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The Effect of High Frequency Repetitive Transcranial Magnetic Stimulation on Gait Abilities in Incomplete Spinal Cord Injury Patients: A Randomized Controlled Trial

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This study was conducted to investigate the effects of high frequency repetitive transcranial magnetic stimulation (rTMS) on gait abilities in incomplete spinal cord patients. 16 subjects were randomly assigned to each of 8 experimental and control groups. 20 Hz high frequency rTMS was applied to the experimental group for 20 minutes per day, 5 times a week for a total of 4 weeks and sham rTMS was applied to the control group. The subjects were assessed for gait abilities by 10 meter walk test (10MWT), 6 minute walk test (6MWT) and community walk test (CWT). A significant improvement in 10MWT, 6MWT and CWT was observed after intervention in the experimental group ($p < 0.05$), and there was a significant improvement in all evaluation items compared to the control group ($p < 0.05$). The results of this study suggest that high frequency rTMS applied to primary motor cortex (M1) positively affects gait abilities in incomplete spinal cord injury patients.

Keywords : community ambulation, gait, high frequency repetitive transcranial magnetic stimulation, magnetic field, spinal cord injury

1. Introduction

There are about 2.5 million patients with spinal cord injury (SCI) worldwide. The biggest problem with SCI is that it remains a serious impairment due to loss of motor and sensory [1]. Patients with SCI have loss of spontaneous movement and sensation, a result of communication problems between the brain and the damaged spinal cord. Lesions are divided into complete injury with no function of nerves below the damaged level and incomplete injury with some nerve functions remaining. Patients with SCI are characterized by long-term hospitalization and follow-up, and limited social participation [2]. This results in functional independence and poor quality of life, and therefore requires an effective rehabilitation program in both acute and chronic patients [3].

American Spinal Injury Association Impairment Scale (AIS) is classified from A to E according to the severity of SCI and is widely used in clinical practice [4]. AIS C and D grades refer to incomplete damage, in which the function below the level of neurological damage remains incompletely. In case of damage below L1 level, it is possible to walk after wearing braces, but it requires a considerable amount of energy [5]. The quality and ability of ambulation in patients with SCI is affected by sensorimotor dysfunction, such as spasticity, weakness of lower extremity muscle strength, sequencing disorder of muscle activation [6].

Community ambulation is defined as the ability of ambulation and independence in activities such as crossing the street, shopping and walking at specified velocities within the community [7]. Class D patients in AIS have a good prognosis for walking, but not all patients are able to ambulation in the community. Previous studies have shown that walking speed and endurance are the major indicators of community ambulation. But patients with incomplete spinal cord injury (iSCI) are slower and less efficient of walking [8].

One way to restore function after SCI is to improve neuroplasticity. The studies of neuroplastic changes after SCI are not as much as that after brain lesion. However, previous studies on animals with iSCI reported collateral

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sprouting of spared exons and cortical remapping [9]. In another study, after hemi-section of the cervical spinal cord, it has been observed that injured motor tracts sprout collaterally and integrate into propriospinal circuits [10].

In addition, according to previous study, even patients with incomplete SCI in chronic phase showed improvement in walking ability by intervention [11]. Based on the results of these previous studies, the subjects of this study were selected as chronic iSCI patients more than 6 months after SCI.

However, spontaneous plasticity after SCI is not sufficient for functional recovery, so it is necessary to improve the strength of synaptic connections through stimulation of the brain or spinal cord [12].

rTMS is a non-invasive, painless brain stimulator that has been reported to improve neurological and functional outcomes in patients with neurological disorders with motor deficit such as SCI [13]. Especially, high frequency rTMS enhances synaptic plasticity, activity dependent meta-plasticity, network excitability and activation of feedback loops [14].

Repetitive transcranial magnetic stimulation (rTMS) is effective in forming neurological recovery because it selectively stimulates specific pathways along the central nervous system. rTMS uses biphasic magnetic pulses to stimulate the corticospinal tract, primary motor cortex, and spinal cord to reorganize nerve system [15]. Therefore, rTMS has been in the spotlight as an interventional method to improve the output of voluntary movement of patients with movement disorders [16].

