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Review Article

The Role of Electrical Stimulation in Peripheral Nerve Regeneration: Current Evidence and Future Directions

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The role of electrical stimulation in peripheral nerve regeneration is reviewed, including a brief background and proposed mechanism of action. Studies in animal as well as human models are reviewed. Current recommendations and future directions are addressed.

Peripheral nerve injuries may lead to profound motor and sensory deficits, and even with surgical intervention, functional outcomes are often suboptimal. The mechanisms underlying limited recovery are multifactorial, including (1) impaired axonal growth across surgical coaptation sites as well as nerve gaps and grafts, (2) inadequate neurotrophic factors and supportive cell types such as Schwann cells in the microenvironment to promote axonal regeneration, (3) decreased regenerative potential of nerves following chronic axonotomy, and (4) irreversible motor end plate degeneration and atrophy of the target muscles. Over the past few decades, many research efforts have attempted to accelerate the rate of axonal regeneration. One such technique that has gained traction in recent years is direct electrical stimulation of peripheral nerves.

Brief History and Potential Mechanism of Action of Nerve Stimulation

Peripheral nerves communicate sensory and motor information bidirectionally between the spinal cord and the skin and muscles of the extremity. When a peripheral nerve injury occurs, the first sign of injury transmitted to the neuronal cell body is via the immediate influx of intra-axonal calcium that propagates proximally.[1] Subsequent signaling is mediated by the retrograde transport of various proteins, particularly neurotrophins and cytokines, from the site of axonal injury back to the cell body.[2] Together, these signals trigger neurons to switch to a regenerative phenotype, with notable changes in gene expression inducing a cascade of molecular changes that stimulate neurite outgrowth.

Early studies of direct electrical stimulation of nerves demonstrated an overall positive effect, with greater axon sprouting, more rapid muscle reinnervation, and faster functional recovery.[3,4] The underlying mechanisms have been attributed to the following: (1) enhanced specificity of axon guidance and accurate reinnervation of motor versus sensory targets, (2) axons crossing the surgical coaptation site more rapidly, with no change in speed of regenerating axon elongation, and (3) upregulation of key neurotrophic factors.[5–11] Of note, electrical stimulation seems to only jump-start axonal regeneration, as increasing the period of stimulation from a single hour to 2 weeks did not further improve outcomes; in fact, a longer duration of stimulation was detrimental for sensory neuron regeneration.[5,8] Furthermore, the benefits of electrical stimulation were eliminated with the use of sodium channel blockers, including tetrodotoxin and lidocaine, which may have implications for the intraoperative use of local anesthetics.[5,12]

Evidence in Human Studies of Peripheral Nerve Regeneration

To date, four randomized controlled trials have investigated brief electrical stimulation after surgical interventions in hand and upper extremity clinical applications (Table 1).[13–16] These studies

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Table 1
Randomized Controlled Trials Examining Electrical Stimulation of Peripheral Nerves With Hand and Upper Extremity Surgery

Study	Nerve and Clinical Application	Sample Size	Surgical Intervention	Follow-Up Duration	Electrodes	Stimulation Parameters	Electrodiagnostic Outcome Measures	Functional Outcome Measures	Anesthesia
Gordon et al[13]	Median nerve—carpal tunnel syndrome	21 patients (11 ES, 10 control)	Open carpal tunnel release	1 y	Postoperative ES via electrodes implanted intraoperatively	1 h, 20 Hz continuous train; stimulation intensity at tolerance limit (4-6 V, 0.1–0.8 ms pulse duration)	Significant increase in MUNE in ES patients compared with control. No differences in CMAP amplitude between groups.	No differences in Semmes-Weinstein monofilament test or subjective sensory improvement on Levine's CTS Questionnaire between groups.	Local anesthesia (1% lidocaine)
Wong et al[14]	Digital nerve, with complete transection	36 patients (18 ES, 18 control)	Direct nerve repair within 14 d of injury	6 mo	Postoperative ES via transcutaneous electrodes implanted intraoperatively	1 h, 20 Hz train of balanced biphasic pulses; stimulation intensity at tolerance limit (<30 V, 0.1–0.4 ms pulse duration)	N/A	Significant improvement in static 2-point discrimination, Semmes-Weinstein monofilament detection threshold, quantitative cold and warm detection threshold in ES patients compared to control. Significantly more ES patients achieving S4 sensation. No difference in DASH disability and work scores.	General anesthesia (no local anesthesia)
Power et al[15]	Ulnar nerve—cubital tunnel syndrome with muscle denervation	31 patients (20 ES, 11 control)	In situ ulnar nerve decompression ($n = 23$), submuscular transposition for ulnar nerve subluxation ($n = 8$)	3 y	Postoperative ES via transcutaneous electrodes implanted intraoperatively	1 h, 20 Hz train of balanced biphasic pulses; stimulation intensity at tolerance limit (<30 V, 0.1 ms pulse duration)	Significant increase in MUNE and amplitude of maximum CMAP in ES patients compared with control	Significant improvement in grip and key pinch strength, and McGowan-Goldberg grade in ES patients compared to control	General anesthesia (no local anesthesia)
Zhang et al[16]	Ulnar nerve—cubital tunnel syndrome with muscle denervation	176 patients (89 ES, 87 control)	In situ ulnar nerve decompression	6 mo	Intraoperative ES following decompression	15 min, alternative high- and low-frequency ES (100 mA, 2 Hz/15 Hz)	Significant improvement in MCV and CMAP in ES patients compared with control	Significant improvement in grip and key pinch strength, BMRC motor and sensory function recovery, and Lovett muscle strength grade in ES patients compared to control	General anesthesia

BMRC, British Medical Research Council; CMAP, compound muscle action potential; CTS, carpal tunnel syndrome; DASH, Disabilities of the Arm, Shoulder, and Hand; ES, electrical stimulation; MCV, motor conduction velocity; MUNE, motor unit number estimation.

examined carpal tunnel syndrome, cubital tunnel syndrome, and digital nerve transection in a total of 264 patients, with follow-up periods ranging from 6 months to 3 years. Despite its use across different clinical diagnoses and variations in electrical stimulation parameters, these clinical trials demonstrated generally positive effects on both motor and sensory examination as well as quantitative electrodiagnostic measures in patients receiving brief electrical stimulation compared with control.

