Novel Uses of Nerve Transfers

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Abstract

Nerve transfer surgery involves using a working, functional nerve with an expendable or duplicated function as a donor to supply axons and restore function to an injured recipient nerve. Nerve transfers were originally popularized for the restoration of motor function in patients with peripheral nerve injuries. However, more recently, novel uses of nerve transfers have been described, including nerve transfers for sensory reinnervation, nerve transfers for spinal cord injury and stroke patients, supercharge end-to-side nerve transfers, and targeted muscle reinnervation for the prevention and treatment of postamputation neuroma pain. The uses for nerve transfers and the patient populations that can benefit from nerve transfer surgery continue to expand. Awareness about these novel uses of nerve transfers among the medical community is important in order to facilitate evaluation and treatment of these patients by peripheral nerve specialists. A lack of knowledge of these techniques continues to be a major barrier to more widespread implementation.

Key Words Nerve injury · nerve transfer · sensory reinnervation · spinal cord injury · supercharge end-to-side transfer · targeted muscle reinnervation

Nerve Transfers

Surgical management of nerve injuries continues to evolve, with the available surgical armamentarium continuing to expand. With this evolution, some of the strategies once utilized only for traumatic nerve injuries are now being utilized for the treatment of other pathologies, such as spinal cord injuries and strokes. One of the major advances in the treatment of nerve injuries that has, in some circumstances, dramatically improved outcomes and has also increased the number of injuries amenable to treatment was the development of nerve transfers. Nerve transfers were originally designed as an alternative strategy to nerve graft repair for the restoration of motor function.

A motor nerve transfer utilizes a functioning nerve with an expendable or duplicated function, duplicated by either another nerve or with intraneural duplication in the case of a fascicular transfer, and transfers that functioning nerve to an injured nerve.

The ideal donor nerve for a motor transfer meets the following criteria: 1) it is a motor nerve; 2) it can be directly coapted to the injured nerve without the use of an intervening nerve graft; 3) the direct coaptation can occur in a tension-free manner; 4) it has a large number of motor axons; 5) it will not result in functional loss, because the function is either expendable or duplicated; and 6) it has a synergistic (rather than antagonistic) function with the recipient nerve [1]. One of the mantras of Dr. Susan Mackinnon is “donor distal, recipient proximal” [2]. This mantra guides the way that nerve transfers are performed. By transecting the donor nerve distally and the recipient nerve proximally, additional length is gained in order to facilitate direct coaptation without an intervening graft in a tension-free fashion.

From the time of the injury, a variety of changes begin to occur in the injured nerve, at the neuromuscular junction, and in the denervated muscle [3]. With prolonged axotomy, axonal sprouting is decreased following nerve repair [4]. With prolonged denervation, there are loss of myofibrils and, eventually, death of the muscle cell [5]. Once these changes have occurred, it is impossible to re-establish a functional nerve-muscle unit. Thus, the goal of any reconstructive strategy designed to restore motor function is to restore a functional nerve-muscle unit before these irreversible changes occur. Typically, the coaptation point in a nerve transfer occurs very near the target motor end plates, transforming a proximal injury into a more distal injury. Herein lies one potential advantage of nerve

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transfers. By performing the coaptation near the denervated motor point, the time required for reinnervation is shortened.

The indications for motor nerve transfers are expanding, with some indications still being controversial. One well-established indication is avulsion injuries. Nerve graft repair relies on the proximal portion of the injured nerve having an intact connection with the spinal cord. In cases of avulsion, there is not a proximal nerve stump that can be utilized for nerve graft repair. Nerve transfer is a viable alternative in these circumstances. Another established indication is for patients presenting in a delayed fashion. With delayed presentation, much of the time window to re-establish a functional nerve-muscle unit before irreversible changes occur has elapsed. By transforming the injury into a distal injury and getting functional axons near the denervated motor endpoint, nerve transfers expand the period of time during which reconstruction can still be effective. A third established indication includes proximal injuries that have a long distance between the injury and target motor end plates. For example, lower trunk brachial plexus injuries are not amenable to nerve graft repair in adults due to the distance of axonal regeneration required. Distal nerve transfers can be considered to bring regenerating motor axons near the target, again transforming a proximal injury into a distal injury.

