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Updates in peripheral nerve surgery of the upper extremity: diagnosis and treatment options

Ruth En Si Tan^, Shubashri Jeyaratnam^, Aymeric Y. T. Lim

Department of Hand and Reconstructive Microsurgery, National University Health System, Singapore, Singapore

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Correspondence to: Ruth En Si Tan, MBBS. Department of Hand and Reconstructive Microsurgery, National University Health System, Level 11, Tower Block, 1E Kent Ridge Road, Singapore 119228, Singapore. Email: ruth_tan@nuhs.edu.sg.

Abstract: The loss of function resulting from peripheral nerve injuries confers a significant burden to the patient and society. The treatment of peripheral nerve injuries requires an accurate diagnosis and formulation of a functional reconstructive plan. Advances in peripheral nerve imaging complement electrodiagnostic studies, and provide us with detailed information regarding the status of nerve injury, repair, and regeneration in order to prognosticate recovery and determine the need for surgical intervention. When direct nerve repair is not possible, the methods for bridging a nerve gap are the nerve autograft, allograft and conduit. While current research supports the use of conduits and nerve allografts for shorter nerve gaps, the nerve autograft still remains the gold standard for bridging a nerve gap. When direct nerve repair or nerve grafting fails, or is anticipated to be insufficient, nerve transfers are an alternative for reconstruction. Knowledge of axonal counts, upper limb innervation patterns, location and clustering of upper limb peripheral nerves allows for the design of new nerve transfers. The options of nerve transfers for radial, ulnar and median nerve injuries are outlined, as well as their outcomes. Nerve transfers are an attractive option for restoring motor and sensory function while minimizing donor site morbidity. However, one must consider their limitations, and preserve donor sites for secondary tendon transfer options. This article presents the latest information regarding the imaging of peripheral nerves, methods to bridge a nerve gap, and nerve transfers to aid the peripheral nerve surgeon in choosing a reconstructive plan.

Keywords: Nerve imaging; nerve autograft; nerve allograft; nerve conduit; nerve transfer

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Introduction

Significant functional loss and socio-economic consequences result from peripheral nerve injuries (1). Common etiologies include trauma, iatrogenic injuries, tumors and inflammatory diseases. The patient's ability to reincorporate the affected limb into daily activities is determined by successful functional reconstruction, including the reinnervation of the motor and sensory end organs after the insult. Despite significant advances in technology, imaging and surgical techniques, recovery remains unpredictable and attaining full functional recovery remains a challenge to the medical and surgical fraternities (2).

This article presents the latest updates in peripheral nerve surgery in 3 key areas:

(I) Advances in diagnostic modalities;

(II) Methods for bridging a nerve gap;

^ ORCID: Ruth En Si Tan, 0000-0002-0857-3167; Shubashri Jeyaratnam, 0000-0002-7026-9588.

(III) Nerve transfers for radial, ulnar and median nerve injuries.

Advances in diagnosis

The imaging of nerve injuries has advanced significantly in the last few decades and the ease and availability of scans to help with diagnostic and treatment modalities has opened new avenues of monitoring and therapeutics. Modalities now common in clinical practice include ultrasound, magnetic resonance imaging (MRI), nerve conduction studies and electromyography. Yet, there are still missed injuries, difficulty with tracking regenerative processes and challenges with monitoring post-surgical recovery as well as determining a threshold for surgical intervention (3).

MRI

MRI is now commonplace in most centres. While it does offer excellent anatomical delineation which can be useful for pre-operative planning, one may not have adequate time afforded for a scan in a time-critical emergency, and obtaining a scan after office hours may not be possible. The role of MRI in diagnostic and post-operative monitoring is still fraught with uncertainties including the optimal timeline for performing a scan, when the signal change from a nerve lesion becomes appreciable, and whether the MRI signal evoked by the nerve after a lesion can return to normal without surgical intervention (4).

Magnetic resonance neurography (MRN) has emerged as a better option to provide anatomic delineation of peripheral nerves due to its ability to isolate the entire peripheral nerve from surrounding structures and vasculature, by harnessing the principle of longer T2 isolation time in nerve tissue (5). With the fine-tuning of fat suppression techniques and emergence of new contrast agents like supramagnetic iron oxide and gadaflourine M which are nerve-selective (6), its ability to differentiate nerve from other pathologies, locating the segment of injury and tracking of progression or deterioration with serial studies has proven to be a significant improvement from previously (7,8). In the pediatric population in particular, missing a nerve injury that may present more subtly can have drastic long term implications on the patient, and one may consider MR neurography in a closed peripheral nerve injury to guide the need for operative intervention (e.g., hematoma, pseudoaneurysm) (9).

