

REVIEW ARTICLE

REVIEW OF EFFECTIVE NERVE ELECTROSTIMULATION PARAMETERS APPLIED FOR TREATMENT OF PATIENTS AFTER INCOMPLETE SPINAL CORD INJURIES

PRZEGLĄD SKUTECZNYCH PARAMETRÓW ELEKTROSTYMULACJI NERWÓW STOSOWANYCH DO LECZENIA CHORYCH PO NIECAŁKOWITYM URAZIE RDZENIA KRĘGOWEGO

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ABSTRACT

Introduction

About half a year in patients after incomplete spinal cord injury (iSCI), clinical observations and neurophysiological studies show symptoms indicating the consequences of degeneration of motoneurone cell bodies and axons. This is manifested by adverse results of nerve impulse transmission studies in peripheral motor fibers originating from neuromers below the level of spinal injury. These phenomena can be inhibited by using nerve electrostimulation procedures, maintaining the function of impulse transmission towards the effector on orthodromic way and by antidromic action towards the cell body of the motoneurone.

Aim

The aim of the study is to compare the currently used nerve electrostimulation algorithms that give positive, documented therapeutic effects and the selection of optimal parameters, taking into account the current state of knowledge and pilot own results.

Material and methods

A review of the literature in PubMed regarding data on the effectiveness of peripheral nerve electrical stimulation, especially in patients after spinal cord injuries was performed. Only articles containing complete data on the parameters of the applied nerve electrostimulation in patients after incomplete spinal cord injuries were selected and analyzed. In 11 patients after incomplete spinal cord injuries at the level from C8 to Th11 neuromers, pilot sessions of repetitive tibial and peroneal nerves electrostimulation were performed on both sides with individually selected parameters based on the results of surface electromyography (mcEMG) and electroneurography (ENG). The average duration of the session was 15 minutes, 10 sessions per week, stimuli frequency 10–60 Hz, rectangular stimulus sequences lasting 2–4s, intervals between sequences 2–3s, duration of a single stimulus 16ms on average and intensity in the range 25–45mA. The results of mcEMG and ENG tests were compared before and after 12 months of controlled nerves electrical stimulations.

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Results

Literature descriptions lack a uniform, optimal algorithm that would be rationally justified from the point of view of the physiology of nerve impulse transmission and the activities of motor units of innervated lower limb muscles, personalized for an certain patient. Stimulus nerve electrostimulations are used with a duration of single stimulus from 0.1 to 500ms, a frequency of 1 to 100Hz and an intensity up to 250mA. The pilot algorithm of applied electrostimulation of lower limb nerves proposed in this work led to an improvement in the motor transmission of nerve impulses and the activity of muscle motor units of the lower limbs in patients with iSCI.

Conclusions

Personalized electrostimulation within nerve motor fibers enables the therapy of patients after iSCI to maintain the proper function of nerve impulse transmission in a period awaiting for repair phenomena at the level of the damaged spinal cord. This study draws attention to the need to both standardize and personalize the applied nerve electrostimulation algorithms, the location of electrode application and their size in order to achieve the best therapeutic results.

Keywords: electrostimulation, incomplete spinal cord injury, nerve stimulation parameters

STRESZCZENIE

Wstęp

Około pół roku u chorych po niecałkowitym urazie rdzenia kręgowego (iSCI), w obserwacjach klinicznych i badaniach neurofizjologicznych stwierdza się objawy wskazujące na następstwa degeneracji ciała i aksonów motoneuronów. Przejawem tego są niekorzystne dla chorych wyniki badań przewodnictwa impulsów nerwowych we włóknach ruchowych obwodowo, biorących początek z neuromerów poniżej poziomu uszkodzenia rdzenia. Zjawiska te można zahamować stosując zabiegi elektrostymulacji nerwów, podtrzymując funkcję przewodnictwa impulsów w kierunku do efektora na zasadzie przewodnictwa ortodromowego oraz poprzez działanie antydromowe w kierunku ciała motoneuronu rdzeniowego.

Cel

Celem pracy jest porównanie stosowanych aktualnie algorytmów elektrostymulacji nerwów dających pozytywne, udokumentowane efekty terapeutyczne oraz wybór optymalnych parametrów, biorąc pod uwagę obecny stan wiedzy jak i pilotażowe wyniki własne.

