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Management of nerve gaps: Autografts, allografts, nerve transfers, and end-to-side neurorrhaphy

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Introduction

Since its introduction in the late 1870's, surgical restoration of function following peripheral nerve injury has made significant progress (Naff and Ecklund, 2001). The development of the operating microscope, improved microsurgical techniques, and a greater understanding of the internal topography of peripheral nerves has greatly improved functional outcomes. In addition, advances in basic science and clinical research have furthered our understanding of the pathophysiology of nerve injury, recovery, and repair.

There are several factors that influence recovery following a nerve injury: time elapsed, patient age, mechanism, proximity of the lesion to distal targets, and associated soft tissue or vascular injuries (Gilbert, et al., 2006, Hentz and Narakas, 1988, Slutsky, 2006). All these factors must be carefully considered in order to optimize the operative approach used in each unique patient. Prompt repair of nerve injuries leads to improved outcomes by allowing for earlier distal motor end plate and sensory receptor reinnervation. In younger patients, the more robust regenerative capacity typically results in better outcomes compared to the elderly. Mechanism of damage is an important determinant of the longitudinal extent of the injury. More proximal lesions must traverse longer distances to reinnervate the distal target. And finally, concomitant soft tissue or vascular injuries can result in significant distortion and scarring, seriously complicating exploration of the affected area.

The ultimate goal of any peripheral nerve reconstruction is the restoration of function as promptly and completely as possible, while minimizing donor site and systemic morbidity. In cases where a tension-free primary end-to-end neurorrhaphy is not possible, several alternatives exist. This review summarizes these options for repair including interpositional nerve grafting, transfers and end-to-side neurorrhaphy (Fig. 1).

Timing of nerve repairs (Open vs. Closed)

The process of determining optimal timing for nerve repairs begins as soon as the patient presents. Information regarding the mechanism of injury or onset of symptoms will guide the

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clinician towards the most suitable treatment modality. Patients presenting with open injuries and neurological deficit require early exploration (Figure 2). While concomitant vascular injuries may necessitate emergency exploration, in general it is appropriate to wait to explore open injuries with neurological defects until appropriate expert surgical staff and operative support is available. In cases that require intraoperative stimulation of distal nerves to identify motor fascicles (e.g. distal facial nerve branches), exploration must be performed within 72 hours while residual neurotransmitters are still present in the distal nerve. In sharp transection injuries, primary repair should be performed. With blunt or mangled injuries (e.g. table saw injury), however, the proximal and distal ends of the nerve can be marked and approximated in an initial exploratory procedure. Once scar tissue has helped to declare the full extent of the injury approximately three weeks later, a secondary nerve grafting procedure is then usually performed. Reapproximating the nerve ends during the primary procedure helps maintain proper orientation and decreases the amount of retraction, ultimately minimizing the length of the final nerve graft. Extremely severe injuries involving multiple tissues may occasionally require the acute placement of a nerve graft if returning to the wound at a later date might compromise ultimate recovery. In such cases, since the injury has not had sufficient time to fully declare its true extent, it is imperative that nerve ends be trimmed back proximally and distally to ensure that the nerve graft will be placed outside the zone of injury.

An understanding of the classification of nerve injury (Table 1) is absolutely essential in the management of nerve injuries. First, second, and third degree injuries will recover without the need for surgery, where fourth and fifth degree will require surgical intervention. Initial management of closed injuries is expectant (Figure 3), with baseline electrodiagnostic evaluation at six weeks. Fibrillations will appear approximately four to six weeks after injury, while motor unit potentials (MUPs) and nascent units take several weeks to appear. MUPs indicate reinnervation from collateral sprouting from nearby intact axons, while nascent units represent direct reinnervation from the original injured axons. We frequently encounter cases in which a closed nerve injury followed with electrical studies revealed MUPs or nascents, yet the surgeon misinterpreted this as an indication for surgery, it is not. While fibrillations suggest axonal injury, MUPs and nascent units indicate nerve regeneration and suggests a second or third degree type of injury. With closed injuries, if clinical or electrical evidence of recovery is not seen by three months post-injury, surgery may be recommended. Exploration of gunshot wounds is delayed until four months, since these injuries rarely involve actual transection of neural elements. The initial injury is often secondary to heat and stretch from the projectile (Kline, 2009, Midha, 2008).

