachioradialis muscle to expose the branches of the radial nerve. These nerves can be identified by stimulation, with contraction of the supinator confirming its branches and PIN stimulation not causing contraction of the EDC, ECU, EPL and EIP in the setting of injury. The supinator branch is then divided distally, and the PIN is divided proximally to allow for tension-free coaptation[19].

Outcomes: The supinator to PIN technique is widely documented in the literature and described as the most reliable technique for achieving good outcomes for restoring finger extension[19]. In 2015, Bertelli *et al.* described a case series of 7 patients and thirteen limbs that received supinator to PIN transfer[37]. After 19 months, 12/13 achieved at least MRC grade 3 thumb and finger extension, with 8 achieving MRC grade 4 thumb extension. The last limb regained MRC grade 2 function[37]. In another series by Bertelli *et al.*, 7 patients with tetraplegia received nerve to the supinator to PIN or gracilis muscle transfer to the extensor compartment of the forearm[38]. After 26 months, 3/3 upper limbs receiving nerve transfer recovered MRC grade 3 thumb and finger extension, compared to none of the patients with gracilis transfer scoring above MRC grade 2[38]. In 2018, Emamhadi *et al.* described a case report of a patient with tetraplegia after a C6 burst fracture who received brachialis to AIN and supinator to PIN nerve transfer[36]. From the supinator to PIN transfer, the patient achieved MRC grade 3 on thumb extension and MRC grade 4 on finger extension.

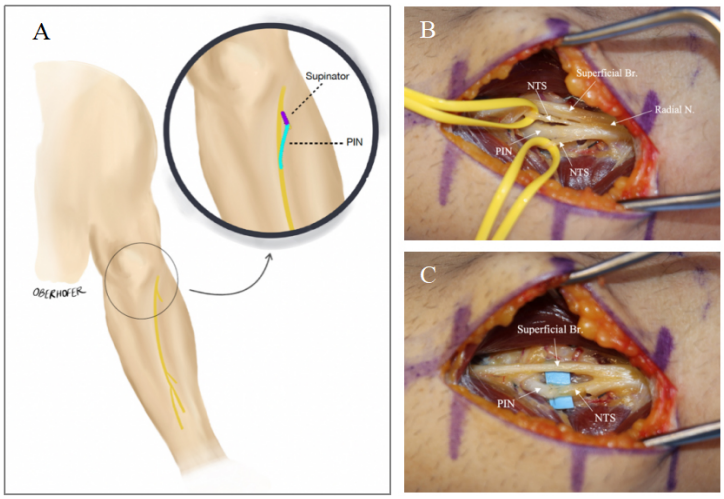

Figure 4. (A) Illustration of relevant anatomy for nerve to supinator to PIN nerve transfer technique. (B) Identification of the nerves prior to transfer: Radial Nerve (Radial N.), Superficial branch of the radial nerve (Superficial Br.), nerve to supinator (NTS), and posterior interosseous nerve (PIN). (C) The donor nerve to the supinator (NTS) is transferred to the recipient PIN.

The patient also achieved MRC grade 4 on thumb and finger flexion with brachialis to AIN transfer[36]. In another investigation, van Zyl *et al.* reported a case series of 16 participants with spinal cord injury and 59 total nerve transfers[39]. Of the nerve transfers, supinator to PIN had the highest-rated satisfaction. In these cases, 19/21 limbs receiving supinator to PIN nerve transfers achieved MRC grade 3 or higher finger extension, and 17/21 achieved at least MRC grade 3 thumb extension at 24 months follow-up[39]. Khalifeh *et al.* reported worse outcomes in a case series of 17 participants and 42 nerve transfers after spinal cord injury[40]. Thirteen out of forty-two nerve transfers were supinator to PIN, and only 7/13 achieved MRC grade 3 or higher finger extension[40], although this could be attributed to the longer delay from the time of injury to surgery[19]. Finally, Souza *et al.* reported a case series of 11 patients with lower brachial plexus injuries who received brachialis to AIN and supinator to PIN within 13 months of injury[22]. After 12 to 24 months postoperatively, 8/11 patients achieved MRC grade 3 or better finger extension with supinator transfer and finger flexion with brachialis transfer. There was no significant loss in donor site function[22].

Summary: Supinator to PIN is one of the most widely documented upper extremity nerve transfer techniques and has shown good outcomes, with 50/62 cases achieving at least MRC grade 3 finger extension and 33/38 achieving at least MRC grade 3 thumb extension. Although results are similar to FCR to PIN, this technique is more widely documented and has been reported to have very high patient satisfaction scores.

CONCLUSION

Distal nerve transfer techniques provide new options to restore function after median and radial nerve injuries. The ECRB to AIN nerve transfer has shown the most promising results for restoration of finger flexion, with all cases examined recovering MRC grade 4 finger flexion.

Regarding transfer techniques for radial nerve injuries, supinator to PIN is a well-documented method for reinnervation of finger and thumb extension. Moreover, it is often used in conjunction with other nerve transfer techniques for finger flexion restoration in the cases of spinal cord or brachial plexus injuries. Although FCR to PIN has shown promising outcomes, there have been few descriptions of this technique published in the past few years, partially due to the popularity of the supinator to PIN. The FCR to PIN nerve transfer does have a role in proximal radial nerve injuries where the supinator branches are not

available as an expendable donor nerve. For wrist extension, both FDS to ECRB and distal AIN (PQ) to ECRB can be used to regain MRC grade 4 extension. The choice of donor nerve will depend on the mechanism of injury.

Although specific nerve transfer methods may be reported more than others, it is essential to remember that the optimal donor nerve may vary in different patients. Available donor nerves would vary in patients with tetraplegia, brachial plexus injury or proximal median or ulnar nerve injury. Nerve transfers should be tailored to the requirements of the patient to potentially achieve the best possible outcome. While physical examination remains the most important method for determining the candidacy of donor nerves, imaging techniques such as magnetic resonance imaging may have a role in decision making[18].

CLINICAL RECOMMENDATIONS

Median and radial nerve transfers are reliable methods for upper extremity reanimation after nerve injury. The authors recommend that decisions on the technique used for nerve transfer should be made on a case-by-case basis depending on injury patterns and available donor nerves. Based on the comprehensive review, if there are multiple nerve transfer options for reinnervation of the AIN, we recommend ECRB to AIN as it has better overall reported outcomes compared to brachialis to AIN. Supinator to AIN is another option, but only a few cases have been published.

For wrist and finger extension restoration, we recommend supinator to PIN as a well-documented, reliable method with good results and high overall reported patient satisfaction. FCR to PIN also has good results. We believe it can still be considered when supinator to PIN is not possible with proximal radial nerve injuries or when imaging or physical exam suggests FCR to be a better donor nerve. When only wrist extension restoration is indicated, we recommend distal AIN (PQ) to ECRB as it has good outcomes and is more widely reported than FDS to ECRB, although the latter has good outcomes as well.

Lastly, we reiterate that our clinical recommendations are based on the current documented outcomes in the literature and may evolve as more cases are reported. We recommend that the final decision for choosing a nerve transfer technique should be based on the clinician's best judgment by utilizing physical exam and imaging to choose a donor nerve that allows a technically feasible dissection and coaptation with the highest return to function and least donor site morbidity.

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Authors' contributions

Made substantial contributions to the article including data curation, background research, interpretation, writing, editing, and revising: Bryan J
Made substantial contributions to writing, editing, and revising: Nichols DS
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Plastic and Aesthetic Research

Review

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Complex upper extremity injuries: targeted muscle reinnervation, free functional muscle transfer, and vascularized composite allotransplantation

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Abstract

Restoration of upper extremity function poses a unique surgical challenge. With considerations ranging from ensuring appropriate skeletal support and musculotendinous and ligamentous anatomy, restoring adequate vascularity and innervation, and providing sufficient soft tissue coverage, upper extremity injuries present a diverse range of reconstructive problems. Recent history has been marked by an expansion of novel techniques for addressing these complex issues. Sophisticated modalities, such as targeted muscle reinnervation, free functional muscle transfer, and vascularized composite allotransplantation, have become some of the most powerful tools in the armamentarium of the reconstructive surgeon. This review article aims to define the distinguishing features of each of these modalities and reviews some of their unique advantages and limitations.

Keywords: Targeted muscle reinnervation, free functional muscle transfer, vascularized composite allotransplantation

INTRODUCTION

Disabling upper extremity injuries encompass a broad spectrum of clinical conditions. These injuries have devastating functional consequences for the patients who sustain them and present complex reconstructive and rehabilitative challenges to the clinicians who treat them. Whether of a traumatic, congenital, ischemic, or oncologic nature, the partial or complete loss of hand and upper extremity function brings with it physical, psychological, and emotional barriers for patients and their providers to work through together.

Algorithmic approaches have been proposed for the initial management of serious traumatic upper extremity injuries[1-4]. However, the long-term restorative and rehabilitative management of each patient represents a unique clinical situation and must be handled as such. Patients' needs, desires, and abilities will differ dramatically based on a host of patient-specific variables, as will the reconstructive options available for a given injury and degree of functional loss.

Historically, the choices available to patients who sustained truly devastating hand and upper extremity injuries were limited. Before the 1970s, problems such as amputations, devascularizing or denervating trauma, or mangled bony and soft tissue injuries were either managed by formalized amputation and body-powered or early electric prostheses[5] or by limb salvage to heal wounds and fractures followed by rehabilitation to attain the most meaningful possible use of the injured extremity. The 1960s saw the first replantation of an upper extremity at the level of the shoulder by Ronald Malt in 1962[6] and the first successful digital reattachment by Komatsu and Tamai in 1965[7]. The first successful microsurgical transplant of a segment of omentum in a human by Harry Buncke and Donald McLean in 1969 opened the door to an entirely new array of techniques involving free tissue transfer[8,9]. Within the past few years, there has been a considerable increase in the options within the armamentarium of the reconstructive upper extremity surgeon. Improvements in prosthetic technology brought about with the advent of myoelectric prostheses[5] combined with progress in peripheral nerve surgery, such as regenerative peripheral nerve interfaces[10-12] and targeted muscle reinnervation (TMR)[13-17], have markedly improved the functional outcomes following amputation[18]. At the same time, widespread refinement of microsurgical techniques has made possible the transfer of vascularized and neurotized muscle, termed free functional muscle transfer (FFMT), with the aim of restoring specific upper extremity functions[19-23]. Furthermore, in the two decades since the first successful hand transplant by Jean-Michel Dubernard in 1998 ushered in the era of vascularized composite allotransplantation (VCA)[24], there have been significant advances in the availability and feasibility of hand and upper extremity transplantation.

With the many novel and highly sophisticated reconstructive options now available as well as the rapid pace at which technology is evolving and adapting, it can be challenging for surgeons, therapists, and prosthetists alike to remain abreast of the most recent developments. This article explores three methods for reconstruction and restoration of upper extremity function, namely, TMR and a myoelectric prosthesis following traumatic or elective amputation, FFMT, and VCA. In reviewing them, the goals are to define each modality and explore their benefits as well as current limitations.

TARGETED MUSCLE REINNERVATION

TMR refers to the surgical transfer of nerves, often following amputation of an extremity, to a new "target" in the form of a remaining muscle. While the fundamental technique was successfully described as early as 1917[25], the ability to harness its full potential has only recently started to be realized. TMR is now widely performed in both the upper and lower extremities, given its proposed two-fold benefits of reducing post-amputation neuroma pain and phantom limb pain and of facilitating improved control of a myoelectric prosthesis[26]. The mechanistic underpinnings of reduced residual limb pain result directly from guiding the

process of axonogenesis in severed nerves to a specified target, described by Cheesborough *et al.* as giving "... the nerves somewhere to go and something to do"[14]. With regard to facilitating enhanced control of the prosthesis, harnessing the power of TMR allows redirection of neural signals intended for a missing limb into input fed to a predefined target muscle that has been surgically stripped of all additional motor input. This in turn reliably and predictably generates electromyographic signals that can be detected by the prosthetic device. It is through this creation of "control sites" that electrodes from a myoelectric prosthesis can translate neural input into meaningful movements and functions. These include transfer of a distal branch of the radial nerve to the lateral head of triceps with the intention of facilitating hand opening and transfer of the median nerve to the short head of biceps to drive hand closure[27]. It is worth noting that, at present, the limited sophistication of the lower extremity prosthetics available in comparison with those for the upper extremity has constrained the extent to which the promise of TMR can be realized in below-knee and above-knee amputations.

In the upper extremity, TMR is most frequently performed in patients who have sustained an injury that has left them with no or significantly limited function proximal to the wrist[28]. These patients can be divided into three groups: those who have undergone an amputation in whom TMR is performed in anticipation of eventual use of a myoelectric prosthesis; those who already use a prosthesis and desire improved control of their artificial limb; and those opting for an elective amputation because of dissatisfaction with their current level of upper extremity function post-injury. Amputations can be at the transradial, transhumeral, or shoulder disarticulation level, and each TMR procedure differs with respect to the anatomy, technical aspects, and number of control sites that can be created.

The success of TMR, and even the ability to offer it to a given patient, remains dependent on several potentially limiting factors. Post-injury anatomy must be such that the residual nerves that will be coapted to target muscles have not sustained damage that would preclude meaningful reinnervation, as could be present in those with multilevel injuries or amputations involving an avulsion mechanism. Furthermore, the patient's residual limb must be able to tolerate a prosthetic device, which can be challenging in patients with systemic conditions such as diabetes mellitus and peripheral vascular disease or burn injuries[27] in whom the soft tissue is compromised. Finally, a variety of socioeconomic factors warrant consideration before pursuing TMR with a myoelectric prosthesis. Despite evidence that these devices can have a cost-benefit over the lifetime[29], they are associated with a significant upfront cost burden, particularly for those without adequate health insurance coverage[30]. They also require a substantial time investment to learn how to attain maximum functionality and are associated with high rates of abandonment[31,32]. However, regardless of an individual's ability to attain or operate a myoelectric prosthesis, TMR still offers the benefit of less neuropathic pain following amputation and should be considered whenever feasible.

FREE FUNCTIONAL MUSCLE TRANSFER

FFMT entails the transposition of viable innervated tissue intended to restore some of the function that has been lost. In upper extremity reconstruction, a typical candidate for FFMT is an individual with an avulsive brachial plexus injury, loss or aberrant development of upper extremity musculature, or a time course of injury and characteristics that preclude use of nerve or tendon transfers[22]. The muscles used and the specific techniques employed vary according to the individual's reconstructive goals. However, common aims include the restoration of shoulder abduction, elbow flexion/extension, and flexion/extension of the digits.

There are several well-established workhorse flaps for each of the above aims. Shoulder abduction is often addressed by transfer of the latissimus dorsi muscle or a combination of adductor longus and gracilis[33].

Restoring elbow flexion is the most common indication for functional muscle transfer in the upper extremity[34]. While the free gracilis flap and free or pedicled latissimus dorsi flap are overwhelmingly the most popular options[35,36], use of rectus femoris and vastus lateralis has also been described. Loss of elbow extension, although a less common indication for FFMT, has also been addressed with the gracilis muscle flap[37]. Purposeful movement of the hand and fingers can be addressed via free gracilis muscle transfer, which is facilitated by attaching the distal tendinous portion of gracilis to the tendons of the digital flexors or extensors[38,39].

With FFMT, the reconstructive surgeon must also carefully select which donor nerve will be used to power the transferred muscle (a consideration that does not necessarily apply in pedicled functional muscle transfer). The choice of nerve will depend on the goals of a particular procedure and the options available in that setting, considering that the donor nerves available will differ substantially between a patient with a total brachial plexus avulsion and a patient with loss of elbow flexion following an oncologic extirpation. As described by Mackinnon and Novak in their 1999 seminal paper on nerve transfers, the ideal donor nerve should be expendable, located in close proximity to its intended target, contain the specific fiber types desired, and in the case of motor nerves, derive from a donor muscle that is synergistic with its destination[40]. There are several popular options for upper extremity FFMT, including but not limited to intercostal nerves, the spinal accessory nerve, the contralateral C7 root, or spared roots of the ipsilateral brachial plexus[37,38,41].

However, while a number of donor nerves have demonstrated success in FFMT, the evidence suggests that they are not universally interchangeable. Among the factors that are critical to consider when selecting a donor are whether the nerve originates within the brachial plexus (intra-plexal) or outside of it (extra-plexal) and the axon count ratio of the donor to recipient nerves. Intra-plexal donors include the ipsilateral brachial plexus roots as well as the medial pectoral, thoracodorsal, and ulnar nerves, while common extra-plexal nerves chosen are the contralateral C7 root along with the spinal accessory and intercostal nerves[42-44]. A 2016 paper by Nicoson *et al.* that reviewed outcomes using several different donor nerves in free functional gracilis muscle transfer to restore elbow flexion following brachial plexus injury described intra-plexal donors as the best choice for achieving better motor strength[45]. Regarding the proposed advantages of intra-plexal donors, the authors cited the quality and quantity of axons in these nerves as well as their proximity to the transferred muscle, which can subvert the need for a nerve graft. However, despite these theoretical benefits, extra-plexal nerves have also shown promise in FFMT, with a paper by Cho *et al.* showing no differences in outcomes pertaining to motor strength across 38 patients undergoing FFMT for brachial plexus injuries according to whether the spinal accessory or ulnar nerves were used as donors[46]. With respect to axon counts in donor and recipient nerves, the 2015 paper by Schreiber *et al.* has provided much of the evidence pairing axon count ratios with functional outcomes[44]. In reviewing average axon counts for the donor nerves frequently used in upper extremity FFMT, they observed that the axon counts are generally higher for intra-plexal donors than for extra-plexal donors. They found that increased donor nerve axon counts tended to increase the likelihood of a meaningful functional outcome, and ultimately advised a donor-to-recipient ratio of at least 0.7:1 for the best chance of regaining useful muscle strength[44].

The complexity of functional muscle transfer derives largely from the numerous variables that must be carefully considered and addressed to achieve a meaningful functional outcome. Preoperatively, this begins with obtaining a thorough understanding of a patient's history of injury and meticulous evaluation of their anatomy and examination, with attention paid to abilities and deficits. Observation of the patient performing occupational tasks or other activities of daily living can be informative, and coordination with a hand and occupational therapy team is essential. Surgical planning must aim to anticipate potential

challenges that may necessitate deviations or conversions to secondary options, such as tendon grafting or use of alternative donor nerves. Intraoperatively, success is contingent not simply upon meticulous microsurgical dissection and anastomosis of the vessels and nerves but upon correct positioning of the muscle and tensioning of tendons to enable their excursion and provide the desired movement. In the early postoperative period, careful monitoring of the transferred muscle is critical to ensure its survival and successful healing of the recipient and donor sites. If all the above are accomplished, the final and most important component will involve the rehabilitation and retraining process, which will demand intimate and coordinated collaboration with hand and occupational therapy colleagues to achieve a meaningful functional outcome.

VASCULARIZED COMPOSITE ALLOTRANSPLANTATION

In keeping with the oft-cited surgical principle of replacing "tissue losses in kind"[47], VCA of the hand and upper extremity seeks to restore form and function following limb loss in a manner that is not possible with other reconstructive modalities. Although fewer than 25 years have passed since the first successful hand transplant, the procedure has now been performed in at least a dozen countries and on more than 100 patients. High mortality and devastating graft loss rates have been reported for combination VCA procedures that involve upper extremity transplantation in conjunction with a craniofacial or lower extremity transplant; however, isolated unilateral or bilateral upper extremity VCA has proven to be a more reliably attainable goal. The patient survival rate has been reported to be 99%, while overall long-term graft survival is approximately 85% across all recipients and more than 95% with stringent adherence to an immunosuppressive medication regimen[48,49].

However, it is that same regimen of immunosuppressive agents that underpins the shortcomings and drawbacks of VCA. Since its inception, the field of transplantation has been plagued by the need for lifelong use of these medications. Their well-described toxicities leading to both graft and organ damage as well as increased susceptibility to infection and malignancy are certainties that all transplant recipients accept. While much progress has been made towards inducing chimerism and tolerance[50,51], at present, these remain theoretical goals, the promise of which has yet to be fully realized. Until the ability to minimize or eliminate immune responses to transplanted tissue in the absence of pharmacologic intervention becomes a reality, constant diligence will remain necessary to balance the harmful effects of immunosuppressants against the risk of graft rejection.

With respect to VCA specifically, discussions of its ethics and risk-benefit profile often cite that, unlike transplantation of a solid organ, such as a liver or kidney, VCA involving the face or an upper extremity is life-changing but not life-saving. Nonetheless, the psychosocial benefits of VCA demonstrate the substantial impact that transplantation can have on an individual's life, in many circumstances easing the burdens of isolation, loneliness, and loss of personhood that may accompany the "social death" experienced following a disfiguring injury[52,53]. In 2016, Breidenbach *et al.* performed a statistical analysis of hand transplantation with the aim of discerning whether the procedure met the necessary threshold to be deemed the standard of care[54]. The group concluded that when considered against solid organ transplants, hand transplantation demonstrates a superior ability to attain adequate immunosuppression and has a lower risk of chronic graft rejection and a decreased incidence of renal failure. This finding, in combination with a functional ability that was superior to that of the prosthetic devices available at the time, suggested that hand and upper extremity VCA had merits.

Despite the wealth of literature published on the subject and the growing number of centers globally that are offering the procedure, assessment of functional outcomes following hand transplantation has proven

challenging. Multiple authors cite inconsistencies in the metrics used, variations in the anatomic level at which transplantation is performed, and the proposed theory that a recipient will only attain maximum function after years of post-transplant therapy and rehabilitation[48,49,55]. Furthermore, the standards that define an acceptable functional outcome inevitably differ between unilateral and bilateral transplant recipients. The concept of bilateral hand transplantation is fairly widely accepted as an indication, given the disabling nature of bilateral hand/arm loss. However, the morbidity of immunosuppression, substantial economic burden associated with VCA, and ever-improving prosthetic technology raise questions about the practice of unilateral hand transplants[56]. Nonetheless, the evidence suggests that following unilateral or bilateral hand transplantation, most patients attain a reasonable degree of sensation and strength, have DASH (Disabilities of the Arm, Shoulder and Hand) scores indicating an ability to perform most activities of daily living, and demonstrate continued improvement with increasing time since transplant[49,57].

CONCLUSION

Despite the ever-evolving sophistication of the methods used for hand and upper extremity reconstruction, the devastating sequelae of mutilating injuries and amputations continue to pose substantial challenges. The past few decades have seen remarkable refinements in the ways surgeons are able to restore form and function using techniques such as FFMT and VCA. At the same time, advances in prosthetic technology paired with the leveraging of peripheral nerves through TMR offer the promise of meaningful functional outcomes for those in whom limb salvage or transplantation is not a viable option. In summary, these techniques represent the pillars of the new era of upper extremity reconstructive surgery.

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Systematic Review

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Efficacy of targeted muscle reinnervation for treating and preventing postamputation pain - a systematic review

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Abstract

Aim: Targeted muscle reinnervation (TMR) is a procedure pioneered to improve control of myoelectric prostheses and was fortuitously found to improve postamputation pain by transferring residual nerve ends from an amputated limb to reinnervate motor nerve units in denervated muscles. This study sought to perform a systematic review of the literature regarding the postamputation pain-related outcomes following TMR.

Methods: PubMed database was queried using the key term "targeted muscle reinnervation". Articles were chosen based on the following criteria: (1) clinical studies on TMR; (2) greater than one subject; (3) studies were case-controls, comparative cohort analyses, controlled trials, or randomized controlled trials; and (4) studies included one or more outcomes of interest: prosthetic use and functionality, improvement or persistence of pain, indications, complications, donor nerves, and technical aspects of TMR.

Results: Overall, 9 studies including 101 upper extremity and 252 lower extremity nerve transfers were analyzed, with nerve transfer type, amputation location, and specific neurotizations reported. Four studies assessed the efficacy of TMR in addressing phantom limb pain (PLP) and residual limb pain (RLP), with 3 out of 4 studies reporting significant improvements in PROMIS (Patient Reported Outcome Measurement Information System) scores in TMR subjects compared to controls. Five additional studies did not analyze PROMIS scores but reported subjective improvements in pain outcomes.

Conclusion: Included studies demonstrated TMR had lower maximal pain and pain intensity, behavior and interference compared to the standard of care. Secondary TMR used to treat patients with established painful neuromas also reported improvement in pain compared to baseline.

Keywords: Targeted muscle reinnervation, postamputation pain, neuroma pain, phantom limb pain, residual limb pain

INTRODUCTION

Targeted muscle reinnervation (TMR) is a nerve transfer procedure originally pioneered to improve the myoelectric control of upper limb prostheses by transferring residual mixed or sensory nerve ends from an amputated limb to reinnervate target motor nerve units in denervated muscles[1-3]. Once surgically relocated, the fascicles of the transferred nerve will grow into the recipient muscle motor end plates[4]. This procedure allows the creation of additional signals that can be used to enhance myoelectric prosthetic control and optimize function[5]. In addition to more intuitive control of myoelectric prostheses, patients who underwent TMR reported better outcomes with common amputation complications, particularly neuroma pain. As a result, TMR has recently been adopted as an effective strategy for the management and prevention of postamputation pain, including neuroma pain, phantom limb pain (PLP), and residual limb pain (RLP)[6,7].

There are multiple distinct types of pain that a patient may experience postamputation. PLP is defined as the perception of burning, tingling, discomfort, or electrical shooting pain in the missing portion of the limb[6,8,9]. This pain may be localized to just one region of the missing limb or may extend over the entire missing area. PLP typically occurs within the first 6 months postamputation, although its prevalence several years after surgery has been reported to be as high as 85%[10-12]. RLP, also known as "stump" pain, is localized to the portion of the limb remaining after the amputation. RLP is typically described as a sharp, electrical, burning, or "skin-sensitive" pain that may be localized superficially at an incision or deep in the residual limb. It can also encompass the entirety of the residual limb. The reported incidence of stump pain can be as high as 74% and, like PLP, may persist for years after initial development[10-13]. RLP may also be driven by terminal symptomatic neuromas that become irritated by pressure, light touch, and hot or cold temperatures[8,9]. Although neuromas may be a cause of RLP, neuroma pain is distinct from RLP and occurs due to uncoordinated attempts of nerve fibers to regenerate, resulting in disorganized axons encased within scar tissue at the site of nerve transection or injury. They are responsible for much of the RLP experienced postamputation and may be difficult to treat with high recurrence rates[1].

Despite the increasing use of TMR for improvement of postamputation pain, there are few studies comparing the functional outcomes of patients who underwent TMR procedures primarily for this purpose. This study sought to perform a systematic review of the literature regarding the outcomes of postamputation pain in patients who have undergone TMR procedures, including RLP, PLP, and neuroma pain.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14]. The PubMed database was queried for articles published in English as the primary language in May 2021. A Boolean operator with the key term "targeted muscle reinnervation" was employed to conduct the search. 588 articles were found and sorted using the "Best Match" criteria. For each relevant article, additional articles were searched for using the "Similar Articles"

section as part of the systematic screening process to identify articles that may have been missed by the original search query. Articles were chosen based on the following criteria: (1) studies were clinical studies on TMR; (2) studies included greater than one subject; (3) studies were either case-controls, comparative cohort analyses, controlled trials, or randomized controlled trials; and (4) studies included one or more outcomes of interest. Outcomes of interest included: prosthetic use and functionality, improvement or persistence of pain, indications, complications, donor nerves, and technical aspects of TMR. Case reports and letters to the editor were excluded. There were no restrictions on the year of publication. After the articles identified through the original query through the PubMed database were screened, the full-text articles were assessed for eligibility and inclusion in qualitative synthesis. Twenty-seven additional articles were surveyed from "Similar Articles"; of the 615 total studies, 9 studies met the final inclusion criteria [Figure 1]. In accordance with PRISMA guidelines, 2 reviewers independently assessed the quality and methodology of each study[14].

