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The Effect of Low-Frequency (1 Hz) rTMS on the Cerebellar Cortex in Patients with Ataxia After a Posterior Circulation Stroke : Randomized Control Trial

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To assess the Safety, feasibility, and efficacy of low-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the cerebellum in patients with acute posterior circulation stroke. Thirty ataxic patients with acute posterior circulation stroke were randomized to experimental (EG = 15) and control groups (CG = 15). All subjects received a 30-minute mirror therapy in common, which consisted of lower limb strengthening exercises and balance enhancement program related to functional tasks. During this intervention, mirrors were placed on the front and side walls to provide visual feedback about their movement. EG applied 1HZ real rTMS for 15 minutes to the cerebellum before mirror treatment and sham rTMS for CG. Intervention was performed once a day, five times a week for four weeks. Static balance test, Wisconsin gait scale, 6 minute walk test (6MWT) and time up go test (TUG) were performed before and after the intervention. At post-test, Static balance test (98.53.68 ± 6.94 versus 110.53 ± 16.83), Wisconsin gait scale (25.61 ± 4.86 versus 29.54 ± 5.82), 6 minute walk test (181.47 ± 34.52 versus 165.72 ± 35.63), time up go test (24.47 ± 4.55 versus 28.93 ± 3.13) was a significant difference in the experimental group than in the control group ($p < 0.05$). There was a significant difference between the pre-test and post-test scores for all variables in both groups ($p < 0.01$). The results of this study show that 1 Hz rTMS application to the cerebellum is safe and feasible and may have beneficial effects on the balance function of stroke patients with posterior circulation dysfunction.

Keywords : transcranial magnetic stimulation, ataxia, cerebellar cortex

1. Introduction

Balance disorders commonly seen after stroke increase the risk of falls and have a negative impact on walking and activities of daily living [1, 2]. Balance disorders can also cause pathological problems such as fracture due to falls [3]. Therefore, recovery of balance ability is an important focus of stroke rehabilitation [4]. Ataxia is one of the common disorders after posterior circulation stroke (PCS), which causes restriction of daily living activities or movement [5]. In particular, ataxic gait is caused by postural stability, ie, lack of balance and impaired lower limb movement [6]. Repetitive transcranial magnetic stimulation (rTMS) has been studied as a therapeutic intervention for neurological problems such as motor deficits after stroke [7]. The stimulation site of rTMS is determined by the damage desired to be recovered [8].

The cerebellum not only participates in motor adaptation and learning, but also plays an important role in balance and gait control [9]. Since ataxia after PCS is associated with impairment of the cerebellum or cortico-ponto-cerebellar projections [10], the cerebellum is considered to be a stimulus site of rTMS suitable for ataxia recovery [11].

This is possible because rTMS is a method of directly applying microcurrents to human brain cells using magnetic fields generated by electromagnetic coils to cause depolarization of neurons located in the cerebral cortex [1]. Two protocols can be used in rTMS: one to apply excitatory (high-frequency) stimulation to lesion hemispheres and the other to apply inhibitory (low-frequency) stimulation to non-lesioned hemispheres [7].

There is a previous study that applied low-frequency rTMS to the cerebellum of a patient with spinocerebellar degeneration improved walking ability as a result [11]. It can be assumed that low frequency rTMS application is useful as a functional approach to rehabilitation of stroke patients. However, studies on the effect of rTMS on the

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cerebellum of ataxia patients after PCS are rare.

The aim of this study was to investigate the additional effect of low frequency rTMS combined with mirror therapy on the improvement of balance ability of ataxia patients after PCS.

2. Materials and Methods

Thirty patients with sub-acute stroke who had ataxia after PCS participated in this study. They were randomly assigned to either experimental group (EG=15) or a control group (CG=15). Initially, 52 patients were recruited, but 22 were excluded because they did not regularly participate in the treatment session, and data from the remaining 30 subjects were used for statistical analysis.

The inclusion criteria is a patient with ataxia due to the first cerebellar or brain stem stroke, less than 6 months of age. The exclusion criteria are ischemic stroke in several vascular regions, severe ataxia that interferes with functional evaluation, increased intracranial pressure, pacemaker insertion, and history of seizure. All subjects were informed of the study and provided written consent. A double-blind, randomized, sham-controlled trial was performed. Subjects were randomly assigned to receive either real rTMS or sham rTMS on the cerebellum. We used unequal randomization to obtain more data on compliance and side effects in the real rTMS group [12]. Randomization was done using an opaque envelope. This process was performed by a investigator who was not involved in patient selection, intervention, or assessment. All patients and investigators who participated in the study were blinded to group assignments.

