Emerging Techniques for Nerve Repair: Nerve Transfers and Nerve Guidance Tubes

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Peripheral nerve injury is a serious health concern for society, affecting 2.8% of trauma patients, many of whom acquire life-long disability.[52] For example, approximately 360,000 people in the United States experience upper extremity paralytic syndromes yearly, resulting in 8,648,000 and 4,916,000 restricted activity days and bed/disability days, respectively.[23] Because peripheral neurons spontaneously sprout new axons after injury, patients with milder severity nerve injuries improve spontaneously, but many patients have more severe injuries that have a poor natural history to recover.[16] Most severe injuries are associated with nerve injury gaps or lengthy scar within the nerve that prevents regenerating axons from effectively innervating the distal nerve stump.[44] These are managed with a nerve repair of the divided nerve or, for the usual scenario of gaps longer than 1 cm or scar segments that need to be resected, placement of interposed nerve grafts.[47] The nerve grafts provide a pathway for regenerating axons from the proximal nerve stump to innervate the distal one.[45] However, recovery after nerve graft repair is limited by incomplete and non-specific regeneration and variable clinical results.[27,43]

Based on sound and solid experimental literature over the past half century, peripheral nerve surgeons in the past three decades have been increasingly using alternative techniques to interposed nerve autografts in an attempt to improve outcomes. For lengthy nerve injuries, or for those very proximal ones in which the spinal nerve root has been or are likely avulsed from the spinal cord, the use of nerve transfers has emerged.[35] For short injury gaps, surgeons are using nerve guidance tubes in place of nerve grafts to perform the repair.[6] This chapter reviews the rationale, principles, and theoretical advantages that these state-of-the-art techniques offer to the surgeon and their patient. Readers are encouraged to read other literature and reviews on each of these topics, which are provided in the references cited at the end of this chapter, for more detailed information as appropriate.

NERVE TRANSFERS

Nerve transfers, also referred to as "neurotization," involve the repair of a distal denervated nerve element using a proximal foreign nerve as the donor of neurons and their axons, which will reinnervate the distal targets. The concept is to sacrifice the function of a (lesser valued) donor muscle to revive function in the recipient nerve and muscle that will undergo reinnervation.[50] Since their first report by Tuttle[64] in 1913 and popularization by Narakas[49] three decades ago, nerve transfers have been used increasingly for the repair of brachial plexus injuries, especially in cases in which the proximal motor source of the denervated element is absent because of avulsion from the spinal cord.[43] Increasingly advocated are the use of transfers in situations in which the proximal motor source is available, but the regeneration distance is so long that the outcome would be poor. A nerve transfer into the denervated distal nerve stump close to the motor end-organ would then restore function, which would not be possible otherwise.[51] The use of nerve transfers has, therefore, been a major advance in the field of brachial plexus nerve reconstructive surgery, with many different ingenious transfers associated with improving results, as reported and reviewed recently.[8,21,42,57,62]

The anatomic and physiological principles that underlie nerve transfers are relatively straightforward. Because motor recovery has been the main goal, the choice of a donor nerve element that has a reasonable aliquot of motor fibers is required.[50] The loss of the muscle denervated by transferring the donor nerve must not represent loss of important or critical function.[31] Obviously, the value of the neuromuscular element to be reinnervated must greatly exceed the utility of the sacrificed one. An excellent compromise is achieved if some function of the donor muscle can be retained, by using only a portion of the nerve as the donor, exemplified by the use of only the distal terminal branch of accessory (transferred to suprascapular nerve), thereby sparing proximal branches to trapezius muscle.[43]

There are several important principles to adopt in order to maximize outcome in nerve transfers, the first of which is to reinnevate the recipient nerve as close to the target muscle as possible.[51] An outstanding example of the latter is the

transfer of an ulnar nerve fascicle directly to the biceps branch of the musculocutanoeus, in close proximity to its entry into the muscle.[53] The second principle is to perform a direct repair without intervening grafts, a tactic that seems to be associated with improved outcomes, as reported convincingly with intercostal-musculocutaneous transfers.[22,38,48,55,66] The third principle is to use combinations of similarly behaving neuromuscular units, maximized when agonist donor and recipient are chosen, as cortical readaptation is the physiological basis for functional recovery.[37,39] This may also be the physiological underpinning that explains why intraplexal (e.g., medial pectoral-musculocutaneous) nerve donors may garner superior results as compared with extraplexal (example intercostal-musculocutaneous) nerves.[56]

