Health, Sports & Rehabilitation Medicine
Vol. 21, no. 4, October-December 2020, 244–251

Peripheral nerve injury rehabilitation

Nadina-Liana Pop [1], Daniela-Rodica Mitrea [1], Andrada Elena Urdă-Cîmpean [2], Adriana Filip [1], Simona Clichici [1], Remus Orăsan [1]

[1] Department of Physiology, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Romania
[2] Department of Informatics and Biostatistics, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Romania

Abstract

Peripheral nerve injuries have a large impact on the patient's life quality. Depending on the localization and severity of the injury, patients may experience from moderate pain to severe muscle atrophy, sensitivity problems and impairment. Various treatments are used for the management of peripheral nerve injuries: drugs, physical therapy, electrical therapy, hydrotherapy, surgery. Physicians experience difficulties in successfully treating a peripheral nerve injury due to its different manifestations from one patient to another.

The current paper can become a useful tool for health care professionals to choose the most effective treatment for their patients by presenting the effects of presently used methods in peripheral nerve injury rehabilitation.

This paper is a review of some of the most common rehabilitation treatment strategies currently used for peripheral nerve injuries in which several studies were analysed to establish which of those methods have proven to be effective over time.

Physical therapy and occupational therapy should be used for all peripheral nerve injury patients. Electrical therapy, thermal therapy and hydrotherapy can be used for some patients but have inconsistent results and surgery is mostly the elective treatment for complete injuries.

Peripheral nerve injuries represent a complex medical problem and, although there are some treatment methods that have positive outcomes, the inconsistency regarding dosage and the treatment period and the lack of sufficient studies make recovery after peripheral nerve injuries a real challenge for physicians. More studies are required to fully understand why and also how some treatments have good results only on some patients and for establishing proper treatment protocols.

Keywords: peripheral nerve injuries, rehabilitation, function

Introduction

The most common causes of peripheral nerve injuries include trauma and nerve tumours. The consequences of a peripheral nerve injury depend on the localization, injury degree, patient's age and comorbidities and can vary from moderate to severe pain, sensibility disorder or motor function impairment to an important disturbance of the patient's daily activities and quality of life.

There are three major types of peripheral nerve injuries, according to Seddon's classification (developed in 1943), which investigated the severity of the nerve injury and the time required for recuperation (Seddon, 1943) (Table I).

The current gold standard treatment for peripheral nerve injuries is surgery - nerve autografting, the most used treatment method in these types of lesions. The success of the intervention depends on timing, ideally no more than 24-48 hours from the moment of injury. In many cases, surgery is not the best option for the patient: non-traumatic injuries, too much time elapsed from the moment of injury, or the patient's refusal of surgical intervention (Chen et al., 2007). Unfortunately, nerve autografting presents some disadvantages: limited availability of donor tissue, secondary deformities, potential differences in tissue structure and size, numbness at donor sites. Therefore, the functional results of peripheral nerve repair remain unsatisfactory especially because the development of nerve across large gaps needs a nerve graft to correctly connect the proximal and distal nerve stumps (Shen et al., 2013). The conservative treatment for peripheral nerve injuries consisting of physical therapy and medication should be aimed at all the patient's symptoms and may improve the patient's quality of life and degree of independence.

The present study synthesizes the benefits of different peripheral nerve injury rehabilitation methods that are currently used. Unfortunately, complete rehabilitation or

Received: 2020, October 10; *Accepted for publication:* 2020, October 16
Address for correspondence: Department of Physiology, "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, 1-3 Clinicilor Street, PC 400006, Cluj-Napoca, Romania
E-mail: popnadina@yahoo.com
Corresponding author: Nadina-Liana Pop, popnadina@yahoo.com
https://doi.org/10.26659/pm3.2020.21.4.244

Table I
Types of peripheral nerve injuries (according to Seddon HJ, 1943).

Peripheral nerve injury type	Characteristics
Neurapraxia	- peripheral degeneration does not occur - conserved myelin or axon integrity - fast recovery (from days to a few weeks)
Axonotmesis	- preserved epineurium and other supporting nerve structures (but with complete peripheral degeneration) - recovery starts from the proximal part of the nerve innervation area with good results
Neurotmesis	- complete nerve transection - important damage to all essential nerve structures - fibrous tissue development at the site of injury - difficult recovery (from months to years)

relief of pain is hardly achieved for these patients, and they struggle with severe chronic pain alongside other symptoms that profoundly affect patients' quality of life.

The research was based on analysing recent studies or treatment methods confirmed over time (from 1943 to 2020) that are commonly used in rehabilitation programmes for peripheral nerve injuries. Most analysed studies were experimental model studies because we wanted to observe functional recovery, molecular changes and effects of the rehabilitation treatment techniques. In this way, understanding the cellular changes, the treatment methods used can properly assess peripheral nerve injury symptoms and can enhance the motor function of the affected segment.

