



The potential of electrostimulation in supporting axonal regeneration in the therapy of peripheral nerve paresis

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ABSTRACT

Starting point: Peripheral nerve paresis is a consequence of axonal damage, which leads to muscle weakness, atrophy and functional disability. Nerve regeneration is a slow process influenced by age, location and type of lesion. The aim of this review article is to analyse the current possibilities of using electrical stimulation in the therapy of peripheral nerve paresis with a focus on its potential to influence axonal regeneration.

Methodology: The article is based on a narrative search of the professional literature (PubMed, Scopus, Web of Science) from 2000–2025. Experimental studies on animal models, clinical studies and review papers evaluating the effect of various types of electrical stimulation on peripheral nerve regeneration were included.

Discussion: Current electrical stimulation is mainly important in preventing muscle atrophy and maintaining muscle contractility, not in directly supporting axonal regeneration. In contrast, invasive electrostimulation applied perioperatively directly to the nerve activates intracellular signaling pathways, increases the expression of neurotrophic factors, and accelerates axonal regeneration. Electroacupuncture, as a miniinvasive method, combines neuromodulator effects with the possibility of outpatient application; studies, primarily in animal models, confirm its effect on Schwann cell proliferation, inhibition of apoptosis, and promotion of neuroplasticity.

Conclusion: Invasive electrostimulation and electroacupuncture appear to be the most promising approaches for targeted influence on peripheral nerve regeneration. Further research should be directed towards optimizing stimulation parameters and verifying long-term clinical outcomes, especially in the context of routine practice.

KEYWORDS

electrostimulation, electroacupuncture, peripheral nerve injury, nerve regeneration, Schwann cells, neurotrophic factors.

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1 INTRODUCTION

Peripheral paresis is the result of peripheral nerve damage. Clinically, it is manifested by the loss of active movement in the muscles innervated by this nerve and a change in the perception of movement. It is often directly related to more or less pronounced motor disability, which can negatively affect the quality of patients' life, especially in cases where the strength of the initial muscle is significantly reduced or completely disappeared¹. Direct injury to a peripheral nerve is often an accompanying adverse event in traumatic injury to the upper or lower extremities. Iatrogenic damage is no exception. Local ischemia, oppression or immune or metabolic processes can lead to indirect nerve injury. The ability of the axon to regenerate depends on the patient's age, the mechanism of injury and the site of injury². For example, in the case of digital nerve injury, the prognosis for regeneration is very good, whereas brachial plexus injury is usually functionally devastating³. Currently, the treatment options for peripheral paresis, or rather the restoration of active movement, are insufficient or unsatisfactory³. The first-line treatment is exercise therapy combined with electrical stimulation of palsy muscles.

The aim of the presented article is to point out the current possibilities of electrostimulation of denervated muscle and the perspective of damaged nerve stimulation with an emphasis on electroacupuncture.

1.1 Factors influencing the course of motor recovery

Complete functional recovery of paretic muscles after peripheral nerve injury is rare in clinical practice. Denervated muscles and sensory structures undergo progressive atrophic changes, leading to the replacement of muscle fibers by fibrous or adipose tissue^{4,5}. This process is multifactorial and includes, in particular:

- Prolonged axonal regeneration, which often exceeds the time during which the muscle is able to maintain its structural integrity. Even with regular application of electrostimulation, not all muscle fibers are preserved. This leads to their gradual atrophy and remodeling.
- Low number of regenerating axons that manage to grow to the insertion site in the muscle. This deficit is partially compensated by the ability of reinnervated motor units to expand up to fivefold, which can functionally replace 80% of the loss of motoneurons⁶.
- Non-specific targeting of regenerating axons, which may not always establish connections with the original muscle fibers. Despite the increased sensitivity of the denervated muscle to regenerating axons, so-called accidental reinsertion can occur, when the axon connects with fibers of another motor unit⁷. This phenomenon can lead to the phenomenon of synkinesis, typically observed, for example, in lesions of the facial nerve, when functionally different muscle groups are activated simultaneously.
- Reduced blood flow in denervated muscle, which negatively affects the metabolic environment and contributes to the progression of atrophy⁸.