MRN does not reveal pathophysiologic information about functional integrity of axons in peripheral nerves. However, this can theoretically be overcome with functional MRI techniques like diffusion-weighted imaging (DWI) or diffusion tensor imaging (DTI) which provide objective quantitative information on the physiopathologic status of the involved peripheral nerve segment, including nerve viability and tension of a repair (10). Although promising, this has not yet been applied in routine clinical practice. In rat models, diffusion MRI has been shown to prognosticate the success of nerve repair, which if applied clinically, could help identify patients in whom repairs are less likely to succeed and requiring earlier intervention, hence decreasing the downtime awaiting clinical or electrophysiological recovery (11). This is especially promising given it is a non-invasive modality that can be used to detect nerve recovery as early as one week after injury even in the presence of edema, as seen in an *ex vivo* rat sciatic nerve model (12). DTI has been described in a small case-control study in humans with nerve injuries at the wrist, showing sensitivity to nerve trauma and recovery (13). More recently, a study investigating DTI values before and after cubital tunnel decompression for ulnar neuropathy showed correlation with clinical outcomes (14). A meta-analysis of normal DTI values of peripheral nerves in the upper limb has also been performed in order to form a basis for comparison for future studies (15). With larger scale clinical studies involving more anatomic sites and pathology, as well as technical familiarity, DTI may become an imaging modality applied in routine clinical practice in the future.

Ultrasound

Ultrasound remains an excellent point of care test and has been popularized in the pre-operative evaluation of peripheral nerve lesions. Speed, accessibility, cost, resolution, and the ability to perform dynamic studies are some of the advantages of the usage of ultrasound over MRI (16). In trauma, it is commonly used for evaluating loss of nerve continuity or neuroma (17) and rapid availability is an obvious advantage over the MRI (18). It can also be used to evaluate complications of repair such as the detachment of direct nerve sutures or neuroma growth, as well as determining timing for revision operations (19).

Where an MRI or computed tomography (CT) scan may already have been done prior, technology also exists in some centres to fuse this data with real-time ultrasound. The ultrasound can be used intra-procedurally or operatively and can be especially useful in post-tumor irradiated fields where both anatomical distortion and post-surgical

enhancement add technical complexity in deciding which area to biopsy or resect (20).

Positron emission tomography

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a non-invasive imaging modality which uses radioactive tracer uptake in tissue dependent on metabolic activity to identify potential sites of pathology. Where it has established roles in tumor staging and surveillance, its role in peripheral nerve injuries is less defined and still largely limited to animal studies as an alternative non-invasive diagnostic modality. Lee *et al.* (21) described a study model on the rat sciatic nerve, utilizing the principle of glucose hypermetabolism in denervated skeletal muscle. It was found that the signal intensity of ^{18}F-FDG uptake in denervated skeletal muscle was strongly related to nerve injury severity in partial nerve injury, although the temporal relation of FDG uptake and its clinical utility remains to be defined. Nam *et al.* (22) performed a rat study evaluating peripheral neuropathic pain and suggested that a fused MRI PET scan may help with the objective diagnosis of neuropathic pain from peripheral nerve injury and clarify the anatomic location of interest better.

Choosing an imaging modality

Ultrasound and MRI remain the commonest modalities for peripheral nerve imaging to date. While ultrasound has obvious accessibility advantages, the anatomical delineation provided by the MRI remains superior. One may consider what information is critical, the timeline for intervention, the need for serial monitoring and choose an imaging modality accordingly. For instance, an ultrasound could be used as a point of care measure in a critical revascularisation that is combined with a nerve injury, to make an index assessment of the nerve injury pre- or intra-operatively given that there would be no time for a pre-operative MRI. This may be done by the surgeon and the images saved for future reference. Once the patient is stable and the limb is out of danger, one can follow up with an MRI for more complex pre-operative planning for the final reconstructive procedure of choice. In a non-time critical scenario where recovery may be taking longer than usual and the viability of the nerve reconstruction is in question, potential combination modalities such as an index MRI and serial ultrasounds to monitor treatment and progress are also a viable option especially with the advent of technology that can fuse this data. The availability of an ultrasound machine in the clinic can also help with a baseline assessment of the state of the nerve as part of the surgeon's initial evaluation and decide if further imaging is warranted. The strength of the abovementioned advancements in these imaging modalities is the ability to detect and prognosticate nerve injury and recovery earlier than electrodiagnostic studies, and could potentially be powerful tools if translated into clinical practice.

Methods for bridging a nerve gap

Nerve autograft

Direct end to end epineural suture is still the preferred method of nerve coaptation to restore sensory and motor function. This is not feasible in situations where the zone of injury is wide, such as in crush and avulsion injuries.

In such situations, autografts are currently considered the gold standard for bridging a nerve gap (2). The autograft is essentially native nerve harvested from a dispensable location in the patient's body. It has the endogenous components required for nerve growth and regeneration, including Schwann cells, an internal scaffold consisting of the epineurium, fascicles and endoneural tubes, as well as surface adhesion molecules.

Common donor nerves include the distal posterior interosseous nerve (for digital nerve defects), medial and lateral antebrachial cutaneous nerves and sural nerves (for nerves of larger diameter and gap) (23). For the reconstruction of nerves of larger diameters, the smaller donor nerves need to be 'cabled' or layered in order to achieve a similar diameter to the recipient nerve. Nerve grafts are typically reversed in the proximal to distal direction to prevent regenerating nerves from growing down a branch into a dead end (23). An epineural repair is most commonly performed as fascicular repair has not been shown to be superior. Although it is regarded as the gold standard for bridging a nerve gap, the autograft carries the disadvantages of donor site morbidity and reduced availability.