Materiał i metody

Dokonano przeglądu literatury w PubMed dotyczącej danych na temat skuteczności zabiegów elektrostymulacji nerwów obwodowych szczególnie u chorych po urazach rdzenia kręgowego. Wybrano tylko artykuły zawierające kompletne dane na temat parametrów zastosowanej elektrostymulacji nerwów u chorych po niecałkowitych urazach rdzenia kręgowego i poddano je analizie. U 11 chorych po niecałkowitych uszkodzeniach rdzenia kręgowego, na poziomie neuromerów C8 do Th11 przeprowadzono pilotażowe sesje powtarzalnej elektrostymulacji nerwów piszczelowych i strzałkowych obustronnie z indywidualnie dobranymi parametrami na podstawie wyników badań elektromiografii powierzchniowej (mcEMG) i elektroneurografii (ENG). Średni czas trwania sesji wynosił 15 minut, 10 sesji w tygodniu, częstotliwość bodźców 10–60Hz, stosowano ciągi stymulacji bodźcami prostokątnymi trwające 2–4s, przerwy pomiędzy ciągami 2–3s, czas trwania pojedynczego bodźca średnio 16ms a natężenie

w zakresie 25–45mA. Porównano wyniki testów mcEMG oraz ENG przed i po 12 miesiącach kontrolowanej elektrostymulacji nerwów.

Wyniki

W opisach literatury brak jest jednolitego, optymalnego algorytmu, który byłby racjonalnie uzasadniony z punktu widzenia fizjologii przewodnictwa impulsów nerwowych oraz czynności jednostek ruchowych unerwianych mięśni kończyn dolnych, spersonalizowany dla usprawnionego chorego. Stosowane są elektrostymulacje nerwów pojedynczymi bodźcami o czasie trwania od 0,1 do 500ms, częstotliwości od 1 do 100Hz i natężeniu aż do 250mA. Proponowany w tej pracy, zastosowany pilotażowy algorytm elektrostymulacji nerwów kończyn dolnych, doprowadził do poprawy parametrów przewodnictwa w włóknach ruchowych nerwów oraz czynności jednostek ruchowych mięśni kończyn dolnych u chorych z iSCI.

Wnioski

Spersonalizowana elektrostymulacja w obrębie włókien ruchowych nerwów umożliwia w procesie terapii chorych po iSCI podtrzymanie prawidłowej funkcji przewodnictwa impulsów nerwowych w oczekiwaniu na zjawiska naprawcze na poziomie uszkodzonego rdzenia. W niniejszym opracowaniu zwrócono uwagę na konieczność zarówno ujednoczenia jak i spersonalizowania stosowanych algorytmów elektrostymulacji nerwów, lokalizacji przyłożenia elektrod i ich wielkości w celu osiągnięcia jak najlepszych wyników terapeutycznych.

Słowa kluczowe: elektrostymulacja, niecałkowite uszkodzenie rdzenia kręgowego, parametry stymulacji nerwów

Introduction

Incomplete spinal cord injuries (iSCI) occur most often in young people, resulting in significant neurological abnormalities. They cause disability, which is a serious medical and social problem. The peripheral and central nervous systems are functionally integrated regarding the consequences of a nerve injury peripherally, a peripheral nerve lesion often results in profound and long-lasting central modifications and reorganization processes (Wall *et al.*, 2002). Within six months after the injury, consequences of degeneration of motoneurone cell bodies and axons can be detected (Kim *et al.*, 2017; Hayta and Elden, 2018), although MRI studies do not confirm reasons of direct injuries in ventral horn cells at L4-S1 spinal levels or within the ventral spinal roots. Pathologies are manifested by unfavorable peripheral nerve impulse test results below the level of damage (Kim *et al.*, 2017). These phenomena are not explained to

the end, but can be inhibited by using nerve electrostimulation treatment supporting their function of impulse transmission towards the effector based on the orthodontic principle and by antidromic action towards the body of the motoneurone (Lee *et al.*, 2015). The transmission of impulses in motor nerve is sustained when the structure and functions of neurotubules and neurofilaments responsible for axoplasmic transport within the axons are preserved. Electrostimulation of nerves aims to counteract the effects of secondary degenerative changes in patients with iSCI (Nogajski *et al.*, 2006), but the uniform description of the effective algorithm has not been provided. This physiotherapeutic procedure not only stimulates peripheral motor axons to activate muscles but also sensory axons that return to the spinal cord and activate both motoneurons and interneurons, as well as the brain.

