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Anatomical and Histomorphometric observations on Nerve Transfers in the Distal Forearm for the Reconstruction of Hand Function

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1. Introduction

Peripheral nerve injuries (PNI) are common and affect all age groups. Loss of motor function and sensation in the hand has a devastating impact on the hand function. The injury may not only lead to problems in everyday life, but also will severely impair the patient's professional life[10]. There are many different types of surgical techniques in the management of the peripheral nerve injury, including primary end-to-end repair, external neurolysis, nerve conduits, nerve grafting and tendon transfer.[11] So far, the tension-free, primary end-to-end repair is the optimal treatment for nerve reconstruction.[8] Autologous nerve graft is widely accepted as a gold standard for nerve reconstruction to bridge the gaps. Proximal nerve lesions reconstructed with direct anatomic repair or nerve grafting often result in poor prognosis because of a long distance for nerve regeneration.[12]

Nerve transfers convert a high level nerve injury into a low level injury hence providing a shorter distance for the regenerating axons to reach the motor endplates and reduce reinnervation time.[13] With a greater understanding of the internal topography of the peripheral nerve, nerve transfers have been successfully used in the operation for reconstruction of upper extremity function in brachial plexus injuries.[8,14] It was first described by Wilfred Harris in 1903, who transferred parts of fascicles from the 5th root of the brachial plexus to the 6th root.[15] R.I. Harris was the forerunner who advocated transferring the normal functional nerves to the adjacent injured nerves to reconstruct the arm function.[16] Oberlin described the partial transfer of the ulnar nerve to the motor branch of biceps brachii to restore the elbow flexion in brachial plexus injury, without ulnar nerve deficiency.[17] In addition, various nerve transfers were introduced by others to treat brachial plexus palsies.[18,19]

Due to these satisfactory results, nerve transfers have become a favorite topic for reconstruction of hand function, especially for restoration of hand intrinsic muscles after injury of the ulnar nerve or median nerve.[20-23] After median nerve injury at the wrist or forearm, the motor function to the thenar muscles is rarely satisfactory following direct anatomic repair or nerve grafting. The primary reason for such cases is that the median nerve is mainly composed of sensory fibers at this level,

and the regenerating motor axons may grow into wrong endoneurial tubes.[12,24-26] In these situations, opponensplasty is the most common treatment. Thumb opposition can be reconstructed by tendon transfers.[27] But as discussed previously in the literature, these transfers may lead to limited function frequently, because only a part of the thenar function is restored and persistent thumb contractures can occur.[28,29]

With this substantial limitation, in recent years, surgeons pay more attention to distal nerve transfers.[28,30] Their rationale was that a distal nerve transfer can approximate the donor axons to the target end-plate and avoid misdirection of motor axons by using a relatively pure motor donor nerve to connect with a relatively pure motor recipient nerve. In accord with this, the AIN as a donor was transferred to the TBMN with an end-to-end (ETE) coaptation to reconstruct the thenar muscles' function.[22,31] The principal indication for this transfer is that the low median nerve, suffers a complete injury in the proximal forearm distal to the origin of the anterior interosseous nerve.[22,32] Recently a concept of supercharged end-to-side (SETS) coaptation was introduced to augment the partial recovery for incomplete injuries of the ulnar nerve, which involves transferring the AIN to the side of the deep motor branch of the Ulnar nerve (DBUN).[33,34]

Loss of sensation in the hand is a major limitation to the function of the hand and the patients' quality of life. For sensation of the hand, the median nerve has the highest importance, followed by the ulnar nerve and radial nerve. The deficit of thumb sensation alone results in a loss of 20% of the hand function.[35] Consequently, nerve transfers have been reported, where branches from the dorsum were redirected to the palm of the hand.[35-37] While being most frequently indicated in open injuries, sensory nerve transfers have also been applied in patients suffering from burns or leprosy.[38,39]

However, in the last decade extra-anatomic reconstructions by transferring peripheral nerves have gained clinical importance. A group of motor nerve transfers to regain motor function of the hand has been described.[13,23,40] But the treatment of high-grade nerve injuries of the upper extremity remains a surgical challenge, especially large nerve gaps of motor nerves in the distal forearm.[29] Moreover, only few attempts of sensory nerve transfers are known. It lacks reports about the

anatomic and histomorphometric data of the nerves in the distal forearm which can be used as a basis and theory for nerve reconstruction.

1.1 Nerve anatomy

In order to manage patients with peripheral nerve injuries (PNI), it is crucial to give a brief description about the relevant anatomy, pathophysiology, and basic injury types.[11] The knowledge of anatomy is important for understanding the pathophysiologic concepts which help to evaluate and manage peripheral nerve injuries.[41,42]

1.1.1 General feature

The peripheral nerve system (PNS) is an important construction which connects central nervous system and periphery. It transfers information from the central nerve system to the motoric or sensoric targets, and collects information from these terminal targets and feeds them back to the central nerve system.[41] The PNS is the part of the nervous system that is made up of cranial and spinal nerves. There are 12 pairs of cranial nerves which are numbered I-XII and generally named according to their structure or function. The cranial nerves innervate the head and neck areas, which exchange information between the brain and parts of the body and control activities of the head and neck.[43] There are 31 pairs of spinal nerves which are concerned with containing both sensory and motor fibers. Each spinal nerve is formed from the combination of nerve fibers from anterior and posterior nerve roots, the anterior root carries motor information from the brain while the posterior root send sensory information back from internal organ or from external stimuli to the brain.[44]

1.1.2 Microscopic structure

The peripheral nerve is composed of its nerve fibers and connective tissue which supplies mechanical and trophic support for the nerve fibers.[45] The connective tissue is built by three supporting structures: The epineurium, which is composed of collagen fibers, fibroblasts and fat cells, is the outermost and a thick layer to

separate from the external tissue.[46] The perineurium is the second layer of structures which organizes the axonal fibers in one or more fascicles, which is composed of flattened cells.[47] The endoneurium is deep to the perineurium to form the third layer of structures, which envelop the individual myelinated axons and groups of unmyelinated axons.[48] These arrangements provide supportive structures to protect the axons against the nerve injuries.

A nerve fiber is an axon-Schwann cell unit that is surrounded by an acellular basal lamina. Peripheral nerve fibers have been classified into three groups which are reflected in their conduction velocity. Fibers that transmit signals to muscles spindles have a largest diameter up to 20 μm and fastest conducting, which is known as Group A; Group B consist of fibers up to 3 μm; Group C have the smallest diameter with around 1 μm and slowest conducting.[49,50] A nerve fiber may be myelinated or unmyelinated, but it is closely associated with Schwann cells which form myelin sheaths in the PNS. The myelin sheaths enwrap around the segment of larger axons along their length and create small gaps in-between each segment named the node of Ranvier which represent of the point of contiguity of adjacent Schwann cells.[49] The remaining unmyelinated fibers travel in deep gutters along the surface of Schwann cells.[51]

Blood supply to the peripheral nerves include extrinsic vessels and intrinsic vessels.[52] Generally the extrinsic vessels run in loose connective surrounding nerve while the intrinsic vessels supply nerves by a series of longitudinal branches that originate from local and regional arteries.[51] Although both extrinsic and intrinsic blood vessels supply the PNS, the intrinsic blood is the primary system for PNS.[52]

1.2 Peripheral nerve injuries (PNI)

1.2.1 Types of PNI

The basic types of PNI include stretch-related injury, laceration, and compression.[41] In general, the most common type of PNIs are stretch-related injuries in which the continuity of peripheral nerve is retained, however, the continuity will be lost when the energy imparted to the nerve is great enough.[41] The second common type of PNI is laceration caused by glass, knife or fractured bone.

Its continuity can be complete or partial transection. Another common type of PNI is compression with completely retained nerve continuity.

The type of PNI can be also classified as closed and open which depend on whether the cutaneous-in-continuity has been disrupted or not.[53] The open injuries are more frequently associated with laceration or transection and should be acutely repaired, especially if proximally located. In closed injury the nerve is more frequently still in continuity, thus the patient should be followed three months and surgery is indicated when no recovery is identified.[53,54] Classical examples of closed injuries with in continuity lesions are stretch, compression, electrical injection and iatrogenic injuries; Conversely, the examples of open injuries include those provoked by knives, propellers, piece of glass, and iatrogenic scalpel lesions.[55]

1.2.2 Classification of PNI

The classification of PNI depends on the extent of injury which assists in prognosis and therapy strategy. There are two widely accepted classification schemes for PNI which were introduced by Seddon in 1943 and Sunderland in 1951.[56,57] Seddon classified nerve injuries into 3 types: neurapraxia, axonotmesis, and neurotmesis (Fig.1). Sunderland reorganized Seddon's classification to 5 degrees of nerve injury (Fig.2). More recently, Mackinnon introduced a new classification scheme for PNI (Fig.3).[2] An overview of grading systems as below aims for a clear understanding of the PNIs.

Classification of Nerve Injury

Sunderland	Seddon	Mackinnon	Injury
Degree I	Neurapraxia	Degree I	Conduction block, resolves spontaneously
Degree II	Axonotmesis	Degree II	Axonal rupture without interruption of the basal lamina tubes
Degree III		Degree III	Rupture of both axons and basal lamina tubes, some scar
Degree IV		Degree IV	Complete scar block
Degree V	Neurotmesis	Degree V	Complete transection
		Degree VI	Combination of I–V and normal fascicles

Table 1: Classification of nerve injury[2]

1.2.2.1 Seddon Classification

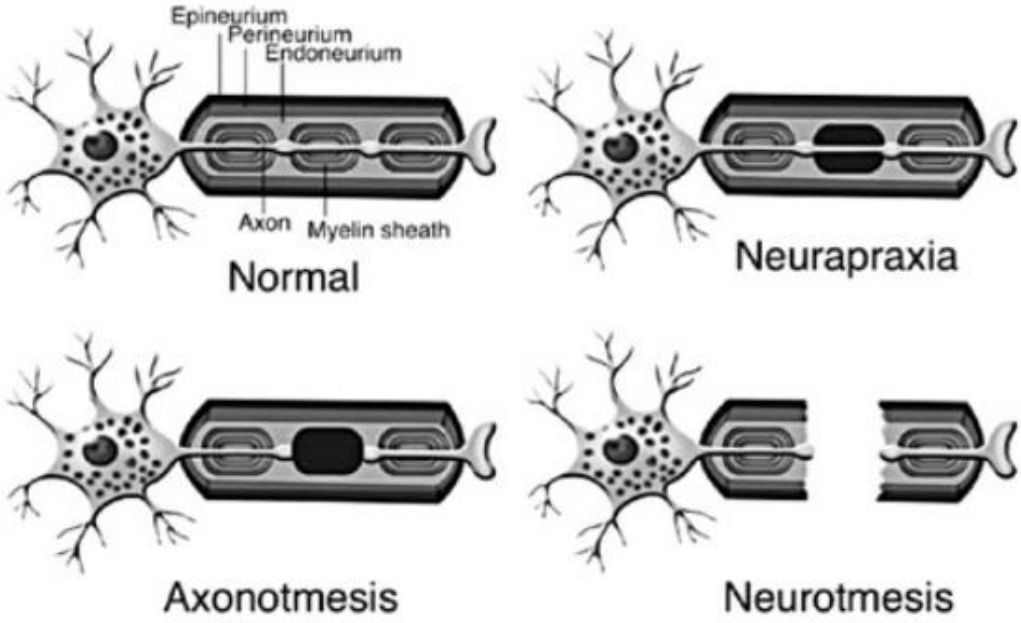


Figure 1: **Seddon Classification. Schematic representation of a normal nerve fiber and the three grades of nerve injury** [53]

Neuropraxia: It's the mildest type of PNI. It involves in temporary physiologic block of nerve conduction without loss of axonal continuity. This transient loss of function is thought to be due to a local conduction interruption at the injury site. Full regain of functions is expected if the conduction is intact in the distal and proximal segment as well as the three layers of peripheral nerve.

Axonotmesis: It involves interruption of nerve conduction from proximal site of injury to the distal site with loss of anatomical continuity of axon and surrounding myelin. But the two outer structures of the peripheral nerve including the perineurium and epineurium are preserved. Wallerian degeneration occurs in the distal segment of injury nerve which results in complete denervation of muscles and sensation. However, the prospect of recovery is excellent for because the intact neural tube provides a path for the sprouting axons to reach the terminal target.[58-60]

Neurotmesis: It's the most serious type PNI. It involves the complete transaction of the axon and connective tissue. Wallerian degeneration was found in both proximal and distal segment of injury nerve. Function recovery does not unlikely occur because of scar formation and the loss of intact neural tube that can direct axonal

regeneration. Surgical intervention is recommended for surgeons to make a treatment plan.

1.2.2.2 Sunderland Classification

- First-degree: equivalent to "Seddon's neurapraxia"
- Second-degree: equivalent to "Seddon's axonotmesis"
- Third-degree: this type places a degree between Seddon's axonotmesis and neurotmesis, nerve fiber is interrupted, the endoneurium is also partial injury, the epineurium and the perineurium remain complete. Functional recovery depends on the extent of endoneurium injury and surgical intervention is necessary.
- Fourth-degree: Only epineurium is intact, the axon and all the supporting tissue are disrupted. Without surgery, functional recovery is not possible.
- Fifth-degree: equivalent to "Seddons's neurotmesis"

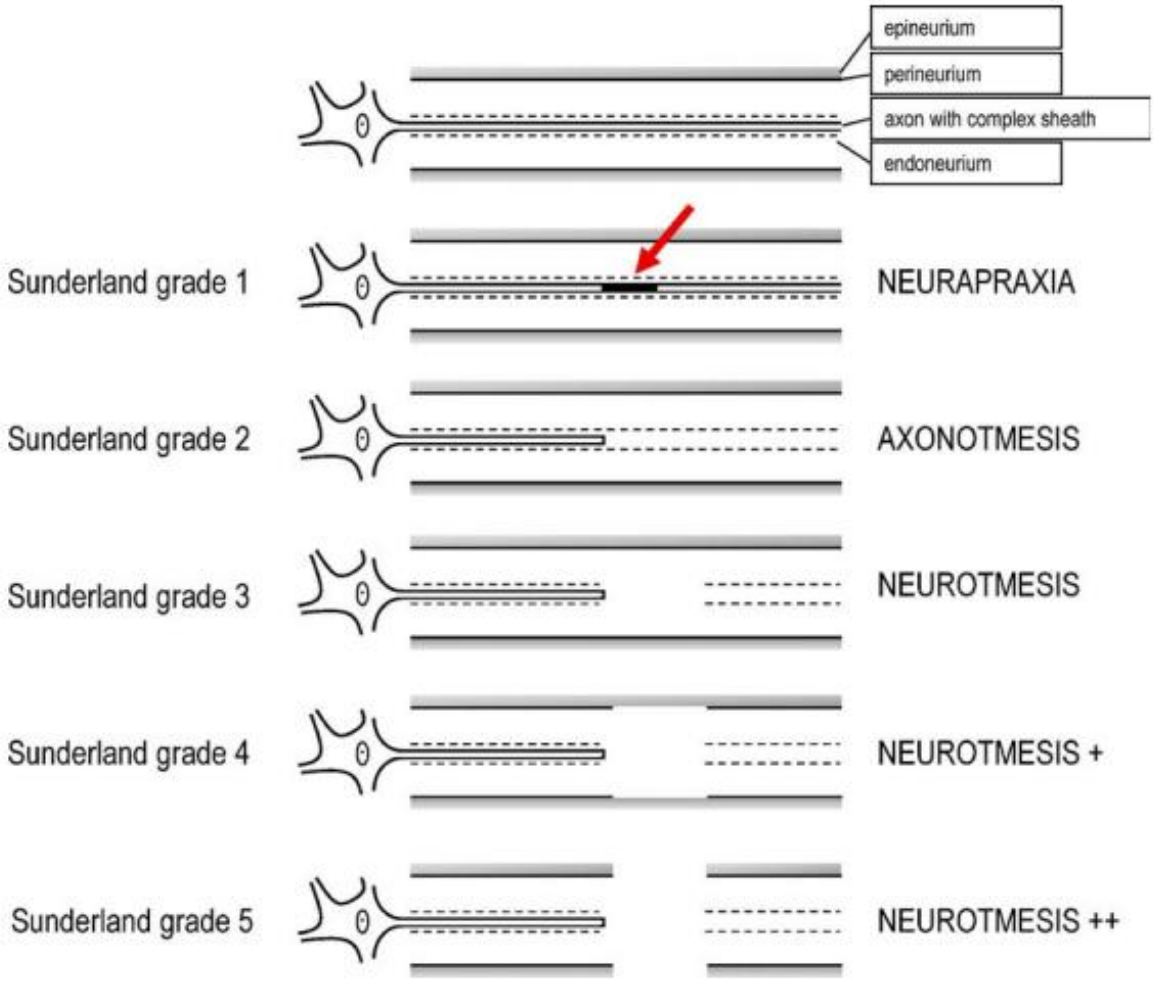


Figure 2: Sunderland Classification. Schematic drawing of a five degrees of nerve injury according to sunderland.[61]

1.2.2.3 Mackinnon Classification

Based on the Sunderland Classification, Mackinnon described a 6th degree of nerve injury which combines a variety of nerve injuries within a single nerve.[62]

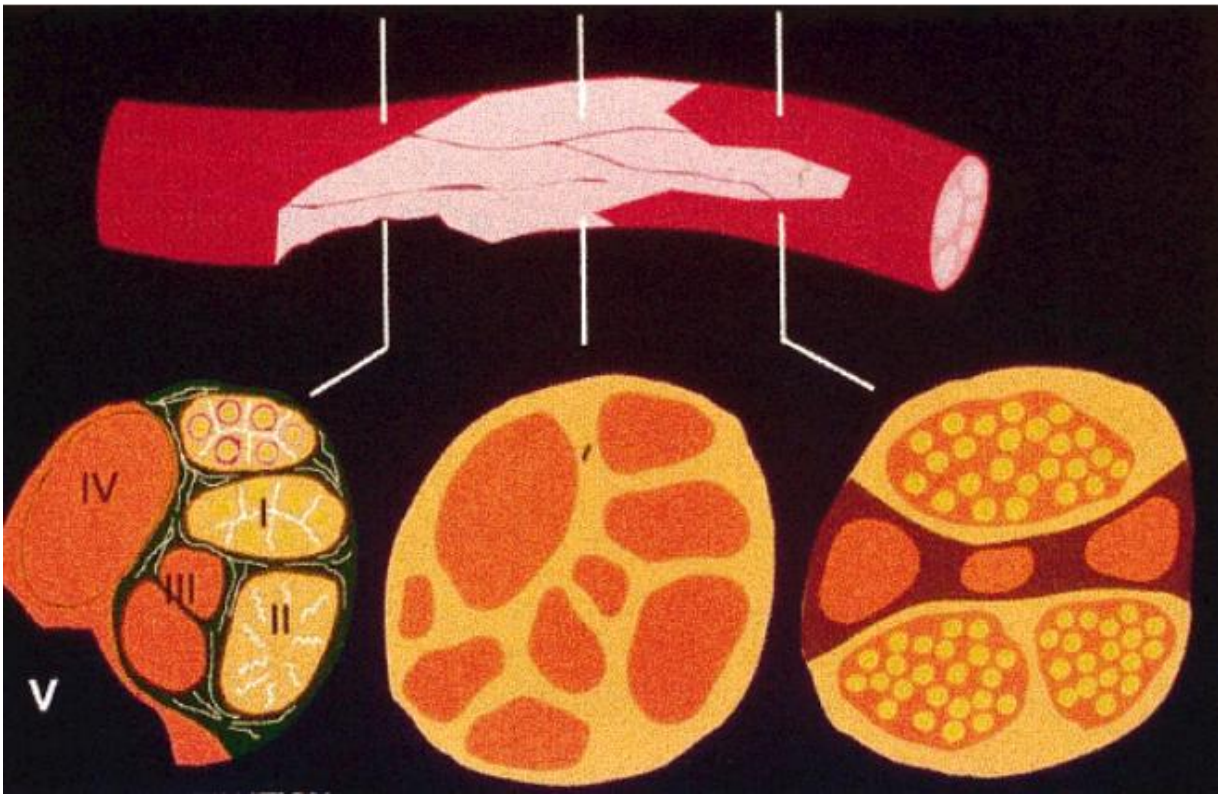


Figure 3: Six-degrees of nerve injury.[7]

This picture indicates the varying degree of fascicular injury that can occur within the same nerve.[7]

1.3 Neurobiology of PNI

1.3.1 Degeneration

Following traumatic injury to peripheral nerves, Wallerian degeneration involving axon and myelin breakdown begins within hours of injury, both at the proximal and distal segment of the injured nerve.[61] Myelin disintegration is in advanced by 36 to 48 hours but it lags slightly behind of axons, which axonal continuity is lost and conduction of stimulus is impossible by 48 to 96 hours post injury.[41] Both Schwann cells and macrophages play a key role in the Wallerian degeneration but the mechanisms and time-course of their action are different.[63] Schwann cells are the major cellular participants within 24 hours of injury, which divide and proliferate rapidly to form dedifferentiated daughter Schwann cells that contribute to the

removal of degenerated axonal and myelin debris and then pass it on to macrophages.[41] Thereafter, macrophages become the major contributors. By one week to several months, Schwann cells and macrophages cooperate to phagocytose and clear the traumatic site; the Wallerian degeneration process is usually complete in 5 to 8 weeks.[41]

