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Orginal paper

Usprawnianie chorych po urazach rdzenia kręgowego z wykorzystaniem przezczaszkowej stymulacji magnetycznej rTMS

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STRESZCZENIE

Wstęp

Niecałkowite uszkodzenie rdzenia kręgowego (iSCI) wywołuje złożone upośledzenie funkcji motorycznych i czuciowych z następstwami objawów spastyczności, bólu i dysrefleksji autonomicznej. U chorych z iSCI najczęściej występuje częściowe zachowanie czynności sensorycznej i/lub motorycznej ośrodków nerwowych w neuromerach poniżej urazu, w których powrót funkcji może być możliwy dzięki zjawiskom plastyczności funkcjonalnej struktur nerwowych oraz ich funkcjonalnej regeneracji stymulowanymi wieloma różnymi czynnikami. Dysfunkcja pęcherza wydaje się być najpoważniejszym problemem dla pacjentów z iSCI. Dlatego przywrócenie koordynacji funkcji zwieracza powinno być priorytetem w rehabilitacji neurologicznej opartej na metodach neurofizjologicznych, takich jak powtarzalna przezczaszkowa stymulacja magnetyczna (rTMS). Metoda diagnostyczna współczulnych potencjałów skórnych (SSR) umożliwia oszacowanie zachowania i poprawy funkcji rdzeniowych ośrodków i szlaków autonomicznych u chorych z iSCI.

Cel

Praca ma na celu przedstawienie rTMS jako terapii, która może wspomagać procesy regeneracyjne rdzenia, w tym funkcję ośrodków i szlaków autonomicznych, których przewodnictwo zbadano z wykorzystaniem SSR u chorych po niecałkowitym uszkodzeniu rdzenia przed i po terapii rTMS.

Materiał i Metody

Wykonano badania porównawcze SSR u 25 chorych po iSCI z uszkodzeniem na poziomach neuromerów od Th2 do L1 przed terapią rTMS i powtórzono je po roku.

Wyniki

Zaobserwowano istotną statystycznie poprawę parametrów amplitudy i latencji SSR zarejestrowanych w kończynach dolnych prawych (p=0,04) i lewych (p=0,03) u chorych z iSCI, u których zastosowano terapię rTMS.

Wnioski

Za pomocą porównawczych badań SSR, zweryfikowano hipotezę, że aplikacja rTMS o częstotliwości 20-22 Hz efektywnie poprawia przewodnictwo impulsów nerwowych z ośrodków nadrdzeniowych związanych z kontrolą prawidłowej czynnością ośrodków rdzenia i szlaków autonomicznych, a więc i sprawność funkcjonalną u pacjentów po niecałkowitym uszkodzeniu rdzenia kręgowego.

Słowa kluczowe: niecałkowite uszkodzenie rdzenia kręgowego, przezczaszkowa stymulacja magnetyczna, współczulne potencjały skórne, funkcja ośrodków i szlaków autonomicznych

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Treatment of patients after spinal cord injuries using transcranial magnetic stimulation rTMS

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SUMMARY
Introduction
Incomplete spinal cord injury (iSCI) causes a complex impairment of motor and sensory functions with the consequences of spasticity symptoms, pain and autonomic dysreflexia. Partial sensory and/or motor function of the spinal centers in the neuromers below the trauma most often occurs in patients with iSCI. The return of function, in such cases, may be possible due to the phenomena of functional plasticity in nerve structures and their functional regeneration stimulated by many different factors. Bladder dysfunction seems to be the most serious problem for patients with iSCI. Therefore, restoring coordination of sphincter function should be the priority in neurological rehabilitation based on neurophysiological methods such as repetitive transcranial magnetic stimulation (rTMS). The diagnostic method of sympathetic skin responses (SSR) allows to assess the function and improvement in the spinal centers and the autonomic pathways in patients with iSCI.
Aim
The work aims to present rTMS as a therapy that can support the regenerative processes in the spinal cord, including the function of autonomic centers and pathways, which transmission was investigated using SSR in patients following incomplete spinal injury before and after rTMS therapy.
Material and methods
Comparative SSR studies were performed in 25 patients after iSCI with injuries at levels from Th2 to L1 neuromers before rTMS therapy and they were repeated after a year.
Results
A statistically significant improvement in SSR amplitude and latency parameters was recorded in the right ($p = 0.04$) and left ($p = 0.03$) lower extremities in patients with iSCI who received rTMS therapy.
Conclusions
By means of comparative SSR studies, the hypothesis was verified that the rTMS application with a frequency of 20-22 Hz effectively improves the transmission of nerve impulses from supraspinal centers associated with the control of the spinal centers function and autonomic pathways, and thus, functional efficiency in patients after incomplete spinal cord injury.