I will emphasize the approaches for repair of brachial plexus injuries, as this is the scenario in which nerve transfers have been used most frequently. Surgery entails a complete and thorough exposure of the plexus, including intraforaminal dissection and external neurolysis of the nerve in-continuity followed by intraoperative electodiagnostic studies.[44] The intraoperative electrical tests and operative findings are used in concert with the preoperative clinical exam, EMG, and imaging[10] to determine the extent of injury and presence of root avulsion to guide operative decisions about the type of nerve reconstruction. For instance, even in the complete severe palsy, the C5 spinal may be singularly spared thus allowing it to be used as the source of axons for a plexoplexal repair to distal elements.[17,24] There are, however, many cases in which the integrity of the proximal root stump as being suitable to graft out from is unclear. The use of very proximal intraforaminal dissection of the nerve roots is invaluable in assessing the nerve anatomically.[25] This, along with frozen section of the very proximal stump to assess fascicular pattern and absence of ganglion cells, has been useful in decision making. However, in uncertain circumstances, the use of a nerve transfer is preferred rather than using a questionable proximal stump. The possible permutations and combinations for repair, therefore, include intraplexal grafts alone from a single (or multiple) functioning root(s), intraplexal grafts along with selective transfers or transfers alone.

The nerve transfer options available can be divided into three categories: extraplexal, intraplexal and fascicular (*Table 18.1*). Extraplexal sources include accessory,[1–3,50] intercostals,[15] hypoglossal, cervical plexus,[71,72] and phrenic.[11,65] Intraplexal donors include C7 (ipsilateral[24,26,60] and contralateral[12,19,20]), pectoral nerves,[9] and others, including thoracodorsal.[56] Nerves from which fascicles have been used with increasing frequency as donors are the ulnar, median, and triceps branches of the radial nerve, as detailed below.

FASCICULAR TRANSFERS

One of the most exciting recent developments in the neurotization field has been the transfer of portions of func-

TABLE 18.1. Commonly used donor nerves for transfer to repair brachial plexus injuries

Extraplexal
   Accessory (XI)
   Hypoglossal (XII)
   Phrenic
   Cervical plexus (C3-4)
   Intercostals
Intraplexal
   C7 spinal nerve (ipsilateral and contralateral)
   Medial pectoral nerves
   Thoracodorsal
Fascicular
   Proximal ulnar (Oberlin)
   Proximal median
   Triceps branch of radial nerve

tioning distal plexal elements to directly reinnervate nerve branches going to critical muscles that are paralyzed. This era really began relatively recently with Oberlin's anatomical studies of the fascicular pattern and then the application in several patients where a single ulnar nerve fascicle ("redundant" to flexor carpi ulnaris muscle) was transferred to biceps branches in the medial arm to restore elbow flexion (*Fig. 18.1*).[54] The initial report of excellent results have subsequently been validated by several other authors.[21,29,30,59] Most impressive have been the results reported by Sungpet[59] who
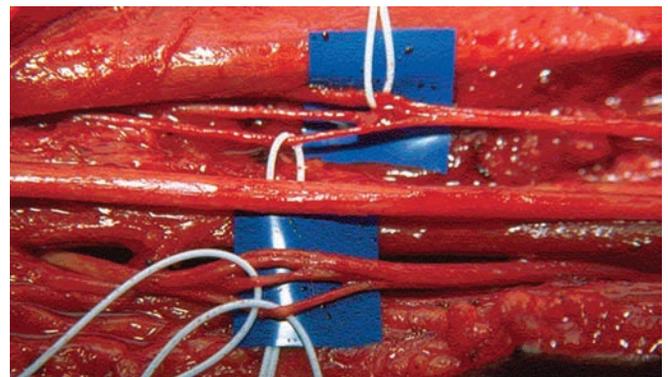