Disadvantages of nerve autografts have led to a search for substitutes which are able to rival the autograft in its ability to promote nerve regeneration while eliminating the above disadvantages. The two alternatives are the nerve allograft and nerve conduit—these do not have donor site morbidity and or availability issues, but have an associated monetary cost for the product used (24).

Table 1 Types of grafts and conduits

Type	Examples
Autografts	Posterior interosseous nerve, medial and lateral antebrachial cutaneous nerves, sural nerve
Processed nerve allografts	Human nerve allograft (Avance, AxoGen Corporation, USA)
Conduits	
Autologous tissue	Muscle, vein
Endogenous materials	Collagen (Neuragen, Ingtegra Neurosciences, USA), fibrin, fibronectin, laminin, hyaluronic acid
Naturally occurring biomaterials	Porcine small intestinal submucosa matrix (Axoguard, Cook Biotech Products, USA), silk fibroin, keratin, alginate, chitosan
Synthetic biomaterials	PGA (Neurotube, Synovis Micro Companies Alliance, USA), PLCL (Neurolac, Polyganics Inc., Netherlands), PVA (Salubridge/SaluTunnel, Salumedica LLC, USA), PLA, PLLA, PLGA, PU, Silicon

PGA, polyglycolic acid; PLCL, poly(D,L-lactide-co-ε-caprolactone); PVA, polyvinyl alcohol; PLA, polylactic acid; PLLA, poly-l-lactic acid; PLGA, poly(lactic-co-glycolic acid); PU, polyurethane.

Nerve allograft

Nerve allografts are human cadaveric nerves used as an alternative for bridging a nerve gap. Due to the requirement and risks of systemic immunosuppression of fresh nerve allograft transplantation (25,26), the type of nerve allograft that is used most commonly in clinical practice today is the processed nerve allograft (PNA), which is essentially a decellularized allograft, without the cellular components that produce immunogenic reactions. The extracellular matrix and basal lamina are maintained, together with the internal structure of the epineurium, fascicles and endoneural tubes. Laminin, which is also retained, provides axonal support and guidance cues for nerve regeneration (27). PNAs have become more commonly used in clinical practice to avoid the drawbacks of the autograft (24), and research concerning allografts has been targeted at proving their equivalence to autografts in terms of functional outcomes.

Nerve conduits

A nerve conduit is essentially a 'hollow tube' in its most basic form, providing a scaffold for nerve regeneration. Materials that may be used as conduits include autologous tissue, materials endogenous to the human body, as well as naturally occurring and synthetic biomaterials (see *Table 1*). Although still mainly limited to animal models and *in vitro* testing, developments in the fabrication of nerve conduits (2) aims to mimick the natural process of nerve regeneration by enhancing the functional capability of conduits, creating more than just a 'hollow tube'. This is achieved through a combination of methods. Firstly, the release of biological substances or neurotrophic growth factors from the conduit can promote and regulate nerve growth (28,29). Secondly, the microstructure of the nerve conduit's surface can be specifically designed with guidance cues to promote growth of the axon and proliferation of Schwann cells (30-32). Thirdly, exogenous electrical stimulation, used in combination with a conductive conduit can also aid in Schwann cell proliferation, adhesion and neuronal protein expression (31).

Classification

Table 1 provides a classification and examples of various materials used to bridge a nerve gap (2). Regardless of the origin, an ideal material used to bridge a nerve gap should have the following properties in order to support nerve regeneration and direct axons growth from the proximal to distal site:

(I) Biocompatible with surrounding tissues;
(II) Should not degrade faster than the nerve regeneration rate;
(III) Allow for vascularization of regenerating tissue;
(IV) Limit scar tissue formation and ingrowth of fibrous tissue;
(V) Provide directional guidance, release of growth factors, and allow for adhesion and proliferation of relevant cell types (e.g., Schwann cells) in order to promote nerve regeneration;
(VI) Readily available;
(VII) Cost-effective.

Outcomes

Studies on digital nerves alone

It is generally accepted that a 4mm gap is the maximum length for digital nerves to be repaired end to end with minimal tension (33). Factors affecting sensory recovery include (34) age, severity and mechanism of injury, gap length (more than 3–5 cm in length), and timing of repair (better 2 point discrimination results with repairs within 15 days of injury) (35).

Currently, choosing a technique for bridging a gap in digital nerves is dictated by gap length, donor site morbidity from graft harvesting, operation time and surgical expertise (34). Randomized controlled trials comparing the outcomes of autograft, allograft and conduit are limited. The current literature suggests that autografts and PNAs are similar in sensory recovery for digital nerve repair for gaps of 20 mm or less. Conduits tended to perform inferiorly to autografts and PNAs for longer gaps, but had similar outcomes for shorter nerve gaps of 10 mm or less. Hence, artificial or biological conduits are therefore more suited for short nerve defects, especially for vein grafts which have a propensity to collapse. Autografts are still preferred for longer defects.

None of these modalities are complication-free, although the highest rate of complications occurs with conduit use (24). Complications related to conduits were related to extrusions requiring removal, whereas complications for autografts and processed allografts were mainly related to donor site neuromas and infections. *Table 2* provides a summary of the best quality evidence for outcomes comparing direct repair, autograft, allograft and conduit for digital nerves and sensory nerve defects in the hand.