The earliest human clinical trial focused on direct bipolar postoperative electrical stimulation of the median nerve after open carpal tunnel release.[13] Patients receiving electrical stimulation demonstrated a significant increase in the number of innervated motor units in the thenar musculature, as quantified by motor unit number estimation (MUNE), compared with controls. On the other hand, there was no difference in compound motor action potential (CMAP) amplitudes between groups, and both groups demonstrated rapid clinical improvements as measured by Semmes-Weinstein monofilament testing and Levine's Carpal Tunnel Syndrome questionnaire. These relatively modest effects of electrical stimulation may be in part due to study design; patients were recruited with a clinical diagnosis of carpal tunnel syndrome, but those with electrophysiological evidence of a conduction block across the carpal tunnel were excluded. Additionally, open carpal tunnel release was performed under local anesthesia. In animal studies, propagation of action potentials via sodium channels was necessary for electrical stimulation to show a benefit; hence, blockade of this signaling with local anesthetic may have affected the underlying mechanism of action and, subsequently, the observed functional outcomes.[5]

Two clinical trials have examined the ulnar nerve in the context of cubital tunnel syndrome accompanied by muscle denervation on electromyography.[15,16] Both studies showed significant improvements in electrodiagnostic measures with electrical stimulation, including MUNE, CMAP, and motor conduction velocity (MCV). Moreover, grip and key pinch strength improved significantly in patients receiving electrical stimulation. Interestingly, significant differences in these measures between groups were observed as soon as 1 month after surgery, and improvements continued to be observed even 3 years after surgery. Of note, the electrical stimulation parameters varied, particularly in a duration of 15 minutes versus 1 hour, suggesting that a shorter duration of intraoperative stimulation may be sufficient. Importantly, for both studies, procedures were performed under general anesthesia to avoid the potential mechanism limiting the effects of local or regional anesthesia on electrical stimulation.

Only one of these studies, focusing on digital nerve injury, explored complete nerve transection; this most closely resembles the nerve injury and repair experiments previously carried out in animal models.[14] Paralleling the data from animal studies, patients receiving electrical stimulation after digital nerve repair showed not only faster functional recovery over time but also superior improvement overall at the final follow-up compared with controls, as measured on testing of static two-point discrimination, Semmes-Weinstein monofilaments, and cold and warm detection thresholds. Impressively, recovery after electrical stimulation led to a near-normal sensation by 6 months after surgery.

Evidence in Animal Models of Nerve Gaps

No human studies have been published to date examining the use of electrical stimulation after reconstruction of a nerve gap. In rodent studies of nerve gap reconstruction, electrical stimulation increases the percentage of regenerating axons across the nerve gap by boosting axonal arborization while having no effect on regeneration speed or distance.[17] Electrical stimulation is beneficial, regardless of the method for nerve graft reconstruction, including autografts, isografts, hydrogel-filled silicone conduits, and chitosan scaffolds, and has been investigated in nerve gaps up to 20 mm in animals.[18–21] Functionally, improvements are observed after electrical stimulation in walking as quantified by the sciatic functional index and in electrodiagnostic measurements including CMAP and nerve conduction velocity.[18–20] Interestingly, one single session of electrical stimulation intraoperatively is sufficient for these benefits, and a second session added no further improvements.[21]

Current State and Future Directions

The therapeutic efficacy of brief electrical stimulation of peripheral nerves has not yet been definitively demonstrated. A multicenter, double-blind, randomized controlled trial is currently ongoing to further investigate the effects of electrical stimulation in a larger cohort of patients undergoing ulnar nerve release at the elbow (ClinicalTrials.gov ID NCT04662320) as well as several other clinical trials that will rapidly change this exciting field. Several clinical trials to date have yielded promising results, and this is supported by animal data elucidating potential mechanisms of action for its observed benefits. As such, many peripheral nerve surgeons advocate for the use of intraoperative electrical stimulation with a handheld nerve stimulator with alternating current. Typical stimulation parameters are a duration of 10 minutes, with a 2-mA current and pulse duration of 100 μs, delivered just proximal to the site of surgical nerve repair or decompression.

Even if clinical efficacy is established, two notable barriers exist to the widespread adoption of intraoperative electrical stimulation: cost and type of anesthesia. Increased costs associated with electrical stimulation are associated both with increased surgical time to deliver the stimulation, as well as with the cost of the handheld device itself. Fortunately, a number of recent animal studies have shown that electrical stimulation for 10 minutes is equivalent to older studies using 1 hour, which is more feasible for clinical translation.[10,11,22] The device itself may be cost-prohibitive if there is no other indication for its use in a specific clinical context, particularly in outpatient surgery centers. Of equal importance, many hand and peripheral nerve surgeries are performed under local or regional anesthesia. With basic science data suggesting that sodium channel blockers extinguish any beneficial effects, electrical stimulation may need to be limited for cases performed under general anesthesia.[5,12] In turn, the risks of general anesthesia must be carefully weighed against the potential benefits for nerve recovery.

Conflicts of Interest

No benefits in any form have been received or will be received related directly to this article.

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