

# Polyethylene Glycol Fusion of Nerve Injuries: Review of the Technique and Clinical Applicability

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## Abstract

Traumatic peripheral nerve injuries present a particular challenge to hand surgeons as mechanisms of nerve-healing pose serious limitations to achieving complete functional recovery. The loss of distal axonal segments through Wallerian degeneration results in the loss of neuromuscular junctions and irreversible muscle atrophy. Current methods of repair depend on the outgrowth of proximal nerve fibers following direct end-to-end repair or gap repair techniques. Investigational techniques in nerve repair using polyethylene glycol (PEG) nerve fusion have been shown to bypass Wallerian degeneration by immediately restoring nerve axonal continuity, thus resulting in a rapid and more complete functional recovery. The purpose of this article is to review the current literature surrounding this novel technique for traumatic nerve repair, paying particular attention to the underlying physiology of nerve healing and the current applications of PEG fusion in the laboratory and clinical setting. This article also serves to identify areas of future investigation to further establish validity and feasibility and encourage the translation of PEG fusion into clinical use.

## Keywords

- ▶ basic science
- ▶ peripheral nerve repair
- ▶ polyethylene glycol fusion
- ▶ traumatic nerve injury

## Introduction

Over the past several decades, our understanding of peripheral nerve function, anatomy, and mechanisms of regeneration have advanced greatly, but our methods of treatment for traumatic peripheral nerve injuries have remained largely unchanged. The gold standard for treatment currently consists of restoring continuity of the nerve tissue with microsutures or glue.<sup>1</sup> Depending on the location and extent of injury, this can be achieved with a direct end-to-end repair, or a variety of surgical techniques to guide axonal growth across gaps in nerve continuity. In general, clinical outcomes for traumatic peripheral nerve injuries are suboptimal because of the difficulties in overcoming the downstream effects of Wallerian degeneration.<sup>2</sup> This organized deconstruction and clearance of all axonal elements of the distal nerve segments leaves behind only the empty honeycomb-shaped endoneurial tubes and renders the sensory or motor end-target organ denervated. Reinnervation is dependent on each axon navigating the path to the target organ. However, without the aid of perfectly matched endoneurial tubes and with intervening scar tissue, up to 50% of axons across each neuroorrhaphy

site can get lost or blocked from reaching their destination. As a result, even with strict adherence to standard protocols, recovery is often slow and incomplete. Recent data from studies utilizing polyethylene glycol (PEG) to fuse axon membranes during surgical repair indicates that it can help prevent or reduce Wallerian degeneration and restore more complete functionality. The purpose of this review is to characterize the current body of literature regarding PEG fusion and its potential for use in the clinical setting.

## Polyethylene Glycol Fusion Mechanism

### Physiologic Response to Peripheral Nerve Injury

In general, peripheral nerve injuries can be classified into three basic categories: neuropraxia, axonotmesis, and neurotmesis.<sup>3</sup> Neuropraxia involves loss of nerve function with intact axons, usually due to stretching or bruising with injury to Schwann cells resulting in loss of myelination. This injury typically heals over the course of several weeks as myelin is restored, and recovery is typically complete due to lack of injury to the underlying axons. Axonotmesis involves damage to nerve axons, but the surrounding perineurium and

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epineurium remain intact. Wallerian degeneration of the distal nerve segments occurs for each damaged axon, and recovery consists of 1 to 2 mm per day outgrowth of proximal axonal projections through the intact nerve endoneurial tubes. Recovery is variable depending on many factors including the degree of axonal involvement as well as the location of injury along the nerve path. Neurotmesis involves the complete severance of axons and surrounding nerve tissue. Wallerian degeneration of the distal segment always ensues, and recovery is dependent on surgical intervention and is usually incomplete.<sup>4</sup>

