Peripheral Nerve Healing: So Near and Yet So Far

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Abstract

Peripheral nerve injuries represent a considerable portion of chronic disability that especially affects the younger population. Prerequisites of proper peripheral nerve injury treatment include in-depth knowledge of the anatomy, pathophysiology, and options in surgical reconstruction. Our greater appreciation of nerve healing mechanisms and the development of different microsurgical techniques have significantly refined the outcomes in treatment for the past four decades. This work reviews the peripheral nerve regeneration process after an injury, provides an overview of various coaptation methods, and compares other available treatments such as autologous nerve graft, acellular nerve allograft, and synthetic nerve conduits. Furthermore, the formation of neuromas as well as their latest treatment options are discussed.

Keywords
► peripheral nerve
► injury
► repair
► review

Peripheral nerve injury (PNI) is a common condition that often affects a younger and otherwise healthy individual, with 83% of the patients being under 55 years old and an equal male to female ratio.1 It is estimated that approximately 5% of all patients admitted to a Level I trauma center have a PNI.2 Common etiologies include penetrating trauma, crush, ischemia, and traction, while injuries from electric shock and vibration are less frequent.3 Their typical symptoms are sensory/motor function deficits that could result in the development of intractable neuropathic pain, with devastating impacts on patients’ quality of life. Multiple factors predict the outcome after a peripheral nerve repair including age, gender, materials utilized, repair time, type of nerve injured, defect size, and duration of follow-up.4

The peripheral nervous system has regenerative potential. However, for optimal healing to occur, an appropriate environment must be provided physiologically or surgically. In this article, we review the peripheral nervous system response to injury, and discuss surgical repair options and their applications.

Peripheral Nerve Injury Classification

Classically, after a focal injury to the peripheral nerve, one of two consequences to the axon is observed: conduction block or axonal degeneration.5 In the former, the axon remains anatomically intact; the conduction of action potentials is blocked in the zone of injury, while it persists distal to it. In this case, if the underlying cause (i.e., ischemia, traction) is removed, spontaneous recovery is expected. On the other hand, in a nerve transection, axonal degeneration happens through Wallerian degeneration,6,7 a rapid and active process which takes place in the distal nerve stump secondary to separation of the nerve axon from its cell body. Nerve recovery in a degenerative lesion depends on the basal lamina preservation. In other words, if the basal lamina remains intact, the proximal axon may grow in an organized fashion into the distal tube once the insulting injury is eliminated. However, when there is an interruption in the basal lamina, spontaneous regeneration will not be organized or may not occur at all.

In 1943, Seddon et al proposed three fundamentally distinct groups of PNs. He coined the terms neurapraxia, axonotmesis, and neurotmesis. Neurapraxia refers to a nerve conduction block, axonotmesis refers to a degenerative injury with an intact continuous basal lamina, and neurotmesis indicates nerve injury leading to disruption of the basal lamina.8 In 1951, Sunderland9 refined this classification and introduced five types of PNI based on increasing...
severity of damage to the nerve structure. Mackinnon and Dellon\textsuperscript{10} introduced a sixth injury pattern that combines any of the Sunderland’s classes and therefore variable degrees of recovery is witnessed (\textsuperscript{Table 1}). A Type 2 or greater Sunderland PNI presents a diagnostic and decision-making challenge, as Wallerian degeneration and subsequent nerve scarring begins within 48 to 72 hours following injury.\textsuperscript{11,12} For a nerve to fully regenerate, axons are required to grow in an antegrade fashion within the endoneurial tube. However, in the presence of excessive intraneural fibrosis, normal neural migration and growth can be delayed or diverted.\textsuperscript{13,14}

While crush and traction injuries may leave nerves in continuity, penetrating injuries can be more complex. They can present as isolated nerve transection, or be associated with crush and traction. These mixed lesions may obscure the diagnosis. While Sunderland introduced an elaborate system of classifying injury, clinically, it is simpler to categorize the injury to “degenerative” and “nondegenerative,” as this is the more important question that should be initially answered by the peripheral nerve surgeon.