Axonal injury not only affects the muscular system but also leads to complex changes at the central nervous system (CNS) level, including cortical reorganization⁹. After peripheral nerve injury, spinal motoneuron cells undergo apoptosis due to oxidative stress and increased expression of apoptosis-regulating genes, including the TNF receptor. However, glial cell-derived neurotrophic factor (GDNF), located in the vicinity of motoneuron cells, has been shown to prevent axotomy-induced motoneuron atrophy¹⁰. In response to the inflammatory reaction following peripheral nerve injury, microglia proliferate in the spinal cord. Nerve growth factor (NGF) plays an important role in the regeneration of damaged peripheral nerves. It is the first discovered and best described neurotrophic factor, known to have a critical protective role in the development and survival of sympathetic and cholinergic forebrain neurons¹¹ and plays a key role in peripheral nerve regeneration¹².

1.2 Neurophysiological context of axon regeneration

The classification of peripheral nerve lesions according to Seddon distinguishes three basic types of damage: neurapraxia, axonotmesis and neurotmesis. Neurapraxia represents the mildest form of conduction disorder, which does not require specific treatment and usually resolves spontaneously within a window of several hours to two weeks. In contrast, axonotmesis and neurotmesis are associated with a disruption of axonal continuity, which leads to Wallerian degeneration - a process in which the distal axon stump is fragmented and subsequently phagocytosis occurs by Schwann cells (SCs) and macrophages¹³⁻¹⁵.

Neurotmesis is further divided according to the extent of damage to the nerve sheaths (endoneurium, perineurium, epineurium)¹⁶. Partial regeneration may occur when the endoneurium is damaged, but lesions of the perineurium and epineurium usually require surgical revision. Surgery on the peripheral nerve is also performed in cases where conservative therapy is ineffective¹⁷. It was found that after direct nerve suturing, 42% of axons regenerated into the muscle, compared to only 25% when using an autograft¹⁸.

Axon regeneration is influenced by axonal transport and neurotrophic growth factors secreted by the SC after nerve injury. The rate of regeneration is theoretically 1-3 mm/day. However, clinical practice does not correspond to this and the rate depends on a number of factors. A realistic rate of 25 mm in 8-10 weeks can be assumed¹⁹. In the case of peripheral nerve suture, a latent period of 3-7 days must also be taken into account, during which axons pass through the surgical site²⁰⁻²². The neuronal response of the SC to injury is associated with the expression of neurotrophic factors, transcription factors, growth-stimulating substances, cell adhesion molecules (e.g. N-cadherin), extracellular matrix components, intracellular signaling enzymes and cytoskeletal cell surface regulatory proteins²³⁻²⁵. The greatest secretion of growth factors from the SC is reached on the 15th day after injury and returns to normal on the 35th day after injury²⁶. However, the ability of SCs to express growth factors gradually decreases over time, and continued denervation leads to atrophy and apoptosis of SCs²⁷. SC atrophy causes a delay in axonal growth²⁸. However, there is a possibility that growing axons can reactivate SCs, for example in the case of delayed neurosurgery²⁵.

Another factor contributing to the delayed axonal regeneration are the endothelial cells forming the blood-nerve barrier. Its disruption contributes to the delay of axonal regeneration²⁹. Last but not least, it may be the state of the endoneurial tube after the inflammatory reaction of macrophages. Long-term absence of axons endoneurially can lead to the collapse of the endoneurial space or to excessive formation of collagen fibers. These fibrotic changes cause thickening of the nerve sheaths, an increase in the content of collagen and connective tissue, which reduces their elasticity and leads to less effective axon sprouting³⁰.