In the cases of axonotmesis and neurotmesis, the disruption in the axon's outer lipid bilayer membrane (the axolemmal membrane) activates a series of cellular and molecular responses designed to limit damage and promote healing. To prevent the influx of cytotoxic substances and lysosomal activation, disruptions in the axolemmal membrane must be sealed.<sup>5</sup> Over the course of 5 to 20 minutes following axonal damage, vesicles from within the axon are released, plug the holes in the membrane, and cap off the end of the axon via a calcium-dependent mechanism.<sup>4</sup> The open breaches in the axolemmal membrane of the distal segments and the disconnection from the cell body allow recognition by the immune and complement systems. Schwann cells breakdown the myelin sheath, and macrophages are recruited to clean up axonal debris. This process can take up to 7 days to begin, but once the committed step in Wallerian degeneration—which is the granular disintegration of the axonal cytoskeleton—has begun, the process is complete in an all or none fashion within hours and thereafter distal innervation is lost.<sup>6-8</sup> Myelin and axonal debris inhibit axonal regeneration, which cannot begin until this process is complete. In the case of achieving motor recovery, the neuromuscular junction (NMJ) must be reestablished prior to motor end plate demise, which may occur within 12 to 18 months.<sup>9,10</sup> Without reinnervation, muscle atrophy and subsequent fibrosis progresses over the course of approximately 2 years.

### **Polyethylene Glycol Fusion Fundamentally Alters the Physiologic Response to Nerve Injury**

PEG fusion makes it possible to bypass some of the maladaptive physiologic responses to peripheral nerve injury (PNI) by immediately restoring continuity of nerve segments and preventing Wallerian degeneration. Although the mechanism is not completely understood, it is hypothesized that the hydrophilic nature of the PEG polymers removes water molecules away from the lipid bilayer, thereby lowering the activation energy for membrane fusion.<sup>11</sup> Via a series of studies over the past few decades, it has been shown that the use of PEG during neurotmesis with microsutures induces rapid and permanent repair of axonal membranes *in vitro* and *in vivo*.<sup>12,13</sup> With the proximal and distal ends of the nerve segments rejoined, combined action potentials (CAPs) demonstrate a restoration of conduction within minutes. Using rat sciatic nerves as a model, PEG fusion not only results in near-immediate return of CAPs, but also a rapid return of function in the days following repair with incremental improvement to near normal levels over the subsequent

weeks.<sup>14,15</sup> These improvements, both immediate and long term, are significantly better than the functional improvements from control animals who underwent neurotmesis without PEG fusion.

It is important to note that during PEG fusion, proximal and distal ends of severed nerves are rejoined in a non-specific manner. While some proximal motor axons may reconnect with distal motor axons with projections to the appropriate target, it is also the case that many motor axons will reconnect with sensory axons or other motor axons to inappropriate targets. Using retrograde neuronal labeling, this nonspecific reconnection can be visualized. For example, in uninjured rats, retrograde labeling of the tibialis anterior nerve fibers localizes neuronal cell bodies in the L3 spinal cord segment. However, for rats with PEG-fused sciatic nerves, retrograde labeling of tibialis anterior nerve fibers localized to spinal cord segments from L3 to L6. Additionally, there was also inappropriate labeling of L3 to L6 dorsal horn spinal cord segments, indicating anomalous reconnection of distal motor axons to proximal sensory axons.<sup>16</sup> However, the behavioral recovery that is observed in the weeks following PEG fusion may be attributed to CNS plasticity, allowing inappropriately connected neurons to alter their dendritic connections to relearn the functions that were lost.

While there is reorganization of connections within the spinal cord, one of the defining features of PEG fusion is the maintenance of the NMJ. Studies to visualize the NMJs after PEG fusion demonstrated maintenance of approximately 80% of NMJs in PEG-fused sciatic nerves after 21 days compared with uninjured animals.<sup>17</sup> In contrast, after 21 days, animals undergoing neurotmesis without PEG fusion demonstrated sparse and small diameter axons in the distal segment with no visualization of intact NMJs. The muscle fibers in PEG-fused individuals also demonstrate significantly less muscle atrophy compared with non-PEG-fused controls. From these data, it can be inferred that the PEG fusion is successful in reducing Wallerian degeneration. Bypassing Wallerian degeneration provides for continuous innervation of distal axonal targets and prevents the extensive atrophy and loss of NMJs following PNI.