Management of Nerve Gaps

When tension free primary repair is not possible, a suitable alternative must be pursued. The surgical technique employed in these alternatives is similar, whether it be a nerve graft, conduit, or nerve transfer. The proximal and distal nerve ends are trimmed until normal fascicular structure is revealed (Fig. 4A–C), allowing the surgeon to achieve appropriate realignment. While considerable attention to detail is typically devoted to the microsurgical technique of a nerve repair, an understanding of the longitudinal extent or zone of injury is equally important. We frequently encounter meticulously performed primary nerve repairs that have unfortunately been performed within the zone of injury (Fig. 4A). “Bread-loafing” proximally and distally reveals about one centimeter of scar tissue before a normal fascicular pattern is noted. In the case of a failed primary repair, a 4cm nerve graft is typically needed to ensure that the graft is placed completely outside the zone of injury, and to minimize tension on the repair throughout a full range of motion at the joint.

A thorough understanding of nerve topography is also critical for any successful nerve repair. For example, at the wrist the ulnar nerve consists of 40% motor and 60% sensory fibers.

Therefore, improper realignment of the ulnar nerve during a repair could result in excellent regeneration but poor functional recovery if motor and sensory fascicles are not properly oriented. In addition, all nerve reconstructions should be performed in a tension-free manner to allow for early protected postoperative movement to minimize any scar adherence that could affect recovery. Finally, as a nerve regenerates it will often “hold” or “stall” in an area of known nerve compression, such as the carpal or cubital tunnels. Decompression or transposition of nerves at these known areas of entrapment will frequently enhance functional recovery.

Autogenous Nerve Grafts

Autogenous nerve grafting has long been considered the “gold standard” for repair of irreducible nerve gaps. Autogenous grafts act as immunogenically inert scaffolds, providing appropriate neurotrophic factors and viable Schwann cells (SCs) for axonal regeneration. The choice of autogenous graft is dependent on several factors: the size of the nerve gap, location of proposed nerve repair, and associated donor-site morbidity. Although the sural nerve is the most commonly used autograft, there are many other suitable nerves that can be used as interposition grafts including: the medial and lateral cutaneous nerves of the forearm, dorsal cutaneous branch of the ulnar nerve, superficial and deep peroneal nerves, intercostal nerves, and the posterior and lateral cutaneous nerves of the thigh (Mackinnon, 1988, Norkus, et al., 2005). As with all repair techniques, when utilizing an interposition graft it is critical to avoid any tension at the repair site, for even minimal tension can negatively impact the functional outcome (Terzis, et al., 1975).

Our institution attempts to use noncritical portions of an injured nerve to provide graft material in order to decrease morbidity from nerve grafting. For example, the third web space component of the median nerve can be used as nerve graft material to reconstruct the more critical radial portion of the median nerve. If grafting is performed within a few months of injury, the distal nerve will still contain viable SCs. The proximal portion of the nerve will always contain viable SCs. The anterior branch of the medial antebrachial cutaneous nerve provides an ideal donor for upper extremity reconstruction; this technique limits scarring and donor-site morbidity to the same extremity as the injured nerve. Leaving the posterior branch of the medial antebrachial cutaneous nerve intact preserves sensibility in the ulnar border of the forearm. We are always conscious of the distal end of the sensory nerve that we have not reinnervated such as the distal donor nerve or the third web space component of the median nerve when we are reinnervating just the radial side of the median nerve. The distal, uninnervated nerve is turned end-to-side to a normal adjacent sensory nerve so that even minimum collateral sprouting from the end-to-side repair will provide some sensation to the area and prevent deafferent pain (Dorsi, 2008).

