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The Effect of High Frequency Repetitive Transcranial Magnetic Stimulation Combined with Treadmill Training on the Recovery of Lower Limb Function in Chronic Stroke Patients: A Randomized Controlled Trial

Si A Lee[1] and Hyun Gyu Cha[2]*

[1] *Department of Physical Therapy, College of Rehabilitation Sciences, Daegu University, Jillyang, Gyeongsan, Gyeongbuk 38453, Republic of Korea*
[2] *Department of Physical Therapy, Joongbu University, Geumsan 32713, Republic of Korea*

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This study was conducted to investigate the effects of high frequency repetitive transcranial magnetic stimulation (rTMS) combined with treadmill training on recovery of lower limb function in chronic stroke patients. 13 subjects were randomly assigned to 7 in the experimental group and 6 in the control group. The experimental group was applied 5 Hz high frequency rTMS of 15 minutes and treadmill training of 20 minutes, and the control group was applied sham rTMS of 15 minutes and treadmill training of 20 minutes per day, 5 times a week for a total of 4 weeks. The subjects were assessed for gait speed by 10-meter walk test (10MWT), gait endurance by 6-minute walk test (6MWT) and ability of dynamic stability by Timed up and go test (TUG). A significant improvement in 10MWT, 6MWT and TUG 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) combined with treadmill training has a positive effect on the recovery of lower limb function in chronic stroke patients.

Keywords : stroke, gait, high frequency repetitive transcranial magnetic stimulation, magnetic field, magnetic stimulation, lower limb function

1. Introduction

Stroke is one of the leading causes of morbidity and mortality in adults, and is the leading cause of disability, particularly disorder of lower extremity function and gait [1]. Stroke patients have difficulty walking due to impaired movement of the legs, poor balance and postural control due to damage to the central nervous systems. In particular, normal gait patterns become more difficult due to the occurrence of compensating action of the non-paralyzed leg to compensate for impaired movement of the paralyzed leg [2].

Nowak *et al.* reported that both hemispheres must be reciprocally inhibited in order to function normally but stroke patients collapsed in the interhemispheric balance, resulting in further suppression of the affected hemisphere, resulting in motor control and dysfunction [3].

About two-thirds of patients after stroke have gait disturbances, which include reduced step length and number of steps per minute, asymmetrical patterns in both lower extremities [4]. And asymmetric movements of the lower limbs require more energy and increase the load on the joints. This problem persists even in the chronic stage and adversely affects the level of daily living [5]. Therefore, recovery of lower extremity function for efficient walking is often a key goal of rehabilitation.

The central nervous system (CNS) may be able to expect to recover to some extent through plasticity mechanisms and reconstruction of residual nerve pathways after injury, but has limitations. Therefore, it is necessary to apply an aggressive therapeutic approach that can improve the plasticity of the CNS to patients with CNS injury [6].

Previously, the intervention method of stroke patients was limited to functional induction, but recently, as a treatment method based on neuroplasticity has been

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*Corresponding author: Tel: +82-41-750-6748
Fax: +82-41-750-6166, e-mail: guychk@naver.com

developed with the advancement of science, it has attracted attention as an approach for the recovery of functions of patients with central nervous system injury.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of stimulating nerve cells in the target brain region with electric currents induced in the tissue by rapidly alternating magnetic fields (electromagnetic induction). The effect by rTMS causes a change not only in the target cortical region, but also in the area away from it [7]. rTMS can achieve the desired effect through the regulation of different neural excitability of the brain region according to the frequency of stimulation. High-frequency rTMS activates neural excitability, while low-frequency rTMS suppresses neural excitability [8]. rTMS can cause long-term potentiation and long-term depression associated with brain neuroplasticity, and especially long-term potentiation increases synaptic connections, positively affecting motor learning [9].

Several studies have reported improvement in leg function after applying high frequency rTMS to stroke patients. Lomarev *et al.* reported that gait speed was significantly improved by applying high-frequency rTMS to patients with brain injury [10]. Yang *et al.* investigated the effects of high-frequency rTMS in combination with treadmill training on the cortical excitability and gait in 20 patients with brain injury. As a result, there was a significant effect on the modulation of corticomotor inhibition and improvement in gait speed and dynamic balance [11].