An alternative, though sometimes complementary strategy, is the use of tendon transfers. To appropriately treat nerve injuries, one must be aware of not only all the nerve surgery options but also the tendon transfer options to address a given deficit. This is particularly relevant because as nerve transfer options expand, harvest of some donor nerves eliminates the potential for tendon transfer. In these cases, the surgeon must be certain that the outcomes associated with nerve transfer are better than, or at least equal to, the corresponding tendon transfer option.

Despite the fact that nerve transfers have been around since early in the 20th century, the nerve transfer that firmly established the technique by producing consistently good outcomes was originally described by Christophe Oberlin and involves transferring a fascicle of the ulnar nerve to the biceps branch of the musculocutaneous nerve, now referred to as the Oberlin transfer [6, 7]. Oberlin originally described using 10% of the cross-sectional area of the ulnar nerve to transfer to the biceps branch of the musculocutaneous nerve [7]. This morphed over time to selecting one or two fascicles of the ulnar nerve that supplied predominantly the flexor carpi ulnaris when tested with direct stimulation in the operating room [6]. In one of Oberlin's early series, 30 of 32 patients (94%) achieved at least Medical Research Council (MRC) grade 3 elbow flexion after the Oberlin transfer with or without a Steindler flexorplasty. No clinical sensory or motor deficits were observed related to the donor ulnar nerve [8]. The success of this transfer and the demonstrated safety led to continued development of additional nerve transfer strategies.

The Oberlin transfer nicely demonstrates a number of the principles that are important for motor nerve transfers to address

traditional nerve injuries. The donor nerve is a motor nerve. Individual fascicles of the ulnar nerve are stimulated intraoperatively to ensure a motor fascicle is selected. The ulnar nerve and musculocutaneous nerve are in close proximity to each other in the arm. By isolating length of the donor nerve fascicle and cutting it distally and by isolating length of the recipient biceps branch and cutting it proximally, the coaptation can be accomplished in a tension-free manner without the use of an intervening graft. The fascicle that is selected is ideally purely supplying the flexor carpi ulnaris, though this may not in reality exist. This function is both internally and externally duplicated. Multiple fascicles within the ulnar nerve typically supply the flexor carpi ulnaris. Furthermore, wrist flexion is also achieved via the flexor carpi radialis which is innervated by the median nerve. In reality, the fascicle that is selected for transfer is the fascicle that steals the least function from the hand intrinsic and flexor digitorum profundus and predominantly supplies the flexor carpi ulnaris. The function of the flexor carpi ulnaris is synergistic to the function of the biceps (wrist flexion and elbow flexion). Finally, the coaptation point of the nerve transfer is very near the denervated motor point of the biceps muscle, bringing regenerative axons near the target (Fig. 1).

More recently, the applications of nerve transfers have expanded beyond motor reconstruction and beyond traumatic nerve injuries. The focus of this review will be these novel uses of nerve transfers that have been more recently developed. The goal is to increase awareness of these novel techniques, particularly among referring physicians so that these techniques can be offered to a larger number of appropriately selected patients.

Nerve Transfers for Sensory Reinnervation

Although deservedly much of the focus is given to motor deficits following a nerve injury, resulting sensory deficits can also

Fig. 1 Intraoperative photograph showing the Oberlin transfer. A fascicle of the ulnar nerve (UF) primarily supplying the flexor carpi ulnaris is coapted to the biceps branch of the musculocutaneous nerve (BB). There is a good size match between the donor and recipient nerves. The coaptation point is very near the biceps motor point (MP), shortening the distance required for regenerating axons to reach the target. UN = ulnar nerve

be very debilitating. The loss of protective sensation can lead to further injuries and can even ultimately compromise the limb. For those reasons and others, restoration of sensation has increasingly become a priority following nerve injuries.