1.3 Diagnosis of peripheral paresis

The current diagnosis of peripheral paresis is based on a combination of clinical examination, electrophysiological methods and imaging techniques. A comprehensive approach begins with a quality medical history and clinical examination by a physician, followed by a specific physiotherapeutic examination, including kinesiological analysis. This approach includes the assessment of muscle strength, range of motion, reflexes, sensory functions and is supplemented by specific functional tests. Part of the functional diagnosis of peripheral nerve lesions is the assessment of nerve mechanosensitivity³¹. A key part of the diagnosis is needle electromyography (EMG), which can detect even very small changes in the transmission of information from the peripheral nerve to the muscle. EMG is considered the gold standard for accurately determining the nature and localization of the nerve lesion. Surface electromyography can also be used as part of a comprehensive functional examination³². Imaging methods include, for example, ultrasound of peripheral nerves or magnetic resonance imaging, which allow the detection of compression, neuroma or changes after trauma.

2 EXISTING TREATMENT OPTIONS FOR PERIPHERAL PARESIS

The principles of clinical treatment after nerve damage have not changed in a broader context over the past 35 years, despite a significantly greater understanding of neuropathophysiology and corresponding clinical outcomes^{3,4}. In the case of complete lesions, when the macroscopic integrity of the nerve is impaired, surgical intervention is indicated, while partial or compressive lesions are usually treated conservatively - rehabilitation including electrical stimulation of denervated muscles. This therapy is rather supportive and tries to delay atrophic changes in the muscle, maintain its elasticity and thus movement in the joint. If reinnervation does not occur, it is important to find a compensatory mechanism.

The effect of electric current on tissue can cause a change in the membrane potential of nerve and muscle fibers, leading to their depolarization. If the depolarization exceeds a threshold value, an action potential is generated, which leads to the generation of a nerve impulse or muscle contraction in the case of a nerve fiber.

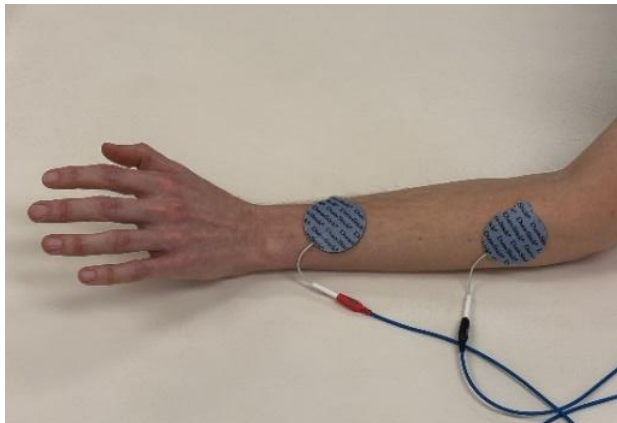
Historically, the effectiveness of electric current on muscle tissue was first described in the 18th century by Luigi Galvani, which laid the foundation for modern electrotherapy. One of the first pieces of evidence that low electric currents accelerate nerve regeneration after peripheral nerve injury was provided by Pomeranz et al.³³. The direct effect of electrical stimulation on peripheral nerve regeneration, especially on axonal growth, has so far been mainly observed in experimental studies on animal models and has not been clearly demonstrated in clinical practice. Current evidence suggests that short-term electrical stimulation can accelerate axonal growth and improve functional recovery, but its widespread use in clinical rehabilitation requires further research and standardization of protocols³⁴.

In recent decades, various types of currents have been used with respect to intensity, frequency, nature and localization of application. Electrostimulation can be divided into several categories according to the type of application.

2.1 Non-invasive forms of electrostimulation

2.1.1 Muscle electrostimulation

Selective electrostimulation of denervated muscle is a non-invasive therapeutic approach in which an electric current is applied through the skin. This term is also known as electrostimulation according to the I/t curve (intensity–time). This expresses the relationship between the intensity of the stimulation current and the pulse duration necessary to induce muscle contraction. This concept allows for targeted stimulation



