AVAILABLE RECONSTRUCTION METHODS OF NERVE INJURIES – A LITERATURE REVIEW

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Abstract

Nerve reconstructive methods include in addition to surgical technique also a close postoperative follow up and a good understanding of nerve regeneration. Direct reconstruction involves the neurorrhaphy of the nerve stumps if they have a proper vascularization and the suture can be done without tension. There are several suturing techniques like end-to-end, end-to-side and side-to-side coaptation. End-to-end neurorrhaphy is the procedure of choice, due to a higher axonal regeneration and better outcomes. When the surgeon faces a major injury with an extensive nerve loss, the reconstruction is made using nerve grafts. The autologous graft has superior results compared to the non-autologous grafts. It has the benefit of being an immunologically inert structure, contains Schwann cells, neurotrophic factors and adhesion molecules that help the nerve to regenerate better. Currently the researchers concentrate on the development of a synthetic material that will successfully replace the autologous graft. The substituents are represented by nerve ducts or conduits and cadaveric allografts, which have the advantage of adequate microarchitecture and neurotrophic factors beneficial to axonal regrowth, but require up to 2 years of immunosuppressive therapy. This branch is in a continuous progress, and maybe in the future the patients will benefit from a close-to-ideal synthetic nerve graft to replace the available grafts. Another technique is the nerve transfer that involves the use of a distal nerve branch anastomosed with the injured nerve near the neuromuscular junction in order to transmit a nerve impulse and thus the muscle to resume its function. The results of nerve transfer are promising, being an adjuvant method for patients with unsatisfactory initial results.

Keywords: neurorrhaphy, nerve reconstruction, nerve graft, autograft, nerve transfer, peripheral nerve injury

Introduction

Nowadays, the prevalence of peripheral nerve injuries is increasing, due to the modern traumatic events escalation. They occur more frequently in males and are found in 2.8% of the total number of trauma patients. The

annual incidence is about 13 to 23 per 100,000 people per year, affecting especially the upper limb [1,2]. The peripheral nerve lesion has serious implications for the paediatric population, mainly because of the more pronounced psychological impact, but also the different perception of the disease.

Nerve reconstructive techniques have been considerably developed since their first introduction in 1870, mainly due to the advancement of microscopic technology and the better understanding of the pathophysiology of the nerve structure and its lesions [3].

The aim of the study is to emphasize the importance of a suitable treatment every time we face an injury of the nerve. Moreover, a deep understanding of the condition is needed in order to offer the patient an ideal treatment with best outcome in the future. We intend to focus on the available surgical approaches on restoring peripheral nerve integrity after traumatic or iatrogenic transection and to highlight the current problems using the information made available by current studies

Surgical approach

When it comes to nerve laceration, the main surgical objective is the nerve reconstruction, keeping in mind that the full recover of its function is an unpredictable process which depends on a lot of external and internal factors. [4] In the situation of a mixed nerve transection, the sensory and motor fibers should be accordingly aligned for a satisfying recovery in the future. The misconnections will lead to poor results, whereas the sensory fibers develop through the former motor fibers and cannot produce the same effect on the motor end plate of the muscle. [5]

Other variables that influence the functionality of the nerve are the age of the patient, the mechanism of the trauma or how the nerve injury occurred, the type of injury or its location, the distance between the distal end and the proximal end of the nerve, when it comes to a loss of substance but also the elapsed time from the traumatic event to the surgical intervention with curative purpose.

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Nerve reconstruction without grafting

End to end neurorrhaphy is the procedure of choice when the stumps of the nerve are vascularized accordingly and can be sutured without tension [2]. Direct repair, ideally in the first 3 days, consists either of epineural micro sutures with thick alignment between the nerve ends or accurate matching of individual fibers of the nerve [4, 6]. The nerve stumps still contain neurotransmitters within the first 72 hours, and their architecture does not deteriorate during this time, so the ends can be better aligned [6]. The tension free suture with individual connection of the fascicles promotes the nerve healing and have a better axon regeneration at the distal part. Thus, it may ameliorate the long-term recovery [7].

However, the theoretical advantages of the fascicular repair are counterbalanced by a high occurrence of nerve branch damage and scars due to the tissue dissection, conditions which could have an impact on the restoration [2]. Many authors share the belief that the epineural suture presents the same functional results as the fascicular one and there are no significant differences between them [2, 6, 7, 8].