After applying rTMS to patients with iSCI, previous studies found long-lasting changes in the cerebral cortex and cortical spinal cord, and showed improved corticospinal synaptic transmission, decreased spasticity, and improved sensorimotor function [17-19]. Benito *et al.* applied 15 session rTMS over primary motor cortex (M1) to subjects with iSCI. The results of the study showed significant improvement in the evaluation of the AIS and gait function [19].

There have been previous studies applying rTMS to patients with iSCI but few, and a little study on the effects of community ambulation. Therefore, the purpose of this study was to investigate the effects of high frequency rTMS over M1 area of patients with iSCI on gait speed, gait endurance and community ambulation.

2. Materials and Methods

2.1. Participants

This study was conducted in 16 patients with SCI who are admitted to a rehabilitation hospital.

The inclusion criteria for selection are as follows: (1) incomplete SCI (AIS D) by trauma, (2) thoracic or lumbar SCI, (3) more than 6 months after SCI, (4) Mini-Mental State Examination (MMSE-K) score of 21 points or more, and (5) independent walking with / without using device. Patients with orthopedic problems such as joint contracture or fracture were excluded. All subjects had no history of brain-related diseases (e.g., stroke), either current or previous.

Informed consent was obtained from all patients according to the ethical standards of the Declaration of Helsinki.

2.2. Study design

After the initial evaluation, subjects were randomly assigned to experimental groups (n = 8) or control groups (n = 8). Sealed envelopes marked with 1 or 2 were used for randomization, the subjects who choose the envelope marked with 1 were assigned to experimental groups and received real rTMS. All subjects were blinded to their group until the study was completed, and randomization and pre- and post-treatment assessments were performed by clinician 1 who was blinded to the group allocations. And the application of real rTMS and sham rTMS was performed by clinician 2 blinded to the group.

The patient received rTMS before treadmill training. The rTMS intervention was conducted for 20 minutes at a time, five times a week for 4 weeks.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation (rTMS)

Participants received rTMS using Magstim Rapid2 (Magstim Co Ltd, Wales, United Kingdom) with an angulated figure-eight-shaped coil. rTMS was applied over the bilateral lower limb motor area (i.e. vertex, Cz) localized in M1 in

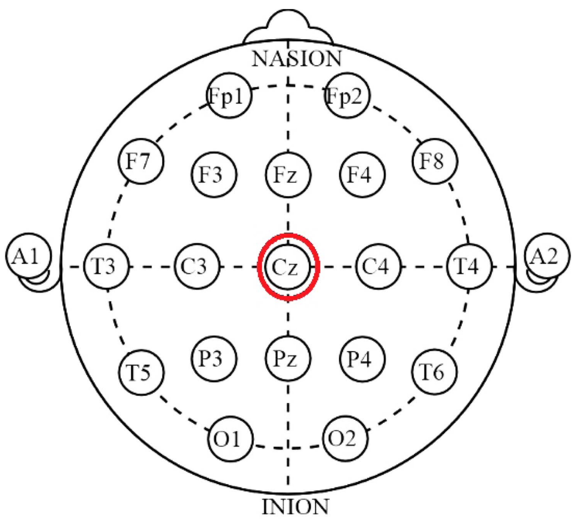

Fig. 1. (Color online) International 10-20 EEG system.

order to stimulate both lower limbs, based on the vertex position of the International 10-20 EEG system (see Fig. 1) [20]. The coil was placed tangential to the scalp for real rTMS and at 90° for sham rTMS.

Resting motor threshold (RMT) was assessed as the lowest stimulation intensity of TMS needed to elicit 5 or more electromyographic responses ≥ 50 μV on the extensor hallucis longus within 10 trials. In this study, the intensity was set to 100 % of the individual's RMT.

rTMS was delivered at 20 Hz as 10 s trains separated by 10 s for 20 minutes. Participants received rTMS before treadmill training using the same equipment during the same time of day.

