Recent Advances and Developments in Neural Repair and Regeneration for Hand Surgery

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Abstract: End-to-end suture of nerves and autologous nerve grafts are the 'gold standard' for repair and reconstruction of peripheral nerves. However, techniques such as sutureless nerve repair with tissue glues, end-to-side nerve repair and allografts exist as alternatives. Biological and synthetic nerve conduits have had some success in early clinical studies on reconstruction of nerve defects in the hand. The effectiveness of nerve regeneration could potentially be increased by using these nerve conduits as scaffolds for delivery of Schwann cells, stem cells, neurotrophic and neurotropic factors or extracellular matrix proteins. There has been extensive *in vitro* and *in vivo* research conducted on these techniques. The clinical applicability and efficacy of these techniques needs to be investigated fully.

Keywords: Conduits, Grafts, Repair, Neurotrophic factors, Schwann cells.

INTRODUCTION

Peripheral nerve injury affecting the upper limbs is a significant problem requiring efficient management in order to avoid disability. The function of the hand is especially dependent on its sensory and motor nerves [1-2]. Some studies have reported that more than 60% of peripheral nerve injuries occur in the upper limbs [1, 3]. These injuries are more common in the dominant hand and occur most commonly in young men [1, 4]. The commonest aetiological factors reported are motor vehicle accidents and sharp objects. The most commonly affected nerves are the ulna, radial and digital nerves [1, 3, 5]. Several new techniques in the management of peripheral nerve injuries such as the use of fibrin glue or nerve conduits have been developed in recent years [6].

ANATOMY

Peripheral nerves conduct information to and from the environment and the central nervous system. Neurons receive signals *via* dendrites and process them within the cell body. Action potentials are transmitted away from the cell body to targets *via* axons. Schwann cells surround the axons and provide trophic support. Myelinated nerve fibres have a continuous series of Schwann cells that ensheath individual axons and form myelin. Unmyelinated axons have Schwann cells covering many different axons without creating the myelin layers. Myelin enhances the conduction velocity of action potentials. Peripheral nerve fibres are surrounded by three connective tissue coverings - the endoneurium, the perineurium and the epineurium. The endoneurium surrounds each axon and its Schwann cell layer. The perineurium covers each bundle of peripheral nerve fibres

(fascicle). The epineurium is the outermost covering of the nerve and is primarily a protective layer [7, 8].

The hand is supplied by the median, ulnar and radial nerves. The median nerve originates in the brachial plexus and is formed as a branch when the lateral and medial cords join. It enters the hand through the carpal tunnel. Distal to the carpal tunnel the median nerve supplies the first and second lumbricals, opponens pollicis, abductor pollicis brevis and the superficial head of the flexor pollicis brevis. It also provides sensation to the skin of the palmar and distal dorsal aspect of the radial three and a half digits and the adjacent palm. The ulnar nerve arises from the medial cord of the brachial plexus and enters the hand on the volar surface of the flexor retinaculum. The palmar cutaneous branch arises from the ulnar nerve just proximal to the wrist joint and supplies the skin of the medial aspect of the palm. The dorsal cutaneous branch of the ulnar nerve supplies the medial half of the dorsum of the hand, the little finger and the ulnar half of the ring finger. The ulnar nerve divides into superficial and deep branches at the distal border of the flexor retinaculum. The superficial branch supplies the skin on the volar aspect of the little finger and the ulnar half of the ring finger. The deep branch supplies the hypothenar muscles, the third and fourth lumbricals, the adductor pollicis and the dorsal and palmar interossei. The radial nerve arises from the posterior cord of the brachial plexus. The superficial branch of the radial nerve travels deep to the brachioradialis muscle and supplies sensation to the skin of the radial half of the dorsum of the hand and thumb as well as the proximal portions of the dorsal aspects of the radial one and a half digits. Within the hand, the radial nerve does not supply any muscles [8].

CLASSIFICATION OF NERVE INJURIES

Nerve injuries were classified into three types by Seddon in 1943 [9]. The three injury types are neuropraxia, axonotmesis and neurotmesis. Sunderland's classification in 1951 classified nerve injuries into five degrees which

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overlap and provide more detail to Seddon's classification [2, 10].

Neuropraxia (first degree injury) is the mildest form of nerve injury. There is transient conduction block without disruption of the anatomical structure of the nerve. Wallerian degeneration does not occur distal to the injury. Full nerve function is expected without intervention within twelve weeks [2, 9].