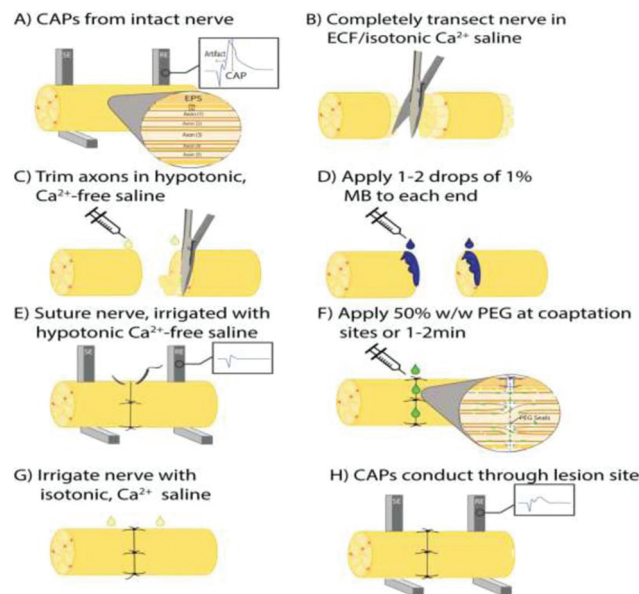
### **Technical Considerations for Polyethylene Glycol Fusion**

PEG fusion involves very precise alterations in the natural physiology of nerve repair. Thus, technique and adherence to very specific procedures are critical to ensure successful axonal reconnection. First, axonal membranes must be open at the time of PEG application. Because membranes are sealed within 5 to 20 minutes of being disrupted, nerve ends must be trimmed immediately prior to microsuture repair.<sup>18</sup> Due to the calcium-dependent nature of axolemmal repair and membrane sealing, the trimmed nerve ends must be washed in a calcium-free solution with methylene blue. Following apposition of nerve endings with microsutures, the repair site is then bathed in a calcium-free solution of 500 mM 2 to 5kD PEG for 1 to 2 minutes to facilitate axonal membrane fusion. Lastly, the repair site is bathed in an isotonic, calcium-containing solution to help seal any

remaining axolemmal disruptions.<sup>19</sup> An illustration of this process is depicted in ►Fig. 1. Technical ability and experience have been shown to play a significant role in the success of PEG fusion. According to Bittner et al, approximately 30% of student surgeons compared with 70% of board-certified surgeons are successful in learning and applying the PEG fusion protocols to achieve functional improvement in >80% of surgical subjects.<sup>20</sup> Some recent studies have cast doubt on the reliability of PEG fusion protocols to result in axonal membrane fusion and behavioral recovery.<sup>21-23</sup> However, critics of these studies point to the technical requirements, the need for experienced surgeons, and the robust controls and validation studies needed to produce and confirm successful PEG fusion.<sup>20</sup>

### Adjuvant Therapies for Polyethylene Glycol Fusion

Several studies have investigated ways to optimize PEG fusion and the resulting behavioral recovery by introducing adjuvant therapies at the time of nerve repair. For example, the use of antioxidant compounds has been tested as a means to increase the number of successfully fused axons. Antioxidants such as methylene blue, among others, have been shown to decrease the rate of membrane sealing, resulting in a higher percentage of open axon membranes at the time of PEG application.<sup>18</sup> By using these antioxidants, in conjunction with calcium-free solutions, the rate of successful PEG fusion is increased. As a result of the successful use of antioxidants, a 1% methylene blue solution has become part of the standardized protocol for PEG fusion.<sup>19</sup> Other adjuvant therapies that have been used to keep membranes open during repair include P2X7 receptor inhibitors.<sup>21</sup> Blocking these receptors involved with regulating calcium influx to peripheral nerve axons was shown to result in improved functional outcomes for PEG fusion.



**Fig. 1 (A–H)** An illustration of the PEG fusion surgical technique. This illustration depicts the key steps and materials needed for experimental severance and subsequent repair of peripheral nerves using PEG fusion. PEG, polyethylene glycol (reproduced with permission from Ghergherechi et al<sup>39</sup>).

Other studies have looked at ways to increase the structural integrity of the nerve repair site. Immediately following PEG-fusion the only mechanical support to the newly fused axon membranes comes from the microsuture repair. A recent study analyzing the use of tubularized nerve conduit with PEG fusion demonstrated that rats showed better behavioral recovery with a higher concentration of nerve fibers in the distal nerve segment.<sup>24</sup> The increased stability at the nerve repair site may contribute to increasing the amount of axons able to maintain their reconnection through the nerve-healing process. Another recent study looked into the use of spastin, a protein involved in microtubule reorganization.<sup>25</sup> One of the reasons that distal nerve segments undergo Wallerian degeneration is the disruption of axonal transport. Even if membranes are rejoined, if cytoskeletal integrity is not achieved, then the axonal transport cannot occur and Wallerian degeneration may still happen. Spastin added in conjunction with PEG fusion was shown to improve behavioral recovery as well as increase the concentration of healthy axons in rats.