However, most of the previous studies had a short intervention period, and few studies were conducted with chronic stroke patients on the effects of rTMS in combination with treadmill training.

Therefore, the purpose of this study is to investigate the effect of 5 Hz high frequency rTMS in combination with treadmill training on the lower extremity function of chronic stroke patients and provide them as basic data for the treatment of magnetic stimulation in stroke patients.

2. Materials and Methods

2.1. Participants

This study was conducted in 13 patients with stroke who are admitted to a rehabilitation hospital.

The inclusion criteria for selection are as follows: (1) diagnosed with stroke, (2) 6 months or more and less than 12 months after stroke (chronic stage), (3) Mini-Mental State Examination (MMSE-K) score of 21 points or more (understanding the inspector's instructions), (4) no neurological deficits in cerebellum or brainstem, and (5) independent walking with/without using aids.

The exclusion criteria for selection are as follows: (1) orthopedic problems such as joint deformity or contracture, (2) a device inserted into the cerebrovascular system (3) a cardiac pacemaker, and (4) a history of seizure.

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 = 7) or control groups (n = 6). Randomization was performed using a computer program, and all subjects were blinded to their group until the study was completed. Randomization and pre- and post-treatment evaluations were performed by clinician, and the application of real rTMS and sham rTMS was performed by other clinician. Both were blind to the subject's group allocation.

The patients received real rTMS or sham rTMS before treadmill training. The rTMS intervention was conducted for 15 minutes at a time, five times a week for 4 weeks.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation (rTMS)

Magstim Rapid2 (Magstim Co Ltd, Wales, United Kingdom), and a figure-of-eight coil with a diameter of 70 mm was used for rTMS intervention.

The subjects in the experimental group received real rTMS for 15 minutes followed by treadmill training for 20 minutes per day. The subjects in the experimental group received training five days per week for four weeks. The subjects in the control group received sham rTMS for 15 minutes and followed by treadmill training for 20 minutes per day on the same days.

To measure the motor-evoked potential, the recording electrode was attached on the tibia anterior muscle of the paralyzed side lower limb, the reference electrode was attached parallel to the direction of muscle fiber 30 mm away from the recording electrode, and the ground electrode was attached to the center of the instep of a foot of the same side [12].

After finding the hot spot inducing the strongest motor-evoked potential at the lowest intensity, the peak amplitude of 50 μV more than 5 times by stimulating 10 times was defined as the resting motor threshold.

The stimulation of this study was at 90 % of the resting motor threshold, and the primary motor cortex (M1) region of the brain was stimulated according to the International 10-20 EEG system with a train of 900 pulses during each treatment session. The train duration was 12 seconds with a 48 seconds intertrain interval.

When applying sham rTMS, the coil was placed at a 90-degree position in the subject's scalp so that no actual rTMS stimulation was induced [13].

2.3.2. Treadmill training

Subjects were trained on a motorized treadmill (Biodex, Shirley, New York) with a safety harness immediately after real or sham rTMS. The treadmill gait training consisted of 5 minutes of warm-up phase of 50 % of the patient's normal ground walking speed, 10 minutes of training phase of 80 % of the patient's normal ground walking speed, and 5 minutes of cool down stage of 50 % of the patient's normal ground walking speed. Treadmill training was performed by one physical therapist, and the physical therapist observed the subject's gait pattern during training and provided verbal feedback as needed [14].

2.4. Outcome measure

In this study, the subject’s gait speed was evaluated by the 10 meter walk test (10MWT), gait endurance was evaluated by the 6 minute walk test (6MWT) and dynamic balance ability was assessed by the Timed up and go test (TUG). All measurements were performed before rTMS intervention and after rTMS intervention for 4weeks.

