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ORIGINAL ARTICLE

Improving outcomes in traumatic peripheral nerve injuries to the upper extremity

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Abstract

Peripheral nerve lesions of the upper extremity are common and are associated with devastating limitations for the patient. Rapid and accurate diagnosis of the lesion by electroneurography, neurosonography, or even MR neurography is important for treatment planning. There are different therapeutic approaches, which may show individual differences depending on the injured nerve. If a primary nerve repair is not possible, several strategies exist to bridge the gap. These may include autologous nerve grafts, bioartificial nerve conduits, or acellular nerve allografts. Tendon and nerve transfers are also of major importance in the treatment of nerve lesions in particular with long regeneration distances. As a secondary reconstruction, in addition to tendon transfers, there is also the option for free functional muscle transfer. In amputations, the prevention of neuroma is of great importance, for which different strategies exist, such as target muscle reinnervation, regenerative peripheral nerve interface, or neurotized flaps. In this article, we give an overview of the latest methods for the therapy of peripheral nerve lesions.

Keywords Peripheral nerve · Nerve injury · Trauma · Nerve reconstruction · Nerve treatment

Abbreviations

ADM	Abductor digiti minimi
AIN	Anterior interosseous nerve
ALT	Anterolateral thigh
ANA	Acellular nerve allograft
ANG	Autologous nerve graft
APB	Abductor pollicis brevis
BR	Brachioradialis
CE	Conformité Européenne
DASH	Disabilities of the arm, shoulder, and hand
DIEP	Deep inferior epigastric perforator
ECRB	Extensor carpi radialis brevis
ECRL	Extensor carpi radialis longus
EDC	Extensor digitorum communis
EN	Electroneurography
EPL	Extensor pollicis longus
FCR	Flexor carpi radialis
FCU	Flexor carpi ulnaris
FDA	Food and Drug Administration
FDP	Flexor digitorum profundus
FDS	Flexor digitorum superficialis
LAF	Lateral arm flap
MRN	Magnetic resonance neurography
NS	Neurosonography
PL	Palmaris longus
PNI	Peripheral nerve injury
RPNI	Regenerative peripheral nerve interface
TMR	Targeted muscle reinnervation
VDMT	Vascularized denervated muscle target

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Introduction

Peripheral nerve injuries (PNI) require complex and individualized therapy. If inadequately treated, these injuries are often accompanied by incomplete healing resulting in long-term physical consequences manifested in chronic pain, impaired motor function, allodynia, persistent sensory dysfunction, and cold intolerance. However, the socioeconomic costs to society and the health-care system are also high, and the psychosocial burden on patients is significant due to long hospital stays, costly therapies and rehabilitation, long periods of sick leave, potential occupational redeployment, and difficulties with activities of daily living [1].

These long-term effects are often preventable with adequate surgical treatment and a precise diagnosis in the early stage. However, "time is muscle," as the time frame for successful regeneration of the motor endplate is limited to 12–18 months. Taking into account that peripheral nerve regeneration is limited to 1–2 mm/day, the importance of accurate and early diagnosis is even more crucial. In particular, high PNI at the upper arm or brachial plexus suffer under a limited prognosis for distal reinnervation due to the physiological condition of peripheral nerve regeneration. However, still today, there is evidence that, especially in closed injuries or in severe injuries of multiple structures, nerve lesions often remain undetected during the primary clinical examination [2].

Continuous technological advancement based on neurosonography (NS) and magnetic resonance neurography (MRN) improves the diagnosis, especially in the early stage of the PNI, and can guide decision-making [3]. Therefore, optimal treatment is based on detailed clinical examination, an exact interpretation of the neurophysiological findings, and precise visualization of the PNI by NS or MRN.

The exact epidemiology of traumatic PNI is currently unknown as the current literature provides only partial information [2]. Almost 90% of PNIs are localized to the upper extremity, with the digital nerves most affected. Distally located upper extremity lesions are often associated with tendon and vascular injuries, while proximal lesions are more commonly associated with fractures. Male patients are significantly more likely to be affected than female patients and are mainly of working age [4]. Children are also affected, with a prevalence of 5.7% among all patients with PNI. Injuries to the finger nerves, caused by cuts and lacerations, are most common [5].

At present, only a few specialized centers provide individualized comprehensive patient care through early diagnosis, optimal timing, and a wide range of therapeutic options, leading to a current lack of care in large regions. This article overviews the diagnostic possibilities and surgical techniques currently used to treat PNI.

Diagnostic evaluation of PNI

In diagnosing PNI, bedside clinical evaluation, electroneurography (EN), NS, and MRN are essential.

