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Effects of Repetitive Transcranial Magnetic Stimulation on Neuropathic Pain and Walking Ability in Patients with Incomplete Spinal Cord Injury

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The purpose of this study was to investigate the effects of rTMS on neuropathic pain and walking ability in patients with iSCI. 10 subjects were assigned to each of the experimental group (10 Hz rTMS) and the control group (5 Hz rTMS group). The rTMS intervention was administered 5 times a week for 20 minutes each time for 6 weeks. All measurements were performed before rTMS intervention and 6 weeks after rTMS intervention. In this study, VAS (Visual Analog Scale) and SF-MPQ (Short Form - McGill Pain Questionnaire) were applied to evaluate the pain of patients with spinal cord injuries. Gait endurance was evaluated by the 6-minute walking test (6MWT), and walking speed was evaluated by the 10-m walking test (10MWT). In the comparison between each group, the experimental group showed significant differences in the post-intervention SF-MPQ, 6-minute walking test, and 10-meter walking test ($p < 0.05$), and the control group showed a significant difference in the 10-minute walking test ($p < 0.05$). In the comparison between the two groups, there was no significant difference in all variables after intervention ($p > 0.05$). High-frequency rTMS can help reduce neuropathic pain in clinical practice and improve walking ability in patients with incomplete spinal cord injury.

Keywords : neuropathic pain, repetitive transcranial magnetic stimulation, spinal cord injury.

1. Introduction

Incomplete Spinal cord injury (iSCI) is when a part of the motor or sensation below the damaged area is preserved due to partial damage or compression of the spinal cord. The causes of iSCI include sports injuries, car accidents, falls, and industrial accidents. The body and brain transmit signals through the spinal cord and peripheral nerves. iSCI is a disease caused by interruption of signal transmission between the brain and muscles. When the nerve pathways are damaged, motor signals from the brain are not transmitted to the spinal cord and the body's sense of touch is not transmitted to the brain, resulting in sensory and motor control impairments below the level of injury after spinal cord injury. In addition, it causes many secondary problems such as the respiratory system, circulatory system, urinary system, and musculoskeletal system [1, 2].

To recover sensory and motor function in patients with iSCI, repetitive transcranial magnetic stimulation (rTMS) can be applied along with conservative physical therapy and exercise therahy [1]. rTMS has been reported to have long-term potentiation or depression effects on neural circuit activity [2]. High-frequency rTMS more than 30 Hz increases the neuronal activity of axons in the corticospinal pathway, and low-frequency rTMS less than 20 Hz decreases neuronal activity in the corticospinal pathway [3].

One of the serious complications after iSCI is neuropathic pain, which can have a serious impact on limiting daily life [4]. Various pharmacological and interventional therapies have been tried to solve neuropathic pain, but there are limitations in reducing pain [5]. In a study on the mechanism of neuropathic pain after iSCI, it was reported that the upstream caused by changes in the brain and downstream caused by the changes in the damaged nerve root were related to neuropathic pain. Pain in patients with iSCI is divided into pain from nociceptors and neuropathy pain from somatosensory [6]. Patients with spinal cord injury with neuropathic pain are difficult to treat clinically because it is difficult to analyze the mechanism of pain [7]. However, non-invasive brain stimulation, especially rTMS, has been reported to be helpful in treating central neuropathy pain or trigeminal

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neuralgia after stroke [8]. Spinal cord injury causes sensorimotor impairment, which reduces the walking ability of iSCI patients [9]. iSCI patients can only walk a short distance indoors or outdoors, so they need the assistance of another person or a walking device [10]. Therefore, improving the walking ability and quality of iSCI patients is very important for rehabilitation goals. According to previous studies, rTMS has been shown to be effective in improving the walking ability of iSCI patients [11].