Axonotmesis corresponds to second, third and fourth degree injuries. The axons are disrupted and Wallerian degeneration occurs. In second degree injuries, the endoneurim and perineurium are intact and complete regeneration and functional recovery occurs. In third degree injuries, the axon and endoneurium are damaged, but the perineurium and epineurium are intact. This results in disorganized regeneration which can result in obstruction or diversion of axons from their correct paths. Fourth degree injuries involve damage to all structures, however, continuity of the nerve trunk is bridged by a mass of connective tissue, Schwann cells and regenerating axons. Conduction down the nerve is not possible [2, 9, 10].

Neurotmesis (fifth degree injury) is complete division of the nerve. In addition to this, a sixth degree of injury has been described by MacKinnon [11]. This refers to lesions with a mixed pattern of injury where there are varying degrees of injury in different sections of the nerve [12].

PATHOPHYSIOLOGY OF NERVE REGENERATION

Wallerian degeneration is a sequence of cellular events which occurs in the distal segment of a nerve fibre after injury that has resulted in loss of axonal continuity [13]. The axons disintegrate, undergo apoptosis and release vesicles of cytosol and organelles [7]. The debris is cleared by Schwann cells and macrophages that migrate across local vessels and create long, clean endoneurial tubes. The Schwann cells proliferate and grow in ordered columns along the endoneurial tube to form bands of Büngner. This provides a clear pathway for directed axonal regeneration [7, 14].

Within 24 to 48 hours, axonal sprouts form at the proximal stump and grow on the surface of Schwann cells or to the inner surface of the basal lamina of the bands of Büngner. If the proximal and distal segments are apposed, the axonal sprouts may grow until they enter the distal stump. If the axonal sprouts do not elongate through the distal Schwann cell tube, they will grow in a more random manner which may lead to neuroma formation [14]. Additionally, axonal regeneration is regulated by various factors molecules including neurotrophic and neurotropic factors, cell adhesion molecules and extracellular matrix proteins [15, 16].

DIAGNOSIS OF NERVE INJURIES

A thorough knowledge of the anatomy of the nerve as as well as the muscles and zones of sensation supplied by the nerve is essential in making an accurate diagnosis [17]. The first step in diagnosing a nerve injury in the hand is to take an accurate thorough history from the patient. This should include the patient's age, occupation, hand dominance, hobbies, mechanism of injury and past medical history. The physical examination should include a sensory and motor assessment of each nerve comparing the findings with the contralateral side. The sensory evaluation should include two point discrimination [2]. The motor assessment should include power and range of motion. Palpation or inspection of the muscle belly under consideration is useful to avoid inaccuracy of assessment due to substitution or trick movement [17]. The Tinel sign can be used to localise the nerve injury. A positive Tinel sign suggests that regenerating axonal sprouts that have not obtained complete myelinization are progressing along the endoneurial tube. Electrodiagnostic tests may be performed if the clinical findings are unclear and to diagnose the injury and determine the severity [2, 17].

CONVENTIONAL SURGICAL TREATMENT OF NERVE INJURIES

Fourth to sixth degree injuries have a poor prognosis for recovery of function without surgical intervention. Repair of sixth degree injuries is particularly challenging due to the risk of disrupting fibres with first to third degree injuries whilst attempting to correct areas of fourth and fifth degree injury [17].

End-to-End Nerve Suture

Apposition of the nerve ends and repair by suturing should be possible if there has been a sharp clean transection and exploration is undertaken within 72 hours. It is advisable to delay repair by two to three weeks in the case of blunt transection. At this stage it will be possible to determine the amount of stump resection that is required to achieve healthy nerve tissue [18]. Nerve suture should be performed using an atraumatic microsurgical technique using an operating microscope and 10-0 monofilament suture material [2]. The lesion is repaired using epineurial or perineurial sutures. Epineurial repair results in approximation of the nerve ends, however fascicular coaptation is often poor and this may result in a reduced number of axons regenerating across the junction due to problems such as internal gaps, overlapping and buckling of the fascicles [19]. Perineurial suturing allows fascicles/groups of fascicles to be repaired in an attempt to achieve more accurate axonal alignment. However, the increased dissection required for this approach could potentially result in increased scarring and damage to the blood supply [19, 20]. There is little clinical evidence that perineurial repair results in superior clinical outcomes to epineurial repair [20, 22]. Techniques to facilitate fascicular matching include intraoperative nerve stimulation and staining of nerve ends with blue SAb, carbonic anhydrase and cholinesterase for example [12].