Aim

The aim of the study was to compare the currently used nerve electrostimulation algorithms that give positive, documented therapeutic effects and the selection of optimal parameters, taking into account the current state of knowledge and pilot own results.

Material and methods

A review of the literature in PubMed regarding data on the effectiveness of peripheral nerve electrical stimulation, especially in patients after spinal cord injuries was performed. Only articles containing complete data on the parameters of the applied nerve electrostimulation in patients after incomplete spinal cord injuries were selected and analyzed.

Additionally, in 11 patients after incomplete spinal cord injuries at the level from C8 to Th11 neuromers, pilot sessions of repetitive tibial and peroneal nerves electrostimulation were performed on both sides with individually selected parameters based on the results of individual surface electromyography (mcEMG) and electroneurography (ENG). The average duration of the sessions was 15 minutes, 10 sessions per week, stimuli frequency 10–60 Hz, rectangular stimulus sequences lasting 2–4s, intervals between sequences 2–3s, duration of a single stimulus 16ms on average and intensity in the range 25–45mA. The electrostimulation device was chosen from available, medical market to permit the possibility of applying, the personalized for the patient algorithm of electrostimulation and control of using it during the whole therapeutic period.

The results of mcEMG and ENG tests were compared before and after 12 months of controlled peroneal and tibial nerves electrical stimulations. Patients were examined with neurophysiological methods in the Department of Pathophysiology of the Locomotor Organs of the Poznan University of Medical Sciences. mcEMG and ENG recordings were performed using the KeyPoint Diagnostic System (Medtronic A/S, Skovlunde, Denmark). mcEMG recordings from tibialis anterior, gastrocnemius, and extensor digiti muscles were

bilaterally performed during their maximal contraction attempts lasting 5 seconds. The parameters of average amplitude and frequency index were analyzed. ENG examinations of motor fibres transmission within peroneal and tibial nerves were performed (CMAP, M waves recordings). Nerves were stimulated during diagnostic test with electrical pulses (rectangular, 0.2ms duration, at 1 Hz, intensity from 0–80 mA) bilaterally; evoked potentials were recorded from tibialis anterior and extensor digitorum longus muscles bilaterally. M-waves (CMAPs) amplitudes, latencies and stimulus strengths to evoke impulses in nerves were calculated and compared with normative values recorded in a group of healthy volunteers, based on the methodology described elsewhere, where principles also the mcEMG recordings and analysis were presented (Huber *et al.*, 2011).

The study was performed in accordance with the Declaration of Helsinki and was approved by the Bioethics Committee of the Poznan University of Medical Sciences (decision number 559/20180).

Results

The currently available literature lacks comparable descriptions that would be rationally justified from the point of view of the physiology of nerve impulse conduction in a particular rehabilitated patient and experimental results (Table 1). Stimuli nerve electrostimulations were used with a duration of single stimulus from 0.1 to 500ms, a frequency of 1 to 100Hz and an intensity up to 250mA. The use of such algorithms would reduce the risk of iatrogenic nerve damage suffered during electrostimulation and would allow achieving the best possible clinical results, which would improve the long-term effects of rehabilitation in patients after iSCI. Developing them, however, requires further research, because only little data was provided on efficiency of electrostimulations therapies evaluated with functional tests.

Initial tests that have already been conducted on 11 patients using the following parameters, frequency 10–60 Hz (average 35 Hz),

Table 1. Examples of electrostimulation parameters described in the papers from PubMed database to evoke positive effects in subjects after iSCI, selected for analysis of common properties.