\textbf{Repair Cascade}

When the continuity of a peripheral nerve is interrupted, its distal and proximal ends retract, and Schwann cells in both stumps orchestrate an inflammatory response that clears the debris and begins the process of neuronal remodeling.\textsuperscript{14} Proximal to the injury, Schwann cells de-differentiate and transform from a myelinating supporting role to a progenitor-like cell and become repair cells.\textsuperscript{15} These cell changes, characterized by the downregulation of the myelin protein, and upregulation of growth-promoting factors,\textsuperscript{16–18} are triggered by the injury signal\textsuperscript{19} or by axonal signal loss.\textsuperscript{20} A retrograde signal is sent to the nucleus to stimulate the transcription factors in the injured neuron.\textsuperscript{21} In particular nerves, the length of axons presents a special challenge, as these signals have to travel more than 50 cm to reach the nucleus.\textsuperscript{20}

On the other end, tube-like structures (bands of Büngner) are formed at the distal stump, which act as “channels” to direct the regenerating axons back to their original targets. In the case of a transection, however, guidance of axons into the bands of Büngner will be more complex.\textsuperscript{22} The two stumps are joint by a “bridge” of inflammatory cells and matrix,\textsuperscript{23} which does not provide sufficient directional capacity for axonal regrowth. Schwann cells become responsible for guiding the axons across this bridge region.\textsuperscript{24} While Schwann cells from both proximal and distal nerve stumps migrate until they bridge the gap, Schwann cells from the proximal stump attract the growing axons. Fibroblasts organize this migration at the wound level, via ephrinB/EphB2 signaling, which gives Schwann cells an adhesive behavior necessary for their orchestrated migration.\textsuperscript{24} Macrophages respond to the hypoxia created within the bridge and secrete vascular endothelial growth factor A, which triggers vascularization within the bridging zone.\textsuperscript{23} This neovascularization acts as tracks, guiding Schwann cells to cross the bridge, directing the sprouting axons to the distal stump. With vascularization begins a crucial part that guides Schwann cell migration; when this system is disrupted, the blood vessels may misdirect Schwann cells to grow into surrounding tissues, and suboptimal healing inevitably occurs.\textsuperscript{23,24}

\textbf{Muscle Reinnervation and Motor Unit Territories}

Cross-section of motor nerves branching is similar to cross-section of a tree and its roots. Motor nerves begin to branch within the intramuscular nerve sheath of their destined skeletal muscle.\textsuperscript{25} This branching takes the nerve to various muscle fascicles. Motor units are territories of all muscle fibers that are innervated by one motor neuron. These spatial territories specify the number of muscle fibers reinnervated by a nerve after injury.\textsuperscript{26–28} The number of muscle fibers in each motor unit has a direct correlation with the size of the

\textbf{Table 1 Classification of nerve injuries}

<table>
<thead>
<tr>
<th>Seddon</th>
<th>Sunderland</th>
<th>Injury</th>
<th>Recovery</th>
<th>Need for surgical repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropraxia</td>
<td>Type 1</td>
<td>Focal demyelination and conduction block. No WD</td>
<td>Complete</td>
<td>No</td>
</tr>
<tr>
<td>Type 2</td>
<td>Axonal discontinuity + WD</td>
<td>Complete - up to 12 wk</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Axonotmesis</td>
<td>Type 3</td>
<td>Axonal and endoneurial disruption + WD</td>
<td>Partial - up to 12 wk</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Type 4</td>
<td>Perineurial rupture with fascicle disruption + WD</td>
<td>None</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Neurotmesis</td>
<td>Type 5</td>
<td>Nerve truck discontinuity + WD</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Mackinnon</td>
<td>Type 6</td>
<td>Mixed</td>
<td>Some</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: WD, Wallerian degeneration.
unit territory; in a muscle cross-section, this territory can take up to 30% of the surface area.26

If reinnervation is provided shortly postinjury, motor units will not significantly reduce in number.15 On the other hand, if a muscle suffers from prolonged denervation, the number of motor units will drastically drop, affecting the structure and function of the reinnervated muscle.29 In chronic denervation, the intramuscular portion of the nerve sheath can no longer support the regenerating axons.15 Other contributing factors have been recognized, namely reduced number of Schwann cells and failure to maintain their regenerative role, disintegration of muscle spindles,30 irreversible atrophy, and muscle fiber necrosis.31,32 All these factors contribute to unsatisfactory functional recovery.

**Functional Recovery after Nerve Injury**

A functional recovery signifies a nerve has regained its physiologic state preinjury. This is largely dependent on three major factors: reinnervation of the end organ, timing of the injury, and distance to target organ.