In the distal nerve segment, neuron degeneration has been termed as Wallerian degeneration. Interestingly, despite the occurrence of Wallerian degeneration, the Schwann sheath and blood vessels remain intact but the endoneurial tubes remain denervated for prolonged periods.[41,64] Within approximately 3 to 4 months post injury, the endoneurial tubes complete the process of shrink; and if the endoneurial tubes lose the contact with peripheral axon, it will be wiped out by progressive fibrosis.[41] Upon depriving of axon contact, Schwann cells proliferate, align with the empty basement membrane of the endoneurial tube and form linear arrays (band of Büngner) which finally become important guides for sprouting axons during regeneration.[61]

Axonal degeneration in the proximal segment of the injured nerve varies depending on the severity of the injury and the proximity of the injured segment to the cell body.[41] This retrograde axonal degeneration in the proximal segment may extend for several millimeters which range from the injury site to the next node of Ranvier or even extend to the cellular body following severe trauma.[61] In the severe trauma, the entire proximal segment suffers Wallerian degeneration if the complete cell degenerates, and the proximal segment axon may demonstrate a reduction in diameter when the functional connections to appropriate terminal organs are not reconstructed [41]

1.3.2 Regeneration

During peripheral nerve regeneration, the sprouting axons which are formed at the proximal segment grow into the distal endoneurial tube and finally reach the terminal end organs. The optimal outcome of function after peripheral nerve regeneration depends largely on the severity of the injury and pathological changes. In less severe injuries, the regenerative and repair processes begin almost immediately.[51] Within a few hours of axotomy, axons begin to sprout from the

terminal nodes of Ranvier, pass through the injury site left by partial retraction of the Schwann cells and grow down the endoneurial tubes.[65] Because the endoneurial tubes and Schwann cell basal lamina are usually intact in mild injuries, regenerating axons remain in their original tubes and are guided accurately back to their targets, therefore functional recovery is complete in these milder injuries.[65] In more severe injuries, however, a series of Wallerian degeneration of the isolated axons and myelin sheaths of the injured nerve must be completed before the occurrence of nerve regeneration, this is the prerequisite to provide a right growth environment for axon regeneration.[63] In contrast to the milder injury, the endoneurial tubes are disrupted in the severe nerve injuries, and the regenerating axons may wander into surrounding tissue or grow into inappropriate tubes which may fail to reach their proper end organs, thus the functional outcome is compromised.[41]

The injury site and the rate of axonal regeneration are other factors which compromise the functional outcome. In proximal peripheral nerve injuries, especially in injury sites close to the spinal cord and far from the end organs, functional recovery is poor because of the long duration for regenerating axons to sprout and grow over the long distance to reach their end organs. These injuries include avulsion-type injuries, nerve lacerations and nerve contusions.[25] In these proximal injuries, injured neurons regenerate their axons at a very slow rate of 1 mm/d, thus it may take months or even years for the regenerating axons to reach the functional motor unit or sense organ.[66] During prolonged periods of time, the injured neurons remain without targets (chronic axotomy) and Schwann cells in the distal nerve segment remain chronically denervated (chronic denervation); Gordon et al. found that chronic axotomy impairs the regenerative capacity of motoneurons by 66% and chronic denervation of the Schwann cells impairs the capacity of supporting axons by 90% which fully account for the absence of functional recovery in the proximal injuries.[12]

1.3.3 Misdirection

A further issue, of functional significance, is that regenerating axons may regenerate into the inappropriate endoneurium. Regenerating axons growing into the right endoneurial tubes that guide them back to their original end organs is an important prerequisite for successful functional outcome.[25] In crush injuries in which the

endoneurial tubes were not disrupted so that the grow cones grow along the Bünger's bands into the appropriate tubes and reach their original targets, thus the functional outcomes are best.[65] However, injuries that disrupt the continuity of peripheral nerve are more complex for axonal regeneration and with compromised functional outcomes.

Misdirection of regenerating axons into the inappropriate endoneurial tubes plays a key role in reducing functional outcomes.[25] Although microsurgical apposition of the proximal and distal nerve segment was aided to repair the continuity of the peripheral nerve and bridge the Bünger's bands between the nerve segments, the grow cones do not succeed in entering the correct tubes.[12] Because one single neurons may many as 20 axons in the distal nerve stump, these daughter axons may grow into several different endoneurial tubes or enter into a single tube, which lead to the random reinnervation of denervated targets by this complex misdirection of regenerating axons.[12] In the case of sensory axons that enter into pathways leading to the muscle rather than the skin, synapses will not be formed on muscle fibers at the level of gross mismact, the original number of functional motor units will not be restored, therefore the muscle isometric forces will not recover.[25,65]

1.4 PNI at upper extremity

1.4.1 The median nerve and its injury

The median nerve is formed by inputs from both the lateral and medial cord of the brachial plexus. It contains the fibers from C6, C7, C8 and T1 and occasionally from C5 fibers.[67] In the arm it passes vertically down and closely accompanies with the brachial artery on medial side.

It then runs through the cubital fossa lateral and enters into the forearm between the two heads of the pronator teres. The nerve passes through the forearm between flexor digitorum superficialis and flexor digitorum profundus. Here it gives off the anterior interosseous nerve and palmar cutaneous nerve.[68] The AIN, the largest terminal branch of the median nerve in the forearm travels along the volar surface of the anterior interrosseus membrane between the ulna and radius, supplies the deep layer group of the flexors except flexor carpi ulnaris muscle and ulnar half of the

flexor digitorum prfofundus muscle which were innervated by the ulnar nerve. The median nerve passes through the carpal tunnel into the palm hand, divides into the thenar branch of median nerve to innervate the thenar muscle and the sensory part to supplies the palmar aspects of radial three and a half digits (Fig.4).[5] Here a muscular branch supplies the first and second lumbricals of the hand.

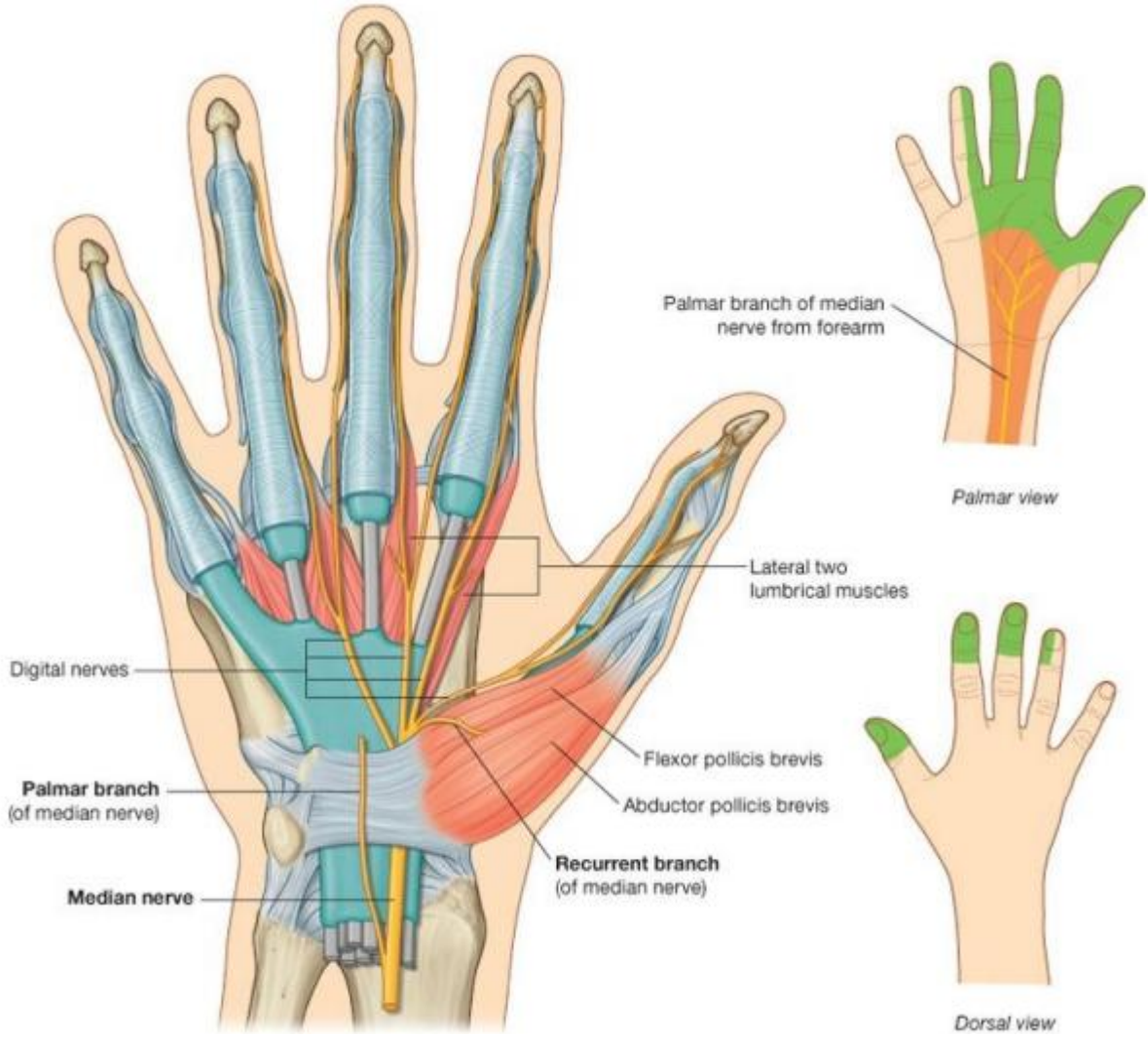


Figure 4: Median nerve in the hand.[5]

Injury of median nerve will lead to different symptoms which depend on the locations of injury. The injury which is proximal to the origin of the anterior interosseus nerve is classified as high median nerve injury.[69] On the contrary, the injury which is distal to the origin of the anterior interosseus nerve is classified into low median nerve injury. Both high and low injury could result in varying motor and sensory deficits. With high median nerve injury, the common pattern of motor deficit will probably involve the pronator teres, flexor carpi radialis, palmaris longus, flexor

pollicis longus muscles, and flexor digitorum profundus muscle to the index.[70] It may also results in sensory weakness of radial palm hand.[67]

In the proximal forearm the median nerve lies deep, its injury usually caused by deep penetrating wounds.[70] Different muscles will be affected in the low median nerve injury. The thenar intrinsic muscles, the abductor pollicis brevis muscle, the opponens pollicis muscle, and the superficial head of the flexor pollicis brevis muscle are involved. Isolated injury to the anterior interosseus nerve will lead to muscle weakness involving the deep group of the flexors and pronator quadrates.[70] Within the wrist, the carpal tunnel syndrome is common mechanism. The median nerve was compressed in the carpal tunnel which mainly result in numbness in radial 3½ digits and motor weakness in flexion abduction and opposition of thumb.[71]

1.4.2 The ulnar nerve and its injury

The ulnar nerve originates from the C7 to T1 nerve roots which form the medial cord of the brachial plexus.[72] It is a mixed motor and sensory nerve. It travels through the posterior compartment of the upper arm and enters the anterior compartment of the forearm.

In the forearm, it runs alongside the Ulna and gives off muscular branches to flexor carpi ulnaris and the radial half of the flexor digitorum profundus.[73] Proximal to the wrist, it sends off the dorsal cutaneous branch of ulnar nerve (DBUN) to supply the sensation of the poster medial side of the hand and the posterior aspect of the little finger and medial half of ring finger as well as the anterior ulnar side of the hand.[74] At the wrist level, the ulnar nerve passes through the Guyon's canal which is formed by the pisiform bone, hook of the hamate and ligaments that to connect them.[73] At the distal aspect of the Guyon's canal, the ulnar nerve branches out a superficial branch to supply the sensation to the palm side of little finger and medial half of ring finger (Fig.5), and gives off the deep motor branch to innervate the intrinsic muscles.[75]

According to the injury location, the injuries of ulnar nerve can be divided into high injuries and low injuries.[76] Low injuries are distal to the motor branches of the flexor carpi ulnaris (FCU) and the innervations of the flexor digitorum profundus (FDP)

muscles for the ring and small finger. It results in a functional weakness including most of the interossei, the medial two lumbricals, the hypothenar and the adductor pollicis and part of the flexor pollicis brevis, and sensory deficit of the small finger and medial half of the ring finger.[77] Consequently, this leads to the development of claw hand deformity of the ring and little fingers with hypertension at the MCP joints and reciprocal flexion at IP joints (Duchenne's sign).[78,79] High injuries associated with paralysis of FCU and FDP result in weakness of wrist flexion and medial half digits flexion, however the claw hand deformity will be less.[77]

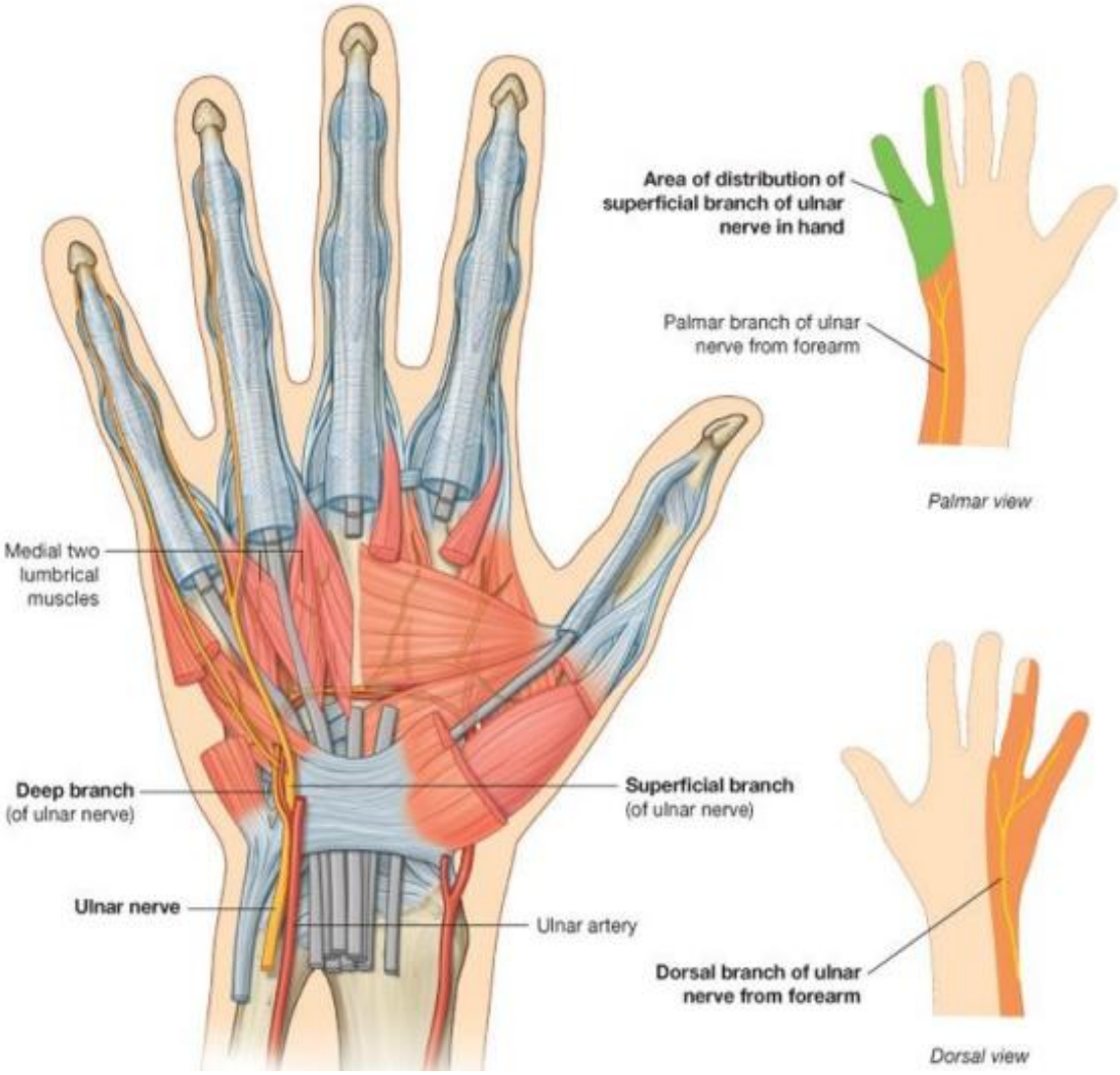


Figure 5: Ulnar nerve in the hand.[4]

1.4.3 The radial nerve and its injury

The radial nerve originates from each nerve root from C5-T1 which is formed by both motor and sensory nerve.[80] It continues as a terminal branch of the posterior cord of the brachial plexus. From the brachial plexus, it provides motor innervation to the triceps muscle and the anconeus, after which it travels posteriorly through the radial groove of the humerus where it gives muscular branches to the brachioradialis muscle. When the radial nerve reaches the forearm, it sends off branches to the extensor carpi radialis longus, extensor carpi radialis brevis and the supinator muscle before bifurcates into a superficial branch and deep branch.

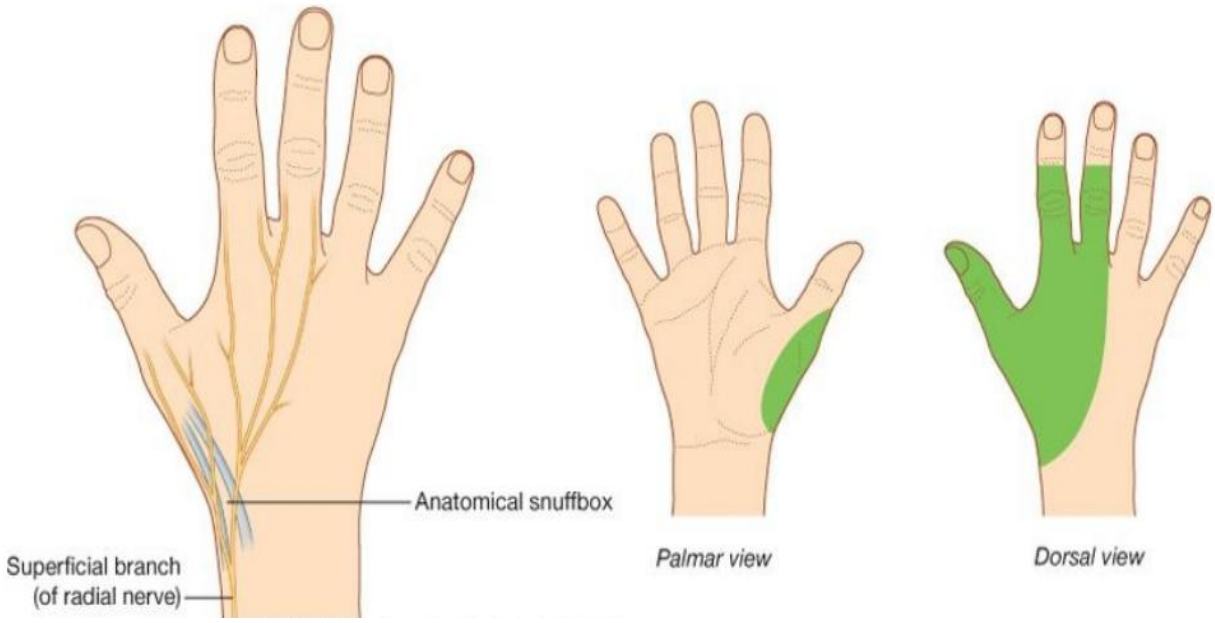


Figure 6: Radial nerve in the hand.[5]

The deep branch pierces the two heads of the supinator muscle to reach the extensor compartment where it turns to posterior interosseous nerve and gives off muscular branches to extensor muscles. The superficial branch of radial nerve (SBRN) descends in the forearm over the radial bone and crosses the brachioradialis to bifurcate in two main branches to supply sensation over the dorsoradial part of the hand and dorsum of the thumb, index, middle and lateral half of the ring finger (Fig.6).[74,81]

Injury to the radial nerve causes a significant disability with motor and sensory deficits. High injuries proximal to the elbow will lead to weakness of supination,

loss of wrist and finger extension, loss of sensibility in posterior forearm, the dorsoradial part of the hand, and dorsum of radial 3½ digits.[80] The injuries located at the axilla will results in loss of forearm extension. Injuries distal to the elbow will lead to deficits of finger extension and sensation respectively.