As such, functional disability and pain, which are the main clinical symptoms of iSCI patients, can be recovered after rTMS, but studies on the effect of rTMS on the mechanism and structure of the central nervous system are insufficient. Therefore, our study was conducted to evaluate the effect of rTMS on neuropathic pain and recovery of walking ability in patients with incomplete spinal cord injury.

2. Materials and Methods

2.1. Participants

The study was conducted on 20 patients with spinal cord injury who are admitted to a rehabilitation hospital, and all participants gave written informed consent to participate in the study. The inclusion criteria for study subjects are as follows. (1) Neuropathic pain below the lesion level (T10-L4) for at least 3 months (2) Incomplete spinal cord injury (ASIA scale D or E grade) (3) Patients who can walk independently without a walking aid. Orthopedic problems such as rheumatoid disease or diabetes or metal insertion into the head or vertebrae, epileptic seizures, and pacemakers were excluded. This study was conducted with the approval of the Bioethics Committee of Joongbu University (JIRB-2022111301-01). The G-Power program (G power version 3.1, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany) was used to calculate the sample size of this study, and a total of 20 subjects participated.

2.2. Study design

This study was designed as a prospective, randomized, double-blind, clinical trial. The sealed envelopes marked 1 or 2 were randomized to separate the subjects. The subjects who selected the envelope marked with 1 were assigned to the experimental group (10 Hz-rTMS), and the subjects who selected 2 were assigned to the control group (5 Hz-rTMS). The rTMS intervention was administered 5 times a week for 20 minutes each time for 6 weeks. The subjects received an additional 30 minutes of neurological physical therapy.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation (rTMS)

For rTMS application, Magstim Rapid2 (Magstim Co Ltd, Wales, United Kingdom) was used, and the cerebral cortex was stimulated non-invasively using a figure 8 coil. rTMS was applied to the M1 lower extremity motor area (i.e. vertex, Cz) based on the brain area coordinates of the International 10-20 EEG system. The resting motor threshold (RMT) was the minimum stimulation intensity that induced electromyographic responses of 50 μV or more 5 times or more after 10 stimulations, and was evaluated in extensor hallucis longus. The intensity of rTMS was set at 100 % of the individual RMT. rTMS was delivered at 10 Hz or 5 Hz as 10 s trains separated by 10 s for 20 minutes [12].

2.4. Outcome measure

In this study, Visual Analog Scale (VAS) and Short Form - McGill Pain Questionnaire (SF-MPQ) were applied to evaluate the pain of spinal cord injury patients. Gait endurance was evaluated by the 6 minute walk test (6MWT) and gait speed was evaluated by the 10 meter walk test (10MWT). All measurements were performed before rTMS intervention and after 6 weeks of rTMS intervention.

2.4.1. Visual Analog Scale (VAS)

A 10-score visual analog scale (VAS) was used to evaluate pain, and “0” and “10” of VAS mean “no pain” and “worst pain”, respectively. The higher the score, the more severe the pain, and the intra-measurement reliability of VAS is r = 0.77 [13].

2.4.2. Short Form - McGill Pain Questionnaire (SF-MPQ)

The short-form McGill Pain Questionnaire (SF-MPQ) can evaluate the intensity and quality of pain, and consists of 15 representative words in the categories of sensation (n = 11) and activity n = 4). The SF-MPQ uses a 4-point Likert scale (0 = no pain, 1 = mild, 2 = moderate, 3 = severe). In addition, the sensory and activity scores are summed, and the higher the score, the more severe the pain. The intra-measurement reliability of SF-MPQ is r = 0.89 [14].

2.4.3. 6 minute walk test (6MWT)

The 6MWT is widely used as a method to evaluate walking endurance. The total distance (meter) that the subject walked a distance of 30-m for 6 minutes was recorded. It has high test-retest reliability in measuring

walking endurance of patients with various neurological problems or cardiopulmonary disease (ICC=0.94) [15].