Upper Extremity Sensation

With upper extremity nerve injuries that result in loss of sensation in the hand, restoration of sensation to the hand is the sensory priority. In cases of lower brachial plexus injuries (C8–T1 ± C7), sensation in the distribution of the ulnar nerve is lost, whereas the majority of the median nerve and radial nerve sensory distributions are preserved due to the continued functionality of C5 and C6. In comparison, sensation in the ulnar nerve distribution is more important functionally and for protection of the hand than sensation in the distribution of the superficial radial sensory nerve. The preserved function of the superficial radial sensory nerve, relatively less important sensory distribution in comparison to the ulnar nerve, and the relative proximity of the two nerves distally make the superficial radial sensory nerve an attractive donor to restore sensation in the ulnar nerve territory. The superficial radial sensory nerve can be coapted directly to the cutaneous portion of the ulnar nerve in the distal wrist, without the need for an intervening graft. Though only reported in a limited number of patients, early reports indicate that this transfer can reliably produce at least protective sensation in the distribution of the ulnar nerve [9]. However, caution should be emphasized in utilizing the superficial radial sensory nerve because this is known to be an unforgiving nerve with regard to neuropathic pain. For that reason, when other donors are available, it may be better to avoid using the superficial radial sensory nerve as a donor.

Branches of the median nerve can also be used as donor nerves in cases of lower brachial plexus injury. Sensation on the ulnar border of the hand is important because often this is the point of support for activities. The hand is often stabilized by resting the ulnar border of the hand against a fixed object. This predisposes this portion of the hand to injury when it is insensate. On that basis, the ulnar proper digital nerve to the fifth digit is a good target for sensory reinnervation. The palmar cutaneous branch of the median nerve or other cutaneous branches to the palm from the median nerve have been used as donors. In a small series of 8 patients, all patients regained at least protective sensation to the ulnar side of the hand [10]. These distal transfers seem to be a reliable method of achieving protective sensation.

With pan-brachial plexus injuries, sensation is lost to the entire hand (C6, C7, and C8 dermatomes). Although irreversible changes occur that preclude long distance axonal regeneration to be functional for the purpose of motor reinnervation, the same limitations may not exist for sensory reinnervation.

The median nerve is made up of contributions from the lateral and medial cords, with the lateral cord contribution being predominantly sensory. One technique for restoration of hand sensation is transfer of the intercostobrachial nerve to the lateral cord contribution of the median nerve. With this technique, the intercostobrachial nerve, which is a branch of the second intercostal nerve, is directly coapted to the lateral cord contribution to the median nerve in the infraclavicular space, without the need for an intervening graft [11]. The goal is restoration of sensation to at least a protective level in the median nerve distribution of the hand. The median nerve distribution is the target due to the large size of the sensory distribution in comparison to the ulnar nerve and also due to the importance of sensation in the thumb and index finger for activities that require pinch. Using the Semmes-Weinstein monofilament test, the red (4.0 g) monofilament is considered to be protective sensation. In one series of 11 patients who underwent intercostobrachial nerve to lateral cord contribution of the median nerve transfer, 10 of the 11 patients regained protective sensation using the Semmes-Weinstein monofilament test. The majority of these patients perceived the area of stimulation in the hand, rather than in the original distribution of the intercostobrachial nerve [12].

A variety of other sensory transfers have been described for the upper extremity including lateral antebrachial cutaneous to dorsal ulnar nerve transfer via a long intervening graft in lower brachial plexus injuries and transfer of the sensory rami of intercostal nerves to the ulnar nerve in lower brachial plexus injuries [13–15]. Further refinements in patient selection and optimization of technique for sensory reinnervation in the upper extremity will likely occur as larger series become available due to the continued and progressive emphasis on sensory reinnervation, not just motor reinnervation.

Lower Extremity Sensation

In the lower extremity, loss of sensation in the tibial nerve distribution can be extremely debilitating. The classic example would be diabetic neuropathy. Loss of sensation from the plantar surface of the foot predisposes to injuries, chronic wounds, and ulcers and ultimately puts the foot at risk. Patients with diabetes are predisposed to these issues for a variety of reasons outside of diabetic neuropathy, including poor vascular supply, but, nonetheless, are an example of the importance of sensation to the foot. The tibial division is often less injured and recovers better than the peroneal division in proximal sciatic nerve stretch injuries [16, 17]. Nonetheless, when tibial nerve sensation does not recover, it is a significant deficit. One major problem with proximal sciatic nerve injuries is the lack of potential donor nerves. In these circumstances, a saphenous nerve to sural nerve transfer has been described [18]. The benefit and results of this technique are unclear. An advancing Tinel's sign in the sural distribution

was demonstrated. The saphenous nerve has also been transferred to the sensory portion of the tibial nerve through an intervening nerve graft. In a single patient, this allowed restoration of vibratory sensation to the plantar surface of the foot [19]. Additional work needs to be done to understand what can be achieved in these situations and how this compares to the natural history of sensory recovery.