1.5 Timing of nerve repair

Surgical timing in a traumatic peripheral nerve injury is important for optimal functional outcome. In every case of acute injury, surgeons must evaluate and make a decision which treatment programs, primary repair or secondary reconstruction, should be implemented. Many factors including the endings of nerve segment, muscles, joints and other tissues of the denervated extremity should be considered before treatment. Based on Martins's theory, surgical timing in peripheral nerve injury is defined by the "rule of three": clean and sharp injuries should be treated immediately within 3 days; blunt/ contusion injuries are treated early within 3 weeks; closed injuries are treated with delayed surgery after 3 months.[53] When the nerve injury type is laceration and there has been a clean cut, primary surgery is favorable in view of that it is easy to judge the rotation of the nerve segment according to the epineurial blood vessels on the surface of the nerve trunk and easy to repair. In injuries caused by a blunt trauma or avulsion, early reconstruction which is delayed for several weeks is preferable because the inflammatory process prolongs for about 3 weeks after the trauma.[53] By that time, neuromas and scarred nerve endings can be identified and resected back to the healthy fascicles, microsurgical intervention can be performed with or without a nerve graft. Closed injuries should be followed up with electromyography or nerve conduction studies for 2-5 months before surgical repair or exploration, because during the initial periods the degree of injury is not unclear.[51]

1.6 Surgical consideration

Although our greater understanding of the peripheral nervous system including anatomy, pathology, pathophysiology and microsurgical techniques, the PNI management still remains a big challenge.[82] There are a number of considerations of surgical management which were used to repair the PNI in different types and

clinical conditions. Current commonly performed surgical treatments are primary anatomic neurorrhaphy, side to side and end to side neurorrhaphy, graft repair, nerve conduit, and nerve transfers. The purpose of nerve repair is to eliminate the gap between the distal segment and proximal segment, and to reconstruct a neural tube for the sprouting axons to reach the terminal target.[64] The success of functional recovery in the hand depends on accurately and correctly axonal sprouts from the proximal segment to the distal segment.[25] Other factors which influence the ratio of successful recovery include: PNI type, location, patient's age and timing of surgery.[82] In the following paragraph we review the microsurgical techniques which are advances in the nerve reconstruction of the hand.

1.6.1 Primary nerve repair

Direct nerve repair is a primary anatomic end-to-end coaptation which if possible remains the optimal method of nerve reconstruction.[83] Usually the injury site is with good blood supply and close to the target organs where the gap is small enough for tension-free neurorrhaphy. When the proximal segment and distal segment were approximated together, the longitudinal vessel which is outside of the epineurium and other connective tissue is used as anatomic landmark for suturing. Nerve surgery is carried out under magnification using 9.0 nylon sutures.[84] The injury type and time are also important factors for surgeon to be considered. Within 3 days to 7 days, a laceration and a sharp should be repaired by primary anatomic coaptation.[38] If a tension-free neurrorrhaphy is not possible due to a gap formation or poor blood supply, another method should be used.

End-to-end nerve repair includes several different microsurgical techniques, such as epineural repair, group-fascicular repair, and fascicular repair. In the so-called epineural repair the lacerated nerves are sutured only in the outer sheath.[85] The goal of epineural repair is to approximate the transected segments with correct alignment of internal fascicles, so that the sprouts from the proximal segments can reach the end-organ.[64] Perineural repair where the identifiable fascicles can be easily copated, provides better alignment of neuronal pathways because surgeons can identify the matching fascicle groups by well localized nerve terminals.[86] The

drawbacks are the greater scar formation and vessel injury at the site of suture.[87] Therefore, a minimal number of sutures should be used.

1.6.2 Techniques to bridge the nerve defect

PNI may result in a nerve gap between the two segments of the severed nerve, which can be due to is nerve tissue deficit but also to the retraction of the two segments.[88] A short nerve gap can be overcome by primary anatomic coaptation with minimal tension. When a direct coaptation leads to a large tension or if large nerve ends can't be approximated at all secondary nerve repair is recommended which include nerve grafting, nerve allografting, nerve conduits, tendon transfer and nerve transfer.[11]

1.6.2.1 Nerve autografting

Nerve autografting is widely accepted as the gold standard for nerve gap management.[8] The axons in the harvested graft undergo wallerian degeneration, the enoneurial tubes and Schwann cells basal laminae are used as supportive structure for axon regeneration.[89] Normal cutaneous sensory nerves are transected from the non-critical areas in the body and sewn to bridge the nerve gap. The best autograft should fulfill the criteria: long and unbranched segment, easily accessible, small disameter and large fascicles.[38] Clinical observations indicate that multiple small grafts results in better recovery because they can easily get revascularization from the nearby tissue bed to decrease the scar formation and improve nerve regeneration.[90] Currently the donor nerves which are used for the autograft including: sural nerve, lateral antebrachial cutaneus nerve (LCAN), dorsal cutaneous branch of the ulnar nerve (DCBUN), and superficial sensory branch of the radial nerve (SSR).[90]

1.6.2.2 Allograft

Allograft is a cadaveric nerve graft in which the donor cellular and noncellular factors were removed to retain the three dimensional scaffold and basal lamina tubular structure.[8] Compared to the autograft, the main advantage of the allograft is unlimited availability and lack of morbidity that patients can be treated exactly with

the same type of nerve from the donor.[91] However, a temporary systemic immunosuppression is necessary while the regenerating axons grow across the allograft until they reach the terminal organ, which is critical for the success of nerve regeneration.[92] Moreover, nerve allograft pretreatment was regarded as an ideal method in order to prevent rejection. Carefully, the delicate balance between the reduction of the expression of major histocompatibilitycomplex (MHC) molecules and the preservation of the extracellular matrix (ECM) should be taken into consideration.[38]

1.6.2.3 Nerve conduit

Nerve conduits are another alternative option for managing the nerve gaps because they can avoid the donor site morbidity of the autograft and the pretreatment and immune reaction of the allograft. Various materials have been used to construct the nerve conduits which include bone, vein, muscles, biologic tubes and silicone, polyglycolic and polyglactin for the bioabsorbable synthetic tubes.[38] The main objective of nerve conduit is to block the external inbibitory factors and combine all kinds of factors that can provide a physical guidance for axonal outgrowth.[93] Currently, the limitation of the nerve conduits is lack of Schwann cells and laminin scaffolding which are important for axonal regrowth, therefore they can only be used for noncritical, small-diameter nerves with a gap less than 3 cm.[38]

1.6.2.4 End-to-side nerve repair

End-to-side (ETS) is a technique based on the concept that axons from the donor nerve grow into the recipient nerve by collateral sprouting.[94] There are different views whether an injury to the donor nerve was needed for the collateral sprouting, some researchers indicated that sensory and motor axon regeneration may require an injury to the outer sheath of the donor nerve, some support that the sensory axons may sprout without injury, but others report that motor axons can only sprout with deliberate injury.[95] Although these conflicting results, a positive outcome was reported in distal sensory nerve by ETS reconstruction.[96]

1.6.2.5 Supercharged end-to-side

Supercharged end-to-side (SETS) nerve transfer is performed when the injury site is at proximal or middle level where regenerating axons take a long time to reach the targets. A donor nerve is cut distally and coapted to the side of an injured recipient nerve by creation of a perineurial window. [34] In theory, the SETS can supply additional motor axons to augment the injured recipient nerve and provide more quickly muscle reinnervation with additional axons to protect the distal motor end plates until native axons from the muscle's original neuron fully regenerate.[97] Experimental models have indicated that axonal regeneration grew across a SETS nerve coaptation, and less-than-optimal recovery is otherwise anticipated.[34] In patients, with a mid-level ulnar nerve injury when a good functional recovery is predicated, the SETS AIN-to-ulnar motor nerve transfer was performed to preserve the distal target and excellent results in this clinical scenario were possible.[33]

1.7 Nerve transfer

Nerve transfers involve sacrifying of a less important nerve and transferring it to reinnervate the distal stump of more valuable nerve.[98] It provides nerve axons closer to the terminal organ which can be directed quickly to the denervated end-organs.[76] In 1903, Harris and low first described the technique by using end-to-side nerve transfer for brachial plexus reconstruction.[15] In 1913, Tuttle introduced the first successful nerve transfer for brachial plexus reconstruction.[99] In 1948, Lurije outlined an important concept of nerve transfer to restore function of axillary, suprascapular and musculocutaneous nerves after brachial plexus injuries, which transferred the normal functioning nerves to the adjacent injured nerves.[100] In the mid-1990s, nerve grafting and tendon transfers with excellent results were accepted as the standard treatment for nerve reconstruction which dominated the literature.[101] However, in the early 1990s, several nerve transfers were used and acquired popularity which included transferring the medial pectoral branches to the musculocutaneous nerve, transferring the AIN to the deep motor branch of the ulnar nerve.[13,102] Therefore, nerve transfers were rapidly expanded and widely accepted for reconstruction of upper extremity function in brachial plexus injuries.

Compared with nerve grafts, nerve conduits and tendon transfers, nerve transfers are an optimal choice especially for a proximal nerve injury which has a poor prospect of recovery because of its long distance between the injury site and the terminal end-organ.[103,104] It offers several advantages including: it can convert the high-level nerve injury into a low level nerve injury, does not depend on the location of injury, avoids operation in scarred areas, can restore the multiple muscle groups with a single nerve transfer.[8] In contrast, the functional outcomes of proximal nerve injury which reconstructed with nerve graft are often poor due to the irreversible loss of the terminal motor endplates by denervation and fibrosis.[105]

In addition, the nerve regeneration depends on the axonal regeneration which has a rate of approximately 1 mm per day.[56] Optimal muscle reinnervation relies on how much regenerating axons reach the target muscles within approximately one year after injury. By two years, muscle fibers are completely broken into fragments and finally replaced by fat cells.[84] Therefore, a surgical technique which can minimize the regeneration distance and time is important. Nerve transfers allow surgery in uninjured field, minimize the distance and time for nerve regeneration before irreversible changes of the terminal end-organ occur.

As the knowledge of the internal topography of peripheral nerves and of new donor sources for motor and sensory restoration is increased, the indications of using nerve transfers are widely expanded.[98] Generally the nerve transfers follow the indications including: [8,98]

- Proximal brachial plexus injuries or spinal cord root avulsion injuries in which grafting is not possible;
- High level nerve injuries that require a long distance for reinnervation of terminal end-organ;
- Avoidance of severely injuried and scarred regions in critical locations with probability for injury to critical structures;
- Major limb injury with segmental nerve tissue loss;
- Delayed treatment with inadequate time for reinnervation of distal targets with grafting;
- Partial nerve injuries with a defined functional loss;
- Long distance nerve defects;

- Sensory nerve deficits in critical field.

Many potential nerve transfers have been introduced for peripheral nerve reconstruction for different level nerve injuries in the upper extremity.[20,22,106] Nerve transfers are based on the theory that it converts the proximal nerve injury into a distal nerve injury by transferring an unimportant nerve to the more critical or important nerve. To ensure a end-to-end tension-free coaptation, the donor and recipient nerve should be mobilized as much as possible.[76] The mantra “donor distal, recipient proximal” should be taken into consideration when plan the nerve transfers.[84] The criteria for motor and sensory nerve transfers are listed as follows:[2,38]

Criteria for motor nerve transfer

- Expendable donor motor nerve
- Donor motor nerve with a large number of motor axons
- Donor nerve near the motor endplates of the target muscle
- Donor nerve innervates a muscle that is synergistic to the target muscle

Criteria for sensory nerve transfer

- Expendable donor sensory nerve
- Donor sensory nerve with a large number of sensory axons
- Donor sensory nerve near the target sensory nerve

1.7.1 Motor nerve transfers in the forearm and hand

Forearm pronation

If the loss of pronation is a separated finding, an expandable motor branch of the median nerve can be used to manage the isolated loss of pronator function.[107] Normally, the flexor digitorium superficialis was transected as the donor nerve to innervate the two branches of the median nerve to the pronator teres (Fig.7).[6] If the median nerve is not functioning at all, redundant portions of the ulnar nerve that innervates the flexor carpi ulnaris and palmaris longus can also be used as donor nerve.[76,107] In addition, extensor carpi radialis brevis branches (ECRB) and supinator branches of the radial nerve (SBRN) can be transferred to the pronator in median nerve palsy.[84]

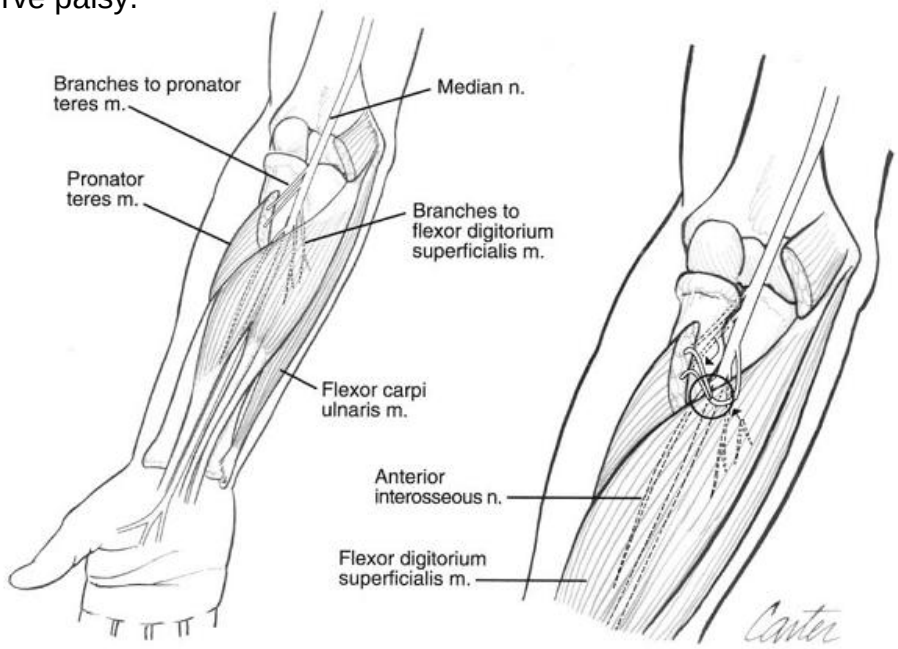


Figure 7: Transfer of redundant branches of the median nerve to restore pronation.[6]

Wrist extension and finger extension

Radial nerve palsies will lead to deficits of wrist and finger extensors and weakness of sensation. Typically, radial nerve injuries are reconstructed with direct anatomical coaptation, nerve graft, or tendon transfers.[6] Beside these techniques, nerve transfers were performed for radial nerve restoration. The flexor carpi radialis and flexor digitorum superficialis branches of the median nerve were transected and

transferred to the posterior interosseous nerve (PIN) and ECRB respectively for finger and wrist extension reconstruction (Fig.8).[9] Intraoperative stimulation was needed before the transaction to confirm lack of radial nerve function.

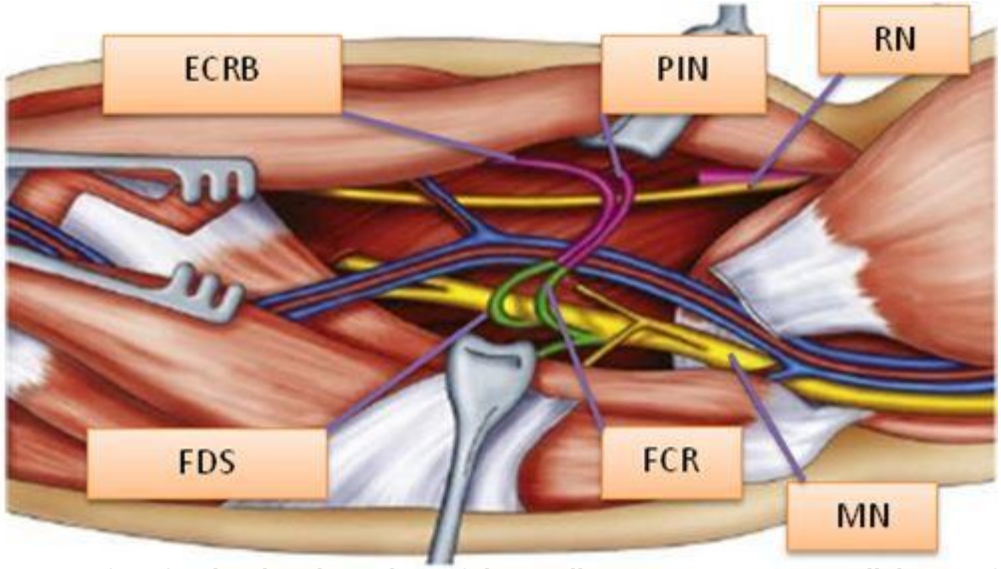


Figure 8: Transfer of redundant branches of the median nerve to restore radial nerve function.[9]

RN=radial nerve, MN=median nerve, FCR=flexor carpi radialis, FDS= flexor digitorum superficialis, PIN=posterior interosseous nerve

Finger flexion

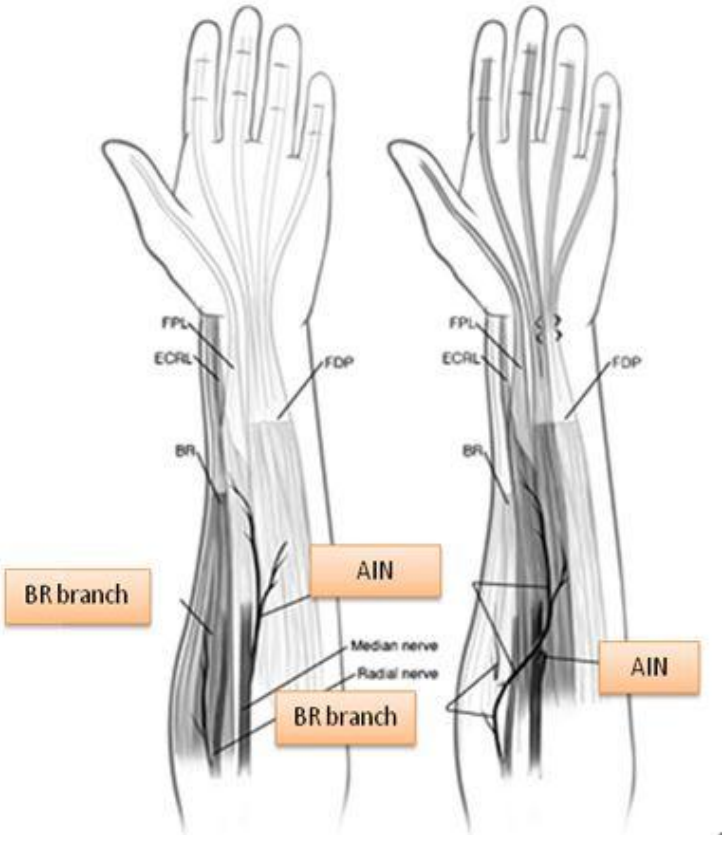


Figure 9: Transfer of the nerve to the brachioradialis muscle to the anterior interosseous nerve to restore the flexion of the thumb, index and middle fingers.[1,2]

Median nerve injuries may result in the common pattern of motor deficit of flexion of radial half of digits and thumb. Tendon transfer was described as treatment which transected and reattached the brachioradialis (BR) to the flexor pollicis longus (FPL) and the extensor carpiradialis longus (ECRL) to the flexor digitorum profundus (FDP) in order to restore the thumb and digit flexion.[108,109] In a nerve transfer procedure, the single nerve which innervates the BR was transected and transferred to the anterior interosseous nerve which can reinnervate a group muscles (Fig.9).[1] In this case, although nerve transfers need time for regenerating axons to reach the target muscles, it avoids sacrifice of multiple muscles for target muscle function reconstruction.

Intrinsic hand function

High level ulnar nerve injuries are associated with poor recovery of intrinsic hand muscles because of the long distance from the injury site to the terminal endplate.[59] Tendon transfers often bring unsatisfactory results with complicated procedures.[20] In this case, nerve transfer is used to convert the high level ulnar nerve injury to a low level ulnar nerve injury. Several reports have shown an anterior interosseous nerve as a distal donor nerve which can be transferred to the deep motor branch of the ulnar nerve (Fig.10).[3,13,23,40] The AIN was transected at the hight of the pronator quadratus, the DBUN was identified and isolated retrogradely until tension-free coaptation of AIN and DBUN. AIN provides a close source of motor axons to reinnervate the intrinsic muscles.