2.4.4. 10 m walk test (10MWT)

The 10MWT is a method for evaluating walking speed. The subject walks a total of 14-m and evaluates 10-m excluding the initial acceleration section of 2-m and the final deceleration section of 2-m. The intra-measurement reliability of the 10MWT is r = 0.88 and the inter-measurement reliability is r = 0.99, which is very high [16].

Independent-t test and chi-square test were used to compare the differences in general characteristics between the experimental group and the control group. Paired-t test was used to evaluate the pre- and post-intervention effects of each group. Independent-t test was used to compare the effects after intervention between the two groups. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). For all analyses, p values < 0.05 were considered significant.

3. Results and Discussions

This study was conducted to investigate the effects of 10 Hz rTMS and 5 Hz rTMS applied to the M1 of iSCI patients on neuropathic pain, gait endurance and gait speed. In this study, iSCI patients with ASIA D and E grades had lower extremity muscle strength of F or higher, and those who could walk more than 30 m on their own were selected.

In this study, VAS and SF-MPQ were performed to evaluate lower extremity neuropathic pain in patients with iSCI. 6MWT was conducted to evaluate walking endurance and 10MWT was conducted to evaluate walking speed.

In Table 1, there was no statistically significant difference in the general characteristics of the subjects before intervention. Table 2 presents the mean and standard deviation data of the two groups before and after intervention.

Table 1. General and medical characteristics of subjects.

	EG (n=10)	CG (n=10)
Age (years)	52.5±6.04[a]	55.7±4.78
Sex (male/female)	6/4	5/5
Duration (month)	1.5±1.25	1.3±1.23
ASIA grade (D/E)	4/6	3/7
SCI level (T10/T11/T12/L1/L2/L3/L4)	(1/1/1/2/1/2/2)	(1/1/1/1/1/3/2)
Quality of Pain (freezing/tingling/Burning/allodynia/pressing/tugging/stabbing)	(1/2/3/1/1/1/1)	(1/1/2/2/1/1/2)

[a]Mean±SD, EG: 10 Hz rTMS, CG: 5 Hz rTMS

In comparison between each group, the experimental group showed a significant difference in the SF-MPQ, 6MWT, and 10MWT after intervention ($p < 0.05$) and the control group showed a significant difference in 10MWT ($p < 0.05$). In the comparison between the two groups, there was no significant difference in all variables after intervention ($p > 0.05$).

rTMS is a non-invasive method that can induce immediate or lasting changes in motor cortex excitability. Applying rTMS to the motor cortex (M1) can reduce neuropathic pain of various causes, such as SCI and post-stroke pain, amputation pain, and brachial avulsion pain [17]. Local excitability changes in the motor cortex induced by rTMS are related to pain [17]. It also reorgination sensory motor cortex after neurological lesions [18]. Various mechanisms for the pain reducing effect of rTMS have been reported. Application of rTMS results in local changes in the brain by restoration of inhibition in the motor cortex [19]. In addition, activation of the perigenual cingulate and orbitofrontal areas that control pain, Activation of gray matter around the brainstem periaqueductal leading to inhibition of descending nerve pathways from the cerebrum to the spinal cord,

Table 2. Comparison of change in characteristics of the experimental group and control group.

	EG (n=10)	CG (n=10)	t	*p*
VAS (score)				
Pre-test	7.10±1.28[a]	7.90±1.19	-1.43	0.16
Post-test	5.80±1.47	7.10±1.52	-1.93	0.06
t	1.99	1.23		
p	0.07	0.24		
SF-MPQ				
Pre-test	38.90±5.52	39.30±4.98	-0.16	0.86
Post-test	30.50±6.65	35.80±7.50	-1.67	0.11
t	4.48	1.40		
p	0.00	0.19		
6-minute walk test (m)				
Pre-test	217.80±26.12	219.10±32.16	-0.09	0.92
Post-test	253.40±36.53	245.00±44.19	0.46	0.64
t	-2.80	-1.49		
p	0.02	0.16		
10-m walk test (s)				
Pre-test	59.80±5.73	61.40±7.08	-0.55	0.58
Post-test	35.10±12.26	47.20±20.12	-1.62	0.12
t	6.52	2.28		
p	0.00	0.04		

[a]Mean±SD, EG: 10 Hz rTMS, CG: 5 Hz rTMS

Activation of mechanisms that promote secretion of endogenous opioids can help reduce pain [19, 20].