2.4. Outcome measure

In this study, gait speed was evaluated by the 10 m walk test (10MWT), and gait endurance was evaluated by the 6 minute walk test (6MWT). The subjects' community ambulation ability was assessed by the community walk test (CWT). All measurements were performed before rTMS intervention and after rTMS intervention for 4 weeks.

2.4.1. 10 Meter Walk Test (10MWT)

The 10MWT is an evaluation tool for evaluating gait speed among gait abilities. Subjects are asked to walk a total of 14 meters, measuring 10 m of time excluding the 2 m acceleration period at the start and the 2 m deceleration period at the end. In this study, three measurements were taken and the average was used as data. The intra-measurement reliability of 10MWT is r = .88, and the inter-measurement reliability is r = .99 [21].

2.4.2. 6 Minute Walk Test (6MWT)

The 6MWT was originally a modification of the 12MWT and was developed to assess and monitor the functional capacity of patients with cardiopulmonary diseases to establish prognosis and to assess the extent of change through treatment. It is now widely used as a standard assessment of gait endurance in patients with various neurological problems as well as patients with cardiopulmonary diseases [22]. The 6MWT records the distance walked in meters for six minutes. In this study, the total distance (m) the subject walked on a 30 m straight line for 6 minutes was recorded. 6MWT has been reported to have high test-retest reliability for travelled distance measurements in patients with neurologic deficits (ICC = 0.94) [23].

2.4.3. Community walk test (CWT)

In accordance with a previous study of community ambulation conducted by Lerner-Frankiel *et al.*, subjects were required to walk at a comfortable pace for 300 m in the community near the hospital where they were admitted [24]. The time taken to walk 300 m was measured using a stop watch, and the coefficient was multiplied according to the level of walking aid used (no aid, ×1; ankle foot orthosis, ×2; mono cane, ×3; quadruped cane, ×4; ankle foot orthosis and mono cane, ×5; and ankle foot orthosis and quadruped cane, ×6) [25].

Differences in general characteristics between the experimental group and the control group before intervention were compared using the Mann-Whitney tests and chi-square tests. The Wilcoxon signed-rank tests were performed to assess the before and after effects in each group. The Mann-Whitney tests were used to assess differences between real rTMS and sham rTMS. For all analyses, p values < 0.05 were considered significant. Data were expressed as the mean ± standard deviation (SD) and statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results and Discussions

This study was conducted to investigate the effects of 20 Hz high frequency rTMS applied to M1 of patients with iSCI on gait speed, gait endurance, and ability of community ambulation. In general, since the posture and gait are anti-gravity activities, muscle strength of grade F or higher is required. AIS D refers to the case where paralyzed muscles have muscle strength of F or higher. In addition, AIS D patients were selected as subjects for this study because 95 % of patients with AIS D are expected to have the possibility of community ambulation [26].

The general characteristics of the subjects are summarized in Table 1, and there were no statistically significant differences in the characteristics of the subjects between the two groups.

In this study, the change in the subject's walking ability was evaluated in three categories: gait speed (10MWT), gait endurance (6MWT) and ability of community am-

Table 1. General and medical characteristics of subjects.

	EG (n = 8)	CG (n = 8)
Age (years)	62.5 ± 12.14[a]	63.5 ± 13.56
Sex (male/female)	5/3	4/4
Duration (month)	3.2 ± 1.23	3.1 ± 1.26
Weight (kg)	68.46 ± 10.02	69.43 ± 8.78
Height (cm)	168.73 ± 8.94	171.52 ± 9.56

[a]Mean ± SD, EG: rTMS + Treadmill training, CG: rTMS (shame Therapy + Treadmill training