Fundamental concepts

When a peripheral nerve, distal to the lesion site, is injured, the trunk calcium-dependent proteases are activated in the axon, which causes rapid loss of Schwann cell myelin sheath and distal axon disintegration, the remaining myelin and parts of the axon being removed by macrophages (Dahlin, 2008).

After the nerve fibre injury, intracellular signal pathways are initiated to control factors that put the neuron and Schwann cells into a regenerative state or into apoptosis. In Schwann cells, near the transection site, the extracellular signal regulated kinase-1/2 (Erk 1/2) is phosphorylated, and, within a couple of days after injury, the activating transcription factor 3 (ATF3) is expressed, leading to the outgrowth of the axon (Dahlin, 2008).

A minor axon defect can be healed by the extension of Schwann cells that proliferate and migrate toward the lesion area, but as more time passes from the moment of injury, it appears that Schwann cells lose their ability to produce the necessary factors for axonal outgrowth. Expression of c-erbB receptors, glial cell-line derived neurotrophic factor (gDNF) and ATF 3 is inhibited in the chronically denervated nerve ends. The same transformations occur in the Schwann cells close to the site of transection. Signals induced by the transection of the axon are transferred up to the nerve cell body within seconds to minutes and continue to be transferred for hours, days or weeks after the injury (Dahlin, 2008).

Axonal transport is a retrograde transport that transfers information from the site of injury. The signals that are transported include factors produced in the axoplasm at the site of injury or chemicals released from cells in the interstice and taken up at the site of injury. Some studies revealed that substances connected to specific nuclear localisation may be activated or conformationally modified and represent positive signals, crucial for the transmission by retrograde transport. These retrograde signals, activated and necessary for transcription in the nucleus, are part of the mechanisms activated in neurons as a stress response, to initiate the nerve regeneration. The signal transduction pathways are still incompletely understood. The loss of information normally transported with retrograde transport is considered to be the "negative signal". Within hours to days after injury, these positive and negative signals reach the cell body.

In the next phase, other positive signals that originate from the surroundings of the formed growth cone or those released by the cells at the lesion site intervene and initiate gene expression in the nucleus of the cell, which has still unknown specific functions. In the final phase, especially when reinnervation of the damaged nerve occurs, signals from the outgrowing axons could be generated suggesting that direct outgrowth of axons may be finalized. During time, there is a spontaneous down-regulation in neurons, such as the transcription factor ATF3, which can explain impaired regeneration when there is a delayed nerve repair. It appears that the reaction of motor and sensory neurons after injury is different regarding regeneration-associated factors and apoptosis: up to 40% of sensory neurons in dorsal root ganglia may die if a nerve injury is not repaired compared to motor neurons, but cell death can be diminished if nerve repair is performed early (Dahlin, 2008).

When the nerve injury is treated by surgery, axon grows from the proximal nerve segment into the distal nerve segment and a growth cone is formed at the end of the transected axon. Finger-like processes –filopodia, attached to the growth cones, palpate the environment to find the best growth direction. In the gap between the proximal and distal nerve segments, an inflammatory response occurs and a fibrin matrix filled with macrophages and other chemicals is formed. Schwann cells can migrate from both ends where the migration of such cells takes part in concert with the outgrowing axons (Dahlin, 2008).

Motor deficit associated with muscle hypotrophy/atrophy causes dysfunctions of the altered anatomic segment. In this case, at the neuromuscular junction,

pathological mechanisms occur, which can persist even after reinnervation and may affect complex and fine movements, representing the most challenging element from the point of view of rehabilitation. Functional disability represents another consequence of the lack of peripheral stimulation with synaptic modifications in the sensitive cortex that appear shortly after the peripheral nerve injury. Therefore, the aim of rehabilitation is to reduce motor deficit and maintain the involved muscle length in order to prevent muscle stiffness and hamstring retraction. The rehabilitation programme also contains different techniques (visual and audio-tactile) that facilitate the ability of the brain to maintain the connection between the sensitive cortex and the peripheral nervous system (Roghani et al., 2012).

Different rehabilitation methods

a) *Physical exercise*

Regardless of the presence or absence of motor deficit, a physical exercise programme is recommended, due to its preventive role because pain and sensibility disorders can lead the patient to "protect" the affected limb and use it less frequently, which will determine the onset of motor deficit. Usually, stretching exercises, aerobic activity, exercises that enhance flexibility, balance and muscle force, exercises that improve proprioception and gait and reduce the risk of fall are recommended.

There are some commonly used methods of kinetic therapy in peripheral nerve damage, presented in Table II (Suszyński et al., 2015).