Picture 1: Muscle electrostimulation

of muscle fibers with different degrees of innervation. In practice, oblique pulses with variable duration are used^{35,37,38}, since denervated muscles have a lower ability to accommodate. The parameters of excitability are monitored, in particular the contraction threshold, chronaxy and rheobase³⁵. The transmission of the stimulation signal occurs through the conductive layers of tissues – epidermis, dermis and subcutaneous tissue – to the target muscle tissue. It has been shown that the cathode has a greater stimulation potential³⁵⁻³⁷, which is why it is often placed above the motor point of the muscle (the area of the muscle in which the largest number of neuromuscular junctions are located). Point electrodes are used for small muscles, and area electrodes for larger muscles. Typical stimulation pulses for denervated muscles range in duration from a few hundred ms^{35,38}. In denervated muscles, it is necessary to apply longer pulses and higher intensity due to the reduced excitability of the tissue, while in healthy or partially reinnervated muscles, shorter pulses with lower intensity are sufficient³⁶. The intensity is chosen so as to achieve a visible contraction without excessive discomfort to the patient. (Picture 1)



Picture 2 Functional electrical stimulation of nervus peroneus to facilitate gait

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2.1.2 NMES (Neuromuscular Electrical Stimulation) and FES (Functional Electrical Stimulation)

NMES and FES are considered non-invasive forms of electrical stimulation but are not intended to stimulate completely denervated muscle in peripheral nerve paresis. However, they can be applied in cases of partial denervation or following at least partial reinnervation, when functional neuromuscular transmission has been restored. While FES is inherently focused on functional tasks and task-specific movements^{36,39}, such as grasping or dorsiflexion

during walking (see picture 2), NMES primarily aims to elicit muscle contraction to facilitate activation, strengthening or neuromuscular control.

2.2 Invasive forms of peripheral nerve electrostimulation

2.2.1 Perioperative invasive electrical stimulation

There are procedures in which stimulating electrodes are placed directly on the peripheral nerve, which requires surgical intervention. These procedures are temporary, applied directly to the nerve during or shortly after surgery in connection with surgical nerve reconstruction. Typical parameters of electrical stimulation used in studies^{34,40-44} are quite consistent: most often a frequency of 20 Hz, a pulse width of 0.1–1 ms, and an intensity in the range of 3–30 V (or around 2 mA) are applied. The duration of stimulation varies between 20 and 60 minutes, with the electrodes placed proximal to the site of nerve damage during or immediately after surgical reconstruction. This procedure is now considered a promising adjunct to neurosurgical operations.

2.2.2 Electroacupuncture

It represents a relatively innovative method in the treatment of peripheral paresis. It is a combination of classical acupuncture with electrostimulation. It can be considered a miniinvasive form of electrostimulation. Unlike invasive peripheral nerve stimulation, electrodes are not placed directly into the peripheral nerve. Electroacupuncture uses the introduction of thin needles into specific (acupuncture) points, thereby overcoming the high skin resistance, which is a certain limiting factor in transcutaneous electrostimulation methods. Thanks to this, the electric current is applied to deeper layers, which allows for more selective stimulation of target neuromuscular structures⁴⁵ (picture 3).



Picture 3: Electroacupuncture

Acupuncture pathways are considered energetic in traditional medicine. Their partial anatomical correlation with the course of peripheral nerves can be pointed out (e.g. nervus radialis – colon pathway, nervus peroneus profundus – stomach pathway, nervus peroneus superficialis – gallbladder pathway)⁴⁶.

2.3 Further insights into influencing peripheral nerve regeneration

Advances in treatment include the application of cell cultures (Schwann cells, mesenchymal cells, bone marrow cells) that produce growth factors to the site of nerve injury⁴⁷. However, conservative pharmacotherapy (B vitamins, methylcobalamin, exogenous neurotrophic factors) has been shown to be ineffective due to the low concentration of drugs at the site of nerve injury⁴⁸⁻⁵⁰.

3 METHODS

This review article is based on a narrative search of the scientific literature focused on the use of electrical stimulation in the therapy of peripheral nerve paresis. The search was conducted in the databases PubMed, Scopus and Web of Science from 2000 to 2025. The main included studies were experimental studies on animal models, clinical studies and review articles that dealt with the effect of different types of electrical stimulation on peripheral nerve regeneration. Studies were selected based on relevance to the topic, availability of full text and presence of measurable outcomes related to axon regeneration. In total, approximately 60 studies were analyzed, most of which focused on electroacupuncture and invasive electrical stimulation.