EN is currently part of the standard diagnosis of peripheral nerve lesions and can provide information about the localization of the lesion, the severity, and the prognosis. However, directly after the PNI, EN cannot differentiate between axonotmesis or neurotmesis by only showing an axonal block in the analysis. For instance, PNI Sunderland type III injuries with the potential for complete healing without additional surgical procedures cannot be distinguished from type IV or type V injuries with nerve discontinuity and the urgent need for surgical intervention.

For direct visualization of the PNI, NS has become the gold standard. Technological advancement led to better visualization of the peripheral nerve, even in demanding anatomic areas like the brachial plexus or the upper arm. However, to provide a less subjective view, NS demands investigator training and substantial expertise for accurate interpretation. Nonetheless, in exceptional cases during the early phase of PNI, the visualization of NS may be limited by the side effects of the trauma, such as swelling, hematoma, or traumatic alternate soft tissue [6].

In these cases, MRN currently seems of great potential, in which nerve lesions can be visualized with excellent definition and first detectable signs of Wallerian degeneration within 48 h after PNI [7]. Decision-making can be accelerated by nearly a month using clinical examination, NS, and MRN as diagnostic tools. Therefore, surgery can be planned and performed earlier, which is of great importance, especially in nerve lesions with a long regeneration distance to the motor endplate [3]. This is relevant during the regeneration process to monitor recovery and apply further rescue strategies as distal nerve transfers in case of incomplete recovery.

Optimizing surgical strategies

Peripheral nerve reconstruction

Tensionless nerve coaptation is of utmost importance for the reconstruction of the peripheral nerve. Ignoring this principle will result in insufficient peripheral nerve regeneration due to inadequate vascularization of the coaptation site and inadequate axonal regeneration [8]. Technically, a microscope and microsurgical instruments are obligatory to obtain precise nerve coaptation including all nerve fascicles. If tensionless nerve coaptation is impossible, bridging the gap with autologous nerve transplantation remains the gold standard [9].

Autologous nerve graft (ANG)

Since Millesi et al. promoted ANGs for tensionless nerve coaptation in 1972, no alternative has shown a superior functional outcome for spanning peripheral nerve defects [10, 11]. The advantages of the ANG compared to bioartificial alternatives are the absence of a potential foreign body reaction and simultaneous transplantation of neurotrophic factors and vital Schwann cells within the nerve graft [9]. Timely revascularization of the nerve graft is crucial for a good prognosis. It is an important factor for the survival of Schwann cells. The survival and function of the ANG are affected by the recipient site's quality and the graft's diameter. If timely revascularization is achieved, graft length does not seem to have an impact [12]. In clinical practice, the most used ANG is the sural nerve due to the ability of gaining substantial autologous material with minimal donor site morbidity. Alternatives are the medial cutaneal brachial nerve, the medial and lateral cutaneal antebrachial nerve, the superficial branch of the radial nerve, the articular branch of the posterior interosseous nerve, the saphenous nerve, and the great auricular nerve. When more autologous material is required or only a small cross-section must be repaired [for example, nerve defects in the hand], these can be considered.

However, the ANG has several disadvantages, making the need for an alternative indispensable. Due to the limited amount of usable autologous nerves and the need to restore the entire cross-section with numerous nerve grafts, this remains a challenge. Furthermore, the second operation site and the donor site morbidity must be considered. Possible techniques for sural nerve harvesting include open techniques with a single longitudinal incision along the nerve or via multiple smaller longitudinal incisions. A minimally invasive procedure like nerve harvesting with a nerve stripper or endoscopic technique has also been described. Each technique has different benefits and limitations, so the technique must be decided based on the situation.

ANG was only used for bridging to reconstruct functional recovery in the first place. In particular, for proximal PNI on the level of the upper arm or the brachial plexus reconstruction will not lead to proper distal functional recovery, for example, intrinsic musculature of the hand. Here, ANG reinnervates proximal musculature such as flexor carpi radialis (FCR) muscle for radial nerve lesion or flexor carpi ulnaris (FCU) muscle for ulnar nerve lesion. The second aim is to prevent future neuroma formation at the lesion site.

After the nerve stumps have been cut back to healthy bleeding endoneurial tissue, the defect length is measured to determine the required graft length. The graft should be approximately 10–20% longer than the defect length. Disadvantages of this technique are the risk of scarring and neuroma formation and the loss of sensibility of the donor's nerve. In addition, donor nerves are limited, and the results are worse than primary end-to-end reconstruction. The second incision required for graft elevation is also an additional risk.

In the case of an amputation, the nerve graft can be taken from the amputation, e.g., in multiple finger amputations. The disadvantages of elevation site morbidity can be overcome by using this spare part surgery (Fig. 1).

