Current Concepts in the Management of Peripheral Nerve Injury

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Introduction: Peripheral nerve injuries are challenging problem which often result in a life long disability. In the past, due to poor understanding of pathophysiology of nerve injuries, the results of its repair were unpredictable. Cajal in early 1900s described the axons regenerating from the neurons which were guided by chemotrophic substances(1).Sunderland in 1945 described the microsurgical techniques in nerve repair which improved the results of nerve injuries (2). Our understanding of nerve regeneration, advances in microsurgical techniques of nerve repair along with molecular biology of nerve injury has helped to improve the overall results of peripheral nerve injury.

Pathophysiology: Nerve injuries fall into 3 broad categories, the traction or stretch injuries, injuries due to penetrative trauma and the compressive nerve injuries. When describing the pathophysiology of nerve injuries it is important to understand the severity of nerve injuries. The severity of nerve injuries have been classified initially by Seddon and later by Sunderland (3,4) (Table 1).

Table 1: Classification of nerve injuries

Degree of injury (Sunderland)	Pathology	Seddon type
1st degree	Focal conduction block without axonal disruption	Neuropraxia
2nd degree	Axonal disruption	Axonotmesis
3rd degree	Axonal disruption with endoneural tube	Axonotmesis
4th degree	Disruption of axon, endoneurium and perineurium	Axonotmesis
5th degree	Complete loss of continuity of nerve	Neurotmesis

Pathophysiology of nerve injury is related to these types of injuries and can be divided into degeneration and regeneration. The success of regeneration depends upon the severity of initial injury and resultant degeneration.

Degeneration: In first degree injury there are no histological changes in nerve fibers and no true degeneration or regeneration occurs. In second degree or more severe injuries Wallerian degeneration occurs in the distal segment of axons. This is a Calcium mediated process which occurs within hours of injury and is characterized by physical fragmentation of axons and myelin. By 48- 96 hours axonal continuity lost and conduction of impulse is no longer possible. Schwann cell and the macrophages play a key role in Wallerian degeneration and are responsible for removal of degenerated axons and myelin at the site of injury. Intrafasicular injuries as in 3rd degree or more, axonal regeneration is impaired and endoneural tube undergo progressive fibrosis for the want of regenerating axons. The stack of Schwann cells, called the Bands of Bugner acts as a guide for the sprouting axons during re-innervation. More severe injury results in disorganized degenerative process leading to incomplete regeneration. The proximal segment undergoes degeneration depending on the severity of injury. The proximal degeneration can be minimal (up to node of Ranvier) or can extend to cellular body. In severe injuries cellular body may degenerate and proximal segment may undergo Wallerian degeneration (5).

Regeneration: In first and second degree injuries recovery is complete. In third degree and more severe injuries regeneration is dependent on severity and site of injury. The regeneration in severe injuries occurs only after the Wallerian degeneration is complete. The sequence of regeneration is in orderly fashion beginning from cell body of the proximal segment proceeding to distal segment through the injury site and finally the end organ. The sprouting axon is a growth cone which contains multiple fingers like projection called filopodia which engage the Schwann cell in the distal segment through which the axons are expected to grow towards the target organ. The rate of axonal growth is estimated to be 1mm per day. Therefore any gap between the two segments will not allow the regeneration to occur. Accurate surgical repair is hence important for a successful outcome.

Neurotrophic factor in nerve regeneration: Nerve growth factor (NGF) was the first neurotrophic factor to be identified. Other neurotrophic factor like brain derived neurotrophic factor, ciliary neurotrophic factor and glial derived neurotrophic factor (GDNF) are important factors in nerve repair. They are released from the target organs and Schwann cells which are believed to be transferred to cell body in a retrograde fashion by the axon (6). Any disruption of the transport of NGF is a trigger factor for the repair process. The neurotrophic factors provide continuous stimulus for growth as well guide for advancing axons. Whitworth et al observed that administration of exogenous NGF resulted in sustained axon regeneration which has been related to reduction in the incidence of neuronal cell death (7). Similarly GDNF has a beneficial effect on axonal regeneration and improves the conduction velocity of motor neurons following regeneration and that of small diameter sensory neurons(8,9).

Diagnosis of nerve injury: Nerve injury clinically manifests itself in form of loss of motor, sensory and autonomic functions. These must be evaluated at the time of nerve injury and findings meticulously documented. It is important to distinguish between neuropraxia, axonotmesis and neurotmesis. While complete recovery is expected in neuropraxia and axonotmesis, neurotmesis will not recover without surgical intervention. This distinction may be difficult at times and hence there is a role of electrophysiological studies in the diagnosis of nerve injuries. They are also helpful in documenting recovery and in the diagnosis of compressive neuropathies.