Adverse events were checked during and after each rTMS session by the investigators. The 1 Hz rTMS for the cerebellum was performed for 15 minutes. Assessments were performed before and after rTMS and one month after the last session by the blinded physical therapist for group assignment. When applied to CG, the magnetic coil was directed to the opposite side of the head of the subject, so that the cerebellum was not stimulated and the sound from the magnetic coil was heard so that the subject did not know that it was sham therapy. All subjects received mirror therapy after receiving real (EG) or Sham (CG) rTMS. Participants from both groups received a mirror therapy program to promote balance function for 30 min. Mirror therapy is described by Dean *et al.* (2000) and Leroux (2005) were modified and used [13, 14].

The program consisted of balanced training and walking training. (i) stepping in various directions, (ii) stepping over obstacles, (iii) forward and backward walking, (iv) extend arms forward to reach the therapeutic ball, (v) weight-bearing training on the affected leg, (vi) exercises in the double-leg stance, (vii) walking training in tandem pattern, and (viii) sit-to-stand training. All participants from were placed in front of a front mirror and a side wall mirror so that they were able to visualize their reflected image while performing the task.Intervention with rTMS and mirror therapy was performed once a day, five times a week for a period of 4 weeks. Before the cerebellar rTMS, the resting motor threshold (RMT) for the abductor pollicis brevis muscle in the non-ataxic side was measured over the M1 of the hemisphere ipsilateral to the ataxic side. RMT was defined as the minimum stimulation intensity that caused 50 μV of response more than 5 times in 10 consecutive stimulations. rTMS was performed through a 70 mm-diameter figure-of-8 coil powered by MagPro® (Magstim, Wales, UK). The coil was placed 2 cm below the inion and 2 cm lateral to the midline on the cerebellar hemisphere ipsilateral to the ataxic side, with the handle pointing superiorly, targeting the posterior cerebellar lobe [15]. 1 Hz cerebellar rTMS, which was performed for a 15 minute, once a day, five times a week for a four-week period. Stimulation in each session was applied at a frequency of 1 Hz and an intensity of 100 % of the patient's RMT for 15 min, achieving 900 stimuli in total per session. For the sham rTMS, the coil was placed perpendicular to the scalp with the same parameters of stimulation to minimize current flow into the skull.

All measurements were performed before and after 4 weeks of training. Static balance test (Gaitview System, Alfus Co., Korea) was used to measure the postural sway in standing posture. Gaitview System is 550 × 480 × 35 mm in total size. The thickness of pressure sensor is 0.15 mm, the size of sensor is 0.73 cm^2, the number of sensor is 2,304 (48 × 48) and the maximum pressure is 100 N / cm^2. Data were analyzed by converting the values measured in Static test mode to Excel using Gait view software version 1.0.1. In order to measure the static balance ability, a foot scan board was installed on the floor, connected to a computer, and then the Gaitview system was run. After selecting the static test mode, the patient was placed on the footboard and verbal instructions were given, "Keep in the good posture" and the postural sway was measured for 10 seconds. The Wisconsin gait scale consists of 14 observable variables for measuring clinically relevant components of gait. Gait characteristics of stroke patients are observed in stance phase and swing phase, respectively. Then they are scored on a 3-point or a 4-point scale. A total of 45 points. The lower the score, the better the function. In this study, a physical therapist

with more than 5 years experiences had observed and evaluated the patient while repeating the 10-m-long walking three times [16]. The 6MWT is a test method that displays the reference point at a distance of 20 m from the starting point to the turning point on the floor of indoor and then repeats the walking for as much as possible for 6 minutes. For objective evaluation, the evaluator informed of the time elapsed per minute, and the measurement recorded the total walking distance in meters (m). This test has a high intra-rater reliability (r = 0.91). To reduce the measurement error, the mean value was calculated by repeating the measurement three times, and the subjects rested for about 2 minutes between each test [17]. The TUG test measures the time it takes to get up from a chair with armrests, walk 3 meters and returns to sit back in the chair. The subject is asked to do it as quickly as possible. TUG has excellent intrarater (r = 0.99) and interrater (r = 0.98) reliabilities [18].