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

	EG (n = 8)	CG (n = 8)	z	p
10-m walk test (m/s)				
Pre-test	0.55 ± 0.03	0.48 ± 0.05	–1.90	0.05
Post-test	0.83 ± 0.04	0.49 ± 0.02	–3.36	0.00
z	–13.87	0.18		
p	0.00	0.85		
6-minute walk test (m)				
Pre-test	172.88 ± 8.31	167.00 ± 9.79	–0.84	0.39
Post-test	235.25 ± 15.70	179.00 ± 6.27	–3.36	0.00
z	–9.80	–3.34		
p	0.00	0.01		
Community walk test (min)				
Pre-test	53.50 ± 7.15	45.37 ± 2.97	–1.84	0.06
Post-test	28.75 ± 1.58	40.12 ± 1.64	–3.37	0.00
z	11.28	4.10		
p	0.00	0.00		

[a]Mean ± SD, EG: rTMS + Treadmill training, CG: rTMS (shame Therapy + Treadmill training

bulation (CWT). The values of 10MWT, 6MWT and CWT in the experimental and control groups are summarized in Table 2.

As a result of 10MWT, about 0.28 m/s increased in the experimental group, and there was a significant improvement between pre-test and post-test ($p < 0.05$). It also showed a significant improvement in comparison between groups ($p < 0.05$). The results are shown in Fig. 2.

As a result of 6MWT, about 62 meters increased in the experimental group, and there was a significant improvement between pre-test and post-test ($p < 0.05$). It also showed a significant improvement in comparison between groups ($p < 0.05$). The results are shown in Fig. 3.

As a result of CWT, about 25 minutes decreased in the experimental group, and there was a significant improvement between pre-test and post-test ($p < 0.05$). It also showed a significant improvement in comparison between groups ($p < 0.05$). The results are shown in Fig. 4.

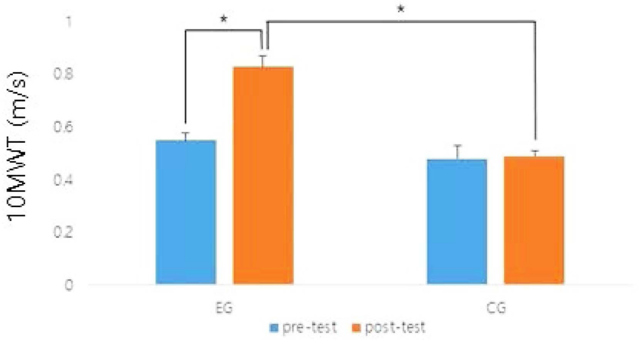

Fig. 2. (Color online) Comparison of change in 10MWT of the experimental group and control group.

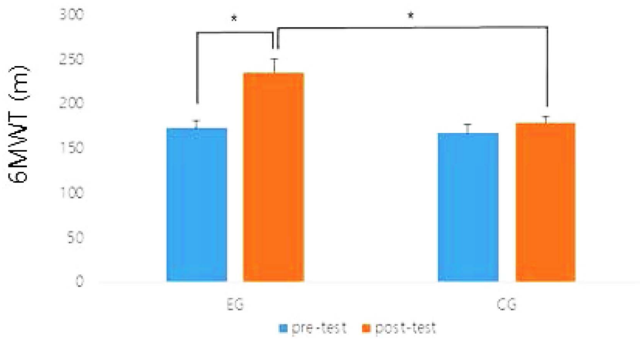

Fig. 3. (Color online) Comparison of change in 6MWT of the experimental group and control group.

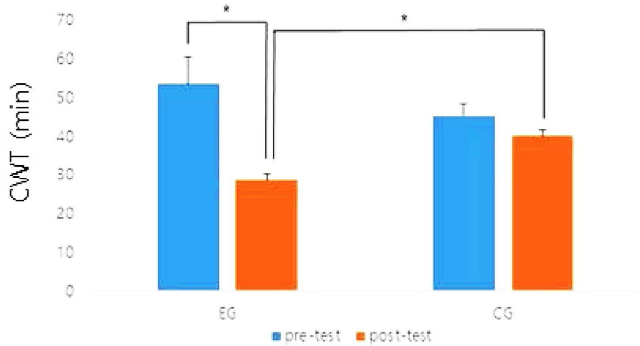

Fig. 4. (Color online) Comparison of change in CWT of the experimental group and control group.