To facilitate reinnervation, a nerve repair must primarily guide the regenerating axons to their original endoneurial tubes.33 Motor and sensory nerves can find their correct path to a motor unit or sensory dermatome, respectively. Despite this capacity, motor fibers occasionally fail to follow their respective pathway and, consequently, fibers never meet the preinjury target organ.34 This misdirection can happen even after surgical repair of a nerve, which poses a major long-term functional deficit.35,36

Although sensory nerves reinnervate their specific organs, it is unlikely for them to reach their original mechnoreceptor. With a portion of healing consisting of misguid- ed afferent fibers, misinterpretation of tactile stimuli and poorly localized sensation may occur. This is observed in patients with severe brachial plexus injury, in particular patients who report “wrong-way” sensation.37 Similarly, the efferent motor fibers may reinnervate a different muscle. This has a particular clinical importance following complete transection of large mixed sensory and motor nerves. Random reinnervation was observed in patients’ hand muscles after surgical approximation of a transected ulnar nerve at the wrist, and result in simultaneous antagonistic muscles contractions.38

While the regeneration of sensory nerves can still happen with delayed repairs over months to years,39 the timing of reinnervation is particularly important for motor nerves, as the regenerated nerve muscle and sensory end organ to its denervated target (i.e., motor endplate) in a timely manner.15,40 In motor nerves, a significant delay in regeneration becomes a major challenge to functional recovery.15,40,41 In chronic denervation, newly generated axons approach the motor endplate of the target muscle, but cannot form functional connections or synapses.42 This is possibly due to the ir reversible Schwann cells in the end plate that no longer support reinnervation. This is observed clinically in patients with complete brachial plexus palsy with almost no functional recovery in repairs delayed beyond 12 months follow-

![Fig. 1](image-url) Schematic presentation of proximal and distal nerve stumps: (A) grouped fascicular repair, suture coapting the corresponding a group of fascicules using the perineurium; (B) fascicular repair; and (C) standard epineural repair, stumps are aligned based on the anatomy of vessels.

- **Primary Nerve Coaptation**

The ideal nerve repair occurs after trimming the proximal and distal nerve ends to healthy fascicular structures. The topographic anatomy must be restored to decrease the risk of aberrant reinnervation.52 This can be achieved by realigning the vasa nervorum, and by visually identifying known fascicular groups within the nerve. Whenever possible, a tension-free, precisely aligned, and atraumatic primary neurorrhaphy is favored.53,54 - Fig. 1 describes three main categories of primary direct nerve repair and their...
subcategories. Although there is theoretical advantage of precisely realigning each fascicle in interfascicular neurosurgery, the formation of excessive internal scarring has proven to adversely affect the clinical outcome of such repair. Today, the epineural repair is the mainstay of primary neurosurgery.

Fibrin glue is sometimes used instead of standard microsurgical suturing. The first commercially available fibrin sealant was introduced in the 1970s, and since then, its use in nerve repair has increased. Potential benefits of fibrin glue utilization are: shorter procedure time, reduced recovery time, possible barrier to invading scar tissue, minimal trauma and scarring, and subsequently decreasing fibrosis and inflammation. The main disadvantage of this technique is its inferior holding strength. Currently, most available studies are from animal models and a well-controlled human study is lacking. Most of this literature demonstrates similar clinical outcomes for fibrin glue and microsutures in small diameter peripheral nerve coaptations. Fibrin glue can also be used as an adjunct to microsuturing to reduce the total number of sutures, thus theoretically reducing the chance of suture-induced fibrosis. That being said, there is a dichotomy in the evidence, while some works show the ease of use and noninferiority of fibrin glue to suturing, others show that it can lead to an inflammatory response and a high degree of scarring. This paucity in strong literature and human studies, warrants further studies to better investigate their comparative efficacy.

Even when optimal end-to-end microsurgical coaptation is done, scar tissue formation postoperatively can lead to excessive collagen deposition, fibrosis of the epineurium, and nerve compression that eventually impedes regeneration. Pathophysiology of epineural scarring and compression are due to three main reasons: (1) vascular compromise, (2) tethering forces, and (3) direct nerve compression. Few of the regenerating axons may escape the coaptation and create a neuroma. To prevent this, nerve wraps were introduced to support repairs and minimize fibrosis and scarring. Wraps potentially offload tension from the repair site and distribute it across a larger length of the nerve. They can also act as a barrier and reduce axonal escape. Currently, different nerve wraps are being utilized with autologous tissue or vessels, and more recently biodegradable materials such as collagen, have been widely investigated. Autologous vein grafts impart minimal donor site morbidity, and serve as a conduit that facilitates cellular migration between the cut nerve ends, bridging gaps up to 3 cm. The advantages of synthetic nerve conduits include no donor site morbidity and the elimination of donor size discrepancy. However, they are limited to the defect size, with defects > 2 cm are better treated with autologous nerve grafting. Processed allograft is a decellularized and sterile extracellular matrix obtained from human peripheral nerve tissue which requires no immunosuppressive therapy. Clinical data support their use in noncritical nerve defects up to 5 cm.