Studies on mixed and motor nerves

The range of meaningful recovery reported after autografting of mixed and motor nerves is less predictable than digital nerves. Results vary widely across studies due to heterogeneity in terms of age, injury mechanism, time to reconstruction, nerves injured, level of nerve injury, repair technique and length of follow-up. In a review of studies reporting outcomes of autografting for motor or mixed peripheral nerve defects, Huayllani *et al.* (41) reported Medical Research Council (MRC) grade 3 or greater recovery in 48% to 84%, and grade 4 or better outcomes in 21% to 51% of patients for motor function (41-44). In another review, Geissler and Stevanoic found that recovery of motor function of MRC grade 4–5 and sensation of S3+ to 4 was estimated at 45% (23). It is upon these benchmarks to which the outcomes of PNAs are compared.

In the two largest clinical studies to date, Leckenby *et al.* (45) and Safa *et al.* (46) studied 171 and 475 PNA repairs respectively at various anatomical sites. Leckenby *et al.* reported 77% of patients achieving a sensory recovery of S3 or more and 36% of patients with motor recovery of grade 3 or more, while Safa *et al.* reported 84%, 71%, and 83% of meaningful recovery for sensory, mixed and motor nerves respectively, with a meaningful recovery defined similarly as S3 or grade 3 or more (using the Mackinnon and Dellon modification of the Medical Research Council Classification sensory and motor scales). The average gap length was 27 and 24 mm respectively in these two studies. Safa et al subdivided repairs into gap lengths of <15, 15–29, 30–49 and 50–70 mm, and found that the group with gap length of <15 mm had the best meaningful recovery of 91%, compared to 69% in the group with gap length of 50–70 mm in the upper limb. Similarly, Leckenby *et al.* found a negative correlation between allograft length and outcome. Additionally, the diameter of the PNA was also found to correlate negatively with outcome. This makes logical sense as PNAs, like autografts, are affected by inadequate revascularisation when used for longer lengths and larger calibers due to central necrosis (47). In addition, both studies recorded poorer functional outcomes on PNAs used in the lower limb compared to the upper limb.

Apart from restoring motor or sensory function, Leckenby *et al.* (45) in the same study mentioned above reported the use of PNA for alleviating neurogenic pain. A reduction of the median numeric rating pain score from 7 to 3 was found, with a significant reduction in requirement of pain medications, as well as 57% of patients having a meaningful sensory recovery (S3 or more).

At present, there is a paucity of randomized controlled trials and comparative studies reporting the outcome of autograft and PNA for mixed and motor nerve gaps. The majority of studies involving allografts are derived from the RANGER® registry, an industry sponsored multicenter clinical registry which collects data for peripheral nerve injuries repaired with PNAs (Avance Nerve Graft, AxoGen Corporation, USA). Further comparative studies are required to establish the true equivalence of allografts and autografts for specified nerve gaps, locations and types of nerves. In summary, the current literature (see *Table 3*), albeit with its limitations, supports the use of PNAs in mixed motor and sensory nerves for gaps of up to 30 mm on average.

Table 2 Randomized controlled trials, systemic reviews and meta-analyses reporting outcomes in the use of autograft, allograft and conduits for digital nerve gaps

Author	Type of nerve and gap	No. of repairs	Follow-up	Outcomes	Author's conclusions
Randomized controlled trials					
Weber *et al.* [2000] (33)	Nerve defects in the hand; average 5 mm gap	56 AG and DR; 46 PGA conduits	AG and DR 8.1, PGA conduit 9.4 months	M2PD: ≤4 mm gap: PGA 3.7, DR 6.1; 5–7 mm gap: PGA 8.9, DR 6.0; ≥8 mm gap: PGA 6.8, AG 12.9	PGA conduit better moving sensory recovery than AG for ≥8 and ≤4 mm, but overall no significant differences
Bertleff *et al.* [2005] (36)	Nerve defects in the hand; gap ≤20 mm for all patients	21 Neurolac (PLCL), 13 DR	12 months	S2PD and M2PD no difference between both groups	Nerve gaps of up to 20 mm in the hand can be treated with a nerve conduit instead of a nerve graft
Calcagnotto and Braga Silva [2006] (37)	Digital nerves, average gap 15 mm	25 sural nerve graft, 25 vein conduit with interposition of PIN nerve segment	10.4 months	S2PD and M2PD no difference between both groups	Outcomes were equal in both groups. Both patient age and age of the nerve lesion independently affected results
Rinker and Liau [2011] (38)	Digital nerves, average gap 10 mm	36 PGA conduit, 32 autologous vein conduit	12 months	S2PD and M2PD no difference between both groups	Sensory recovery was equivalent in both groups with fewer complications noted in autologous vein conduit group
Means *et al.* [2016] (27)	Digital nerves, average gap 12 mm	6 PNA, 9 hollow conduit	12 months	MP2D: PNA 5 mm, Hollow conduit 7 mm; S2PD: PNA 5 mm, Hollow conduit 8 mm	PNAs produced more consistent functional sensory outcomes compared with hollow conduits
Systemic reviews and meta-analyses					
Paprottka *et al.* [2013] (34)	Digital nerves with gap of up to 4 cm	2,997 nerves: 384 AG, 115 artificial conduit, 102 vein conduit, 56 muscle and muscle in vein reconstructions, 31 ETS repaire, 2 digital artery reconstructions, 924 digital replantation, 1,383 DR	At least 12 months	No difference in sensory outcomes overall. However, DR and AG had slightly more S4 (using the Mackinnon and Dellon sensory scale) than other methods	Authors recommendation for gaps of <10 mm: vein graft or artificial conduit; 10–30 mm: artificial conduit or PIN graft; >30 mm: AG or ETS coaptation
Kim *et al.* [2018] (35)	Digital nerves; average gap 15 mm	818 nerves, including: 31% nerve graft, 11% synthetic conduits, 10% vein conduit, 35% DR	22 months	81% had sensory recovery of S3+/S4 (using the Mackinnon and Dellon sensory scale). Significant better S2PD seen in nerve reconstructions performed within 15 days of injury and defect length of <13 mm	Digital nerve reconstruction provides good to excellent sensory recovery in up to 81% of patients. No significant functional differences across age, follow-up time, injured digit or side, or reconstructive technique