FIGURE 18.1. Medial arm exposure showing the biceps muscle (uppermost), adjacent musculocutaneous nerve, median nerve (center), and ulnar nerve (lowermost). For the transfer of an ulnar nerve fascicle to biceps muscle nerve in the medial arm, the common epineurium of the ulnar nerve is opened under microscopic magnification, several fascicles displayed and one of two redundant fascicle (that maximally stimulate flexor carpi ulnaris and not hand intrinsic muscles) chosen to transfer directly to the adjacent biceps nerve branch (uppermost vessel loop) of the musculocutaneous nerve. (Picture courtesy of Susan Mackinnon, by permission).

used a single ulnar nerve fascicle directed to biceps and obtained MRC Grade 3 or better outcome in 34 out of 36 patients. Also noted in this study was that time to reinnervation began as early as 3.3 months and that hand function and ulnar assessment using a series of tests and functional tools was not compromised in the long-term follow-up period. A recent report indicates that elbow flexion function will be further augmented (especially in delayed surgery cases) by also concomitantly reinnervating brachialis muscle via a graft from the medial pectoral nerve.[63] Another alternative to using the ulnar fascicle is to use a fascicle of the adjacent median nerve to transfer to biceps or brachialis muscle nerve (*Fig. 18.2*), with good results ranging from 64%[21] to 80% of patients.[58] An emerging transfer is the direct repair of the anterior branch of the axillary nerve by the nerve that goes to the long head of triceps in the posterior arm.[28,70] This transfer, when combined with accessory to suprascapular transfer, may herald a much better outcome in dynamic shoulder function than was previously possible with the flail shoulder after long graft repair from C5 and C6 injuries.[28] Indeed, the most recent series demonstrate the benefit of several targeted transfers in individual patients with plexus avulsions.[8] Finally, transfers for restoration of rudimentary hand function in lower brachial plexus palsies are emerging.[18]

WHICH NERVE TRANSFERS TO USE

Much of the literature related to brachial plexus surgery is in the form of retrospective case reviews, anecdotal experiences, a few, rare prospective studies, and no randomized studies of different surgical techniques. Moreover, the field has been in considerable evolution with traditional plexo-
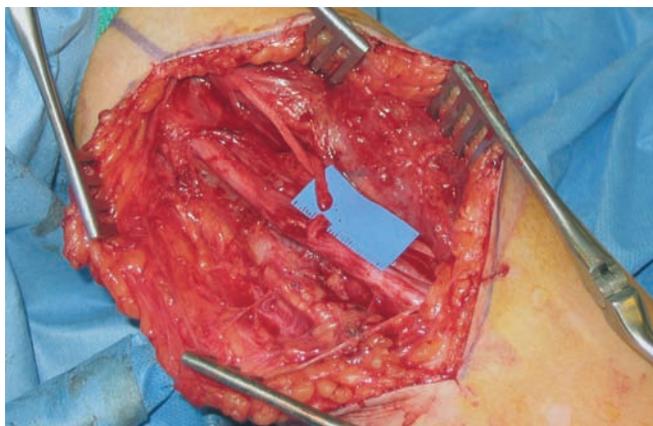

FIGURE 18.2. Two fascicles, primarily innervating flexor carpi radialis as determined from intraoperative stimulation and evoked muscle responses, of the median nerve are in position to be transferred to the brachialis branch of the musculocutaneous nerve in a patient with complete Erb's palsy associated with C5 and C6 spinal nerve root avulsions and lack of elbow flexion.

plexal repairs[24,26] being gradually replaced by a much more liberal use of nerve transfers.[8,21,42,57,62]