### In Vivo Polyethylene Glycol Fusion Repair Techniques

#### Current Techniques for Peripheral Nerve Repair

To better understand the possible applications of PEG-fusion, it is important to understand the current methods of nerve repair and their limitations. In general, current methods can be categorized into either direct repair or gap repair. The goal with any nerve repair is to achieve tensionless restoration of nerve continuity.<sup>26,27</sup> Direct repair with microsutures has been demonstrated to provide superior functional recovery compared with gap repair techniques in the setting of sharp laceration.<sup>28</sup> This is largely because direct repairs require one neurorrhaphy site, whereas gap repairs require two, and up to 50% of axons can be lost across each coaptation. Additionally, it is believed that having axon outgrowths regenerate through native, matched endoneurial tubes allows for better recovery and reinnervation of distal nerve targets. However, the issue with direct repair is nerve tension. Even with a sharp laceration, there is inevitable nerve retraction and a zone of injury making direct neurorrhaphy difficult. Additionally, posttraumatic fibrosis within a nerve can lead to decreased nerve elasticity and increased tension and ischemia during moments of nerve stretching.<sup>29</sup> Moreover, with complex lacerations and crush injuries, there may be lengthy segments of nonviable nerve-making direct neurorrhaphy not possible. Similarly, chronic nerve injuries, such as neuromas, require nerve resection again making direct neurorrhaphy not possible. While direct repair can provide superior results, these factors make direct repair technically challenging and often impossible. Techniques to bridge gaps in nerve injuries include nerve autografting, synthetic nerve conduits, or decellularized nerve allografting. Selection of the nerve gap repair technique will be dependent on several factors, including the length of the nerve gap and the function of the injured nerve. Current in vivo studies have demonstrated promise for PEG fusion with nerve graft repairs as well.<sup>13,14,30-32</sup>

### Current In Vivo Applications of Polyethylene Glycol Fusion

Initial validation studies for PEG fusion examined direct repair of sciatic nerves in rats.<sup>13,14,30</sup> Direct repair of severed sciatic nerves with PEG fusion demonstrate immediate recovery CAP conduction, as well as an immediate, partial return of function with continued improvement over the next several weeks. Due to the importance of strict adherence to tensionless repairs outside of the zone of injury, direct repairs are less often a viable option than gap repairs. The first studies evaluating the application of nerve grafting with PEG fusion looked at the use of autografts in rat sciatic nerves. In this model, a 1-mm segment of nerve was ablated and reinserted via PEG fusion after trimming damaged ends.<sup>33</sup> Successful PEG fusion with a nerve graft requires the successful fusion of membranes at two discrete locations simultaneously. This initial study noted that while PEG fusion was successful with autografting, as determined by CAP and behavioral assessment, there was evidence of increased loss of distal neurons, suggesting that axonal fusion with autografting was not as complete as with previous direct repair studies. Additionally, behavioral recovery was not as robust. The authors suggest that this could be the result of increased nerve tensioning from the need to trim the ends of the proximal and distal nerve segments, as well as each end of the nerve autograft. Increased tension has the potential to reduce proper apposition of axonal membranes at the time of PEG fusion, as well as hinder recovery over the subsequent days to weeks. It is important to note that this model of nerve autografting is not translatable to clinical practice. Clinical use of autografting would involve harvesting remote sensory nerve tissue, thus decreasing the issue of tension in autografting. However, this method of autografting requires donor site morbidity and, if used for motor nerve gaps, then mixes sensory and motor nerve tissue. Thus, alternative methods for gap repair could prove beneficial.