RESULTS

As part of the systematic review, nerve transfer type, amputation location, and specific neurotizations were reported [Table 1]. Overall, 101 upper extremity nerve transfers were analyzed (with 11 of these specifically reported as primary TMR for the upper extremity and 8 reported as secondary TMR for the upper extremity). Specified amputation locations included trans-radial (19), trans-humeral (38), shoulder disarticulation/glenohumeral (32), above-elbow (8), below-elbow (5), elbow disarticulation (1), and CMC joint (1) amputations. Neurotizations for the upper extremity primarily involved the ulnar, median, radial, and musculocutaneous nerves, although additional nerves (including the medial cord, lateral cord, posterior cord, radial, intercostal, and intercostal brachial cutaneous) were also involved in nerve transfer. A variety of muscle targets for the upper extremity were identified, and selected based on amputation level, patient-specific anatomy, zone of injury, mechanism of injury, and nerve length[7,8,15-21].

For lower extremity amputations, 252 were reported, with specific amputation sites including below-knee (48), above-knee (50), hip disarticulation (1), trans-tibial (82), trans-femoral (15), and knee disarticulation (1). Neurotizations for the lower extremity primarily involved the tibial, saphenous, sciatic, and peroneal nerves, although additional nerves including the posterior femoral cutaneous nerve, femoral, and sural nerve (among others) were used as well[7,8,15-20].

A total of four studies assessed the possible benefits of TMR in PLP and RLP via PROMIS (Patient Reported Outcome Measurement Information System) [Table 2][7,8,20,21]. PROMIS is a self-reporting tool to capture respondents' perception of pain through its impact on multiple components of daily life including physical, social, and emotional pillars. It utilizes three aspects-intensity, behavior, and interference. Intensity is represented by standardized pain rating scales (verbal, numerical, visual analog). Pain Interference applies a numerical rating score for degree of impedance in professional, familial, emotional, and recreational life. Pain behavior applies a similar numerical rating in the context of how one specifically acts or reacts through observable displays or phonation. All these studies, with the exception of Dumanian *et al.*, reported significant improvements in PROMIS parameters in TMR subjects compared to controls[7]. PROMIS analysis was also performed for the subcategory of worst pain, as outlined in Table 3.

Several studies included in the systematic analysis did not analyze PROMIS scores, however, still reported patient subjective improvements in pain outcomes including neuroma pain [Table 4]. Janes et al reported that of the 10 patients who underwent TMR for chronic neuroma pain, 7 patients (those not lost to follow-up) were seen an average of 4 months postoperatively, with 2 reporting reduced neuroma pain and 5 reporting complete resolution of pain[15]. Of the 7 patients who underwent acute TMR at the time of

Table 1. Included studies in systematic review

First author, year	Amputation location (*n*), Primary/Secondary TMR	Amputation location (*n*)	Neurotizations
Alexander, 2019[6]	Upper extremity (9), Primary	Trans-radial (1) Trans humeral (4) Shoulder disarticulations (4)	Not specified
	Lower extremity (22), Primary	Below-knee (7) Above-knee (14) Hip disarticulation (1)	Not specified
Dumanian, 2019[7]	Upper extremity (4), Secondary	Above-elbow (3) Below-elbow (1)	• Not specified
	Lower extremity (26), Secondary)	Above-knee (10) Below-knee (16)	• Not specified
Janes, 2020[15]	Lower extremity (17)	Trans-tibial (7), Secondary Trans-femoral (10), Primary	• Saphenous nerve → Medial soleus muscle, medial gastrocnemius biceps femoris, vastus medialis, gracilis
Kubiak, 2019[16]	Upper extremity (6), Primary	Trans-radial (3) Trans-humeral (2) Glenohumeral (1)	• Median cord, lateral cord, posterior cord, musculocutaneous, ulnar, median, radial, SBRN, intercostal brachial cutaneous nerves
	Lower extremity (46), Primary	Trans-tibial (37) Trans-femoral (9)	• Sciatic, femoral, tibial, common peroneal, deep peroneal, superficial peroneal, saphenous, sural
Morgan, 2016[17]	Upper extremity (5)	Trans-radial (3), Primary; (2) Secondary	• Median nerve → FDS, FDP • Ulnar nerve → FCU, FPL • SBRN → Extensor carpi radialis, FDS
Pet, 2014[18]	Upper extremity (11), Primary	Elbow disarticulation (1) Long trans-humeral (3) Short trans-humeral (4) Above-elbow (1) Shoulder disarticulation (2)	• Median nerve → Medial biceps, biceps, FDS, pectoralis major, lateral biceps, upper pectoralis major • Radial nerve → Teres minor lateral triceps, medial triceps, serratus anterior, lateral triceps, brachialis, triceps, latissimus dorsi, lateral FDS • Ulnar nerve → Medial triceps, serratus, lower pectoralis major, teres minor, triceps, posterior triceps, pectoralis minor, triceps, FDS • Musculocutaneous nerve → Clavicular head of pectoralis major, medial biceps, lateral biceps, biceps
	Upper extremity (8), Secondary	CMC joint (1) Trans-radial (3) Trans-humeral (3) Shoulder disarticulation (1)	• Median nerve → Clavicular head of pectoralis major, medial biceps, FDS, FDP • Radial nerve → Lateral triceps, medial triceps, brachialis, FDS • Ulnar nerve → Medial triceps, posterior triceps, FDS
	Lower extremity (1), Primary	Knee disarticulation (1)	• Tibial nerve → Medial hamstring, hamstring • Peroneal nerve → Lateral hamstring
	Lower extremity (15), Secondary	Above-knee (8) Below-knee (7)	• Sciatic nerve → Lateral hamstring, medial hamstring • Tibial nerve → Medial hamstring, hamstring • Peroneal nerve → Lateral hamstring
Souza, 2014[19]	Upper extremity (26), Secondary	Trans-humeral (16)	• Median nerve → Biceps brachii (short head) • Ulnar nerve → Brachialis • Radial nerve → Triceps brachii (lateral head)
		Shoulder disarticulation (10)	• Musculocutaneous nerve → Pectoralis major (clavicular head) • Median nerve → Pectoralis major (split sternal head) • Ulnar nerve → Pectoralis major (split sternal head), pectoralis minor, latissimus dorsi, serratus anterior • Radial nerve → Latissimus dorsi, serratus anterior, pectoralis major (split sternal head)
Valerio, 2019[20]	Upper extremity (15), Primary	Above-elbow (4) Below-elbow (4) Shoulder disarticulation (7)	Not Specified
	Lower extremity (36), Primary	Above/through knee (18) Below-knee (18)	Not Specified
Obrien, 2021[21]	Upper extremity		• Median nerve → FDS or FDP • Ulnar nerve → FCU or FPL

(16), Primary	Trans-radial (5)	• SBRN → Lateral head of triceps • MABC nerve → Brachioradialis, FDP, ECRL LABC nerve → ECRL, ECRB
	Transhumeral (5)	• Median nerve → Short head of biceps • Ulnar nerve → Brachialis • Radial nerve → Lateral head of triceps • Medial antebrachial cutaneous nerve → Brachialis • Musculocutaneous nerve → Short head, long head of biceps
	Shoulder disarticulation (6)	• Musculocutaneous nerve → Clavicular head of pectoralis major • Median nerve → Sternal head of pectoralis major • Ulnar nerve → Sternal head of pectoralis major • Radial nerve → Tibial nerve, latissimus dorsi

TMR: Targeted muscle reinnervation; SBRN: superficial branch of radial nerve; FCU: flexor carpi ulnaris; FDP: flexor digitorum profundus; FDS: flexor digitorum superficialis; FPL: flexor pollicis longus; MABC: medial antebrachial cutaneous; LABC: lateral antebrachial cutaneous; ECRL: extensor carpi radialis longus; ECRB: extensor carpi radialis brevis.

Table 2. PROMIS analysis - worst pain

First author, year		Worst pain at baseline	Worst pain at 1 year	Change from baseline	Worst pain at last follow-up	Change from baseline
Dumanian, 2019[7]	PLP TMR	5.8 (SD 3.2)	2.6 (2.2)	3.2 (2.9)	2.3 (2.3)	3.5 (3.1)
	Standard	3.9 (SD 2.7)	4.1 (3.0)	-0.2 (4.9)	4.4 (3.3)	-0.5 (5.3)
	RLP TMR	6.6 (2.0)	3.7 (2.0)	2.9 (2.2)	3.6 (2.1	3.0 (2.1)
	Standard	6.9 (2.5)	6.0 (2.5)	0.9 (3.3)	5.7 (3.0)	1.2 (3.5)

PLP: Phantom limb pain; RLP: residual limb pain; TMR: targeted muscle reinnervation; PROMIS: Patient Reported Outcome Measurement Information System.

amputation for prevention of neuroma pain and postamputation pain, the 3 patients not lost to follow-up (seen on average 6.67 months postoperatively) denied development of neuroma pain.

Additional studies reported outcomes for neuroma pain[15-19]. Kubiak et al reported postoperative outcomes in a total of 90 patients, with 45 of these patients acting as controls and 45 undergoing TMR[16]. 6 control patients (13.3%) developed symptomatic neuromas in the postoperative period, compared with 0 patients in the TMR group ($P = 0.026$). 23 TMR patients (51.1%) reported the development of PLP, compared with 41 control patients (91.1%; $P < 0.0001$)[16]. Likewise, Morgan et al reported that among 3 patients undergoing revision amputation with TMR for treatment of painful neuromas and 2 patients undergoing elective amputation with concurrent TMR, all 5 patients reported improvement in pain[17]. Although all 5 reported improvements in pain, only 4 were able to use a prosthesis following the procedure. Souza *et al.* reported that of 15 patients presenting with preexisting neuroma pain, 14 experienced complete resolution of pain after TMR, with 1 patient having improvement of neuroma pain. No patients reported new-onset neuroma pain following the TMR procedure[19]. Pet 2014 analyzed 12 patients undergoing primary TMR for neuroma prevention and 23 patients with established neuromas who underwent neuroma excision with secondary TMR and reported that at follow-up, 11 of 12 patients (92%) after primary TMR and 20 of 23 patients (87%) after secondary TMR were free of palpation-induced neuroma pain. Of the cohort undergoing primary TMR, 6 out of 12 patients did develop PLP. For those undergoing secondary TMR, PLP was present in 8 patients before secondary TMR and in 8 patients afterward, showing persistent PLP in 7 patients with new onset of phantom pain in 1 patient, and resolution of preoperative phantom pain in 1 patient[18].

Table 3. PROMIS analysis - pain intensity, behavior & interference

		Pain intensity	Pain behavior	Pain interference	Follow-up
Alexander, 2019[6]	PLP (mean differences)	5.855 (95%CI 1.159, 10.55; *P* = .015)	5.896 (95%CI 0.492, 11.30; *P* = .033)	7.435 (95%CI 1.797, 13.07; *P* = .011)	> 1 year
	RLP (mean differences)	5.477 (95%CI 0.528, 10.42; *P* = .031)	6.195 (95%CI 0.705, 11.69; *P* = .028)	6.816 (95%CI 1.438, 12.2; *P* = .014)	> 1 year
Dumanian, 2019[7]	PLP (mean differences)	11.7 (-0.3, 23.7)	1.1 (-8.3, 10.5)	4.7 (-5.0, 14.3)	At 1 year
		9.3 (-1.4, 20.0)	4.3 (-4.7, 13.2)	4.7 (-5.6, 15.3)	At last follow-up
	RLP (mean differences)	5.8 (-0.9, 12.4)	-0.5 (-7.2, 6.1)	-0.9 (-8.5, 6.7)	At 1 year
		5.8 (-0.3, 11.2)	-0.7 (-7.5, 6.1)	0.5 (-7.0, 8.1)	At last follow-up
Valerio, 2019[20]	PLP (median *t*-score)	TMR 36.3 *vs.* control 48.3	TMR 50.1 *vs.* control 56.6	TMR 40.7 *vs.* control 55.8	
	RLP (median *t*-score)	TMR 30.7 *vs.* control 46.8	TMR 36.7 *vs.* control 57.3	TMR 40.7 *vs.* control 57.3	Median 330 days (TMR group)
O'Brien, 2021[21]	PLP (median *t*-score)	33.5 *vs.* control 46.8 *P* = < .05	50.1 *vs.* control 53.1 *P* = < .05	40.7 *vs.* control 50 *P* = < .05	Average 23.1 months (for TMR group)
	RLP (median *t*-score)	33.5 *vs.* control 46.8 *P* = < .05	36.7 *vs.* control 53.1 *P* = < .05	40.7 *vs.* control 48.2 *P* = .146	

PLP: Phantom limb pain; RLP: residual limb pain; TMR: targeted muscle reinnervation.

Table 4. Subjective patient outcomes

First author, year	Type of study	Nerve transfer	Outcome
Janes, 2020[15]	Case series	Lower extremity (17) ● Primary treatment for neuroma pain (10) ● Secondary treatment (7)	Primary treatment 7 total follow-up patients: 5 reported resolution of symptoms, 2 reported improvement in pain Secondary treatment: all denied development of neuroma pain
Kubiak, 2019[16]	Retrospective cohort	Primary treatment Upper extremity (10) Lower extremity (80)	0 patients in treatment group developed symptomatic neuroma *vs.* 13.3% of control 51.1% of TMR patients developed PLP *vs.* 91.1%
Morgan, 2016[17]	Case series	Upper extremity (5) ● Primary treatment for neuroma pain (3) ● Secondary treatment (2)	All patients reported improvements in pain symptoms
Pet, 2014[18]	Retrospective review	Upper extremity (19) ● Primary treatment (11) ● Secondary treatment (8) Lower extremity (16) ● Primary treatment (1) ● Secondary treatment (15)	92% of primary TMR treatment neuroma free. 50% developed PLP 87% of secondary TMR treatment neuroma free. Equivocal findings regarding PLP
Souza, 2014[19]	Retrospective Review	Secondary treatment Upper extremity (26)	93% of patients with existing neuroma pain experienced resolution of symptoms

TMR: Total muscle reinnervation; PLP: phantom limb pain; avg: average.

DISCUSSION

This systematic review of currently available literature supports the use of TMR to minimize PLP and residual limb pain (RLP) after upper and lower extremity amputation. Included studies demonstrated

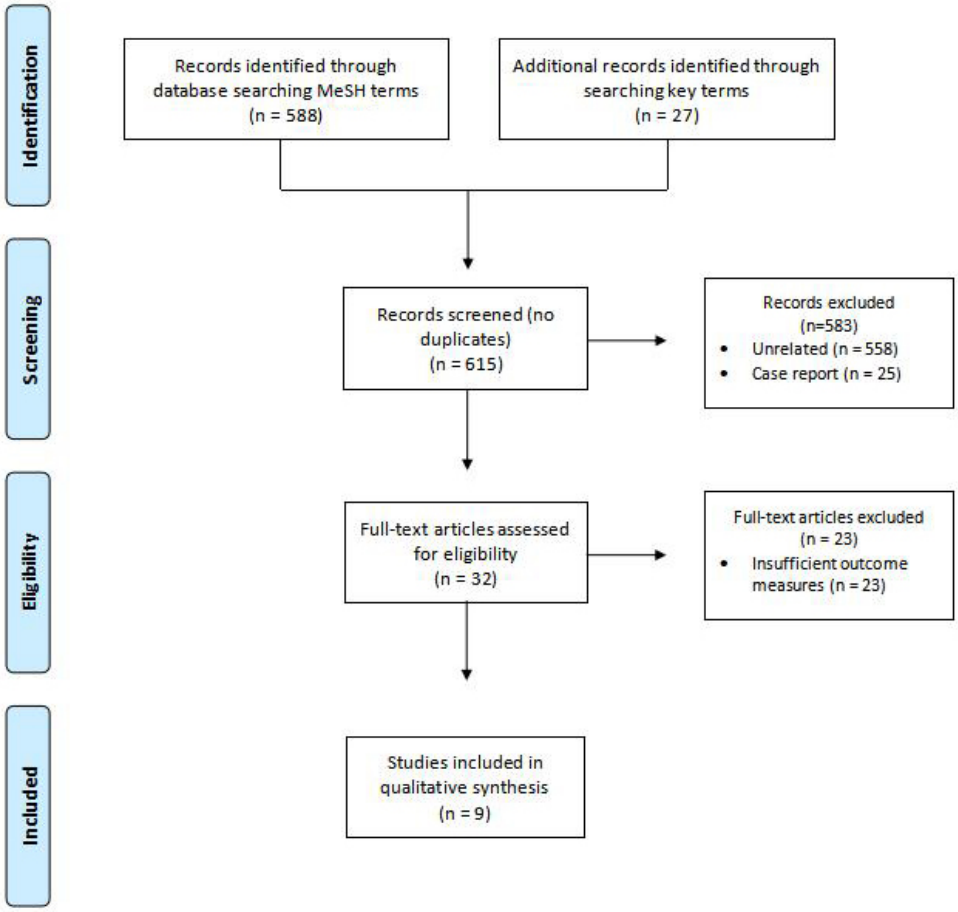

Figure 1. PRISMA flow diagram of included studies.

patients undergoing TMR had lower maximal pain and pain intensity, behavior and interference compared to the standard of care of burying the cut nerve in muscle. Secondary TMR used to treat patients with established painful neuromas also reported an improvement in their pain compared to their preoperative baseline. With encouraging outcomes having been reported throughout multiple randomized controlled trials, TMR is emerging as a leading surgical technique for pain prevention in patients undergoing major limb amputations and pain management in patients with preexisting amputations.

TMR has proven a useful tool in accentuating myoelectric potential in prosthesis as well as improving pain outcomes, specifically in regard to PLP and RLP[22,23]. The overall morbidity of PLP and RLP in amputees has been reported in several studies with rates as high as 67% and 25%, respectively[24]. This systematic review serves to specifically identify outcome parameters related to these debilitating sequelae of amputation, inclusive of diverse etiologies and timing related to index and subsequent procedures. While studies measure TMR outcomes in a variety of manners, our review underscores PROMIS for its versatility and inclination to the multifaceted nature of PLP and RLP. Developed by the NIH, The PROMIS explores person-centered agency using physical, mental, and social facets of one's health. Researchers involved in TMR have found this tool particularly relevant in capturing holistically the devastating effects of PLP and RLP on physical and emotional well-being.

Our investigation identified four studies meeting inclusion criteria assessing PLP/RLP; all of which showed improvements in outcome parameters. Only one study, Dumanian et al, with limited patient enrollment (n = 28), did not demonstrate statistical significance in improvements related to PROMIS specifically[7]; however, the study did report significant change in PLP from baseline related to Numerical Rating Scale in 1 year post surgery[8]. While this study represents randomized controlled data, its limited enrollment (with diverse amputation locations, levels, and timing) likely affected outcomes trending in favor of TMR without statistical significance. This study was unique in being the only one to assess patients with existing amputations; thus, subjects likely were predisposed to longstanding behavioral adaptions, which possibly prolonged calculable improvements in PROMIS parameters.

The remaining studies were retrospective cohort studies and demonstrated statistical significance across PROMIS components including pain intensity, pain behavior, and pain interference. Alexander *et al.* uniquely studied amputations related to oncologic treatment with concurrent TMR and incorporated follow-up to 1 year[6]. This study also had limited total patients (31 TMR). Although TMR was done at the time of amputation, only 16 patients underwent TMR at index surgery. The remaining underwent secondary amputation related to recurrence or infection. These patients were also affected by neoadjuvant/adjuvant chemotherapy and radiation.

Valerio *et al.* focused on the general amputee population with larger patient numbers totaling 438 subjects, 51 of which had TMR performed at index procedure[20]. Subjects represented diverse ages, levels of amputation, and indications for amputation. The aggregate data perhaps favors a more generalized representation, emphasizing marked improvements in PROMIS reporting across intensity, behavior, and interference. The follow-up ranged 3 months to 5.3 years (> 1 year 64.7%). One limitation, however, is that the follow-up survey of the non-TMR cohort was noted to be longer after surgery, given the retrospective nature. Long-term data are needed to determine if TMR results are consistent over time without recurrence of functional limitation. This likely introduced respondent reporting biases.

The latest 2021 study by O'Brien et al was also a retrospective cohort study, which included 16 patients who underwent TMR at index amputation compared to 55 controls. 62% of the TMR patients had no PLP versus 24% of controls. Similarly, half of TMR patients were without RLP versus 36% of controls. PROMIS scores across all parameters, with the exception of RLP interference, significantly favored TMR[21].

Although PROMIS scores offer a tremendous metric for assessing the debilitating pillars of RLP and PLP, it is not without limitations. Its design remains predicated on an objective iteration of subjectively assigned values in a presumably standardized manner. Moreover, the processes for all the above-mentioned studies were reliant upon patients' ability to distinguish PLP from RLP, which at times may be tenuous.

Limitations of this study include the lack of meta-analysis, which was not feasible given the wide variation in data points collected among the different studies. Additionally, the information does not allow for outcome conclusions comparing specific nerve transfers. Generally, target motor nerves in both upper and lower extremity TMR are ideally those which have redundancy in motor function to maintain physiologic continuity. The target nerve should be an expendable nerve preserving another nerve that has similar functions. This is particularly relevant in below knee amputation, where the larger medial gastrocnemius is preserved to provide adequate protective bulk for prosthesis fitting. Despite the statistical limitations and inability to compare transfers across multiple studies, this review supports the use of TMR in the prevention and treatment of RLP and PLP.

This study includes new literature not evaluated in prior reviews. This is critical given the recent increase in the adoption of and research related to this technique[25,26]. This study is also unique due to its strict inclusion criteria of control groups to underscore clinical and patient-reported outcome measures in standard practice. Additionally, our appraisal of the literature emphasized specifically studies that assessed PROMIS, a metric we believe is especially meaningful in capturing the multifaceted nuances of living with postamputation pain syndromes.

This systematic review adds to the literature supporting the efficacious use of TMR, both as a technique to improve postamputation pain compared to previously established standards of care and as a treatment for established postamputation neuromas.

DECLARATIONS

Authors' contributions

Writing, review and editing: Di Valerio E, Lautenslager L, Vonu P, Mustafa C, Chim H, Satteson E
Original draft and methodology: Di Valerio E, Lautenslager L, Vonu P, Satteson E
Data curation: Di Valerio E, Lautenslager L
Formal analysis: Lautenslager L, Vonu P
Conceptualization: Vonu P, Mustafa C, Chim H, Satteson E
Supervision, project administration, resources: Satteson E

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Plastic and Aesthetic Research

Review

Open Access

Advances in lower extremity peripheral nerve surgery

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Abstract

Peripheral nerve injury (PNI) is a common source of pain and disability in patients. While many patients are affected by PNI, peripheral nerve surgery advancements in the lower extremity have lagged behind the upper extremity. Subsequently, principles that have demonstrated success in the upper extremity have been implemented in the lower extremity. Interventions with recent advances include the advent of novel nerve transfers in the lower extremity and using stem cells and electrical stimulation (ES) for nerve regeneration. This article focuses on advances in nerve transfers for lower extremity PNI and provides details on the basic science and clinical applications of newer interventions.

Keywords: Stem cells, peripheral nerve, surgery, nerve transfer, electrical stimulation, nerve repair, nerve regeneration

INTRODUCTION

Patients with traumatic injuries may experience pain and disability due to PNI. One recent study found that 1.2% of patients with lower extremity trauma experience PNI, and these patients are more likely to

experience chronic pain and require physical and occupational therapy[1]. Therefore, proper diagnosis and treatment are crucial for improving outcomes in these patients. Historically, more attention has been paid to peripheral nerve reconstruction of the upper extremity, with less attention focused on the lower extremity. The longer distances between nerves in the lower extremity make nerve transfers in the leg more challenging. The increased distance required for regeneration can also lead to worse outcomes, as the target muscle(s) may be atrophied by the time of regeneration[2]. Research into nerve regeneration and factors that improve outcomes is crucial for overcoming these obstacles.

There are various options for repair of lower extremity nerve injuries depending on the extent of nerve damage and subsequent nerve gap. Direct repair is the preferred treatment modality in cases where a tensionless repair is possible with a neglectable nerve gap[3]. However, in cases of severe nerve damage, nerve conduits are preferred for gaps less than 3 cm, and auto- or allografts are used for gaps of more than 3 cm[3]. However, the capacity for nerve regeneration and functionality can be limited after reconstruction by scar formation, hemostasis, and infection[3]. Interventions have been proposed to improve nerve regeneration, including adipose-derived stem cells (ADSCs)[4-7], and electrical stimulation[8-10]. Although these interventions have demonstrated potential for improving axonal regeneration and functional nerve recovery, their use in clinical settings remains unclear.

In cases with significant scarring preventing nerve graft surgery, nerve transfers may be viable interventions for restoring muscle function. Nerve transfers have the possibility of earlier reinnervation with restoration of function[11]. Anatomical and clinical studies have investigated new sites for nerve transfers and reported promising results in traumatic cases[12-14] and patients with acute flaccid myelitis[15,16]. The variability of lower extremity nerve injuries requires a personalized approach and understanding of each therapy's unique advantages and disadvantages. In this article, we will focus on the recent advances in nerve transfers and provide additional details regarding interventions to improve axonal regeneration.

NERVE TRANSFER

In upper extremity injuries, nerve transfers have been increasingly performed to restore motor function[11]. Nerve transfers allow the surgeon to avoid operating in the zone of injury, which may have scarring[11]. Another advantage is the potential for faster recovery, due to a nerve coaptation site closer to the target. Developments in nerve transfers for the lower extremity have lagged behind the upper extremity due to inherent anatomical challenges, such as increased distance for nerve regeneration and fewer nerve branches to serve as donor nerves following spinal cord injuries[2]. Other advantages of nerve transfer surgery in the lower extremity over nerve grafts arise because these injuries often require long nerve grafts, leading to a degeneration of the target distal motor endplate before reinnervation can occur[17]. Ambulation, as well as bowel and bladder control, are priorities for lumbosacral plexus injuries[2]. Examples of promising advances have been reported and are discussed below [Table 1].