Treadmill walking/running may have positive effects on peripheral nerve injuries. One study published in 2009 concluded that one hour of treadmill running during the first two weeks (5 days/week) following sciatic nerve transection and direct repair in mice increases the number of regenerated motoneurons, which could still be observed in high numbers by the end of the four-week experiment. Treadmill exercise also enhances functional outcome by preventing misrouting of the regenerating sciatic nerve motoneurons (English et al., 2009; de Ruiter et al., 2008).

In an experimental model on rats, after sciatic nerve transection and direct repair, treadmill walking exercise (5 m/min) during a four-week period increases the density and number of myelinated nerve fibres in the tibial nerve. When treadmill exercise is combined with acute electrical stimulation (a single one-hour session immediately after the nerve injury) it induces faster and enhanced muscle reinnervation and, in this way, improves functional outcome (Asensio-Pinilla et al., 2009). In other studies, treadmill exercise has been shown to decrease the levels of pro-inflammatory cytokines in diabetic humans (Dekker et al., 2007; Balducci et al., 2010) and rats (Teixeira de Lemos et al., 2009), but the exact mechanism of this effect is not yet elucidated.

Passive mobilization is recommended for patients with severe peripheral nerve injury with the purpose of maintaining joint range of motion and muscle strength and it can be replaced by *assisted mobilization* if patients recover from total paralysis. Passive mobilization, initiated the immediate day after injury, was demonstrated, as early as 1989, to stimulate axonal regeneration, improve end-plate structure and reinnervation (Pachter & Eberstein, 1989).

Passive cycling during the first four weeks after sciatic nerve neurotmesis and end-to-end repair promoted the regeneration of sciatic motoneurons and muscle reinnervation of rat hind leg muscles, with effects on M-wave amplitude and latency and the magnitude of the electrically-elicited H-reflex that are comparable in magnitude to that of treadmill exercise (Udina et al., 2011).

Tofthagen et al. evaluated the results of strength and balance training for adults with chemotherapy-induced peripheral neuropathy and high risk of fall. The authors showed that aerobic and strength and balance exercises can reduce neuropathic symptoms, which increases quality of life by enhancing the blood, the oxygen and glucose supply to the mitochondria, generating less frequent neuropathic symptoms and increased strength and balance (Tofthagen et al., 2012).

Other studies observed the connection between exercise and brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family of growth factors, related to the nerve growth factor (NGF). Several studies demonstrated that exercise training elevates BDNF expression in the central nervous system (Gomez-Pinilla et al., 2012;

Table II

Kinetotherapeutic techniques for peripheral nerve injuries (adapted from an original review by Suszyński et al., 2015).

Technique name	Method/principle	Effects
Jacobsen (Jacobsen & Edinger-1982)	points of strong pressure applied around the coil and nerve plexus	- eliminates venous stasis
Neuromuscular re-education (Brunnström & Mauritz-1993)	muscle synergy usage	- control of voluntary movements
Bobath (Brunnström & Mauritz-1993)	key point manipulation using supporting techniques	- restores muscle tone and proprioceptive sensation - normal movement patterns
Rood (Brunnström & Mauritz-1993)	successive patterns of movement using exteroceptive stimulation	- neuromuscular re-education
Proprioceptive neuromuscular facilitation (Lustig et al.-1992)	activation of nervous system receptors and movement, using nervous system plasticity	- proprioceptive neuromuscular facilitation
Vojta (Brunström & Mauritz-1993)	reflex exercises	- reflex activation of innate motor patterns reception areas

Rothman et al., 2012) and skeletal muscles (Gomez-Pinilla et al., 2012). BDNF seems to have an important role in the regeneration of injured peripheral axons (Wilhelm et al., 2012) and exercise is able to increase BDNF expression in affected motor (but not sensory) neurons (Keeler et al., 2012). Cobianchi et al. (2013) demonstrated that aerobic exercise training reduced the levels of BDNF in the dorsal root ganglion and reduced neuropathic pain in rats with peripheral nerve injury. Aerobic exercise was presented by Detloff et al. as a factor that can normalize the spinal levels of glial cell-derived neurotrophic factor (GDNF), which can prevent the excessive sprouting of pain afferents and may reduce tactile allodynia in rats following spinal cord injury (Detloff et al., 2014).

b) *Aquatic exercise*

In an experimental model performed in rats with induced sciatic peripheral nerve injury, Kuphal et al. applied a 25-day hydrokinetotherapy and swimming programme with positive effects in reducing the intensity of neuropathic pain (Kuphal et al., 2007). In another study, swimming exercise accelerated nerve regeneration and synaptic elimination after axonotmesis and resulted in a larger axon diameter in animals that were put to swim after nerve injury, compared to the no swim group (Teodori et al., 2011).