Differences in general characteristics between the experimental group and the control group before therapy were compared using independent t-tests and chi-square tests. Comparisons of balance before and after training within each group were made using the paired samples t-test. Comparisons of pre- and post-test differences in balance between the experimental group and the control group were made using the independent samples t-test. The statistical software, SPSS 20.0 (SPSS, Chicago, IL, USA), was used for statistical analysis. The level of significance was chosen as 0.05.

3. Results

Figure 1 shows a flow chart of the study. All subjects signed a written informed consent agreement before participating in this study. Table 1 summarizes the detailed demographic and clinical information of the subjects.

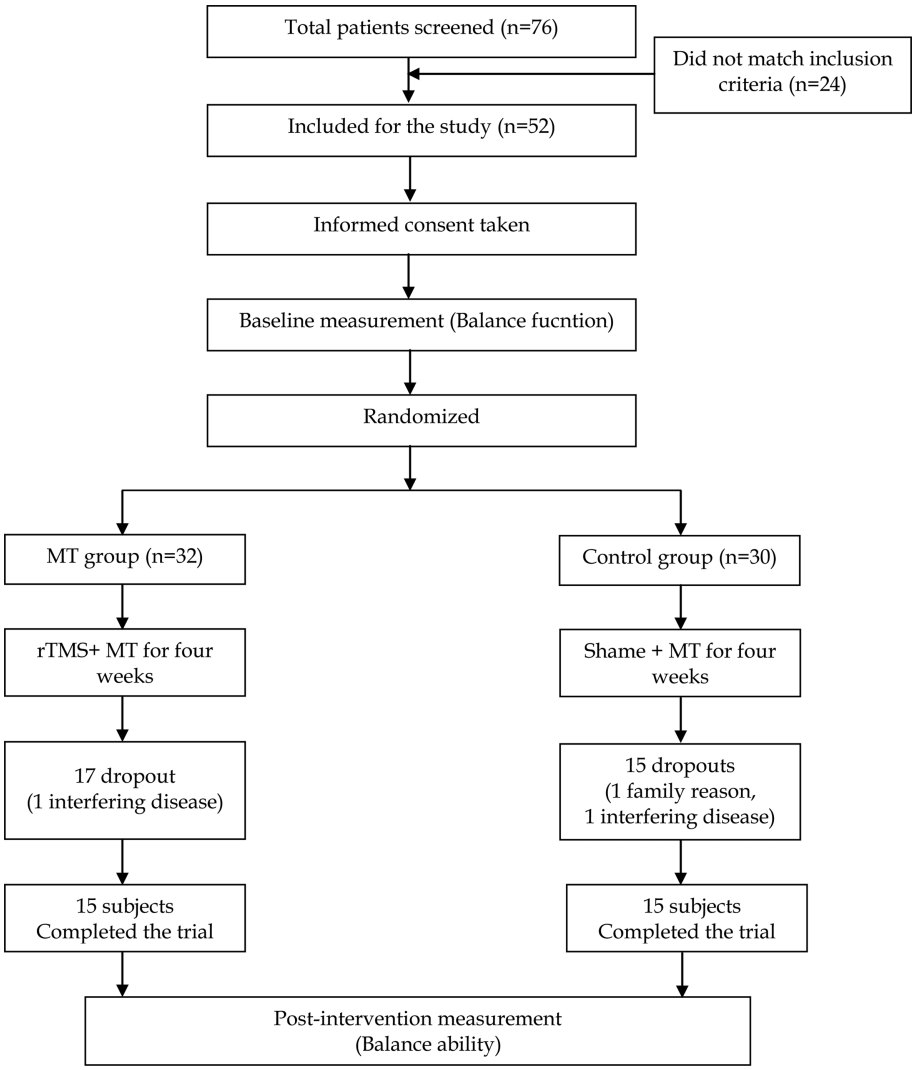

Fig. 1. Study flowchart. MT, mirror therapy; ST, shame therapy; rTMS, repetitive transcranial magnetic stimulation.

Table 1. Participant's Demographic and Clinical Data.

	EG (n = 15)	CG (n = 15)
Age (years)	61.60 ± 7.76[a]	63.73 ± 6.10
Onset duration (day)	75.20 ± 12.91	77.20 ± 10.02
Gender (Male/Female)	8/7	7/8
Stroke type (Infarction/Hemorrhage)	10/5	9/6
Stroke lesion		
Cerebellum	8	8
Pons	3	5
Medulla	4	2

[a]Mean ± SD, EG: experimental group, CG: control group

Table 2. Comparison of the outcome measures within groups and between groups.