Keywords: incomplete spinal cord injury, transcranial magnetic stimulation, sympathetic skin potentials, function of autonomic centers and pathways

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Introduction

Spinal cord injury (SCI) is a life-altering trauma characterized by the presence of complex impairment of motor and sensory functions associated with spasticity, pain and autonomic dysreflexia. According to the Global Burden of Diseases Study (2019), SCI is the sixth position among 15 other, the most common neurological disorders worldwide. Data updated by National Spinal Cord Injury Statistical Center in 2018 show that currently, approximately 288,000 persons with SCI live in the US, with 78% being men in the average age of 43 years. Although the current efforts and neurosurgery interventions have decreased morbidity and mortality rates in SCI cases, there are still many unsolved problems regarding the functional abilities of patients with SCI (Burns and O'Connell, 2012). Bladder dysfunction seems to be a major problem for iSCI patients. Thus, restoration of sphincter function should be the priority in the evidence-based neurological rehabilitation supported by the objective neurophysiological methods such as repetitive transcranial magnetic stimulation and sympathetic skin response. The combination of both these methods may allow to assess neural damage and reduce dysfunction due to the therapeutic effects of brain stimulation. Therefore, it should be crucial to investigate the effectiveness of new methods that trigger the long-term potentiation or depression of the neuronal tracts; thus, improve functional recovery after iSCI (Oudega and Perez 2012).

The transcranial magnetic stimulation (TMS) is a non-invasive method of brain stimulation (Tazoe et al. 2015). The TMS coil held over the head acts as the magnetic field generator which induces an electrical current in the brain. The electrical current in the brain stimulates cortical layers. So, if the coil is over the area of the motor cortex, the stimulus causes a muscle twitch or motor evoked potentials elicited by TMS as the consequence of efferent transmission in the spinal descending pathways. Preliminary, the primary motor cortex (M1) is being excited, then the impulse is transmitted via two major motor control pathways, namely corticospinal tract and rubrospinal tract. The concept of repetitive magnetic stimulation (rTMS) assumes applying trains of many stimuli to increase primary motor cortex and corticospinal excitability. The series of stimuli seems to modulate corticospinal inhibition, and it may enhance recovery and spinal cord regeneration. As a clinical outcome, it seems to reduce spasticity and improve motor and possibly also sensory functions; hence, it seems to improve the functional abilities of a patient with iSCI (Bunday et al. 2012, Oudega 2012). rTMS does not require surgery, implantation of electrodes, nor sedation with anaesthesia. A patient lies comfortably, and he or she is conscious and relaxed during all the procedure, if parameters of stimulation are included in physiological limits and algorithm of applied stimuli and stimulus strength does not evoke hyperexcitability in the central nervous system. Tazoe et al. (2015) summarised available and currently effectively applied modes of rTMS stimulation. They concluded that frequency at 20-22 Hz seems to induce excitation of all efferent fibres in the spinal tracts providing optimal motor and sensory responses, what was also mentioned by Ellaway et al. (2014) concerning the bladder function improvement in patients with iSCI.