Liao et al. (2017) investigated the effects of various swimming exercise methods on nerve regeneration in a rat sciatic nerve transection model and presented the beneficial effects of moderate swimming rehabilitation therapy (10 or 20 minutes/3 times/week) in the improvement of an acute nerve injury.

It seems that aquatic exercise consisting of different swimming exercise methods can stimulate peripheral nerve regeneration after injury. However, there are insufficient data to establish an aquatic exercise programme protocol regarding the duration of swimming sessions, the number of sessions/week, the total duration of the programme that can be applied to all patients suffering from peripheral nerve injury.

c) *Transcutaneous nerve stimulation (TENS)*

Transcutaneous nerve stimulation (TENS) is a frequently used, well tolerated procedure, which appears to reduce neuropathic pain by activating the central mechanisms. Low-frequency TENS stimulates K-opioid receptors in the spinal cord and brainstem, and high-frequency TENS activates C-opioid receptors. The European Federation of Neurological Societies published a guideline about the use of therapeutic electrical neurostimulation techniques in chronic neuropathic pain, which suggests that the success of TENS application depends on the intensity, frequency, duration and number of sessions (Akyuz & Kenis, 2014).

A complex study published in 2018 by Su et al. presented the effects of TENS application after experimental sciatic nerve injury and showed that immediate high-frequency electrical stimulation significantly improved motor function and increased nerve myelination, but caused a predisposition to neuropathic pain. High-frequency electrical stimulation causes a higher expression of inflammatory response in the dorsal root ganglion and brain, increases evoked potential in the somatosensory cortex and increases expression of synaptophysin, TNF-α and NGF in dorsal root ganglion cell culture. It also seems that TENS effectively decreased chronic neuropathic pain originated from median nerve injury in a rat experimental model (Lee & Song, 2013).

In a 2017 Cochrane Database Syst Rev, the authors evaluated 15 studies on TENS role in the management of neuropathic pain in adults, with a total of 724 human participants (Gibson et al., 2017). They found a wide range of treatment protocols in terms of duration of care, application times and intensity, which prevented them from elaborating a synthesis from this point of view. The authors recommend future TENS studies which can reduce the uncertainty relating to the effectiveness of this treatment modality (Gibson et al., 2017).

TENS seems to have a positive effect on pain management for peripheral nerve injuries. However, the lack of data regarding the effects of TENS treatment on peripheral nerve injuries results in low quality evidence and a low level of confidence in this procedure, and future studies are required in order to change this result.

d) *Low-level laser therapy*

Laser biostimulation has a positive outcome on neuropathic pain because it appears to decrease the hypoxia level induced by 1-α factor, which reduces inflammation (Akyuz et al., 2014). Several studies were analysed regarding the effects of low-level laser (LLL) therapy on peripheral nerve injuries, presented in Table III (Shen et al., 2013; Rosso et al., 2017; Suszyński et al., 2015).

LLL therapy seems a viable treatment for peripheral nerve injuries, reducing inflammation and pain level, and may have a role in nerve regeneration. However, the authors who studied this subject applied LLL therapy in various ways, from different intensities to a different number of irradiation points and applications per day, and different treatment periods. Despite all recent findings, there is still no consolidation of the LLL therapy application protocols, and more studies are needed.

e) *Therapeutic ultrasound*

Lowdon et al. studied the effects of continuous ultrasound irradiation on an experimental model of tibial nerve in rats following a compression lesion and demonstrated that the velocity of conduction recovered significantly earlier with the intensity of 0.5 W/cm² and significantly later with the intensity of 1 W/cm², concluding that low intensity therapeutic ultrasound can speed nerve regeneration, but a high intensity irradiation can delay it (Lowdon et al., 1988).

Raso et al. (2005) studied in rats the effects of ultrasound therapy on sciatic nerve regeneration after a controlled crush injury and found that pulsed ultrasound irradiation (0.4 W/cm², 2 minutes duration) ameliorates the sciatic functional index (SFI) and increases nerve fibre density. Chen et al. (2015) showed (in a peripheral nerve injury in rats) that 1 W/cm² application may decrease thermal and mechanical sensitivity and can stimulate tumour necrosis factor-α, substance P and interleukin-6.

Daeschler et al. investigated the therapeutic effects of ultrasound and shock wave therapies on motor nerve regeneration and concluded that ultrasound significantly increases nerve conduction, axonal regeneration with

Table III
Low-level laser therapy effects on peripheral nerve injuries.