Electromyography (EMG): The recording of muscle action potential can help in documenting the extent of denervation as well as its distribution (10). EMG studies should be done after 2-3 weeks of injury for the muscle to show denervation changes. Complete denervation is characterized by low amplitude sharp waves or fibrillation potential with muscle at rest and absent evoked muscle action potential (MUAP). With reinnervation these changes begin to reverse.

Nerve conduction studies (NCS): They play an important role in identifying the type and age of peripheral nerve injury. In neuropraxia compound muscle action potential (CMAP) amplitude remains normal distal to the site of injury and drops to zero with proximal site stimulation. In axonal injury the CAMP is present in the first week and thereafter falls rapidly after Wallerian degeneration has occurred (11).

Management of nerve injuries: When a nerve injury is identified, the dilemma is when to operate, and what kind of repair should be undertaken. If the nerve injury is due to penetrating trauma with neurological deficit, immediate exploration and repair of nerve is indicated. However, if the mechanism is due to blunt trauma the serial examination is necessary for allowing spontaneous recovery to occur. In these circumstances delayed repair can be done. Electrophysiological studies are helpful in deciding the timing of surgery in these patients.
Surgical repair: The core issue in a peripheral nerve surgery is tension free coaptation of nerve ends with minimum number of nonabsorbable monofilament sutures. The tension in the suture line is associated with increased with fibrotic reaction and poor regeneration (12). Best results of nerve repair are possible with correct matching of motor and sensory component. Intraoperative motor-sensory differentiation is possible with immunohistochemical and electrophysiological methods (13).

A divided nerve gap can be bridged by number of means which include direct repair, nerve grafts and nerve conduits. However in cases where these are not feasible nerve transfers and neurotisation can be resorted to for good functional recovery (14).

Direct nerve repair: Three techniques are described for direct nerve repair viz epineural repair, perineural repair and group fascicular repair.The epineural repair is the commonest form of nerve repair and is associated with certain advantages in terms of short operating time, technical ease and avoids injury to intraneural tissues and fascicles. The perineural repair is indicated in nerve grafting and nerves with less than 5 fascicles. The group fascicular repair can be performed at a site where nerve has given branches and individual fascicles can be identified in the main trunk. Theoretically motor and sensory fascicles can be matched and hence motor-sensory cross innervations avoided .

Repair by nerve grafts: When nerve gap exceeds 2 cms and direct nerve repair is under tension nerve grafts are indicated to bridge the divided nerve ends(15,16). Three common types of nerve grafts are cable grafts, trunk grafts. Cable grafts are multiple small caliber grafts from relatively dispensable nerves. The commonly used nerve are sural, superficial radial sensory nerve, anterior branch of median antebrachial cutaneous nerve and lateral femoral cutaneous nerve. The graft length should be 10-20% longer than the nerve gap to allow for shortening due to fibrosis. The micro neural sutures are then used to co-apt the multiple cables to match the diameter of the nerve (Fig 1 to 7). Reversal of nerve grafts reduces the axonal disruption through the distal nerve branches.

The trunk grafts are whole nerve grafts in a non functional nerve which can be used to reconstruct a nerve likely to function. However due to its thickness and ability to vascularise from the bed, they are associated with poor results. Vascularised nerve grafts consists of an entire nerve with its vascular pedicle used to restore nerve functions. Doi et al in their series of vascularised vs non vascularised nerve grafts concluded that vascularised nerve grafts are indicated when the nerve gap is more than 6 cms and associated with massive skin loss and poor tissue bed vascularity(17).