Table 2 (*continued*)

Table 2 (*continued*)

Author	Type of nerve and gap	No. of repairs	Follow-up	Outcomes	Author's conclusions
Herman and Ilyas [2020] (39)	Digital nerves; average gap: PNA 15.4 mm, AG 24.7 mm, conduit 13.4 mm	611 nerves analysed for S2PD outcomes: 125 AG, 138 PNA, 90 conduit, 258 DR	9.4 to 23.2 months	Highest percentage of patients with S2PD ≤6 mm was seen in the autograft group (28%), followed by PNA (23%), conduits (19%)	AG and PNA are comparable, both superior than conduit repair
Mauch *et al.* [2019] (24)	Digital nerves; average gap: AG 22 mm, allograft 13 mm, conduit 12 mm	70 AG, 66 PNA, 101 conduit, 569 DR	13 to 42 months	Percentage of patients with sensory recovery of S3+ to S4 (using the British Medical Research Council Sensory Scale) was similar in AGs (88%) and PNAs (86%), compared to conduits (77%)	AG and PNA repairs demonstrated similar rates of normal or near normal sensation. Conduits resulted in a higher rate of incomplete recovery of sensation and complications
Braga Silva [2021] (40)	Digital nerves; gaps stratified into subgroups: <5.49, 5.5–10.99, 11–17.99 mm	961 digital nerves, including: 158 AG, 299 PNA, 114 PGA tubes, 152 collagen tubes, 113 vein graft, 122 DR	6 and 12 months	Conduits and AGs had no significant differences in S2PD and M2PD outcomes. However, the group with 11–17.99 mm gap had significantly greater improvement in M2PD for AG group compared to conduit	Data insufficient to guide treatment, many studies not able to identify the better treatment due to small sample sizes and low quality evidence

AG, autograft; DR, direct end-to-end repair; PGA, polyglycolic acid; PLCL, poly(D,L-lactide-co-ε-caprolactone; S2PD, static 2 point discrimination; M2PD, moving 2 point discrimination; PIN, distal posterior interosseous nerve; PNA, processed nerve allograft; ETS, end to side.

Table 3 Studies reporting use of processed nerve allograft for mixed and motor nerve injuries

Author	Type of nerve and gap	No. of repairs	Follow-up	Outcomes	Author's conclusions
Cho *et al.* [2012] (48)	35 sensory, 13 mixed, 3 motor nerves. Average gap 23 mm (range, 5–50 mm)	51 PNA	296 days	S3 or M4 and above achieved in 86%. MR in 89% of digital nerve repairs, 75% of median nerve repairs, and 67% of ulnar nerve repairs	PNAs effective for nerve gaps of 5 to 50 mm. Outcomes compare favorably with those reported in the literature for nerve autograft, and exceed those reported for tube conduits
Brooks *et al.* [2012] (49)	49 sensory, 18 mixed, 9 motor nerves. Average gap 22 mm (range, 5–50 mm)	76 PNA	264 days	MR in 87%. Mixed nerve injuries: M4–5 motor function recovered in 47% of cases and M3 in 32% of cases. No significant differences in percentage of MR when stratified by gap length, nerve type, age, mechanism of injury	PNAs effective for nerve gaps of 5 to 50 mm. Outcomes compare favorably with those reported in the literature for nerve autograft, and exceed those reported for tube conduits
Zhu *et al.* [2017] (50)	39 sensory, 19 mixed, 6 motor nerves. Average gap 27 mm (range, 10–60 mm)	64 PNA	355 days	MR in 75%. Gap length (≤30 *vs.* ≥50 mm) and site of injury (low versus high) had significant correlation with outcome	PNAs effective for nerve gaps of 10–60 mm in the hand and upper extremity
Leckenby *et al.* [2020] (45)	135 acute nerve injuries, defined as <6 weeks (of which there were 110 sensory and 25 motor nerves),	171 PNA	417 days	MR in 77% for motor recovery, 36% for sensory recovery. Graft length and diameter, usage in the LL were negatively correlated with reported outcomes	Allografts are useful for wide application of nerve problems (including chronic pain)
	10 delayed nerve injuries			Patients treated for chronic pain had significantly lower analgesia requirement, 57% had MR in sensation	Caution must be applied to the use of long grafts with larger diameters
	26 chronic nerve injuries. Average gap and diameter of the allografts used was 27 mm (range, 8–100 mm) and 2 mm (range, 1–5 mm) respectively				
Safa *et al.* [2020] (46)	386 sensory, 77 mixed, 12 motor nerves; average gap 24 mm (maximum 70 mm)	475 PNA	Subjects had follow-up assessments at a time-point commensurate with the approximated distance for reinnervation, based on 1–2 mm/day regeneration to the target zone of reinnervation	MR in 82%. In the UL, significant differences were noted between mechanism of injury subgroups (MR in 74% of complex injures compared to 85% in lacerations and 94% in neuroma resections) and by gap length (MR in 91% of gap <15 mm compared to 69% of gap 50–70 mm)	Results support use of PNA of up to 70 mm, results comparable to historical literature for nerve autograft and exceed that of conduit