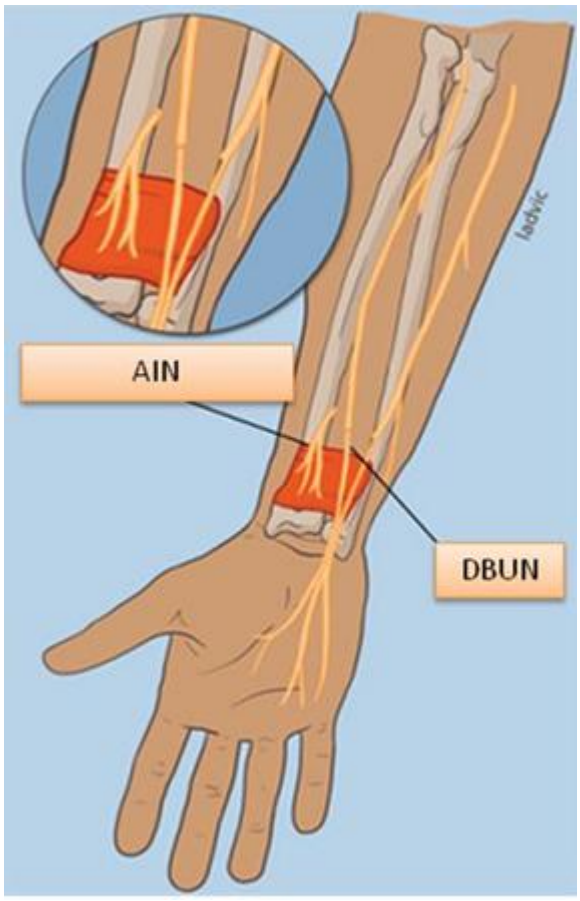


Figure 10: Transfer of the anterior interosseous nerve to the deep motor branch of ulnar nerve to restore intrinsic hand function.[3]

1.7.2 Sensory nerve transfer in the hand

Median nerve deficit

Median nerve injuries lead to sensation deficit in the hand. Many donor nerves including the fourth web space fascicle of the ulnar nerve, the dorsal branch of the ulnar nerve, and the sensory radial nerve can be used for sensation reconstruction with sacrifice of non-critical sensory nerve.[110] The proprioception is important for pinch so that the sensation in the thumb and first web space was normally first reconstructed. Kirsty used the dorsal cutaneous branch of the ulnar nerve for sensation restoration in the thumb and first web space in an end-to-end way, and coapted the third web space fascicle of the median nerve to the main sensory portion of the ulnar nerve in an end-to-side manner (Fig.11A).[8] Renata transected

and transferred the fourth web space fascicle of the ulnar nerve to the first web space nerve in an end-to-end way (Fig.11B).[2]

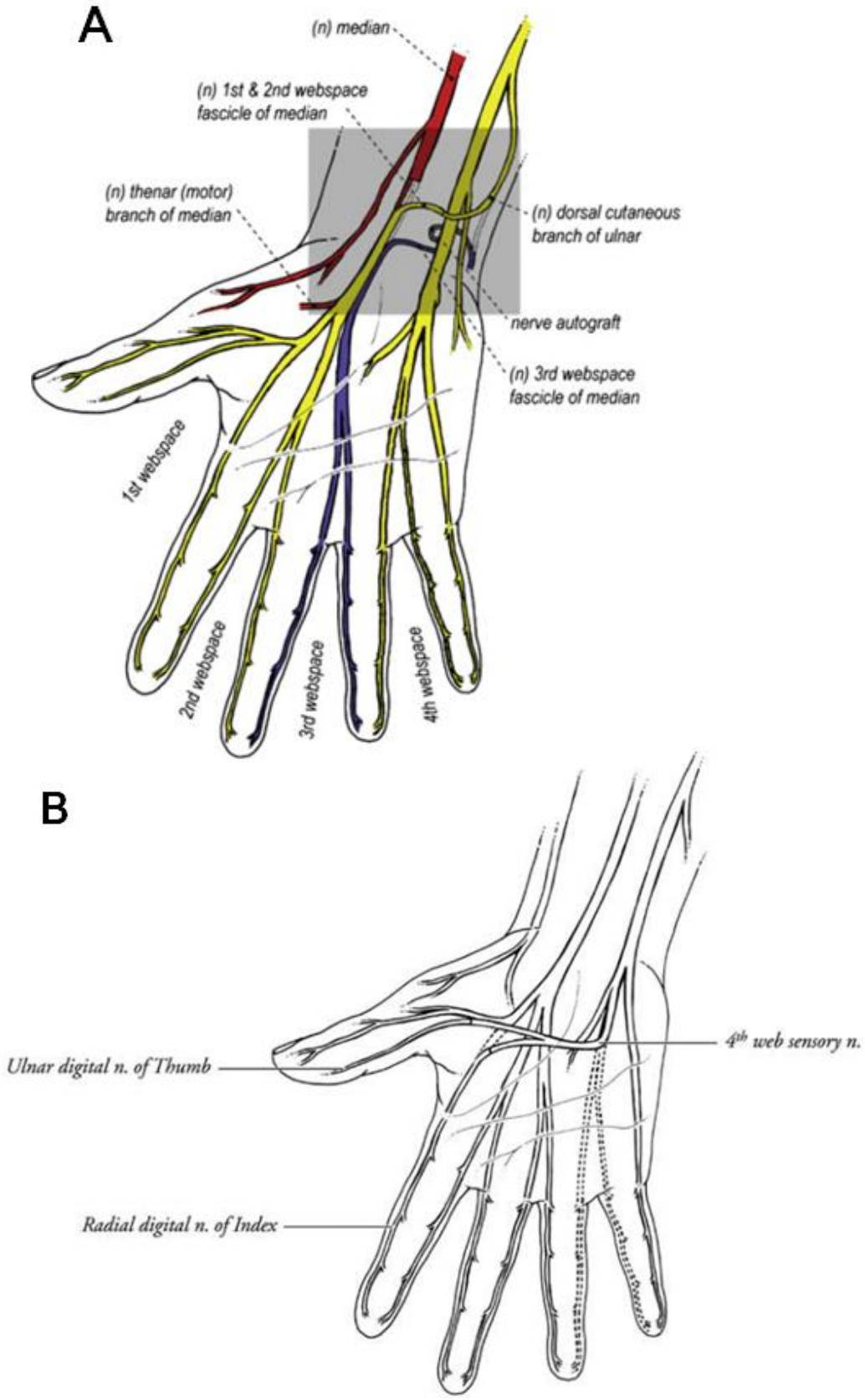
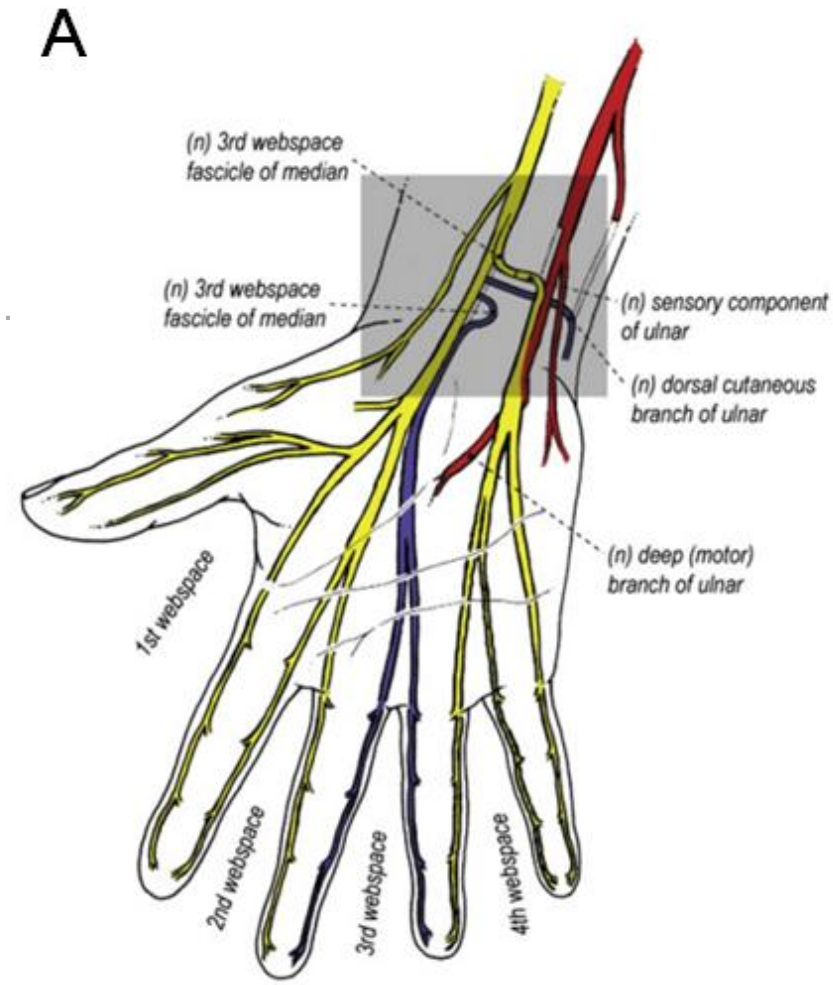


Figure 11 (A,B): Sensory nerve transfers to restore median nerve deficits.[8, 2]

Ulnar nerve deficit

Ulnar nerve injuries result in sensory weakness in the ulnar side of the hand. Several nerve transfer options were described for ulnar nerve sensation reconstruction. Kirsty used third web space fascicle of the median nerve as the donor nerve for sensory reconstruction of the superficial branch of the ulnar nerve in an end-to-end manner, and coapted the DBUN in an end-to-side way to the main portion of the median nerve (Fig.12A).[8] Renata reconstructed the sensation of the ulnar nerve by coapting the SBUN and DBUN to the main portion of the median nerve in an end-to-side manner (Fig.12B).[2]



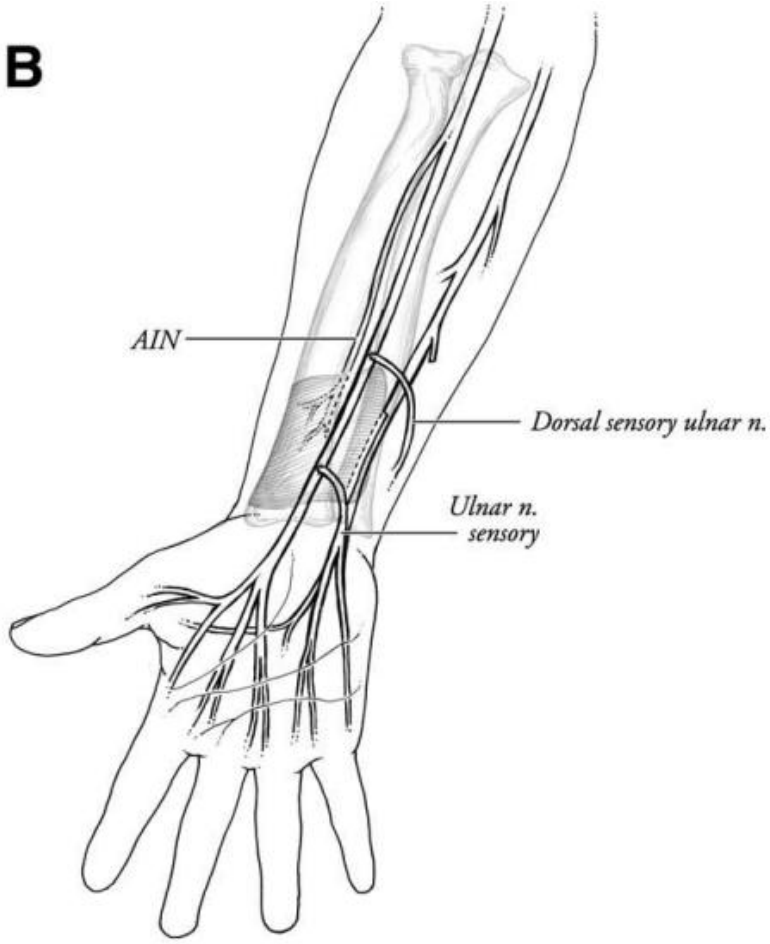


Figure 12 (A,B): Sensory nerve transfers to restore ulnar nerve deficits.[8, 2]

1.8 Postoperative management of PNI

Postoperatively, nerve reconstruction with nerve conduit, graft or nerve transfer are advised to protect by splinting the extremity for 2-6 weeks, which depend on the peripheral nerve injury site and the risk for tension of the nerve repair.[10,111] After immobilization rehabilitation is carried out to realize full passive and active range of motion.

The surgeon should follow the advancement of regenerating axons by Tinel's sign and check the rehabilitation of the patient including physiotherapy and occupational therapy.[112] Moreover, a patient's functional demands at work and daily life should be taken into consideration. The degree of functional recovery of motor and sensory can be evaluated by Medical Research Council (MRC) System, motor recovery is graded

from M0 to M4 and sensory is graded from S0 to S4; of these, M0/1 and S0/1 are “bad”, M2 and S2 are “poor”, M3 and S3 are “fair”, M2 and S2 are good”.[52]

Relearning is an important rehabilitation process in postoperative management of peripheral nerve injury. Its success effect depends on multiple biological and environmental factors including type of injury, type of nerve, injury site, patient’s age, axonal regeneration rate, and rehabilitation without delay.[113] In addition, the results of relearning process rely highly on the motivation of the individual patient. Relearning and reeducation techniques are needed for brain to interpret the new language which is spoken by the hand after nerve reconstruction because of dramatic and extensive functional reorganizational changes in the brain.[112] The rehabilitation program can be started early before reinnervation of the hand and late after some reinnervation of skin in the postoperative period.[10]

1.9 Object of this study

This contribution focuses on the anatomical and histomorphometric background of the nerve transfer of the anterior interosseous nerve (AIN) to the Thenar branch of the median nerve (TBMN), the dorsal cutaneous branch of ulnar nerve (DCBUN) to the sensory part of the median nerve (SMN) or the superficial branch of radial nerve (SBRN). Based on the anatomic and histomorphometric results of these three different nerve transfers, surgeons can better estimate the possibility of these treatments and perform the nerve transfer successfully.

2 Methods

2.1 The AIN Transfer to the TBMN

2.1.1 Anatomic dissection and measurement

We used 15 fresh specimens for anatomic measurements and transected the upper limbs right above the epicondyle. After removing the skin and subcutaneous tissue, nerves were exposed in the palmar aspect of the distal forearm. The AIN was identified on the interosseous membrane. It was isolated from the connective tissues and transected at the proximal edge of the pronator quadratus muscle (PQ). The carpal tunnel was dissected in a longitudinal way to expose the median nerve, the thenar branch of the MN was separated from the sensory part of the MN and traced proximally until possible tension-free coaptation between the AIN and the TBMN.

Following the coaptation, its location was documented by measuring it in relation to anatomic landmarks (Fig.13). The distances from the lateral epicondyle to the takeoff of the thenar branch, to the styloid process of the radius and to the proximal edge of the PQ were recorded. (n=15)

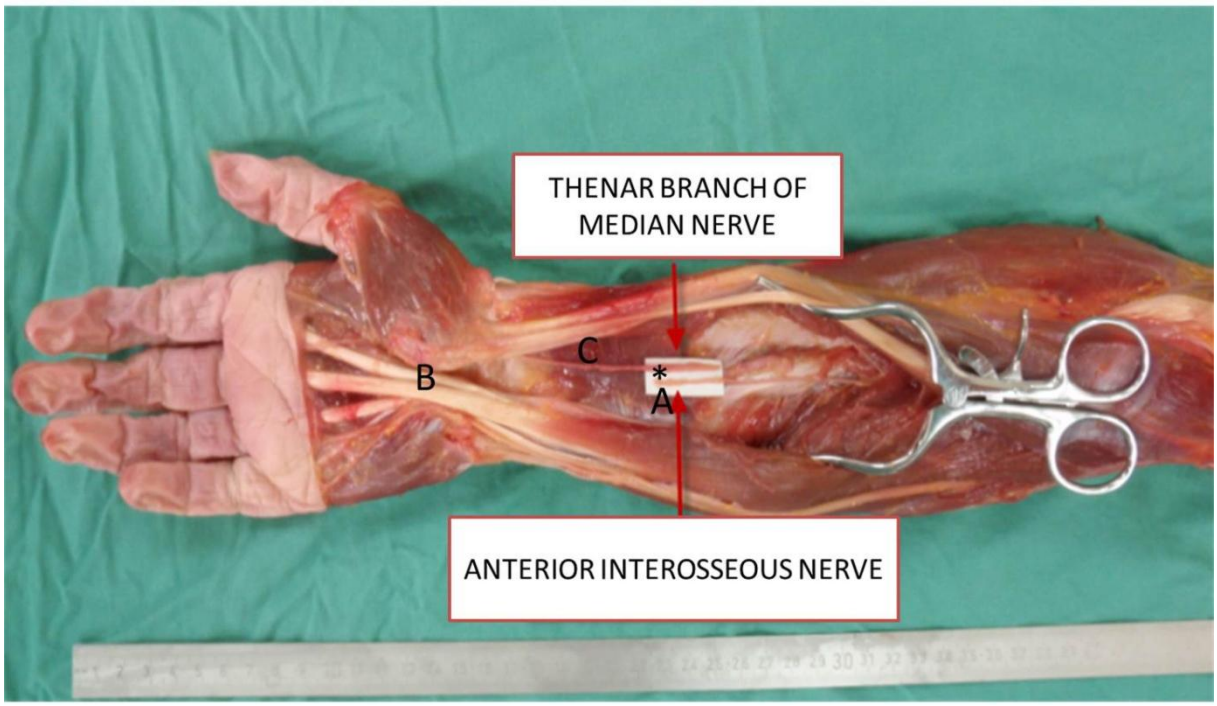


Figure 13 : Transfer of the AIN to the TBMN

The AIN was identified and cut at the level of proximal margin of the PQ (A). The carpal tunnel was opened by a longitudinal incinsion to expose the MN (B). The TBMN was identified and dissected proximally (C). *Coaptation site. (n = 15)**.**

2.1.2 Histomorphometric Analysis

For histomorphometric evaluation, nerve samples of 2-3 mm length were harvested from the coaptation site where the donor and recipient nerves were sutured together. They were fixed with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer for 60 min at 4°C (pH 7.4; Science Service, Munich, Germany). Following postfixation in a 2% aqueous osmium tetraoxide solution (Science Service, Munich, Germany), Nerve samples were transferred to an ascending alcohol series from 30-100% and propylene oxide for dehydration. Then samples were embedded (Merck, Darmstadt, Germany) and cured for 24 hours at 60°C. A series of semi-sections (1µm) were cut by using an ultramicrotome (Reichert Jung) and stained for 1 min with 1% toludine blue (Fig.14). At a 20x magnification, all stained sections were scanned. The diameters, the cross-sectional areas of the nerves and the individual fascicles were measured at a 200x magnification. The cross-sectional areas were determined by a polygon approach (Pannoramic Viewer 1.15; 3DHISTECH,

Hungary). The total fascicle areas were estimated by summarizing the cross-sectional surfaces of all fascicles. At a 600x magnification, the myelinated axon numbers were obtained semi-automatically with a low cut-off value for inclusion of 4 µm. (ImageJ version 1.42; NIH, Bethesda, MD, USA). For all samples, axon density was calculated as the ratio of total axon number and total fascicle area. The ratio from donor to recipient of all nerve specimens were recorded for histomorphometric comparison. The results of ratio was compared to the commonly accepted successful threshold of 1:3. A statistical analysis of the difference between the donor and the recipient was performed using a two-tailed t-Test with $p \leq 0.05$ being considered as significant. All data is given as the mean ± Standard Error of the Mean (SEM). (n=13)

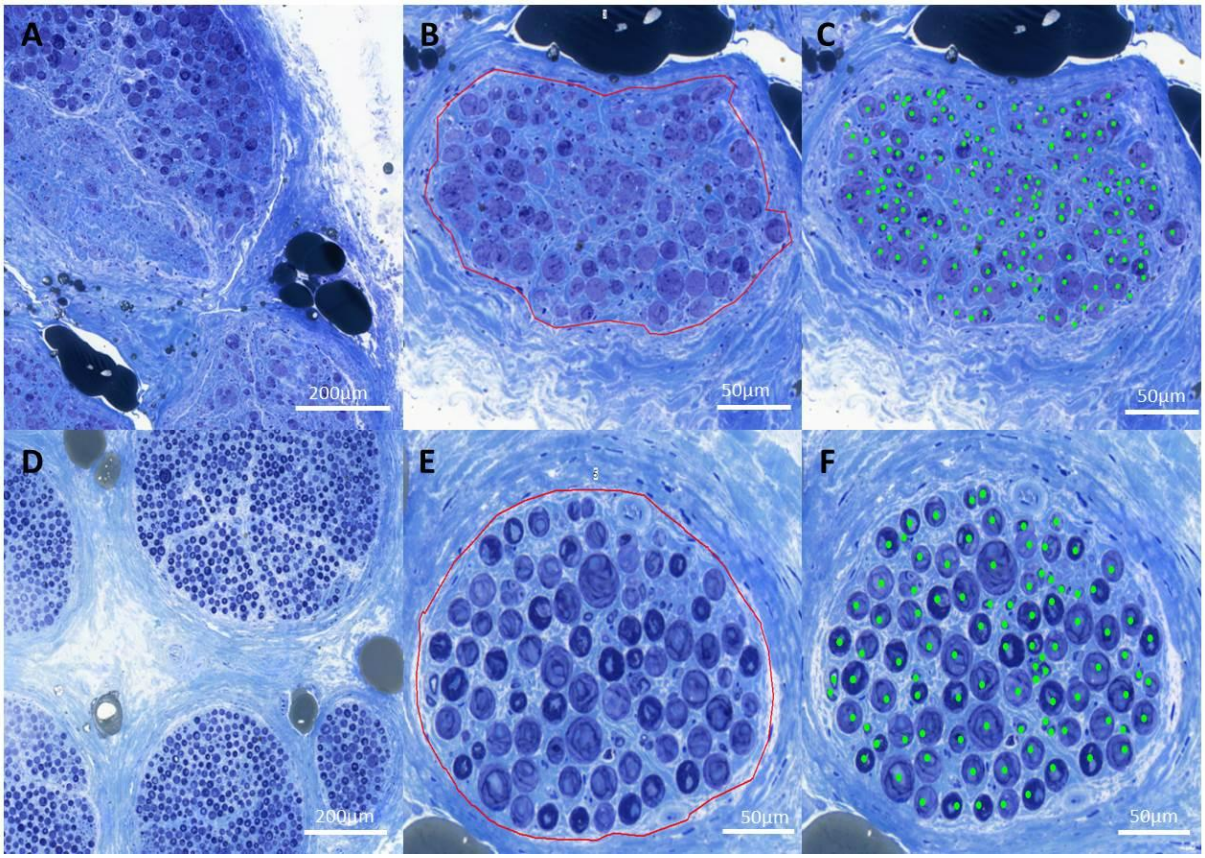


Figure 14: Histologic pictures of stained nerve sections from the AIN and the TBMN.

A series of semithin sections of the AIN (A, B, C) and the TBMN (D, E, F) from the coaptation site were collected and stained with toluidine blue. The nerve diameters, cross-sectional nerve areas and fascicle numbers were measured at ×200 magnification (A, D). At ×600 magnification, semiautomatic method was used to aid axon counting and a polygon approach was applied for determination of the cross-sectional areas of individual fascicles (B, C, E, F) (n=13).