For optimal results, the anastomosis principles must be respected. The surgeon must have an adequate workspace so as to differentiate the damaged structures from the healthy ones. A good nerve dissection is necessary as seen in figure 1. The ends of the traumatized nerve must be trimmed to healthy tissue (Fig. 2), which can be attested by the visualization of the nerve fibers and the dotted bleeding from the edges of the nerve. With careful neurolysis the surgeon separates the nerve from the scar tissue. The suture should not deform the nerve and the nerve fibers should not exit from the plane of the nerve. Postoperatively the part of the body that has undergone the intervention must be immobilized for 4 weeks [6].

End to side and side to side neurorrhaphy are also presented in several clinical trials as convenient surgical techniques for the repair of peripheral nerve damage.

End to side suture consists of the coaptation between the distal end of the injured nerve and the trunk of a nerve located in the proximity. It is described as a good alternative when conventional techniques such as autologous nerve graft or terminal to terminal neurorrhaphy, are not feasible due to large laceration or when the proximal stump of the nerve is unavailable. The cited literature recommends the use of this technique only in selected cases, due to the discrepancy between the clinical results and the experimental studies. It is presumed that because of the end to side anastomosis the axonal growth is diminished and the regenerative process is delayed leading to functional disturbances [9, 10].

A further clinical trial (Tateshita T. et al., 2018) compares the results of end-to-side and end-to-end neurorrhaphy between two nerves of different caliber. The results were analyzed at 6 weeks and 12 weeks after the surgical intervention. The end to end anastomosis revealed a higher rate of axonal regeneration at 6 weeks in the

detriment of end-to-side suture. The rate gets even at 12 weeks. This thereby attests the superiority of end-to-end neurorrhaphy due to early axonal regeneration that impedes peripheral muscle atrophy and thus may have a better functional recovery in comparison with the end-to-side neurorrhaphy [11].

Several clinical trials certify the preventive action of side-to-side neurorrhaphy on early muscular atrophy [12, 13]. The anastomosis is performed distally from the initial injury on a nearby nerve trunk that will serve as the donor nerve. A longitudinal incision is made on the epineurium and partially on the adjoining perineurium, and then sutured together side by side. This technique does not damage the donor nerve and facilitate a better motor and sensorial recovery [12, 13].

Rönkkö H. et al. (2016) confirms the superiority of end-to-end anastomosis through an experimental study made on rats. The tibial and peroneal nerve were sectioned and then sutured accordingly. Although the test animals regained their limb functionality, there were notable differences between the side-to-side and end-to-side anastomoses compared to the end-to-end type which had better outcomes in the walking track analysis, superior regeneration of the axons confirmed by histopathological examination and an adequate connection with the muscle fibers [14].

Nerve reconstruction with autologous graft

In case of a major injury with an extensive nerve loss, the use of a nerve graft is needed in order to restore its continuity (Fig. 3). The graft consists either of biosynthetic materials or autologous tissue harvested from the patient. This represents the current standard in peripheral nerve reconstruction, especially when the nerve stumps cannot be approximated to achieve a tension-free suture [15]. The nerve graft meets the standards of an ideal nerve structure because it contains Schwann cells, neurotrophic factors, and adhesion molecules that promote nerve regeneration. Moreover, the autogenous graft is immunologically inert [3]. The graft is selected according to the diameter of the recipient nerve and then interposed between the ends of the injured nerve to restore its continuity. The most commonly used are the sural nerve and the medial cutaneous antebrachial nerve [4].

Autografting has superior results compared to biosynthetic conduits when the nerve gap exceeds 3 centimeters or when the lesion is located proximally on the nerve trunk. After harvesting, the donor graft is reversed and then sutured, which maximizes the regeneration of a larger number of axons through distal canalization (Fig. 4). Graft gathering produces functional disorders at the level of the donor site, therefore a sensitive nerve is usually sacrificed to regain a much more important motor function (Fig. 5). Other complications may be loss of sensitivity in the area served by the donor nerve, scarring and painful neuromas.