Source	Experimental group	Frequency of stimuli	Duration of a single stimulus	Duration of series of stimuli	Duration of pause between series of stimuli	Stimulus intensity (mA)	Voltage (if available)	Therapy frequency
(Zuo et al., 2020)	36 rats	20Hz	0,1ms	-	-	-	3–5V	1h
(Han et al., 2015)	64 rats	20Hz	100ms	-	-	-	3V	1h
(Mödlin et al., 2005)	40 patients	2Hz	120–150ms	5s	2s	-	160Vpp	once a day, 15 mins session, later – 20–30 mins sessions
		5Hz	70ms	-	-	-		
		20Hz	40ms	-	2s	-		
(Pieber et al., 2015)	24 patients	1Hz	200ms	-	-	5.4 mA	-	1–2 minute sessions
		1Hz	500ms	-	-	5.3 mA		
	24 patients	1Hz	200ms	-	-	8.0 mA		
		1Hz	500ms	-	-	8.3 mA		
(Bochkezanian et al., 2018)	5 patients	30Hz	-	2s	2s	40mA		12 weeks of therapy, twice a week
						30–99mA		
(Kern et al., 2010)	25 patients	-	120–150ms	-	-	250mA	-	5 times a week, 30 mins sessions
(Gorgey et al., 2018)	22 patients	30Hz	0.45ms	-	0.05ms	intensity that causes the 50% of maximal flexion in knee joint	-	therapy 2 to 7 times a week, 20–60 mins sessions
		33.3Hz	0.35ms			100–140mA		
(Lee et al., 2015)	22 patients	100Hz	0.45ms	2s	2s	12–30mA	-	6 weeks of therapy, 5 times a week, 30 mins sessions
(Kern et al., 2005)	1 patient	2Hz	120ms	-	-	-	-	therapy 5 times a week, 15 mins sessions
		20 Hz	40 ms	2s	2s	200mA	-	therapy 5 times a week, 15 mins sessions

duration of a single stimulus 16ms on average, intensity in the range 25–45mA (28mA on average), brought statistically significant improvement of impulse transmission parameters in motor fibers and activity of muscle motor units in distal lower limb muscles (Figure 1).

Discussion

According to the PubMed analyzed literature, a wide variety of nerve electrostimulation parameters were applied in treatment of subjects and in experimental studies after iSCI (duration of a single stimulus between 0.1 and 500ms, the frequency from 1 to 100Hz and the intensity of up to 250mA). Single stimuli with a duration of 200ms rather caused complete

tetanus spasm, which, with a prolonged stimulation, can lead to irreversible changes in neuromuscular synapses. 100mA is the standard, safe maximum intensity of stimulus in electroneurographic tests stimulating all axons, however, this value could be sometimes increased up to 150mA in iSCI patients with moderate advanced neurogenic pathological changes. The 20Hz frequency caused an induction of a slight incomplete tetanic spasm in the muscle. In addition, at the moment, there is no uniform strategy for nerve electrostimulation algorithm, concerning the localization of electrode application, their size, and method of stimulation (percutaneous or internal).

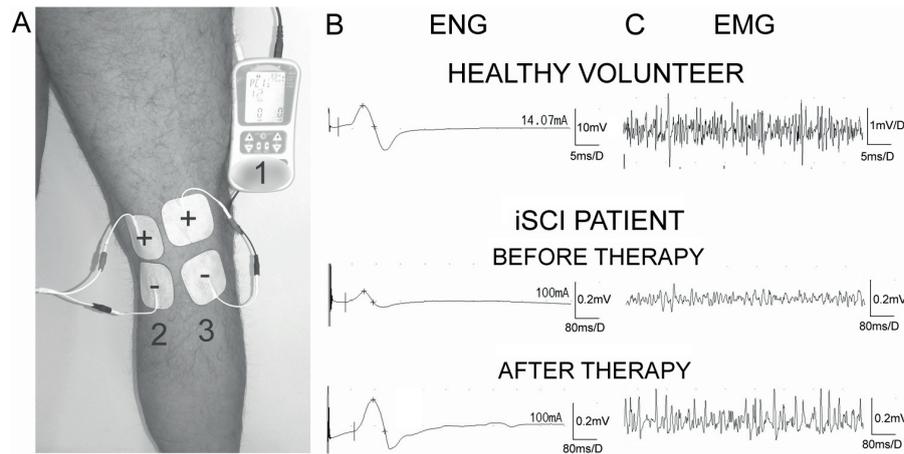


Figure 1. A – Photograph of electrotherapy device (1) and the placement of the stimulation electrodes over anatomical passage of the tibial (2) and peroneal (3) nerves. Examples of electroneurography (B) and electromyography (C) recordings performed in a healthy volunteer and compared with one of the iSCI patient before and after therapy. Note the different amplifications of the recordings indicated near vertical bars.