Alternatives to autologous graft

Strategies to bridge a gap

Due to the disadvantages of the ANG mentioned above, developing bioartificial nerve conduits is still subject to current research. In 2003, Schmidt and Leach defined three requirements for the ideal nerve conduit: inner guidance, the material's biocompatibility, and toxic-free degradation [13]. Over the past decades, materials from autologous veins or amniotic membranes [14] to synthetic or bioartificial

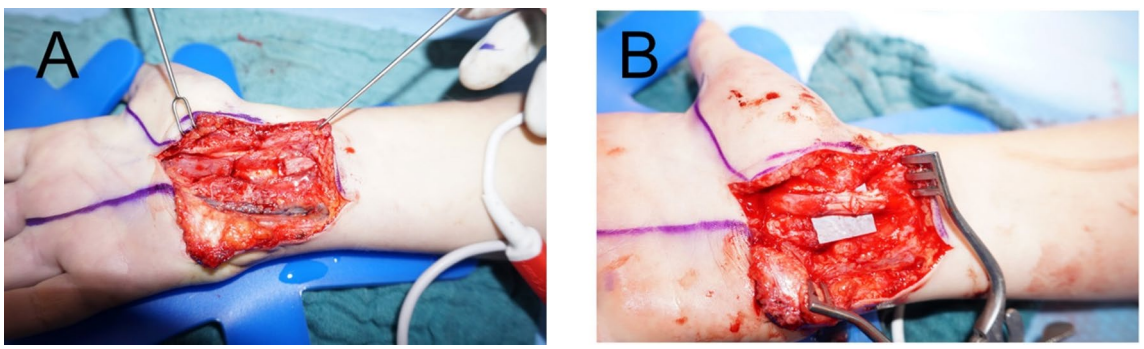

Fig. 1 Patient with a traumatic injury of the median nerve. Resectioning the median nerve's proximal and distal nerve ends led to a nerve defect of approximately 1.5 cm (**A**). ANG harvested by the sural nerve bridges the peripheral nerve defect (**B**)

materials such as polyglycolic acid or polyhydroxybutyrate have been used [15]. Materials can also be separated by their capacity for biodegradation. Non-biodegradable materials include silicone, polytetrafluoroethylene, plastic, and polyvinyl alcohol. However, due to severe foreign body reactions leading to extensive scar tissue formation and resulting nerve compression, non-biodegradable should not be used in the future. Biodegradable materials can be subdivided into synthetic polymers (polyglycolic acid, polylactic acid, polyhydroxybutyrate, polycaprolactone, etc.) or biological polymers (collagen, chitosan, creatin, quinine, gelatin, hyaluronic acid, etc.) [15]. The preferred material must be toxic-free, customizable, and adapted to the requirements of peripheral nerve regeneration. Materials like polylactic acid have shown impairment of peripheral nerve regeneration due to the lowered pH during reduction. Nevertheless, clinically no autologous or synthetic material has showed superior results to the gold standard of the ANG. Strategies with additional seeding of Schwann cells [16], mesenchymal stromal cells, preadipocytes, or olfactory nerve ensheathing cells or growth factors (nerve growth factor and brain-derived neuropathic factor) regularly show superior results on the microscopic level for the seeded nerve guides but not on functional outcome [17]. Furthermore, different strategies for external guidance have also been tested in the literature to provide guided axonal regeneration. Advances in tissue engineering make biomimicking of the physiological nerve with a resulting guided axonal regeneration possible by developing inner guidance with porous structures, filaments, or channels.

Current Food and Drug Administration (FDA)—and Conformité Européenne (CE)—approved nerve conduits include collagen-, polycaprolactone-, polyglycolic acid-, and chitosan-based nerve conduits [18]. Usually, FDA- and CE-approved nerve conduits are used for small nerve defects smaller than 3 cm (i.e., in the hand) and only for sensory reconstruction. All approved nerve conduits showed biocompatibility with cells of the PNS and were biodegradable, fulfilling the requirements of Schmidt and Leach [13]. However, currently, no approved nerve conduit provides an inner structure for guided axonal regeneration. Interestingly, due to the heterogeneity of study designs, types of PNI, and outcome parameters, a direct comparison of the performance of the current nerve conduit to each other and, in particular, to the ANG is hard to make. Therefore, for reconstructing peripheral nerve defects larger than 3 cm, ANG remains the gold standard.