Neuroma Formation

In situations where regenerating axons cannot successfully reenter the distal stump, the biologic response of the proximal stump leads to neuroma formation. This swelling of the terminal bulb of the proximal stump contains Schwann cells, fibroblasts, blood vessels, and most importantly, regenerating axons.

Severe neuropathic pain is normally not provoked if a main nerve fiber is cut sharply. Nonetheless, significant pain is almost always unavoidable after accidental damage to the terminal branch of the same type of cutaneous nerve. Some susceptible cutaneous sensory branches are: medial cutaneous nerve of the forearm, superficial radial nerve, sural nerve, and the long saphenous nerve. As the name implies, in complete neuromas (fully transected), the nerve trunk has been divided, whereas partial neuromas (neuroma in continuity) contain a portion of intact fibers.

The most commonly performed treatment of a neuroma is excision and anastomosis of the two ends. Recent studies have compared various surgical options including: excision alone, traction neurectomy, excision and cap, excision and transposition, excision and repair with allograft or autograft, and neurolysis and coverage, showing no superiority of one to another. The current concept supports the shift to attempt to heal rather than hide the injured nerves.
A neuroma that has no distal nerve stump for a reconstruction of the resected nerve segment with a graft can be treated with a regenerative peripheral nerve interface or targeted muscle reinnervation (TMR). The former involves wrapping the cut nerve end with a small free muscle graft, which allows nerve ingrowth and innervation. In TMR, the nerve stump is coapted to a small target motor nerve within a nearby muscle. In both modalities, the goal is to create a new functioning nerve–muscle interface for the transected nerve to innervate, thereby conferring it a new “job” to facilitate normal nerve healing and to prevent its dysregulated growth into a painful neuroma. TMR, in particular, has been shown in randomized controlled trials to decrease the incidence of postamputation neuroma pain and phantom limb pain compared with traditional traction neuectomy. 80

Strategies to Enhance Nerve Healing

There are several strategies to improve functional recovery after a nerve injury. As previously mentioned, a distal babysitting nerve transfer was initially proposed by Terzis and Tzafetta. 85 To decrease the risk of muscle atrophy and endplate loss in a high motor nerve injury, the procedure utilizes an end-to-side neurorrhaphy between a healthy donor located close to the motor target and the distal injured nerve to rapidly restore efferent stimuli to the denervated muscles, thereby preventing irreversible atrophy. This method has multiple applications, for instance, ipsilateral hypoglossal to facial nerve transfer is performed with cross-facial nerve grafting, anterior interosseous nerve to distal motor branch of the ulnar nerve transfer is done with high ulnar nerve laceration repair, and many other.

Emerging evidence demonstrates accelerated axon outgrowth across injury sites with brief electrical stimulation. 86 Electrical stimulation of the injured nerve can enhance the functional recovery even after delayed surgical repair. 87 A more recent study also supported the accelerating effect of immediate electrical stimulation in TMR with daily stimulation right after denervation. 88 These promising findings anticipate more rigorous clinical studies regarding their practicality and application. If proven to be clinically successful, intraoperative and postoperative brief electrical stimulation may become the standard of practice.

Low-intensity pulsed ultrasound (LIPUS) has demonstrated some benefit in different therapeutic applications such as pseudarthrosis, bone fractures, and various soft tissue conditions. 89 Although further studies are required to clearly demonstrate clinical efficacy, there are some promising reports on animal models indicating that LIPUS use accelerates peripheral nerve regeneration. 90

One of the most recent biologic agents administered to assist nerve regeneration is FK506, a Food and Drug Administration approved immunosuppressant. While FK506 has proven to enhance nerve regeneration, side effects of the systemically delivered FK506 has averted clinicians from its routine use. The current research is focused on developing innovative routes of local medication delivery such as using a fibrin gel matrix to significantly reduce the biodistribution, thereby reducing the chance of FK506 systemic toxicity. 91 Until this milestone is reached, its wide use in nerve repairs is unlikely.

Conclusion

During the last several decades, our knowledge of peripheral nerve pathophysiology has expanded drastically, and parallel to our refined microsurgical skills, we have discovered strategies to enhance its healing. We have become more consistent in achieving satisfactory reinnervation and functional outcomes in short nerve gap reconstructions, and recently have found new venues to repair larger defects. Future approaches should focus on new methods to improve the outcome in more challenging scenarios such as chronic injuries and delayed nerve repairs, for the aim of offering a better quality of life to a large portion of our trauma patients.

Conflict of Interest
None declared.

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