For isolated tibial nerve injuries, the use of the superficial peroneal nerve and/or the sural nerve as a donor remains possible. An anatomic feasibility study demonstrated that it is possible to divide the sural nerve and superficial peroneal nerve at the level of the ankle and to swing the nerves over to be coapted directly to the distal tibial nerve in the tarsal tunnel. The results for this technique have not yet been presented [20]. The deep peroneal nerve provides sensation to the first webspace of the foot. Loss of this patch of sensation would theoretically be well tolerated by patients and may make the deep peroneal nerve an attractive option as a donor. This technique has also been described in a limited number of patients [21]. As opposed to the upper extremity, the donor options are extremely limited in the lower extremity. An attempt at restoring tibial nerve sensation should be undertaken whether by proximal repair, accepting the long duration needed for recovery, or by the novel use of a nerve transfer depending on the available donors.

Corneal Sensation

The cornea can become insensate for a variety of reasons, some congenital and some acquired. When the cornea is insensate, chronic ulceration typically occurs, with blindness eventually occurring secondary to chronic scarring of the cornea [22, 23]. Thus, re-establishing or preventing loss of sensation to the cornea is important in maintaining vision. Nerve transfer options have now been developed to reinnervate the cornea using the supratrochlear or supraorbital nerves as donors for direct neurotization of the cornea. Different than traditional nerve transfer options in which both the donor and recipient are nerves, in these operations, the function of the supratrochlear or supraorbital nerve is transferred to the cornea by directly implanting the terminal end of the donor nerve into the cornea. The ultimate goal is restoration of a protective level of sensation to the cornea.

In vivo confocal microscopy has shown that this nerve transfer technique can successfully reinnervate the cornea [24]. Initial small series have shown that all operated patients have had improvement in corneal sensation postoperatively [25, 26]. This has led to restoration of protective sensation and halted progression of corneal anesthesia-related complications. Though reports are limited to small patient numbers, this is a significant triumph in the treatment of patients with this previously untreatable pathology.

Nerve Transfers for Spinal Cord Injuries

Spinal cord injuries can be thought of as having three separate anatomic and pathophysiologic regions [1]. Above the level of the injury, both the upper motor neuron and lower motor neurons are intact and continue to function. Below the level of the injury, there is no injury to the lower motor neurons, but there is loss of function due to loss of the upper motor neurons. Due to the fact that there is not an injury to the peripheral nerve (lower motor neuron), Wallerian degeneration does not occur within the peripheral nerve and a nerve-muscle connection remains intact at the motor end plates that prevents the irreversible changes from occurring that were discussed previously in association with peripheral nerve injuries. At the level of the injury, there is typically a mixed injury to both upper and lower motor neurons. The involved nerve roots will thus undergo Wallerian degeneration, and the changes in the nerve, neuromuscular junction, and muscle that are associated with peripheral nerve injuries will begin to occur. A novel use of nerve transfers that has been developed is the use of functioning nerves supplied above the level of the spinal cord injury as donors to reinnervate muscles supplied by nerves originating from the level of the injury or below. These nerve transfers can be thought of as an alternative or a complementary strategy to the more traditional tendon transfers. When targeting muscles supplied from below the injury, the time constraints do not apply that are typical for peripheral nerve injuries, whereas if targeting muscles supplied at the level of the injury, the time constraints do apply, because the peripheral nerve is involved in the injury.