Acellular nerve allograft (ANA)

Recently, ANAs have been put into focus as a suitable alternative for ANG. The subgroup of the RANGER study included 22 nerve repairs with a 1-year follow-up. Safa et al. published results of ANAs in the mixed and motor nerves in the upper extremity. Safety and functional recovery were shown [19]. Currently, the ANAs fulfill the concept of biomimicking the physiological nerve. However, there is still a lack of evidence on the performance of ANAs, particularly in comparison with the ANG. Yet, only for small finger defects, functional recovery similar to the ANG was shown for ANAs [19]. The use of ANAs should be critically considered for long-distance PNI and mixed or motoric nerves due to a lack of knowledge of the functional outcome [20]. Additionally, the allograft has high associated costs, and ethical issues may be apparent with cadaveric nerve implantation.

Nerve transfer

General principles

Nerve transfer is indicated for high nerve lesions and may be performed in combination with local nerve reconstruction when necessary. Nerve transfers are used for the primary treatment of preganglionic nerve root avulsions and the reconstruction of postganglionic nerve root avulsions. When determining the indication, it must be noted that regeneration of the motor endplates can be expected within 18 months after the nerve injury.

A dispensable, intact nerve is used as an axon donor, and coaptation is performed as distally as possible to the defective nerve. Intraoperative monitoring is essential to assess the donor and recipient nerves' function accurately. To ensure tension-free coaptation, the donor nerve must be prepared as distally as possible and the recipient nerve as proximally as possible. However, nerve transfer is not intended to replace proximal nerve reconstruction at the target site. To establish sensory reinnervation, reach proximal target muscles, and prevent neuroma formation, proximal nerve reconstruction is typically combined with distal nerve transfer. Also, a combination of tendon transfer and nerve transfer is possible (i.e., median to radial nerve transfer).

The advantages of nerve transfer compared to tendon transfer are seen in the preserved biomechanics of the innervated muscle as a functional unit. The surgery-related soft tissue dissection is usually less, there is no risk of tendon rupture, and early postoperative exercise is, therefore, possible. Additionally, nerve transfers do not impair the balance of the tendon system. Disadvantages include a limited time window for the procedure of about 12 months after the nerve lesion and a longer surgical time. The functional result can only be observed after reinnervation, resulting in long waiting times for the surgeon and the patient.

In general, nerve transfers can be performed end-to-end or end-to-site. Depending on the aim, end-to-end nerve transfers can restore function without the support of

proximal axonal regeneration (i.e., median to radial nerve transfer). End-to-side nerve coaptation was first described in 1992 and has remained the domain of individual experts. The technique can be used when no nerve stump is available proximally for nerve suturing or grafting [9]. This is mainly relevant in subtotal amputation. Here, the distal stump of the transected nerve is coapt end-to-side to an intact donor nerve by opening the epineurium of the donor's nerve and, if necessary, the perineurium. An opening of 4–5 mm allows the ingrowth of larger axons [21]. Oligofascicular nerves show the best results [22]. End-to-side coaptation is mainly useful in recovering minimal sensory deficits, due to the fact that end-to-side coaptation remains still controversial [9, 23].

Common nerve transfers

Brachial plexus

Nerve transfers in brachial plexus injury are indicated when ANG is not possible, or reinnervation distance is not within the timeframe of 12–18 months. The main focus for brachial plexus injury is to gain shoulder stability and elbow flexion. Therefore, several nerve transfers have been described. For high brachial plexus injuries, nerve transfers accessory nerve to the suprascapular nerve [24]. The accessory nerve is identified at the ventral border of the trapezius muscle and dissected after the first branch to the trapezius muscle and the branch to the sternocleidomastoid muscle to not denervate the muscles completely. For elbow flexion, double fascicular nerve transfers with fascicles of the FCU branch of the ulnar nerve and FCR branch of the median nerve are transferred to the biceps and brachialis branches of the musculocutaneous nerve in high nerve trunk lesions. Combination with local nerve reconstruction is possible; however, the exact effect on muscle strength is controversially discussed. For example, Srampickal et al. presented a significantly improved strength of elbow flexion compared to the single transfer [25]. In contrast, Sneiders et al. showed no benefit on the muscle strength for an additional FCR branch to the brachialis motor branch [26].

Alternatively, when the median and ulnar nerve are unavailable, the intercostal nerve transfer to the branches of the musculocutaneous nerve is suitable. However, due to the lower amount of motor axons and the need for an ANG [lower intercostals] [27], the intercostal nerve should not be the first choice for innervating the musculocutaneous nerve.