Sympathetic skin response (SSR) is a neurophysiological method that objectively evaluates the function of the sympathetic nervous system. Electrical and sound stimuli, such as a bell ring, are used to evoke the physiological sympathetic skin response recorded from upper and lower extremities. The examination is possible due to the temporary changes in the electrical skin resistance caused by the application of an unexpected external stimulus followed by the sweat glands excitation (Wiertel-Krawczuk et al. 2016). The results of SSR

studies seem to be a perfect tool for evaluation of function of the autonomic centers and pathways in patients with iSCI following the application of certain type of rehabilitation, including rTMS.

Aim

The current study aims to present the results of SSR recordings in 25 patients after iSCI, who underwent rTMS therapy. It was assumed that rTMS supports spinal cord regenerative mechanisms and improve the neural transmission in descending spinal pathways. The hypothesis has been put forward that rTMS verified by the neurophysiological evaluation such as SSR may be practical for modulation of the autonomic activity and trigger functional recovery after iSCI.

Material and methods

The results of treatment of 25 patients with chronic iSCI at Th2-L1 levels were evaluated in this study. The main inclusion criteria were MRI results showing at least 1/3 preservation of spinal structures at thoracic or lumbar levels, time from injury less than a year, and an individual agreement for participation in the project not less than a year. All patients underwent surgical interventions that led to the stabilisation of the broken spine. Before participation in the study, the patients signed written informed consent. Everyone was informed and understood the risk of all procedures and the potential for no benefit. All patients reported a stable psychological and social status and met the general criteria to be qualified for the SSR neurophysiological examination and rTMS treatment. No written incongruity, pregnancy, oncological episodes, the presence of a pacemaker, cochlear implant, epilepsy, psychotropic drug intake before admission, stroke, inflammatory diseases and previous cervical spine injuries nor myelopathies before the incident of SCI, were the contraindications for the participation in this study. The Bioethics Committee of Poznan University of Medical Sciences approved the study (decision number 532/2018). All procedures were performed in accordance with the Declaration of Helsinki. The four-channel Key Point System for recordings in neurophysiological studies (SSR examination) and MagPro X100 with MagOption Medtronic (Medtronic A/S, Skovlunde, Denmark) with a biphasic current waveform for magnetic stimulation (rTMS purposes) were used.

rTMS therapy and SSR studies were conducted in the Department of Pathophysiology of Locomotor Organs of the Poznan University of Medical Sciences. The treatment consisted of monthly rTMS sessions. The whole observation period lasted a year. SSR recordings were performed before the rTMS treatment and after a year since the first measurements. Patients were awake and cooperating during both SSR and rTMS sessions. All patients reported that they feel the magnetic stimulation as painless. The trains of impulses that were transmitted uni- and contralaterally down to lower extremities were commonly described by the participants.

For the rTMS stimulation, a circular coil (C-100, 12 cm in diameter) was used. It was placed over the scalp in the area of M1 targeted with an angle for the corona radiate excitation. The fibres of the corticospinal tract for upper and lower extremities are described as originated in this area. The hotspot position was marked on a patient's head and used in all subsequent sessions of stimulation. The coil was placed above the skull of the subject lying in a prone position with a custom coil holder, while the head was slightly elevated and secured to limit head movements. Every patient had a monthly course made up of 3-5 sessions of rTMS (up to 9 monthly meetings in the observation period). A single session consisted of bilateral stimulation of motor cortex for about 10 minutes and a 10 minutes pause. During each session, every patient received 1600 biphasic pulses, 800 pulses for each side. The parameters of each session were as follows: 20-22 Hz - frequency of applied stimuli, 2s trains of 40 pulses, 28s - the interval between trains of stimuli, strength at about 70-80% of the resting motor threshold (RMT).