Autologous Nerve Grafting

Nerve grafting is indicated if primary end-to-end closure of the two transected nerve ends is not possible without excessive tension. Terzis *et al.,* compared suturing of rat sciatic nerve under varying degrees of tension to nerve grafting and showed that superior conduction velocities and amplitudes of evoked potentials were achieved with nerve grafting than with nerve suturing under excessive tension [23]. A section of nerve can be harvested and placed between the two nerve ends. Autologous nerve grafts are considered the 'gold standard' [18]. Suitable donor sites for autologous nerve grafts include the sural nerve, anterior branch of the

medial antebrachial cutaneous nerve the lateral femoral cutaneous nerve and the superficial radial nerve. The graft should be approximately 10 to 20% longer than the defect to be grafted in order to overcome the effect of connective tissue fibrosis. Several grafts may need to be placed in parallel to reconstruct the nerve if it has a large diameter relative to the graft obtained [20]. A series of interfascicular autologous nerve grafting by Millesi *et al.,* reported useful motor recovery in 82% of 38 patients after median nerve grafting and 37 out of the 38 regained protective sensibility. 100% of 39 patients who underwent ulnar nerve grafting and 77% of 13 patients with radial nerve lesions regained useful motor recovery. The cases with poor results were generally found to be associated with the presence of unfavourable factors such as advanced age, severity of original trauma and a long time interval before repair [24]. Other studies have shown that patient age, width of contusion and length of time before surgery have significant effects on both nerve repair and reconstruction with grafting [25-27].

An appropriate blood supply is required for successful nerve grafting. Revascularization of a nerve graft may occur by vessels from the surrounding tissue bed growing into the nerve graft or by vessels from the end of the graft sprouting into the existing vascular tree [28]. Free nerve grafts may be hindered by delayed establishment of blood supply to the nerve graft leading to fibrosis, development of central necrosis and finally failure of nerve regeneration [23]. Vascularized nerve grafts may be used to avoid this. However, the procedure is time-consuming and it may be difficult to obtain a suitable, well-vascularized expendable donor. Taylor recommended that vascularized nerve grafts are only used when there is a high risk of graft necrosis. It may be considered in situations where the nerve gap is large, the recipient bed is scarred, or the free transfer of a thick nerve is desired [29, 30]. A study of 151 vascularized ulnar nerve grafts performed over a period of 23 years reported better outcomes when compared to conventional nerve grafts. The best outcomes were observed for pedicled ipsilateral nerve grafts for single targets [28].

RECENT ADVANCES IN PERIPHERAL NERVE REPAIR

Sutureless Nerve Repair

Peripheral nerve suture may be complicated by foreign-body inflammatory reaction leading to impaired nerve regeneration [6, 31]. A variety of tissue glues or laser to perform sutureless nerve repair have therefore been investigated as an alternative. The use of cryanoacrylate glue, for example, has been tested, but was unsuccessful as it also caused a foreign-body reaction and fibrosis [32]. Fibrin glue, which is more biocompatible than cryanoacrylate has shown more promising results [6, 31]. Ornelas *et al.,* compared the use of bovine and human fibrin glues to microsutures for repair of rat median nerves. They showed that nerve repairs performed using fibrin glues were quicker and technically easier to perform and were associated with less inflammatory response and fibrosis. Additionally, the fibrin glue repairs resulted in better axonal regeneration and fibre alignment [33]. Laser-activated protein solders containing bovine serum albumin have also been successfully used for sutureless peripheral nerve repair in

rats and have been tested as an alternative to fibrin glue as they result in a greater adhesion strength [31, 34, 35]. A chitosan-based laser-activated adhesive has also been shown to produce successful sutureless anastomosis *in vivo* in rat tibial nerves. The activation temperature range of the the chitosan-based adhesive is around $5^{\circ}C$ lower than for albumin solders and it has been proposed that consequently there may be a reduced risk of tissue thermal damage [31]. Borzorg *et al.,* carried out a clinical study of the use of fibrin glue for facial nerve repair and reported good results after a mean follow-up period of 50 months [36]. However, long-term clinical evidence of sutureless peripheral nerve repair in hand surgery in humans is needed.