Radial nerve

Due to the long distance to gain long finger extension and thumb extension, nerve transfer plays a crucial role in high radial palsy. In particular, median branches from the flexor digitorum superficialis (FDS) and the branch to the FCR can be used to restore finger extension and extensor pollicis longus (EPL) function. Regularly, the FDS branch is coapted to the extensor carpi radialis brevis (ECRB) branch and the FCR branch to the posterior interosseus nerve. Donors are prepared distally and recipients proximally to perform a direct nerve coaptation and avoid the need for an autologous nerve transplant. In the 12-month follow-up, median to radial nerve transfer has shown good up to excellent results for 18 patients in the wrist and 12 patients in the finger/thumb function [28].

Ulnar nerve

For high ulnar nerve lesions, transferring the anterior interosseous nerve (AIN) to the motor branch of the ulnar nerve is a workhorse transfer to restore the intrinsic function of the hand. The transfer can be performed end-to-end or as a "babysitter" end-to-side nerve transfer. Davidge et al. presented a significant improvement in grip strength, pinch grip, and disabilities of the arm, shoulder, and hand (DASH) outcome for 55 patients after 8 months of recovery [29].

Surgical indications are not only limited to traumatic nerve lesions but also to chronic nerve compression syndromes on the level of the cubital tunnel. Xie et al. [29] showed in a prospective randomized study of 48 patients a significant improvement in strength and pinch grip for patients treated with a "supercharged" end-to-side motor nerve transfer with advanced cubital tunnel syndrome. As previously mentioned, this is still a controversial topic [23].

Besides shortening the regeneration length, the allocation of the motor donor nerve to the motor recipient nerve is another advantage of this nerve transfer. The AIN at the pronator quadratus level includes nearly only motor neurons making it a favorable donor nerve for transfer to the motor branch of the ulnar nerve.

Median nerve

Reconstruction of high median nerve injuries often aims to restore AIN function by an ECRB to AIN transfer in cases where the radial nerve is not injured [30]. However, the median nerve should be reconstructed by ANG proximally to restore sensory regeneration and prevent neuroma formation at the lesion site. Classic nerve transfers to the median nerve focus on the reconstruction of the thumb opposition [31, 32]. If there is no injury of the ulnar nerve, retransfer of the branch to the abductor digiti quinti to the thenar branch of the median nerve is a common nerve transfer. Bertelli et al. recovered 75% of the normal side grasp and pinch strength [33]. In attempt to avoid the need of ANG and the disadvantages of a second nerve coaptation side, the thenar branch has to

be prepared proximally with an intraneural preparation to gain length of the recipient nerve. The branch of the abductor digiti quinti must be prepared as distal as possible in the muscle (Fig. 2).

Secondary reconstruction strategies

General principles

Secondary reconstruction can be used for subtotal amputations with incomplete nerve lesions or incomplete recovery after replantation. In general, the decision on which secondary reconstruction to use depends on the individual patient and his or her expectations. Different secondary and primary reconstruction procedures can be combined to achieve the best possible result for the patient needs.

Tendon transfers are indicated in cases where nerve reconstruction is no longer possible or has failed. Individual patient characteristics, such as age, comorbidities, and preferences, should be considered. This technique repositions an expendable donor muscle that performs only one function. The muscle should ideally be an agonist to achieve a physiological movement pattern. Sufficient strength and similar amplitude are important. There should be a moderate overcorrection of the tendon transfer, and care should be taken to ensure that the line of contraction is as direct and similar as possible to the original tendon. It should be noted that reinnervated muscles after a nerve lesion have less strength and endurance than prior to injury as not all motor units regenerate, and target end-plate remodeling occurs [34].

Tendon transfers for radial nerve lesions

The goals are to restore wrist, thumb, and digital extension.

Here, reconstruction of the EPL muscle is usually achieved by a tendon transfer of the palmaris longus (PL) tendon, when present. However, it should be noted that the PL muscle is not present in about 20% of patients. Typical donor tendons include the pronator teres muscle, the FCU muscle, FDS, and the FCR muscle. Typical tendon transfers include pronator teres to ECRB for wrist extension, PL or FDS to EPL for thumb extension, and FCR or FCU to extensor digitorum communis (EDC) for digit extension.

Tendon transfers for ulnar nerve lesions

In ulnar nerve lesions, the goals of a tendon transfer are to correct the claw position, reconstruct the flexor digitorum profundus (FDP)-4/5 function, and reconstruct the key grip.

The FDS tendon can be transposed into the extensor apparatus or as a loop around the A1 or A2 annular ligament (dynamic Zancolli) to correct the claw position. Another option is to transpose the ECRB/extensor carpi radialis longus (ECRL) tendon (Brand) or split the tendon (Riordan) into the extensor apparatus.