2.4.1. 10-Meter Walk Test (10MWT)

10MWT is one of the most used evaluation methods to evaluate walking speed. Subjects are required to walk a total of 14 meters, and it is evaluated for the remaining 10 meters except for the initial acceleration section 2 meters and the last deceleration section 2 meters. In this study, the average value was used as the data after 3 repeated measurements. The intra-measurement reliability of 10MWT is r = .88, and the inter-measurement reliability is r = .99 [15].

2.4.2. 6-Minute Walk Test (6MWT)

The 6MWT is widely used as an assessment of gait endurance, evaluating the total distance walked for 6 minutes. In this study, it was evaluated at a straight line distance of 30 m, and the total distance the subject walked round-trip was recorded. 6MWT has been reported to have high test-retest reliability for gait measurements in patients with neurologic deficits (ICC=0.94) [16].

2.4.3. Timed Up and Go (TUG) test

TUG test is an evaluation method used to measure a subject's mobility or dynamic balance ability. The TUG test measures the time it takes for a subject to get up from a chair with armrests, walks 3 meters as fast as possible, and then return to sit on the chair. In this study, the average value was used as the data after 3 repeated measurements with a rest interval of 2 minutes. According to the time taken, mobility is divided into four grades: (1) normal mobility (< 10 seconds), (2) good mobility (< 20 seconds, can go outside alone or do not need walking aids), (3) limited mobility (< 30 seconds, cannot go outside alone or requires walking aids, and (4) dependent mobility (> 30 seconds, most of daily activities and mobility are dependent). TUG test has excellent intrarater (r = 0.99) and interrater (r = 0.98) reliabilities [17].

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 experimental and control group. 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 5Hz high frequency rTMS applied to M1 combined with treadmill training on recovery of lower limb function in chronic stroke patients.

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 lower limb ability was evaluated in three categories: gait speed (10MWT), gait endurance (6MWT) and ability of dynamic balance (TUG). The values of 10MWT, 6MWT and TUG in the experimental and control groups are summarized in

Table 1. General and medical characteristics of subjects. There was no statistically significant difference between the two groups as a result of using Mann-Whitney and chi-square tests.

	EG (n = 7)	CG (n = 6)
Age (years)	66.85 ± 4.05[a]	64.00 ± 3.57
Sex (male/female)	4/3	3/3
Duration (month)	7.57 ± 1.81	8.16 ± 1.72
Weight (kg)	66.71 ± 4.02	66.83 ± 9.41
Height (cm)	162.7328 ± 8.80	159.83 ± 8.23

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

Table 2. Comparison of change in characteristics of the experimental group and control group. When there was a statistically significant difference using Wilcoxon signed-rank and Mann-Whitney tests, symbols * and † were used to indicate.

	EG (n = 7)	CG (n = 6)	z	p
10-m walk test (s)				
Pre-test	34.42 ± 7.06	39.66 ± 1.96	–.21	.82
Post-test	26.71 ± 5.83	33.50 ± 5.24	–2.51	$.01^{\dagger}$
z	–2.37	–1.89		
p	$.01^{*}$	.05		
6-minute walk test (m)				
Pre-test	169.86 ± 3.53	165.83 ± 7.91	–1.21	.22
Post-test	244.00 ± 27.20	199.66 ± 33.64	–2.97	$.00^{\dagger}$
z	–2.37	–1.57		
p	$.01^{*}$	.11		
Timed up and go test (s)				
Pre-test	42.00 ± 6.06	40.00 ± 4.73	–.86	.38
Post-test	30.29 ± 2.75	35.00 ± 5.55	–2.01	$.04^{\dagger}$
z	–2.37	–2.20		
p	$.01^{*}$	$.02^{*}$		

Mean ± SD, EG: rTMS + Treadmill training, CG: rTMS (sham Therapy + Treadmill training

Table 2. Comparison of change values of 10MWT, 6MWT, and TUG test between the experimental and control groups are shown in Fig. 1.

As a result of 10MWT, about 7.7 seconds 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. 2.

As a result of 6MWT, about 74 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 TUG, about 11.7 seconds 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.