- *Pros* - nonimmunogenic, bridge nerve gap
- *Cons* - sensory loss, scarring, neuroma formation, second incision, limited supply, inferior to tension free primary repair

Nerve Transfers

Nerve transfers convert a proximal injury into a distal one by transferring “near by” redundant nerve function to a distal denervated nerve close to the target. The concept of nerve transfer itself is not new (Kotani, et al., 1971, Tuttle, 1913), but has gained significant momentum over the past decade with many authors reporting good outcomes (Brandt and Mackinnon, 1993, El-Gammal and Fathi, 2002, Samardzic, et al., 2002, Waikakul, et al., 1999). The use of nerve transfers for proximal upper extremity and brachial plexus reconstruction is now well established. Although there are no definitive guidelines for when to use nerve transfers, we follow a general set of parameters to tailor each patient’s procedure. Indications include: brachial plexus injuries or other proximal injuries, long distance from target motor end plates,

delayed presentation, significant limb trauma resulting in segmental loss of nerve function, and previous injury with significant scarring around vital bony or vascular structures. The use of nerve transfers provides some indemnity for return of function in cases where use of nerve grafts or primary repair may prove unreliable. In a proximal radial nerve injury it is possible to restore distal radial nerve function with redundant motor branches from the median nerve (Figure 5A–D). A proximal ulnar nerve injury can be especially problematic, and even early repair typically provides only protective sensation to the digits without returning meaningful function to intrinsic hand muscles (Weber, 2006). In these cases, a distal nerve transfer of the anterior interosseous nerve (AIN) can provide reinnervation prior to degeneration of the neuromuscular junction. Novak et al. (Novak, 2002) described the use of the distal AIN to pronator quadratus (Fig. 6A and C), and directed it to the distal ulnar motor fascicle (Fig. 6B and D). Complex injuries may require even more novel reconstructive strategies (Figure 7A–D). Table 2 shows the most common upper extremity transfers we currently utilize.

With all transfers, when selecting the appropriate donor nerves several criteria must be considered: proximity of donor nerve to the recipient nerve motor end plates, availability of redundant or expendable donor nerve, synergism of donor muscles to target muscles, similarity in number of motor or sensory axons between donor and recipient nerves, and size matching (Table 3).

- *Pros* - typically avoids donor autografts and associated morbidity, proximity of donor nerves to target motor endplates provides earlier reinnervation
- *Cons* – possible loss of function from donor nerve site, donor muscle is no longer an acceptable donor for muscle transfer

End-to-Side Coaptation

Described over a century ago (Balance, 1903, Harris, 1903) end-to-side coaptation is an alternative in cases where the proximal nerve stump is not available or inaccessible; instead, the injured distal stump is coapted to the side of an uninjured donor nerve. In 1994, Viterbo et al. sparked new interest in this technique by reporting axonal regeneration with the use of end-to-side neurorrhaphy in a rat model (Viterbo, et al., 1994). This revitalized interest has given rise to a substantial amount laboratory and clinical work investigating its application (Amr and Moharram, 2005, Lundborg, et al., 1994, Luo, et al., 1997, Tham and Morrison, 1998, Yan, et al., 2002, Zhao, et al., 1997). Although this technique continues to have many advocates, some authors have reported disappointing results. Bertelli and Ghizoni reported their experience in a rat facial nerve model, as well as several clinical cases involving brachial plexus, radial and peroneal nerve lesions. Both experimentally and clinically, they found no evidence of reinnervation from end-to-side coaptation (Bertelli and Ghizoni, 2003, Bertelli and Ghizoni, 2006). Despite these mixed reviews the controversy surrounding end-to-side has primarily focused on the requirement for donor nerve axotomy.

In an end-to-side repair, the term “collateral sprouting” refers to novel axonal regeneration into the recipient stump originating from the donor nerve; the exact origin of these new axons is disputed. Hayashi et al designed an end-to-side coaptation rat model that left the donor nerve intact. Evidence of collateral sprouting was initially reported even in the absence of donor nerve injury (Hayashi, et al., 2004). However, when repeated in a more sophisticated model, it was shown that only sensory axons sprouted de novo without injury (Hayashi, et al., 2008). Matsumoto et al also demonstrated that although collateral sprouting occurs in the absence of donor nerve axotomy, only sensory reinnervation occurs (Matsumoto, et al., 1999). In our laboratory, Brenner et al used a rodent model to demonstrate that donor nerve injury is required for motor regeneration following end-to-side repair (Brenner, et al., 2007). Furthermore, in a recent review by Dvali and Mykатыn on end-to-side repair, the authors concluded motor sprouting following end-to-side repair relies upon donor nerve axotomy, while sensory

sprouting does not (Dvali and Myckatyn, 2008). Therefore, we believe that in order for motor fibers to regenerate, a donor nerve axotomy must be performed. Our current clinical practice has yielded excellent results with low morbidity using well planned nerve transfers and we generally limit the use of end-to-side repairs to reconstruction of noncritical sensory deficits.