Clinically, in the results of 10MWT, it is considered that indoor walking is possible when it is less than 0.4 m/s, indoor and limited outdoor walking is possible when it is 0.4-0.8 m/s, and outdoor walking is possible when it is 0.8 m/s or more. The experimental group showed that the outdoor walking ability was improved because the result of 10MWT after the experiment was increased to 0.8 m/s or more, and it can be said that it is directly related to the improvement of the evaluation of community walking ability (CWT) [21].

The mechanism by which high-frequency rTMS improved the gait function of iSCI patients is considered to be due to the descending control of spinal excitability through synaptic plasticity and neural reorganization of cortical and subcortical networks. Therefore, it was possible to promote neural connections responsible for motor function [27].

According to Belci *et al.*, a key mechanism for this functional effect is that rTMS modifies corticospinal projections by increasing motor cortical excitability, resulting in altered spinal excitability [28]. Recent animal studies have reported that the application of rTMS results in upregulation of N-methyl-D-aspartate (NMDA) receptors and an increase in brain-derived neurotrophic factor (BDNF) signaling, which also affects cortical excitability and synaptic connectivity [29, 30]. Furthermore, in this study, treadmill training was performed immediately after the application of rTMS. Thus, it is speculated that not only changes in synaptic connectivity through rTMS but also enhanced neural activity through motor learning were induced [31].

As with the results of this study, previous studies have reported improvement of gait ability through the application of high frequency rTMS in various diseases. In previous studies using high frequency rTMS, Lomarev *et al.* showed improvement in gait speed in patients with brain injury, and Yang *et al.* showed improvement in gait speed and dynamic balance [31, 32]. Chieffo *et al.* showed that lower limbs motor function was improved by applying a high frequency rTMS of 20 Hz to the cortical motor area of patients with chronic stroke [33]. Another study has shown improvement in 6MWT by applying high-frequency rTMS to patients with multiple sclerosis [34].

Especially, several previous studies have shown that the application of high frequency rTMS to SCI patients improves gait or motor function. In a previous study of patients with AIS D grade SCI, 20 Hz high frequency rTMS was applied to the experimental group and sham rTMS to the control group. The experimental results showed significant improvement in MAS, 10MWT, cadence, step length, and TUG [19]. Ji *et al.* reported that applying 10 Hz rTMS to subacute stage iSCI patients had a positive effect on motor recovery in lower extremities [35]. In another study, the authors demonstrated a significant improvement in the lower-extremity motor score, 10 MWT, and MAS by applied 20 Hz rTMS in the leg motor area of patients with iSCI for 15 days [36]. These results are consistent with a significant improvement in gait abilities by the high frequency rTMS applied to the motor area of patients with iSCI as in this study.

This study has some limitations. First, the number of samples was small. This resulted in a statistically significant improvement before and after intervention in the experimental group, but attention should be paid to the significance of the comparisons between the groups. Second, because of the absence of a follow-up after rTMS intervention period, so the duration of the effect could not be determined. Future study needs to address these limitations and provide more specific guidelines for applying rTMS to iSCI patients.

4. Conclusion

In terms of restoring the function in iSCI patients, gait is particularly important because it relates to quality of life. AIS Class D iSCI patients are many possibilities for outdoor walking represented by community ambulation as well as indoor walking, but there are many limitations due to various kinematic problems. The results of this study showed that 20 Hz high frequency rTMS can improve gait speed, gait endurance, and ability of community ambulation in AIS Class D iSCI patients. Based on the results of this study, we suggest that applying high frequency rTMS to the M1 region of iSCI patients is positive as an adjuvant therapy to improve gait ability. In future studies, if the measurement of brain activity using functional magnetic resonance imaging is added, more objective data will be obtained.

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