Small gains involving specific movements or functions can lead to large gains in independence and quality of life for patients with spinal cord injuries. Nerve transfers in spinal cord injuries are targeted at restoring these specific movements that have large impacts on function and independence. One such deficit associated with cervical spinal cord injuries is loss of diaphragmatic function due to loss of phrenic nerve innervation (C3, C4, and C5). These patients then require chronic mechanical ventilation. One technique to address loss of phrenic nerve function is the use of phrenic nerve pacing. However, this depends on an intact phrenic nerve that is free from axonal loss. In cases where the spinal cord injury happens at the C3–C5 level, axonal loss can occur in the phrenic nerve, rendering phrenic nerve pacing impossible. Restoring phrenic nerve innervation via nerve transfer is one method to potentially circumvent this problem. With axonal continuity from the donor nerve through the phrenic nerve to the diaphragm, pacing is then possible. In one series of 6 patients with C3–C5 spinal cord injuries and another series of four similar patients, intercostal nerves were used as donor nerves for nerve transfer to the phrenic nerve. All patients in both series showed improvement, with periods of ventilator independence [27, 28]. The T6–T8 intercostal nerves not only

innervate the intercostal muscles but also contribute to innervation of the anterior abdominal wall. This may make them an attractive choice among the intercostal nerves due to the higher number of motor axons [28]. Overall, though the technique is in its infancy, these series suggest this may be a viable technique in appropriately selected patients.

Restoration of specific upper extremity movements can also be achieved using nerve transfer strategies. Management of patients with spinal cord injuries requires a multidisciplinary approach, and the patient's physiatrist should be involved in developing an individualized treatment strategy that may include nerve transfers. Decisions must be made regarding which specific movements would be most beneficial and lead to the largest gains in quality of life. The most common movements targeted include elbow extension, wrist extension, finger flexion, and finger extension.

Elbow extension is a very useful function for patients with spinal cord injuries, as elbow extension can help the patient participate in transfers and also can aid in powering a wheelchair. Triceps motor branches from the radial nerve serve as the recipient nerves in nerve transfers aimed at restoring elbow extension. The specific branch that is chosen as the recipient should be based on preoperative electromyography. The recipient nerve should supply the head of the triceps that shows denervation and no volitional motor unit potentials. If any volitional motor units are present, that head of the triceps will be under volitional control and, though it may be small, may contribute to active elbow extension [29]. The teres minor branch of the axillary nerve, the posterior branch of the axillary nerve to the posterior deltoid, and the brachialis branch of the musculocutaneous nerve have been described as donors [29–33]. In one series of 13 limbs undergoing nerve transfer for elbow extension using branches of the axillary nerve to the deltoid as donors, 11 (85%) achieved M4 elbow extension, while the remaining two (15%) achieved M3 strength [30]. Given that the ability to aid in transfer is the target, at least M4- strength should be considered the target, with M4 really required to be useful. Even by these criteria, the vast majority of patients in the series achieved useful elbow extension. Only a single case report exists detailing the use of the brachialis branch of the musculocutaneous nerve through a medial upper arm approach as the donor for elbow extension. This patient recovered elbow extension very quickly after the nerve transfer, achieving M3 elbow extension by 3 months after the operation. The coaptation point was 5 mm from the motor point of the medial head of the triceps, facilitating this rapid recovery. Ultimately, the patient recovered M4 elbow extension [33]. Two case reports exist detailing the use of the teres minor branch of the axillary nerve through an axillary approach as a donor [31, 34]. In one, the operation was performed bilaterally and resulted in M4 elbow extension bilaterally, and in the other, the operation was performed unilaterally and also resulted in M4 elbow extension. There was no detectable

weakening of external rotation. Recovery of triceps function was more delayed due to the coaptation point being further from the motor end plate. The first detectable contraction of the triceps was not observed until 5 months after the operation [31]. Again, although limited to case reports and case series, all three methods have the potential to restore elbow extension function sufficient to be functionally useful.

Wrist extension is an important target in patients with cervical spinal cord injuries. The tenodesis effect from wrist extension can be taken advantage of, particularly to drive key pinch between the thumb and the index finger. The primary nerve transfer that has been described for this purpose is the brachialis branch of the musculocutaneous nerve to the extensor carpi radialis longus (ECRL) branch of the radial nerve transfer [29, 35]. The branch to the brachialis serves as a good donor for a number of reasons. First, elbow flexion is duplicated by both the biceps and brachioradialis muscles, making it expendable when these muscles are preserved. Additionally, the brachialis is not a good tendon transfer option for most applications. Finally, the brachialis branch can be directly coapted to the branch to the ECRL without an intervening graft. In one case report using this technique, the patient achieved M3 wrist extension by 5 months after the operation and had the desired tenodesis effect [35]. No large series are available to determine the efficacy or typical results of this transfer.