During SSR recordings, every patient was lied in a supine position in an air-conditioned room with an average temperature of 23°C. There was always 15 minutes of relaxation in silence before a test. The time base was set on 1s/D and 200 ms/D and amplifications from 0.5 to 1mV, respectively. The surface bipolar stimulating electrode was used for every test along the anatomical course of the right median nerve at the wrist. Single rectangular electrical pulse with the intensity of 10mA, duration of 0.1ms, frequency 3Hz was used. The impendancy between the skin and the surface electrode was never higher than 5 kΩ. The recording surface for AgCl adhesive disposable bipolar electrodes was 7 x 4 mm. The electrodes were covered with isotonic gel to reduce the resistance. The active recording electrodes were between the second and third metacarpus and metatarsus. The reference electrodes were in the centre area of the dorsal sides of feet and hands. The ground electrodes were placed on the one side on the wrist and the ankle. There were always three attempts for recordings from lower and upper extremities on both sides. The presence of response within a normal range, the lower amplitudes and longer latencies, and no response were scored. Principles of methodology and analysis of the parameters described above are described elsewhere (Wiertel-Krawczuk et al. 2016).

A comparison of SSR parameters average values using the Student t-test before and after the rTMS therapy was applied. It is assumed that the comparison of the mean value at $p \leq 0.05$ determined the significant statistical differences between averages, pointing to the positive impact of the rTMS.

Results

All patients tolerated rTMS sessions and SSR measurements without complications. None of the patients reported any side effects nor pain. SSR recordings with parameters of amplitudes and latencies were marked as follows: the potentials within a normal range according to the original paper published by Wiertel-Krawczuk et al. (2016) received a score 1, the potentials with lower amplitudes and longer latencies but recordable received a score 0,5; finally, no recorded responses received a score 0 (Figure 1).