2.2 The DCBUN Transfer to the SMN and the SBRN

2.2.1 Anatomic dissection and measurement

The DCBUN was isolated from the connective tissues; it was divided proximally from the main part of the ulnar nerve and transected at the ulnar dorsal aspect of the wrist. The point of the first branch of the DCBUN was taken as the point of the transaction, the distance from medial epicondyle of the humerus to this point was recored. The SBRN was identified at palmar aspect of the distal forearm and carefully traced distally until its first branch. The SBRN was dissected sharply and coapted accurately to the DCBUN without tension. The carpal tunnel was dissected in a longitudinal way to expose the SMN. The SMN was separated from the motor part of the MN and traced proximally until tension-free coaptation to the DCBUN.

Following the coaptations, their locations were measured in relation to anatomic landmarks (Fig.15, 16). The distances from the medial epicondyle to the takeoff of the DCBUN, to the division of the dorsal branch into its smaller branches, to the point where the DBUN crosses under the flexor carpi ulnaris muscle， the distances from the lateral epicondyle to the crossing (distally) of the SBRN underneath the brachioradialis muscle, from the lateral epicondyle to the nerves distal diversion into its smaller branches and the distances from the medial epicondyle of the humerus to the division of the SMN and the thenar branch were documented. (n=15)

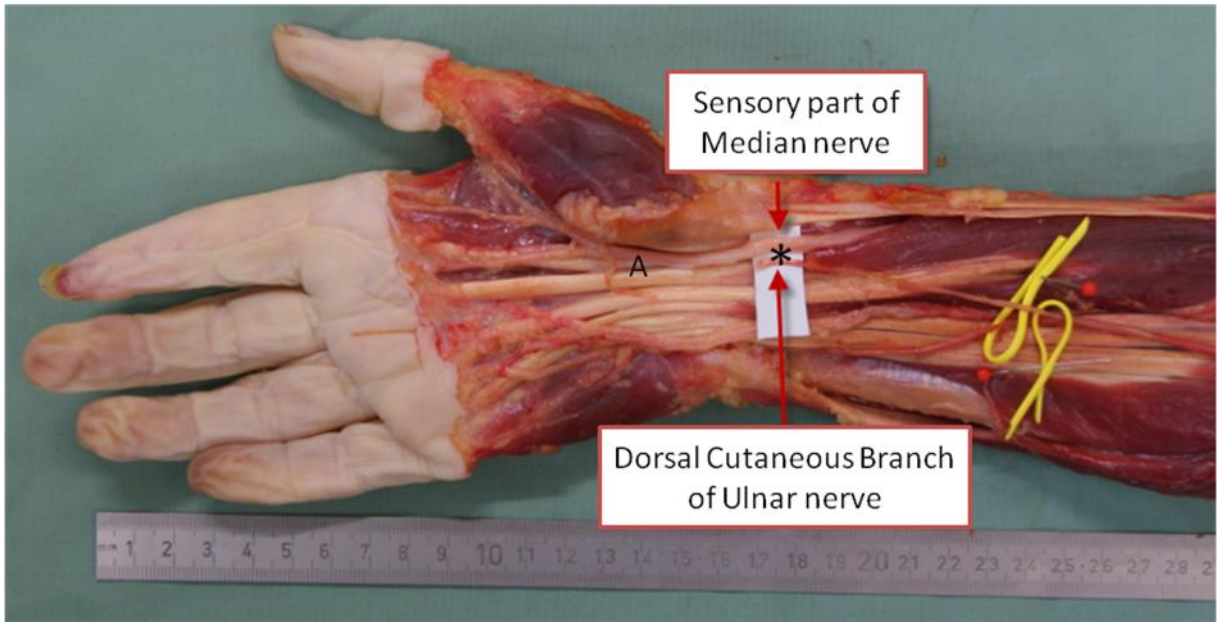


Figure 15 : Transfer of the DCBUN to the SMN.

The DCBUN was identified and dissected proximally to its first bifurcation at the distal ulnar forearm. The carpal tunnel was opened by a longitudinal incinsion to expsose the MN. The SMN was identified and dissected proximally (A). The DCBUN and the SMN was coapted without tension in the distal forearm. *Coaptation site. (n = 15)

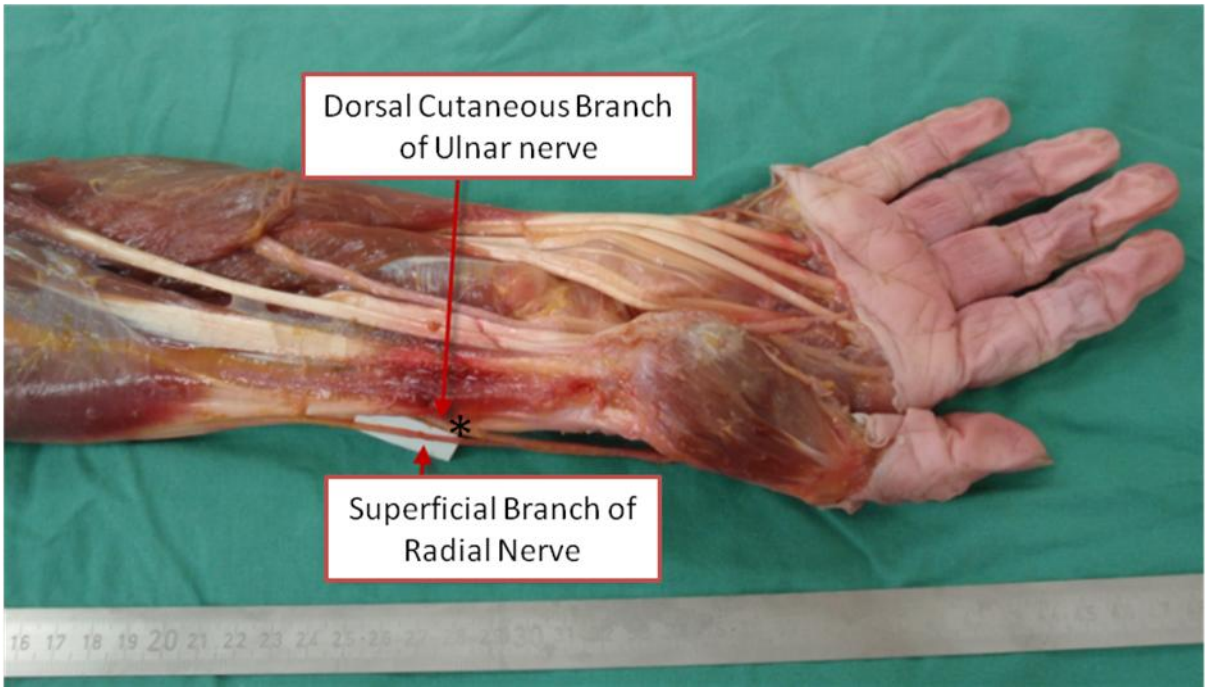


Figure 16 : Transfer of the DCBUN to the SBRN.

The DCBUN was identified and dissected proximally to its first bifurcation at the distal ulnar forearm. The SBRN was dissected proximally to its first bifurcation at the distal radial forearm. The DCBUN and the SBRN was coapted at the distal radial side of the forearm. *Coaptation site. (n = 15)

2.2.2 Histomorphometric Analysis

For histomorphometric evaluation, nerve samples of 2-3 mm length were harvested from the coaptation site where the donor and recipient nerves were sutured together. Followed the same procedure which was described in the 2.1.2 (histomorphometric analysis), samples from the DCBUN, SMN and SBRN were fixed, dehydrated and embedded. A series of semi-sections (1 µm) were cut by using an ultramicrotome (Reichert Jung) and stained for 1 min with 1% toludine blue (Fig. 17). At different magnification, the diameter, cross-sectional area and the myelinated axon numbers were measured. For all samples, axon density was calculated as the ratio of total axon number and total fascicle area. The ratio from donor to recipient of all nerve specimens were recorded for histomorphometric comparison, the results of ratio was compared to the commonly accepted successful threshold of 1:3. A statistical analysis of the difference between the donor and the recipient was performed using a two-tailed t-Test with $p \leq 0.05$ being considered as significant. All data is given as the mean ± Standard Error of the Mean (SEM). (n=13)

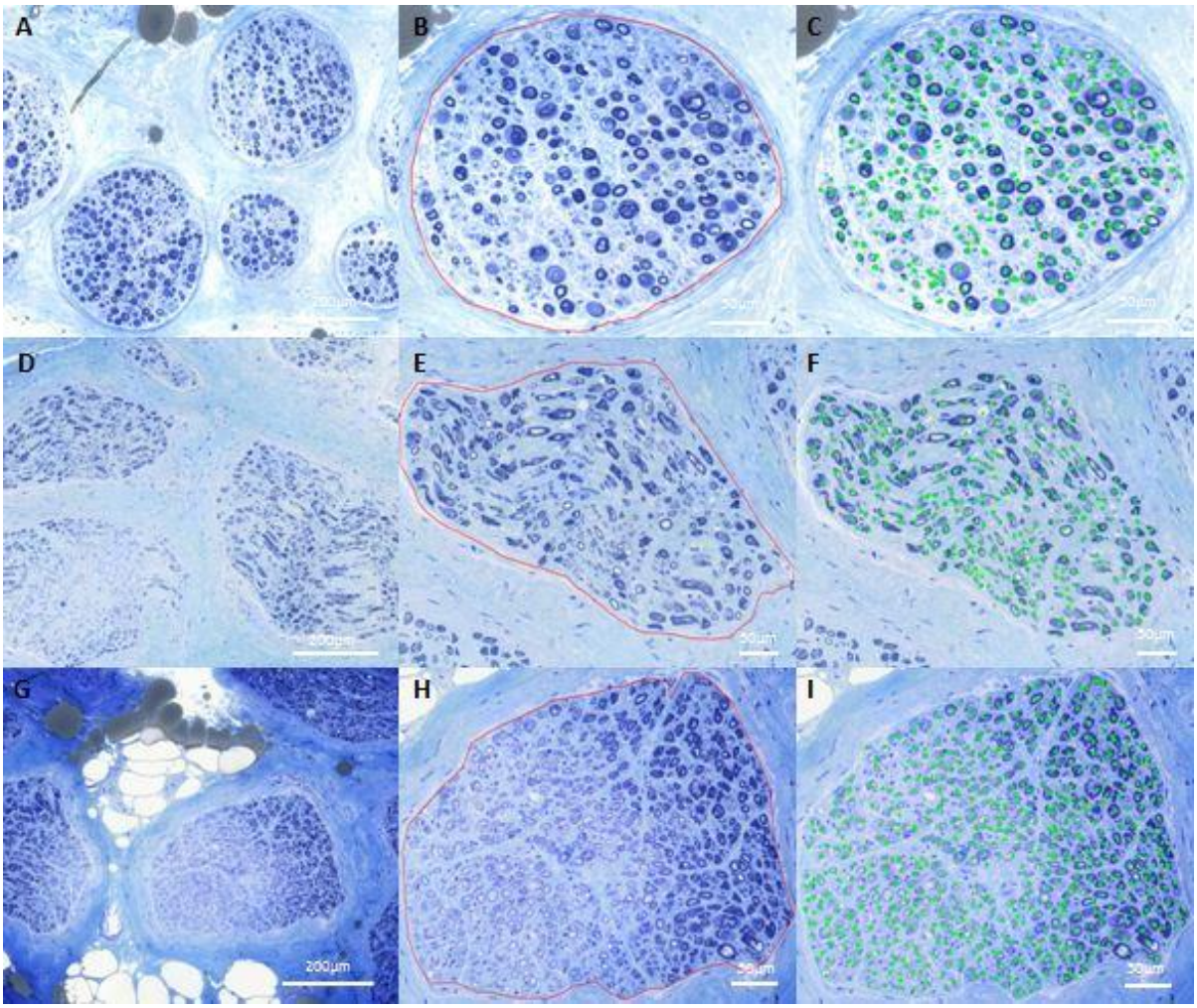


Figure 17: Histologic pictures of stained nerve sections from the DCBUN, the SMN and the SBRN.

A series of semithin sections of the DCBUN (A, B, C), the SMN (D, E, F) and the SBRN (G, H, I) from the coaptation site were collected and stained with toluidine blue. The nerve diameters, cross-sectional nerve areas and fascicle numbers were measured at × 200 magnification (A, D, G). At × 600 magnification, a semiautomatic method was used to aid axon counting and a polygon approach was applied for determination of the cross-sectional areas of individual fascicles (B, C, E, F, H, I) (n=13).

3 Results

3.1 The AIN Transfer to the TBMN

3.1.1 Anatomic Dissection

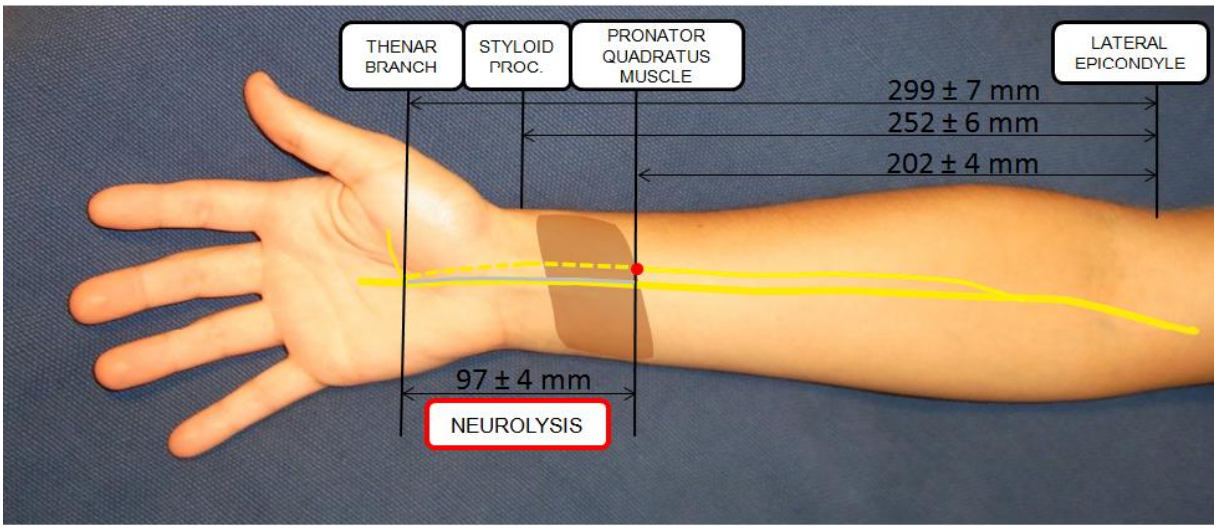


Figure 18: Schematic presentation of the measurements of the transfer from the AIN to the TBMN

The takeoff of the TBMN was found at 299 ± 7 mm distance to the lateral epicondyle of the humerus. From this point, the sensory part of MN and TBMN were severed proximally over a distance 97 ± 4 mm so that the coaptation are tension-free. The AIN and TBMN were transferred to each other at the proximal margin of the PQ which was 202 ± 4 mm distally to the lateral epicondyle of the humerus. The course of the TBMN before the transposition is shown in grey. Its course after the transfer is shown as interrupted lines and the coaptation site is illustrated by a red dot. Pronator quadratus muscle is underlined in brown. (n=15).

In all cadavers the AIN and the TBMN were identified without anatomic variations. The overall length of the forearm was 252 ± 6.0 mm which was measured from the lateral epicondyle of the humerus to the styloid process of the radius (Fig.18). Before tension-free coaptation, the TBMN had to be separated from the median nerve over a length of 97 ± 4.0 mm to reach the coaptation site. The associated landmark for beginning the TBMN dissection is the takeoff of the thenar branch which was located

299 ± 7.0 mm distal from the lateral epicondyle of the humerus. Following transection, it appears that an optimal site for coaptation of the AIN and the TBMN is at the proximal edge of PQ. This point was recorded as 202 ± 4 mm distal from the lateral epicondyle of the humerus. At the level of the coaptation site, the nerve diameters were 0.80 ± 0.10 mm for the AIN and 1.30 ± 0.10 mm for the TBMN (Fig.19). Despite the different size between donor and recipient, it was possible to suture the nerves by microsurgical method.

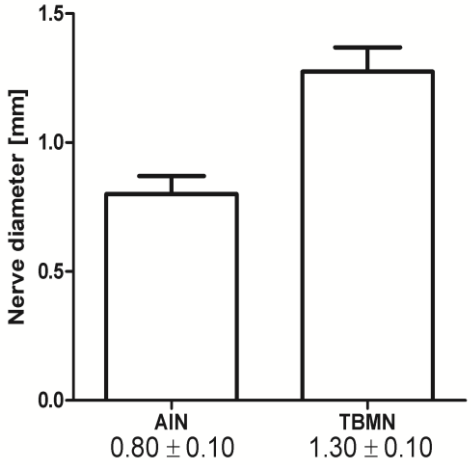


Figure 19: Comparison of AIN and TBMN nerve diameter.

All data presented as Mean ±SEM

3.1.2 Histomorphometric Results

The cross-sectional nerve area was 0.50 ± 0.10 mm^2 for the AIN and 1.30 ± 0.20 mm^2 for the TBMN (Fig.20A). The fascicle numbers was 2.40 ± 0.40 in the AIN and 3.90 ± 0.70 in the TBMN (Fig.20B). The total fascicle area was 0.30 ± 0.10 mm^2 in the AIN and 0.70 ± 0.10 mm^2 in the TBMN (Fig.20C). The AIN presented 580 ± 70 myelinated axons and the TBMN presented 2160 ± 370 myelinated axons respectively (Fig.20D). The density of axons was estimated to be 2300 ± 210 fibers/mm^2 for the AIN and 3010 ± 210 fibers/mm^2 for the TBMN (Fig.20E). The nerve diameter, nerve and fascicle cross-sectional area of the AIN was smaller when compared to the TBMN. In addition, the AIN has less axons and density than the TBMN. Differences were significant with respect to $p < 0.05$. Comparison of donor to recipient showed no significant differences ($p < 0.05$) in terms of fascicle

number. In this study, the axon ratio of AIN to TBMN was 1:3.7, which was close to the commonly accepted threshold for the nerve transfers 1:3. The axon count ratio of the individual donor toward recipient showed that almost half of the specimens (6 out of 13) had a good ratio no less than 1:3. Only one specimen had a poor ratio less than 1:9. Other specimens presented a ratio between 1:4 and 1:6 (Fig.21).

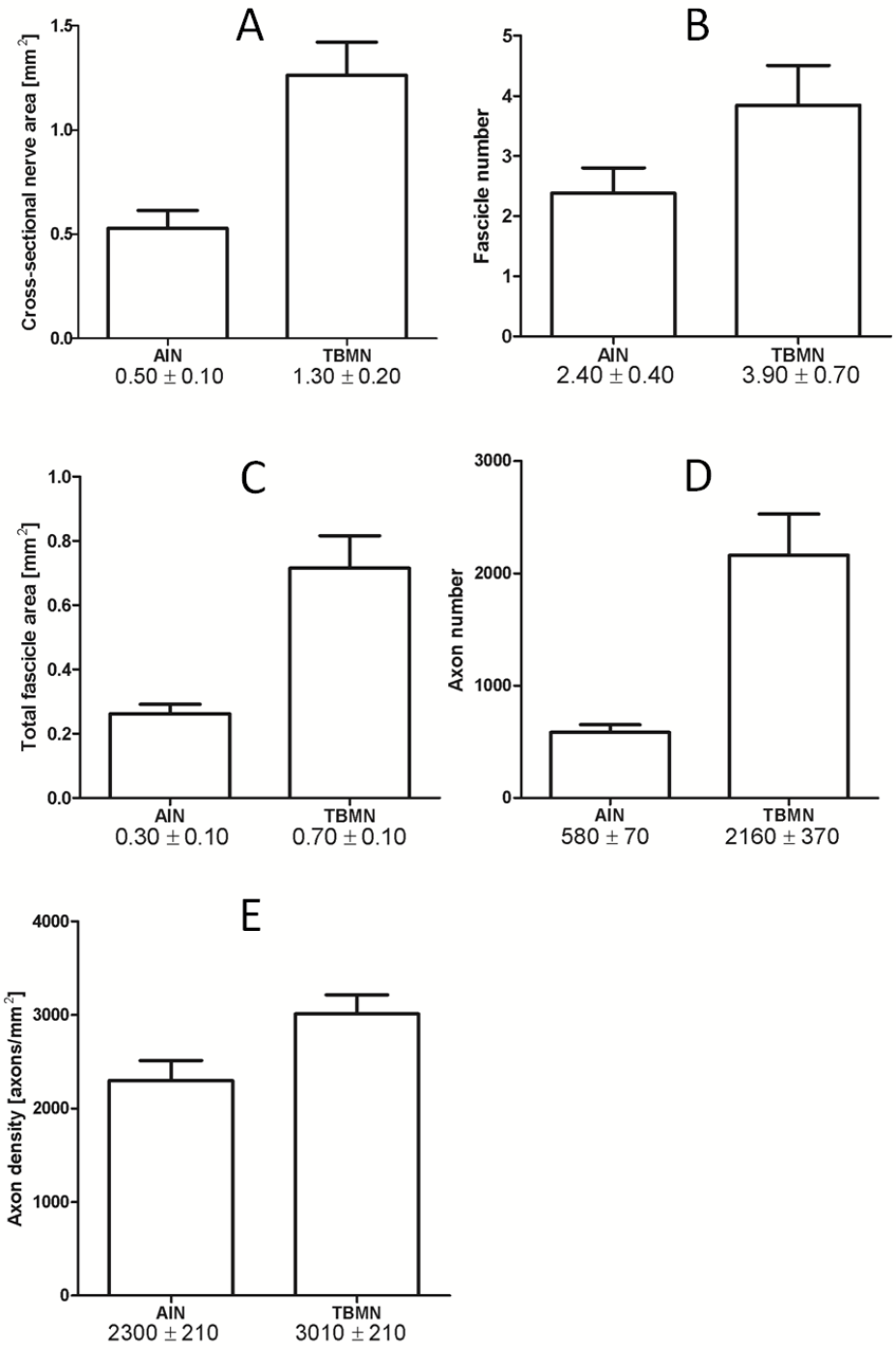


Figure 20 : Comparison of donor (AIN) to recipient (TBMN) - Histomorphometric results

Comparison of donor to recipient nerve in terms of cross-sectional nerve area (A), fascicle number (B), total fascicle area (C), axon number (D), axon density (E). The AIN had significantly lower values in all parameters except of fascicle number. All data presented as Mean ± SEM. $p < 0.05$, (n=13). AIN: anterior interosseous nerve; TBMN: thenar branch of median nerve

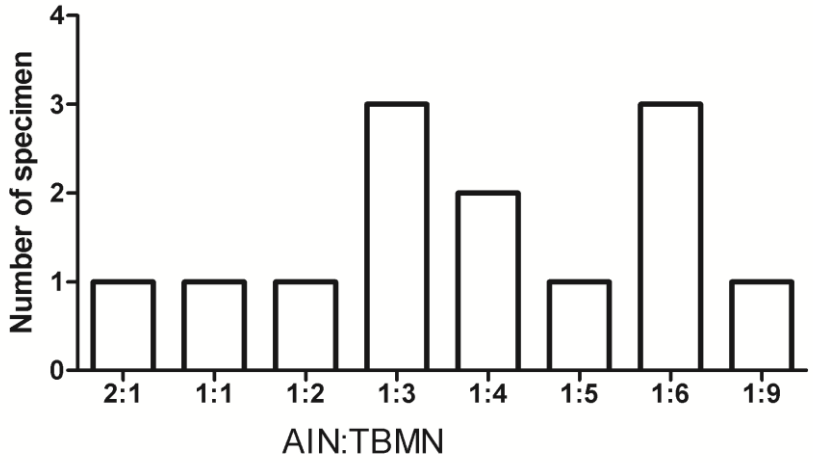


Figure 21: The frequency of the individual axon ratios between AIN and TBMN.