4 DISCUSSION

The direct effect of electrical stimulation in the area of damaged nerve on regeneration, or rather on axonal growth, has so far been mainly observed in experimental studies on animal models. Current evidence suggests that short-term electrical stimulation can accelerate axonal growth and improve functional recovery, but its widespread use in clinical rehabilitation requires further research and standardization of protocols ²⁵.

4.1 Potential of electrostimulation of denervated muscles

Although muscle electrical stimulation is widely used, its effect on axon regeneration itself remains controversial. The aim of this stimulation is to preserve the contractile ability of the muscle, slow its atrophy, and extend the time window for peripheral nerve reinnervation.

Application of NMES to partially reinnervated muscle may further contribute to improving muscle strength, increasing perfusion, and preserving muscle volume ⁵¹.

In functional electrical stimulation (FES), the effect of electrical stimulation is enhanced by stimulating the muscle during movement ⁴³. While systematic reviews demonstrate that FES supports motor learning and neuroplasticity mainly in patients with central nervous system lesions, in peripheral nerve paresis the primary benefit lies in functional movement facilitation and improvement of movement patterns rather than in direct induction of motor learning ⁵².

4.2 The potential of invasive electrical stimulation for peripheral nerve regeneration

Perioperative electrical stimulation has been shown to be an effective tool for promoting peripheral nerve regeneration ⁴⁰⁻⁴⁴. Direct postsurgical electrical stimulation has been shown to have a positive effect on axonal regeneration, as brief stimulation (typically 20 Hz for 20–60 min) applied immediately after nerve suturing activates intracellular signaling pathways (e.g., cAMP elevation) that promote growth factor expression and accelerate axonal regeneration. It also stimulates the SC, creating an optimal environment for remyelination and reinnervation of target muscles ⁴³. Clinical studies have shown that this method leads to faster recovery of sensory and motor functions compared to standard surgical reconstruction without stimulation, without significant adverse effects. This approach is therefore considered a promising adjunct to neurosurgical procedures to improve the functional outcome of peripheral nerve regeneration ^{40,43,44,53,54}.

The positive effect of electroacupuncture on axonal regeneration in combination with rehabilitation procedures has been repeatedly demonstrated in experimental studies on animal models ⁵⁵⁻⁵⁷. Electroacupuncture in patients with peripheral facial nerve palsy has led to a better prognosis of functional recovery compared to conventional methods ⁵⁸. The mechanisms of action include inhibition of neuronal apoptosis and reduction of the peripheral inflammatory response, which promotes nerve fiber regeneration and accelerates the recovery of muscle function ⁵⁹. Furthermore, it has been found that electroacupuncture stimulates the proliferation of Schwann cells, which play a key role in the process of remyelination and axonal growth ^{60,61}. The regenerative potential is mediated by the increased expression of neurotrophic factors, especially nerve growth factor (NGF), and other molecules that migrate towards the cathode ⁶². Another important mechanism is the influx of Ca^{2+} ions into the proximal end of the severed axon, which activates growth-promoting signaling pathways ⁶³. Placing the cathode distal to the lesion site accelerates regeneration, while its proximal position slows this process ⁶³. Electroacupuncture is more effective than classical acupuncture, not only in terms of peripheral regeneration, but also in its effect on the reorganization of the somatosensory cortex, which suggests its ability to support neuroplasticity of the central nervous system ⁶⁴⁻⁶⁶. The parameters used for electroacupuncture range from a frequency of 5–20 Hz, an intensity of 0.2–2 mA, a duration of one application of 15 minutes, with a frequency of 5–6 times a week for a period of 4 weeks to 4 months ^{57,62,65,66}.

Our current clinical experience and available evidence also point to the positive effect of electroacupuncture on accelerating the return of motor function. This method appears to be the most promising for the possibility of directly influencing nerve regeneration. The advantages of electroacupuncture include mini invasive and relatively simple application by an erudite physician. Its minimal invasive nature allows for safe and repeated outpatient application. We have not encountered any major complications or adverse effects while using this method. It can also be used for muscle electrostimulation.