- *Pros* – useful when minimal sensory recovery is needed
- *Cons* - will not result in motor recovery without donor axonal injury

Nerve Conduits

A considerable amount of research has been devoted to the development of a viable synthetic or biologic nerve conduit, and currently several commercially available options exist. The authors limit their use of nerve conduits to the repair of noncritical small diameter sensory nerves, gaps less than 3cm, and as a nerve repair wrap. We believe the concentration of neurotrophic factors is critical to advancing nerve regeneration, and if the volume of a conduit increases beyond a critical size (Fig. 8), regeneration is inhibited unless the length of the conduit is dramatically shortened. As surgeons achieve clinical success with short-gap, small diameter nerve injuries, the clinical front is being extended to include larger diameter nerves at longer gaps, and we are beginning to see the failed results of such procedures (Fig. 9A–C)(Moore, 2009).

- *Pros* - Readily available, avoids donor site morbidity, bridges a nerve gap, barrier to scar tissue infiltration, may allow for accumulation of local neurotrophic factors
- *Cons* - Variable outcomes, lack of laminin scaffold and Schwann cells, limits its use to short nerve gaps

Nerve Allografts

The use of donor related or cadaveric nerve allografts is reserved for devastating or segmental nerve injuries. Like all tissue allotransplantation, nerve allografts require systemic immunosuppression; the associated morbidity of immunomodulatory therapy limits the widespread application of nerve allografting. Several techniques (e.g. cold preservation, irradiation, lyophilization) to reduce nerve allograft antigenicity have been described (Anderson and Turmaine, 1986, Campbell, et al., 1963, Evans, et al., 1995, Hiles, 1972, Lawson and Glasby, 1995, Marmor, 1964, Martini, 1985, Singh and Lange, 1975, Wilhelm, 1972, Wilhelm and Ross, 1972). Our clinical protocol is ABO matched donors, small diameter donor nerves, cold preservation (4°–5° C for 7days), three days of pretreatment with FK506 and continued immunosuppression until the tinell sign has crossed the distal graft site.

In contrast to autografts, the use of nerve allografts relies upon the viability of both host and donor SCs. The donor SCs play a dual role following nerve transplantation, acting as support cells for remyelination and as facultative antigen presenting cells. This dual role prohibits a complete removal of these presumed primary sources of major histocompatibility complex (MHC) II molecules and simultaneously maintains the requirement for systemic immunosuppression (Gulati, 1998, Gulati and Cole, 1990, Lassner, et al., 1989, Mackinnon, et al., 1982, Pollard, et al., 1971, Trumble and Shon, 2000, Yu, et al., 1990).

Despite the morbidity associated with systemic immunosuppression, nerve allografting remains an area of intense interest. Unlike solid organ transplantation, nerve allotransplantation requires only temporary immunosuppression. Once adequate host SC migration has occurred into the nerve allograft at approximately 24 months, systemic immunosuppression can be withdrawn. Furthermore, despite the morbidity of immunosuppressive therapy, the commonly utilized immunosuppressive agent FK-506 (Tacrolimus) has been demonstrated to augment neuroregeneration (Feng, et al., 2001, Gold, et al., 1995, Mackinnon, et al., 2001). The

combination of FK-506 with cold preservation of allografts has produced reliable, robust clinical outcomes (Mackinnon, et al., 2001). Current research efforts are aimed at understanding the host response to nerve allotransplantation and mechanisms to modify host and/or donor alloantigen recognition and presentation. This understanding may lead to further refinement of the current immunomodulation strategies and may eventually provide an unlimited supply of nerve graft material.