Pathophysiology of iSCI

Spinal cord injury results in two stages of pathologies, direct mechanical trauma and secondary pathophysiological changes. Immediately after the injury, ischemia, edema, reactive oxygen species production, inflammation and excitotoxicity of glutamate may occur (Figure 2). As the injury progresses, demyelination and apoptosis of neurons become more significant, and the reactive proliferation of astrocytes causes a glial scar to create an obstacle inhibiting the transmission of nerve impulses (Alizadeh *et al.*, 2019).

Long-lasting denervation in muscles causes their atrophy and the muscular tissue is replaced with fat and connective tissue. However, there is an evidence that skeletal muscle fibers survive up to six years after denervation

(Carraro and Kern, 2016), what makes the introducing of electrostimulation treatment reasonable. Denervated muscle tissue shows an increase in chronaxia above ms, what can be an indication for choosing the optimal single stimulus duration parameter.

Electrostimulation

The personalized electrostimulation within the nerve whose axons show a change in function of impulses transmission enables the therapy of patients after spinal injuries to maintain correct peripheral function while waiting for the repair phenomena at the level of the damage in the spinal cord. In patients after spinal cord injury, electrostimulation has a lot of different purposes: increasing muscle mass showing the atrophic effect,

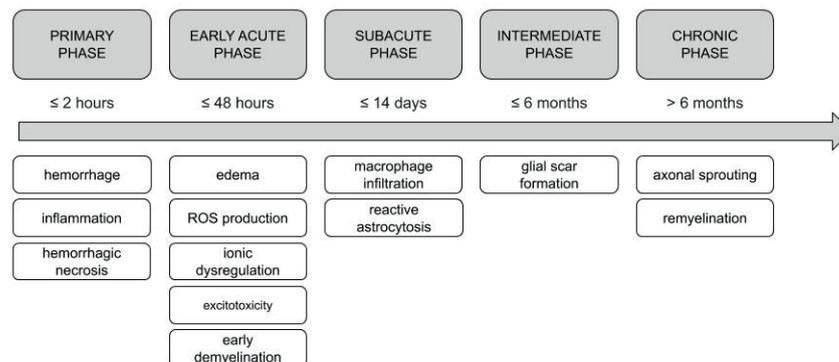


Figure 2. Sequence of pathophysiological changes after incomplete spinal cord injury.

improvement of contracture, pressure ulcer prevention and treatment, neuromodulation, motor learning, coughing stimulation, improving motor limb function, preventing orthostatic hypotension, reducing spasticity (Bersch *et al.*, 2015). Previous work on the effectiveness of nerve regeneration indicates three main ways of therapy: FES (Functional Electrical Stimulation), NMES (Neuromuscular Electrical Stimulation), TENS (Transcutaneous Electrical Nerve Stimulation), which vary in the location of the electrodes, stimulated area (nerve or muscle) and direction of the current flow.

In spite of many publications describing the effects of electrostimulation, only few of them include the influence of physiologically data on the applied parameters. An optimal algorithm for nerve electrostimulation adjusted to the patient's individual functional state should include:

- **the frequency** of stimulation with rectangular bipolar stimuli (which resembles the morphology of the action potential in the nerve the most) should not be higher than 40 Hz in an advanced cases of muscle injury, and should not exceed 90 Hz which is recorded in mcEMG tests in cases of healthy muscle motor units.
- **the duration** of the rectangular pulse cannot be longer than 200ms, because the normative duration of a single action potential of a motor unit varies from 9 to 18ms.
- **the interval** between impulse series with a frequency of 10–80 Hz can be determined from the half-fall in mcEMG amplitude recorded during the maximal contraction, which in people with an intermediate neurogenic muscle disorder it lasts about 2s. The same interval should be introduced between the series of applied impulses used to determine the time needed for resuscitation of acetylcholine content resleased at the level of the neuromuscular synapse.
- **the intensity of stimulus** should be adjusted individually to the patient after electoneurographic tests of CMAP recordings potential also known as the M wave. In

a healthy human, the maximum intensity of a single impulse administered in order to induce a supramaximal response (one where further increase of the stimulus does not bring a visible increase in potential amplitude parameter, indicating that all the motor fibers in the examined motor branch are excited) is up to 20 mA, but in a patient with moderately advanced axonal changes in nerves, this value increases up to 30–40 mA.