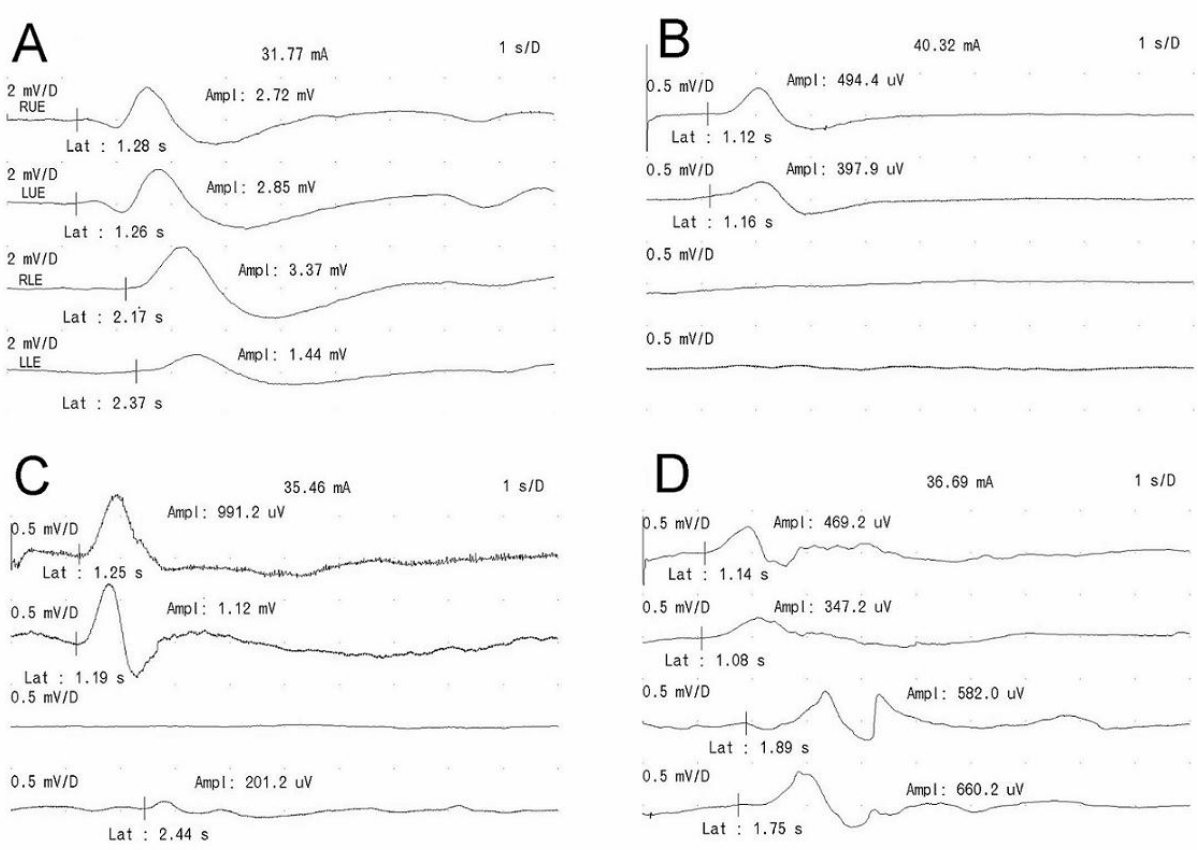

Figure 1. Examples of SSR recordings in A – a normal subject, B – a patient with results scored 0, C and D – a patient with comparative recordings scored 0,5 and 1, respectively, before and after rTMS therapy.

In all patients, there were no observed changes in parameters of SSR recordings from upper extremities on both sides before and after a year due to the levels of iSCI that were mainly in the thoracic area (Figure 2). After rTMS therapy a significant increase of SSR recordings from lower extremities on right (p=0,04) and left (p=0,03) was observed. Before rTMS therapy, the activity of the autonomic centers and pathways in the spinal cord below the level of injury was ascertained at about 30-36%, while after the therapy it reached 50-54%.