Femoral nerve repair

Femoral nerve is the major branch of the L2-L4 lumbar plexus and innervates the hip flexor and knee extensor muscles. It also controls the sensory processing of the anteromedial thighs to the medial compartment of the legs and feet. Injuries to the femoral nerve may result in significant functional impairments depending on the anatomic location of the damaged nerve. Generally, femoral nerve injuries at the pelvis level are classified as high femoral nerve injuries. The first successful employment of nerve transfer for repair of high femoral nerve injury was reported in the study by Campbell *et al.* in 2010[18]. They transferred the ipsilateral obturator nerve to the injured femoral nerve, which was damaged due to a schwannoma[18]. The impressive restoration of functional outcomes after this nerve transfer was the

Table 1. Examples of the published articles on the use of nerve transfer for lower extremity nerve injuries

References	Study design Population characteristics Mean age ± SD, F; M ratio	Clinical outcome
Femoral nerve repair		
Campbell *et al.* (2010)[18]	• Case report • 45-year-old female with a retroperitoneal schwannoma involving lumbar plexus	• Excellent functional recovery and significant quadriceps functions at 2 years after the operation
Goubier *et al.* (2012)[20]	• Cadaveric study • Investigated the anatomical feasibility of obturator-to-femoral nerve transfer in 5 cadavers (10 thighs)	• Confirmed that obturator-to-femoral nerve transfer is anatomically possible and may have clinical implications
Tung *et al.* (2012)[19]	• Cadaveric study • Evaluated the efficacy of obturator nerve transfer to the femoral nerve in both human and cadaveric subjects	• Obturator-to-femoral nerve transfer is a safe and efficient procedure for the treatment of high femoral nerve injuries
Karagiannis *et al.* (2015)[53]	• Case report • 49-year-old man with right-sided femoral nerve palsy undergoing dual gracilis and adductor longus to quadriceps muscles	• Significant functional recovery at 3 years post-operation
Inaba *et al.* (2018)[54]	•Case report • Partial obturator nerve transfer was done for the repair of an excised femoral nerve after resection of a retroperitoneal schwannoma	• Significant quadriceps recovery with 4/5 knee extension and normal gait
Meng *et al.* (2018)[55]	• Animal study (rat) • Investigate the efficacy and feasibility of obturator nerve transfer for repair of injured femoral nerve in rat models	• A significant functional recovery and increase in quadriceps muscle mass in rat models after nerve transfer was observed
Rastrelli *et al.* (2018)[56]	• Case report • Anterior branch of the obturator nerve was transferred to the femoral nerve at thigh level in a 19-year-old female	• Obturator-to-femoral neve transfer is a feasible option when the nerve gap is considerable (≥ 6 cm)
Doi *et al.* (2019)[15]	• Case report • Contralateral obturator nerve transfer to the left femoral nerve due to acute flaccid myelitis	• At 14 months post-op, favorable functional outcome with full knee extension was achieved
Graham *et al.* (2020)[57]	• Case report • A modified obturator-to-femoral neve transfer with cable grafting for a 49-year-old woman with iatrogenic injury to the femoral nerve	• At 4 years post-op, patient recovered knee extension (4/5) and mobilization was successful
Cao *et al.* (2020)[14]	• Case report • Contralateral obturator nerve transfer to femoral nerve after extensive lumbar plexus injury in a 30-year-old male	• Contralateral obturator nerve transfer to femoral nerve is an alternative procedure when the ipsilateral obturator nerve is damaged
Chen *et al.* (2020)[21]	• Cadaveric study • Evaluate the safety and feasibility of sciatic nerve transfer to the femoral nerve in cadavers	• Suggested that the muscle branches of sciatic nerve may be a reasonable candidate for femoral nerve repair
Nicholas *et al.* (2021)[13]	• Case report • Reported two cases of extensive lumbosacral plexus injury accompanied with root avulsion which underwent contralateral obturator-to-femoral neve	• At the last follow-up, patients had 3/5 and 2/5 knee extension, representing this nerve transfer as a therapeutic option for extensive plexal injuries
Peters et el. (2021)[12]	• Retrospective case-series • Reported the functional outcome of 14 patients with femoral nerve palsy that underwent femoral nerve decompression and nerve transfer	• Post-operatively, a significant improvement in knee extension muscle power and pain compared with pre-operation (*P*-value = 0.001)
Lubelski *et al.* (2021)[16]	• Case-series • Demonstrated sciatic-to-femoral nerve transfer using a fascicle of the proximal tibial nerve as the donor for pediatric patients with acute flaccid paralysis	• Sciatic-to-femoral nerve transfer is a feasible option for repair of extensive lumbar plexus damage. However, the clinical outcome of patients are not available
Donaldson *et al.* (2022)[58]	• Case-series • Two patients with femoral nerve injuries underwent concomitant gracilis muscle transfer and obturator-to-femoral neve (adductor longus nerve branch)	• At 6 months post-op, one patient regained significant knee flexion and full knee extension with grade 4/5 power. • At 18 months post-op, patient 2 had full knee flexion and extension with grade 5/5 muscle power
Obturator nerve repair		
Spiliopoulos *et al.* (2011)[27]	• Case report • Femoral-to-obturator nerve transfer was done for a female patient with a iatrogenic obturator nerve injury	• At 1 year post-op, patient gained full limb adduction and full recovery was observed

	after excision of a gynecologic tumor	
Tibial nerve repair		
Koshima *et al.* (2003)[28]	• Case report • First description of nerve transfer for repair of tibial nerve using the deep peroneal nerve	• Significant improvement in patient's functional outcome. Both patients were able to walk at the last follow up
Yin *et al.* (2015)[29]	• Case-series • Evaluated the safety and efficacy of ipsilateral obturator-to-tibial nerve transfer in 5 consecutive patients with sacral plexus injury	• Significant symptom resolution was observed following the transfer • Obturator-to-tibial nerve transfer is a feasible option when direct nerve repair is not plausible
Moore *et al.* (2017)[17]	• Case-series and cadaveric study • Investigated the distal femoral-to-sciatic nerve transfer for proximal nerve injuries	• Efficient and safe transfer procedure for treatment of proximal tibial nerve injuries
Agarwal *et al.* (2018)[59]	• Prospective case-series • Saphenous nerve transfer to the posterior tibial nerve was carried out for 21 patients with loss of sensation at the sole	• At 6 months follow up, significant improvement in sensory perception was observed in most of sole territories
Meng *et al.* (2018)[33]	• Cadaveric study • Investigated the efficacy and safety of femoral nerve transfer to peroneal and tibial nerves for high sciatic nerve injury	• Femoral-to-sciatic nerve transfer is a feasible option for restoring muscle and sensory function for sciatic nerve and its branches
Namazi *et al.* (2019)[60]	• Cadaveric study • Evaluated the safety and feasibility of obturator to tibial nerve transfer with saphenous nerve graft	• This technique is feasible for patients with sacral nerve root avulsion injury. However, no clinical outcomes are available
Peroneal nerve repair		
Ferris *et al.* (2017)[31]	• Case-series • Partial tibial nerve transfer was carried out for 9 patients with traumatic peroneal nerve injury	• Excellent functional outcomes were observed for 7/9 patients. the study recommended nerve transfer as an alternative therapeutic option
Nath *et al.* (2017)[32]	• Retrospective case-series • Investigated the surgical outcomes of 21 patients with foot drop undergoing nerve transfer	• The results of the study showed significant improvement in functional outcome after the operation
Meng *et al.* (2018)[33]	• Cadaveric study • Investigated the efficacy and safety of femoral nerve transfer to peroneal and tibial nerves for high sciatic nerve injury	• Femoral-to-sciatic nerve transfer is a feasible option for restoring muscle and sensory function for sciatic nerve and its branches
Flores *et al.* (2013)[34]	• Retrospective case-series • Investigated the efficacy and outcome of 13 patients with foot drop undergoing tibial-to-peroneal nerve transfer	• Nerve transfer from the soleus muscle to the deep peroneal nerve is not recommended due to unfavorable patients outcomes

inspiration for future surgeons to utilize nerve transfer for femoral nerve injuries when a direct repair is not possible due to a considerable nerve gap. Nevertheless, performing a transfer for an injured femoral nerve at the pelvis can be challenging. Goubier and Tung assessed the anatomical feasibility of obturator-to-femoral nerve transfer and confirmed that this nerve transfer is anatomically possible[19,20]. Since then, a few modifications have been made to the femoral nerve transfer to maximize axonal regeneration and nerve viability.

One of the most robust data on nerve transfer for femoral nerve repair came from the study by Peters *et al.*[12]. They previously reported success in treating high femoral nerve palsy using the motor branches of the anterior obturator nerve to the gracilis, adductor longus, and adductor brevis muscles and the sartorius motor branches to improve quadriceps function[12]. Successful reinnervation to all four quadriceps muscles has been reported in cases where the zone of injury was inaccessible, such as after hip surgery[12]. In this example, femoral nerve decompression was offered in conjunction with nerve transfer surgery as an adjunct therapy for neuropathic pain[12].

In patients with multilevel lumbosacral plexus injuries with concomitant ipsilateral nerve damages, restoration of knee extension has been reported using the contralateral obturator to the femoral nerve

transfer[13,14]. This approach has also successfully restored knee extension in a pediatric patient with acute flaccid myelitis[15]. In cases of femoral nerve injury accompanied by bilateral obturator nerve damage, a cadaveric study by Chen *et al.* suggested the muscle branches of the sciatic nerve may be a reasonable candidate for femoral nerve repair[21]. Lubelski *et al.* demonstrated sciatic-to-femoral nerve transfer using a fascicle of the proximal tibial nerve as the donor for pediatric patients with acute flaccid paralysis[16]. However, the clinical implications and functional outcomes of this nerve transfer remain unclear.

Other proposed donors in cases of femoral nerve injury include the nerve to semitendinosus[21] and the S1 nerve root[22], as well as the intercostal, ilioinguinal, and iliohypogastric nerves[23]. Overall, the main indication of nerve transfer for repair of a high femoral nerve injury is reserved for patients for whom direct nerve repair or nerve graft surgery is not plausible.

Obturator nerve injury

The obturator nerve originates from the L2-L4 nerve roots and innervates the medial compartment of the thigh, which are responsible for adduction and external rotation of the thigh, as well as sensory processing of medial thigh. It enters the thigh after passing across the pelvis and through the obturator foramen. Obturator nerve injuries are rare and occur most commonly from complications during pelvic surgery. Injury to the obturator nerve results in weakness in thigh adduction and external rotation and sensory loss in the medial thigh. Given the surgical setting of these injuries, nerve repair is often performed intraoperatively with direct repair or nerve grafting[24-26]. Nerve transfers are less common interventions in obturator nerve injuries presenting postoperatively, with a conservative approach being preferred. However, one study reported full restoration of hip adduction and medial thigh sensation after nerve transfer of a branch of the femoral nerve to the obturator nerve[27].

Tibial nerve repair

The tibial nerve is a distal branch of the sciatic nerve (L4-S3 nerve roots) and is responsible for motor and sensory innervations to the posterior leg compartment, as well as foot and toe flexor muscles. Injuries to the tibial nerve may result in significant gait disturbance, impaired foot plantar flexion, and sensory losses. In cases of sciatic nerve injury, repair of the tibial nerve is given priority to ensure plantarflexion strength for walking and protective plantar sensation[17]. The first description of nerve transfer for repair of the tibial nerve was in the study by Koshima *et al.* in 2003[28]. They successfully used the deep peroneal nerve to restore sensory functions of the injured tibial nerve. Moore *et al.* described a novel approach for performing nerve transfer of the terminal branches of the femoral nerve supplying vastus medialis and vastus lateralis to the medial and lateral branches of the tibial nerve in cases of tibial and common peroneal nerve palsies after sciatic nerve injury[17]. Obturator nerve transfer to the tibial nerve to the medial head of the gastrocnemius has also been successful in restoring knee and ankle flexion[27]. One cadaver study found feasible targets for restoring tibial nerve function using transfers of the vastus medialis nerve branch to the medial gastrocnemius nerve branch[29]. There is a paucity of data on the utilization of nerve transfer for tibial nerve repair in the current literature. Nevertheless, all published articles reported significant improvements in functional outcomes. Nerve transfer should be taken into consideration as an alternative option, particularly for proximal sciatic nerve injuries.

Peroneal nerve repair

The common peroneal nerve is another major branch of the sciatic nerve, and it provides the motor and sensory processing of anterolateral compartment of legs to the dorsal aspect of feet and toes. The common peroneal nerve is at high risk of injury due to its superficial anatomical course, and it is the most common source of mononeuropathy in the lower extremity[30]. Peroneal nerve palsies arise from trauma, compression, or iatrogenic causes and are classically associated with “foot drop”, which results in gait

disturbance and can lead to falls[30]. In cases where conservative management fails to improve nerve function after 4 months, surgical treatment may be required with nerve decompressions, direct nerve repair, nerve or tendon transfers, or ankle fusion[30].

Nerve transfers can restore function for patients with peroneal nerve palsy. Ferris *et al.* demonstrated improvement in active dorsiflexion in patients with traumatic common peroneal nerve injuries who underwent partial tibial nerve transfer to the motor branches of tibialis anterior[31]. Another study reports successful outcomes in patients with foot drop who undergo superficial peroneal nerve or tibial nerve fascicles transfer to the motor branch of the tibialis anterior and the deep peroneal nerve[32] [Figure 1]. Feasible nerve transfers have been reported in cadaver studies by transferring the vastus lateralis nerve branch to the deep peroneal nerve branch[33]. While there is potential for nerve transfers to help patients, not all nerve transfers have excellent outcomes. Poor outcomes have been reported in the nerve of the soleus muscle to the deep peroneal nerve transfer[34].

These novel techniques demonstrate the innovation required to treat patients with PNI in the lower extremity. Nerve transfers have the potential to restore function in cases where other treatments, such as nerve grafting, are not feasible. To optimize outcomes in nerve transfers, the donor activation focused rehabilitation approach has been suggested in upper extremity nerve transfers[35]. Given the success of these interventions in the upper extremity, advances in the lower extremity are promising.

SURGICAL NEUROLYSIS

Neurolysis is another therapeutic option for patients with intractable pain that are not responsive to conventional treatments. Surgical neurolysis refers to the procedure of releasing the entrapped nerves from the adjacent tissues enabling them to decompress and repair. Pess *et al.* in 1987, described a case of femoral nerve compression following a total hip replacement that was successfully treated with surgical nerve decompression and neurolysis[36]. Since then, the implications of neurolysis for the treatment of lower extremity neuropathic pain have been discussed in the literature with favorable patient outcomes [Table 2]. The main role of neurolysis for lower extremity neuropathic pain is for patients with nerve entrapment. Decompressing the affected nerve from the adjacent fibrous tissues would lead to better functional recovery, symptom relief, and axonal regeneration. Surgical neurolysis is considered a safe and feasible option for nerve decompression [Figure 2]. Complications of surgical neurolysis have been reported rarely, and it mainly depends on surgical technique and the degree of nerve adhesions to the surrounding structures.

STEM CELL THERAPY FOR NERVE REGENERATION

Nerve transfers may provide a definitive surgical resolution to many cases of lower extremity PNI. Alternative therapies to promote axonal regeneration and improve nerve function may be required in cases where nerve transfers are not possible. Stem cells have been investigated as a therapy for PNI due to their potential to regenerate neurons, support glial cells, and release factors to promote nerve regeneration[4]. Schwann cells, in particular, play a vital role in the regenerative response, although there are challenges associated with harvesting autologous Schwann cells[37]. Schwann cells are procured by harvesting donor nerves and cell culturing, requiring the loss of a functional nerve[37]. For this reason, there have been significant advances in lower extremity nerve regeneration using stem cells and the results have been satisfactory.

Embryonic stem cells

Embryonic stem cells (ESC) are pluripotent cells and can be extracted from the inner embryonic blastocyte layer. They can actively differentiate into almost all cell lineages including neurons and glial cells, which

Table 2. Examples of published articles on the implications of nerve neurolysis in the lower extremities

References	Study description	Clinical outcome
Pess *et al.* (1987)[36]	• Case report • A patient underwent nerve decompression and neurolysis after femoral neuropathy following the use of pressurized cement in total hip arthroplasty	N/A
Montgomery *et al.* (2005)[61]	• Case report • Late surgical neurolysis for a female patient with sciatic nerve injury after total hip arthroplasty	• Full functional recover and pain alleviation after the procedure
Volpi *et al.* (2005)[62]	• Case report • Laparoscopic sciatic nerve neurolysis in a 37-year-old female due to nerve entrapment after endometriosis	• Significant improvement at the last follow up
Possover *et al.* (2007)[63]	• Case series • Laparoscopic neurolysis of proximal sciatic nerve and sacral plexus due to endometriosis infiltration	• Laparoscopic neurolysis is a feasible option for sciatic nerve entrapment
Ramanan *et al.* (2011)[64]	• Retrospective case-series • Evaluated 20 patients with commo peroneal injury that underwent surgical neurolysis	• Functional recovery was observed in 74 % and 68% of patients with motor and sensory dysfunction, respectively
Kyriacou *et al.* (2013)[65]	• Prospective cross-sectional • Investigated the functional outcome of 56 patients with sciatic nerve palsy after hip arthroplasty that underwent surgical neurolysis	• The mean VAS score decreased significantly after neurolysis • Surgical neurolysis is associated with improved functional outcome in patients with sciatic nerve injury
Maalla *et al.* (2013)[66]	• Retrospective case-series • Investigated the role of surgical neurolysis for patients with common peroneal nerve entrapment	• Excellent outcome in 9 (60.0%) patients after neurolysis
Aboulfetouh *et al.* (2014)[67]	• Case-series • Evaluate the safety and efficacy of neurolysis for treatment of sciatic nerve entrapment in 11 patients with sciatic nerve injury	• At 1-year follow up, 10 patients (90.9%) had significant motor and sensory improvement • Sciatic nerve neurolysis is a safe and efficient option for neuropathic pain without the risk of major complications
Andrade *et al.* (2015)[68]	• Case report • A 38-year-old female with femoral nerve involvement by endometriosis underwent laparoscopic neurolysis	• Laparoscopic neurolysis could be the first approach for treatment of femoral nerve endometrial infiltration
Ham *et al.* (2018)[69]	• Retrospective case-series • Investigated the outcome of patients with deep gluteal syndrome that underwent endoscopic sciatic nerve neurolysis	• Significant functional outcome with satisfactory pain reduction
Ilizaliturri *et al.* (2018)[70]	• Prospective case-series • Endoscopic sciatic nerve exploration and neurolysis for 15 patients with deep gluteal syndrome	• Excellent functional outcome with significant pain alleviation post-operation
Broekx *et al.* (2018)[71]	• Retrospective case-series • Evaluated the outcome of peroneal nerve neurolysis in patients with foot drop after weight loss	• External neurolysis is a safe and efficient procedure for foot drop with a success rate of 85%
Tarabay *et al.* (2019)[72]	• Case-series • 14 patients underwent surgical neurolysis due to common peroneal nerve entrapment	• 13 out of 14 patients reported significant motor functional recovery after decompression
Park *et al.* (2019)[73]	• Comparative study • Compared functional outcome of patients undergoing neurolysis after acetabular fracture *vs.* deep gluteal syndrome	• Neurolysis was associate with favorable outcomes in both groups; however, patients with deep gluteal syndrome were associated with better outcomes

accounts for their regenerative effects[38]. An animal experiment by Cui *et al.* demonstrated that after the transplantation of ESC-derived neural progenitor cells at the site of sciatic injury, the stem cells differentiated into myelin-producing cells[38]. The transplanted progenitor cells can potentially replace the injured neuron and improve functional outcomes[38]. In another animal study, genetically modified human ESC overexpressing fibroblast growth factor 2 (FGF2) was successfully employed for sciatic nerve injury, which was associated with both sensory and motor resolution[39]. Almost all experimental studies on the use of ESCs for the treatment of lower extremity nerve damage have pointed to their potential regenerative effects [Table 3]. However, a few ethical concerns are limiting the use of ESC in human subjects. The main

Table 3. Key papers regarding the implications of stem cell therapy for lower extremity nerve regeneration

References/Title	Study design	Clinical outcome
ESC		
Cui *et al.* (2008)[38]	• Animal study (rat) • Investigated rat ESC-NPCs' efficacy in repairing severe sciatic nerve injury	• Transplanted ESC can differentiate into myelin-producing cells after cell induction and have the potential to repair damaged peripheral nerve injuries
Mozafari *et al.* (2018)[39]	• Animal study (rat) • Investigating the efficacy of modified ESC with overexpressing FGF-2 for sciatic nerve injury in rat models	• Significant motor and sensory recovery were observed after modified ESC at the damaged sciatic neuron
Jones *et al.* (2018)[74]	• Animal study (rat) • Explorated the results of hESC-derived neural crest in the sciatic nerve regeneration	• *In-vivo* transplantation of hESC-derived neural crest was suggestive of significant regeneration at the site of sciatic injury
Chen *et al.* (2020)[75]	• Animal study (rat) • Described the possible role of hESC-NPCs in the regeneration of sciatic nerve	• hESC-NPCs and their microvesicles have the potential to promote sciatic nerve regeneration
iPSC		
Wang *et al.* (2011)[42]	•Animal study (rat) • Reported electrophysiological results of sciatic nerve injury following NCSC derived from iPSC and ESCs	• Combination of engineered scaffolds and multipotent stem cells has a higher therapeutic potential for nerve regeneration
Huang *et al.* (2017)[43]	• Animal study (rat) • Investigate the regenerative effects of various differential stages of human fibroblast-derived iPSCs in the function of transected sciatic nerve	• iPSC-derived NCSCs were associated with much better short and long-term sciatic nerve regeneration compared with the induced adult Schwann cells
Xia *et al.* (2019)[76]	• Animal study (rat) • Investigated the combination therapy of LIPUS with iPSC-NCSC	• A combination of LIPUS treatment with iPSC-NCSC, GDF5, and PFTBA can provide a satisfactory outcome for sciatic nerve regeneration
Lv *et al.* (2015)[77]	• Animal study (rat) • Investigating the efficacy of LIPUS with iPSC-NCSC for regeneration of transected sciatic nerve in animal models	• Results reported a higher rate of regenerated neurofilaments and vasculature with LIPUS stimulation following iPSCs-NCSC seeding
Yokoi *et al.* (2018)[78]	• Animal study (rat) • Comparing sciatic nerve regeneration in young and old-aged mice following iPSC-derived neurospheres	• Sciatic nerve regeneration was much slower in old-aged mice compared to younger ages. • Adding the iPSC-derived neurospheres to the nerve conduit was associated with better axonal regeneration
Pepper *et al.* (2017)[79]	• Animal study (rat) • Investigating whether motor neurons derived from human iPSCs have the potential to engraft into animal sciatic nerve	• Although EMG studies reported no signs of functional recovery, the motor neurons in 40.6% of rat models had successful engrafted to the denervated muscles
BMMSCs		
Dezawa *et al.* (2001)[45]	• Animal study (rat) • Efficacy of BMMSCs from rat models for regeneration of injured sciatic nerve	• Significant nerve fiber regeneration following administration of genetically engineered BMMSC to the end of transected sciatic nerve
Chen *et al.* (2006)[46]	• Animal study (rat) • Bone marrow-harvested MSCs were genetically engineered and transplanted at the nerve regeneration chamber	• The experiment resulted in an increase in regenerative nerve fibers after differentiation of BMMSCs to Schwann-like cells
Raoofi *et al.* (2021)[80]	• Animal study (rat) • BMMSCs were extracted from axotomy rat models and added to the neve conduit loaded with PCL	• Better nerve regeneration with BMMSC conditioned medium provides satisfactory results for nerve regeneration
Zheng *et al.* (2018)[81]	• Animal study (rat) • Denervated Schwann cells were co-cultured with neurons induced from BMMSCs *in vitro* • The induced neurons were added to the crushed sciatic nerves in rat models (*in vivo*)	• Co-culturing was associated with rapid denervated SC proliferation and enhancing the myelination process
Fernandes *et al.* (2018)[82]	• Animal study (rat) • Compared BMMSC *vs.* ADSC for regeneration of lesioned sciatic nerve in rat models	• Nerve regeneration was not satisfactory for both groups when using Matrigel as a conductor
Cai *et al.* (2017)[83]	• *In vitro* and *in vivo* (animal study) • Schwann-like cells were derived from human BMMSCs and used for sciatic nerve regeneration	• Bone marrow derived SC-like cells has a potential for satisfactory axonal regeneration and augmented myelination
ADSCs		

Karakol *et al.* (2022)[84]	• Animal study (rat) • Investigating the effects of epineural tubulization (ENT) with/without ADSCs for sciatic nerve transection	• Satisfactory axonal regeneration and outcome following ENT+ intratubal ADSC
Soto *et al.* (2021)[85]	• Animal study (rat) • ADSCs were magnetically recruited to the traumatic sciatic nerve for regenartion	• A safe delivery method for neuronal regeneration with satisfactory outcomes
Bucan *et al.* (2019)[86]	• Animal study (rat) • Effects of ADSC-derived exosomes on sciatic nerve remyelination	• Satisfactory axonal regeneration and outcome
Fernandes *et al.* (2018)[82]	• Animal study (rat) • Compared BMMSC *vs.* ADSC for regeneration of lesioned sciatic nerve in rat models	• Nerve regeneration was not satisfactory for both groups when using Matrigel as a conductor
Allbright *et al.* (2018)[87]	• Animal study (rat) • Investigate the role of ADSC with PCL delivery system for repair of sciatic nerve injury	• Enhanced sciatic nerve regeneration and facilitated muscle reinnervation were observed
Luca *et al.* (2017)[88]	• Animal study (rat) • Evaluated the efficacy of ADSCs with a fibrin gel delivery loaded with laminin	• Implantation with laminin was associated with satisfactory axonal regeneration

ESC-NPC: Embryonic stem cell-derived neural progenitor cell; LIPUS: low-intensity ultrasound; hESC: human embryonic stem cell; iPSC: induced pluripotent stem cell; NCSC: neural crest stem cell; EMG: electromyography; BMMSCs: bone marrow-derived stem/stromal cells; MSC: mesenchymal stem cells; PCL: polycaprolactone; SC: schwann cell; ADSC: adipose-derived stem cells.

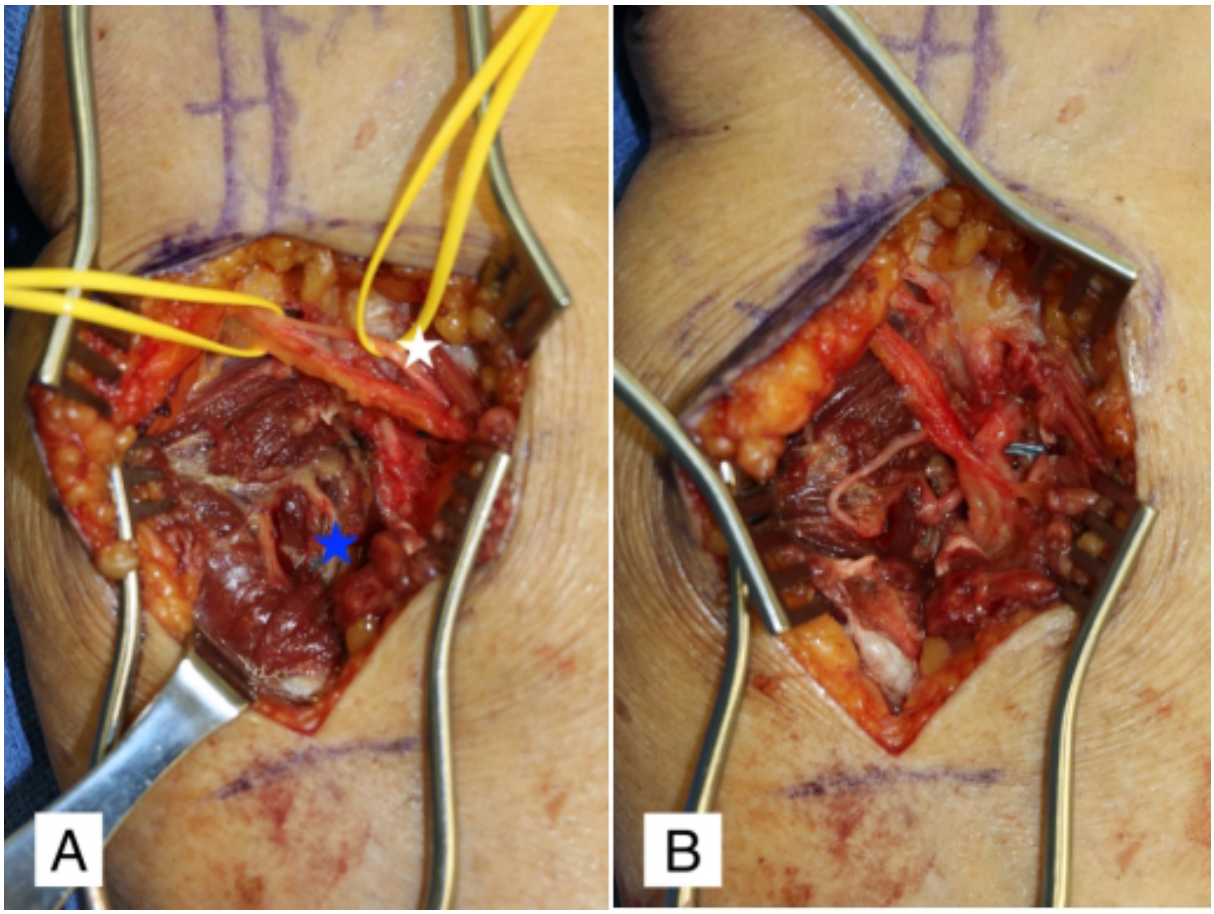

Figure 1. Nerve transfer for common peroneal nerve palsy in a 77-year-old female. A: The tibial nerve branch to lateral gastrocnemius (blue star) and the peroneal nerve branch to tibialis anterior nerve (white star) were identified. B: Nerve transfer of the tibial nerve branch to lateral gastrocnemius to the peroneal nerve branch to tibialis anterior.