According to previous analysis (Günter *et al.*, 2019), chronic peripheral nerve stimulation with a frequency lower than 30 Hz is considered harmless and most studies use frequencies consistent with this premise. However, in previous years, Lee *et al.* introduced the electrostimulation with a frequency up to 100 Hz (with a very short stimulus duration and low intensity) in 22 patients, and it was well tolerated by the subjects (2015). Therefore, it can be assumed that frequencies higher than 30 Hz do not cause any negative effects. In the studies researchers use intermittent pulses more often than series of pulses over 100ms, in order to prevent muscle fatigue and acetylcholine depletion. Attention should also be paid to the shape of the stimulus used during electrostimulation. Rectangular stimuli are mainly used, and according to Pieber *et al.* (2015), there are no studies evaluating effects of a triangular stimulus on a denervated muscle. The advantage of this type of stimulus is the ability to selectively stimulate only denervated muscle fibers and differentiating them with innervated ones (Bc, 1967). It is also suggested, that the way the electrodes are positioned can play a significant role in the effectiveness of the applied electrostimulation. In the case of denervated tibial anterior muscle, better results were observed when the cathode was located proximally on the lower limb. However, the study of extensor digitorum muscle did not bring similar results. A whole group of studies also focuses on the impact of long-lasting implanted electrodes function, that involve

direct nerve stimulation through nerve cuffs electrodes, which are most often performed on very few volunteers. The results are important for engineers who design endoprosthesis controlled by impulses whose parameters are similar to those in the nervous system. Such implants remain functional without causing neuroinfection from 1 month up to 11 years.

Current restrictions on nerves electrostimulations

Despite the many papers referenced above, current knowledge also indicates some limitations. Most studies on peripheral nerve regeneration have been conducted on animal subjects. The effectiveness of nerve electrostimulation has been proven, allowing the axons to regenerate on a distance of up to 20 mm (Zuo et al., 2020). At the same time, it is important to note that such procedure performed later than 1 month after the injury does not bring the expected results due to Schwann cell apoptosis and fibrosis – replacement of nerve fibers with collagen fibers (Han et al., 2015). In addition, under physiological conditions, this regeneration is quite slow: 1 to 3 mm a day, and it becomes even less prominent with time because of the decrease of support coming from Schwann cells. It should be considered whether animal studies give the possibility of using the same stimulation parameters in humans as non-iatrogenic. Current studies focus more on biochemical and histological aspects than on clinical effects of therapy, and the important issue is the fact, that the results of the motor function recreation (i.e. nerve conduction and activities of innervated motor units in muscle tissue) are passive – the effectiveness of electrostimulation in this regard is estimated at about 50%. The effectiveness of stimulation depends on what type of nerve is targeted, since they have a mixed motor-sensory structure. Bersch et al. (2015) draw attention to the problems encountered by patients interested in nerve electrostimulation therapy performed at their own homes. Although this solution is seemingly more

convenient for patients and gives an easy access to regular therapy sessions, the necessity to single-handedly connect the electrodes and operate a complicated, heavy device can be too much of a challenge for patients after neurological injury. In addition, studies by Bochkezanian et al. (2018) show, that the effectiveness of electrostimulation therapy depends on the degree of spinal cord injury and other accompanied movement disorders.

Conclusions

The currently available literature lacks descriptions that would be rationally justified from the point of view of the physiology of nerve impulse conduction in a particular rehabilitated patient. The use of such an algorithm would reduce the risk of iatrogenic nerve damage suffered during electrostimulation and would allow achieving the best possible clinical results, which will improve the long-term effects of rehabilitation in patients after incomplete spinal cord injuries. Developing it, however, requires further research. The pilot algorithm of applied electrostimulation of lower limb nerves proposed in this work led to an improvement in the motor transmission of nerve impulses and the activity of muscle motor units of the lower limbs in patients with iSCI.

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