Tendon transfers for median nerve lesions

The goals of a tendon transfer in median nerve lesions are to repair the opposition of the thumb and the function of the FPL muscle and FDP-2/3 muscle. For restoration of opposition, the vector of tendon pull is crucial, which is why the donor muscle should insert in the aponeurosis of the abductor pollicis brevis for restoring opposition. Classic examples

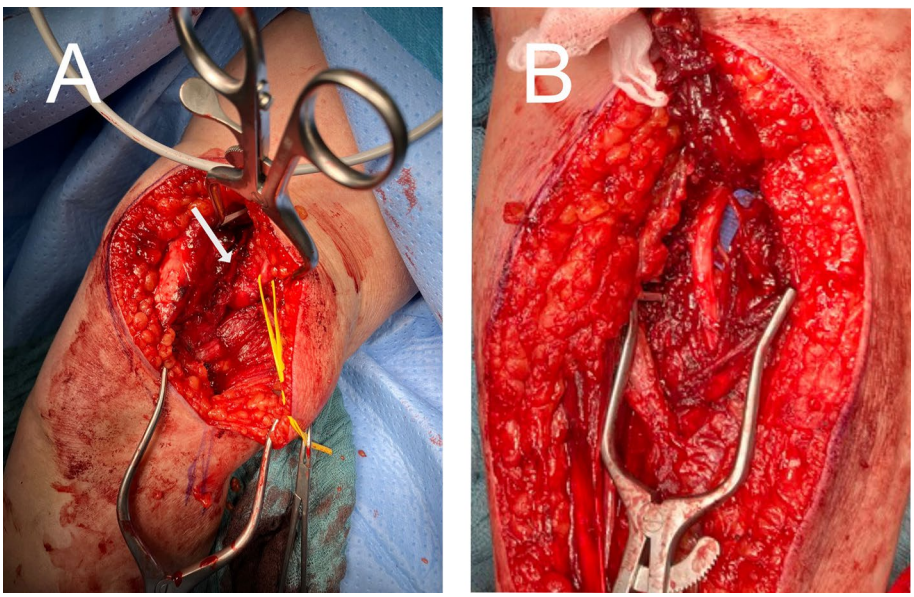

Fig. 2 Iatrogenic trauma of the radial nerve after osteosynthesis. The radial nerve was compressed by osteosynthesis material (white arrow) after a humerus fracture fixation (**A**). Following the removal of the damaged nerve, the peripheral nerve defect was repaired by transplanting five ANG sural nerves to restore the full diameter over a 6-cm distance (**B**)

for the restoration of opponens function are the transfer of the extensor indicis proprius muscle, the transfer of the palmaris longus (PL) muscle (Camitz), the transfer of the FDS muscle, and the transfer of the abductor digiti minimi (ADM) muscle (Huber). Furthermore, for high median nerve lesions, the reconstruction of the FPL muscle can be done by transferring the brachioradialis (BR) muscle. For the reconstruction of the FDP-2/3 function, a side-to-side transfer to FDP-4/5 can be used (Fig. 3).

Free functional muscle transfer

Free functional muscle transfer is an option if nerve reconstruction, nerve transfer, or tendon transfer are not possible. This technique is commonly used in plexus surgery. Interventions of this type are extremely complex and reserved for only a specific subgroup of patients. One reason for this is the postoperative regeneration phase, which takes several months.

Important principles and conditions must be observed. The donor muscle must be an expendable muscle that can provide sufficient strength. Only one function can be replaced with one muscle, and care must be taken to ensure the most linear direction possible in the orientation of the vector of contraction. The donor muscle must have a well-defined motor nerve branch, and tension-free nerve coaptation must be possible. Additionally, adequate flap vessels are obligatory. Preoperatively, the target joints must have a full range of motion, and a sufficient soft tissue envelope must be present. When selecting a suitable donor nerve, a nerve with agonistic function to the target function should be chosen if possible. However, this is not always possible, especially in the case of combined brachial plexus lesions.

In some cases, donor nerves must also be extended via ANG. This can be done in a two-stage procedure to keep the denervation time of the donor's muscle as short as possible. Using the Hoffmann–Tinel sign, the regeneration of the ANG can be monitored, and as soon as the end of the interponate is reached, the definitive transfer of the donor muscle can take place. Suitable donor muscles include the gracilis, latissimus dorsi, tensor fasciae latae, medial gastrocnemius, and pronator quadratus [31].