	EG (n = 15)	CG (n = 15)
Postural sway (mm)		
Pre-test	130.56 ± 15.57 [a]	132.5 ± 17.82
Post-test[b,c]	98.53.68 ± 6.94*	110.53 ± 16.83*
Wisconsin gait scale (score)		
Pre-test	31.21 ± 5.72	32.81 ± 6.95
Post-test[b,c]	25.61 ± 4.86*	29.54 ± 5.82*
6 minute walk test		
Pre-test	120.67 ± 25.67	118.24 ± 30.84
Post-test[b]	181.47 ± 34.52*	165.72 ± 35.63*
Time up go test (s)		
Pre-test	30.40 ± 4.29	31.60 ± 3.56
Post-test[b]	24.47 ± 4.55*	28.93 ± 3.13*

[a]Mean ± SD, EG: experimental group, CG: control group
[b]Significant difference in gains between two groups, *$p < 0.05$
[c]Effect size greater than 0.80

There were no statistically significant differences in age, onset duration between the 2 groups.

The values of static balance test, Wisconsin gait scale, 6MWT, and TUG test of the experimental and control groups are summarized in Table 2. There were significant differences between the two groups in the post test of static balance test, Wisconsin gait scale, 6MWT, TUG test ($p < 0.05$). Furthermore, in the two groups, significant differences were found in the pre- and post-test scores for the static balance test, Wisconsin gait scale, 6MWT, TUG test ($p < 0.05$).

4. Discussion

The purpose of this study was to evaluate the safety, feasibility, and efficacy of low frequency repetitive transcranial magnetic stimulation (rTMS) applied to the cerebellum in patients with acute PCS. As a result of applying rTMS in integrated with mirror therapy for 4 weeks, the balance ability was significantly improved in the experimental group compared to the control group. This result supports our hypothesis that rTMS in integrated with mirror therapy can improve the balance ability of stroke patients.

In this study, quantitative variables of static balance test and Wisconsin gait scale were provided to measure balance function in patients with acute stroke. In the result, static balance test and Wisconsin gait scale showed that the EG significantly improved the balance function compared to the CG, as the degree of postural sway and Wisconsin gait scale score decreased. Therefore, the results of this study suggest that using visual feedback with rTMS improves the balance of PCS patients and improves exercise and functional capacity.

Also, 6MWT and TUG test, which demonstrate the balance capability associated with functional mobility, have been selected as the primary outcome measure to demonstrate the clinical benefit of mirror therapy in balance function. In the TUG, the shorter the time, the better the balance ability. The result in EG showed that the balance ability was improved in both of them. This suggests a positive effect of mirror therapy on functional mobility [19]. This result also suggests that EG subjects have increased independence in gait and functional mobility.

In the post-stroke, balance function may be affected by abnormal joint motion, asymmetric stride time and length during walking, slow speed and coordination disturbances, as well as abnormal control of the vestibular and somatosensory systems. Mirror therapy has been used to maintain body alignment in an upright posture, to take the right posture, and to promote weight shift to the affected side after stroke. Recent studies suggest that mirror therapy, which has a significant effect on balance function, should be performed to promote rehabilitation in patients with post-stroke paralysis [20].

In this study, low frequency (1 Hz) rTMS was applied to the cerebellum as a treatment modality for ataxia improvement. Previous studies have shown that low frequency rTMS application improves 10 MWT in patients with spinocerebellar degeneration [21]. In addition, low-frequency rTMS application of the cerebellum to patients with Parkinson's disease improved performance [22]. Based on these results, a low-frequency stimulation protocol was selected in the current study and led to a significant improvement in EG. However, there are some limitations to this study. First, it is difficult to rule out the possibility of activation of the antidromic corticospinal tract by cerebellar rTMS that can inhibit the contralateral motor cortex. To minimize this effect, the strength of

rTMS is used as 100 % of RMT and the coil is treated at its best, but there is no specific suggestion on how to solve this problem [23]. Second, we did not include neurophysiologic methods, such as the paired-pulse TMS, that could help to alter cerebellar excitability by low-frequency cerebellar rTMS [24]. Third, the subjects were not controlled by medication. So it may have been influenced by it.

Therefore, since the findings of this study cannot be generalized to the entire stroke population, controlled studies with larger sample sizes and longer intervention methods should be performed to verify clinical utility. This paper was supported by Joongbu University Research & Development Fund, in 2017.

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