Study	Experiment type/details	LLL treatment protocol	Effects
Shen et al., 2013	- 15 mm sciatic nerve transection in rats repaired with a biodegradable genipin-crosslinked gelatin nerve conduit annexed using beta-tricalcium phosphate (TCP) ceramic particles (genipin-gelatin-TCP, GGT)	2 min, daily, 10 consecutive days	- significantlly improved walking track analysis (SFI) and compound muscle action potential (CMAP)
Suszyński et al., 2015	- several studies analysed		- facilitating nerve conduction (by increasing ATP formation) - improved microcirculation, nutrition and regeneration of nerve cells - increased endorphin release and concentration of neurotransmitters in the synapses - analgesic effect
Rosso et al., 2017	sciatic nerve injury in rats surgically repaired	gallium-aluminium-arsenide laser (GaAlAs) at three different points in the surgical area (immediately after surgery and followed for 5 weeks with 3 applications/ week)	- anti-inflammatory, anti-oedematous effects - decreased analgesia - positive outcome on morphological and functional recovery of the nervous system

Table IV
ESWT effects in peripheral nerve injuries.

Study	ESWT characteristics	Effects
sciatic nerve injury with surgical repair (Hausner et al., 2012)	300 impulses of 3 Hz immediately after nerve grafting	- significant improvement of functional recovery (increased number of myelinated nerve fibres, well-myelinated regenerating axons, axonal regeneration activation, accelerated Wallerian degeneration)
crushed sciatic nerve injury in rats (Lee & Cho, 2013)	ESWT applied at a dose of 300 impulses at a frequency of 3 Hz and energy flux density of 0.09 mJ/mm^2, daily for 14 days	- improved neural function recovery - prevention of denervation atrophy
crushed sciatic nerve injury in rats (Lee & Kim, 2015)	- ESWT applied at 3 Hz frequency, an energy flux density of 0.09 mJ/mm^2, at 300 impulses, daily, for 21 days - dosage of neurotrophin-3 expression in the spinal cord (important for neuronal development and survival, synaptic functions and neuroplasticity) - SFI evaluation	- stimulation of nerve - regeneration - increased functional activity and NT-3 expression - neuro-reorganization - redistribution
sciatic nerve crush injury in rats (Daeschler et al., 2018)	300 impulses at 3 Hz frequency and 0.09-0.1 mJ/mm^2 energy, right after the injury or six/ten times during 14 days post-injury	- improved motor function - significantly increased number of myelinated nerve fibres (three weeks after surgery) - increased nerve conduction velocity (three months after surgery in some animals) - increased proliferation rate and expression of regenerative phenotype-associated markers (glial fibrillary acidic protein in Schwann cells)

thicker myelin and improves motor function on the sciatic functional index scale (Daeschler et al., 2018). LLL therapy seems to have better effects on healing processes compared with those of therapeutic ultrasound in an experimental sciatic nerve injury model by Oliveira et al., 2012.

Our conclusion is that therapeutic ultrasound has a positive effect on regeneration after peripheral nerve injury, but the effect is dose-dependent and has a large variation interval. Therefore, more studies are necessary in order to clearly establish the constant dose and treatment period for achieving maximum benefits.

f) *Extracorporeal shock wave therapy*

Low energy extracorporeal shock wave therapy (ESWT), widely used for osteoarticular pain, is currently investigated in different nervous system conditions.

Several experimental studies (sciatic nerve injury in rats), were analysed regarding ESWT treatment in peripheral nerve injuries (Table IV).

It appears that ESWT has positive effects on injured nerve regeneration, with a significant improvement of functional recovery (Hausner et al., 2012), prevention of denervation atrophy (Lee & Cho, 2013), increased functional activity and neurotrophic factor neurotrophin-3 (NT-3) expression, with effects on neuro-reorganization and redistribution (Lee & Kim, 2015) and an increased proliferation rate and expression of regenerative phenotype-associated markers such as glial fibrillary acidic protein in Schwann cells (Daeschler et al., 2018).

Our opinion is that extracorporeal shock wave can be used as an efficient treatment for peripheral nerve injuries. Research regarding the effects of ESWT on peripheral nerve injuries is at the beginning and therefore, a conclusion cannot be formulated because more studies are needed in order to establish the constant treatment dose and the application period.

Psychological impact

An important aspect of peripheral nerve injuries is the psychological impact that can manifest through insomnia, anxiety, depression and overall, a decreased quality of life. Studies demonstrated that disregarding the psychological problems caused by peripheral nerve injuries can lead to the emergence of chronic cortical pain and the reduction of brain plasticity of the hippocampus. To prevent this, different cognitive rehabilitation techniques can be used (Novak et al., 2011; Kodama et al., 2011).

Peripheral nerve injuries can have different effects in different patients, even when they suffer from the same nerve damage. Patients describe the impact of a peripheral nerve injury from moderate and temporary to significant and life changing, depending on the severity and location of the injury and patient-specific factors. The quality of life for these patients is substantially reduced, around 25% of patients are still out of the workforce 1.5 years after surgery (Davis et al., 2011). Peripheral nerve injury induces in most patients loss of function of the affected limb, persistent pain, hyperesthesia, hyperalgesia, or allodynia. To ameliorate all these symptoms, rehabilitation following peripheral nerve injury is essential (Ewald & Beckmann-Fries, 2017).