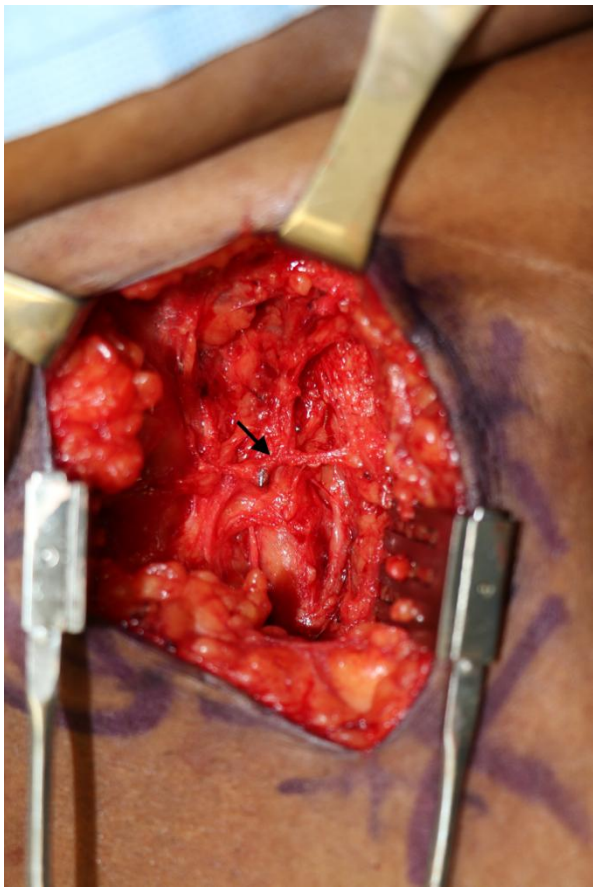

Figure 2. Femoral nerve neurolysis. A 39-year-old patient experienced traumatic neuropathic pain and a 2/5 Medical Research Council (MRC) score in knee extension. The patient had improvement in knee extension to MRC 4 function and resolution of pain following femoral nerve (black arrow) neurolysis.

controversy is the potential moral status of the embryo that prohibits ESC harvesting from the inner blastocytes cell line[40].

Induced pluripotent stem cells

To avoid these ethical concerns, Takahashi *et al.* were the first to induce pluripotent stem cells from animal (mouse) embryonic or human fibroblasts using transcription factors[41]. Their study was one of the first steps toward pluripotency control in somatic cells and providing a safe method for patient-specific stem cell generation. The first use of iPSC for lower extremity nerve regeneration was the study by Wang *et al.*, in which they used iPSCs and ESCs to derive natural crest stem cells (NCSC) for the regeneration of sciatic nerve damage in rat models[42]. They observed that NCSCs can promote nerve myelination and regeneration[42]. Huang *et al.* conducted an experiment to investigate the regenerative effects of various differential stages of human fibroblast-derived iPSCs in the function of transected sciatic nerve[43]. They observed that the iPSC-derived NCSCs were associated with much better short and long-term sciatic nerve regeneration than the induced adult Schwann cells[43]. That said, there is one major concern regarding the employment of iPSCs and their derivatives in human subjects. Compared with ESCs, iPSCs and their derivations are susceptible to oncogenic transformations due to the pluripotency induction and overexpression of oncogenic factors[44]. Although various strategies have been introduced to diminish the potential tumorigenicity, their use has been limited to animal models only. A summary of the implications of iPSC for lower extremity nerve regeneration is obtained in [Table 3].

Bone marrow-derived mesenchymal stem cell

Bone marrow-derived mesenchymal stem cells (BMMSCs) are another source of pluripotent cells that are located in the stromal bone marrow compartment. Under specific experimental conditions, they have the potential to differentiate into mesenchymal lineages, which accounts for their extensive application in cell-based therapies. The first use of BMMSCs for lower limb nerve regeneration was described by Dezawa *et al.* in 2001[45]. They observed significant nerve fiber regeneration following administration of genetically engineered BMMSC to the end of transected sciatic nerve[45]. The same observation was made by Chen *et al.* using BMMSCs from rat models for regeneration of injured sciatic nerve[46]. The experiment resulted in an increase in regenerative nerve fibers after differentiation of BMMSCs to Schwann-like cells. Regardless of their potential beneficial effects, they are limited by their harvesting difficulties, which are usually quite painful. In addition, bone marrow aspirations provide low amounts of stem cells, most of which may get lost due to unsuitable post-translational microenvironment.

Adipose-derived stem cells

Contrary to BMMSCs, adipose-derived stem cells (ADSCs) are the preferred method due to the ease of harvest in great numbers[37]. However, ADSCs are acquired after 2-3 weeks of cell culturing[5]. To address this problem, a stromal vascular fraction (SVF), which is obtained by treating subcutaneous adipose tissue with collagenase, has emerged as a potential source of ADSCs that are immediately available and do not require cell culturing [Figure 3][5].

In 2020, Mathot *et al.* demonstrated enhanced neoangiogenesis of decellularized sciatic nerve graft defects with ADSCs in rats[48]. Notably, their protocol for cell harvesting is approved for harvesting ADSCs from patients as part of a future clinical trial[48]. ADSCs have also shown potential for improving nerve regeneration in rat studies when delivered to fibrin[6] and nerve conduits[7]. Furthermore, in another study by Shimizu *et al.*, both ADSCs and SVF were shown to have excellent effects on nerve regeneration in a rat model with nerve conduits[5].

Clinical trials investigating the use of ADSCs are limited by the Food and Drug Association, which has not approved using ADSCs that have been enzymatically altered[49]. These federal regulations limit the availability of ADSCs for research, warranting further investigation into alternative sources[37]. One target source of mesenchymal stem cells is the olfactory nerve[50]. An additional intervention showing potential is the use of fat grafting as a source of ADSCs[37]. This is an evolving field of research, and more studies are needed to investigate patient outcomes[49].

ELECTRICAL STIMULATION

An additional intervention to encourage nerve regeneration after PNI is pulsatile ES, which has shown potential as an adjunct therapy by accelerating axonal regeneration and promoting recovery[10]. Keane *et al.* found that ES accelerated functional recovery when applied at the time of nerve graft surgery in rats[8]. Immunohistochemistry of the harvested nerve revealed increased axonal regeneration and macrophage accumulation[8]. Furthermore, Jo *et al.* found that ES improved nerve regeneration in a rat model and was comparable to the changes seen with systemic tacrolimus administration[9].

One challenge in the translation of ES at the time of surgery to a clinical setting is that the current protocol tested is one-hour in duration, which adds a significant time and cost burden for clinical trials[10]. Roh *et al.* found a possible solution to this problem by investigating the benefit of a 10-minute ES session in a rat model[10]. They found accelerated recovery in both the 10- and 60-minute ES groups compared to the control group, with evidence of early axon regeneration in both groups[10]. While no clinical trials have been

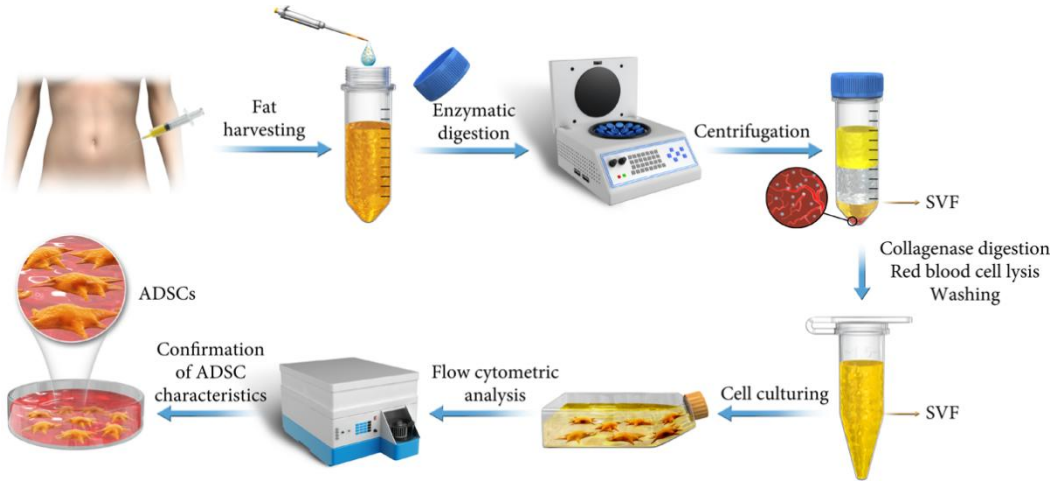

Figure 3. Subcutaneous adipose tissue can be harvested and treated with collagenase to produce SVF, which can be cultured for 2-3 weeks to produce undifferentiated ADCSs[37,47]. These cells can be differentiated into ADSCs, which can in turn promote nerve regeneration[37].

published investigating ES in PNI in the lower extremity, one recent clinical trial found improved outcomes in patients treated with adjuvant ES during surgery for severe cubital tunnel syndrome[39]. However, more clinical trials are needed to evaluate the clinical applications of electrical stimulation in the lower extremity.

ES can be provided at the time of nerve repair or as part of a long-term approach with a neuroprosthesis. For example, in a case series by Possover *et al.*, 29 patients with spinal cord injuries had long-term low-frequency ES of the pelvic somatic nerves with a neuroprosthesis implanted laparoscopically at the time of surgery[51]. While some patients were reported to have improved sensory and motor function recovery, this study was limited by its design, and further studies are needed to confirm the benefits of ES[51]. Notably, one concern with implantable neuroprosthesis is an induced foreign body reaction, which can compromise benefits by provoking an inflammatory response[52]. However, systemic dexamethasone treatment for 2 weeks in rats was found to significantly attenuate the inflammatory response, demonstrating a potential adjuvant therapy to improve the function of neuroprostheses[52].

CONCLUSION

There have been many significant advancements in peripheral nerve surgery, though advances in the lower extremity have lagged behind the upper extremity. Nerve transfers have been successfully performed in the upper extremity and translated to the restoration of function in the lower extremity. Meanwhile, new targets are being evaluated for their anatomical feasibility through cadaver studies, with case reports of successful implementation in surgery. Nerve regeneration has been researched, primarily through basic science studies, as a critical step that can be improved through ADSCs and ES.

Given the impact of lower extremity PNI on patient well-being, there must be a concerted effort to investigate the benefit of the discussed interventions through continued research. While there are challenges in translating basic science research to the clinical setting, the proposed interventions can be optimized. One key challenge in using ADSCs is finding a source of cells that is readily available and complies with federal regulation, thereby leading to investigations into fat grafting[37]. In ES, the current protocol relies on an hour-long session at the time of surgery, leading to research into a possible shortened duration as a solution[10]. Innovative solutions like these can promote continued advancement; however, clinical trials are

necessary before these interventions become standard practice.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the review: Garbuzov A, Nichols DS, Chim H

Review of literature, manuscript writing and critical revisions: Shekouhi R

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

Not applicable.

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Original Article

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An analysis of the role of targeted muscle reinnervation (TMR) in quality of life and pain outcomes: a case series

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Abstract

Aim: Targeted muscle reinnervation (TMR) surgery has fundamentally changed the management of patients who have suffered or are about to undergo amputation. Providing nerve stumps with a muscle target has been shown to have profound effects on levels of post-amputation pain in relation to phantom limb pain (PLP) and neuroma pain (NP). The primary objective of this report was to quantify pain parameters for this population and to measure the impact on health-related quality of life (HRQol) before and after TMR surgery. In this case series, we evaluate the role of TMR in addressing both pain and the impact of the surgery on the patient's quality of life.

Methods: A retrospective analysis of 15 upper limb amputee patients who underwent TMR by the Relimb Unit in London, UK. Participants' perceptions of pain were determined using the 11-point numerical (Pain) rating scale (NRS) and HRQoL was calculated using the Euroqol EQ-5D-5L questionnaire at two time points, comparing both pain and perceived quality of life pre and post surgery. The Wilcoxon Signed Rank Test was used for the NRS data and a paired sample *t*-test was used for the EQ-VAS data.

Results: A total of 15 patients completed the evaluation. We observed statistically significant reductions in both PLP (pre-operative mean: 7.6, post-operative mean: 2.7, $P < 0.05$) and NP (pre-operative mean: 6.4, post-operative mean: 2.5, $P < 0.05$) in these patients. Similarly, HRQoL observed on the EQ-VAS scale demonstrated a significant

improvement in quality of life, from 68 pre-operatively to 78 post-procedure ($P < 0.05$).

Conclusion: This is the first quantified evaluation of changes in HRQoL after TMR surgery for upper limb amputation. There appears to be a significant improvement in both HRQoL and overall perception of pain. This finding may have important implications for funding and national resource allocation for TMR surgery.

Keywords: Amputation, TMR, targeted muscle reinnervation, quality of life, QALY

INTRODUCTION

There are an estimated 10,000 upper limb amputations annually in the United Kingdom[1]; most are digital amputations, with approximately 300 major limb amputations (e.g., transhumeral or transradial). The adverse impact of an upper limb amputation on mental health and pain is well established[2]. There are additional functional sequelae associated with the loss of the limb, which adversely impact health-related quality of life (HRQoL)[3]. Functional reconstruction can be achieved through upper limb prosthesis; however, their accessibility may be precluded by high upfront and running costs, even in a developed nation such as the UK. These costs are difficult to determine due to a wide range of available devices and the extent of prosthesis required, which in turn is dependent on the level of amputation[4]. In the United States, one source has estimated the mean cost of a myoelectric prosthesis for partial hand amputations at $18,703, $20,329 for transradial amputations, $59,664 for Transhumeral amputations, and approximately $62,000 for shoulder and forequarter amputations[5]. Overall, prosthesis-related expenses can range between £31,890 to $117,440, clearly highlighting a significant financial burden on both the patients and the healthcare system[4].

The nerve-related pain experienced after upper limb amputation can be both persistent and debilitating[6]. The two main nociceptive sensations after amputation are neuroma pain (NP) and phantom limb pain (PLP), which can be differentiated based on their character, location and triggers[7]. NP is typically initiated by direct pressure over the end of the injured nerve, while PLP is any pain or discomfort that is perceived to occur in the now absent limb[8]. The sustained and persistent nature of these two types of pain has been demonstrated to adversely impact the patient's HRQoL[9]. Although the introduction of neuropathic agents (e.g., gabapentin) has had a transformational effect on the management of both of these types of pain, these drugs cannot abolish pain and patients often suffer from a variety of debilitating side effects or may be completely intolerant of the medication[10]. Chronic use of the medication is also costly for many healthcare systems.

Targeted muscle reinnervation (TMR) has shown great promise in the treatment of both types of nerve-related pain[11]. By providing a muscle target to the regenerating nerve stumps after amputation, TMR surgery appears to reduce the reformation of painful neuromas while simultaneously providing feedback to the central nervous system (CNS), which appears to reduce the perception of PLP. However, to date, there has been no work to quantify the impact of TMR surgery on the quality of life in this population.

METHODS

We performed a retrospective review of all upper limb amputees with NP and/or PLP who underwent TMR surgery between October 2013 and September 2021 by the Relimb Unit, Royal Free Hospital, London, United Kingdom. Data were collected from patient records and telephone interviews. Additional baseline characteristics were also collected from the study participants, including; age, gender, date of procedure and indication for TMR. Our primary outcome measures evaluated pain and quality of life. Subjects were

contacted and asked to complete the surveys at two time points: pre-operatively, and at the time of interview. For pain measures, we used the 11-point numerical (Pain) rating scale (NRS), where 0 indicates "no pain" and 10 indicates "the worst possible pain". Pain levels were identified separately as either NP and PLP, pre-operatively and at the time of the interview. As previously indicated, NP was defined as pain occurring within the stump – located over the ends of the nerve stumps, and PLP was defined as painful sensations perceived in the absent limb.

Quality of life was evaluated using the EuroQol EQ5D-5L questionnaire (with permission from EuroQol). The seven metrics provided by the EQ-5D questionnaire were evaluated (five domains, an index score, and a Visual Analogue Scale/VAS score).

Surgical technique

The surgical techniques used by the Relimb unit are based on Kuiken and Dumanian's description of TMR surgery[12] and these have been described previously[13].

Statistical analysis

A statistical analysis was performed with IBM SPSS Statistics (IBM Corporation, Armonk, New York, USA). The NRS data were evaluated using the Wilcoxon Signed Rank Test, identifying any changes pre and post-surgical intervention. The EQ-5D VAS data were analysed using a paired sample *t*-test, evaluating HRQoL pre and post-surgical intervention.

RESULTS

A total of 15 patients completed the evaluation. The mean age of the study participants was 55.8 years, and five of the 15 participants were female (33%). All patients underwent TMR surgery between October 2013 and September 2021. The indication for TMR in these patients was for secondary treatment of NP or residual limb pain (RLP) and/or PLP, sequelae of upper limb amputation. As such, TMR surgery was offered to our patients several years after their initial amputation surgery.

The data show a statistically significant reduction in both PLP (pre-operative mean: 7.6, post-operative mean: 2.7, $P < 0.05$) and NP (pre-operative mean: 6.4, post-operative mean: 2.5, $P < 0.05$) [Figure 1].

Table 1 demonstrates the changes in score across each of the EQ-5D domains. The green colour denotes an improvement in a domain and red denotes a reduction in domain function. A total of 12 patients experienced a change in their EQ-5D domains. Nine patients noted improvements and five patients noted reductions in functionality.

Ten of the 11 patients reporting changes in pain as part of their EQ-5D found an improvement in this domain. Changes in HRQoL were observed for the EQ-VAS scale, and these demonstrate an improvement in quality of life from 68 pre-operatively to 78 post-procedure ($P < 0.05$).

DISCUSSION

In many instances since 2008, the evaluation of the quality of life has been based on the EQ-5D, Euroqol questionnaires[14]. Ernstsson and colleagues evaluated the use of EQ-5D questionnaire to assess HRQoL following lower limb amputation surgery. They highlight the correlation between factors such as pain due to NP/RLP or PLP, reduced mobility and impaired activities of daily living with poor HRQoL. The authors conclude that the EQ-5D-5L questionnaire has high validity and feasibility to assess HRQoL, particularly in lower limb amputees[15]. Globally, access to healthcare can be challenging due to limited resources,

Table 1. Demonstrating the change in pre- and post-operative EQ-5D

	Change in EQ-5D					
Patient number	**Mobility**	**Self-care**	**Usual activities**	**Pain**	**Anxiety**	**VAS**
1	0	-1	-1	-2	-1	15
2	0	0	1	0	0	0
3	n/a	n/a	n/a	n/a	n/a	n/a
4	n/a	n/a	n/a	n/a	n/a	n/a
5	0	0	0	-2	0	15
6	0	-1	-1	-3	0	20
7	1	0	-2	-1	0	5
8	0	0	0	0	0	0
9	0	0	0	-1	1	50
10	0	0	1	-1	0	10
11	0	0	0	0	0	0
12	-2	-2	-1	-2	-2	55
13	n/a	n/a	n/a	n/a	n/a	n/a
14	1	0	0	1	0	0
15	0	0	0	-3	0	0
16	0	0	0	0	0	0
17	n/a	n/a	n/a	n/a	n/a	n/a
18	n/a	n/a	n/a	n/a	n/a	n/a
19	0	0	0	-1	-2	30
20	0	0	0	-2	-2	35

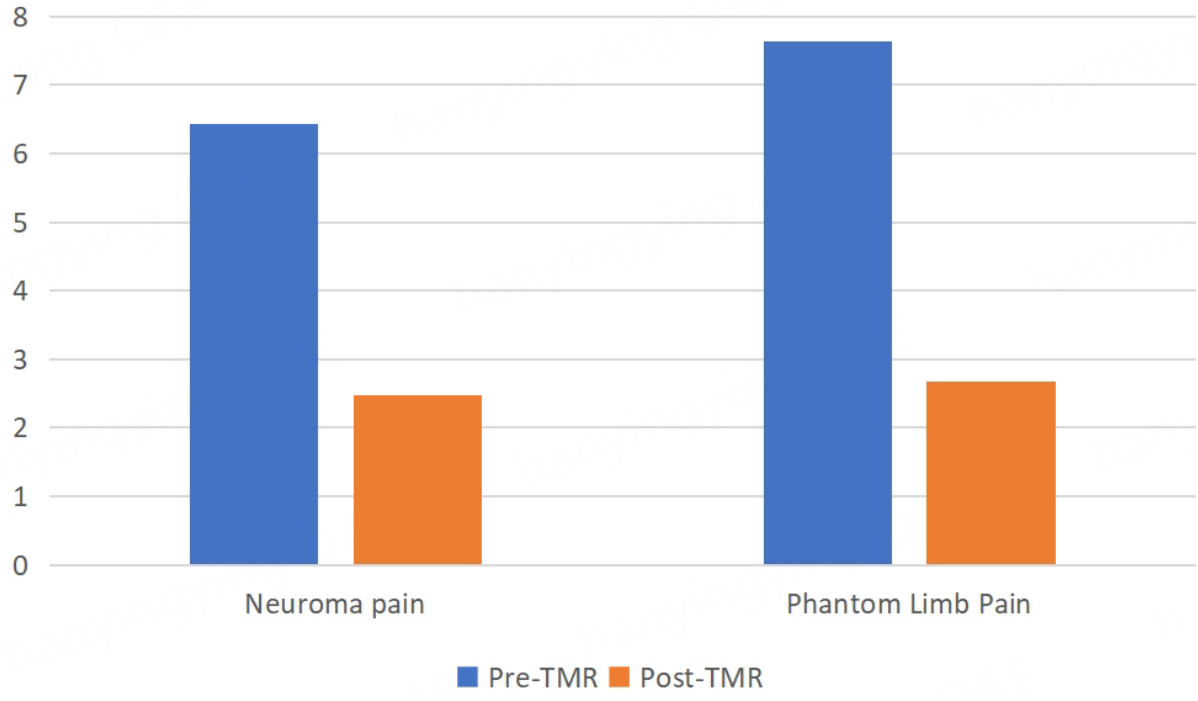

Figure 1. Demonstrates the changes in NP and PLP both prior to and after TMR intervention. NP demonstrated a reduction from 6.4 to 2.5 and PLP from 7.6 to 2.7 after TMR. TMR: Targeted muscle reinnervation; PLP: phantom limb pain; NP: neuroma pain.

healthcare provider expertise and funding. A recent study identified an average cost of $28,961 to the

patient for upper extremity amputation. Equally, the healthcare system saw an overall cost of $166 million over a 15-year period[16]. Lifetime costs to an amputee patient can exceed $500,000[4]. The EQ-5D-5L questionnaire is a reproducible and informative resource that provides practical insight into the impact on a patient's quality of life. The international impact of the EQ-5D and its applicability is a testament to its wide-ranging benefits and further supports policy makers at national and firm levels in their decision making to fund the interventions.

Previous articles have already established the reproducible nature of TMR in improving symptoms of NP and PLP after amputation. However, there has been no work specifically evaluating the interplay between the chronic pain caused by NP and PLP on quality of life after upper limb amputation. Moreover, while recognised by NICE as a key metric[17], assessing changes in (pain) quality of life is not routinely performed after upper limb amputation. Our study highlights the efficacy of TMR in improving HRQoL, with 66% of patients reporting an overall improvement following their intervention. It is important to assess why five (33.3%) patients reported a decrease in functionality for some domains such as pain, mobility and usual activities following TMR. We hypothesise that this could be multifactorial. Some reasons may include individual patient perception towards domains such as pain and anxiety, extent of the initial injury, degree of amputation and site of injury. Other reasons include non-specific questions such as mobility, which some patients may have perceived as pertaining to lower limb mobility rather than upper limb, and further could be a function of other confounding variables as it may sometimes be challenging to discern the changes patients experience from surgery versus over time. In addition, the retrospective nature of our study gives rise to the potential impact of recall bias. Patients may not recall the impact that TMR may have had on their HRQoL, particularly if a number of years have elapsed since their surgery. Our study was conducted in December 2021 on patients who initially had their TMR operation as far back as October 2013. Amongst the five patients with a reduction in domain function, three (60%) demonstrated positive improvements in other domains [Table 1]. Therefore, despite these drawbacks, most patients in our study reported an overall improvement in their HRQoL following TMR, as evidenced by their Q-5D-5L domain scores and VAS. Our study provides precedence for further investigation into the HRQoL benefits associated with TMR surgery for secondary NP/RLP and/or PLP associated with upper limb amputation. Ideally, this should be performed in the context of a multi-centre randomised control trial.

For this analysis, we used a numerical (pain) rating scale (NRS) which was simple, reproducible, and easily understood (by patients and researchers) to perform surveys over the telephone. This was necessary because of the restrictions on face-to-face contact during the COVID-19 pandemic. However, we accept that further work could be done to evaluate the complexity of the questionnaires we administered, their reproducibility and error rate to create a better framework for future trials.

Funding for TMR surgery in the UK is currently determined on a local level. Since there are no OPCS codes for this procedure, the codes for a number of different procedures (e.g., nerve repair, nerve transfers, free tissue transfer) are often put together to cover the cost of the TMR procedures. However, the absence of any uniformity of what constitutes a TMR procedure may contribute to further inequities in healthcare provision in the future. As a first step towards reducing these inequities, we have tried to quantify the size of the improvements in quality of life produced by TMR surgery after upper limb amputation. Based on our analysis, we believe that there is sufficient evidence to inform any future Health Technology Assessments and Appraisal, and this may enable NICE to make recommendations on the future (national) provision for TMR surgery. However, the complex nature of the surgery (especially in the upper limb) means that it is likely to need that such care will only ever be possible on a tertiary or quaternary basis.

Limitations

The main limitation of this study is its retrospective nature. Our methodology draws on the (validated) retrospective use of the EQ-5D questionnaire in an orthopaedic population[18]. Our small sample size and the lack of a control group could be enhanced with future work, although it is important to note that the novelty of the intervention precluded greater patient recruitment.

Conclusions

In this study, TMR appears to have improved the quality of the lives of a small cohort of upper limb amputees with NP and PLP. This improvement was evident across many metrics, and more broadly in quality-of-life assessments. The implications of these findings require further analysis, including randomized control trials to potentially inform policy and national commissioning to ensure equitable access to this type of surgery for patients who have experienced limb loss.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Zargaran D, Nagra R, Zargaran A, Akella M, Ajam Y, Woollard A, Kang N

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

All patients agreed to participate in this study.

Consent for publication

Informed consent of the patient has been obtained.

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Review

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The neurobiology of targeted muscle reinnervation for post-amputation pain

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Abstract

Targeted muscle reinnervation (TMR) is a peripheral nerve procedure that can prevent and treat postamputation pain. The nerve transfer allows for organized nerve regeneration and repair after amputation surgery. The procedure can successfully prevent neuromas despite large size mismatches between the donor and recipient nerves. Here, we discuss the fundamentals of peripheral nerve injury and regeneration as it pertains to TMR. We propose axonal pruning to explain axon behavior when there are large size mismatches between transferred nerves. Given the increasing use of TMR for amputees, future studies should investigate the basic science of peripheral nerves in TMR. Advances in this field have the potential to significantly improve clinical outcomes for these patients.

Keywords: Targeted muscle reinnervation, peripheral nerve injury, nerve regeneration, axonal pruning

INTRODUCTION

More than 2 million amputees live in the United States, and approximately 185,000 amputations occur in the United States each year[1]. Pain is a significant problem affecting more than 70% of amputees[2]. Peripheral nerve injury and subsequent improper axon regeneration result in a disorganized bundle of nerve tissue, known as a neuroma[3]. Neuromas are a known cause of postamputation pain, which includes

residual limb pain (RLP), phantom limb sensations (PLS), and phantom limb pain (PLP)[3]. RLP is pain at the site where amputation occurred, often due to nerve injury and neuroma formation[3]. PLS are non-painful sensations in the amputated limb, which may lead to PLP[3]. Meanwhile, PLP represents neuropathic pain localized to the lost limb[3]. Postamputation pain contains significant overlap, and patients with neuromas are significantly more likely to suffer from PLS and PLP[4,5]. Postamputation pain has a significant impact on patient outcomes, including prosthetic use, return to work, and overall quality of life[6].