Finger extension reconstruction is important to facilitate grasp and release. When the supinator muscle remains functional following a spinal cord injury, the branch or branches to the supinator can be used as the donor in a nerve transfer to the posterior interosseous nerve as the recipient. The supinator is itself supplied by a branch of the posterior interosseous nerve but receives its innervation from C5 and C6, whereas the thumb and finger extensors are supplied by C7–T1. Similar to other nerve transfers in spinal cord injury patients, we are limited to case reports and small case series [30, 34, 36]. However, although it is a limited number of reported patients, good results have been observed. In the largest series, 62% of patients achieved M4 thumb extension and an additional 31% achieved M3. M4 metacarpal extension was observed in 92% of patients, and the authors noted that this represented a significant improvement in hand span [30]. Given that the supinator is supplied by the posterior interosseous nerve, this transfer can be done through a small incision and without the need for any intervening graft. As these transfers become more prevalent, not only will surgical technique surely improve but so will the care and rehabilitation provided in the postoperative period. Some centers have already started to develop protocols for postoperative rehabilitation and training tailored towards the specific nerve transfer that was performed [37].

In patients with cervical spinal cord injury, loss of finger flexion results in weak or absent pinch and grasp. Restoration of this function significantly improves patients' quality of life and ability to perform a wide variety of daily activities. The

anterior interosseous nerve innervates the flexor pollicis longus and the flexor digitorum profundus to the second and third digits. Restoring the function of these muscles can significantly improve pinch function, and thus, the anterior interosseous nerve serves as a good target for nerve transfer. Two potential options for the donor nerve have emerged, including the brachialis branch of the musculocutaneous nerve and the extensor carpi radialis brevis (ECRB) branch of the radial nerve [1, 29, 38–40]. The largest series involved 8 nerve transfers using the brachialis branch as the donor and five nerve transfers using the branch to the ECRB as the donor. Using the brachialis branch, 50% of patients achieved M3 or better finger flexion, compared to 100% of those patients who had the ECRB branch used as the donor. The authors observed co-contraction of the ECRB when the fingers were flexing in the patients for whom the branch to the ECRB was used. They believe that this actually helps to stabilize the wrist and augment finger flexion [41].

Currently, the literature is limited to case series describing the various nerve transfers in spinal cord injury patients and the associated results. Additional data are needed to refine the indications for nerve transfers, especially to support specific indications for nerve transfers versus tendon transfers. Many times, a prolonged period of immobilization is required following tendon transfers which significantly increases the dependence of the patient, limiting the number of patients who undergo tendon transfers. Nerve transfers may have an advantage in this regard, because prolonged immobilization is not required. This may expand the number of spinal cord injury patients that could benefit. However, additional data are needed to further demonstrate the efficacy before the specific indications can be established. Given that spinal cord injury patients routinely prioritize restoration of hand function over all other potential functional gains, including bladder function, walking, and trunk strength stability, expanding the availability of nerve transfers for spinal cord injury patients, developing specific indications, and honing postoperative rehabilitation programs should be a priority [42, 43].

Supercharge End-to-Side Transfers

Nerve transfers have traditionally been performed by transecting the donor and the recipient nerves and then coapting them in an end-to-end fashion. When a nerve transfer is performed in this manner, it precludes any spontaneous recovery through the injured nerve, because the injured nerve is transected to perform the nerve transfer. A more recent technique involves performing a supercharge end-to-side (SETS) nerve transfer, whereby a donor nerve is coapting to the injured nerve in an end-to-side fashion through an epineurial window. This technique may allow axons to grow into the distal injured nerve and stave off the irreversible changes that occur at the

neuromuscular junction and in the muscle. By staving off these changes, axons can spontaneously regenerate down the intact injured nerve, even over long distances because the irreversible changes have been prevented, allowing more complete reinnervation of the distal muscles.