Six specimens had a ratio greater or equal to the threshold of 1:3. Four specimens showed poor ratios of less than 1:6.The remainder had a ratio range from 1:4 to 1:5. (n=13)

	AIN :TBMN
Nerve diameter [mm]	1:1.6
Cross-sectional nerve area [mm^2]	1:2.4
Fascicle number	1:1.6
Fascicle area [mm^2]	1:2.7
Axon number	1:3.7
Axon density [axons/mm^2]	1:1.3

Table 2: Histomorphometric results of comparison between donor and recipient.

The AIN has a comparable fascicle number with the TBMN. But the nerve diameter, the cross-sectional nerve areas, total fascicle areas, axon numbers and axon density of the AIN were inferior to the TBMN (n=14).

3.2 The DCBUN Transfer to the SMN and the SBRN

3.2.1 Anatomic Dissection

In all cadavers the DCBUN, SMN and SBRN were identified without anatomic variations. The overall length of the forearm was 252 ± 6.0 mm which was measured from the medial epicondyle of the humerus to the styloid process of the radius (Fig.18).

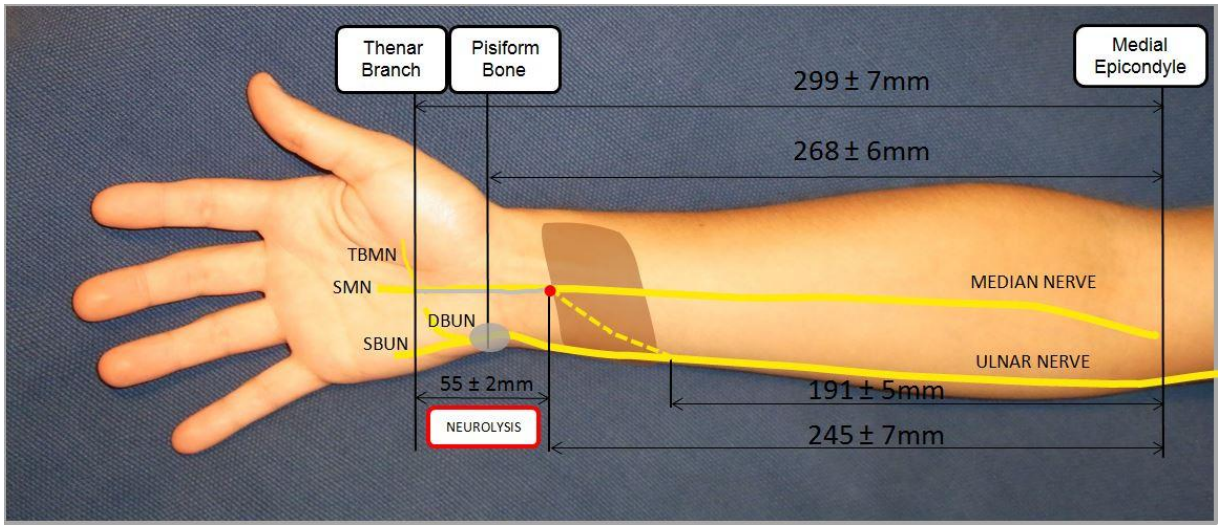


Figure 22: Schematic presentation of the measurements of the transfer from the DCBUN to the SMN.

The takeoff of the TBMN was found at 299 ± 7mm distance to the medial epicondyle of the humerus. From this point, the SMN and TBMN were dissected from each other proximally over a distance 55 ± 2 mm to allow a tension-free coaptation. The course of the SMN before the transposition is shown in grey. Its course after the transfer is shown as interrupted lines and the coaptation site is illustrated by a red dot which was 245 ± 7 mm distal to the medial epicondyle of the humerus. (n=15).

From the medial epicondyle of the humerus to the separation of the ulnar nerve and the DCBUN the mean distance measured was 191 ± 5 mm. The mean distance measured from the medial epicondyle to the point where the DCBUN crosses under the flexor carpi ulnaris muscle was 221 ± 8 mm, and to the division of the dorsal branch into its smaller branches was 245 ± 7 mm.

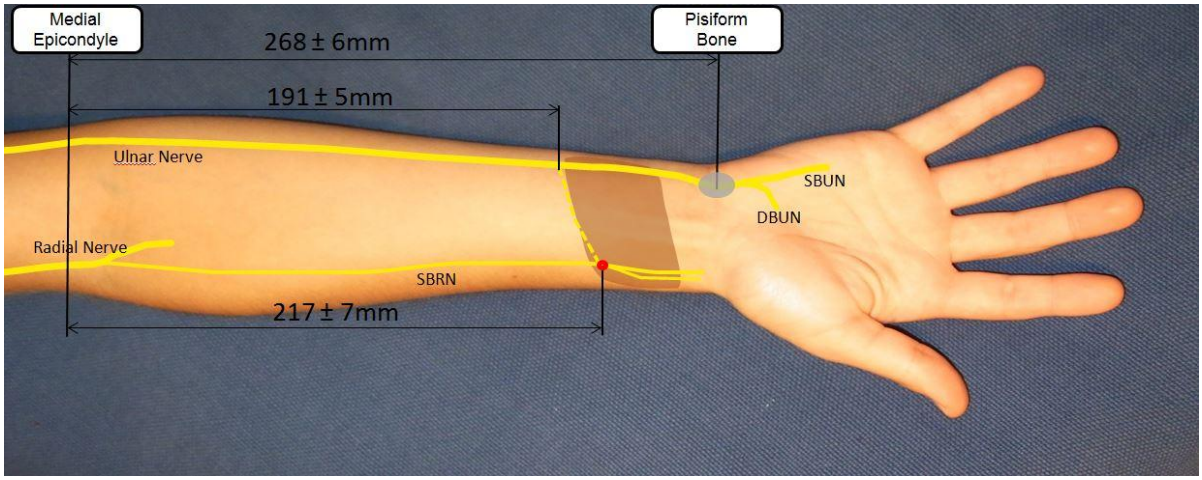
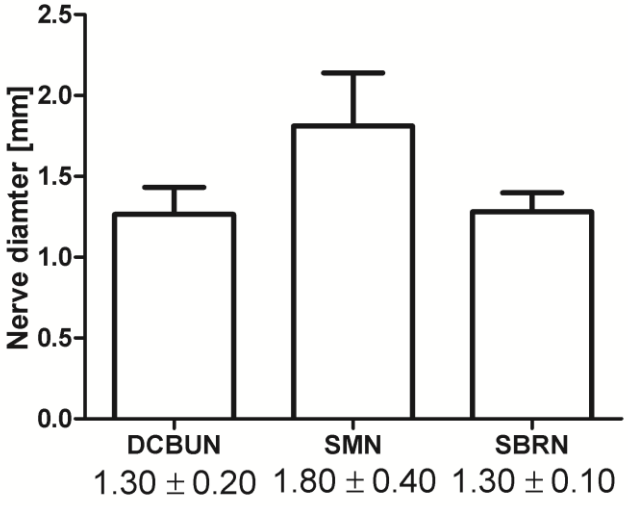


Figure 23: Schematic presentation of the measurements of the transfer from the DCBUN to the SBRN.

The DCBUN was transected before its first bifurcation. Interrupted lines illustrate their positions after the transfer. The coaptation site is illustrated by a red dot which was 217 ± 7 mm distal to the Medial epicondyle of the humerus. (n=15).

The mean distance measured from the lateral epicondyle of the humerus to the crossing (distally) of the SBRN underneath the brachioradialis muscle is 173 ± 5 mm and to the nerve's distal diversion into its smaller branches is 217± 7 mm. The SMN was separated from the main trunk of the median nerve over a distance of 55 ± 2 mm to reach the DCBUN. Following transection, it appears that an optimal site for coaptation of the DCBUN to the SBRN and the SMN is at the radial of the distal forearm. The points were recorded as 217 ± 7 mm and 245 ± 7 mm distal from the medial epicondyle of the humerus respectively (Fig.22, 23). The target nerves weren't mobilized because with the transposition of the DCBUN, the donor and recipient can be coapted with no tension. At the level of the coaptation site, the nerve diameters were 1.30 ± 0.20 mm for the DCBUN, 1.30 ± 0.10 mm for the SBRN, 1.80 ± 0.40 mm for the SMN (Fig.24). Despite the different sizes of donor and recipient, the nerves could be sutured microsurgical.



All data presented as Mean ±SE.

Figure 24: Comparison of donor to recipient nerve diameter.

3.2.2 Histomorphometric Results

The cross-sectional nerve area was 1.20 ± 0.20 mm^2 for the DCBUN, 1.30 ± 0.20 mm^2 for the SBRN, 2.60 ± 0.80 mm^2 for the SMN (Fig.25A). The fascicle numbers were 6.90 ± 1.50 in the DCBUN, 5.50 ± 0.90 in the SBRN, 4.80 ± 1.40 in the SMN (Fig.25B). The total fascicle area was of 0.60 ± 0.10 mm^2 for the DCBUN, 0.50 ± 0.10 mm^2 for the SBRN, 1.30 ± 0.40 mm^2 for the SMN (Fig.25C). The number of axons was 1990 ± 360 for the DCBUN, 1510 ± 230 for the SBRN, 2450 ± 670 for the SMN (Fig.25D).The density of axon was estimated 3290 ± 340 fibers/mm^2 for the DCBUN, 3470 ± 240 fibers/mm^2 for the SBRN, 2160 ± 250 fibers/mm^2 for the SMN (Fig.25E).

The comparison of DCBUN to SBRN and SMN indicated that there were no significant differences ($p < 0.05$) in terms of total fascicle number, fascicle area, nerve diameter, nerve area and axons. The axon density of the DCBUN was more when compared to the SMN, but no significant differences were found ($p < 0.05$) in terms of density between DCBUN and SBRN. In this study, the DCBUN to SBRN axon ratio was 1:0.8, and the DCBUN to SMN axon ratio was 1:1.2 (Table.3). Both

ratios are better than the commonly accepted threshold of 1:3. Differences were significant with respect to $p \leq 0.05$. The axon count ratio of the individual donor toward recipient showed that 82% cases of in the transfer of the DCBUN to the SBRN had a good ratio more than 1:3, in the transfer DCBUN to the SMN presented that 78% cases had a good ratio. (Fig.26)

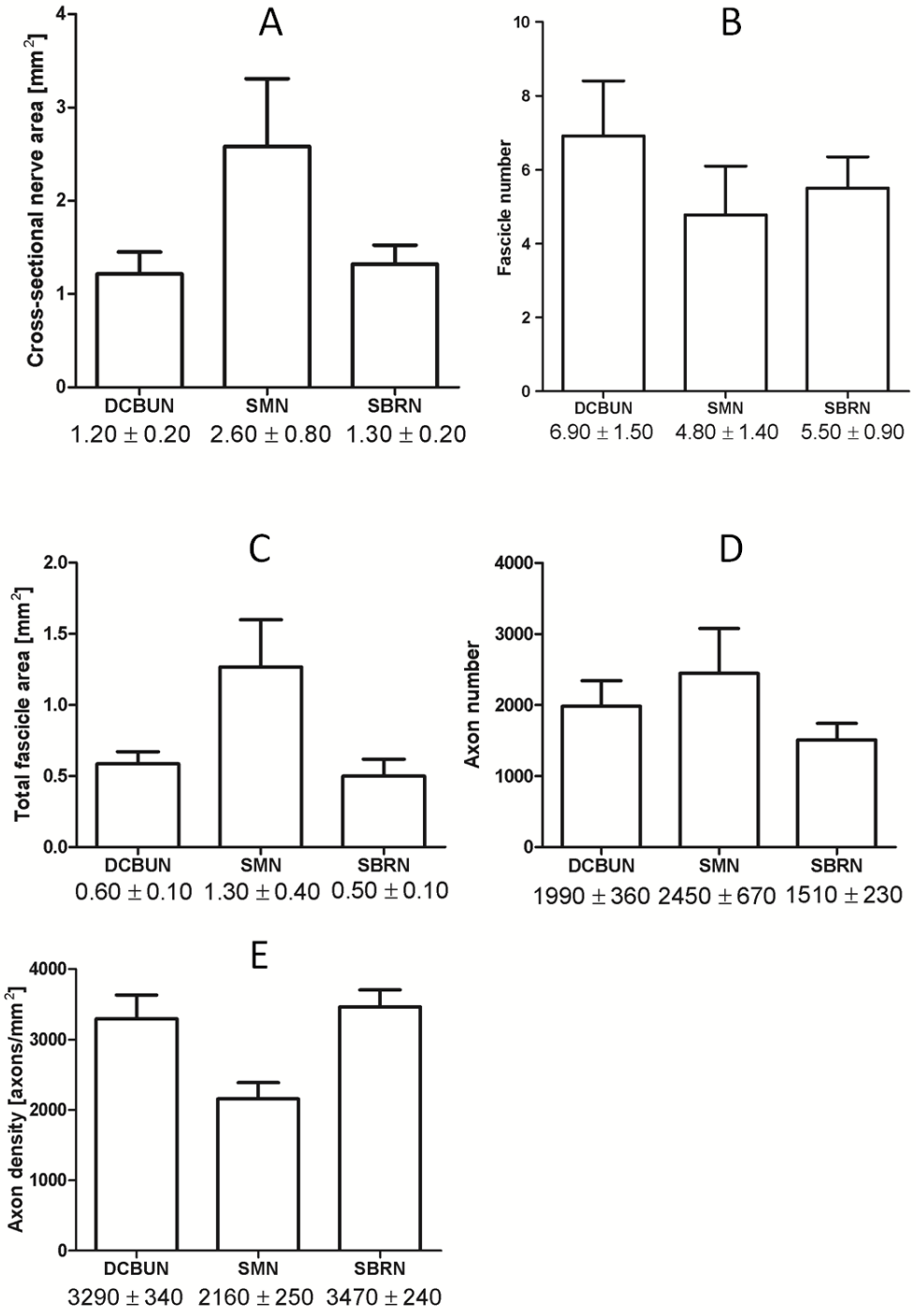


Figure 25: Comparison of donor (DCBUN) to recipient (SMN and SBRN) – Histomorphometric Results.

Comparison of donor to recipient nerve in terms of cross-sectional nerve area (A), fascicle number (B), total fascicle area (C), axon number (D), axon density (E). The DCBUN had no significantly difference with SBRN and SMN, except that the axon density of the DCBUN was less than the SMN. All data presented as Mean ± SEM. $p < 0.05$, (n=12). DCBUN= dorsal cutaneous branch of ulnar nerve; SBRN= superficial branch of radial nerve; SMN= sensory part of median nerve.

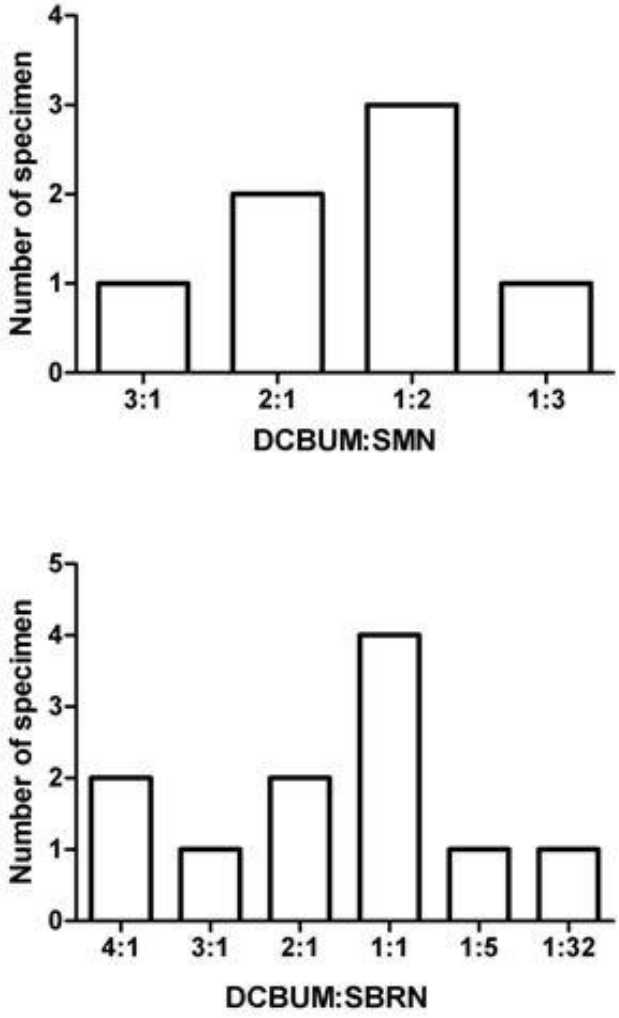


Figure 26: Frequency of the individual axon ratios between the DCBUN and the SMN, the DCBUN and the SBRN.

In the transfer of the DCBUN to the SMN, seven specimens had a ratio greater than or equal to the threshold of 1:3. In the transfer of the DCBUN to the SBRN, nine specimens had a ratio greater than the threshold of 1:3. (n=12)

	DCBUN:SMN	DCBUN:SBRN
Nerve diameter［mm］	1:1.4	1:1.0
Cross-sectional area［mm^2］	1:2.1	1:1.1
Fascicle number	1:0.7	1:0.8
Fascicle area［mm^2］	1:2.2	1:0.9
Axon number	1:1.2	1:0.8
Axon density［axons/mm^2］	1:0.7	1:1.1

Table 3: Donor-to-target (DCBUN : SMN and DCBUN : SBRN) ratios of histomorphometric nerve characteristics.

Comparison of the DCBUN to the SBRN and the SMN, no significant differences in the terms of nerve diameter, cross-sectional nerve areas, fascicle number, fascicle area and axon numbers was found. The axon density of the DCBUN was higher than the SMN and slightly inferior to the SBRN (n=13).

4 Discussion

Nerve transfers are widely accepted for reconstruction of upper extremity function in brachial plexus injuries.[8,14] Proximal level nerve lesions reconstructed with direct anatomic repair or nerve grafting often result in poor prognosis because of the long distance for nerve regeneration.[12] Nerve transfers convert a high level nerve injury into a low level injury by dissecting a healthy nerve and connecting it to the injured nerve, hence providing a shorter distance for the regenerating axons to reach the motor endplates and reduce the reinnervation time.[13] R.I. Harris was the forerunner who advocated transferring normal functional nerves to the adjacent injured nerves to reconstruct the arm function.[16] Oberlin described the partial transfer of the ulnar nerve to the motor branch of biceps brachii to restore the elbow flexion in brachial plexus injury, without ulnar nerve deficiency.[17] In addition, various other nerve transfers were introduced by other experts to treat brachial plexus palsy which intensively improve the development of nerve transfer in the clinic.[18,19]

4.1 The AIN Transfer to the TBMN

Satisfactory results from other transfers stimulated the inventiveness for distal nerve transfers for restoration of hand intrinsic muscles. In 1972, Schultz first reported a patient got successful results of thenar function by transferring of the third lumbrical motor branch to the TBMN.[28] Huang was the first to investigated the transfer of the distal AIN to the TBMN in the rhesus monkey model in 1992.[30] In 1997, Wang and Zhu performed this transfer in a patient to restore the thenar muscle function for patient on clinical application.[23] Üstün in 2001 and Wood in 2004 used cadaveric research to prove the possibility of this procedure.[22,32] Vernadakis described reconstruction of a median nerve neuroma-in-continuity by transferring the AIN to the TBMN with a nerve graft in 2004. However, when the motor fascicles of the median nerve have been disrupted, the defect repaired with ‘blind’ graft has been proved leading to axon misdirection with limited function.[29] In order to increase the

success rate of reinnervation of the thenar muscles, one should put a lot of effort to avoid the mismatching of sensory and motor fibers during the nerve suture.[24,25,114] Moreover, a new nerve transfer technique of supercharged end-to-side (SETS) that have been utilized for DBUN restoration may also work for the TBMN in less severe.