Boada et al. hypothesized that persistent activation of peripheral nociceptors after an injury could develop a chronic pain state that impairs attention-related behaviour and could induce changes in peripheral neuron phenotypes. Experiments performed on rats with partial L5 spinal nerve ligation presented impaired attentional performance, produced by persistent hypersensitive nociceptors (decreased threshold, increased activity to a given stimulus, spontaneous activity). Persistent nociceptive activation causes a re-emergence of impairment in the attention-related task associated with electrophysiological abnormalities in peripheral nociceptors, consistent with the development of chronic pain characterized by cognitive impairment (Boada et al., 2020).

The psychological impact of peripheral nerve injury should not be ignored by the patient or by the physician, because it can profoundly affect patients' quality of life, causing severe disabilities.

Conclusions

1. Peripheral nerve injuries can develop into a debilitating condition if treatment is not initiated shortly after the injury occurrence, preferably within the first 24 hours. After a peripheral nerve injury, the rehabilitation treatment plays a major role in the patient's quality of life and enhances the effects of surgery and/or pharmacological treatment.

2. As analysed above, several treatment methods are used in order to properly assess the symptoms of a peripheral nerve injury. Most of these methods have positive effects regarding functional recovery and pain management. However, the analysed studies contain different treatment dosages, different treatment periods and therefore it is difficult to formulate a precise conclusion about the treatment methods mentioned above. Unfortunately, this inconsistent evidence with a low to moderate level of confidence puts the physician in the situation of recommending and applying these methods mostly based on a personal decision depending on the characteristics of each case.

3. As a conclusion, there is currently no well-established and accepted rehabilitation protocol for peripheral nerve injuries, and the treatment methods and procedures are left to the physician's choice. Therefore, more research and studies are needed in this domain in order to find the most adequate treatment protocol.

Abbreviations

ATF3 - activating transcription factor 3; BDNF - brain-derived neurotrophic factor, Erk ½ - extracellular-signal regulated kinase-1/2; ESWT - extracorporeal shock wave therapy; gDNF - glial cell-line derived neurotrophic factor; LLLT - low level laser therapy; NGF - nerve growth factor; SFI - sciatic functional index; TENS - transcutaneous nerve stimulation; TNF-α - tumour necrosis factor alpha

Conflicts of interests

None declared.

Acknowledgments

The present article represents the partial results of the first author's PhD thesis, research which is in progress at *Iuliu Haţieganu* University of Medicine and Pharmacy in Cluj-Napoca.

References

Akyuz G, Kenis O. Physical Therapy modalities and rehabilitation techniques in the management of neuropathic pain. Am J Phys Med Rehabil 2014;93(3):253-259. doi: 10.1097/PHM.0000000000000037.

Asensio-Pinilla E, Udina E, Jaramillo J, Navarro X. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. Exp Neurol 2009;219(1):258-265. doi: 10.1016/j.expneurol.2009.05.034.

Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, Fallucca S, Alessi E, Letizia C, Jimenez A, Fallucca F, Pugliese G. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight

loss. Nutr Metab Cardiovasc Dis. 2010; 20(8):608-617. doi: 10.1016/j.numecd.2009.04.015.

Boada MD, Ririe DG, Martin CW, Martin SJ , Kim SA , Eisenach JC , Martin TJ . Nociceptive input after peripheral nerve injury results in cognitive impairment and alterations in primary afferent physiology in rats. Pain. 2020;161(5):960-969. doi: 10.1097/j.pain.0000000000001782.

Chen YW, Tzeng JI, Huang PC, Hung C-H, Shao D-Zi, Wang J-J. Therapeutic ultrasound suppresses neuropathic pain and upregulation of substance P and neurokinin-1 receptor in rats after peripheral nerve injury. Ultrasound Med Biol. 2015;41(1):143-150. doi: 10.1016/j.ultrasmedbio.2014.07.022.

Chen ZL, Yu WM, Strickland S. Peripheral regeneration. Annu Rev Neurosci. 2007;30:209-233. doi: 10.1146/annurev.neuro.30.051606.094337.

Cobianchi S, Casals-Diaz L, Jaramillo J. Navarro X. Differential effects of activity dependent treatments on axonal regeneration and neuropathic pain after peripheral nerve injury. Exp Neurol 2013;240:157-167. doi: 10.1016/j.expneurol.2012.11.023.