This technique has been best described for high ulnar nerve injuries. With proximal ulnar nerve injuries, the distance of axonal regeneration that is required to reinnervate the ulnar-innervated hand intrinsic muscles is substantial. This distance means that the hope for recovery is low. In these cases, a SETS transfer can be performed, coapting the distal anterior interosseous nerve (donor) to the side of the distal ulnar nerve [44–47]. The distal anterior interosseous nerve is followed to its point of branching within the pronator quadratus muscle and transected in that location. The nerve is then swung over to be coapting to the side of the ulnar nerve ~8–9 cm proximal to the wrist crease [44]. For proximal ulnar nerve transection injuries, the SETS technique shows promise, with the limited available data suggesting a significant improvement in the likelihood of regaining intrinsic function compared to repair without using the SETS technique [45]. In fact, 85% of patients regained hand intrinsic function in one study when a SETS transfer was performed, compared to only 15% when no SETS transfer was performed [45]. If these data are supported by further larger studies, this would represent a major advance in the treatment of an injury that previously had poor outcomes.

This same technique may be applicable for severe cubital tunnel syndrome [48, 49]. Further data are needed to elucidate specific indications. Furthermore, the concept of a supercharge end-to-side transfer may be applicable for other nerve injuries aside from ulnar nerve injuries. If the technique continues to be supported, there will surely be additional SETS transfers that will be conceived of and employed.

Nerve Transfers for Stroke and Other Spastic Hemiparesis

Ischemic strokes can result in spastic paralysis that is typically unilateral. Spastic paralysis of the upper extremity makes completing many activities of daily living difficult, including dressing oneself and performing daily hygiene. Furthermore, pain due to the posture of the affected arm can result and reduce quality of life [50–54]. Recently, it has been hypothesized that recovery of hand function following a stroke may be augmented by creating a functional connection between the contralesional cerebral cortex and the affected hand [55]. Transfer of the contralateral C7 nerve has been used with varying degrees of success in the setting of brachial plexus injuries. Theoretically, this same concept could be applied in the setting of an ischemic stroke to establish a functional connection between the affected hand/arm and the ipsilateral cerebral cortex.

Zheng and colleagues [55] performed a randomized, controlled clinical trial randomizing ischemic stroke patients (also traumatic brain injury and cerebral palsy patients) with upper extremity spastic paralysis to standard rehabilitation or standard rehabilitation plus contralateral C7 nerve transfer. In this operation, the C7 nerve root on the unaffected side was transected distally and tunneled through the prevertebral space to the contralateral side. The affected C7 nerve root was transected proximally. The distal portion of the transected nerve was then directly coapted to the C7 nerve root from the contralateral side. This nerve transfer is possible because the functions of C7 have large overlap with the remaining four nerves of the brachial plexus. This allows the C7 nerve root to be utilized as a donor, typically with only minor, transient weakness and numbness. The primary outcome measure used in the study was the Fugl-Meyer upper extremity scale. Patients in the nerve transfer group showed a significant improvement in Fugl-Meyer score compared to control (rehabilitation alone). The authors postulate that there are two potential mechanisms for the observed improvement. First, sectioning the C7 nerve on the affected side may help relieve spasticity by transecting gamma motor neurons that help maintain the spastic tone. Second, the contralateral C7 nerve may supply muscles in the affected extremity, leading to the observed increase in motor function. This is supported by the fact that the authors observed activation of the ipsilateral cerebral hemisphere on functional imaging when using the affected limb [55].

Ischemic stroke represents an exciting new frontier for the use of nerve transfers to aid in functional recovery. The positive results thus far using a contralateral C7 nerve transfer will likely lead to an expansion of this technique and allow further evaluation. However, it will also likely lead to the conception of new nerve transfer ideas that can be used in patients with ischemic stroke. Given the size of the population of patients who unfortunately suffer ischemic strokes, the number of patients who can be helped through nerve transfers may significantly expand.

Targeted Muscle Reinnervation

In the USA, there are more than 185,000 amputations annually. One quarter of these are complicated by the formation of painful terminal neuromas at the cut ends of transected nerves [56]. Pain related to postamputation neuromas can be very difficult to manage. The pain results from hyperexcitable nerve tissue within the neuroma that is exquisitely sensitive to pressure and also from the deafferentation that occurs when the nerve is cut. When conservative measures are exhausted, a wide variety of surgical strategies have been employed. These surgical strategies have been broadly divided into four categories: 1) implantation of the terminal end of the nerve into a surrounding structure (e.g., muscle, vein, bone), 2) closure/

capping of the terminal end of the nerve, 3) neurotaphy, and 4) alternate target reinnervation [56]. Most strategies, until recently, have been associated with mixed results, but generally poor. More recent strategies including “nerve to nowhere,” regenerative peripheral nerve interfaces, and targeted muscle reinnervation have had more dramatic success in relieving pain and preventing recurrence [57–60]. Falling into the alternate target reinnervation category is a nerve transfer strategy referred to as targeted muscle reinnervation.