4.1.1 Anatomic Dissection

The AIN passes along the volar surface of the anterior interrouseus membrane between the ulna and radius. This anatomic location makes the AIN not easily injured by trauma.[30] We harvest the AIN at the proximal border of the PQ in order to maximize the axon numbers (Fig 13), while some authors harvest the AIN within the PQ [20,32] which we think is only suitable for individual cases.[115] This technique will result in loss of partial pronation force, but it can be compensated by the pronator muscle.[32] In all specimens, the branches of the AIN to the long flexors were not affected when the AIN was transferred to the radial-proximal border of the PQ; tension-free copatation between AIN and TBMN were obtained without loss of relevant length in both ETE and SETS nerve transfers.

From the wrist to the distal forearm, the TBMN is in the volar-radial position accompanied with the sensory nerve to the index finger and the thumb. The ratio of the pure sensory and the pure motor parts of the median nerve decrease due to the interconnection between different fascicles.[26,114] Therefore, the motor fascicles at this level often can't be identified reliably by electrical stimulation.[116] In order to obtain purely motor fascicle, the TBMN and the sensory part were divided retrogradely over a length of 97 ± 4.0 mm (Fig.18). This intraneural fascicular dissection allows clear motor fibres identification at the stated length and a tension free coaptation between the TBMN and the AIN at the proximal border of the PQ without need for an interposition graft as reported by others.[23,32,114] During the intraneural dissection, minor plexuses were found between sensory and motor fascicles of the median nerve, these are considered as expendable, but care should

be taken not to injure the sensory part of the median nerve.[117] As surgeons, we have to keep in mind that mismatching of mixed fascicles or a nerve graft may substantially downgrade the outcome of a nerve transfer.[40,118]

One of the basic principles for motor nerve transfers is that the donor nerve should be in close proximity to the denervated end-plate.[6] By performing the presented procedure, we greatly shorten the distance required for axonal regeneration to the thenar muscles, thereby it may minimize the regeneration time and provide faster reinnervation. In the rhesus monkey model, in comparison to the direct anatomic coaptation, transferring the AIN to the TBMN resulted in lower incidence of ulceration and better and earlier recovery of intrinsic muscle function.[30] Our measurements indicate that a suitable coaptation site of the AIN and the TBMN is located 202 ± 4 mm distal from the lateral epicondyle of the humerus (Fig.18). This will permit estimation of the reinnervation distance and time according to the rate of nerve regeneration.[56] We can hereby calculate the time span until regain of hand function after performing the nerve transfers in the forearm. We speculate, with this strategy, the thenar muscle will be reinnervated 100 days postoperatively.[12] More importantly, based on these anatomic data, surgeon and patient can tailor a treatment plan with the information of when the endpoint of recovery can be expected.[119] An attractive feature of choosing the AIN as a donor is that it has a function synergistic to the motor function of the thenar muscles which will facilitate the postoperative re-education.[120] Moreover, this technique has an additional advantage that the coaptation site is away from the injury site which reduces scar formation and have a well vascularized environment for nerve regeneration.[23] The drawback of nerve transfers is the creation of a secondary defect when harvesting the donor nerve. It has to be carefully reflected if the possible gain of function outweighs the created defect.

4.1.2 Histomorphometric Analysis

Histomorphometric analysis is the far most common method for nerve regeneration research.[121] Axon number and density are particularly important since they relate to the functional outcome of nerve recovery.[122] Clinical experience of an optimal axon ratio of donor to recipient is generally expected at ratio higher than 1:3. The favorable diameter of the donor should be close to diameter of the recipient. We attempted to assess the donor-to-recipient ratio after transferring the AIN to the TBMN. Similar nerve transfers were reported in the previous literature, which demonstrated that the axon number was 866 ± 144 in the AIN whereas 1120 ± 97 in the TBMN.[23] Our study indicated that axon numbers are 580 ± 70 in the AIN and 2160 ± 370 in the TBMN. The quantitative assessment of nerve axons were may be different between studies due to different inclusion-exclusion rules and the influence of embedding procedures.[123] We calculated axon ratios of this nerve transfer from data of previous studies[22,106] (Table 4). Interestingly, in previous studies the TBMN was transected at different levels, but the AIN was cut always proximal to PQ at the coaptation site. In this study the nerve samples were taken directly from the coaptation site. Comparing the AIN to the TBMN, the AIN has significantly less axon density, smaller diameter, fascicle and nerve cross-sectional area, but comparable fascicle number. The axon ratio of the AIN to the TBMN is 1:3.7 (Table.2).

	n	**AIN : TBMN**	**Location of sample collection**	
			AIN	**TBMN**
Our data	n=13	1:3.7	Proximal to PQ at the coaptation	Proximal to PQ at the coaptation
Üstün et al[22]	n=10	1:1.1	Proximal to PQ at the coaptation	Proximal to PQ at the coaptation
Wang et al[106]	n=8	1:1.3	Proximal to PQ	Takeoff of the thenar branch

Table 4: Histomorphometric results of comparison between donor and recipient.

In this table, the axon ratios of the AIN to the TBMN were calculated from the data of previous reports, which were compared with the data from our study. In addition, the location of sample collection in different studies presented that all studies took samples from AIN at the proximal board of the PQ, but the samples from the TBMN were taken from different levels.

The question is, is this axon ratio for a nerve transfer too low? Previous studies of different authors aimed at the question of what a sufficient donor to recipient axon ratios is. Lutz tested the axon ratio relationship between donor and recipient in an animal model and showed that the threshold for relevant motor recovery begins at 1:3.[124] Jiang and colleagues reported that up to 3 - 4 collaterals can be developed by one axon.[125] Fu and Gordon also indicated that few motor-neurons enlarge the reinnervated motor units 3-5 times to compensate for the reduced motor neurons and axons.[126] These reports are based on the fact that axons send off more than one collateral axon that grow into the motor end-plate.[125] Based on these reports, one could conclude that nerve transfers with a ratio between 1:3 and 1:5 may be regarded as having a chance for successful reinnervation.[127] In consequence, we assumed that 9 out of 13 of the specimens in our study would quality for transferring the AIN to the TBMN to reconstruct the thenar muscles.

Of interest, the discrepancy of individual donor-to-recipient axon ratio in our study was apparent (Fig.21), which may explain why the same nerve transfer resulted in varied outcomes in different patients. 17 cases of transferring the AIN to the recurrent branch of the median nerve (RBMN) and DBUN were followed up over 2 to 7 years by Wang and Zhu. 10 out of 17 cases had received normal electromyogram results, 7 out of 17 cases had poor myodynamic performance results.[31] Other researchers used only a part of the AIN as a donor to reinnervate the TBMN without noticeable PQ deficit. Huang transferred half branches of the AIN to the TBMN in two rhesus monkey models, the function outcomes of the thenar muscles are similar between the half branch transfer and the whole branch transfer.[30] It may provide a new choice, but the axon number of the branches and more cases should be included into further investigation. Recently, the SETS AIN-to-DBUN transfer has been performed in an incomplete injury of the ulnar nerve.

Reports of excellent results of this clinical scenario give hope for a new treatment option of intrinsic hand atrophy.[33] A similar approach can be taken in less severe or incomplete median nerve injuries. The SETS AIN-to-TBMN transfer may help to preserve the motor units by axonal sprouting until the native axons reach the motor end plates.

4.1.3 Conclusion

Our anatomic data demonstrate that the AIN is a suitable donor for the TBMN. Histomorphometric results show that donor-to-recipient axon ratio were slightly below the commonly accepted threshold of 1:3 in most specimens. But some studies have reported that one axon can develop 3 - 4 collaterals and grow into target end-plates which might further strengthen the feasibility of transferring the AIN to the TBMN to restore the thenar muscle function.[125] The satisfying outcomes, which were reported in the clinic and in animal models, also indicate that this particular nerve transfer is possible even with a slightly lower axon ratio.[23,32,40,128] Based on these results, the anterior interosseous nerve may be a valuable donor nerve for nerve transfer to the thenar branch of the median nerve. The method of intraneural fascicular dissection decreases the misdirection between motor and sensory axons which improve the functional outcomes. Surgeons who will perform this nerve transfer need to keep in mind that this operation should be used only when the injuries distal to the site of origin of the anterior interosseous nerve. Certainly, further clinical studies are necessary to prove the superiority to tendon transfers. Taken together, nerve transfers from the AIN to the TBMN are expected to be a simple solution for low median nerve injuries and helpful for the individual patient’s hand function.

4.2 The DCBUN Transfer to the SMN and the SBRN

Loss of sensation in the hand is a major limitation to the function of the hand and the patients' quality of life. Especially the sensation deficit of thumb leads to 20% reduction of hand function.[35] For nerve injuries located proximally on the upper limb and for large nerve defects, extra-anatomic nerve transfers were introduced at the beginning of the twentieth century.[15]

But nerve transfer procedures for sensory restoration are less widely applied than motor nerve transfers.[129] Among the previously described sensory nerve transfers are variations of the ulnar to radial digital nerve transfer, dorsal to the palmar transfers, and palmar cutaneous branch of the median nerve to the ulnar-palmar aspect of the ulnar nerve.[38,39,129-131]

For sensation of the hand, the median nerve has the highest importance, followed by the ulnar nerve. Consequently, nerve transfers have been described which redirect branches from the dorsum to the palm of the hand.[16] While being most frequently indicated in open injuries, sensory nerve transfers have also been applied in patients suffering from burns or leprosy.[38,39,130]

The results of the sensation reconstruction by nerve transfer were different. Wood reported that sensory transfers rarely bring sensibility that topographically matches to the recipient nerve area. The mismatch confusing between donor and recipient will lead to reduction of functional usefulness of the nerve transfers.[130] But Brunelli indicated that sensory nerve transfers are quick operations that can restore sensation in more than 80% of the cases in hand injuries.[98] During the years 1980-1985, R.Matloubi performed sensory nerve transfers of SRBN to median nerve and ulnar nerve in 37 patients. 25 of 37 patients were re-examined postoperatively including eighteen with median nerve injuries and seven with ulnar nerve injuries. 10 cases were judged as the satisfactory, 5 cased were considered

as good, 7 cases were considered as excellent. The recovery of sensitivity which supports the nerve transfer even though a long time between injury and operation. 3 cases were observed with poor results while the multiple injuries and bad environment for transfer.[132] In 2004, Brunelli reported that he operated 21 cases of patients with sensory nerve transfer after brachial plexus injury and tested the outcome with Gnostic rings, he indicated that the transfers from radial nerve to the median nerve and ulnar nerve to the median nerve resulted in better recovery than the transfer from DCBUN to the median nerve.[98]

Based on these clinical cases, we find that partial hand sensation to critical area can be restored by sensory nerve transfers after severe partial brachial plexus injuries. Comparison with island and pedicle flaps, which are best used for the anaesthetic area that is nearby, the advantage of sensory nerve transfer lies in the possibility of implement one single coaptation.[98,132]

4.2.1 Anatomic Dissection

The dorsal cutaneous branch of the ulnar nerve (DCBUN) is a terminal branch of the ulnar nerve, which arises from the ulnar side of the ulnar nerve at the distal third of the forearm.[133-135] Previous anatomic studies have indicated that it passes the antebrachial fascia from volar to the ulna and then emerges at the dorsal ulnar sider of the flexor carpi ulnaris, just distal to the wrist, it supplies sensation to the dorso-ulnar aspect of the hand, to the ulnar side of the ring finger and both sides of the little finger.[133,134] Because it composed by pure sensory axons, therefore it can work as an ideal candidate of donor nerve for nerve transfer.

Many researchers have reported different anatomic datas about the origination of the DCBUN, Botte showed that the DCBUN arose at an average distance 8.3 cm from the proximal border of the pisiform,[135] Puna and Corroller indicated that the DCBUN originated on average 5.1 cm and 5.7 cm respectively proximal to the ulnar

styloid process.[133,136] Our study would suggest that the DCBUN arose at an average distance 191.3 mm distal to the medial epicondyle of the humerus, and this originated point was around 72 mm proximal to the midpoint of pisiform bone (Fig.22). We harvested the DCBUN prior to its first bifurcation to maximize axon number and subsequently improve donor to target histomorphometric ratios. The division of the dorsal branch into its first branch was located 245 mm to the medial epicondyle of the humerus, we can calculated that the distance from the transaction point to the origination was 53 mm which DCBUN can be transferred freely for tension free coaptation to the SMN and SBRN.

As investigated and confirmed anatomic results by Chow in 1986, at the level of the wrist and distal forearm median nerve were made up of three fascicular groups and two sensory fascicular groups lied at the ulnar side which send branches to the third and second web spaces, the TBMN was in the volar-radial position accompanying with the sensory nerve to the index finger and the thumb.[114] In order to suture the SMN to DCBUN in a tension-free manner and avoid the motor and sensory axon mismatching, the special attention should be taken to the intraneural topography of the median nerve. SMN is a predominantly sensory nerve with a palmar motor branch which supplies the lateral two lumbricals, but these two small muscles can be also innervated by ulnar nerve.[67] In our study, the SMN was retrogradely separated from the TBMN starting at carpal canal where median nerve separate to motor and sensory branches. Totally a distance of 55 ± 2 mm of the median nerve was interfascicularly separated so that the SMN can be transferred for tension-free coaptation with DCBUN and thus the misdirection of sensory axons to the motor axons can be decreased. (Fig.22). Although the risk of damaging both the sensory and motor fascicles, the function of the TBMN was conserved in which it was not affected by the injury. If the thenar branch was affected, an addition nerve transfer from AIN to TBMN is suggested.

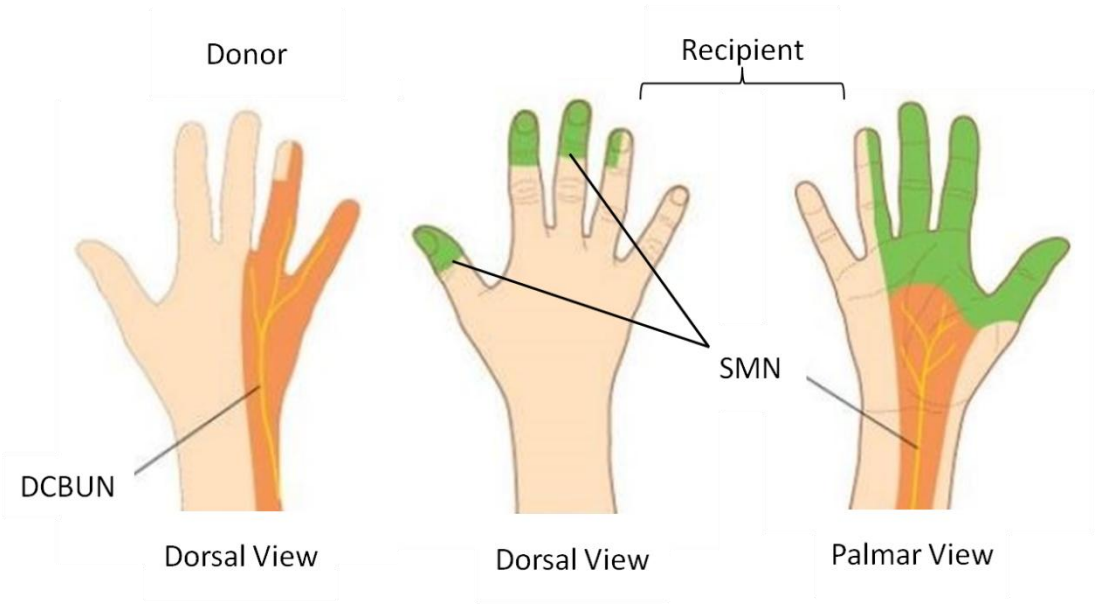


Figure 27: Sensation area of donor nerve and recipient nerve in the nerve transfer of the DCBUN to the SMN.

In the transfer of the DCBUN to the SBRN, the sensation of the poster medial side of the hand (donor area) was sacrificed to reconstruct the sensory function of the SMN. The palmar aspects lateral three and a half digits (recipient area) will regain the sensation if the daughter axons from the DCBUN grow in to the SMN successfully.

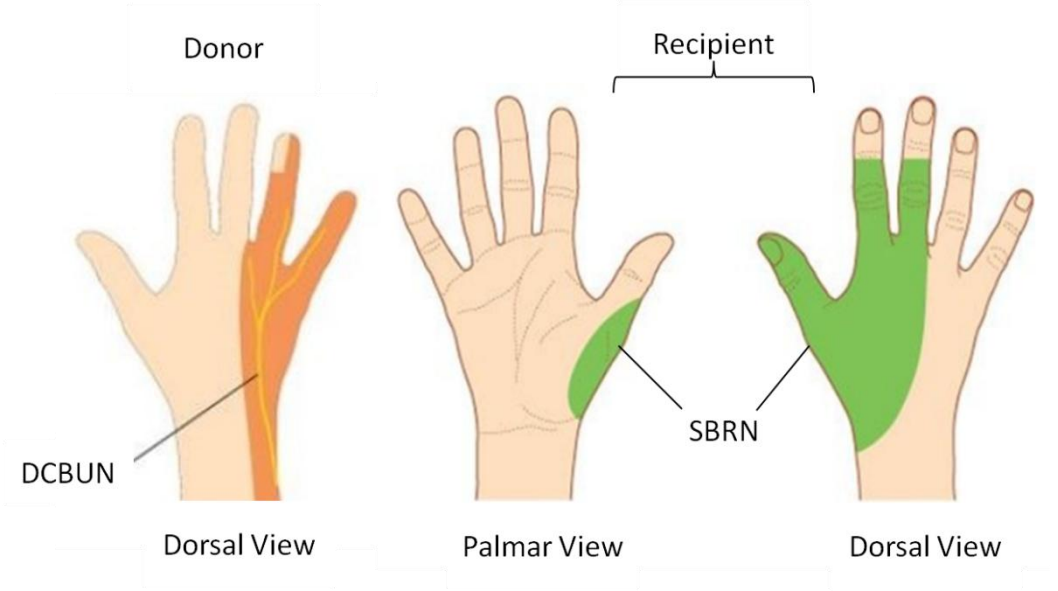


Figure 28: Sensation area of donor nerve and recipient nerve in the nerve transfer of the DCBUN to the SBRN.

In the transfer of the DCBUN to the SBRN, the sensation of the poster medial side of the hand (donor area) was sacrificed to reconstruct the sensory function of the SBRN. After reinnervation of sensory axons from the DCBUN, the sensation over the poster lateral side of the hand (recipient area) will be regained.

The SBRN separates from the deep motor branch of radial nerve at distal part of the humerus, passes underneath the brachioradialis muscle to become a subcutaneuous nerve which send two main branches to extend over the dorsal side of the index finger and the thumb as well as the dorsoradial part of the hand.[74,81] Because of anatomic mechanism that the SBRN superficially lies on the lateral side of the distal forearm, which results in the SBRN a frequently injured nerve.[137] In our studies indicated that the SBRN sends its first bifurcation at level of 217.6 mm distal to the the medial epicondyle of the humerus (Fig.23). We transected the SBRN before its first bifurcation when transferred it to the DCBUN so that the donor nerve can reinnervate the whole SBRN.