Luft *et al.* showed that activation of the non-lesional sensorimotor cortex increased significantly as the gait function improved in stroke patients [18]. Similarly, in the study of Enzinger *et al.*, the activation of sensorimotor cortex in both hemispheres increased as the gait function of stroke patients recovered [19]. Based on these studies, it can be said that neural activation of the leg motor areas are important for the recovery of gait function in stroke patients.

rTMS is used as a therapeutic approach for restoring motor function of stroke patients by inducing depolarization in brain cells by changing the sensitivity of the brain cortex through repeated stimulation [20]. High-frequency rTMS causes not only changes in the plasticity of synapses, but also metaplasticity, excitability of neural networks, and activation of feedback loops [21]. When rTMS is applied to the primary motor cortex, corticospinal neurons and pathways are activated, and a motor evoked potential may be generated in the target muscle. It also activates intracortical inhibitory and excitatory neural circuits [22].

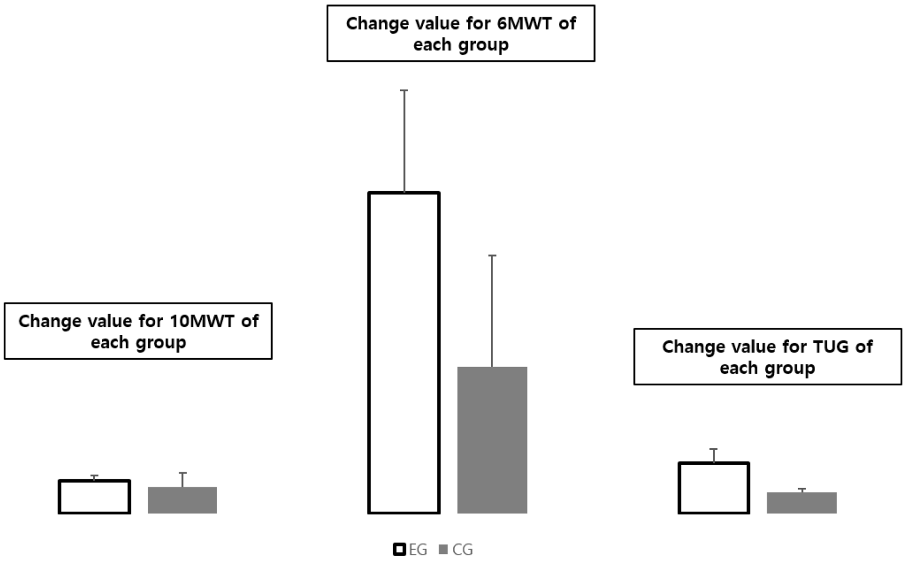

Fig. 1. Comparison of change values of 10-meter walk test, 6-minute walk test, and Timed up and go test between the experimental and control groups.