A meta-analysis conducted on the nerve transfer literature noted that, for restoration of shoulder abduction, it is best to use an accessory nerve transfer to the suprascapular nerve, whereas, for elbow flexion, intercostals without graft should be performed.[42] In the grim scenario of complete avulsions, the addition of a contralateral C7 transfer with an interposed vascularized ulnar nerve graft directed to the entire or perhaps the lateral root of median nerve in the axilla could be considered.[61] Alternatively, some lower intercostals or cervical plexus elements could be directed to the sensory aspect of the median nerve. This set of transfers is certainly appropriate for the situation in which the patient has a complete flail arm with all five spinal nerve roots avulsed. However, it is most important in the case of the completely flail arm patient to ensure that the C5 spinal nerve is, in fact, avulsed and not ruptured extraformainally.[25] To deny an intraplexal repair from a useable C5 spinal nerve to its distal outflow would be a disservice given the relatively poor number of extraplexal transfer possibilities available. In uncertain cases, the repair from C5 to distal elements can be augmented by the transfers of accessory and intercostal nerves.[24] Although the above strategy is appropriate for the pan plexus injury, the tactics are very different for the isolated Erb's palsy. If C5 and C6 are avulsed, but C7 is clearly intact, intraplexal graft repairs from the C7 may be considered to reinnervate the shoulder abductors and elbow flexors.[24] Alternatively, directed discrete transfers should be performed. Based on the most recent literature, this seems to be an emerging approach. A combination of distal accessory to suprascapular, ulnar nerve fascicle to biceps nerve (augmented by a portion of medial pectoral nerve via graft to brachialis nerve or direct median nerve fascicle transfer) and long head of triceps nerve to the anterior portion of the axillary nerve may be performed.[8]

NERVE TUBES

In the 1940s, Weiss championed the use of non-nerve tissues as an alternative to suture repair of nerve, also demonstrating their effect over very short gaps to successfully bridge the proximal and distal nerve stumps.[69] Since then, multiple biological conduits for nerve repairs have been attempted with varying success in experimental animals, including the use of arteries, veins, muscle, collagen and other materials (reviewed in[14]). Synthetic tubes have been constructed from biodegradable material, such as polyglycolic acid (PGA), laminin, polylactide-caprolactone and non-biodegradable material, such as silicone, as we have recently reviewed.[7]

Clinical translation for the use has occurred in the past two decades. In pioneering studies reported in the early 1990s, Lundborg[33,34] demonstrated the feasibility and success

of ulnar and median nerve reconstruction using short silicone conduits in a few patients. However, these impermeable, non-biodegradable tubes elicited an inflammatory and fibrotic reaction and produced chronic nerve compression,[41] requiring their removal after regeneration had occurred through them. Surgeons have, therefore, increasingly used biodegradable materials for clinical use. Based on promising primate and clinical experience,[13,36] PGA tubes were found to be comparable to nerve autografts in the repair of digital nerves with defects up to 3 cm in a prospective randomized clinical study.[67] PGA tubes (Neurotube; Neuroregen LLC, Bel Air, MD) and subsequently collagen nerve tubes (NeuraGen; Integra Life Sciences, Plainsboro, NJ)[4,5] have been approved in the United States for the repair of peripheral nerve injuries. In 2001, SaluMedica (Atlanta, GA) and Collagen Matrix (Fraklin Lakes, NJ) each received approval for their tubular constructs used in repairing peripheral nerves. Using a repeated freeze-thawing technique, SaluMedica produces a hydrogel tube made from polyvinyl alcohol (PVA), whereas Collagen Matrix has developed a collagen nerve cuff made from collagen fibers. Most recently, Polyganics (Groningen, Netherlands) used a dip coating procedure to manufacture a resorbable poly (DL-lactide-caprolactone) tube (Neurolac). Although approved for human use, the efficacy, and thus the indications, for all the tubes marketed to date are limited to the repair of short defects (<3 cm) of mainly the small-caliber nerves.[40]

Nerve tubes are, therefore, appropriate for use in the repair of the smaller diameter (e.g., distal extremity nerves, such as radial, ulnar, and their terminal branches in the wrist, hand, or fingers) nerve injuries in which gap lengths are less than 3 cm. To undertake the repair with a nerve tube, the nerve ends are trimmed until a good fascicular pattern is visible at each nerve stump. An appropriate diameter nerve tube is chosen so that the inner luminal diameter is approximately 20% larger than the cross-sectional diameter of the nerve to be repaired, and cut to have its length slightly longer than the nerve gap to be bridged (*Fig. 18.3A*). The nerve ends are then inserted into each end of the tube. This requires the placement of a single microsuture placed in a "U" fashion from outside to the inside of the tube then through the epineurium of the nerve 1 to 2 mm back form the nerve stump, then again from the inside of the nerve tube to the outside where the knot is tied (*Fig. 18.3B*). This type of stitch at each end keeps the nerve stumps constrained within the lube lumen (*Fig. 18.3C*). The interior of the lumen is then filled with saline, to flush out any air bubbles. The ends of the nerve tube and nerve junction can be further reinforced, if necessary, with fibrin glue.