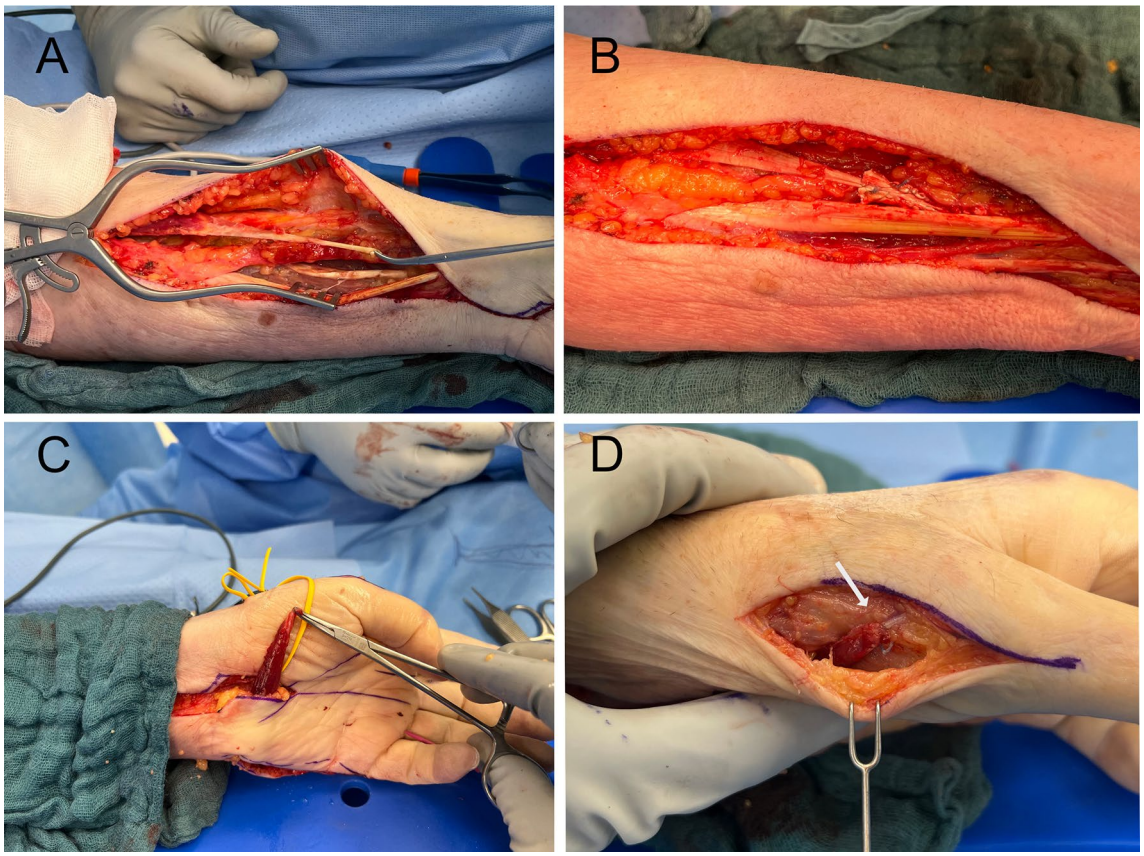

Fig. 3 Patient with a high median injury with an elapsed time frame prohibiting nerve transfers. The patient suffered from a high median injury and presented in our outpatient clinic 24 months after trauma. Thumb flexion reconstruction was performed with a tendon transfer of the brachioradialis tendon to the flexor pollicis longus tendon (**A**, **B**). Opposition reconstruction was achieved with transfer of the abductor digiti minimi muscle to the tendon of the abductor pollicis brevis (**C**, **D**)

Management of nerve lesions in amputations without replantation

General principles

In the case of amputation when replantation is not possible, the proximal nerve endings should be managed to prevent painful neuroma formation. Neuromas develop due to undirected axon growth when the regenerating axon does not reach the distal nerve stump resulting in a missing guidance structure. In the case of amputation, the distal nerve part is no longer present, and a stump neuroma is formed. Hypesthesia and hyperalgesia may develop due to dysfunctional excitability. Only neuromas involving sensory nerves become clinically symptomatic. Painful neuromas after finger amputation occur in approximately 7% of patients [35]. The etiology of painful neuromas has not been finally identified, but predisposing risk factors, such as age, trauma mechanism, and the affected finger, have been identified [35]. However, treatment of symptomatic neuromas is challenging, and results are unsatisfactory. The recurrence rate is high, with a reoperation rate of more than 25% [36].

Surgical therapy can be divided into reconstructive and ablative procedures. Ablative procedures are intended to protect the proximal nerve stump and are utilized when the distal nerve stump can no longer be used or is absent such as in the case of amputation. Various surgical treatment options outlined below are used in clinical practice, although none have demonstrated superiority [37].

Neuroma excision and retraction

A simple and practicable method to prevent a neuroma is the excision and retraction of the proximal nerve endings. This technique is often used in the region of the digital nerves. Compared to other methods described in the literature, this method was not shown to be inferior [37].