Previous work reported that the DCBUN was transferred to the first webspace fascicle of the median nerve in a end-to-end manner, while the distal stump of the DCBUN was coapted back to the ulnar nerve in a end-to-side way which can partially preserve the sensation.[138] The approach taken by us was we harvested the DCBUN as far as possible and the recipient nerve (SMN and SBRN) as proximally as possible before the bifurcation in order to not only maximize the length of each nerve for directly end-to-end tension-free coapatation but also maximize the axon number of the donor nerve which will growth into the recipient nerve. The mantra “donor distal, recipient proximal” is important to follow. Based on these theories, we passed the DCBUN under the skin of the distal forearm to reach the SMN and mobilized the DCBUN under the flexor digitorum superficialis to reach the SBRN without loss of length. The coaptation site was located 217 ± 7 mm and 245 ± 7 mm distal to the the medial epicondyle of the humerus for SBRN and SMN respectively (Fig.22, 23). This distance which allows to calculate the reinnervation time and distance for the nerve transfers because of the regeneration speed of the peripheral nerve was approximately 1 mm per day.[56] The mean diameter of the donor nerve and recipient nerve at the coaptation site were closed, thus there was no suture problem by microsurgical technique. (Table.3)

4.2.2 Histomorphometric Analysis

Functional recovery of injured peripheral nerve are often incomplete and unpreidictable, despite the advance in microsurgical techniques.[139] Many factors have an impact on the functional recovery of the injured peripheral nerve, which include the gap of nerve defect, the environment of injured site, the age of the patients and duration of preoperative treatment. Therefore, it is important for surgeons to take anatomic and histomorphometric topography into consideration in order to win a better outcome. As stated above, histomorphometric analysis is the far most common method for nerve regeneration research.[121] For donor nerve and recipient nerve of the nerve transfer, the axon number, the axon density, the cross-sectional area as well as the the distance of the coaptation site to the target organ are all crucial factors which may influence the functional recovery. But most of the cognition of histomorphometric results were obtained by motor nerve transfers, there are rare histomorphometric data of sensory nerve transfers.[140]

Some researchers have investigated the histomorphometric data of the sensory nerve at the distal forearm, because they think that morphometric analysis is necessary for the successful surgical nerve repair as well as for the other diagnostic application of computed tomography (CT) scan, ultrasound and magnetic resonance imaging (MRI).[141-143] In current study, nerve samples were harvested bilaterally from the coaptation site and the transverse semi-thin sections were analyzed for the nerve diameter, cross-sectional nerve area, fascicle number, total fascicle area, axon number and density (Fig.17). Comparing the DCBUN to the SBRN and SMN, our results indicated that the DCBUN has a comparable cross-sectional nerve area, total fascicle area, fascicle number, axon number and revealed that density of the DCBUN was significantly more than the SMN but comparable to the SBRN. (Table.5)

researchers	n	Location of sample colletion	Axon number	fascicular areas［mm^2］
DCBUN				
Current study	n=12	Proximal to the first bifurcation	1990 ± 360	0.60 ± 0.10
Oliveira et al.2011	n=14	1–3 cm distal to the styloid process of the ulna	2104 ± 907	0.44 ± 0.19
SBRN				
Current study	n=12	Proximal to the first bifurcation, 5.1cm above the wrist	1510 ± 230	0.50 ± 0.10
Marx S et al.2010	n=30	5 to 6 cm above the wrist	No data	0.90 ± 0.03
Chentanez et al.2010	n=21	the point emerging from beneath the brachioradialis tendon and the branching point	6495 ± 474.	No data
SMN				
Current study	n=12	Coaptation site	2450 ± 670	1.30 ± 0.40

Table 5: Comparison of donor-to-target axon number and fascicular areas with previous reports.

The axon ratio of the DCBUN to the SBRN and SMN were 1:0.8 and 1:1.2 respectively, which were much better than the commonly accepted threshold for successful nerve transfers-a donor to recipient axon ratio 1:3.[124] In the previous studies, different authors have reported that axons send off more than one collateral axon that reinnervated the target organ which means that successful reinnervation is possible with lower number of axons in the donor than the recipient.[125]

Axon ratio of donor to recipient was not calculated for the transfer of the DCBUN to the SBRN and SMN in other studies, but they have represented data about the axon numbers and fascicular areas. Oliveira discussed the DCBUN with the axon numbers (2104 ± 907), fascicular areas (0.44 ± 0.19) and fascicle number (5 ± 2) which were comparable to our data (Table.5), but the myelinated fiber density of the

DCBUN varied from 5,910 to 10,166 fibers/mm^2 with an average of 8,170 ± 393 fibers/mm^2 which was higher than our data 3290 ± 340 fibers/mm^2.[144] It was notable that in our study, the DCBUN and the SRBN were transected before the first bifurcation; the SMN was transected as proximal as possible in order to reach a tension-free coaptation with the DCBUN. In Oliveira's study, the DCBUN nerve samples were taken at the height of 1 - 3 cm distal to the styloid process of the ulna, which was also the main trunk of the DCBUN.[144]

Chentanez et al in 2010 investigated the SBRN on 21 human bodies and transected the nerve samples at the point emerging from beneath the brachioradialis tendon and the branching point which was the same to our study that we cut the SBRN just before the first bifurcation[145]. In his study, the axon number (6495 ± 74), the fascicle number (rang 2 to16) and the density (8872.9 ± 167.4/mm^2) were great more than our results.[145]

Marx et al presented in 2010 the number of fascicles in SBRN ranged from 6 to 12 by ultrasonography,[146] Folber CR et al. reported that the SBRN has an average of 6.6 at the wrist which was comparable to the current study.[147] While Sunderland and Campero indicated that the SBRN composed of three fascicles at the forearm.[66,148]

Marx et al. reported that the cross-sectional area of the SBRN was investigated at antecubital fossae with 2.63 ± 0.05 mm^2 on the right side and 2.68 ± 0.04 mm^2 on the left side,[141] Visser also discussed the total cross-sectional area of the SBRN in a same way which showed 2 ± 0.5 mm^2 in healthy individuals[149]. These data were bigger than 1.30 ± 0.20 in our histomorphometric results as well as the fascicular areas. The quantitative assessment of nerve fascicular area were different may due to the epineurium and the perineurium of the peripheral nerve may shrink during the embedding procedures, moreover the ultrasonography for the health individuals was more exactly to test the cross-sectional area, another important reason is that Visser and Marx tested the cross-sectional area of SBRN at the antecubital fossae,

but we transected the nerve samples from the coaptation site which more distal in the forearm.

With respect to the individual donor-to-recipient axon count ratios, 7 specimens have the ratio more than 1:3 in transfer of the DCBUN to the SMN, and 9 specimens have the ratio more than 1:3 in transfer of the DCBUN to the SBRN (Fig.26). Based on these data, we can assume that the DCBUN was an optimal donor nerve for nerve transfer to the SMN and the SBRN. Although two specimens presented with an low donor-to-recipient axon ratio in the transfer of the DCBUN to the SBRN, the 1:5 which can be considered to be close to the commonly accepted threshold 1:3, however the specimen with axon ratio 1:32 might explain the poor cases in the clinic. In according with this data, we can indicate that the SMN can be reconstructed by nerve transfer with the DCBUN other than the SBRN,[98,132] more importantly the SBRN also can be reinnervated by the DCBUN when it is injured.

4.2.3 Conclusion

In conclusion, the anatomic and histological results indicate that the DCBUN is a suitable donor for the SMN and the SBRN. Normally, the loss of sensation to the dorsal medial side of the hand is not considered as heavily deficient when compare to the sensation weakness in the palm side of the thumb, especially in the lateral side of the index finger and medial side of the thumb. For this reason, the uncritical sensation area of the DCBUN was sacrificed for the critical sensation area in the thumb and index finger. The anatomic measurements demonstrate the possibility of tension-free coaptation between the DCBUN and the SMN, the SBRN, which avoid a graft for connection. The anatomic landmarks help to plan the nerve transfer and calculate the re-education time after the operation. The intraneural fascicular dissection of SMN prevents the mismatching of sensory axons and motor axons during the regeneration as well as preserves the function of the TBMN which finally will improve the hand function recovery.

The histomorphometric results show that although the slightly inferiority of the cross-sectional area, the DCBUN still can work as a satisfying donor nerve for the SBRN and the SMN, because the size inferiority can surgically overcome by high axon density of the DCBUN. In previous studies, they have discussed the axon number, axon density and fascicle area of the sensory nerve in the distal forearm, but they didn't compare the axon ratio between the different sensory nerves.[142,145,147] In our study we have investigated the histomorphometric data of the donor nerve and recipient nerve which supply a basic theory for this nerve transfer. If we take into consideration that one axon can develop 3 - 4 collaterals into consideration, surgeons could tailor the nerve transfer by just using part of the DCBUN as a donor nerve to reinnervate the SMN and the SBRN, which can not only win the sensation reconstruction in the critical area but also preserve the sensation the donor side.

5 Summary

In the past century, significant understanding in the field of peripheral nerve surgery has been made with the increasing advances of microsurgical techniques and knowledge of topography of peripheral nerves as well as the cellular and molecular events. As our understanding of nerve injury and repair increases, new techniques of nerve repair including nerve autograft, nerve allograft, tendon transfers and nerve transfers have been performed in the clinic. Although autografting is still the gold standard of nerve repair when possible, nerve transfers have gained great popularity among surgeons especially in the distal forearm for wrist and hand functional reconstruction. The most frequently distal nerve transfer is the transfer of the AIN to the DBUN for intrinsic hand reconstruction.[23,40,84,98]

Specific successful nerve transfer of the AIN to the DBUN has stimulated us to transfer the AIN to the TBMN to reconstruct the thenar muscle function and transfer the DBCUN to the SBRN or the SMN for sensory reconstruction. As previously reported, the AIN can be sacrificed because the loss of pronation function in the forearm can be compensated by the pronator teres muscle and the DCBUN can be cut because the medial dorsal side of the hand is a non-critical area[23]. This feature of the AIN and the DCBUN allows us to use them as donor nerves which meet the technical point of nerve transfer in the upper extremity ‘donor distal, recipient proximal’.[150] Therefore we cut the AIN at the proximal border of the pronator quadratus muscle and the DCBUN before the first bifurcation in order to maximize the axon number and decrease the regeneration distance. For the recipient nerve, we transected the SMN and the TBMN proximally enough so that they can be mobilized to allow a tension-free coaptation. Moreover, divided proximally can avoid necessity for nerve grafting as well as axon misdirection, which could substantially downgrade the functional recovery.

There are two sides for everything and that certainly is time for nerve transfers as well. The major drawback of nerve transfers is sacrificing a viable nerve for an injured one, losing or diminishing the function of a muscle for more important functions, or to sacrifice a non-critical area's sensation for critical area's sensation. For surgeons, we need to take a risk-to-benefit ratio into consideration before we perform the operation. Therefore the anatomic and histomorphomoetric data of the nerves are crucial for us when we tailor the plan for the patient individually. In keeping with this, anatomical and histomorphometric data of nerve transfers including the motor nerve transfer from the AIN to the TBMN and sensory transfer from the DCBUN to the SBRN and the SMN were tested and documented in our study, which provided a basis for managing the peripheral nerve lesions in the hand.

The nerve transfers were performed in 15 fresh cadaver specimens.The overall length of the forearm was documented 252 ± 6.0 mm from the lateral epicondyle of the humerus to the styloid process of the radius. Nerve samples were transected from the distal side of the donor nerve and proximal side of the recipient nerve at coaptation site for histomorphometric observation. The tension-free coapation sites were measured with relation to the anatomical landmarks.

In the motor nerve transfer study, our anatomic data indicate that the AIN is a suitable donor nerve for the TBMN. Donor nerve and recipient nerve can be coapated in a tension-free manner after the SMN and the TBMN were proximally divided and mobilized over a length of 97 ± 4.0 mm to reach the coaptation site. It appears that an optimal site for coaptation of the AIN and the TBMN is at the proximal edge of the PQ which was recorded as 202 ± 4 mm distal from the lateral epicondyle of the humerus. Comparison of the AIN to the TBMN, the AIN has significantly less density, smaller diameter, fascicle and nerve cross-sectional area, but a comparable fascicle number. The axon ratio of the AIN to the TBMN is 1:3.7 which was slightly less than the commonly accepted successful threshold 1:3, but multivariate analyses have shown that 3-4 collaterals can be developed by one

axon; hence we think that the AIN is a suitable donor nerve for the TBMN. In addition to the directly end-to-end suture, the SETS AIN-to-DBUN transfer has been described with excellent result in an incomplete injury of the ulnar nerve.[33] This clinical scenario provides us a new choice for the reconstruction of thenar muscle by the SETS AIN-to-TBMN transfer.

In the sensory nerve transfer, our anatomic data show that the DCBUN was a suitable donor nerve for the SMN and the SBRN. In order to maximize the axon number of the donor nerve, the DCBUN was cut prior to its first bifurcation.The SBRN was transected prior to its first bifurcation, which made the donor nerve axons grow into the whole recipient to supply the lateral dorsal hand. The SMN was separated from the TBMN over a distance of 82 ± 6 mm which ensured a tension-free copatation with the DCBUN. Histomorphometric data indicate that there were no significant differences ($p < 0.05$) between donor and recipient in terms of total fascicle number, fascicle area, nerve diameter, nerve area and axons. Based on these results, the DCBUN can be accepted as a suitable donor nerve for sensation restoration in the hand.

In the past decade, accompanying with the development of nerve reconstruction from nerve grafts to nerve transfers, the difficulties and possibilities of motor or sensory nerve transfers were concern by many peripheral nerve surgeons. One of the greatest concerns of surgeons was the nerve reeducation after operation. Clinically, many transfers are performed with little or even with no training.[24] But it is known that rehabilitation is helpful by recruiting the donor muscle groups preoperatively and repeating these activities until reinnervation is recognized. In keeping with this, early rehabilitation of the motor and sensory functions should be encouraged for the patient. With the increasing understanding of the nerve topography and redundancy as well as the advances of the basic science and clinical research, potential nerve reconstructions with end-to-end, end-to-side and reverse end-to-side transfers will continue to be expanded and become available.

Zusammenfassung

Im vergangenen Jahrhundert haben der zunehmende Entwicklungsfortschritt der mikrochirurgischen Technik, zunehmende Kenntnisse der Topographie peripherer Nerven und zellulärer und molekularer Ereignisse zu einem erheblichen Aufschwung des Verständnisses im Bereich der peripheren Nervenchirurgie geführt. Durch unser verbessertes Verständnis von Nervenverletzung und -heilung sind neue Techniken der Nervenreparatur wie Nervenautografts, Nervenallografts, Sehnen- und Nerventransfers in der Klinik möglich geworden. Obwohl die spannungsfreie Primärnaht von Nerven und die ggf. notwendige Autotransplantation immer noch der Goldstandard der Nervenreparatur ist, werden Nerventransfers bei Chirurgen immer beliebter. Dies gilt insbesondere für den distalen Unterarm und das Handgelenk. Der häufigste Nerventransfer ist der Transfer des N. interosseus anterior zum Ramus profundus N. ulnaris zur Wiederherstellung der intrinsischen Handmuskulatur.

Spezifische erfolgreiche Nerventransfers des N. interosseus anterior auf den Ramus profundus N. ulnaris haben uns dazu angeregt, die Möglichkeiten eines Transfers des N. interosseus anterior auf den Ramus thenaris N. medianus zur Wiederherstellung der Oppositionsfunktion des Daumens zu untersuchen. Zudem wurden als Möglichkeiten der sensiblen Rekonstruktion, die Transfers des Ramus dorsalis N. ulnaris auf den Ramus superficialis N. radialis oder den N. medianus nach Abgang des Thenarastes untersucht. Der größte Nachteil von Nerventransfers ist das Opfern eines gesunden Nervens und somit den Verlust oder die Verminderung der Funktion eines Muskels oder Verlust der Sensibilität im entsprechenden Hautareal. Der N. interosseus anterior eignet sich als Spendernerv, da die Pronationsfunktion im Unterarm durch den M. pronator teres kompensiert werden kann. Der Ramus dorsalis N. ulnaris eignet sich als Spendernerv, da die mediale dorsale Seite der Hand einem vergleichsweise unkritischen Areal angehört. Aufgrund dieser Eigenschaften des N. interosseus anterior und des Ramus dorsalis N. ulnaris bieten sie sich als Spendernerven an. Sie beide können auf Grund Ihrer distalen Lokalisation die

wichtige Voraussetzung erfolgreicher Nerventransfers an der oberen Extremität erfüllen, dass Sie im Sinne eines "Spender distal, Empfänger proximal” Prinzips Anwendung finden können. Aus diesem Grund kann der N. interosseus anterior am proximalen Rand des M. pronator quadratus und der Ramus dorsalis N. ulnaris vor seiner ersten Gabelung abgesetzt werden, um die Axon-Anzahl der Spendernerven zu maximieren und die Regenerationsentfernung zu reduzieren. Für die Empfängernerven haben wir den N. medianus nach Abgang des Thenarastes und den Ramus thenaris N. medianus sowie den Ramus superficialis N. radialis ausreichend proximal durchtrennt, so dass sie so weit mobilisiert werden konnten bis eine spannungsfreie Koaptation möglich war.

Die Nerventransfers wurden an 15 frischen Unterarmpräparaten durchgeführt. Nervenproben wurden an den Lokalisationen der Koaptationen vom distalen Ende des Spendernervens und proximalen Ende des Empfängernervens entnommen und histomorphometrisch untersucht. Die Lokalisationen der spannungsfrei durchgeführten Koaptationen wurden vermessen und in Bezug zu anatomischen Landmarken beschrieben. Für den untersuchten motorischen Nerventransfer deuten unsere anatomischen Daten darauf hin, dass der N. interosseus anterior ein passender Spendernerv für den Ramus thenaris N. medianus sein kann. Spender- und Empfängernerv können spannungsfrei am proximalen Rand des M. pronator quadratus, welcher 202 ± 4 mm distal vom lateralen Epicondylus des Humerus liegt, koaptiert werden, wenn Ramus thenaris N. medianus und N. medianus über eine Länge von 97 ± 4 mm von einander interfaszikulär neurolysiert werden.

Im histomorphometrischen Vergleich weist der N. interosseus anterior eine signifikant geringere Dichte, einen kleineren Durchmesser, eine kleinere Faszikel- und Nervenquerschnittsfläche als der Ramus thenaris N. medianus auf. Jedoch hat der N. interosseus anterior eine vergleichbare Faszikelanzahl. Das Axon-Verhältnis des N. interosseus anterior zum N. medianus nach Abgang des Thenarastes beträgt 1:3,7, was etwas kleiner ist als das allgemein akzeptierte Mindestverhältnis von 1:3. Da die Differenz zu diesem Verhältnis nicht sehr hoch ist, folgern wir dass der N. interosseus

anterior als passender Spendernerv für der Ramus thenaris N. medianus fungieren könnte. Neben der direkten End-zu-End-Naht wurde für den Transfer des N. interosseus anterior auf den Ramus profundus N. ulnaris auch eine End-zu-Seit Variante als Behandlungsoption für unvollständige Verletzungen des N. ulnaris beschrieben. Diese Therapieoption eines End-zu-Seit Nerventransfers könnte analog auf den N. interosseus anterior auf Ramus thenaris N. medianus Transfer übertragen werden.

Für die untersuchten sensiblen Nerventransfers zeigen unsere anatomischen Daten, dass der Ramus dorsalis N. ulnaris ein passender Spendernerv für den sensiblen Anteil des N. medianus und für den Ramus superficialis N. radialis sein könnte. Um die Axonzahl des Spendernervens zu maximieren, wurde der Ramus dorsalis N. ulnaris vor seiner ersten Bifurkation abgesetzt. Das Durchtrennen des Ramus superficialis N. radialis vor seiner ersten Bifurkation soll es den Spendernervenaxonen ermöglichen in den gesamten Empfängernerven einzuwachsen, um die dorsale laterale Hand zu reinnervieren. Der N. medianus wurde von unmittelbar nach dem Abgang des Thenarastes von diesem über einen Abstand von 82 ± 6 mm getrennt, um hierdurch eine spannungsfreie Koaptation mit dem Ramus dorsalis N. ulnaris zu ermöglichen. Unsere histomorphometrischen Daten zeigen, dass es keine signifikanten Unterschiede ($p<0,05$) zwischen Spender und Empfänger in Bezug auf die Gesamtzahl der Faszikel, Faszikelfläche, Nervendurchmesser, Nervenfläche und Axonzahl gibt. Basierend auf diesen Ergebnissen kann der Ramus dorsalis N. ulnaris als geeigneter Spendernerv zur Resensibilisierung der Hand beschrieben werden.

Diese anatomischen und histomorphometrischen Daten der beschriebenen Nerventransfers sollen die behandelnden Chirurgen in ihrer individuell auf den Patienten angepassten Therapieplanung unterstützen.

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Appendix

List of all products, devices and drugs:

Epoxy resin	(Merck, Darmstadt, Germany)
Glutaraldehyde	(Science Services, Munich, Germany)
ImageJ version 1.42	(NIH, Bethesda, MD, USA)
Mirax Scannner	(Carl Zeiss, Jena, Germany)
Osmium tetraoxide	(Science Services, Munich, Germany)
Pannoramic Viewer 1.15	(3DHISTECH, Hungary)
Propylene oxide	(Science Services, Munich, Germany)
Sodium cacodylate buffer	(Science Services, Munich, Germany)
Toluidine blue	(Sigma-Aldrich, Taufkirchen, Germany)
Ultramicrotome	(Reichert Technologies, Munich, Germany)

Figures

Tables

List of Abbreviations

AIN	anterior interosseus nerve
BR	brachioradialis
CNS	central nervous system
DBUN	deepmotor branch of the Ulnar nerve
DCBUN	dorsal cuntaneous branch of ulanr nerve
ETE	end-to-end
ETS	end-to-side
ECRB	extensor carpi radialis brevis branches
ECRL	extensor carpiradialis longus
FCR	flexor carpal radialis
FDS	flexor digitorum superficialis
FCU	flecor carpi ulnaris
FDP	flexor digitorum profundus
FPL	flexor pollicis longus
MN	median nerve
MCP	metacarpophalangeal
PIN	posterior interosseous nerve
PQ	pronator quadratus muscle
PNS	peripheral nervous system
PNI	peripheral nerve injuries
RN	radial nerve
SMN	sensory part of Median Nerve
SBRN	superficial branch of radial nerve
SETS	supercharged end-to-side
TBMN	thenar branch of median nerve

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Eidesstattliche Versicherung

Shenyu, Lin

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Anatomical and Histomorphometric observations on

Nerve Transfers in the Distal Forearm for the Reconstruction of

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