Unfortunately, postamputation pain is complex and poorly understood, and treatment of postamputation pain remains difficult[4,7]. Targeted muscle reinnervation (TMR) is an emerging surgical procedure to manage nerves and treat pain in amputees. TMR involves transferring the proximal stump of transected major peripheral nerves to nearby motor nerves of muscles that lack function after amputation[8]. In surgery, the major peripheral nerve being managed with TMR is identified, dissected, and cut distally to healthy fascicles. The recipient motor nerve is identified using a nerve stimulator and cut just proximally to any areas of branching into muscle. The small recipient motor nerve is sutured to the center of the large donor nerve in an end-to-end fashion. Fibrin glue is used to reinforce the coaptation and prevent collateral axonal sprouting and neuroma formation. TMR was originally performed by Kuiken *et al.* in 2004 to improve myoelectric prosthetic control[9]. Incidentally, TMR was found to successfully treat and prevent neuroma pain in amputees, sparking an explosion of new research into TMR[4,7]. Recent literature shows the clinical success of TMR, the expansion of its use, and improvements in surgical technique[4,5,8]. However, there is a paucity of literature exploring the basic science of nerve regeneration pertaining to TMR and how the procedure actually prevents neuroma formation. Surprisingly, the procedure can be successful in preventing neuromata despite a large size discrepancy between donor and recipient nerves[4,10]. No known studies have explained a possible mechanism for axon behavior when there is a large size mismatch between transferred nerves. The purpose of this review is to attempt to explain the process of nerve regeneration in TMR for postamputation pain and to propose axonal pruning as a potential mechanism for axon behavior in the setting of a large size mismatch between coapted nerves.

PERIPHERAL NERVE ANATOMY

The main functions of the PNS are to send sensory information to the CNS, transmit motor commands to voluntary striated muscles in the body, and regulate autonomic functions such as blood pressure[11]. Therefore, the PNS contains motor, sensory, and autonomic nerve fibers that combine to form motor, sensory, or mixed nerves[11,12].

The PNS is myelinated by Schwann cells that increase the speed of action potential propagation[11]. Schwann cells are the supporting cells of the PNS that surround and protect axons[13]. In addition to myelin, peripheral nerves are surrounded by three well-organized connective tissue layers: endoneurium, perineurium, and epineurium[11] [Figure 1]. The endoneurium is the innermost compartment surrounding individual nerve fibers, and it forms the blood-nerve barrier[13]. The nerve fibers are grouped into fascicles, which are enveloped by concentrically arranged perineurium[13]. The epineurium is the outermost layer of peripheral nerves, containing several nerve fascicles and the nerve's blood supply[13]. The well-organized peripheral nerves and their tissue are essential for proper neurotransmission, as well as normal nerve regeneration following peripheral nerve injury.

PERIPHERAL NERVE INJURY

Peripheral nerve injury (PNI) can have a significant impact on a patient's quality of life[15]. PNI frequently develops into neuropathic pain, which is a complex form of pain that is modulated by both the PNS and CNS[15,16]. Sunderland *et al.* were the first to classify peripheral nerve injuries and offer a prognosis for nerve

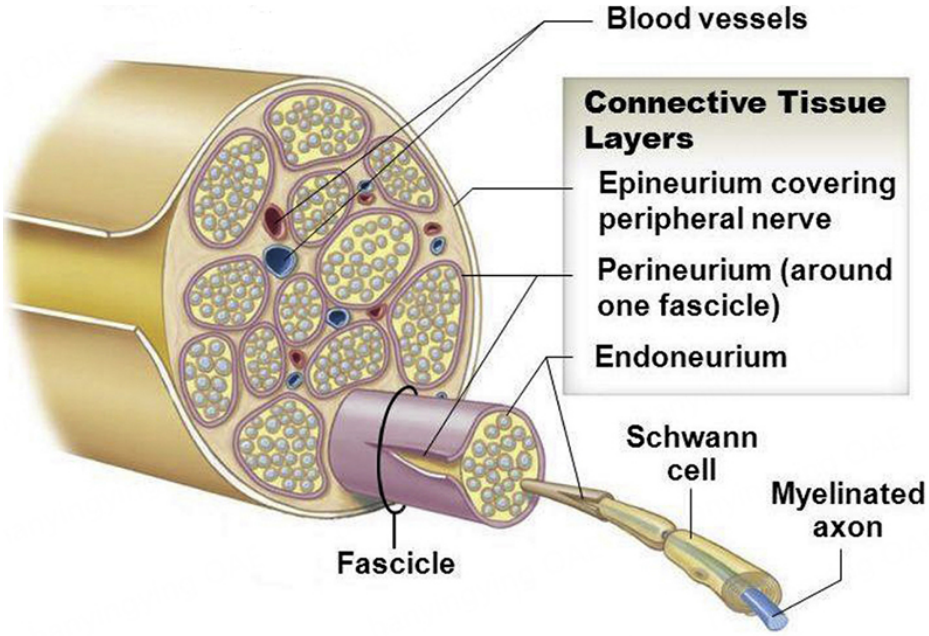

Figure 1. Schematic presentation of a peripheral nerve. Source: Nicholls *et al.*[14].

repair based on the degree of connective tissue disruption[16] [Figure 2].

Since mature neurons are terminally differentiated cells that are incapable of mitosis, a nerve injury to the cell body cannot be repaired and results in apoptosis[13]. However, there are two main mechanisms for axonal regeneration: terminal sprouting from injured axons and collateral axonal branching from intact axons[13,18,19]. This is largely because Schwann cells, unlike neurons, can undergo mitosis if injured[13]. Understanding the fundamentals of peripheral nerve degeneration and regeneration after injury will help inform targeted muscle reinnervation for the treatment of postamputation pain.

In limb amputation, peripheral nerve injury is unavoidable[8,20]. Amputation requires nerve transection and can be considered a Sunderland grade 5 nerve injury, in which all connective tissue layers are disrupted and the distal target for nerve regeneration is removed[16] [Figure 2]. Injury begins the peripheral nerve degeneration cascade. Within hours, degeneration of the axon and myelin begins in both directions from the site of injury in a complex process known as Wallerian degeneration[13]. Wallerian degeneration is the rapid, vigorous process of degeneration of distal and some proximal segments of axon after nerve injury[13,17] [Figure 3]. The disruption of the axon plasma membrane causes the influx of extracellular calcium ions, which triggers proteolysis, fragmentation, and degradation of the myelin and axons[21]. Schwann cells dissociate from the axon and transition into repair cells to help digest myelin[21]. Schwann cells initially phagocytose debris before the macrophages are recruited and enter through the leaky blood-nerve barrier[21]. Macrophages are critical to Wallerian degeneration as they rapidly engulf and digest debris, clearing the path for nerve regeneration to occur[17,21]. Wallerian degeneration begins within 24 h of injury and completes after 3 weeks[22].

Wallerian degeneration traditionally refers to the degeneration of distal detached axon segments after nerve injury but has also been found to extend proximally from the site of injury[13]. Wallerian degeneration proceeds proximally for about two internodes before the axon is sealed within hours of injury[13]. This is thought to protect the intact axon and cell body from the extracellular environment and apoptosis while

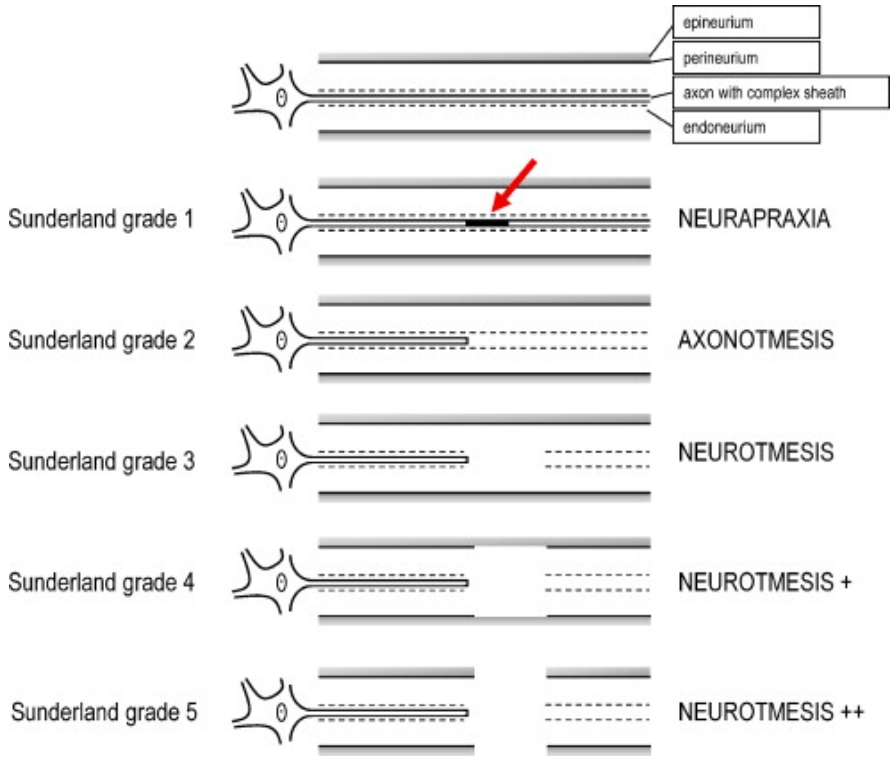

Figure 2. Sunderland peripheral nerve injury classification. Source: Deumens *et al.*[17].

allowing retrograde chromatolysis to proceed[13,22].

The chromatolytic changes seen in PNI include disintegration of Nissl bodies (cisterns of the rough endoplasmic reticulum) in the cytoplasm, an eccentric nucleus, a prominent nucleolus, and an increase in RNA and protein synthesis[17]. In peripheral nerve injury, these chromatolytic changes reflect a shift of metabolic activity away from the synthesis of proteins for neurotransmission and towards proteins required for growth and axon sprouting[17]. Depending on the environment and degree of injury, retrograde chromatolysis may cause the neuron to produce apoptotic proteins, in which case nerve regeneration fails and the neuron undergoes programmed cell death[17]. If the neuron survives, the retrograde reaction peaks at 2-3 weeks after the nerve injury[13,17]. In this instance, nerve degeneration quickly transitions to nerve regeneration[17].

PERIPHERAL NERVE REGENERATION

Nerve regeneration begins when Schwann cells undergo mitosis and rapidly proliferate[17] [Figure 3]. After assisting with the initial degradation of the injured axon and myelin, Schwann cells align from both ends of the damaged nerve to form new endoneurial tubes across the injury site[17]. These are known as bands of Bü ngner, through which new axon sprouts can grow[17].

Once retrograde chromatolysis has peaked, regenerative terminal sprouting and collateral axonal branching can begin[17-19]. Axon sprouts grow along the bands of Büngner at an average rate of 1-3 mm/day towards their distal targets[17]. Distal nerve stumps and target tissues have attractive forces on axon sprouts that likely drive chemotaxis[17]. Since axon sprouting and growth cones require an organized endoneurial tube, the extent of endoneurial tube disruptions during injury determines the healthy regeneration of the nerve axons

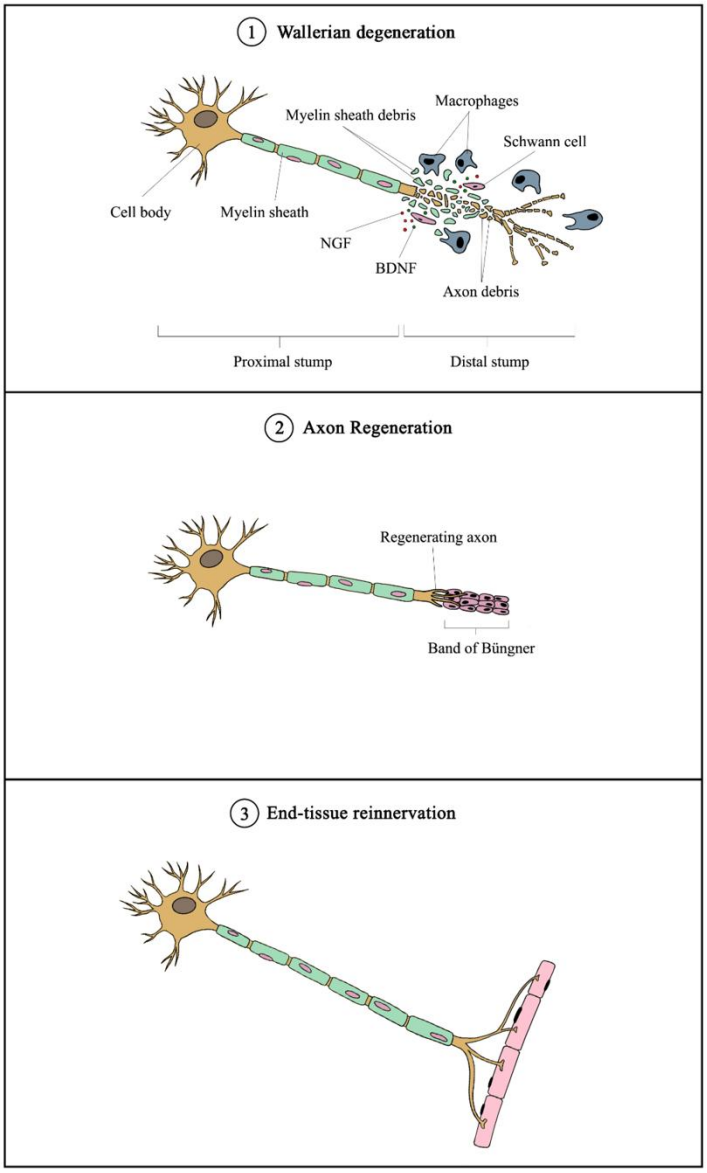

Figure 3. Overview of the mechanism of peripheral nerve injury and regeneration. Source: Yow *et al.*[23].

to their intended targets[16]. Depending on the distance the axon sprouts must travel, sprouts may take weeks to months to traverse the axon injury gap and re-enter appropriate endoneurial tubes[24]. Eventually, the axon sprouts extend through the distal target nerve with support from Schwann cells in the bands of Büngner[24].

Collateral axonal branching occurs via a different mechanism[18,19]. The de novo branches stem from the main axon of the injured neuron or from the axons of nearby uninjured neurons[18]. The outgrowths are formed by actin filament protrusions that become invaded by stable microtubules[18]. The microtubules allow the branches to mature and continue extending toward their target[18]. Collateral branches enter Schwann cell tubes, which guide reinnervation to their target in a similar way to terminal sprouting[25].

Successful nerve regeneration is established when neurotransmission through the injured neuron is restored[17,21]. Axon sprouts that successfully enter the distal target will become re-myelinated and grow stronger with use[13]. Once regeneration is complete, chromatolysis is reversed and cell function returns to normal[17].

NEUROMA FORMATION/FAILURE OF REGENERATION

Nerve regeneration can fail at any step in this process[17]. If the cell body is injured, retrograde chromatolysis may result in the production of apoptotic proteins and cell death[17,26]. If regenerative axon sprouts fail to cross the injury site due to large gaps, a physical barrier formed by scarring, or other factors, the axon sprouts will form a neuroma[17]. Aberrant sprouting may occur in limb amputation when nerves are not given a new target[10]. Neuromas are a common cause of postamputation pain and may negatively impact the function and quality of life of amputees[3,4].

Collateral axonal branching is frequently misdirected and can cause improper innervation of distal targets[27,28]. For instance, nearby sensory nerves can branch to reinnervate the distribution of an injured or cut motor neuron[27,28]. This can produce painful hyperalgesia that is often misinterpreted as neuroma pain[28]. The hyperalgesia due to the collateral branching of sensory axons produces a burning sensation and hypersensitivity to touch[28]. However, collateral branching does not contribute to neuroma formation and is not amenable to surgery. It can be treated with desensitization therapy[28].

PHANTOM LIMB SENSATIONS AND PAIN

PLS are any non-painful sensations that occur in the missing body part after amputation[29,30]. Over 90% of amputees experience PLS in the first 6 months[30]. Phantom sensations may include feelings of movement, touch, tingling, itching, or paresthesia in the missing limb[31].

The causes of phantom sensations are not well understood and are thought to involve both peripheral and central mechanisms. After amputation surgery, neuroma formation and abnormal spontaneous neuronal activity at the proximal end of the cut peripheral nerves may contribute to phantom sensations[32,33]. Neuromata have been shown to correlate with increased duration and intensity of phantom sensations and phantom limb pain[33]. Also, injured peripheral nerves have upregulated sodium channels, causing increased sensitivity to mechanical stimulation and abnormal firing[32,33]. The increased sensitivity of the injured nerves decreases the pressure pain threshold, which may explain why some amputees experience increased PLS and PLP with prosthetic use[32,33].

PLS are also thought to be modulated via central mechanisms. The somatosensory homunculus in the cortex of the brain receives sensory, positional, and movement information from peripheral nerves[34]. The cortical representation of an amputated limb likely persists for some time after limb amputation resulting in a phantom limb[34]. Reorganization of the somatosensory cortex may also underlie phantom sensations[35]. Neurons in the somatosensory cortex that previously responded to signals from the missing limb can begin to respond to signals from other nearby neurons[35]. As a result, stimulation of nerves in other parts of the body can be aberrantly received by the neurons of the amputated limb in the somatosensory cortex, causing sensations to be improperly perceived[35]. Phantom limbs usually change and fade over time, and most PLS disappear after 2 to 3 years[4]. However, PLS may become painful and develop into phantom limb pain in about 45% of patients[34,36].

Phantom limb pain is a complex interplay between neuromas and the central nervous system. PLP is a type of neuropathic pain that can include burning, throbbing, crushing, cramping, or sharp pain in the missing limb[36]. Cortical reorganization is a key component of PLP, and it is even more difficult than neuroma pain to prevent or reverse[4]. Therefore, treating neuromas may prevent cortical reorganization and further centralization of PLP[4,34]. In a prospective, multicenter, randomized clinical trial, Dumanian *et al.* found evidence that TMR significantly decreases phantom pain in major limb amputees compared to standard treatment at 1 year[4]. Therefore, TMR may prevent PLS and PLP by addressing the contribution of peripheral nerve injury to these experiences.

SIZE MISMATCH AND AXONAL PRUNING

TMR often involves a size mismatch between the donor and recipient nerves at the nerve coaptation site[37] [Figure 4]. The ideal nerve coaptation is a 1:1 diameter ratio and the recommended size ratio is less than 2:1[20]. However, the current practice is to accept large size mismatches in TMR[37]. Depending on the available anatomy, the physiological and clinical implications of the size mismatch are unknown, but Kim *et al.* and Dumanian *et al.* found that patients having TMR did not develop symptomatic neuromas at nerve coaptation sites despite large size mismatches[4,10]. No prior works have addressed why TMR is successful despite large size mismatches between the donor and recipient nerves. Kim *et al.* posited that there is likely a critical mass effect where TMR is successful after enough targets are provided for the regenerating nerve sprouts[10]. However, this does not explain what comes of the growing nerve sprouts that fail to reach their targets.

A possible theory to explain why TMR works despite a large size discrepancy between transferred nerves is the process of axonal pruning. Axonal pruning is selective axon degeneration that removes unnecessary, misguided, or excessive axon sprouts while maintaining the integrity of the cell body[26,38,39] [Figure 5]. Singh *et al.* showed that during axon competition, active (i.e., winning) axons can eliminate less active, competing axons by axonal pruning[40]. Axonal pruning is well established in the development of the CNS and PNS[26,40]. Selective degradation of axons that unsuccessfully innervate their targets or are no longer necessary allows for optimal wiring of neural connections in the developing nervous system[26].

Axonal pruning has previously been described in the context of nerve injury. Following an injury to a mixed peripheral nerve, regenerating motor axons will preferentially enter both sensory and motor Schwann cell tubes over regenerating sensory axons[42]. The preferential motor reinnervation of distal targets - known as preferential motor reinnervation (PMR) - is made possible by the pruning of sensory axon sprouts while maintaining motor axons[27,42] [Figure 6]. We believe axonal pruning may explain the elimination of misguided axonal sprouting in TMR, allowing for successful reinnervation despite large size mismatches between the donor and recipient nerves.

Axonal pruning is distinct from Wallerian degeneration and neuronal apoptosis, although all three processes result in axon degeneration[26]. A key feature of axonal pruning is the selective, controlled degradation of axon fibers without inflammation or damage to the cell body[26]. As previously described, Wallerian degeneration is an inflammatory reaction that occurs in response to nerve injury[17], while apoptosis is the programmed death of the entire neuron, including the axon and cell body[26]. The apoptosis pathway is highly restricted after development as neurons cannot regenerate[44]. Axonal pruning, however, is critical to adult neural plasticity, as it permits the selective loss of specific axon sprouts while maintaining nearby axon segments and the integrity of the cell body[26]. Therefore, axonal pruning is the most likely mechanism to explain the behavior of axon sprouts at nerve coaptation sites in TMR.

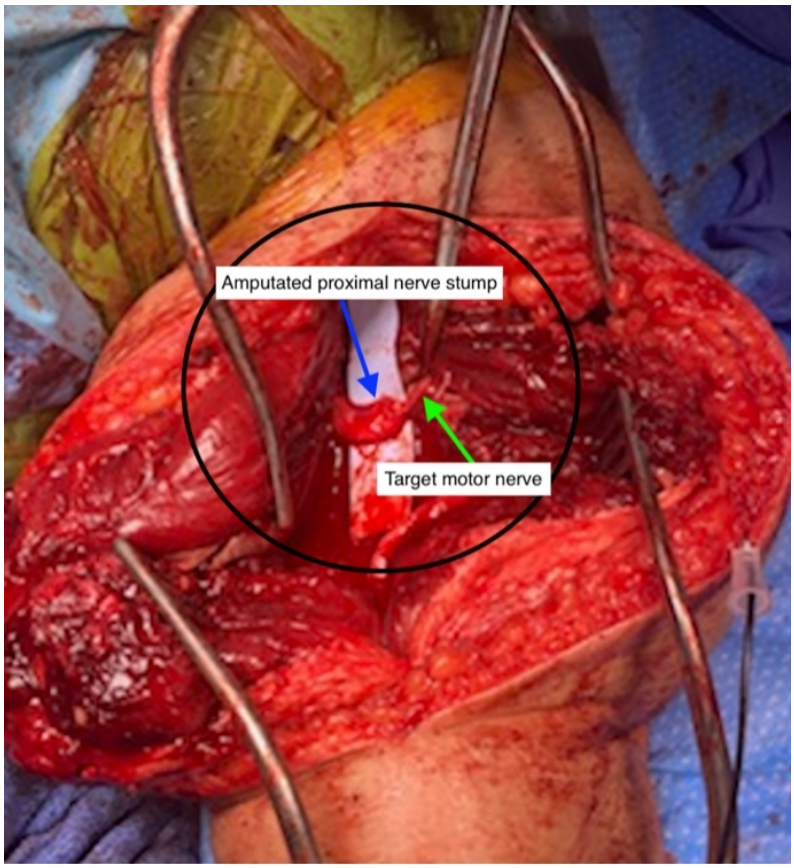

Figure 4. Size mismatch between transferred nerves in TMR.

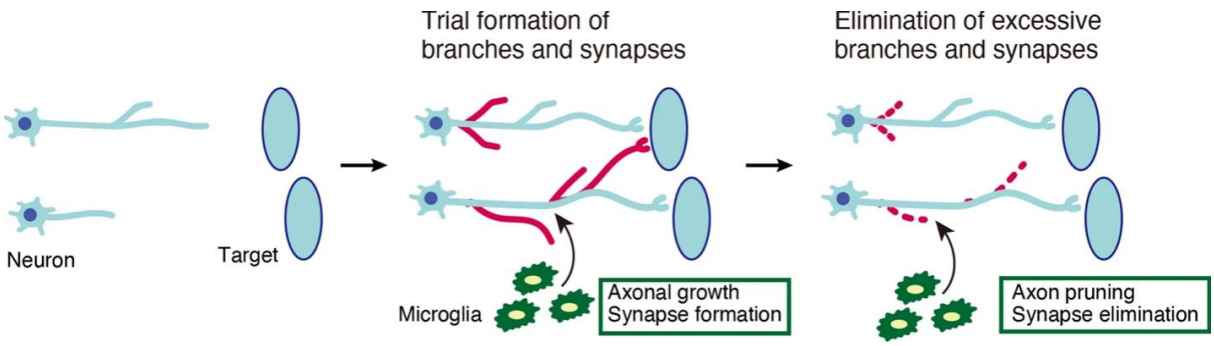

Figure 5. Schematic model illustrating axonal pruning for refining neural connections. Source: Fujita *et al.*[41].

DISCUSSION

Targeted muscle reinnervation is a major surgical advancement in the field of amputation surgery. Since its introduction in 2004, the use of TMR has been growing rapidly with the main goals of treating and preventing painful neuromas and improving the function of amputees. There has been an abundance of research into the clinical success of TMR and its growing indications for use. However, there is a gap in the basic scientific descriptions of peripheral nerve behavior in TMR. Our review aims to fill this gap and provide a better understanding of neurobiology as it pertains to TMR.

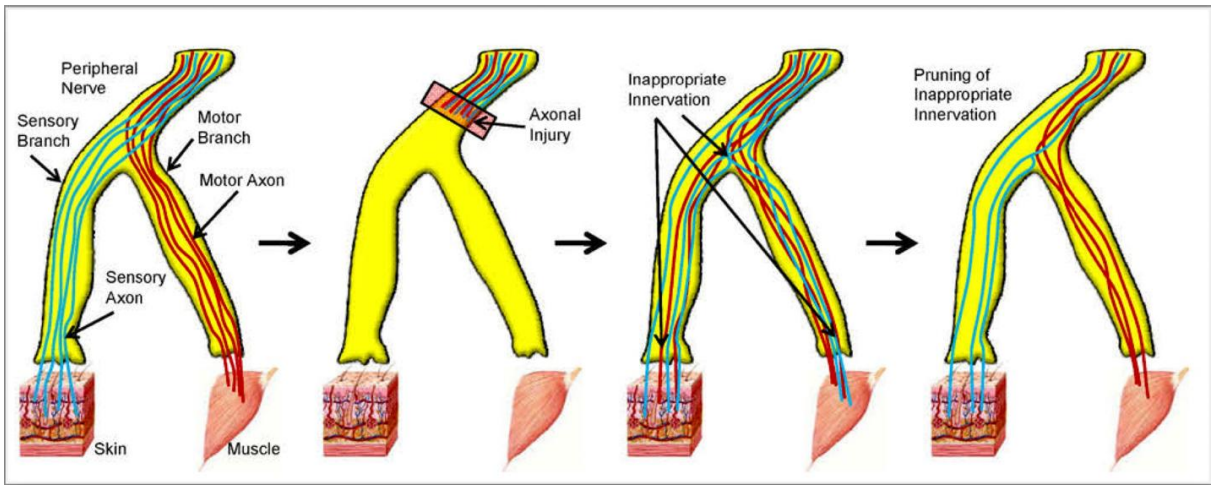

Figure 6. Preferential motor reinnervation. Following an injury to a mixed peripheral nerve, regenerating axons will preferentially reinnervate modality-matched targets driven by target signals. Regenerating axons that inappropriately innervate mismatched sensory or muscle targets undergo axonal pruning. Source: Mackinnon *et al.*[43].

Injured peripheral nerves will always attempt to reach a distal target after injury. Amputation surgery requires the transection of nerves and eliminates a distal target for organized regeneration, creating a high-risk environment for neuroma formation[4,8]. TMR provides a physiologically appropriate environment for regenerating axons and establishes a new distal target, thus preventing neuroma formation. Advances in the understanding of peripheral nervous system pathophysiology can further improve TMR techniques and treatment for patients.

Based on the principles of peripheral nerve injury and regeneration, it is surprising that several clinical studies have found that TMR can successfully prevent neuromas despite large size mismatches between the transferred nerves[4,8]. This is unexpected given the many sprouting axons from the larger proximal peripheral nerve stump that are left without organized connective tissue or a distal target to guide normal regeneration. Here, we propose axonal pruning as a viable explanation for the process of eliminating misguided or unnecessary sprouts when there is a significant size mismatch between transferred nerves in TMR. Axonal pruning may explain why TMR prevents neuroma formation and allows an optimal highway to the new target to form. However, no studies have been performed to support this theory, and further study is necessary to determine the mechanism preventing neuroma formation when there is a large size mismatch between the transferred nerves in TMR.