Fig 1 Wrist drop following Radial nerve injury

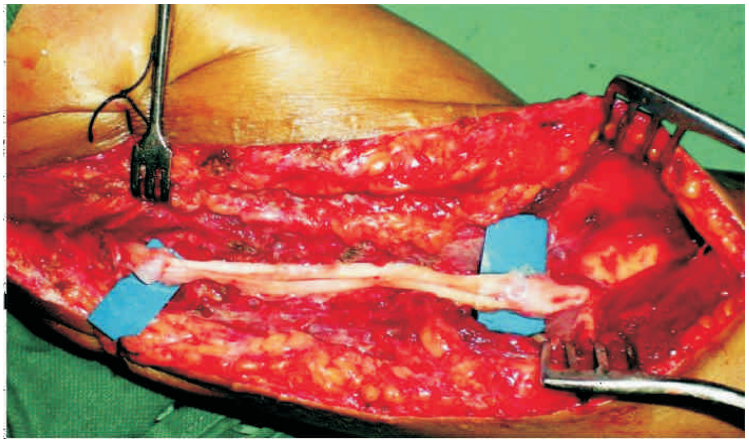

Fig 2- Nerve grafting

Fig 3- Wrist drop corrected

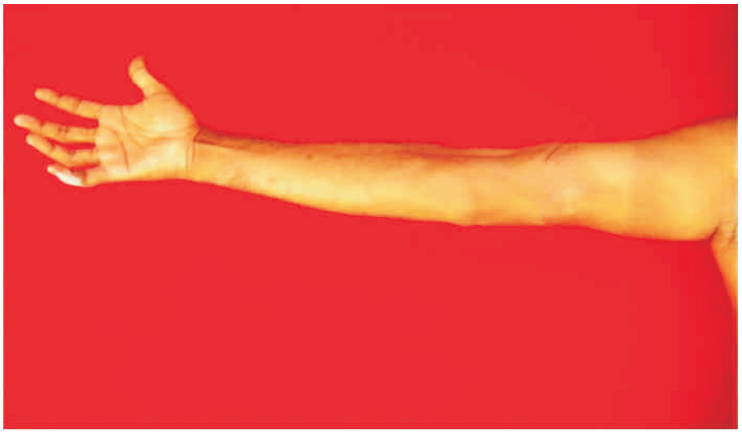

Fig 4- Ulnar nerve injury

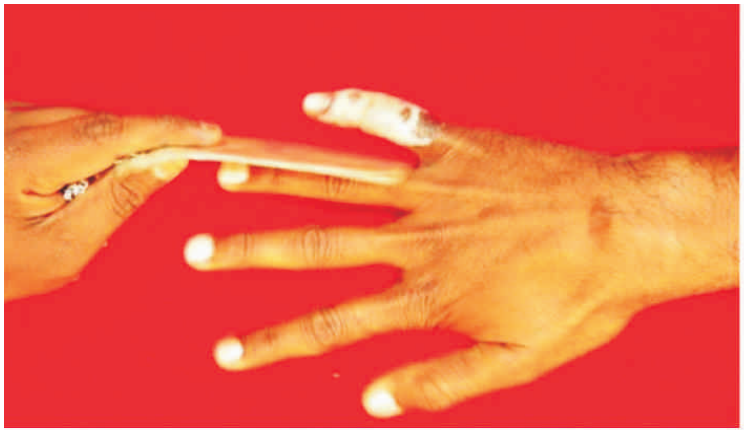

Fig 5- Ulnar nerve injury

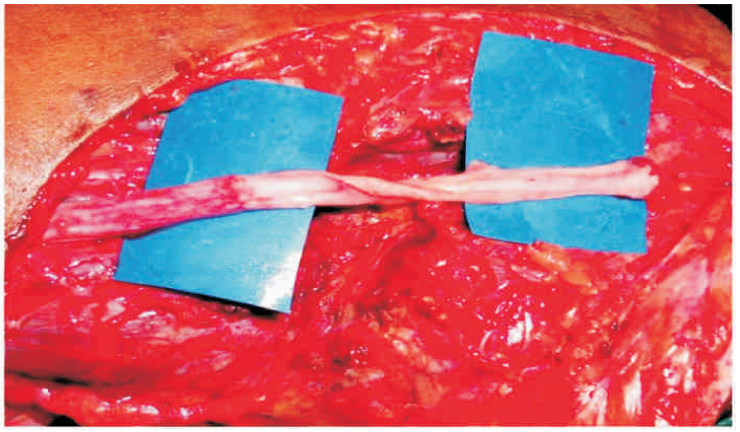

Fig 6- Nerve grafting

Fig 7- Good hand grip following repair

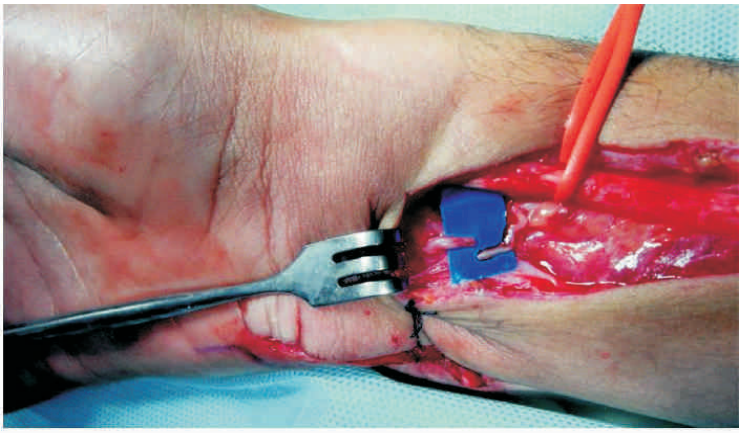

Fig 8- Distal nerve transfer for ulnar nerve injury

Nerve transfers:

Neurotization involvs use of proximal functioning nerve as donor nerve to repair the distal denervated nerve element. The procedure therefore reinnervates the target organ from healthy functional nerve. The technique popularised by Narakas has been used extensively in brachial plexus injuries to reinnervate the distal muscles in cases of root avulsion or roots not found repairable (18) (Fig 8).