Unless otherwise stated, MR, meaningful recovery, and refers to sensory recovery of S3 and above, or M3 and above on the Mackinnon and Dellon modification of the Medical Research Council Classification sensory and motor scales. PNA, processed nerve allograft; LL, lower limb; UL, upper limb.

Table 4 Nerve transfer options for radial, ulnar and median nerve injuries

Injured nerve	Functional deficit	Recipient nerve	Donors	Outcomes
Radial nerve	Wrist extension	Branch to: ECRB, ECRL	Branch to: FDS, PL, FCR, PT, PQ	Garg *et al.* (52): wrist extension: 92.59% ≥ grade 4, ≥96% grade 3; finger extension: 56.52% ≥ grade 4, ≥78% grade 3
	Finger and thumb extension	PIN		
Ulnar nerve	Intrinsic function	Deep motor branch of the ulnar nerve	AIN	Thakkar *et al.* (53): 85% of patients with end to end transfers and 75% of patients with end to side transfers recovered intrinsic function of ≥ grade 3
	Sensory	Ulnar sensory nerve; dorsal ulnar cutaneous nerve; ulnar digital branch of the little finger	3rd webspace sensory branch of median nerve (ETE, ETS or STS with nerve graft); proper median nerve (ETS); palmar cutaneous branch of median nerve (ETE) Superficial radial nerve (ETE)	Flores (54): 40% S3+ or S4 sensation; Sallam *et al.* (55): 58.3% S3 or greater
Median nerve	Thumb opposition	RMB	Branch to: ADM, FDM, ODM, ulnar nerve branch to the 3rd lumbrical	Bertelli *et al.* (56): grade 4 abductor pollicis brevis strength restored
	Thumb and index finger flexion	AIN	Branch to: supinator, ECRB, brachioradialis, brachialis	Multiple case series (57-62): grade 2–4 for FDP, grade 3–4 for FPL
	Sensory	Index finger RDN and thumb UDN	SRN; 4th webspace CDN; dorsal sensory ulnar nerve	Bertelli and Ghizoni (63): protective or better sensation restored for all patients

ECRB, extensor carpi radialis brevis; ECRL, extensor carpi radialis longus; FDS, flexor digitorum superficialis; PL, palmaris longus; FCR, flexor carpi radialis; PT, pronator teres; PQ, pronator quadratus; PIN, posterior interosseous nerve; AIN, anterior interosseous nerve; ETE, end to end; ETS, end to side; STS, side to side; RMB, recurrent motor branch of median nerve; ADM, abductor digiti minimi; FDM, flexor digiti minimi; ODM, opponens digiti minimi; FDP, flexor digitorum profundus; FPL, flexor pollicis longus; RDN, radial digital nerve; UDN, ulnar digital nerve; SRN, superficial radial nerve; CDN, common digital nerve.

Recommendations

While the data on usage of PNAs continues to grow and ongoing research into better nerve conduits appears promising, the autograft still remains the gold standard for bridging a nerve gap. In general, current research supports the use of conduits in digital nerve gaps of 10 mm or less and the use of PNAs for mixed, motor or sensory nerves in gaps of 30 mm or less.

Nerve transfers for radial, ulnar and median nerve injuries

Tendon or nerve transfers are utilised when direct nerve coaptation or grafting techniques fail or are anticipated to be insufficient in restoring function. Although tendon transfers for radial, median and ulnar nerve injuries have had a predictable outcome and are not time-sensitive, disadvantages include sacrifice of a functional muscle unit, scarring, and adhesions (51). Nerve transfers have been popularized in the last two decades as an alternative option for restoring function while minimizing donor site morbidity. This section reviews the options and outcomes of nerve transfers for radial, median and ulnar nerve injuries (see *Table 4*).

