Emerging Strategies on Adjuvant Therapies for Nerve Recovery

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Current strategies for promoting faster and more effective peripheral nerve healing have utilized a wide variety of techniques and approaches. Nerve grafts, conduits, and stem cell therapy all have their respective advantages. However, there are still some difficulties in attaining complete functional recovery with a single treatment modality. The utilization of adjuvant treatments, in combination with current standard-of-care methods, offers the potential to improve patient outcomes. This paper highlights the current landscape of adjuvant treatments for enhancing peripheral nerve repair and regeneration. *(J Hand Surg Am. 2018;43(4):368–373.* *Copyright © 2018 by the American Society for Surgery of the Hand. All rights reserved.)*

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PERIPHERAL NERVE INJURY

Every year, 20 million Americans suffer from peripheral nerve injuries that result in an average yearly cost of $150 million.[1] Injury to peripheral nerves occurs via a variety of mechanisms, most commonly lacerations, motor vehicle accidents, and crush injuries. Failure to repair these injuries in a timely fashion is characterized by paralysis, chronic pain, and neuropathies, resulting in severe disability and decreased quality of life.

Following the injury of a peripheral nerve, the distal stump undergoes Wallerian degeneration. Through this process, the axon and the myelin surrounding the distal stump undergo degeneration through a cellular cascade mediated via Ca^{2+} influx and calpain activation, followed by a clearing of cellular debris by macrophages and Schwann cells (Fig. 1).[2] Schwann cells that remain following the injury proliferate and contribute to regeneration.[2] Unfortunately, there are multiple barriers that prevent this physiological mechanism of regeneration from yielding an effective recovery. With a physiological regeneration rate of approximately 1 mm/d, a brachial plexus neurotmesis or axonotmesis injury leading to paralysis of the upper arm requires close to 2 years to fully regenerate the affected nerve.[3] In addition to the slow rate of regeneration, muscle atrophy arises from long-term denervation. Thus, full functional recovery of major nerve injuries in adults is uncommon.

Current repair techniques for bridging gap defects in nerves include tensionless epineurial suture repair, nerve grafts, nerve transfers, conduits, stem cells, small biological molecules, and other pharmaceuticals. However, each of these techniques has its own limitations and no method has yet proven to be completely effective at treating these injuries. Trauma of major nerves in adults that warrants nerve transfer rarely results in full functional recovery.[4] At present, we discuss current options for implementation of nerve grafts, conduits, stem cells, and U.S. Food and Drug Administration (FDA)–approved pharmaceuticals that have potential for facilitating peripheral nerve repair and regeneration (Fig. 2).

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NERVE GRAFTS

In patients with large nerve gap defects, autologous nerve grafts remain the gold standard for treatment. Nerve grafts offer the advantage of providing a physiological scaffold for Schwann cells and axon regeneration. Graft types include cable grafts and vascularized nerve grafts, some more effective than others. Sensory donor nerves are most commonly used, especially the sural nerve. Allografts can also be employed when insufficient donor nerve graft is available. Allografts also have the advantages of a greater supply of donor material, less invasive surgery for the patient, and elimination of a donor site. However, allografts do have potential for immune rejection. Current strategies to prevent the development of immune rejection include ABO blood typing and irradiation of grafts. Allografts have demonstrated the most success in sensory nerve recovery, whereas autografts have shown better efficacy in motor nerves.[5] Despite these successes for allograft, further research is warranted in this area to determine their clinical utility and use over autograft for peripheral nerve repair.

NERVE CONDUITS

Nerve conduits have been developed over the past 20 years as a treatment option for peripheral nerve injuries. Conduits range from veins to pseudosheaths to bioabsorbable tubes. Conduits function by forming a hollow tube around the injury site, which promotes a fibrin cable to form and fill with proliferating Schwann cells and capillaries. The requisite features for effective nerve conduits include low antigenicity, availability, and biodegradability. Conduits potentially offer advantages over grafts by minimizing the amount of surgery required and increasing the concentration of neurotrophic factors within the conduit. However, conduits are effective only for small nerve gaps.[6]

Vein grafts have been successful in treating nerve defects of less than 3 cm, showing sensory recovery by the imperfect Highet classification, although less robust than comparable autologous nerve grafts.[7] Biodegradable polyglycolic nerve tubes have also been used with some success in primate models and clinical trials to repair 3 cm nerve gap defects.[8]

STEM CELL THERAPY

Nerve grafts and conduits offer the potential for effective repair and regeneration of small nerve gaps. In contrast, stem cell therapy offers a potential solution for defects larger than effectively repairable by conduits alone. Replacing Schwann cells at the site of the injury currently offers the most promise in terms of regeneration. However, this method is constrained by the limited nerve tissue available for harvest.[9]

As such, researchers are exploring alternative cell sources (eg, embryonic, neural, induced pluripotent, and mesenchymal stem cells) to acquire the necessary number of Schwann cells. Neural stem cells have the additional effect of producing glial cell–derived neurotrophic factor and neurotrophin-3, important neurotrophic factors for nerve regeneration. Mesenchymal stem cells are also effective in this context with the added benefit of not conferring the additional risk of teratoma formation and nonspecific differentiation of stem cells.[9] The most common sources for mesenchymal cells have been bone marrow and adipose tissue. Further study is warranted to determine the most effective cell type, with the lowest patient risk, to implement following peripheral nerve injury.

PHARMACEUTICALS

A list of FDA-approved pharmaceuticals with the potential to serve as adjuvant therapies for nerve recovery is presented in Table 1 and discussed in the following sections.

Immunosuppressants

Tacrolimus: Tacrolimus (FK506) is indicated for the prevention of allograft rejection during organ transplantation. It functions by modulating the immune system via T-cell inhibition and binding FK proteins. Thus, FK506 and hyaluronic acid prevented scar formation and promoted neurite elongation following sciatic nerve transection and surgical repair in a rabbit model, suggesting improved peripheral nerve regeneration as a result of decreased scar tissue formation.[10]

Sirolimus: Sirolimus (rapamycin) has a mechanism of action similar to that of tacrolimus, with milder systemic toxicity but stronger anti-CD40L monoclonal antibody–induced tolerance. Subcutaneous injection of either tacrolimus or sirolimus improved functional recovery of murine tibial nerves, with tacrolimus found to be slightly better than sirolimus.[11]

Dexamethasone: Dexamethasone is currently used as an anti-inflammatory. Several studies have demonstrated the ability of this drug to minimize inflammation following peripheral nerve injury in an effort to enhance regeneration and repair. Intramuscular injections of dexamethasone in a rat sciatic nerve crush injury model led to improved gait, higher gastrocnemius muscle mass, reduced Wallerian degeneration, and enhanced regeneration of myelinated nerve.[12] The suggested mechanism was a reduction

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