Careful patient selection and cautious application of these techniques must be emphasized. The senior author (S.E.M) has significant clinical experience with nerve allografts. Since 1988, eleven patients have undergone major reconstructive procedures utilizing cadaveric nerve allografts. Ten of the eleven patients experienced good functional recovery at 24 month follow-up. One patient developed subacute rejection secondary to subtherapeutic immunosuppression and the graft was promptly rejected.

- *Pros* - readily accessible, unlimited supply, bridge nerve gap, avoids donor site morbidity,
- *Cons* – potential side effects of host immunosuppression

Rehabilitation following Nerve Repair/Graft/Transfer

Postoperative rehabilitation and re-education are critical following any nerve repair or transfer. Early goals involve protected range of motion exercises to prevent adhesions at the nerve repair site and to avoid joint stiffness and contractures. Subsequent goals of rehabilitation include sensory and motor re-education. It is well established that re-education is critical for optimizing outcomes following nerve repair or transfer (Oud, et al., 2007). The capacity to re-establish association networks and cortical plasticity facilitates motor and somatosensory reorganization of function (Beaulieu, et al., 2006, Malessy, et al., 2003). This re-organization is dependent on the patient's active participation in sensory and motor rehabilitation.

Conclusion

Advances in laboratory and translational research will undoubtedly continue to shape current clinical practices. While each repair strategy has its own advantages and disadvantages, careful consideration of outcome goals and individual patient factors usually affords a directed surgical approach. The appropriate intervention is ultimately determined by injury type, patient characteristics, and surgeon preferences.

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Figure 1.

Summarizes the various options for nerve repair. Nerve allografts are utilized for large, otherwise irreparable injuries. Nerve transfer use redundant nerve fibers for a proximal nerve injury. The autograft is used to reconstruct a nerve gap. Direct repair is used when there is no intervening nerve gap to create tension. Both end-to-side and nerve conduits are used for noncritical sensory injuries.

Figure 2.
Treatment algorithm for patients with open injuries.

Figure 3.
Treatment algorithm for patients with closed injuries.

Figure 4.

A) Photograph of resected neuroma with disruption of architecture. Sutures are evident from a previous repair, B) Step-wise removal of scar tissue until healthy nerve fascicles are encountered, C) Healthy nerve outside the zone of injury, depicting organized architecture with healthy fascicles prior to nerve grafting. (Images courtesy of Allen Van Beek)

Figure 5.

A and C) Illustration of the exposed median and ulnar nerve, the posterior interosseous nerve (PIN) and extensor carpi radialis brevis (ECRB) are depicted in pink and the anterior interosseous nerve (AIN) and flexor digitorum superficialis (FDS) are seen in green, B and D) Median nerve (green) transfer to the radial nerve (pink). (Adapted by permission from Hand Clinics; Elsevier. 2008 Nov; 24(4):319–340, Brown, JM, Mackinnon, SE. Nerve transfers of the forearm and hand)

Figure 6.

A and C) Illustration and photograph demonstrating the AIN in yellow and the deep motor branch of the ulnar in pink, B and D) Transfer of the AIN (yellow) at the level of the pronator quadratus to the motor branch of the ulnar nerve (pink) (Adapted by permission from Hand Clinics; Elsevier. 2008 Nov; 24(4):319–340, Brown, JM, Mackinnon, SE. Nerve transfers of the forearm and hand)

Figure 7.

A) Large neuroma in continuity of the proximal median nerve, B) microdissection of the injury and the distal branches, C and D) Illustration and photograph of the finished repair utilizing the LABC as both nerve graft and nerve transfer to the sensory branch of the median nerve, the ECRB was transferred to the PT and the supinator was directed to the AIN. The sensory portion of the median nerve to the 3rd web space was not injured and was protected.

Figure 8.

Illustrates the importance of diameter in the volume of a nerve gap. The formula for volume is $V = \pi r^2 L$, thus doubling the radius (conduit B) requires a length $\frac{1}{4}$ of conduit A to maintain an equal volume. (Symbols: V = volume, r = radius, π = pi (~ 3.14), L = length). (Permission for reproduction from Hand; Springerlink 2009 Jan 10, Epub, Moore, AM et al. Limitations of conduits in peripheral nerve repairs.)

Figure 9.