The creation of an augmented artificial nerve tube, built on our fundamental knowledge of axonal guidance, may provide an improved alternative to current nerve guidance tubes. Various strategies have been implemented in experi-
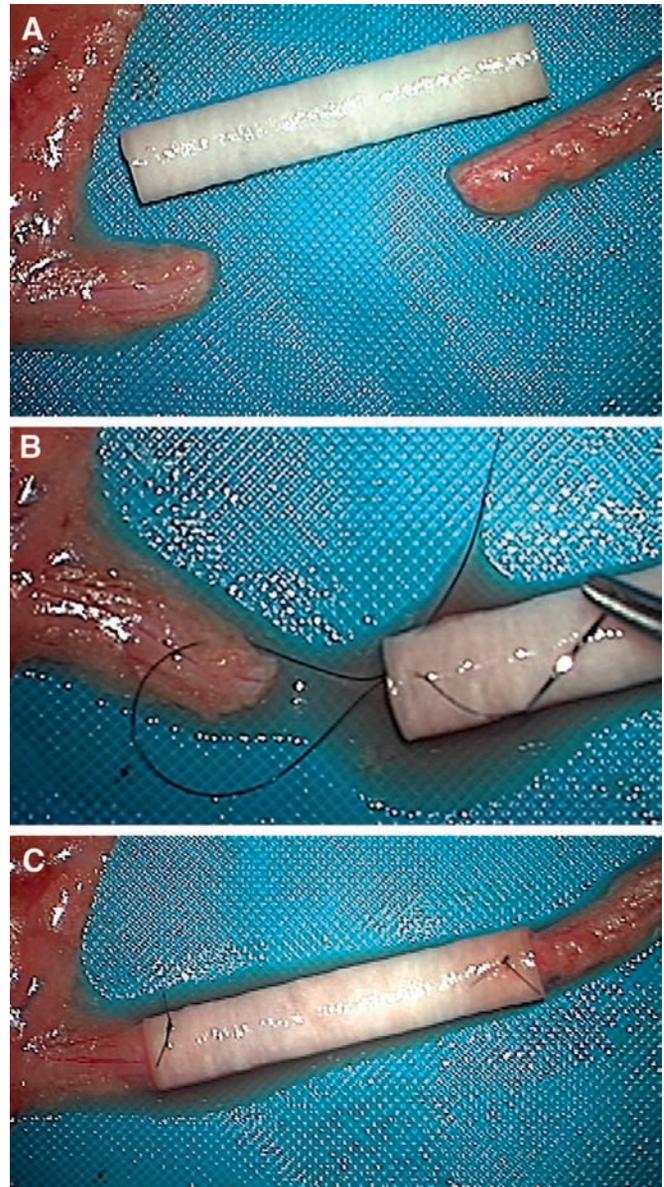

FIGURE 18.3. A, nerve tube repair (using NeuraGen, Integra Life Sciences) of a nerve injury gap, with the chosen tube slightly longer than the gap length and about 20% larger in internal diameter than the diameter of the nerve being repaired. B, repair technique, illustrating the placement of a "U" stitch. C, the final repair with each of the nerve stumps pulled 1 to 2 mm within the lumen of the tube.

mental models that attempt to enhance the regenerative effectiveness of artificial conduits. These include the use of scaffolds, integration of contact-mediated cues within the channel, and incorporation or delivery of exogenous growth factors into the tube lumen uniformly or as gradients.[6] As an example, neurotrophic factors, not only favor neuronal cell survival following injury, but also display chemotactic prop-

erties, by providing appropriate directional cues to regenerating axons.[32] Growth factors placed within the lumen of guidance tubes have been used with considerable success to obtain improved regeneration, compared to autografts, by others (reviewed in[7,40]) and by us.[46] Hence, in the future, we can look forward to advances in tissue engineering and biotechnology providing for the generation of enhanced nerve tubes, leading to better outcomes from nerve repair in our patients.

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