General principles

For a nerve transfer to be successful, the donor nerve should reach the recipient nerve within a reasonably short distance in order for reinnervation and motor recovery without a graft. Sacrifice of the donor nerve should also have minimal

or acceptable loss of function, and should have sufficient axons to reinnervate the recipient (64). Cheah *et al.* (64) and Lee *et al.* (65) have provided a blueprint for the design of suitable nerve transfers in their analysis of axonal counts, upper limb innervation patterns, location and clustering of upper limb peripheral nerves. Motor nerve transfers should be performed early, accounting for the time required for reinnervation prior to significant motor end plate degeneration. Comparatively, sensory transfers can be performed relatively later, and can be successful even several years after injury, although the exact timing is unknown (66,67).

Several factors affect the outcome of nerve transfer surgery. Firstly, factors that reduce the time required for nerve renegeration have a more favorable outcome. These include a shorter time from injury to surgery, proximity of the nerve transfer coaptation site to the motor end plates of the recipient musculotendinous unit, and younger age of the patient (68,69). Secondly, factors that affect the quality of nerve regeneration can also predict a more favorable outcome. These include adequate strength of the donor nerve (more than MRC grade 4), use of pure motor or sensory fascicles in the donor nerve (depending on whether motor or sensory function is to be reconstructed), and avoidance of an intermediary nerve graft (70). In addition, the patient should be free of joint and musculotendinous contractures, and be cognitively able to and willing to participate in post-operative rehabilitation (70).

Radial nerve

Humeral fractures and iatrogenic insults account for most radial nerve injuries in the arm (52), resulting in loss of wrist, finger and thumb extension. A systemic review by Garg *et al.* (52) reviewed the outcome of 7 articles (of level IV and V evidence) with a total of 28 patients following distal nerve transfer of median nerve branches to restore wrist and finger extension respectively. A proportion of 96% (n=27) had high radial nerve palsy and one had low radial nerve involvement. The most common transfer performed for wrist extension was a branch of the flexor digitorum superficialis (FDS) to the extensor carpi radialis brevis (ECRB), while the most common transfer performed for finger extension was a branch of the flexor carpi radialis (FCR) to the posterior interosseous nerve (PIN). These are recommended in view of donor and recipient nerves having synergistic function. The mean follow-up period was 19 months and time to surgery was 6.7 months. A total of 92.59% and 56.52% had at least grade 4 power (as defined by the MRC scale), and 96% and 78% of patients had at least grade 3 power for wrist and finger extension respectively.

Patterson *et al.* (71) compared 30 patients treated with tendon transfers and 16 patients treated with nerve transfers for radial nerve palsy. In the nerve transfer group, 15 of 16 patients received a concomitant pronator teres (PT) to ECRB tendon transfer as an internal splint. The nerve transfer group had a longer follow-up time, but had significantly greater grip strength. The authors surmised that the additional tendon transfer, together with the recovery of wrist extensors from the nerve transfer resulted in improved wrist extension strength, range of motion and grip strength. This unique use of an early tendon transfer at the time of the nerve transfer also provides wrist strength and stability while awaiting regeneration from the nerve transfers.

For radial nerve injuries at the humeral level treated with nerve repair or grafting, recovery of thumb function is often suboptimal (72,73). Using the FCR branch transferred to the PIN, an extension lag at the thumb metacarpophalangeal joint is also commonly observed (74). In order to improve thumb extension, Bertelli *et al.* (75) described a distal nerve transfer from the distal anterior interosseous nerve, passed from volar to dorsal under the mobile wad or through the interosseous membrane, and coapted to the deep branch of the posterior interosseous nerve. This innervated the abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus and the extensor indicus proprius. All 5 patients in this study recovered full motion at the 1st carpometacarpal joint with no or minimal extension lag at the metacarpophalangeal joint. In contrast to the commonly used tendon transfer of the palmaris longus to the extensor pollicis longus for thumb extension, this distal nerve transfer also innervates the abductor pollicis longus, augmenting thumb abduction as well.

In the planning of nerve transfers, one must always consider the possibility of failure and preserve donor sites as secondary options. The presence of multiple 'neuromuscular units' innervated by the median nerve allows for secondary reconstruction with tendon transfers if the index nerve transfer operation is unsuccessful.

Ulnar nerve

Functional recovery in proximal ulnar nerve injuries after

primary repairs and nerve grafts is often poor (42,76). Intrinsic recovery is often incomplete due to the long reinnervation distance between the proximal ulnar nerve injury and the distal motor endplates. The distal pronator quadratus branch of the anterior interosseous nerve (AIN) is a good donor nerve for transfer to the ulnar nerve due to the minimal loss of function and proximity to the ulnar nerve distally in the forearm. An end to end transfer allows for reinnervation by the donor nerve, but not the native ulnar nerve. The supercharged end to side transfer to the ulnar nerve distally first described by Barbour *et al.* (77) may allow for partial recovery and 'babysitting' of the motor end plates to prevent degeneration while awaiting regeneration at the proximal repair site.