4.3 Limits of current evidence

Although available experimental and clinical studies suggest the potential benefit of electrostimulation in promoting peripheral nerve regeneration, the current level of evidence has several significant limitations. Most published studies evaluating the direct effect of electrostimulation on axonal regeneration have been conducted in animal models. These results cannot be directly transferred to clinical practice. Another significant limitation is the considerable heterogeneity of the stimulation parameters used, including frequency, intensity and duration of application, which make it difficult to compare individual studies and formulate uniform recommendations. In the case of electroacupuncture, most of the available evidence is based on experimental studies or clinical studies with a limited number of patients and different methodologies. Although the results suggest a beneficial effect on peripheral nerve regeneration and functional recovery, there is still a lack of high-quality randomized controlled trials that would allow us to clearly determine its effectiveness and optimal therapeutic protocols.

5 CONCLUSIONS

Recent findings suggest that there is sufficient evidence to change the approach to the treatment of peripheral nerve palsy. Selective electrical stimulation of denervated muscle is of primary importance in maintaining muscle activity, preventing atrophy and extending the time window for reinnervation, but not in directly promoting axonal regeneration.

In contrast, invasive electrical stimulation appears to be a promising adjunct to surgical nerve reconstruction, as clinical studies confirm faster recovery of motor and sensory functions with minimal risk of adverse effects. Electroacupuncture represents another promising miniinvasive method that combines neuromodulatory effects with the possibility of outpatient application. Studies show that it not only accelerates the return of motor function, but also supports neuroplasticity of the central nervous system. Both methods – perioperative invasive stimulation and electroacupuncture – thus appear to be the most promising approaches for targeted influence on peripheral nerve regeneration, either directly within the surgical procedure or during subsequent rehabilitation. Further research should be directed towards optimizing stimulation parameters and verifying long-term functional results, especially in the context of clinical practice.

Zusammenfassung

Die Einleitung: die periphere Nervenparese sind eine Folge von Axonschädigungen, die zu Muskelschwäche, Atrophie und letztlich funktioneller Behinderung führen. Nervenregeneration ist ein langsamer Prozess, der durch Alter, Lokalisation und Art der Läsion beeinflusst wird. Das Ziel dieses Übersichtsartikels ist es, die aktuellen Möglichkeiten der Anwendung von Elektrostimulation bei der Behandlung der peripheren Nervenparese zu analysieren, mit Fokus auf ihr Potenzial zur axonalen Regeneration.

Die Methoden: der Artikel basiert auf einer narrativen Literaturübersicht (PubMed, Scopus, Web of Science) von 2000–2025. Experimentelle Studien mit Tiermodellen, klinische Studien und Übersichtsarbeiten, die die Wirkung verschiedener Arten von Elektrostimulation auf die Regeneration peripherer Nerven bewerten, wurden eingeschlossen.

Die Diskussion: die gegenwärtige Elektrostimulation ist besonders wichtig zur Verhinderung von Muskelatrophie und zur Aufrechterhaltung der Muskelkontraktilität, nicht zur direkten Unterstützung der axonalen Regeneration. Andererseits aktiviert invasive Elektrostimulation, die perioperativ direkt auf den Nerv angewendet wird, die intrazellulären Signalwege, erhöht die Expression neurotropher Faktoren und beschleunigt die axonale Regeneration. Die Elektroakupunktur als minimalinvasive Methode kombiniert neuromodulatorische Effekte mit der Möglichkeit ambulanter Anwendung; Studien hauptsächlich an Tiermodellen bestätigen ihre Wirkung auf die Schwann-Zellen, die Hemmung der Apoptose und die Förderung der Neuroplastizität.

Die Schlussfolgerung: invasive Elektrostimulation und Elektroakupunktur scheinen ein vielversprechender Ansatz zur gezielten Beeinflussung der peripheren Nervenregeneration zu sein. Weitere Forschung sollte darauf ausgerichtet werden, die Stimulationsparameter zu optimieren und langfristige klinische Ergebnisse zu überprüfen, insbesondere im Kontext der routinemäßigen Praxis.

Die Schlüsselwörter: Elektrostimulation, Elektroakupunktur, periphere Nervenverletzungen, Nervenregeneration, Schwann-Zellen, neurotrophe Faktoren.

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