There are several limitations to this review since the mechanisms behind TMR and postamputation pain are complex and have not been extensively studied. The information in this review was drawn from a diverse set of orthopedic, neurobiology, and pain studies to better understand the behavior of peripheral nerves in TMR. There is a strong need for basic scientific models of TMR and further investigation in this field. It is our hope to trigger future research to further identify the pathways through which TMR can be clinically effective.

TMR can be considered by surgeons performing amputations and for other indications such as neuroma management. Clinical practice momentum is shifting towards routinely offering TMR at the time of primary amputation. However, before recommending this widespread change in clinical practice, comprehensive high-level evidence to support this practice is needed. In this review, we attempt to bridge

the gap between the literature on the peripheral nervous system and TMR.

CONCLUSION

In conclusion, TMR can be successful in treating neuromata and postamputation pain in amputees. Given the increasing use of TMR for amputees, further research should be done into the basic science of TMR. A better understanding of the mechanism of peripheral nerve injury can help surgeons improve treatments for amputation patients and develop new surgical techniques to prevent pain. Comprehensive, evidence-based knowledge of TMR has the potential to vastly improve the outcomes, function, and quality of life of amputees.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, implementation of the research and interpretation: Tanner N, Ayalon O

Took the lead in writing the manuscript with input and critical feedback: Ayalon O, Tanner N

Discussed the findings and contributed to the final manuscript: Tanner N, Ayalon O

Availability of data and materials

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Financial support and sponsorship

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Conflicts of interest

Both authors have declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Plastic and Aesthetic Research

Review

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Review of current reconstructive approaches for pan-brachial plexus injuries

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Abstract

Pan-brachial plexus injuries present a challenging clinical problem, resulting in severe impairment of motor and sensory function in the upper extremity. Although current literature has outlined several promising methodologies for treatment, a consensus has yet to be reached. In this review, we present three general approaches for reconstructing the upper extremity in these complex cases.

Keywords: Pan-brachial plexus injuries, brachial plexus, reconstructive techniques

INTRODUCTION

Pan-brachial plexus injuries (PBPIs) are severe and life-altering conditions that result in a flail limb. These injuries cause long-lasting physical disability, psychological anguish, and chronic pain, and require a substantial financial investment for treatment. While brachial plexus injuries are overall quite rare, PBPIs constitute approximately 53% of all brachial plexus injuries[1]. These devastating injuries predominantly occur in young males following high-energy motorcycle or motor vehicle accidents[1]. Due to the complete loss of motor and sensory function of the upper extremity resulting from PBPI, the treatment continues to be challenging for surgeons.

Despite our understanding of the epidemiology and presentation of these injuries, the workup can vary significantly. This is seen primarily in the utilization of diagnostic imaging and electromyographic studies. 94% of surgeons surveyed obtained pre-operative advanced imaging. 80% routinely requested CT myelography, 55% a brachial plexus MRI, and 41% obtained both studies pre-operatively. Furthermore, electrodiagnostic studies were only acquired by approximately seven out of ten surgeons[2].

An MRI of the brachial plexus has the benefit of identifying signal changes both at the site of nerve injury as well as a possible lesion distally. A CT myelogram, on the other hand, has the specific benefit of delineating a nerve root avulsion *vs.* rupture. Plexus surgeons should be aware of this as a nerve rupture separates the distal trunk from a healthy nerve root that can be grafted. In contrast, an avulsion injury requires extra-plexal intervention.

Another inconsistency exists in the timing of surgical intervention. A survey completed by Belzberg *et al.* among experienced brachial plexus surgeons revealed an average recommended time for surgery of 2.4 months[2]. However, literature recommendations between 2 weeks up to 6 months have been reported[3-5]. Similarly, the time point after which surgeons recommend against nerve transfer/grafting ranges from six months up to one year, citing concerns over endplate viability, muscle atrophy and joint contractures[2-4,6,7].

One area of agreement is the priority of restoring elbow flexion and shoulder stability/abduction during the initial intervention. These two functions are imperative in restoring the ability to self-feed and in reestablishing rudimentary self-care. However, after this, there appear to be mixed preferences among surgeons for restoration of elbow extension, finger flexion, wrist motion, and hand sensation. Restoration techniques rely heavily on whether a C5 nerve root persists in a graftable state following acute PBPI. The frequency of a graftable C5 nerve root varies in the literature from 15% to 88%. With such a high incidence, most surgeons recommend brachial plexus exploration with a CT myelogram to ascertain C5 nerve root viability prior to finalizing the reconstructive plan[6,7]. Although less frequent, the same applies to the presence of a graftable C6 nerve root and below.

In the case of complete plexus injuries, practical nerve transfer options must come from outside of the plexus itself. This can include the spinal accessory nerve (SAN), the phrenic nerve (PN), the contralateral cervical seventh nerve root (CC7), intercostal nerves (ICN), and/or the hypoglossal nerve in a variety of donor-recipient combinations. Additional reconstructive options include tendon transfers, arthrodesis, and free functional muscle transfers (FFMT). Given the complexity of this clinical topic, the heterogeneity of PBPI, and the many permutations of treatment options that are available, multiple reasonable strategies may be employed in the treatment of PBPI. The following review is not meant to be exhaustive or prescriptive, but rather to describe three reasonable options that may provide a framework for surgeons who care for these challenging injuries.

TREATMENT METHODOLOGIES

Method 1: extra-plexal nerve transfers

The most referenced method for PBPI intervention involves nerve transfers from outside the injured brachial plexus, termed "extra-plexal transfers". According to recent polls of experienced brachial plexus surgeons, the SAN was the most utilized donor nerve, incorporated by 68% of surgeons during PBPI reconstruction, with the suprascapular nerve (SSN) being the most common recipient. The next most common donor was the intercostal nerves. Most often, these were transferred to the musculocutaneous nerve (MCN) and the median nerve. We will describe each of these techniques in further detail based on the function they aim to restore.

Elbow flexion

The favored technique for elbow flexion restoration, while using the SAN to SSN transfer for shoulder motion, is a direct nerve transfer of ICN to the MCN. A 2018 meta-analysis has shown improved function and decreased comorbidity of transferring two ICN over three or four[8]. To accomplish this, a curved incision along the sixth intercostal space from sternum to axilla is completed. Soft tissue is retracted superiorly, and the 5th and 6th ribs are exposed. ICN 5-6 are dissected from the inferior border of their corresponding rib and sectioned at the level of the costochondral junction. Next, a longitudinal incision is made along the proximal medial arm, posterior to the biceps muscle belly. The overlying fascia at the interval between the biceps and the coracobrachialis is incised, and the MCN, along with biceps motor branch, is identified. The MCN is transected at least 1 cm proximal to its insertion into the biceps allowing room for coaptation. The ICN is then reflected into the axilla to the MCN [Figure 1]. The shoulder is abducted to 90 degrees and externally rotated during repair to ensure a tensionless neurorrhaphy. This technique negates the need for an interposition nerve autograft along with donor morbidity and worse associated outcomes[9,10].

Functional results for this transfer have seen improvement over time, with 42%-90% of patients regaining elbow flexion to a British Medical Research Council (MRC) grading system, strength grade 3 or greater. One study showed nearly 40% of patients improved to grade 4[11-13]. In comparison, a meta-analysis from 2001 suggested that the SAN to MCN transfer produced a significantly lower likelihood of obtaining functional elbow flexion[12]. Furthermore, compared to the phrenic nerve transfer, there were no statistical differences in the final MRC grade or EMG results[14]. This is important to note as the ICN transfer does not require a nerve graft and eliminates the possibility of diaphragm paralysis/pulmonary complications with the sacrifice of the phrenic nerve.

Shoulder stabilization/abduction

When addressing shoulder stabilization and abduction, extra-plexal nerve transfers from the SAN to the SSN are preferred. For this procedure, a supraclavicular approach is used, and the proximal brachial plexus is explored. The target SSN is identified as branching from the upper trunk and traversing through the suprascapular notch. The SAN is isolated on the deep surface of the trapezius muscle. The SAN is dissected as distally as possible prior to transecting it to maximize length for coaptation[15-17]. Similarly, the SSN is transected as it branches from the upper trunk, preserving as much length as possible. A tension-free coaptation is then performed between the two nerves [Figure 2].

Previous studies have demonstrated encouraging outcomes, with 70%-90% returning good/excellent abduction results through the supraspinatus. Additionally, SAN to SSN fared significantly better than SAN to axillary nerve transfers in regaining functional shoulder abduction in 92% of patients compared to 69%[12,18].

Elbow extension

To restore elbow extension, ICN 3-4 to the triceps motor nerve is the procedure of choice in this reconstruction methodology. Meticulous dissection along the inferior border of the corresponding ribs from the costochondral junction to the axilla is required to isolate the longest ICN for transfer. The radial nerve motor branch to the long head of the triceps is identified as the radial nerve proper crosses distal to the teres major. Once isolated, this motor branch can undergo direct coaptation to ICN 3-4. Again, this is done with the arm abducted to 90 degrees and externally rotated to ensure tensionless coaptation[9,19].

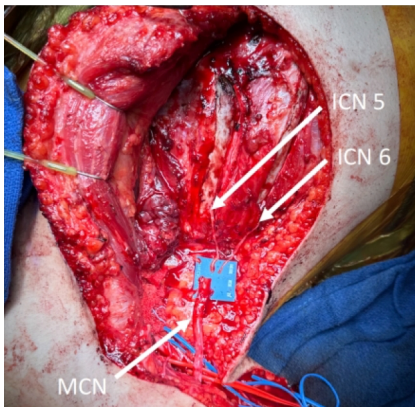

Figure 1. Submammary exposure for intercostal nerve (ICN) five and six transfer to the musculocutaneous nerve (MCN).

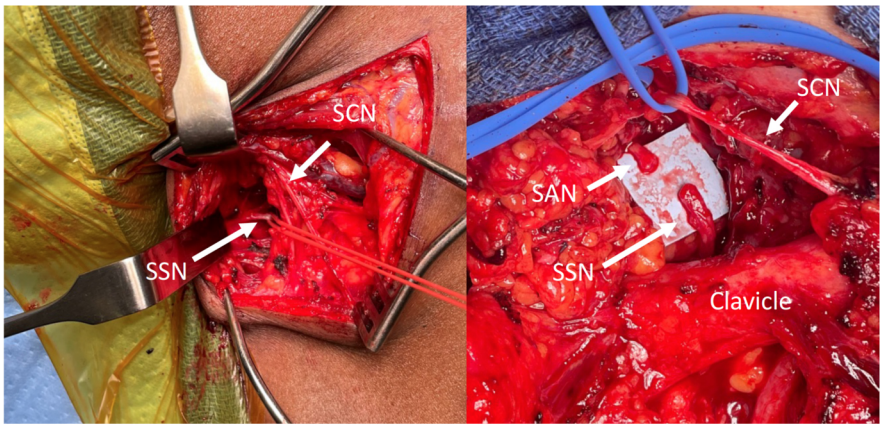

Figure 2. Supraclavicular approach for a direct end-to-end transfer of the spinal accessory nerve (SAN) and the suprascapular nerve (SSN). Supraclavicular nerve (SCN) and clavicle utilized as landmarks.

ICN 3-4 to the triceps motor branch has shown good results, with studies showing 47%-82% of PBPI patients regaining functional elbow extension of M3 or greater[9,19-21]. This suggested method incorporates two ICN branches for the triceps motor transfer. A study by Gao *et al.* demonstrated there was no added benefit, including a third ICN to this specific transfer[21]. An important caveat is that while this ICN transfer for elbow extension and the aforementioned ICN transfer for elbow flexion have demonstrated good clinical outcomes, both procedures cannot be performed on the same extremity. Intercostal motor nerves cannot be utilized to reinnervate opposing functions as simultaneous action of antagonistic muscle contraction will lead to poorer outcomes.

Hand function

Restoration of hand function remains a difficult obstacle for surgeons during the reconstruction of pan-plexus injuries. Many remain unconvinced that nerve transfers can reliably provide a more functional, stable hand than focal arthrodesis. In this method, arthrodesis of the wrist, first carpometacarpal joint and thumb interphalangeal joint is completed as a secondary surgery to create a stable platform for self-care.

Traditional wrist fusion techniques utilize a dorsal locking wrist fusion plate spanning the second or third metacarpal to the distal radius, placing the wrist in neutral to a slightly extended position. This may be augmented with bone autograft, which has been shown to achieve excellent fusion rates[22,23]. The first

carpometacarpal joint should be fused in approximately 35 of palmar abduction, 30 of radial abduction and 15 of pronation. The bone graft can be utilized to aid in fusion which can be achieved by a variety of methods including plates, compression screws, staples or wires[24-26]. Similarly, the thumb interphalangeal joint can be fused with several techniques, including tension bands, staples or compression screws across the decorticated articular surfaces. To optimize function, the thumb should be flexed between 15 and 35.

Several studies have shown exceptional fusion rates at each joint. Furthermore, following a patient self-assessment, 97% of polled PBPI patients were satisfied with wrist stability following fusion and 89% stated the fusion enhanced upper extremity function[27]. A similar study demonstrated subjective patient assessments of disability of the arm, shoulder, and hand (DASH) scores improved from 51 to 23, which was a statistically significant improvement. Additionally, following fusions, patients reported improved appearance, function, hygiene, and satisfaction[26].

Hand sensation

The intercostobrachial nerve (ICBN) is a stout sensory nerve providing cutaneous innervation to the axilla and proximal medial arm. This nerve can be utilized as a nerve transfer to the lateral cord contribution to median nerve (LCMN) to restore hand sensation. To accomplish this, the same submammary incision used to harvest ICN nerves is extended posteriorly along the lateral border of the pectoralis major. In this region within the second intercostal space, piercing superficially through the serratus anterior, the ICBN can be found traveling within subcutaneous fat into the axillary region. The dissection is carried through its terminal axillary branches, where the ICBN is released. The axillary incision is extended until it is in continuity with upper medial arm dissection. The pectoralis major is retracted superiorly, and the pectoralis minor is released off the coracoid as necessary to expose the infraclavicular plexus. The LCMN is identified at its origin and transected. The ICBN is then mobilized with as much length as possible and redirected into the infraclavicular space for direct coaptation[28].

Initial data for this technique has demonstrated impressive results, as 91% of patients registered the return of hand sensation[28]. This is a notable improvement to sensory rami of ICN or supraclavicular nerve reconstruction techniques that afford limited sensation recovery[29-33]. Anatomic data shows that at only 1,000 nerve fibers, and a diameter of 2.7 mm, the ICBN is much smaller than the average 5,300 nerve fibers and 3.7 mm diameter of its target LCMN. However, with more than double the average axon count of the sensory rami of ICN, the ICBN is considered by many to be a superior choice to ICN, even when incorporating two donor ICN[29].

Graftable C5

With an available C5 nerve root, sural nerve grafting to the anterior division of the brachial plexus upper trunk is recommended. This will provide innervation to the MCN and median nerve, aiming to restore elbow flexion, rudimentary grasp, and hand sensation. As above, restoration of shoulder stability will require a SAN to SSN transfer and elbow extension will require ICN 3-4 to triceps transfer[7].

Method 2: double free functional muscle transfer

Initially described by Doi out of Yamaguchi, Japan in the late 1990s, the use of the gracilis FFMT has slowly gained popularity[34,35]. Some authors have demonstrated greater improvements in elbow function over extra-plexal nerve transfers and this reconstructive technique has the benefit of providing secondary improvements to hand function[36-38].

Elbow flexion

The main function of the first FFMT is to maximize elbow flexion. The most common free muscle transfers involve the gracilis. This superficial muscle lies in the medial aspect of the thigh and is supplied by a branch from the profunda femoris, the medial femoral circumflex, and innervated by the obturator nerve. To harvest, the muscle must be released from its origin on the pubic symphysis and its insertion at the pes anserine. The medial femoral circumflex vessels and the obturator nerve can both be harvested at a length of up to 10 cm, which will facilitate easy anastomosis and coaptation at the transfer site. A skin paddle is often taken with the FFMT for postoperative monitoring [Figure 3]. Following the harvest of the gracilis muscle from the medial thigh, the proximal attachment to the clavicle is secured with suture anchors. This first FFMT is routed beneath the mobile wad proximal to the elbow joint and sutured to the extensor digitorum communis (EDC) tendon, allowing for elbow flexion and digit extension. The innervation of the gracilis muscle is accomplished by direct coaptation of the gracilis obturator nerve to the SAN. In addition, vascular microsurgical anastomoses complete a reliable artery and vein. These can include the thoracodorsal, transverse cervical, or thoracoacromial pedicles based on ease of reach and surgeon preference [Figure 4].

In the context of double FFMT, Doi showed good to excellent restoration of elbow flexion in 96% of patients[35]. Furthermore, the work by Maldonado *et al.* further demonstrated FFMT was able to restore M3/M4 elbow function in a greater percentage of patients than ICN to MCN transfers (68% *vs.* 42%)[37]. It is important to inform patients that similar to extra-plexal nerve transfers, reinnervation and initial functional return can be expected within six to nine months postoperatively[39].

Shoulder stabilization/abduction

Restoration of shoulder stability is once again prioritized in this reconstructive method. In the context of double FFMTs, traditional extra-plexal donors to the SSN and axillary nerve (i.e., the SAN and ICN) are being utilized for innervation of the free muscle flaps. With no other good donors for the SSN and axillary, tendon transfers have been historically performed. However, poorly reported outcomes have led to shoulder arthrodesis becoming a more universally accepted and implemented procedure[7,40]. When prepared with a subacromial corticocancellous graft, one study reported successful glenohumeral fusion rates as high as 94%. Following fusion, scapulothoracic abduction and arc of rotation averaged 57 and 50 degrees[41].

Elbow extension

To restore elbow extension, the ICN 3-4 to triceps motor transfer is again selected as in the previously described purely extra-plexal nerve transfer reconstructive method. While recent results for this transfer are promising, it is also important to note that results for these transfers are highly contingent on patient BMI. Several analyses have demonstrated that elevated BMI is inversely related to obtaining functional results[42,43].

Hand function

In the second stage of the technique, an additional FFMT from the contralateral gracilis is attached to the second and third ribs through a series of drill holes. This tendon is tunneled along the medial arm, beneath the lacertus fibrosus, and deep to the pronator teres creating a pulley during muscle contraction. A second forearm incision is made, and the terminal tendon is woven into the flexor digitorum profundus and flexor pollicis longus muscle belly, providing rudimentary grasp capabilities. Options for vascular anastomosis similarly include the regional vessels listed for the first FFMT, while innervation may be provided by ICN 5-6. Utilizing this approach, Doi published results where 65% of his patients achieved > 30 degrees of active finger arc of motion through this second FFMT technique[44].

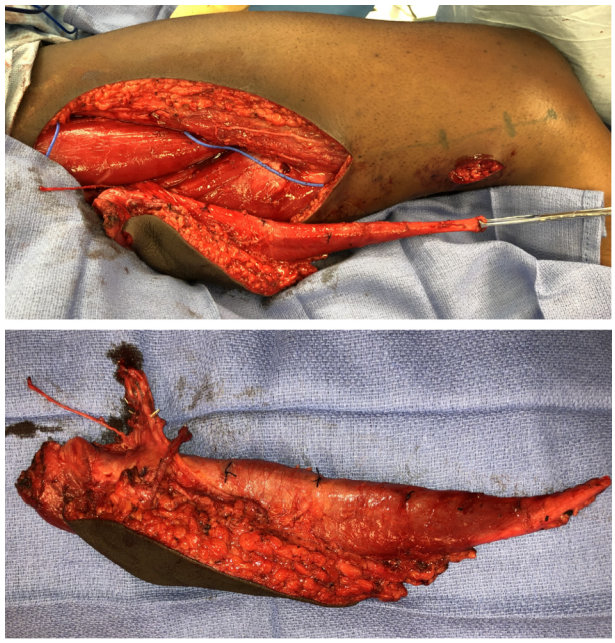

Figure 3. Medial thigh approach and final product of gracilis free functional gracilis muscle harvest. Gracilis FFMT utilizes medial femoral circumflex vessel, obturator nerve and a skin paddle.

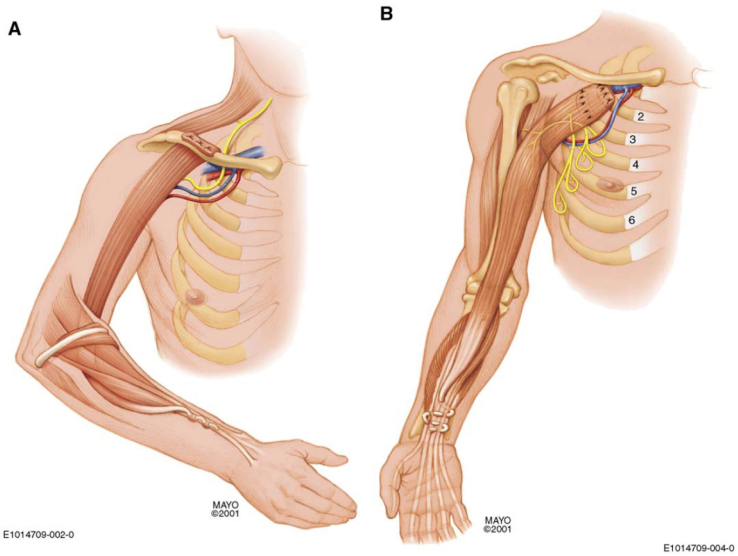

Figure 4. Modified Doi procedure for two-stage double free functional gracilis transfer. A) Stage 1 transfer, innervated by a SAN transfer, attempts to restore elbow flexion and wrist extension. B) Stage 2 transfer, innervated by ICN 5-6, augments elbow flexion while adding finger flexion. Additional ICN 3-4 transfers are performed for triceps neurotization. Copyright Permission: Bishop AT. Functional free-muscle transfer for brachial plexus injury. *Hand Clin.* 2005;21:91-102.

Hand sensation

In the same surgical setting as the second FFMT, sensory rami of the ICN are harvested and transferred to LCMN. These lateral sensory rami pierce the muscles of the lateral thoracic wall and divide into an anterior and posterior sensory branch. Within the submammary flap created for motor ICN harvest lies the sensory nerve branches. Recommended techniques involve the harvest of three sensory rami and direct coaptation with the LCMN.

Although results are sub-optimal, several studies have shown a reliable return of S2 sensation, which is meaningful as this is sufficient enough to provide protective sensation[31,32,45]. Ihara *et al.* demonstrated a more reliable restoration of this S2 level of sensation following ICN nerve transfers compared to supraclavicular sensory transfers[32].

Graftable C5

In the presence of a graftable C5 nerve root, authors who incorporate this technique prefer nerve autograft of C5 to the SSN or posterior division of the upper trunk to attempt to restore shoulder stability and abduction, as opposed to glenohumeral arthrodesis. The remainder of the reconstructive strategy follows as above with a SAN innervated primary FFMT for elbow flexion/wrist extension and a 5th and 6th ICN innervated secondary FFMT for elbow flexion/finger flexion, ICN 3-4 to triceps for elbow extension, and a sensory ICN 3 to LCMN[7].

Method 3: contralateral cervical seventh nerve root transfer

Originally described in 1991 by Gu *et al.* in Shanghai, China, the CC7 transfer has become another viable option for reconstruction in PBPI[46]. While ICN nerve transfers are considered effective options, they are challenging, time-consuming, large dissections with around only 1,300 myelinated axons per donor's nerve compared to the limited dissection and 24,000 axons consistent with a CC7 transfer[47]. Moreover, as most PBPIs occur in high-energy motor vehicle accidents, damage to the chest wall musculature, rib fractures, pulmonary contusions, or diaphragm injuries could be contraindications for and preclude the harvest of ICN.

Elbow flexion

To restore elbow flexion in this technique, the PN is harvested and coapted with the anterior division of the upper trunk. This aims to reinnervate the MCN motor branches to the biceps and brachialis. The PN can be exposed overlying the anterior scalene. It should be released as distally as possible prior to entering the chest cavity. Dissection and isolation of the anterior division of the upper trunk provide the target for this nerve coaptation.

Good/excellent biceps muscle strength was reported by 80% of patients following PN transfer[48]. A recent meta-analysis reported compelling data that PN to MCN transfer is superior to CC7 to MCN transfers in regards to reconstituting M3 or M4 elbow flexion[49]. One concern over this transfer is the pulmonary sequelae of harvesting the PN. However, a series from 2018 demonstrated that this is not a common complication, as no patient developed clinical respiratory problems postoperatively[50].

Shoulder stabilization/abduction

Shoulder abduction may again be accomplished with the transfer of SAN to SSN to reinnervate the supraspinatus and infraspinatus muscle bellies. As one of the most common nerve transfers in brachial plexus reconstruction, there are several studies that have reported encouraging outcomes with this transfer. One study demonstrated good/excellent supraspinatus strength in 79% of patients and good/excellent infraspinatus strength in 55% of patients[18]. Along with strength, the literature has shown that with appropriate coaptation, abduction range of motion recovery can surpass 60 degrees[51].

Elbow extension

This review has mentioned several nerve transfer techniques to reinnervate triceps motor function. While these have shown encouraging results, they are not commonly implemented. Alternatively, it has been an acceptable option to allow elbow extension to be controlled by gravity alone. Coordinated elbow positioning

thus will rely solely on whatever elbow flexion motor function is restored.

Hand function

The CC7 nerve root transfer is an integral part of this third reconstructive method. Targeting the median nerve, the CC7 transfer looks to restore hand function and sensation. The brachial plexus of the unaffected side is explored utilizing an incision just superior and parallel to the clavicle extending cranially along the posterior border of the sternocleidomastoid if needed. Branches of the external jugular vein are identified and preserved. Further dissection exposes the supraclavicular brachial plexus. The inferior muscle belly of the omohyoid is retracted and serves as a landmark for the C7 root. Once identified, CC7 is dissected distally until the anterior and posterior divisions of the middle trunk are exposed. The anterior trunk is sharply divided for transfer. For these CC7 limbs to reach their intended target, an interposition nerve autograft is required. To achieve this, sural, saphenous, or a reversed ipsilateral vascularized ulnar nerve graft can be harvested. Once collected, the CC7 donor is tunneled subcutaneously between the contralateral neck incision to a midaxial incision on the affected arm using a specialized nerve passer. In this midaxial dissection of the injured side, the median nerve is isolated for coaptation. Microsurgical coaptation of the anterior division of the middle trunk of CC7 to the median nerve is then completed[7,46]

In their study of 111 such transfers, Songcharoen *et al.* reported that 30% of patients attained finger and wrist flexion MRC grades of M3[52]. Yang *et al.* reported similar outcomes, with 36% achieving M3 finger flexion and 38% achieving M3 wrist flexion. M4 finger and wrist flexion strength were recovered by only 7% and 11% of patients, respectively[53]. While regaining hand motion is notoriously difficult, this technique has fallen out of favor in many regions of the world. Sammer *et al.* in 2012 published a series of fifteen patients who underwent hemi-CC7 to median nerve transfers with greater than two-year follow-up. Only three out of the fifteen showed electromyographic signs of reinnervation, but none were able to regain M3 grip strength[54]. These underwhelming outcomes have been replicated by other recent publications[55,56]. Regarding contralateral arm deficits following CC7 transfer, triceps and wrist extensor weakness occurred in less than 3% of patients. Sensory deficits were seen primarily in the index finger and were transient in nature, resolving within seven months[52]. This technique has a steep learning curve and its use is noticeably more prevalent in the region of its development[7,57].

Hand sensation

The CC7 transfer to the median nerve provides the secondary benefit of hand sensory reinnervation. A recent meta-analysis reported 56% of patients recovered S3 sensation[53]. These results surpass reported sensation recovery following supraclavicular and ICN sensory rami transfer to the median nerve[31,32].

Graftable C5

Strategy alterations when a viable C5 nerve root is present involve grafting C5 to the posterior division of the middle and lower trunk. This aims to reinnervate axillary and radial motor nerve function, reconstituting shoulder abduction, elbow extension, and wrist extension. Additional support for shoulder stability is obtained through the standard SAN to SSN transfer. PN can be similarly transferred for elbow flexion while CC7 to the median nerve as above for wrist flexion, digit flexion and hand sensation[7].