A previous study reported a 30 % reduction in chronic pain when high-frequency rTMS was applied to the lower extremity motor cortex [21]. In a meta-analysis related to rTMS, it was reported that applying rTMS to the motor cortex helps reduce various neuropathic pain [22]. Our results are consistent with these previous studies and meta-analyses. The application of 10HZ rTMS conducted in this study is thought to have an analgesic effect due to neuroplastic changes in the thalamic nucleus, anterior cingulate cortex, gray matter around the brainstem aqueduct, and motor cortex related to pain control [23, 24, 25].

Application of rTMS increases signals from N-methyl-D-aspartate (NMDA) and brain-derived neurotrophic factor (BDNF) receptors [26]. This has a positive effect on motor cortex excitability and synaptic connections [27]. In this study, significant differences were found in the 6MWT and 10MWT after rTMS was applied. After applying rTMS, it is thought that there was a positive effect on the improvement of gait endurance and gait speed by strengthening neuronal synaptic connectivity. rTMS is helpful in neurological functional connection for movement of the lower limbs.

At 10MWT, when the walking speed is less than 0.4 m/s, it is judged that indoor walking is possible, when it is 0.4-0.8 m/s, indoor and limited outdoor walking is possible, and when it is over 0.8 m/s, outdoor walking is possible [28]. After applying rTMS, the walking speed increased to 0.28 m/s in the experimental group and 0.21 m/s in the control group, respectively. There was no difference between the two groups, but indoor walking ability was improved. It is considered that it was difficult to reach a normal walking speed because the sensory ability of the lower extremities was reduced due to iSCI.

In a previous study, when 20 Hz rTMS was applied to patients with incomplete spinal cord injury, a significant improvement in walking ability was reported in the 10MWT, time up go test [29]. Another study reported that 10 Hz rTMS and 20 Hz rTMS were applied to the lower extremity motor area of patients with incomplete spinal cord injury and helped improve gait ability and muscle tone [30-33].

The limitations of the results of this study are as follows. Due to the small number of participants in this study, it is difficult to generalize the treatment to all patients with incomplete spinal cord injury. In addition, the intervention was conducted for 6 weeks, and long-term effects could not be judged because follow-up was not conducted. Since the subjects were patients in the acute phase within 3 months, the effect of spontaneous recovery on the experiment could not be excluded.

4. Conclusion

In the results of this study, when 10 Hz rTMS and 5Hz rTMS were applied to the lower extremity exercise area (M1), there was no significant difference in pain and walking ability. However, 10 Hz rTMS showed significant differences in pain, gait endurance, and gait speed.

It is thought that high-frequency rTMS can help reduce neuropathic pain and improve walking ability in patients with incomplete spinal cord injury in clinical. In future studies, the strength, frequency, and application time of rTMS should be considered. And it is necessary to secure objective data through functional magnetic resonance imaging or 3-D gait analysis.