Daeschler SC, Harhaus L, Schoenle P, Boecker A, Kneser U, Bergmeister KD. Ultrasound and shock-wave stimulation to promote axonal regeneration following nerve surgery: a systematic review and meta-analysis of preclinical studies. Sci Reports. 2018;8(1):1-9. DOI: 10.1038/s41598-018-21540-5.

Dahlin LB. Techniques of peripheral nerve repair. Scand J Surg. 2008;97(4):310-316. doi: 10.1177/145749690809700407.

Davis K, Taylor K, Anastakis K. Nerve injury triggers changes in the brain. Neuroscientist. 2011;17(4):407-422. doi: 10.1177/1073858410389185.

de Ruiter GC, Malessy MJ, Alaid AO et al. Misdirection of regenerating motor axons after nerve injury and repair in the rat sciatic nerve model. Exp Neurol. 2008;211(2):339-350. doi: 10.1016/j.expneurol.2007.12.023.

Dekker MJ, Lee S, Hudson R, Kilpatrick K, Graham TE, Ross R, Robinson LE. An exercise intervention without weight loss decreases circulating interleukin-6 in lean and obese men with and without type 2 diabetes mellitus. Metabolism 2007;56(3):332-338. doi: 10.1016/j.metabol.2006.10.015.

Detloff MR, Smith EJ, Molina DQ, Ganzer PD, Houlé JD. Acute exercise prevents the development of neuropathic pain and the sprouting of non-peptidergic (GDNF- and artemin-responsive) c-fibers after spinal cord injury. Exp Neurol. 2014;255:38-48. doi: 10.1016/j.expneurol.2014.02.013.

English AW, Cucoranu D, Mulligan A, Sabatier M. Treadmill training enhances axon regeneration in injured mouse peripheral nerves without increased loss of topographic specificity. J Comp Neurol. 2009;517(2):245-255. doi: 10.1002/cne.22149.

Ewald SG, Beckmann-Fries V. Rehabilitation Following Peripheral Nerve Injury. In: Assmus H., Antoniadis G. Haastert-Talini K. Modern Concepts of Peripheral Nerve Repair. Ed. Springer, 2017, 109-125.

Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. Cochrane Database Syst Rev. 2017;9(9):7-63.(CD011976). doi: 10.1002/14651858.CD011976.pub2.

Gomez-Pinilla F, Ying Z, Zhuang Y. Brain and spinal cord interaction: protective effects of exercise prior to spinal cord injury. PLoS One 2012;7(2):e32298. doi: 10.1371/journal.pone.0032298.

Hausner T, Pajer K, Halat G, Hopf R, Schmidhammer R, Redl H, Nógrádi A. Improved rate of peripheral nerve regeneration induced by extracorporeal shock wave treatment in the rat. Exp Neurol. 2012;236(2):363-370. doi: 10.1016/j.expneurol.2012.04.019.

Keeler BE, Liu G, Siegfried RN. Acute and prolonged hindlimb exercise elicits different gene expression in motoneurons than sensory neurons after spinal cord injury. Brain Res. 2012;1438:8-21. doi: 10.1016/j.brainres.2011.12.015.

Kodama D, Ono H, Tanabe M. Increased hippocampal glycine uptake and cognitive dysfunction after peripheral nerve injury. Pain. 2011;152(4):809-817. doi: 10.1016/j.pain.2010.12.029.

Kuphal KE, Fibuch EE, Taylor BK. Extended swimming exercise reduces inflammatory and peripheral neuropathic pain in rodents. J Pain 2007;8(12):989-997. doi: 10.1016/j.jpain.2007.08.001.

Lee JH, Cho SH. Effect of extracorporeal shock wave therapy on denervation atrophy and function caused by sciatic nerve injury. J Phys Ther Sci. 2013; 25(9):1067-1069. doi: 10.1589/jpts.25.1067.

Lee JH, Kim SG. Effects of extracorporeal shock wave therapy on functional recovery and neurotrophin-3 expression in the spinal cord after crushed sciatic nerve injury in rats. Ultrasound Med Biol. 2015;41(3):790-796. doi: 10.1016/j.ultrasmedbio.2014.10.015.

Lee SH, Song CH. The effects of Transcutaneous Electrical Nerve Stimulation (TENS) on the neuropathic pain in peripheral nerve injury. J Korean Soc Phys Med. 2013; 8(1):79-89. doi:10.13066/kspm.2013.8.1.079.

Liao CF, Yang TY, Chen YH, Yao C-H, Way T-D, Chen Y-S. Effects of swimming exercise on nerve regeneration in a rat sciatic nerve transection mode. Biomedicine 2017;7(1):3. doi: 10.1051/bmdcn/2017070103.

Lowdon IM, Seaber AV, Urbaniak JR. An improved method of recording rat tracks for measurement of the sciatic functional index of de Medinaceli. J Neurosci Methods. 1988;24(3):279-281. doi: 10.1016/0165-0270(88)90173-2.