PEG-fusion allografting has also been investigated as an alternative to PEG fusion autografting in animal models. The current clinical use of allografts in nerve repair is limited to decellularized allograft segments to prevent host rejection. Cellular allografts typically undergo rapid rejection within days. Only with tissue matching and systemic immunosuppression have successful results been reported.<sup>27,34</sup> Because PEG fusion requires viable axon segments, it would stand to reason that allografting for PEG fusion would likely result in host rejection. However, pilot studies performed looking into the viability of allografting for PEG fusion have demonstrated promising results. In fact, the best results in terms of behavioral recovery have been shown with the use of allografting.<sup>35</sup> Furthermore, the studies looking at the viability of allografting demonstrated little evidence of tissue rejection in the PEG-fused nerves in contrast to the non-PEG fused nerves.<sup>35,36</sup> From these data, it appears that PEG fusion, by reconnecting axonal membranes, decreases host rejection. While the mechanism of preventing rejection is not entirely understood, it is hypothesized that sealing the axolemmal membranes with PEG prevents recognition by the immune and complement systems necessary for major

histocompatibility complex rejection. More studies need to be performed to confirm and understand the lack of host rejection, but this initial data provide promising results that nerve allografts could have broad applications for a variety of nerve injury patterns and repairs.

### Potential Clinical Application of Polyethylene Glycol Fusion and Future Directions

To date, one clinical study by Bamba et al has been published outlining clinical results of PEG fusion.<sup>37</sup> This study reported the results of four digital nerve repairs utilizing PEG fusion and compared them to retrospectively patient-matched controls. The results demonstrated faster return of sensation as measured by two-point discrimination and monofilament testing. While this study provides support for the use of this new technology in humans, the real value of PEG fusion may be for mixed and motor nerve injuries to avoid motor end plate loss. There are currently three other clinical trials being conducted to investigate PEG fusion; however, these three studies are all examining the repair of sensory nerves (clinicaltrials.gov: NCT03236064, NCT02359825, NCT04270019). Looking at the repair of motor nerve injuries are an important next step in PEG fusion development. Expanding PEG fusion to larger animal models such as porcine models can be used to further establish validity in motor nerve repair before translation into clinical practice.

A unique challenge with PEG fusion is its time sensitivity of application to avoid the committed step of Wallerian degeneration. Some studies have evaluated PEG fusion at various time points after injury, but time-varied investigations in humans is necessary as rates of Wallerian degeneration vary between rodents and humans.<sup>38</sup> In a similar vein, being able to prolong the time course of Wallerian degeneration could expand the window of intervention and improve the recovery potential. Interventions such as limb-cooling devices or immunosuppression have been shown to delay Wallerian degeneration, but application of these interventions in actual clinical practice requires further investigation.<sup>31,32</sup> Because of the very promising results of PEG fusion with unmatched allografts, attention must also be paid to the procurement and handling of nerve. Because of the apparent lack of host rejection of these allografts, the possibility of using fresh cadaveric nerve tissue could be a possibility in the future. Studies have indicated that rat allograft segments can be maintained for up to 3 days and remain viable for PEG fusion.<sup>35</sup> Optimization of the procurement of allografts must be further characterized before PEG fusion allografting can be considered for clinical use.

### Conclusion

PEG fusion for PNI repair appears to be a promising new development to help address the current limitations in nerve repair and functional nerve recovery. Current methods of nerve repair inevitably result in Wallerian degeneration of distal axons segments and denervation of distal targets. Depending on the length of denervation, this can

result in irreversible muscle atrophy and fibrosis. These current methods rely on guided growth of proximal nerve outgrowths back to their initial nerve targets. This can be a long-healing process on the order of months to years, depending on the extent and location of nerve injury with complete recovery typically unattainable. In contrast, PEG fusion provides the possibility for return of function within minutes and a near complete recovery over the subsequent weeks to months. Immediately restoring the continuity of the nerve axonal membrane serves to bypass Wallerian degeneration, maintain innervation of distal targets, prevent irreversible muscle atrophy and allow for more complete functional recovery. The promising results from recent animal studies showing robust functional recovery with nerve allografting without graft rejection is an exciting development. Successful PEG fusion allografting would not only allow for rapid functional recovery, but provide surgeons with a versatile technique to span gaps with cadaveric nerve tissue and forgo morbidity associated with autografting. Further studies are needed to help translate PEG fusion into clinical use, but the possibility for more complete recovery for patients makes this investigation worthwhile.

#### Conflict of Interest

None declared.

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