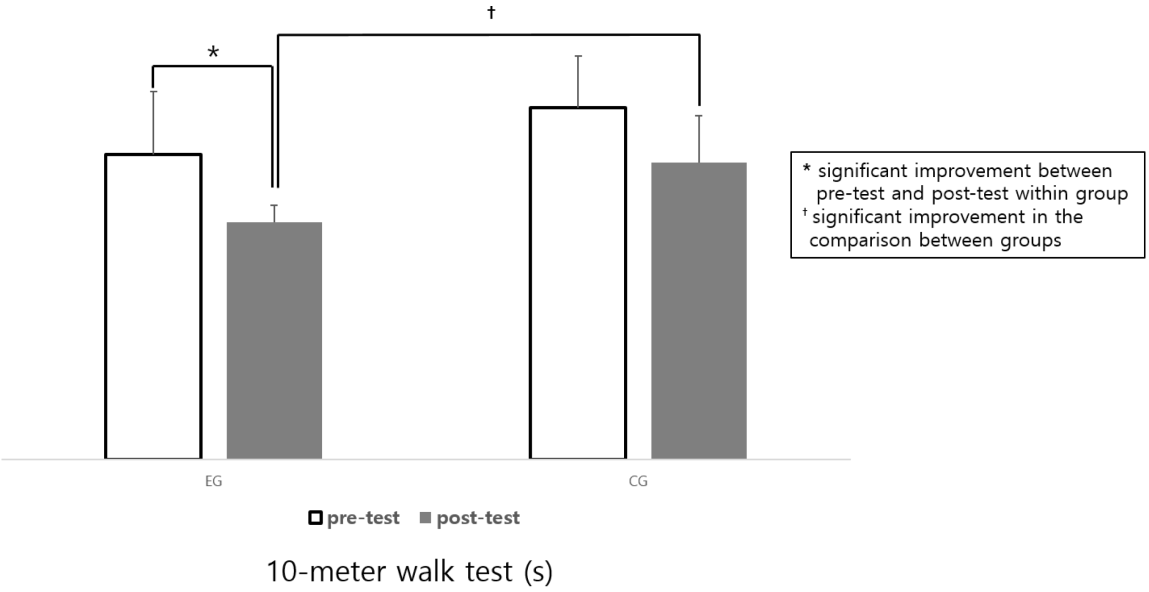

Fig. 2. Comparison of change in 10MWT of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

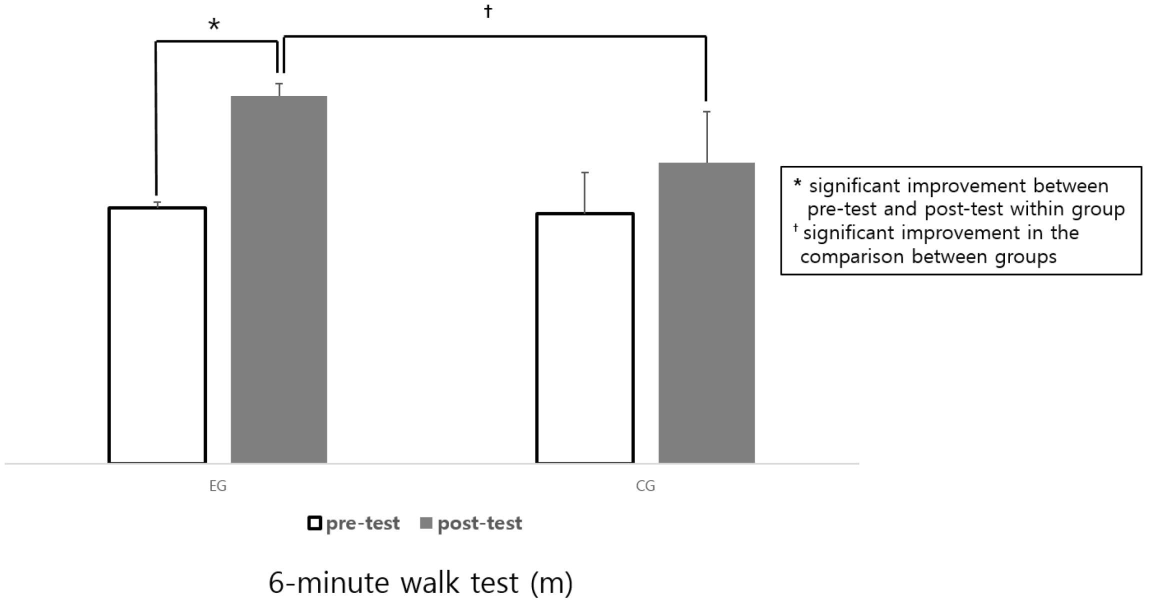

Fig. 3. Comparison of change in 6MWT of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

Therefore, it is considered as a promising technology to improve the spontaneous motor output of patients with movement disorders, and is applied to patients with paralysis after stroke or spinal cord injury [23].

Because the three evaluation methods used in this study have high clinical reliability, it can be considered that a significant improvement in all items indicates a certainly recovery of lower limb function. It is also presumed that this restoration of lower extremity function is due to neural activation in leg motor areas. However, since the neuroimaging study was not applied in this study, it is necessary to clearly confirm the occurrence of beneficial plasticity changes in the brain through neuroimaging studies such as functional magnetic resonance imaging (fMRI) in future studies.