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References

[1] M. Oudega and M. A. Perez, J. Physiol. **590**, 3647 (2012).
[2] M. Belci, M. Catley, M. Husain, H. L. Frankel, and N. J. Davey, Spinal Cord. **42**, 417 (2004).
[3] H. Kumru, N. Murillo, J. V. Samso, and J. Valls-Sole, Neurorehabil. Neural Repair **24**, 435 (2010).
[4] D. D. Cardenas and E. R. Felix, PM&R **1**, 1077 (2009).
[5] D. D. Cardenas and M. P. Jensen, J. Spinal Cord Med. **29**, 109 (2006).
[6] T. N. Bryce, F. Biering-Sorensen, and N. B. Finnerup, Spinal Cord. **50**, 413 (2012).
[7] C. Schuld, S. Franz, and K. Bruggemann, J. Spinal Cord Med. **39**, 504 (2016).
[8] A. Leung, M. Donohue, and R. Xu, J. Pain. **10**, 205 (2009).
[9] L. Davis and J. Martin, J. Neurosurg. **4**, 483 (1947).
[10] L. A. Simpson, J. J. Eng, and J. T. Hsieh, J. Neurotrauma **29**, 1548 (2012).
[11] E. G. Widerstrom-Noga, E. Felipe-Cuervo, and J. G. Broton, Arch. Phys. Med. Rehabil. **80**, 580 (1999).
[12] A. V. L. de Araújo, V. R. N. Barbosa, G. S. Galdino, F. Fregni, and T. Massetti, Trials. **18**, 522 (2017).
[13] A. M. Boonstra, H. R. Schiphorst Preuper, and M. F. Reneman, Int. J. Rehabil. Res. **31**, 165 (2008).
[14] Y. Yakut, E. Yakut, and K. Bayar, Clin. Rheumatol. **26**, 1083 (2007).
[15] K. A. Mossberg, Am. J. Phys. Med. Rehabil. **82**, 385 (2003).

[16] C. M. Dean, C. L. Richards, and F. Malouin, Arch. Phys. Med. Rehabil. **81**, 409 (2000).
[17] J. P. Lefaucheur, Clin. Neurophysiol. **36**, 117 (2006).
[18] K. J. Kokotilo, J. J. Eng, and A. Curt, J. Neurotrauma **26**, 2113 (2009).
[19] J. P. Lefaucheur, X. Drouot, and I. Menard-Lefaucheur, Neurology **67**, 1568 (2006).
[20] L. Garcia-Larrea and R. Peyron, Neuroimage **37**, S71 (2007).
[21] R. Defrin, L. Grunhaus, and D. Zamir, Arch. Phys. Med. Rehabil. **88**, 1574 (2007).
[22] L. Garcia-Larrea, R. Peyron, and P. Mertens, Pain **83**, 259 (1999).
[23] L. Garcia-Larrea and R. Peyron, Neuroimage **37**, 71 (2007).
[24] S. Yang and M. C. Chang, Front. Neurol. **11**, 114 (2020).
[25] Y.-W. Bai, Q.-H. Yang, P.-J. Chen, and X.-Q. Wang, Front. Immunol. **14**, 1172293 (2023).
[26] Y. Z. Huang, J. C. Rothwell, M. J. Edwards, and R. S. Chen, Cereb. Cortex. **18**, 563 (2008).
[27] Y. R. Yang, C. Y. Tseng, S. Y. Chiou, K. K. Liao, and S. J. Cheng, Neurorehabil. Neural. Repair. **27**, 79 (2013).
[28] C. M. Dean, C. L. Richards, and F. Malouin, Arch. Phys. Med. Rehabil. **81**, 409 (2000).
[29] J. Benito, H. Kumru, N. Murillo, U. Costa, and J. Medina, Top. Spinal Cord Inj. Rehabil. **18**, 106 (2012).
[30] S. G. Ji, H. G. Cha, and M. K. Kim, J. Magn. **20**, 427 (2015).
[31] H. Kumru, J. Benito, N. Murillo, J. Valls-Sole, and M. Valles, Neurorehabil. Neural Repair **27**, 421 (2013).
[32] J. Yang, R. Liang, L. Wang, C. Zheng, X. Xiao, and D. Ming, Sec. Environmental, Front. Physiol. **12**, 587515 (2021).
[33] H. Fan, Y. Song, X. Cen, P. Yu, I. Bíró, and Y. Gu, Front. Hum. Neurosci. **15**, 620573 (2021).