DISCUSSION

Pan-brachial plexus injuries present a challenging clinical problem with severe impairment of motor and sensory function to the upper extremity. In this review, we have presented three general approaches to performing reconstructions for these challenging patients [Table 1]. Most strategies aim to maximize shoulder and elbow function, while prioritization of hand function and sensation are variable. As seen in

Table 1. Summary representation of three general approaches to pan-brachial plexus injury reconstructions

	Method 1: extra-plexal nerve transfers	**Method 2: double free functional muscle transfer**	**Method 3: contralateral cervical seventh nerve root transfer**
Elbow Flexion	ICN 5-6 to MCN	FFMT Stage 1 (SAN) FFMT Stage 2 (ICN 5-6)	PN to ADUT
Shoulder Stabilization/ Abduction	SAN to SSN	Shoulder Arthrodesis	SAN to SSN
Elbow Extension	ICN 3-4 to Triceps	ICN 3-4 to Triceps	Gravity
Hand Function	Wrist, 1st CMC and thumb IP joint arthrodesis	FFMT Stage 1 to FFMT Stage 2	CC7 to Median
Hand Sensation	ICBN to LCMN	Sensory ICN to LCMN	CC7 to Median

Intercostal nerves (ICN), musculocutaneous nerve (MCN), spinal accessory nerve (SAN), phrenic nerve (PN), anterior division upper trunk (ADUT), the contralateral cervical seventh nerve root (CC7), suprascapular nerve (SSN), carpometacarpal (CMC), interphalangeal (IP), free functional muscle transfer (FFMT), intercostobrachial nerve (ICBN), lateral cord contribution to median nerve (LCMN)

this review, there is substantial heterogeneity within the group of patients with PBPI, and intraoperative flexibility is a necessity. The greatest variability in operative plans and strategies hinges on the status of C5 roots, which can provide valuable donor axons, in addition to the extra-plexal SAN, PN, ICN and CC7. It is important to note that in rare cases, a graftable C6 nerve root may be present. In this case, in a pan plexus injury with C5 and C6 roots viable, you could reconstitute shoulder motion with C5 to suprascapular/ PDUT and C6 to ADUT.

The literature has outlined several promising methodologies for the treatment of PBPI; however, there remains much progress to be made to support this patient population with more reliable and more restorative interventions.

DECLARATIONS

Authors' contributions

Completed writing of the manuscript, figure/table creation: Mitchell SM
Made substantial contributions to the conception and design of the study: Zumsteg JW
Performed literature review, as well as provided organizational and editorial support: Desai KA

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Not applicable.

Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Informed consent was obtained from all patients.

Consent for publication

Patients have signed a release of intra-operative clinical photos for educational use in publications.

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Review

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Functional muscle transfer for restoration of elbow flexion: a review

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Abstract

Elbow flexion is essential to help position the hand in space and for functional use of the upper extremity. Loss of elbow function can be secondary to many etiologies, including but not limited to brachial plexus injury, traumatic muscle loss, oncologic treatment, poliomyelitis or congenital absence of motor function. The end result is a significant functional limitation of the upper extremity. One method to address the loss of elbow flexion is the use of a functional muscle transfer. These transfers can be performed as pedicled rotational transfers or free functional muscle transfers. This article reviews functional muscle transfers for restoration of elbow flexion as a treatment option for patients with an otherwise unreconstructable extremity.

Keywords: Brachial plexus injury, elbow flexion, functional muscle transfer, pedicled latissimus dorsi transfer, free latissimus dorsi transfer, free gracilis transfer

INTRODUCTION

Elbow flexion is considered one of the most important upper extremity motions to accomplish activities of daily living. As such, loss of elbow flexion significantly limits upper extremity function. These injuries may be caused by obstetric or traumatic brachial plexus injuries, elbow flexor muscle loss due to trauma or oncologic resection, brachial plexus damage from oncologic resection or radiation treatment, poliomyelitis,

or congenital loss of elbow motion, as in arthrogryposis. When muscles required for elbow flexion (specifically biceps brachii and brachialis) are viable, nerve transfers or grafts may be an option for restoration of elbow flexion[1,2]. However, in cases of chronic injuries, muscle loss, atrophy, fibrosis, or extensive brachial plexus injury, nerve transfer or graft may not be sufficient to restore elbow flexion. In these cases, muscle transfer options should be considered[1]. Restoration of elbow flexion should be prioritized to restore function to the upper extremity, followed by finger flexion and finger extension[3]. In general, a single transferred muscle should provide a single function, though in the case of severe brachial plexus injury, this may be impossible due to limited numbers of donor nerves[3].

INDICATIONS

A pedicled latissimus transfer for restoration of elbow function was first described by Schottstaedt *et al.* in 1955 and Hovnanian in 1956[4,5]. Since that time, numerous studies have examined various options for functional muscle transfers. Free muscle functional muscle transfers were used by Manktelow and McKee in 1978 and Zuker *et al.* in 1991 to restore upper extremity function[6,7]. As techniques have progressed, functional muscle transfers can now be used for restoration of shoulder flexion, elbow flexion, elbow extension, finger flexion, finger extension, and thumb motion, either in isolation or in combination to restore muscle functions[8-10]

Patients who are being considered for functional muscle transfer must be motivated and willing to perform the extensive postoperative therapy and rehabilitation required for maximizing function. The recipient site requires full passive motion at the joint the transfer will move, in addition to a soft tissue bed conducive to muscle and tendon gliding. Healthy donor nerves and vessels are required. Functional muscle transfer should be used when no nerve or tendon transfer options are available. Patient age is an additional factor to consider -- while children are more likely to have successful restoration of motor function, there may be a mismatch in growth between the transferred muscle and the humerus, potentially leading to elbow contracture as the child reaches skeletal maturity[9]. Stevanovic and Sharpe recommend an age limit of 45 years old for free functional muscle transfers to optimize recovery of motor function[9] However, Doi *et al.* showed success after free functional muscle transfer in patients aged 62 years old and younger, while Ihara *et al.* had successful outcomes up to age 65[11,12]. Additional factors that are detrimental to outcomes, especially in free muscle transfers, include diabetes, vascular disease, cardiac disease, autoimmune conditions, smoking, and obesity[9].

DONOR MUSCLES

Several donor muscle options are available for restoration of elbow flexion. In the setting of vascular compromise from trauma or irradiation, a pedicled latissimus is preferred to restore elbow flexion without the need for an arterial anastomosis. The pedicled transfer is technically less challenging as it does not require a microvascular anastomosis. When a free flap is required, such as in the case of poor ipsilateral latissimus function, the gracilis is the most commonly used donor muscle. The gracilis has a redundant function in the lower extremity, making it more suitable for transfer than other lower extremity donor muscles. Its size and excursion make it ideal for restoration of upper extremity function, where it may be used in the forearm for restoring wrist or digit flexion or extension, or in the upper arm for restoring elbow flexion.

Latissimus dorsi (pedicled)

The latissimus dorsi muscle is a versatile option for restoring elbow flexion. It can be performed as a rotational muscle transfer or free functional muscle transfer from either the ipsilateral or contralateral side. Prior to surgery, the function of the latissimus muscle must be tested to ensure the transferred muscle can

adequately power elbow flexion, as described by Stevanovic *et al.*[13]. The latissimus dorsi is evaluated by palpating or gently pinching the muscle at the posterior axillary fold during adduction, extension, and internal rotation of the arm. The patient may also be asked to cough while the clinician holds the posterior axillary fold to palpate muscle contraction. Patients may also perform exercises with a physical therapist prior to surgery to maximize the strength of the latissimus dorsi muscle.

A pedicled transfer has the advantage of not requiring microsurgical anastomoses. The patient is placed in the lateral decubitus position, and the entire upper extremity, along with the lateral side from the shoulder girdle to the pelvis, is included in the surgical field. As described in prior studies, the defect in the anterior arm is measured along with the distance from the proximal aspect of the planned incision to the coracoid. This measurement is used to plan the skin paddle location relative to the axis of rotation to ensure coverage of the arm soft tissue[13]. The incision is made from the posterior axillary fold to the midpoint of the iliac crest, allowing identification and exposure of the latissimus dorsi [Figure 1]. With the latissimus in the stretched position (abduction, forward flexion, and external rotation of the arm), marking sutures may be placed at 5 cm intervals along the latissimus prior to mobilization to use for setting tension at the recipient site[13,14]. The latissimus dorsi muscle is then elevated off the thoracic wall, with care to avoid injury to the thoracodorsal artery pedicle, which enters the muscle 10-12 cm from the axilla[14]. The thoracodorsal nerve is also protected to maintain innervation to the transferred muscle [Figure 2]. The serratus anterior can be elevated along with the latissimus dorsi as a chimeric flap when a larger defect requires coverage, though this is not often the case in the upper extremity[15]. After pedicle mobilization, when a bipolar transfer is planned, the insertion on the humerus is released and sutures are placed in the tendon. In cases where a unipolar transfer is planned, the humeral insertion is left intact[1]. A bipolar transfer has the advantage of allowing proximal fixation to the coracoid, acromion, or lateral clavicle which can provide a more direct line of pull while stabilizing the shoulder[1].

To transfer the muscle to the anterior arm, the latissimus is tubularized. An incision is made over the coracoid, where the origin of the transferred muscle is planned. A subcutaneous tunnel is created connecting the posterior and anterior incisions, and the latissimus tendinous insertion is passed below the pectoralis major tendon to the coracoid where it is secured with sutures or suture anchors [Figure 3]. The remainder of the tubularized latissimus is passed to the anterior arm [Figure 4]. Care must be taken to avoid twisting the pedicle while passing the muscle, which may lead to flap ischemia[14]. To set the tension of the transferred latissimus, the muscle is stretched distally, the elbow is extended, and the distal latissimus is secured to the distal biceps tendon [Figure 5]. Since the marking sutures were placed with the latissimus in extension at the donor site, securing the muscle at the recipient site with the elbow in extension should be performed after re-establishing the 5 cm interval between marking sutures[14]. After securing the muscle, the shoulder and elbow are ranged to ensure there is not excessive tension on the pedicle. After closure, the shoulder is immobilized with an abduction pillow and the elbow is immobilized in 90 degrees of flexion[13,14].

Reported outcomes are shown in Table 1. The majority of patients achieved at least antigravity strength with pedicled latissimus transfer, with a low rate of reported complications. Of the studies reporting motor outcomes, 87% of patients achieved at least antigravity flexion strength. Range of motion was inconsistently reported in the literature. In the publications describing final elbow flexion, all but two reports revealed a mean postoperative elbow flexion of 90° or more.

Latissimus dorsi (free)

A free latissimus dorsi transfer allows more flexibility in use for restoration of elbow flexion, but it is technically more demanding than a pedicled transfer, given the need for microsurgical anastomoses. Either

Table 1. Reported outcomes of pedicled latissimus dorsi transfer. MRC: Medical Research Council muscle grade

Reference	Number of patients	Mean age (years)	Pathology	Elbow flexion MRC < 3	MRC 3	MRC ≥ 4	Mean postop elbow flexion (degrees)	Complications
Chuang *et al.*[16]	10	Not specified	Brachial plexus trauma	0	4	6	NR	None reported
Haas *et al.*[17]	2	20	Upper arm amputation	0	2	0	NR	None reported
Haninec *et al.*[18]	2	Not specified	Brachial plexus trauma	0	0	2	90 to 120	None reported
Kawamura *et al.*[19]	10	16.9	8 brachial plexus trauma 1 birth palsy 1 humeral fracture	0	2	8	111	None reported
Martin *et al.*[20]	4 (6 limbs)	Not specified	4 congenital 2 brachial plexus trauma	1	0	5	115	1 revision for muscle dehiscence 2 donor site seroma
Moneim *et al.*[21]	5	29.4	Brachial plexus trauma	0	1	4	92	None reported
O'Ceallaigh *et al.*[22]	1	35	Electrical burn	0	0	1	80	None reported
Schoeller *et al.*[23]	5	35.5	Upper arm amputation	0	2	3	NR	None reported
Stevanovic *et al.*[13]	4	18	Traumatic anterior compartment defect	0	0	4	134	1 infected hematoma
Vekris *et al.*[24]	9	Not specified	Brachial plexus trauma	0	9 (distribution not specified)		NR	2 skin necrosis and infection, distal insertion revision
Zancolli *et al.*[25]	8	Not specified	2 brachial plexus trauma 6 poliomyelitis	0	0	8	128	None reported
Hirayama *et al.*[26]	7	33.3	Brachial plexus trauma	Not specified	4 excellent, 2 good, 1 failure		NR (4 could move hand to mouth)	1 failure (fibrofatty degeneration of transferred muscle)
Rogachefsky *et al.*[27]	1	39	Traumatic anterior compartment defect	NR	NR	NR	135	None reported
Eggers *et al.*[28]	3	32	Brachial plexus trauma	0	0	3	132	None reported
Cambon-Binder *et al.*[29]	7	29	4 traumatic anterior compartment defect 3 brachial plexus trauma	1	1	5	91	None reported
Takami *et al.*[30]	2	22	Brachial plexus trauma	0	0	2	127	None reported
Hochberg *et al.*[31]	1	11	Electric burn	NR	NR	NR	"complete"	None reported
Germann *et al.*[32]	3	28	2 traumatic anterior compartment defect 1 upper arm amputation	1	0	2	105	None reported
Mordick *et al.*[33]	1	16	Traumatic anterior compartment defect	0	0	1	110	None reported
De Moraes *et al.*[34]	6	39	Brachial plexus trauma	1	4	1	73	None reported
Alshammari *et al.*[35]	1	30	Traumatic anterior compartment defect	NR	NR	NR	120	None reported
Lupon *et al.*[36]	1	25	Sarcoma	NR	NR	NR	140	None reported
Kameda *et al.*[37]	1	29	Brachial plexus trauma	0	0	1	135	None reported
Sood *et al.*[38]	1	77	Sarcoma	0	1	0	NR	None reported
Ma *et al.*[39]	20	43	Anterior compartment defect	NR	NR	NR	16 excellent (134)	3 flap edge necrosis and wound

							3 105+ 1 85	breakdown
Minami *et al.*[40]	1	32	Brachial plexus trauma	0	0	1	135	None reported
Bostwick *et al.*[41]	1	Not specified	Musculocutaneous injury, anterior compartment atrophy	0	0	1	"full"	None reported
Botte *et al.*[42]	5	Not specified	3 brachial plexus trauma 1 upper arm amputation 1 arm crush	NR	NR	3	109	Not specified
Stern *et al.*[43]	10	19	3 Erb palsy 3 brachial plexus trauma 1 sarcoma 3 anterior compartment defect	1	3	6	107	1 pedicle twisted and failed

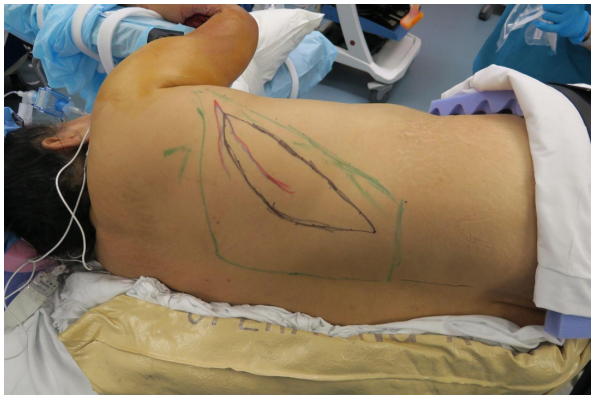

Figure 1. External anatomic landmarks for harvest of the latissimus dorsi flap.

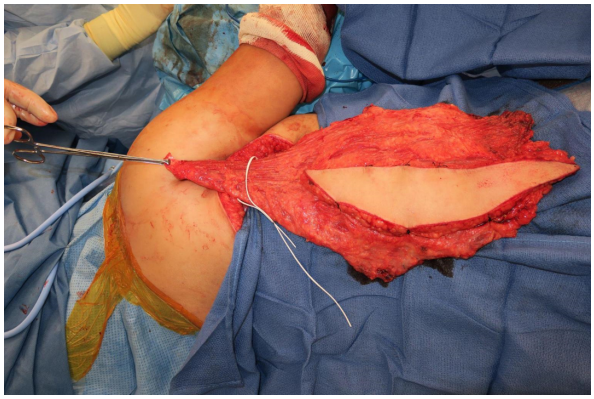

Figure 2. The pedicled latissimus dorsi flap after elevation.

the ipsilateral or the contralateral free latissimus may be used. The contralateral latissimus dorsi muscle is considered in the event of atrophy or injury to the ipsilateral muscle. The approach and surgical dissection are similar to that described for the pedicled rotational latissimus transfer [Figure 6]; however, the patient needs to be repositioned to a supine position after the muscle has been harvested[9]. The latissimus muscle may be neurotized by the distal branch of the spinal accessory nerve, intercostal nerves, contralateral C7

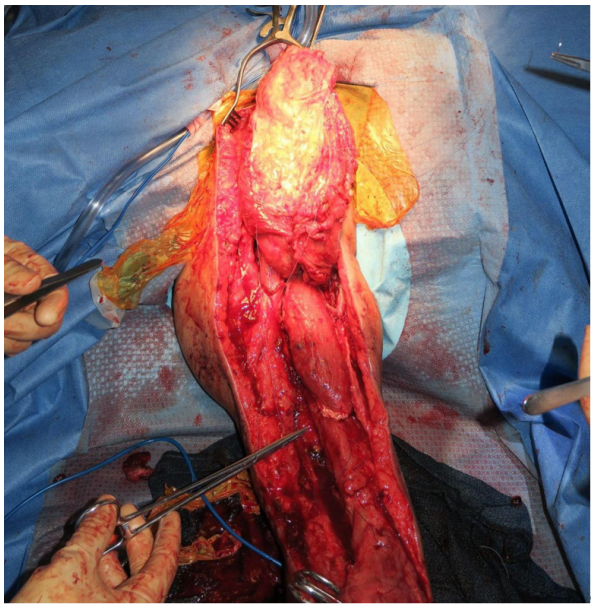

Figure 3. Rotation of the pedicled latissimus dorsi flap to the anterior arm.

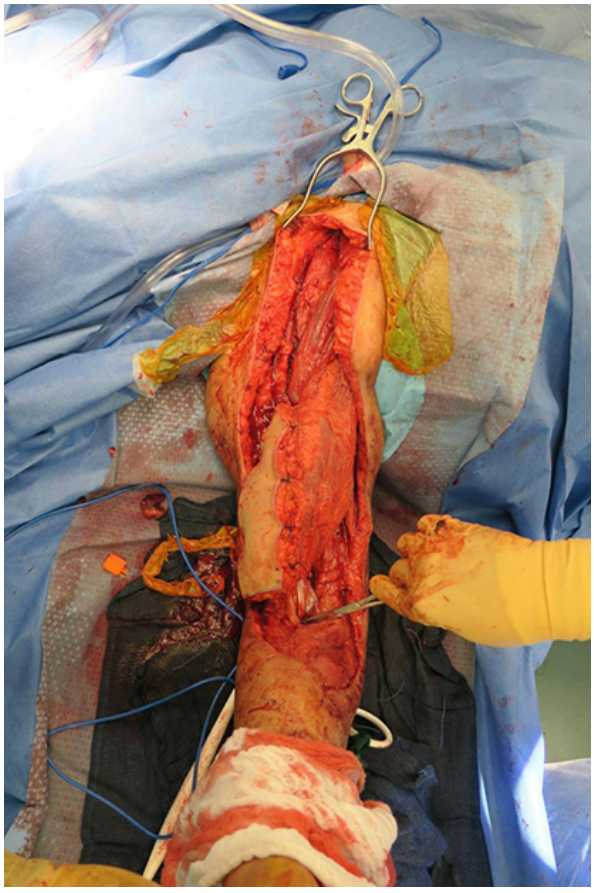

Figure 4. Planned inset of the pedicled latissimus dorsi flap to the anterior arm.

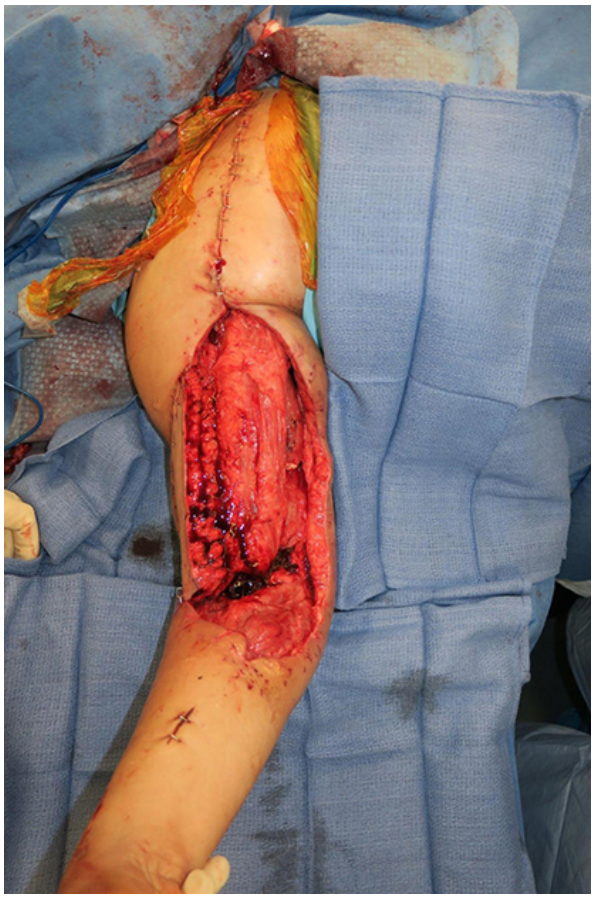

Figure 5. Inset of the pedicled latissimus dorsi flap.

nerve root, contralateral lateral pectoral nerve, or intact ipsilateral cervical nerve roots or intraplexal nerve branches[9,44]. Terzis *et al.* demonstrated increased postoperative mean muscle grade after neurotization of three intercostal nerves compared to two intercostals[44]. The thoracodorsal artery of the transferred latissimus may be anastomosed to the thoracoacromial artery, and the venae comitantes or cephalic vein may be used for venous outflow[9].

Reported outcomes are shown in Table 2. In the studies reporting individual patient motor grades, 83% achieved at least antigravity elbow flexion strength. Mean elbow flexion was 72°.

Gracilis

The gracilis muscle is a commonly used donor muscle for a variety of upper extremity reconstruction indications. Either the ipsilateral or the contralateral gracilis may be used. In cases of double free functional muscle transfer used to restore multiple functions in the extremity, bilateral gracilis can be harvested. However, the direction of the vascular pedicle makes the contralateral gracilis a more desirable option. The gracilis provides knee flexion, internal rotation, and thigh adduction, but is redundant and does not lead to functional deficits in the leg when harvested. Additionally, it may be harvested with a skin paddle, and its length and excursion provide an ideal replacement for elbow flexors. One important aspect to consider when harvesting the gracilis is the short pedicle length. Determining the estimated pedicle length prior to flap harvest is of utmost importance to determine if the gracilis is a viable option. In the event that the pedicle length is insufficient, a vein graft may be utilized.

Table 2. Reported outcomes of free latissimus dorsi transfer. MRC: Medical Research Council muscle grade

Reference	Number of patients	Mean age (years)	Pathology	Neurotization	Vessel anastomosis	Elbow flexion MRC < 3	MRC 3	MRC ≥ 4	Mean elbow flexion (degrees)	Complications
Terzis *et al.*[44]	37	Not specified	Brachial plexus trauma	15 intercostal 7 distal spinal accessory 4 cervical plexus 4 ipsilateral plexus 5 contralateral C7 1 contralateral lateral pectoral	Not specified	Mean muscle grade reported Intercostal 3.33 Distal accessory 3.05 Cervical plexus 2.8 Ipsilateral plexus 2.66 cC7 3.22 Contralateral lateral pectoral 2			NR	2 failures (in 42 transfers for elbow flexion and extension)
Doi *et al.*[45]	4	21	Brachial plexus trauma	Distal spinal accessory	Not specified	0	0	4	90	None reported
Doi *et al.*[46]	3	32	Brachial plexus trauma	Distal spinal accessory	Not specified	0	2	1	83	1 recurrence of nerve palsy
Terzis *et al.*[47]	20	Not specified	Brachial plexus trauma	Not specified	Not specified	NR	NR	NR	NR	3 hematomas 7 seromas
Minami *et al.*[40]	2	Not specified	Brachial plexus trauma	Intercostal nerves (4,5)	Not specified	0	2	0	90	None reported
Botte *et al.*[42]	3	Not specified	Brachial plexus trauma	Not specified	Not specified	2	1	0	23	Not specified

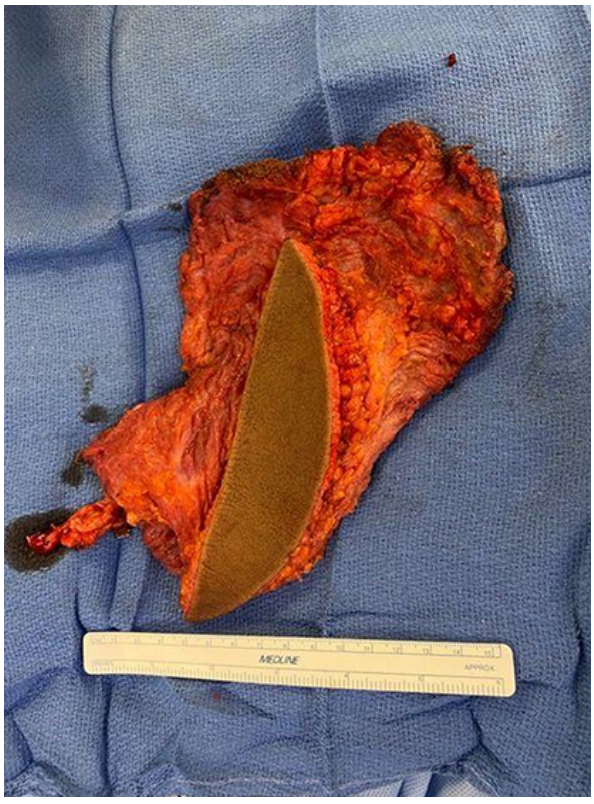

Figure 6. Harvested free latissimus dorsi flap.

The surgical technique for free gracilis transfer has been well described in the literature[3]. The patient is placed in a frog leg position and an incision is created along a line from the pubic tubercle to the medial femoral condyle [Figure 7]. If a skin paddle is used, it is created in the proximal third of the incision and just posterior to the line. The gracilis is the most posterior adductor muscle of the thigh, and is differentiated from the sartorius by its origin on the pubic tubercle, rather than anterior superior iliac spine. The medial thigh fascia is incised and kept with the gracilis muscle to improve independent gliding during contraction. The distal tendon is identified and separated from the other tendons of the pes anserinus. As with the latissimus transfer described above, marking sutures may be used at fixed intervals to help define resting length. Proximally, the neurovascular pedicle is identified 8 to 12 cm distal to the pubic tubercle [Figure 8]. The pedicle is divided after exposure of the recipient site and division of origin and insertion of the muscle to minimize ischemia time[3]. Prolonged ischemia time should be avoided -- Martins-Filho *et al.* demonstrated a trend towards improved results in terms of muscle strength with decreased ischemia time[48]. Additionally, they noted a trend towards poorer functional outcomes with only one venous anastomosis compared to two[48].

The recipient site is prepared with an extensile anterior arm approach including exposure of the lateral clavicle, acromion, and coracoid proximally, and the medial epicondyle and antecubital fossa distally [Figure 9]. The gracilis is attached proximally to the lateral clavicle and acromion or coracoid via suture anchors or bone tunnels. By fixing the muscle proximally first, the muscle can then be stretched to its resting length and the position of arterial anastomosis can be planned to avoid undue tension on the pedicle. Arterial anastomosis may be performed with the thoracoacromial, lateral thoracic, or subscapular arteries in an end-to-end fashion, or the brachial artery in an end-to-side fashion [Figures 10][3]. After anastomosis, distal gracilis is secured to the distal biceps tendon or the radius or ulna, with the restoration of the distance between the previously placed marking sutures while the elbow is held in extension [Figure 11][49]. The orientation of the gracilis may be reversed in the event of prior surgery near the brachial plexus, which allows the anastomosis and nerve coaptation to be performed more distally, out of the region of prior scarring[50,51].The gracilis may also be used for finger flexion when attached distally to the flexor digitorum profundus (FDP) and flexor pollicis longus (FPL), or finger extension when attached distally to the extensor digitorum communis (EDC). Maldonado *et al.* showed that distal tendon attachment (to FDP or FPL tendons with flexor carpi radialis [FCR] tendon autograft) was associated with superior elbow flexion strength and range of motion compared to biceps tendon reattachment[52]. Bertelli showed the gracilis muscle flap can be combined with a Steindler flexorplasty, wherein the flexor-pronator mass origin is transferred proximally to the anterior humerus to improve elbow flexion, to increase strength and decrease time to elbow flexion[51].