Emerging concepts in peripheral nerve surgery

End to side neurorraphy:

This technique of nerve coaptation was described by Letrevant in 1893 in a case of nerves with loss of significant length. This was however abandoned due to poor results. In 1992 Viterbo et al reintroduced this technique which consists of coaptation of distal stump of transected nerve to the trunk of adjacent donor nerve(19). This is considered as an alternative technique when the proximal stump is unavailable or the nerve gap is too long to be bridged by a nerve graft (20).

The nerve regeneration in end to side neurorraphy takes place by collateral sprouting. The regenerated axons emerge from the most proximal node of Ranvier and travel in the epineurium of donor nerve (21,22). In 1993 Viterbo used cross facial nerve graft transplantation using end to side neurorraphy in facial palsy (23). Amr et al reported satisfactory results in 11 cases of brachial plexus injury managed with end to side neurorraphy (24). Other authors have also reported promising results with this technique (25). Nevertheless this is an interesting technique and in the future it may be a viable option in peripheral nerve injuries.

Nerve conduits:

Use of cylindrical tube to bridge a gap between nerve ends has been widely reported in current literature. Through neurotrophism the regeneration of axons occurs within this tube. It avoids the morbidity associated with nerve graft. The semi rigid tube prevents the soft tissue coming in between the nerve ends. Several studies have indicated the comparable results to direct nerve repair and nerve grafts when nerve conduit was used to reconstruct a short segment of nerve(26,27). The limitation of nerve conduits is the distance between the divided ends which can be bridged. The 3-4 cms is the defining upper limit of nerve gap which can be bridged with comparable results (28,29). Conduits from various biological and synthetic sources have been used. The biological tubes include the use of arteries, veins, muscles and modified biological tissues such as laminin and collagen. The limitations of biological conduits in terms of early fibrosis, scar infiltration and tissue reaction have led to emergence of conduits made from synthetic materials. Commonly used synthetic conduits are polyester such as polyglycolic acid, polylactic acid and polygalactin (30). In order to enhance nerve regeneration in these conduits the use of exogenous growth factors and neurotrophic factors have been used(31). However for digital nerve repair excellent to good sensory function in 75% has been reported and for larger mixed nerves functional recovery was obtained in 75% of patients with 1-4 cms nerve gap reconstructed with conduits(26,27). Therefore the use of nerve conduits in selected patients can produce comparable results obviating the need for donor nerves and its resultant morbidity.

Nerve allografts:

The use of nerve allografts have been reported in primates by Bain et al (32). The immunosuppressant FK 506(Tacrolimus) has benefitted the experimental allografting results which are comparable with autografting in animal studies (33). However despite these advances there remains limited indications for its application which include insufficient nerve autografts (34), limb transplantation and pre-existing immunesuppression. The duration of immune suppression required for nerve allograft remains undetermined. Mackinnon reported return of motor and sensory functions in 6 out of 7 nerve allograft transplants to upper and lower limbs (35).

Immune modulators in nerve repair:

The use of immunosuppressant FK 506 (Tacrolimus) has been shown to accelerate the nerve regeneration and functional recovery. It acts via FK 506 binding protein (FKBP) receptors. The FKBP 12 in receptor is responsible for immune suppression (36). The current application of FK 506 is in enhancing the nerve regeneration after nerve repair but its role as an adjunct to nerve allografting is promising. Yan et al in their experimental study on rat demonstrated significant therapeutic impact in short term use of FK 506 in nerve regeneration. In future, the use of FK 506 is likely to play an important role in nerve regeneration (37).

Results after peripheral nerve repair:

The outcomes of nerve reconstruction are influenced by multifactorial variables. In 1991, Sunderland made certain observations regarding nerve repair. He found that outcomes in younger patients, early repair, repair close to target muscle, repair of single function nerve and short nerve graft had better outcomes(2). Kallio et al reported their results of 132 median nerve reconstruction which were managed with nerve grafting and secondary neurorraphy. They reported god to excellent results in 49% , fair results in 11% and poor results in 40% of patients. The poor results were associated with injury proximal to the elbow, age more than 54 years, graft length of more than 7 cms and delayed surgery of more than 23 months (38). Similar results were published by Vastamaki et al in reconstruction of ulnar nerve with 52% of patients achieving useful recovery (39).

Conclusion:

Despite advances in understanding of pathophysiology of nerve injuries and advent of microsurgical techniques, the outcomes of repair have still not reached its zenith, with about 50% of patients achieving useful nerve function. Current research in nerve injuries is challenging and newer modalities are under evaluation to further improve the results of nerve reconstruction.

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