Fig. 1. Nerve dissection

Fig. 2. Proximal stump mobilization

Fig. 3. Proximal and distal nerve ends

At the suture site, improper alignment of nerve fibers, manipulation with surgical instruments as well as suture threads can further traumatize the nerve, thus leading to poor regeneration. It is claimed that 50% of the axons are lost with each anastomosis, so that at a nerve graft with two ends just 25% of the bundles will have the regenerative potential. Usually the nerve graft is 20% longer than the nerve gap. It must be harvested with care just before implantation due to the short survival time of the Schwann cells *ex vivo* [2].

Gosk J. et al. (2010) compared direct end-to-end anastomosis and nerve graft reconstruction in children who have suffered perinatal brachial plexus injury. The results

tend to incline towards the superiority of the direct neurorrhaphy, outcomes supported also by other specialized studies [2, 3, 16]. However, according to Grinsell D. et al. (2014) the autograft is the best option in a nerve gap greater than 3 centimeters. The final result depends on the length of the graft thus a shorter graft under 5, 5 centimeters has good result in 75% of the cases. In contrast to this fact, a longer graft (more than 6 centimeters) has favorable outcomes just in 27% of the cases [17]. Lower success rates of 58% were also reported in the case of proximal radial nerve reconstruction [18].

The results presented in the studies are inconsistent and depend on several factors. Simple lesions usually have good results. Age is an important factor proven in several

studies that reported better functional outcomes in children than adults. Poor patient compliance with recovery treatment as well as low social and educational status hang as negative prognostic factors and have modest outcomes [6]. The type of nerve damage also matters, the sensory type nerves recover better than the motor ones. The ulnar nerve has often poor outcomes after standard reconstruction [19] and a regenerative potential of motor function lower than the median nerve. The sensory function recovers equally in all nerves. Better results have the radial nerve [6, 18]. The proximal end of the nerve has a reduced rate of regeneration compared to its distal segment. The time elapsed until the surgical intervention also influences the final result so that an early repair and a graft under 10 centimeters improves the prognosis [6].

Nerve reconstruction with autograft substitutes

Although autologous nerve grafts have many benefits, more and more researchers focus on the development of alternative grafts that behaves as accurately as a native nerve and overcomes the disadvantages of autograft. The ideal replacement graft should have the following attributes: widespread availability, an exact caliber as the recipient nerve, structural and mechanical properties similar to the genuine nerve, should contains fibroblasts and capillaries and a large number of Schwann cells for regeneration [20].

a) Nerve conduits

There are numerous types of nerve conduits like biological autogenous, biological nonautogenous and nonbiological tubes [2]. Modern conduits are made of polyesters or denatured collagen and aim to form a skeleton or a platform that allows the diffusion of oxygen and micronutrients from the outside to the fibrin matrix. Thus, it allows the local accumulation of neurotrophic factors [3, 20]. Various materials have been manufactured so far but their major disadvantage is the absence of laminin scaffold and the Schwann cells [3]. According to the available studies the outcomes are often reasonable.

Woven polyglycolic acid conduit gave superior results of sensory function compared to direct suturing or autograft when the nerve gap was below 4 mm. Another synthetic material made of denatured collagen obtained favorable evaluation in clinical trials when the difference between the nerve stumps was less than 15 mm. However, studies do not show a significant difference between direct suturing and the collagen graft. Moreover, synthetic materials can give severe complications such as nerve scarring and inadequate regeneration.

Polymer-based tubes have the benefit of being transparent and thus allow a more accurate suture. Although this material has the ability to resorb in a period of 3 to 24 months the results are not very satisfactory even when the lack of substance is less than 20 mm. An increased rate of complications has also been reported, including tube fistulisation, which is why some authors do not recommend this type of material [20].

Mokarram N. et al. demonstrates the efficiency of an immunoengineering technique in the nerve regeneration using an anti-inflammatory recruiting factor, fractalkine. This recruits a subtype of monocytes, which increases the permeability of the polysulfone conduit and stimulates axonal growth [21].