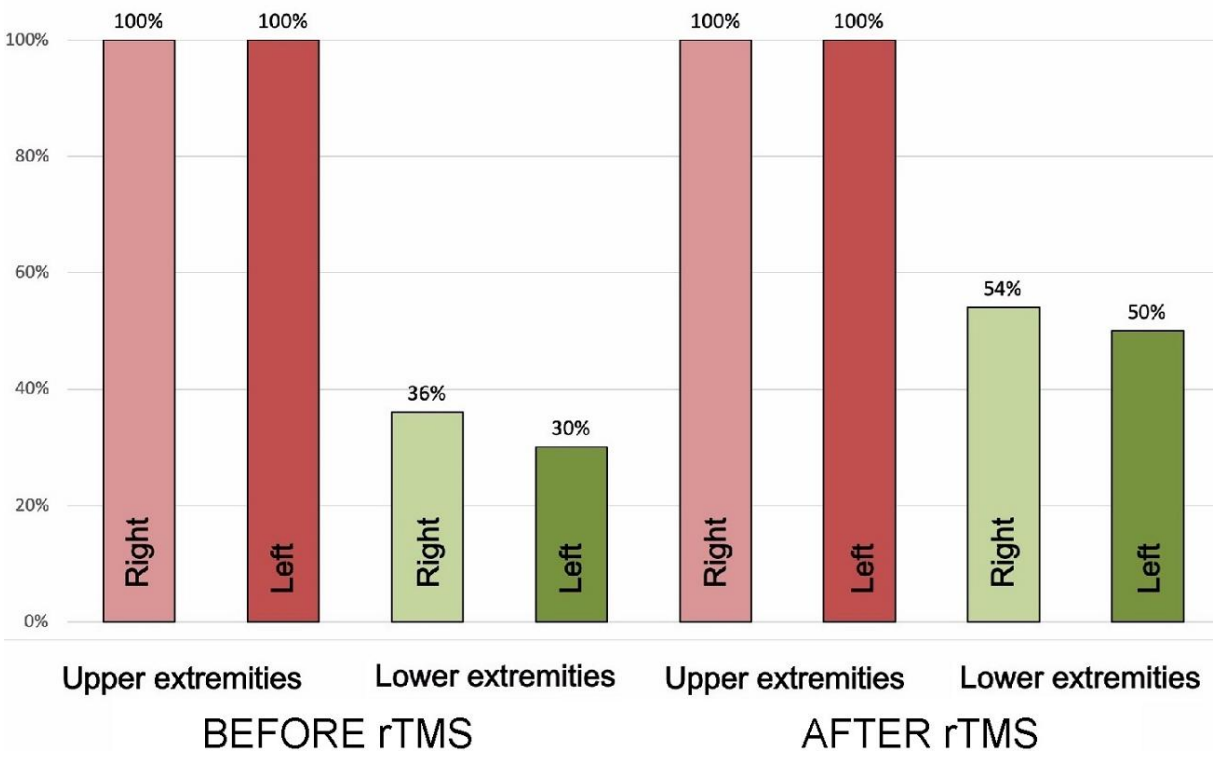

Figure 2. Summary of results from SSR recordings providing data on the function of the autonomic centers and pathways in the spinal cord of patients after iSCI expressed in percentages, before and a year after applying of rTMS therapy.

Discussion

The purpose of this study was to draw attention to the effectiveness of rTMS in patients with iSCI at thoracic levels supported by the results from SSR examinations performed before and after therapy. To our knowledge, similar studies that combine rTMS therapy in iSCI patients and SSR evaluation have not been performed, except the study of Kurt et al. (1996) and Cariga et al. (2002). However, no one of the mentioned researches did not evaluate results of the long term rehabilitation with rTMS. There have been many studies that tested the effectiveness of rTMS in the iSCI subjects concerning the assessment focused on the sensorimotor function improvement (Belci et al. 2004, Benito et al. 2012, Kuppuswamy et al. 2011, de Araújo et al. 2017), and the changes in spasticity (Kumru et al. 2010). Despite the increased use of rTMS in iSCI, its mechanism of action remains elusive and poorly understood. Moreover, no conclusive evidence was observed, mainly because of the heterogeneity of available studies and different rTMS sessions parameters, and the use of subjective evaluation methods such as different scales. It can be concluded that there is no universal and repetitive pattern of rTMS stimuli algorithm based on a neurophysiological and mainly clinical method of treatment evaluation. Therefore, the degree of motor or sensory improvement of patients is different, and it is hard to compare studies and results presented by different authors.

The findings from Silber et al. (2000) illustrate that magnetic coil stimulation of the motor cortex, so the one that it is provided during rTMS therapy, leads to skin sympathetic nerve activity (Silber et al. 2000). It suggests that rTMS may enhance the autonomic nervous system; thus, it may be a promising tool in the restoration of bladder sphincter function. Consequently, it may trigger a functional recovery in iSCI patients (Ellaway et al. 2014). In

addition, SSR as a method that measures the autonomic nervous system function can shed important light onto the functional recovery mechanism in iSCI patients and helps to assess its broader effects, including rTMS safety profile concerning its influence on the autonomic nervous pathways.

Main limitations of the presented study and all studies that use rTMS are also the technical difficulties in performing rTMS in humans. The electrical current induced into the cortex area reaches only a few centimetres in depth. The stimulation is non-selective so, all effects cannot be predicted. Additionally, low number of examined patients and the variation in brain anatomy limit the possibility to design a well-prepared clinical trial.

SSR and rTMS combined studies should be developed, because they may enhance the understanding of the cortical mechanisms of the autonomic regulation and spinal cord regenerative mechanisms. Further studies with rTMS therapy within the autonomic nervous system as a primary outcome will be helpful to understand longer-lasting effects on neuroplasticity. Such approach may allow modulating autonomic activity for therapeutic purposes to improve functional recovery of iSCI patients.

Conclusions

By means of comparative SSR studies, the hypothesis was verified that the rTMS application with a frequency of 20-22 Hz effectively improves the transmission of nerve impulses from supraspinal centers associated with the control of the spinal centers function and autonomic pathways, and thus, functional efficiency in patients after incomplete spinal cord injury.

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