Transposition into surrounding tissue

The proximal nerve stump may be embedded for protection in surrounding tissues, such as muscles or veins. The technique of implanting the proximal nerve stump into the muscle has been used for many years. Stimulation by mechanical irritation should be prevented by the protective tissue increasing the distance between the nerve end and the skin. This can reduce pain and can improve quality of life. Excellent and good results are shown in 82% of treated nerve stumps using transposition into an anatomically deeper muscle [38] and reducing pain [37]. By transposition into a vein, pain reduction can be achieved in 87% of cases [39].

Nerve cap

Efforts have been made to prevent undirected axon growth by using a nerve cap. Here, autologous, biological, and synthetic materials have been evaluated. Currently, there are mainly experimental trials with large human studies lacking.

In animal experiments, applying a vein cap decreased neuroma formation [40]. The vein cap can serve as mechanical protection as in the case of transposition into a vein. Nerve caps made from the outer epineurium as an epineural graft are also described in the literature [41]. Research on bioartificial nerve caps is ongoing in the field of tissue engineering. There is no recommended use of silicone caps [42], due to an insufficient biodegradation and leading to severe foreign body reaction.

However, applying nerve caps based on poly(L-lactic acid-co-ε-caprolactone) shows promising results [43].

Relocation nerve grafting

In this technique, a graft is microsurgically coapted to the proximal nerve stump, and the distal end of the graft is guided away from the surface. Studies show that if a sufficiently long ANA is used during this procedure, axon growth can dissipate in a controlled manner. Here, ANAs with less than 3-cm length could be adequate to sufficiently stop axon growth [44].

Regenerative peripheral nerve interface (RPNI)

In RPNI, a denervated, vascularized muscle cuff is placed around the proximal nerve stump. Originally, this technique was used for improving the signals of myoelectric prostheses. If the muscle is not denervated, axons are unable to grow into the muscle, whereas, in denervated muscles, axons from the proximal nerve stump can build neuromuscular connections [45]. Studies demonstrate that neuromas and phantom limb pain can be prevented using this technique [46]. Only diffusion from the surrounding tissue supplies the muscle when using this procedure. If the muscle cuff has insufficient vascularity, there is a risk of muscle necrosis, scarring, and fibrosis. One proposed solution is the vascularized denervated muscle target (VDMT) method, in which a vascularized, denervated muscle cuff is placed around the proximal nerve stump [47].

Targeted muscle reinnervation (TMR)

During TMR, the ends of the large peripheral nerves are neurotized to surrounding small motor nerve branches allowing axonal growth into the denervated muscle to provide reinnervation. Initially, this technique was used to enhance myoelectric prostheses [48]. However, it has been shown that TMR also improves neuroma pain as well as phantom limb pain in amputations [49]. This technique can be used not only for major amputations but has also been successfully used for ray amputations of the hand. TMR is highly valued in both primary preventions of neuroma and recurrence prophylaxis in revision surgery.

Neurotized flaps

In severe cases of recurrent neuroma in anatomically challenging areas without the possibility for TMR and areas of minimal soft tissue cover, a neurotized free flap can be used to provide a new target for the nerve as described by Aman et al. [50]. By providing free fasciocutaneous tissue that is innervated by the amputated nerve, the challenging soft tissue envelope can be augmented and aid to prevent neuroma in areas such as the superficial radial branch or the infrapatellar branch of the saphenous nerve. Various free flaps (e.g., the anterolateral thigh (ALT) flap, the lateral arm flap (LAF), or the radial forearm flap) can be neurotized and are also helpful in treating therapy-resistant neuromas [50].

Conclusion

The treatment of peripheral nerve lesions is complex and challenging. For an optimal outcome, treatment by an experienced nerve surgeon is essential. This highlights the importance of specialized treatment centers to ensure a high standard of care. Timely treatment of nerve lesions is important to restore motor function even in proximal lesions with a long recovery distance. Recovery surveillance should be done using appropriate diagnostics, such as EN, NS, and MRN.

In amputation injuries, reconstructive strategies depend on the condition and availability of the distal stump. If the distal stump is available, reconstruction should aim to bridge the peripheral nerve defect with an autologous nerve graft to gain functional recovery and prevent neuroma formation. In proximal amputations, adequate nerve reconstruction is more complex, and techniques such as nerve transfers or tendon transfers for secondary reconstruction secondary should be considered. If the distal nerve stump is unavailable, the treatment should focus on neuroma prevention and, in particular cases, supporting the adjustment of a future prosthesis by applied techniques.

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Declarations

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