In conclusion, although the synthetic conduits are a more convenient alternative because of their biocompatibility and protective environment to the nerve ends, their benefits are not spectacular and occur only when the gap is less than 1 cm [20].

b) Nerve allografts

Allografts are used in case of large nerve gaps and require up to 2 years of immunosuppressive therapy, which is why their utility is limited [3]. The cadaveric harvested grafts have an adequate microarchitecture and adjuvant neurotrophic factors for superior axonal regeneration [20]. Irradiation, cold preservation or lyophilisation are some techniques used to preserve the graft and decrease the antigenicity or the immunogenic response of it. However, these methods decrease the number of Schwann cells and thus reduce the chance of a better regeneration [3]. The benefits of nerve reconstruction using a graft gathered from a donor or corpse is safe and effective on sensory nerves with a gap of up to 70 mm, method proved in several studies made on digital nerves. For peripheral nerves, proper functional benefits were also reported with 54% recovery in mixed nerves and up to 71% in motor nerves. Negative results were also observed, some authors informed about reconstructions that did not lead to a recovery of the initial nerve function. Compared to the conduit repair, the allograft has good statistical results, when the gap length stand between 15 mm and 65 mm. Processed nerve allografts are also convenient in other situations like reconstruction of a donor or biopsied nerve, management of neuromas and as extensive grafts in nerve transfer. We can say that allografts are a good alternative, which have promising results even when the length of the lesion exceeds 70mm, but also in simple and complex lesions of the peripheral nerves [20]. However, some studies do not recommend replacing autografts with decellularised allografts in proximal nerve damage or when it comes to a motor nerve reconstruction with a gap greater than 3 cm [2].

Nerve transfer

Nerve transfer technique involves the use of a healthy distal branch of a nerve that transfers to an injured nerve close to its neuromuscular junction [4]. This method has benefits especially when it comes to distal nerve trunk lesions, since the coaptation is near the targeted muscle and thus its re-innervation occurs faster [19]. In case of nerve transfer the results are not concordant for all type of nerve. They depend on the type of nerve, the intervention difficulty and surgeon's experience and also on the initial injury magnitude [22].

Fig. 4. Autograft harvesting

Fig. 5. Sural nerve graft

Some authors [23] recommend the correction of nerve injuries using both nerve graft and nerve transfer to minimize the post-lesion pain. The nerve transfer can be performed using the end-to-end or the reverse end-to-side procedure. The first one is used in high-grade proximal lesions with no expectation of recovery after primary nerve reconstruction, while the second one is used when the nerve can recover some of the initial function after the direct suture, usually in children [19]. The donor nerve must meet several criteria for good functional results. It must be as close as possible to the neuromuscular junction innervated by the injured branch, each fascicle sutured must have the same function sensory or motor, and the number and diameter of the fibers should be approximately between the recipient and donor nerves [19, 22]. Muscle tissue is capable of generating response to a received nerve stimulus as long as the percentage of connections between nerve fibers and the motor plate remains over 20%. This number can be increased by sewing more fibers from the donor nerve or by a double fascicular transfer. Below this percentage the ability to generate muscle tension drops dramatically [22].

Referring to the peripheral nerve traumas of the upper extremity, we will analyse 3 types of lesions as well as the most relevant techniques of reconstruction using nerve transfer.

Soldado F. et al. (2016) exemplify in his article the functional deficits after a proximal injury of the median nerve. Furthermore he explains the reconstruction methods and shows their results after the surgical intervention. The clinical deficits observed after the lesion are not always in agreement with the theoretical ones. According to the literature, all patients present grip and pinch deficiency and flexion impotence of thumb and forefinger. However, pronation is largely preserved at more than 50 degrees, flexion of the wrist and middle finger is complete, and the opposing function of the thumb is maintained at half of its potential. Sensitive deficits are also arguable, with some authors claiming that the patients present general palmar anesthesia, while others claim in their findings that the anesthesia occurs just at the distal phalanx of the first three digits.

The nerve transfer is preferably done in the first 6 months after the injury. If the maximum limit of 12 months is exceeded, another intervention such as tendon transfer can be used.

The author's preferred techniques [23] are the transfer of the nerve corresponding to the extensor carpi radialis brevis to the anterior interosseous nerve, for improvement of fingers flexion; the nerve of the supinator towards the flexor digitorum superficialis, for grasping reestablishment; and the nerve of the abductor digiti minimi to the thenar muscular branch for pinch and thumb opposition restoration. The sensory function is recovered by transferring the ulnar or radial dorsal digital nerve branch to the adjacent median palmar nerve [23].

Pet M. et al. (2016) makes a brief presentation of the radial nerve injuries and their following consequences. The most frequent lesions appear after humeral fractures in 11.8% of the cases. The clinical manifestations are presented as the inability of wrist and fingers to extend [18].