End-to-Side Nerve Repair

End-to-side nerve repair is an approach which has been used in cases where the proximal stump is not available (for example in cases where it is very distant from the distal stump). The distal stump is coapted to the side of an intact donor nerve. The donor nerve does not lose any function. The potential advantage of this technique is that donor site morbidity associated with nerve graft harvest is avoided and the distance travelled by regenerating axons is reduced [37]. However, experimental studies have produced mixed results with some studies demonstrating only limited motor or sensory recovery [38-40]. More research is needed before this approach can be considered an established technique of nerve repair [37].

Nerve Allografts and Xenografts

Autologous nerve grafting may be complicated by donor site morbidity such as scarring, neuroma formation and sensory loss in the distribution of the donor nerve [41]. There may also be an insufficient amount of expendable autologous nerve available for large nerve defects [42]. Nerve allografts and xenografts act as a temporary scaffold across which host axons regenerate [6]. Due to the risk of rejection, the use of appropriate immunosupression is essential [43]. The allograft tissue is eventually completely replaced by the host tissue once regeneration has occurred. At this stage, immunosuppression may be discontinued. The immunosuppressant tacrolimus (FK 506) has shown neurore-generative and neuroprotective effects whilst simultaneously acting as an effective immunosuppressant [6, 41]. Clinical evidence on the efficacy of allografts/xenografts is scarce. However, some early clinical studies of nerve allografts have however shown some success in achieving return of motor function or sensation [41- 44].

Nerve Conduits

Nerve conduits provide a channel for direction of axonal sprouts from the proximal stump to the distal nerve stump. In addition to this, they allow diffusion of neurotrophic and neurotropic factors secreted by the Schwann cells of the distal stump and minimize infiltration of fibrous tissue [6]. Animal models in rats as well as cats and primates, have shown successful nerve regeneration with the use of nerve conduits fabricated from a variety of synthetic materials (e.g. polyglycolic acid, silicon, glycolide trimethylene carbonate, polylactide-co-caprolone) and biological materials (e.g. collagen, laminin, silk, autogenous vein/ muscle grafts) [21, 45-50]. The clinical evidence of efficacy of nerve conduits is

more limited. Mackinnon and Dellon conducted an early clinical study of the use of polyglycolic acid conduits for digital nerves with nerve gaps of up to 3cm and reported excellent or good functional sensation in 86% of patients [51]. Lohmeyer *et al.,* reported excellent results with collagen conduits for nerve gaps in the hand of up to 18mm in 4 out of 6 patients [52]. Bushnell *et al.,* reported good or excellent function in 8 out of 9 patients who had undergone digital nerve repair with a collagen nerve tube at one year follow-up [53]. Weber *et al.,* performed a randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction compared to conventional nerve repair or grafting. 98 patients with 136 nerve transections were included in the study. The overall results showed no significant difference in outcome between the two groups in general. However, improved sensation was found with the polyglycolic acid nerve conduits for nerve gaps of 4mm or less compared to conventional repair or grafting of digital nerves [54].

Molecular and Cell Therapy

Experimental studies have shown that the use of conduits seeded with cultured Schwann cells improve nerve regeneration [55-57]. The use of fetal and adult progenitor neuronal cells and bone-marrow stem cells is an alternative to the use of Schwann cells. Cell therapy is limited by the technical and logistical difficulties in culturing and expanding these cells *in vitro* [55]. Another approach that has been studied is the incorporation of neurotrophic and neurotropic factors e.g. nerve growth factor, brain derived neurotrophic factor and ciliary neurotrophic factor *etc* into nerve conduits in order to improve the regeneration process [7, 12]. The effect of extracellular matrix molecules such as fibronectin, laminin and hyaluronic acid on axonal regeneration as well as the effect of incorporating these proteins into nerve conduits has also been investigated [7, 58-61]. The use of these techniques has been largely experimental to date.

CONCLUSION

The current standard treatment for peripheral nerve injuries of the hand is end-to-end repair with epineurial sutures. End-to-side nerve suturing may be considered when the proximal stump is unavailable. However, studies of end-to-side repair have shown mixed results. Studies on sutureless nerve repair using fibrin glues or laser-activated protein or chitosan-based materials have produced some promising results. Nerve grafting is indicated if suture repair is not possible without excessive tension. As autologous nerve grafting may be associated with donor site morbidity, alternatives such as the use of allografts with appropriate immunosuppression has been sought. Research into the use of nerve conduits is in progress and has shown some success. Molecular and cell therapy is another area which has the potential to improve the future of nerve regeneration. More clinical trials are required to assess these techniques.

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CONFLICT OF INTEREST

None declared.

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