Avenanti *et al.* showed that stroke patients get more functional recovery when combined with rTMS and rehabilitation programs than rehabilitation programs only,

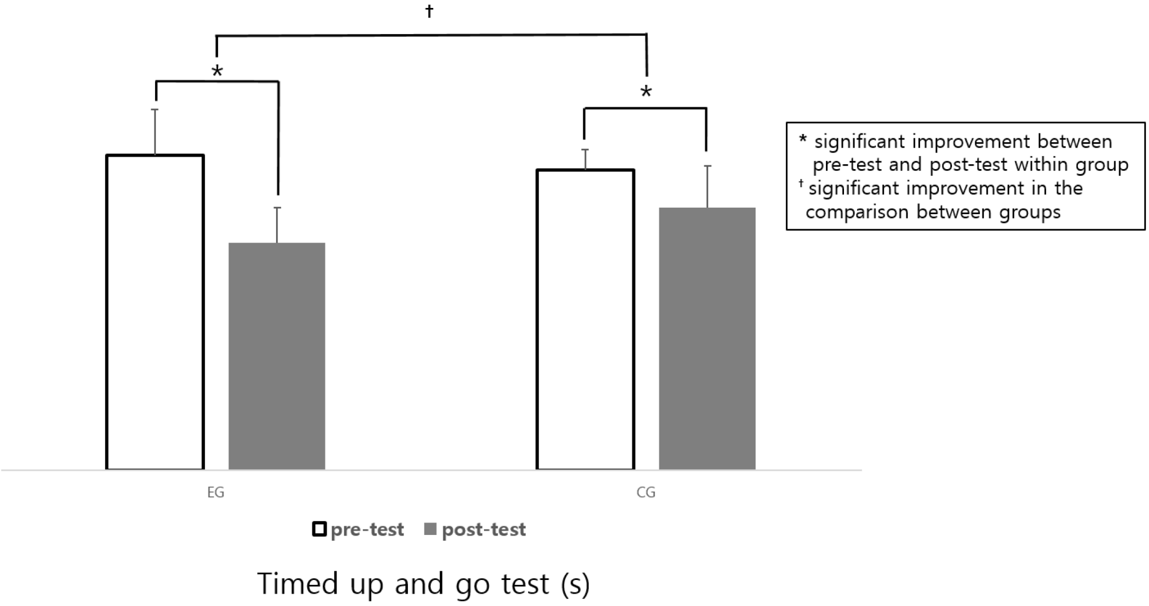

Fig. 4. Comparison of change in TUG of the experimental group and control group. When there was a statistically significant difference, symbols * and † were used to indicate.

and that applying rTMS before a rehabilitation program is more effective than applying rTMS after a rehabilitation program [24]. Based on these results, rTMS was applied to the subjects prior to the gait-related rehabilitation program in this study, and the rehabilitation program focused on treadmill training.

Even in the control group that did not apply rTMS and only treadmill training showed a significant improvement in TUG. This is thought to be because treadmill training causes a significant plasticity change in the brain neural network of stroke patients, as shown in the results of previous fRMI studies [25]. However, the results of this study showed a more significant effect in the experimental group with rTMS.

This study has limitations that need to be addressed. First, since this study did not evaluate the long-term effects of rTMS, it is necessary to perform additional clinical evaluations at a certain time point after application of rTMS. Second, because of the small number of subjects, it is difficult to generalize to all chronic stroke patients. Third, there was no control over individual physical activity outside of intervention.

4. Conclusion

It is important for patients with CNS injuries such as stroke to induce movement and functional recovery through a therapeutic approach that can improve plasticity. In particular, movement of the lower limbs is closely related to gait, and gait is one of the most important goals in rehabilitation of stroke patients because it directly affects the level of daily living.

This study showed that 5 Hz high frequency rTMS has a significant effect on gait speed, gait endurance and dynamic balance. Based on the results of this study, we recommend that applying high-frequency rTMS to the M1 region of chronic stroke patients is positive as an adjuvant therapy to improve the recovery of lower extremity function. In future studies, adding neuroimaging studies may provide more objective data on changes in brain plasticity.

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