Novak CB, Anastakis DJ, Beaton DE, Mackinnon SE, Katz J. Biomedical and psychosocial factors associated with disability after peripheral nerve injury. J Bone Joint Surg Am. 2011;93(10):929-936. doi: 10.2106/JBJS.J.00110.

Oliveira FB, Pereira VMD, da Trindade APNT, Shimano AC, Dias Gabriel REC, Borges APO. Action of therapeutic laser and ultrasound in peripheral nerve regeneration. Acta Ortop Bras. 2012;20(2):98-103. doi: 10.1590/S1413-78522012000200008.

Pachter BR, Eberstein A. Passive exercise and reinnervation of the rat denervated extensor digitorum longus muscle after nerve crush. Am J Phys Med Rehabil. 1989;68(4):179-182. doi: 10.1097/00002060-198908000-00005.

Raso VVM, Barbieri CH, Mazer N. Can therapeutic ultrasound influence the regeneration of peripheral nerves? J Neurosci Methods. 2005;142(2):185-192. doi: 10.1016/j.jneumeth.2004.08.016.

Roghani RS, Rayegani SM. Basics of Peripheral Nerve Injury Rehabilitation. In: Mansoor S. Basic Principles of Peripheral Nerve Disorders. 2012, 257. Available at: https://www.researchgate.net/publication/224829001_Basics_of_Peripheral_Nerve_Injury_Rehabilitation. DOI: 10.5772/39371.

Rosso MP, Buchaim DV, Rosa Junior GM, Andreo JC, Pomini KT, Buchaim RL. Low-Level Laser Therapy (LLLT) improves the repair process of peripheral nerve injuries: A Mini Review. 2017, Int J Neurorehabilitation 2017; 4(2):1-3. doi: 10.4172/2376- 0281.1000260

Rothman SM, Griffioen KJ, Wan R, Mattson MP. Brain-derived neurotrophic factor as a regulator of systemic and brain energy metabolism and cardiovascular health. Ann New Y Acad Sci. 2012;1264(1):49-63. doi: 10.1111/j.1749-6632.2012.06525.x.

Seddon HJ. Three types of nerve injury. Brain 1943;66(4):237-288. https://doi.org/10.1093/brain/66.4.237.

Shen CC, Yang YC, Huang TB, Chan S, Liu BS. Low-Level Laser accelerated peripheral nerve regeneration within a reinforced nerve conduit across a large gap of the transected sciatic nerve in rats. Evid Based Complement Alternat Med. 2013;175629. doi: 10.1155/2013/175629..

Su HL, Chiang CY, Lu ZH, Cheng F-C, Chen C-J, Sheu M-L, Sheehan J, Pan H-C. Late administration of high-frequency electrical stimulation increases nerve regeneration without aggravating neuropathic pain in a nerve crush injury. BMC Neurosci. 2018;19(1):37. doi: 10.1186/s12868-018-0437-9.

Suszyński K, Marcol W, Górka D. Physiotherapeutic techniques used in the management of patients with peripheral nerve injuries. Neural Regen Res. 2015;10(11):1770-1772. doi: 10.4103/1673-5374.170299.

Teixeira de Lemos E, Reis F, Baptista S, Pinto R, Sepodes B, Vala H, Rocha-Pereira P, Correia da Silva G, Teixeira N, Santos Silva A, Carvalho L, Teixeira F, Das UN. Exercise training decreases proinflammatory profile in Zucker diabetic (type 2) fatty rats. Nutrition. 2009; 25(3):330-339. doi: 10.1016/j.nut.2008.08.014.

Teodori RM, Betini J, Salgado de Oliveira L, Sobral LL, Takeda SYM, de Lima Montebelo MI. Swimming exercise in the acute or late phase after sciatic nerve crush accelerates nerve regeneration. Neural Plast. 2011;2011:1-8. doi: 10.1155/2011/783901.

Tofthagen C, Visovsky C, Berry DL. Strength and balance training for adults with peripheral neuropathy and high risk of fall: current evidence and implications for future research. Oncol Nurs Forum. 2012;39(5):416-424. doi: 10.1188/12.ONF.E416-E424.

Udina E, Puigdemasa A, Navarro X. Passive and active exercise improve regeneration and muscle reinnervation after peripheral nerve injury in the rat. Muscle Nerve. 2011;43(4):500-509. doi: 10.1002/mus.21912.

Wilhelm JC, Xu M, Cucoranu D. Cooperative roles of BDNF expression in neurons and Schwann cells are modulated by exercise to facilitate nerve regeneration. Journal Neurosci. 2012;32(14):5002-5009. doi: 10.1523/JNEUROSCI.1411-11.2012.