The surgical treatment consists of transferring the nerve of the flexor digitorum superficialis muscle (FDS) to the extensor carpi radialis brevis (ECRB), a method described in many studies, which improves the hand extension. To aid and relieve the finger extension, a second nerve transfer is needed, which is made from the flexor carpi radialis to the posterior interosseous nerve.[18, 24] Donor muscle deficiency is negligible in both situations, the muscle functions being easily taken over by other muscles. The pronator teres (PT) tendon transfer to the extensor carpi radialis brevis (ECRB) stand as an adjuvant step for a faster extension function recovery and can be added to the nerve transfers (high radial nerve injury - nerve transfers for the restoration of wrist) The three maneuvers are performed in the same operative time and show good results with a proper recovery after the trauma [18].

Other authors support only the transfer of the flexor carpi radialis (FCR) corresponding branch to the posterior interosseous nerve (PIN) along with the end-to-side transfer of the pronator teres (PT) tendon to the extensor carpi radialis longus (ECRL), yet with unsatisfying effect on the extension of the hand [25].

Sensitive branches of the radial nerve are very rarely damaged. When it occurs the sensory deficit is represented by numbness in the distal portion of the dorsal face of the forearm and hand. Surgical treatment is performed by end-to-end anastomosis of the lateral antebrachial cutaneous nerve to the radial sensory nerve or end-to-side anastomosis of the radial sensory nerve to the median nerve [18].

Ulnar nerve injuries are the most common nerve lesions. Unfortunately, these injuries have poor results after conventional surgery, which is why some authors question the usefulness of the intervention [19, 26]. The lesion is clinically noticeable by the occurrence of clawed hand, the patient's inability to flex the metacarpophalangeal joints and to extend the distal interphalangeal joints. This disabilities combined with the 5th finger opposition impotence affects further the grab and pinch function. The sensory deficit appears on the palmar face of the 4th and 5th fingers and may not emerge if the insult only affects the deep ulnar branch [27].

The surgical option for restoring the motor function of the ulnar nerve is represented by the transfer of the anterior interosseous nerve (AIN) to the motor branch of the ulnar nerve, a medial split of the ulnar nerve following the Guyon canal in the proximity of the hamate bone. The anterior interosseous nerve contains approximately 506 nerve fibers at the distal forearm level, while the motor nerve branch of the ulnar nerve contains over 1500, therefore the transfer will lead to weak recovery, but sufficient to prevent the "clawed hand" [26]. The surgical technique consists of a tension free anastomosis using 9-0 suture under the operating microscope. In the case of concomitant lesions of the ulnar and median nerve, the posterior interosseous nerve is mobilized through the interosseous membrane aperture to the motor branch of the ulnar nerve. To regain the ulnar sensory function, the nerve transfer is practiced between the median nerve ramification of the third web space and the sensory branch of the ulnar nerve [19].

The results after nerve transfer are promising, with many authors reporting that the grab and pinch strength of the operated patients increased substantially. It is concluded that nerve transfer is an adjunctive method for peripheral nerve injuries that encounter poor or insufficient results after nerve graft or direct suture [19].

Summary

Nervous injuries are a serious health problem due to their complexity and the effect they have on the individual's life. Both motor and sensory transmission are affected, which have a long-term resonance, their treatment being complex and entail more than one medical branch. Most of the time, in order to see the desired result, the patient has to be compliant to the different medical recovery techniques. Even so, in some cases the long-term sequelae prevent the patient from carrying out his daily activities. The neurosurgical techniques have evolved because of the increasing use of the available technology, operative microscope, and appropriate surgical instruments and suture threads.

In conclusion, we can say that the direct suture of the nerve is ideal as long as it is done in a timely manner. The nerve graft has its role especially when the distance between the nerve stumps is large and classical anastomosis cannot provide a tensionless suture. Thereby, the nerve graft can cover large gaps with satisfactory results. Nerve transfer can be considered as an adjuvant method of direct suture or nerve graft, when there are not adequate outcomes. This method offers the possibility of reconstruction close to the motor plate, which is motivating due to the early recovery and the suitable long-term results.

Nerve repair or neuropathies are complex surgical manoeuvres with variable results that can be pushed to perfection when the principles of the technique are respected.

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