In a systemic review of 16 studies totally 269 patients, Thakkar *et al.* (53) evaluated the outcome of anterior interosseous nerve to ulnar nerve transfer, including end to end transfers and supercharged end to side transfers. End to end transfers were performed more commonly for nerve transection, while supercharged end to side transfers were performed more commonly in compressive etiologies. 85% of patients with end to end transfers and 75% of patients with end to side transfers recovered intrinsic function of grade 3 and above. In another study, McLeod *et al.* (78) compared the results of end to end and end to side transfers for patients with ulnar nerve compression at the elbow. Motor grading for intrinsic function was significantly better when surgery took place within 12 months compared to 12 months or more for both groups. The post-operative MRC score for the end to side group was better (3.2) compared to the end to end group (2.6), but this was not statistically significant.

Studies comparing nerve transfers and sural nerve grafting for proximal ulnar nerve injuries have shown superior outcomes with nerve transfer for motor function, but similar results for sensory reinnervation. Flores *et al.* (54) compared the results of sural nerve grafting to nerve transfers for motor and sensory function (end to end nerve transfer of the AIN branch to ulnar motor branch combined with end to side reinnervation of the superficial branch of the ulnar nerve with the 3rd webspace sensory branch of median nerve). Grade 3 and 4 motor outcomes were observed in a larger percentage of the nerve transfer group (80% versus 22%), while a similar proportion of patients in both groups had recovery of S3+ or S4 sensation (40% versus 30%). In another study, Sallam *et al.* (55) also compared sural nerve grafting with nerve transfers (AIN branch to ulnar motor branch, 3rd webspace sensory branch of median nerve to ulnar sensory branch, and end to side reinnervation of the dorsal ulnar cutaneous nerve to the sensory part of the median nerve on its ulnar side). A proportion of 83.3% of patients in the nerve transfer group regained grade 3 or greater, compared to 57.1% in the nerve grafting group. Sensory recovery of S3 or greater was achieved in 50–60% of each group with no significant differences. Additionally, both authors noted that nerve transfers for sensory reinnervation had the issue of sensory crossed innervation, requiring cortical remapping.

Despite encouraging results on the MRC grading scale, however, nerve transfers for proximal ulnar nerve lesions are not effective in preventing clawing and do not come close to normalizing grip and pinch strength when compared to the contralateral unaffected limb (79).

Median nerve

Although high median nerve injuries classically lead to loss of innervation of many muscles (both pronators, FCR, palmaris longus, FDS, flexor pollicis longus (FPL), flexor digitorum profundus (FDP) of the index and middle fingers, and part of the thenar muscles), the main motor deficit warranting reconstruction is that of thumb and index finger flexion, pinch and grasp, while loss of thumb opposition occurs in only 14–30% of patients (66). Patients also have sensory loss predominantly over the fingertips of the thumb, index, and middle finger, of which the sensation over the radial aspect of the index finger and ulnar aspect of the thumb is most critical for function.

Studies on nerve transfers to the AIN are limited to small case series and case reports (57-62). Heterogeneity in outcome measures, indications and pathology limit comparisons between the different donors (brachialis, supinator, ECRB, and brachioradialis branches) for nerve transfers to the AIN. The best reported outcome was MRC grade 3 for the FPL and grade 2 for the FDP using a branch from the brachioradialis (59), grade 4 for the FPL and FDP using a branch from the brachialis (58), grade 4+ for the FPL and grade 4– for the FDP using a branch from the supinator (60), and grade 4+ for the FPL and FDP using a branch from the ECRB (62). In addition, Bertelli reported an average of 5 kg grasp and 2 kg pinch strength using a branch from the ECRB (61). Use of the nerve to ECRB has been cited as the preferred donor for reinnervation of the AIN (66).

Reinnervation of the thenar musculature is performed not only for thumb opposition but also to increase pinch

strength. When considering the options for nerve transfers to the recurrent motor branch of the median nerve, use of the nerve to the abductor digiti minimi as a donor may be considered over the nerve to the flexor digiti minimi brevis or opponens digiti minimi as these muscles are involved in elevating hypothenar area during thumb opposition (56,66).

Studies with a higher level of evidence and larger cohort of patients are required to support the use of nerve transfers for median nerve injuries and at present, tendon transfers still remain as the workhorse for restoring FPL, FDP and thumb opposition function.

In high median nerve injuries, sensory recovery with primary repair or nerve grafting tends to be poor due to the long reinnervation distance to the sensory receptors at the fingertips. Sensory nerve transfers have the potential to provide at least protective sensation to the thumb and index finger. Of the various options proposed, transfer of the dorsal branches of the superficial radial nerve at the level of the proximal phalanx of the radial side of the index and ulnar side of the thumb to the corresponding digital nerves is the most described transfer, and is hypothesized to decrease the risk of sensory cross innervation and neuropathic pain compared to more proximal transfers (63).

Conclusions

Current research in this field continues to present exciting possibilities for the peripheral nerve surgeon. New imaging techniques allow for more accurate diagnosis and prognostication of nerve injuries, while the development of new surgical techniques in the field of nerve transfers allows for faster reinnervation of distal end organ targets. While nerve autografts are still the current gold standard for bridging a nerve gap, the alternatives (PNAs and conduits) may eventually replace it. In the future, tissue engineering may provide avenues to customize nerve conduits with unique scaffolds containing biological cues for sensory and motor pathways which can be tailored to individual patients' needs (80).

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