Following distal fixation, nerve coaptation is performed. The gracilis may be innervated by a variety of donor nerves, including the distal spinal accessory nerve, intercostal nerves, fascicles of the ulnar or median nerve, the phrenic nerve, or contralateral medial pectoral nerve[3]. In cases where elbow flexion was lost due to anterior compartment trauma or resection, the original musculocutaneous nerve may be used. The authors prefer neurotization with the distal spinal accessory nerve. The spinal accessory nerve is identified after detaching the trapezius insertion from the clavicle and the acromion. The distal branch of the spinal accessory nerve is divided and a coaptation is performed to the motor branch of the gracilis with microsurgical technique.

Reported outcomes are shown in Table 3. The majority of patients, 79% of those reported, achieved antigravity strength or stronger with free gracilis transfer, with a low rate of reported complications.

Table 3. Reported outcomes of free gracilis transfer. MRC: Medical Research Council muscle grade

Reference	Number of patients	Mean age (years)	Pathology	Neurotization	Vessel anastomosis	Elbow flexion MRC < 3	MRC 3	MRC ≥ 4	Mean elbow flexion (degrees)	Complications
Silva *et al.*[53]	87	30	Brachial plexus trauma	45 spinal accessory (4 using sural nerve graft) 10 intercostal nerves (3 with graft) 8 median nerve fascicles 22 ulnar nerve fascicles 2 phrenic nerve	Not specified	32	30	25	NR	3 loss of skin monitoring signal 1 hematoma compressing pedicle 4 infections
Ikuta *et al.*[54]	1	11	Brachial plexus trauma	Intercostal nerves (3, 4)	Lateral thoracic artery, venae comitantes	0	1	0	90	None reported
Krakauer *et al.*[55]	3	30	Brachial plexus trauma	Intercostal nerves (3, 4)	Not specified	1	1	1	72	None reported
Chuang *et al.*[49]	38 (34 gracilis, 4 rectus femoris, results combined)	25	35 brachial plexus trauma 3 traumatic anterior compartment defect	31 intercostal nerves (3 nerves in 23, 2 nerves in 8) 4 glossopharyngeal nerve 3 musculocutaneous nerve (biceps loss, intact plexus)	Lateral thoracic artery or thoracodorsal artery	10 (results combined)		28	NR	None reported
Chuang *et al.*[16]	16	Not specified	Brachial plexus trauma	Intercostal nerves	Not specified	3	6	7	NR	None reported
Barrie *et al.*[56]	22 (15 single gracilis; 7 double gracilis)	25	Brachial plexus trauma	5 spinal accessory 8 intercostal (3, 4) 1 intercostal (4, 5) 1 musculocutaneous 7 combination (spinal accessory and intercostal, double transfers)	7 thoracoacromial 9 brachial 2 axillary 1 lateral pectoral 3 combination (thoracoacromial and brachial)	2	4	16	105	5 failures
Kay *et al.*[57]	33	Median 4.8 (20 children) Median 34 (13 adults)	13 obstetric brachial palsy 12 adult brachial plexus trauma 4 arthrogryposis 2 sarcoma 1 polio 1 radial dysplasia	18 intercostal 12 fascicles of ulnar nerve 2 spinal accessory with graft 1 thoracodorsal	Brachial artery or posterior branch to triceps; vena comitans of brachial artery	6 adults 3 children	7 adults 17 children		NR	3 microvascular failures 6 hematomas 3 infections 1 recipient dehiscence

Sungpet *et al.*[58]	3	28	Brachial plexus trauma	Ulnar nerve fascicle	Brachial artery; cephalic vein	0	0	3	110	None reported
Armangil *et al.*[59]	16	27	Brachial plexus trauma	12 spinal accessory nerve 2 medial pectoral 1 phrenic 1 intercostal (4,5,6)	Thoracoacromial artery, vena comitantes or cephalic vein	5	11		63	2 flap failures
Chen *et al.*[60]	39	27	Brachial plexus trauma	Spinal accessory nerve	Brachial artery, axillary artery, or subclavian artery	2	8	29	107	1 flap failure 1 donor site hematoma
Dodakundi *et al.*[61]	36	29	Brachial plexus trauma	Spinal accessory nerve	Thoracoacromial artery, cephalic vein	0	11	25	119	None reported
Doi *et al.*[62]	34	23	Brachial plexus trauma	Spinal accessory nerve	Not specified	NR	NR	NR	118	None reported
Elzinga *et al.*[63]	2	20	Brachial plexus trauma	Spinal accessory nerve	Thoracoacromial artery and vein	0	0	2	NR	None reported
Hosseinian *et al.*[64]	12	25	Brachial plexus trauma	Contralateral medial pectoral nerve	Brachial artery, basilic vein	4	1	7	25	2 unsuccessful
Yang *et al.*[65]	47	26	Brachial plexus trauma	45 spinal accessory nerve 2 phrenic nerve	Brachial artery, axillary artery, or subclavian artery; comitantes vein	5	1	36	106	2 thrombosis with flap failure (immediately received second transfer)
Maldonado *et al.*[52]	39 (29 biceps attachment, 10 distal attachment)	34 biceps attachment 25 distal (FDP/FPL) attachment	Brachial plexus trauma	13 intercostal 26 spinal accessory	Thoracoacromial artery; cephalic vein	10 (biceps) 0 (FDP/FPL)	9 (biceps) 1 (FDP/FPL)	10 (biceps) 9 (FDP/FPL)	111 (biceps) 127 (FDP/FPL)	None reported
Potter *et al.*[66]	13	32	Brachial plexus trauma	Spinal accessory	Thoracocromial artery; cephalic vein	0	0	13	102	1 venous congestion
Nicoson *et al.*[67]	13	34	Brachial plexus trauma	4 spinal accessory 1 spinal accessory+ intercostal+ rectus abdominis 1 intercostal 3 intercostal + rectus abdominis 1 medial pectoral nerve 2 FCU fascicle of ulnar nerve 1 thoracodorsal	Thoracoacromial artery or brachial artery	3	4	6 (mean 4.5 MPN, 4 TD, 3.3 intercostal, 3 SAN, 3 SAN + ICN, 2 FCU)	NR	None reported
Estrella *et al.*[68]	42	29	Brachial plexus trauma	41 spinal accessory 1 intercostal nerve	Thoracoacromial artery; cephalic vein	5	9	28	107	4 flap failures 1 peroneal nerve palsy

										3 wound dehiscence 3 revision tensioning 2 skin flap necrosis 2 transient sensory disturbance at knee
El-Gammal *et al.*[69]	15	102.5 months	Obstetric brachial plexus palsy	Intercostal nerves (4,5) Phrenic nerve Spinal accessory nerve	Not specified	0	1	14	104	None reported
Chim *et al.*[70]	12	14	Brachial plexus trauma	Intercostal nerves Spinal accessory nerve	Not specified	1	3	8	79 (mean arc)	2 elbow flexion contractures 2 arterial thrombosis (stage 2, double transfer) 1 wound dehiscence
Coulet *et al.*[71]	12	26	Brachial plexus trauma	Intercostal nerves	Not specified	2	0	10	128 (partial injuries) 103 (complete injuries)	2 failures
Sochol *et al.*[72]	1	5	Arthrogryposis	Branch to pectoralis major (lateral pectoral)	Thoracoacromial artery and vein	0	0	1	140	None reported
Martins-Filho *et al.*[48]	23	33	Brachial plexus trauma	18 spinal accessory 3 intercostal nerve	18 thoracoacromial artery 3 thoracodorsal artery 1 brachial artery	5	9	9	NR	None reported
Bertelli *et al.*[51]	24	34	Brachial plexus trauma	Median nerve fascicles or ulnar nerve fascicles	Radial artery; cephalic vein	1	7	16	108	1 arterial occlusion 1 arterial wall rupture 1 epicondyle fracture (during Steindler flexorplasty) 4 hematoma
Madura *et al.*[73]	17	13	Brachial plexus trauma	Spinal accessory nerve	Thoracoacromial artery; cephalic vein	0	3	14	119	3 bowstringing
Cho *et al.*[74]	38	28	Brachial plexus trauma	18 spinal accessory nerve 20 motor fascicles of ulnar nerve	Thoracoacromial artery and vein	12	9	17	NR	2 vascular impairment of skin paddle 2 infection
Nath *et al.*[75]	24	10 obstetric 27 traumatic	13 obstetric plexus palsy 11 brachial plexus trauma	18 median nerve branch 5 radial nerve branch 1 ulnar nerve branch	Not specified	8	11	5	NR	NR
Kimura *et al.*[76]	8	31	Brachial plexus trauma	Spinal accessory or intercostal nerve	Anterior humeral circumflex artery, deep	4	0	4	NR	None reported

					brachial artery, or thoracoacromial vessels					
Potter *et al.*[66]	17	33	Brachial plexus trauma	Spinal accessory nerve	Thoracoacromial artery; cephalic vein	2	0	15	92	1 exploration for venous congestion
Yavari *et al.*[77]	63	23	Brachial plexus trauma	Contralateral medial pectoral nerve + sural graft	Brachial artery	16	26	21	NR	2 flap failures
De Rezende *et al.*[78]	21	32	Brachial plexus trauma	Ulnar nerve fascicle	Thoracoacromial artery and vein	3	5	13	86	None reported

Rectus femoris

An alternative option for free functional muscle transfer to restore elbow flexion is the use of rectus femoris. This may be useful when the gracilis muscles are unavailable for use, whether as a result of injury or after use for a different function. The rectus femoris is a fusiform muscle that generates more force than the gracilis, and may lead to stronger elbow flexion, though comparative studies are lacking[79].

An incision is created along the anterior thigh in line from the anterior inferior iliac spine to the patella. A skin paddle may be incorporated into the incision. The rectus femoris and sartorius muscles are identified below the fascia, and the sartorius is retracted medially. As mentioned above, marking sutures may be placed at fixed intervals to define the normal resting length of the muscle. The descending branch of the lateral femoral circumflex vessels and branches of the femoral nerve are identified medial to the muscle. The rectus femoris is then elevated from distal to proximal and lateral to medial with care to avoid injury to the pedicle. Distally, the muscle is divided 6cm above the patella to preserve the quadriceps tendon[79].

The recipient site is prepared as explained previously. The proximal end of the muscle is fixed to the coracoid or lateral clavicle and acromion with suture, suture anchors, or bone tunnels. As with the free latissimus and gracilis transfers, the pedicle anastomosis can be performed to an available artery in an end-to-end or end-to-side fashion. Similarly, tension is set with the elbow in extension to restore the distance between the previously placed marking sutures and the distal end of the transferred rectus is fixed to the biceps tendon. The donor nerve of choice is then sutured to the motor branch of the femoral nerve innervating the rectus femoris.

Reported outcomes are shown in Table 4. While there are fewer reported cases using a rectus femoris muscle transfer compared to latissimus or gracilis transfer, the results are promising. In the studies which reported individual distributions of motor grades, 83% achieved at least antigravity strength.

Medial gastrocnemius

The medial gastrocnemius muscle is less frequently used as a free functional muscle transfer option for restoration of elbow flexion, which may be used if other

Table 4. Reported outcomes of free rectus femoris transfer. MRC: Medical Research Council muscle grade

Reference	Number of patients	Mean age (years)	Pathology	Neurotization	Vessel anastomosis	Elbow flexion MRC < 3	MRC 3	MRC ≥ 4	Mean elbow flexion (degrees)	Complications
Chuang *et al.*[16]	1	Not specified	Brachial plexus trauma	Intercostal nerves	Not specified	0	1	0	NR	None reported
Akasaka *et al.*[80]	11	Not specified	Brachial plexus trauma	Intercostal nerves (3, 4)	Anterior circumflex humeral artery or profunda brachii artery; cephalic vein or brachial vena comitantes	3	8	0	80+ in 8 100+ in 3	2 failures, thrombosis
Wechselberger *et al.*[79]	1	22	Brachial plexus trauma	Spinal accessory nerve	Brachial artery and vein	0	0	1	110	None reported
Doi *et al.*[81]	7	25	Brachial plexus trauma	Spinal accessory nerve	Thoracoacromial artery; cephalic vein	NR	NR	NR	34	3 skin paddle necrosis
Terzis *et al.*[44]	7	NR	Brachial plexus trauma	4 contralateral C7 2 intercostals 1 cervical plexus	Not specified	Mean muscle grade reported Intercostal 2.77 Cervical plexus 2.33 cC7 3.67			NR	None reported

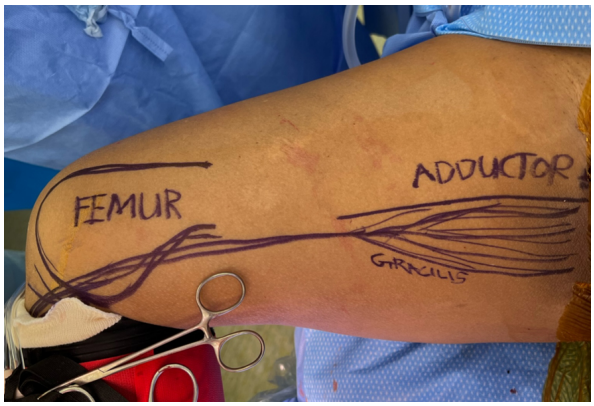

Figure 7. The relevant anatomy and planned incision for harvest of the gracilis muscle.

donors are unavailable. The technique is described by de Moraes *et al.*[34] An incision is made from 8 cm proximal to the popliteal crease to 10 cm proximal to the medial malleolus. The septum between the two heads of the gastrocnemius muscle is identified and dissected, retracting the lesser saphenous vein and sural nerve laterally. Marking sutures may be placed at a fixed distance. The medial sural artery and nerve to the medial gastrocnemius, branching from the tibial nerve, are identified between the heads of the gastrocnemius. Proximally, the medial gastrocnemius muscle is divided at the medial femoral condyle, and distally at the musculotendinous junction[34]. Transfer to the recipient site is performed as described above. De Moraes *et al.* describe functional outcomes similar to pedicled latissimus transfer, where all patients achieved at least antigravity strength [Table 5][34].

DONOR VESSELS

The choice of the donor artery and vein to supply the transferred muscle is variable and depends on

Table 5. Reported outcomes of free medial gastrocnemius transfer. MRC: Medical Research Council muscle grade

Reference	Number of patients	Mean age (years)	Pathology	Neurotization	Vessel anastomosis	Elbow flexion MRC < 3	MRC 3	MRC ≥ 4	Mean elbow flexion (degrees)	Complications
De Moraes *et al.*[34]	7	28	Brachial plexus trauma	Ulnar nerve fascicle Intercostal nerve Spinal accessory nerve	Thoracodorsal artery; thoracodorsal vein and cephalic vein	0	3	4	83	None reported

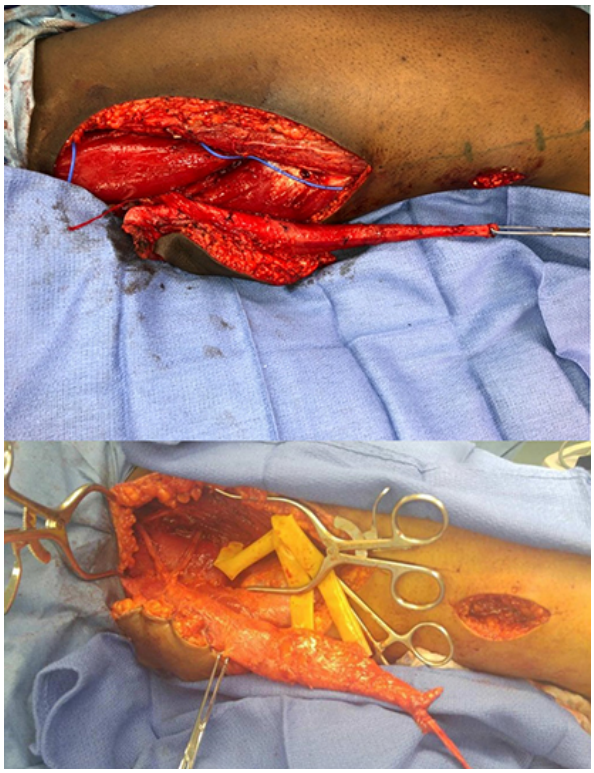

Figure 8. Harvest of the gracilis muscle for free functional muscle transfer.

individual anatomy, the length of the harvested pedicle, and the presence of pre-existing injuries. The anastomosis may be performed in an end-to-end or end-to-side fashion, depending on the chosen vessels. A meta-analysis comparing end-to-end and end-to-side anastomoses showed no significant difference in flap failure[82]. For transfers to restore elbow flexion, the thoracoacromial artery (end-to-end) or brachial artery (end-to-side) are commonly chosen vessels due to proximity and size match [Tables 1-4]. Most importantly, ischemia time and tension on the pedicle should be minimized[48].

DONOR NERVES

As described above, there are a variety of options for innervation of functional muscle transfers for brachial plexus injuries. Mahmood *et al.* evaluated axon counts in the nerve to the gracilis and found that the spinal accessory or two or three intercostals are all sufficient for transfer to the nerve to the gracilis[83]. When the musculocutaneous nerve or other intraplexal nerves are present, these should be used to innervate the transferred muscle, such as when free functional muscle transfer is used for treating anterior compartment

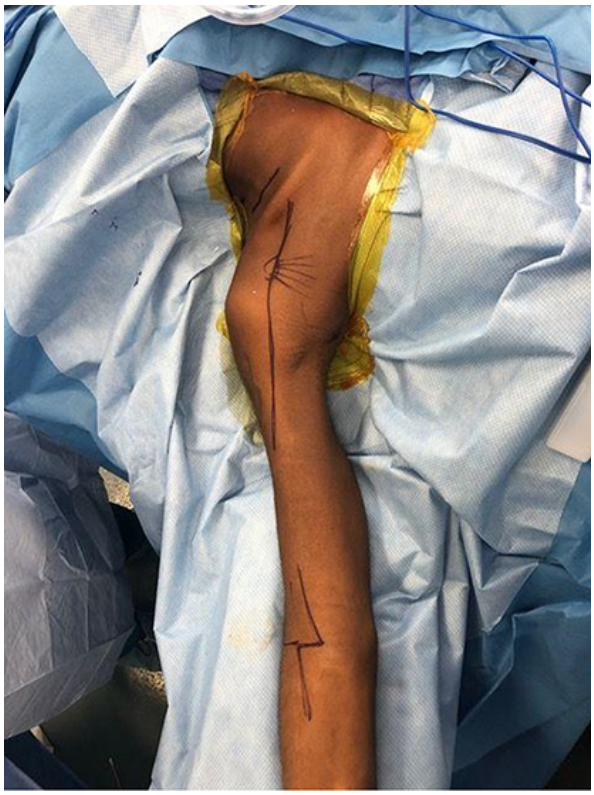

Figure 9. Planned incision for transfer of the gracilis muscle to the anterior arm.

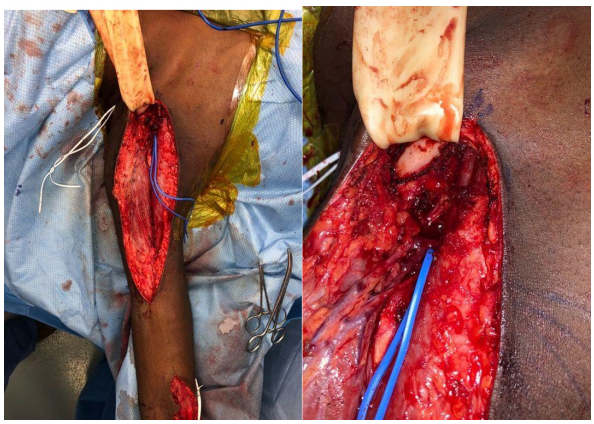

Figure 10. Dissection of the donor artery in the anterior arm for transfer of the gracilis muscle.

loss[49]. Silva *et al.* compared gracilis muscle transfers innervated by the spinal accessory nerve, intercostal nerves, median nerve fascicles, ulnar nerve fascicles, or phrenic nerves. Success rates were similar between groups, with an overall success rate of 65% achieving at least grade M3 strength[53]. Nicoson *et al.* performed gracilis transfers with spinal accessory nerves, intercostal nerves (with or without rectus abdominis nerves), medial pectoral nerves, thoracodorsal nerves, and fascicle of ulnar nerves. They found a mean recovery strength of M4.5 for medial pectoral, M4 for thoracodorsal, M3.3 for intercostal, M3 for spinal accessory, and M2 for ulnar nerve fascicles, but had limited numbers[67]. Cho *et al.* compared neurotization of gracilis transfers by spinal accessory nerves or motor fascicles of the ulnar nerve, with 83% of those with spinal

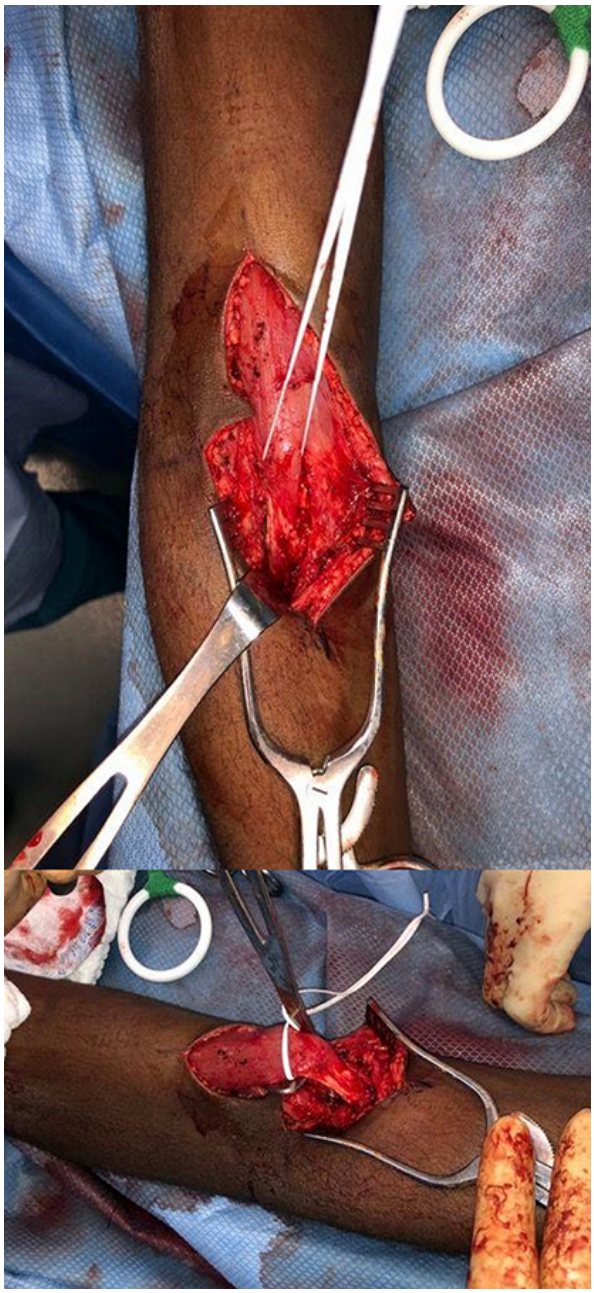

Figure 11. Dissection of the distal biceps tendon for the distal attachment of the transferred gracilis muscle.

accessory nerve transfer and 55% of those with ulnar nerve fascicles reaching M3 strength or greater, but the difference was not statistically significant[74]. Chuang *et al.* showed that transferring three intercostal nerves leads to earlier recovery of muscle strength and higher final power compared to those with two transferred intercostal nerves[49]. This group showed poorer results with the use of the spinal accessory nerve to innervate the free functional muscle transfer -- 0% achieving M4 strength (compared to 78% of those with three intercostal nerves treated). However, they note the use of a nerve graft interposition when using the spinal accessory nerve to achieve the appropriate length of the transferred nerve[49]. Kimura *et al.* also noted a higher number of patients reaching M4 strength when the nerve transfer was performed without an interpositional nerve graft[76]. Terzis and Kostopoulos prefer the use of latissimus dorsi or rectus femoris

transfers in most patients because of the increased strength at recovery and inadequate muscle bulk of the gracilis[44].Similar to Chuang *et al.*, Terzis and Kostopoulos also demonstrated increased strength after latissimus dorsi neurotization with three intercostal nerves compared to two[44].

Oliver *et al.* performed a systematic review and meta-analysis to compare free functional muscle transfers (gracilis, rectus femoris, and latissimus dorsi) innervated by either intercostal or spinal accessory nerves. They found no difference in success rate or muscle strength, with nearly 65% achieving at least grade M3 strength[84]. Despite the success seen with these nerve transfers, one should consider potential risks and complications. Though the use of intercostal nerves is commonly reported, the proximity to vital structures should be noted, as there have been reported pleural tears and effusions, acute respiratory distress syndrome, seroma formation, and rib fractures[85].

POSTOPERATIVE PROTOCOL

Following functional muscle transfer, patients are monitored closely for signs of flap failure, whether the transfer is pedicled or free. A skin paddle is useful in determining if early signs of flap failure are present, and may provide more successful flap salvage in the event of arterial thrombosis or venous congestion[86]. After functional muscle transfer, rehabilitation is vital to optimizing patient outcome. Typically, patients are placed in a splint postoperatively with the elbow in flexion for 1-6 weeks, following which patients begin passive therapy exercises to avoid contracture[3]. Doi *et al.* performed a trial with patients undergoing double free gracilis muscle transfer, comparing those with 6 weeks of immobilization to those with early passive mobilization after 1 week of splinting. They showed that none of the patients in the latter group required tenolysis, compared to 32% in the immobilization group, but the final range of motion was similar[62]. Following muscle reinnervation, retraining is required to train the patient to use the new elbow flexor properly.

CONCLUSIONS

Functional muscle transfer is a viable option to restore elbow flexion in the setting of brachial plexus injury, traumatic muscle loss, oncologic treatment, poliomyelitis, or congenital absence of motor function. Options include pedicled or free functional muscle transfers. Functional muscle transfer has the potential to significantly improve upper extremity function.

DECLARATIONS

Authors' contributions

Performed literature review: Vakhshori V
Prepared manuscript: Vakhshori V, Azad A

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Ethical approval was not applicable, and consent to participate was obtained.

Consent for publication

Consent for publication was obtained.

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Journal articles by individual authors	Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med* 2011;364:412-21. [PMID: 21247310 DOI: 10.1056/NEJMoa1008108]
Organization as author	Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002;40:679-86. [PMID: 12411462]
Both personal authors and organization as author	Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol* 2003;169:2257-61. [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]
Journal articles not in English	Zhang X, Xiong H, Ji TY, Zhang YH, Wang Y. Case report of anti-N-methyl-D-aspartate receptor encephalitis in child. *J Appl Clin Pediatr* 2012;27:1903-7. (in Chinese)
Journal articles ahead of print	Odibo AO. Falling stillbirth and neonatal mortality rates in twin gestation: not a reason for complacency. *BJOG 2018*; Epub ahead of print [PMID: 30461178 DOI: 10.1111/1471-0528.15541]
Books	Sherlock S, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub; 1993. pp. 258-96.
Book chapters	Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. pp. 93-113.
Online resource	FDA News Release. FDA approval brings first gene therapy to the United States. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm. [Last accessed on 30 Oct 2017]
Conference proceedings	Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.
Conference paper	Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. pp. 182-91.
Unpublished material	Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci U S A*. Forthcoming 2002.

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9.1 Initial check

9.1.1 Initial manuscript check

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