The concept of targeted muscle reinnervation involves performing a nerve transfer with the cut end of the nerve as a donor and muscle branches in the local area as the recipients. Targeted muscle reinnervation was not originally conceived as a management strategy for pain, but rather was designed as a mechanism for augmenting electrical signal as a bioamplifier to be harnessed in powering motorized prosthetic devices. Its role in the management of postamputation pain is actually a secondary benefit. For example, for proximal humerus amputations, the musculocutaneous, radial, median, and ulnar nerves can be transferred as part of a targeted muscle reinnervation strategy to different portions of the pectoralis and serratus muscles. Activation of specific regions of the pectoralis and serratus muscles can then be interpreted as activation of the nerve that was transferred to that region. Using this bioamplifier mechanism, the signals from the various regions can then be combined to control a prosthetic device. This method of control has been associated with substantial improvements in prosthetic control [61–63].

Secondarily, by employing this technique, neuroma formation is avoided as the axons are allowed to regenerate into the muscle branches and deafferentation is improved as the axons grow into the muscle and reinnervate the associated receptors, giving the technique a later discovered benefit on neuroma pain. The procedure has since been performed in some instances for a primary indication of neuroma pain control, rather than for prosthetic control. Targeted muscle reinnervation has most often been reported for upper extremity amputations but can be used for either upper or lower extremity amputations [64–66]. For the treatment of postamputation neuroma pain in the upper extremity, in one study, 15 of 16 patients experienced complete resolution of their neuroma pain following targeted muscle reinnervation and the remaining patient had a substantial improvement. However, it is important to note that this assessment was specific for neuroma pain and did not assess phantom limb pain, which also has the potential to significantly affect quality of life in patients with amputations [59]. In another study, 92% of patients were free of pressure-induced neuroma pain following primary (i.e., at the time of amputation) targeted muscle reinnervation and 87% after secondary (i.e., delayed) targeted muscle reinnervation. In the primary targeted muscle reinnervation group, 50% of the patients still developed phantom limb pain. Eight patients in the secondary group had phantom limb pain.

Following targeted muscle reinnervation, one patient had resolution and seven patients had persistent phantom limb pain. In addition, one patient developed new phantom limb pain [67]. Previous studies reporting outcomes for standard nerve burial techniques have been mixed, but some studies have reported comparable rates of pain reduction [68, 69]. Nonetheless, targeted muscle reinnervation is an exciting innovation in prosthetic control that may have a substantial secondary benefit of neuroma pain reduction. However, phantom limb pain does not appear to be affected and targeted muscle reinnervation does not seem to be an effective strategy for either prevention or treatment of phantom limb pain. Thus, it is important to understand the goals of targeted muscle reinnervation when used for treatment of pain in amputation patients.

Conclusions

The advent of nerve transfers was a major advance in the surgical armamentarium available for the treatment of traumatic nerve injuries. With the establishment of motor nerve transfers, novel uses of nerve transfer surgery continue to be explored. This trend will likely continue. While restoration of motor function will always be paramount, increased recognition of the importance of sensory restoration will push us to expand the options and this will almost certainly involve an increase in nerve transfers for sensory reinnervation. New techniques such as supercharge end-to-side nerve transfers may allow some nerve injuries that were previously untreatable with nerve surgery to now be treated. The most exciting aspect of the novel use of nerve transfers is the ability to help new patient populations such as spinal cord injury patients, ischemic stroke patients, and patients with postamputation neuromas. These patient populations represent exciting new areas for growth within peripheral nerve surgery and represent patient populations that will likely be significantly benefitted by nerve transfer techniques. A lack of knowledge of these techniques continues to be a major barrier to more widespread implementation. As awareness of these more recently developed techniques is increased, it is likely that such awareness will help facilitate referral of patients who may benefit from these surgical techniques to peripheral nerve specialists.

Compliance with Ethical Standards

Required Author Forms [Disclosure forms](#) provided by the authors are available with the online version of this article.

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