A) Photograph of a large neuroma in continuity following repair with a large PGA nerve conduit, B) The affected segment of nerve was resected leaving a 6 cm nerve gap, C) A-histology of the distal conduit revealed dense fibrinous scar tissue with no discernable nerve structures, B -the mid-conduit section revealed disorganized architecture with no clear axonal organization, C – proximally, normal nerve architecture was demonstrated, D) Photograph of final repair with interposition graft. (Permission for Reproduction from Hand; Springerlink 2009 Jan 10, Epub, Moore, AM et al. Limitations of conduits in peripheral nerve repairs.)

Table 1

Classification of Nerve Injury

Degree of Injury		Degree of Recovery	Rate of Recovery	Tinel	EMG Nerve Conduction Studies	
I	Neurapraxia	Complete	Fast ≤ 4 months	—	Fib	MUP's
II	Axonotmesis	Complete	Slow, 1" per month	(+) Advances	+	+
III		Incomplete	Slow, 1" per month	(+) Advances	+	+
IV	Neuroma In-continuity	None	None	Stationary	+	—
V	Neurotmesis	None	None	Stationary	+	—
VI	Mixed Injury (I to V)	Mixed	Variable ‡	Depends on degree of injury (I–IV)	+	+

* Recovery can vary from excellent to poor depending on the amount of scarring and the sensory versus motor axon misdirection to target receptors

‡ Mackinnon injury where some fascicles may be injured and others show varying degrees of injury

— EMG= Electromyography, MUP's = Motor unit potentials

Table 2

Nerve Transfer Table

Injured Nerve	Missing Function	Donor Nerve	Recipient Nerve
Suprascapular	Shoulder abduction, external rotation	Distal Spinal Accessory	Suprascapular
Long thoracic	Scapula stabilization, forward abduction	Medial pectoral, thoracodorsal, intercostal	Long thoracic
Axillary	Shoulder abduction	Triceps branch of radial nerve, medial pectoral	Axillary
Musculocutaneous	Elbow flexion	Ulnar nerve fascicle to FCU; Median nerve fascicle to FCR, FDS	Brachialis branch; Biceps branch
Spinal Accessory	Shoulder elevation and abduction	Medial pectoral, C7 redundant fascicle	Spinal Accessory
Ulnar	Intrinsic hand	Terminal AIN (branch to pronator quadratus)	Ulnar nerve fascicles to deep motor branch
Median	Thumb opposition	Terminal AIN (branch to pronator quadratus)	Median (recurrent) motor
Median	Finger flexion	FCU, Brachialis	AIN
Median	Pronation	ECRB, FCU, FDS	Pronator branch
Radial	Wrist and finger extension	FCR, FDS ± PL	ECRB and PIN
Sensory			
Median sensory	Thumb-index key pinch area sensation	Ulnar common sensory branch to 4 th web space	Median common sensory branch to 1 st web space
Median sensory	Thumb-index key pinch area sensation	Dorsal sensory branch of the ulnar nerve	Median common sensory branch to 1 st web space
Ulnar sensory	Ring and small finger sensation	Median common sensory branch to the 3 rd web space	Ulnar common sensory branch to the 4 th web space; ulnar digital nerve to the small finger
Ulnar sensory	Ulnar border of the hand sensation	Lateral antebrachial	Dorsal sensory branch of the ulnar nerve

FCU = flexor carpi ulnaris, FCR = flexor carpi radialis, FDS = flexor digitorum superficialis, AIN = anterior interosseous nerve, ECRB = extensor carpi radialis brevis, PIN = posterior interosseous nerve, PL = Palmaris longus

Table 3

Number of available fibers/axons

C5 - 16,000	Suprascapular - 3500	Radial - 19,000
C6 - 27,000	Axillary - 6500	Spinal accessory - 1600
C7 - 23,000	Musculocutaneous - 14,000 [*]	Thoracodorsal - 2000
C8 - 30,000	Median - 18,000 ^{**}	Intercostal - 1000
T1 - 19,000	Ulnar - 16,000 [‡]	Medial Pectoral - 1170–2140

^{*} ½ motor and ½ sensory axons

^{**} AIN – 900 fibers at the elbow & 600 at the wrist

[‡] fibers at the level of intrinsic – 1200 fibers