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The Effect of 1 Hz Repetitive Transcranial Magnetic Stimulation Combined with Task-oriented Training on Upper Limb Function and Hemineglect in Stroke Patients

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The purpose of this study was to investigate the effect of rTMS on upper limb dysfunction and hemineglect patients after stroke and to find out the most effective application method. This study was conducted with 25 subjects who were diagnosed as a hemiparesis by stroke. Participants in the experimental (12 members) and control groups (13 members) received rTMS and sham rTMS during a 20 minutes session, five days per week for four weeks, respectively, followed by task-oriented training during a 30 minutes session. Motor recovery evaluation was performed by fugl meyer assessment (FMA), box and block test (BBT), albert test (AT) and grip strength test. The experimental group showed significant increments in FMA, BBT, AT, and grip strength test, compared to the pre-intervention results ($p < 0.01$). Furthermore, the control group showed significant increments in the FMA, BBT, AT, compared to the pre-intervention results ($p < 0.05$). A significant difference in the post-training gains in FMA, AT, and grip strength test were observed between the experimental group and the control group ($p < 0.05$). In addition, the effect size for gains in the experimental and control groups was very strong in FMA, AT, grip strength test (effect size = 1.29, 1.45, 0.96 respectively) and the effect size for gains in the experimental and control groups was very weak in BBT (effect size = 0.20). The findings demonstrate that application of 1 Hz rTMS combined with task-oriented training can be helpful in improving upper limb function and hemineglect of stroke .

Keywords : transcranial magnetic stimulation, stroke, hemineglect

1. Introduction

Stroke is a serious disease that also causes death and is one of the major causes of adult disorder. Several studies have estimated that the incidence of stroke, which was 18 per 1000 people in 2000, will increase to 2 per 1000 in 2020 [1]. Stroke is a major cause of long-term physical impairment, and the most prominent dyskinesia after stroke are paralysis of the opposite side of the body with cerebrovascular problems, which can permanently affect the function of the arms and hands [2]. Neurological damage due to stroke results in loss of excitation input to the spinal motor nerve, which results in reduced excitability of the cerebral cortex [3]. These neurological damages are the absolute cause of muscle weakness and ultimately lead to a decrease in upper limb function [4]. Upper limb function is important for delicate movement related to daily activities such as eating and dressing as well as gross movement such as postural control and movement. More than 85 % of all stroke patients have paralysis of one arm and leg, more than 69 % of them experience functional impairment of the upper limb and approximately 56 % of patients suffer from a severe discomfort in daily life due to hemiplegia even after 5 years of stroke [5]. In addition to dysfunction of the upper extremity, one of the disorders that can be experienced after stroke is hemineglect (HN). HN or unilateral HN refers to a complex symptoms in which a patient ignores or does not react to the opposite stimulus of a brain lesion [6]. This does not mean that it ignores all the stimuli opposite the brain lesion. Rather, the stimulus near the body center line is less likely to be ignored, and the extreme opposite stimulus is more likely to be ignored [7]. HN occurs more frequently in patients with unilateral stroke and more in patients with right-side brain damage [8]. As is well known, the right hemisphere is perceived to be highly involved in the spatial perception and orientation [9]. The characteristics of HN patients are omitting the elements on the left when drawing a clock, a face, or a simple picture. Also, when you tell them to divide the horizon,

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they only do what is on the right [10]. It is one of the important problems to be solved through treatment because patients can be in a dangerous situation because they do not see objects or obstacles on the neglecting side if they have HN. Although there are many therapies that address these various physical problems caused by stroke, it has been shown that treatments focusing on the impairments itself or methods of restoring normal movement patterns such as neurodevelopmental treatment (NDT) have little effect [11]. Physical intervention is important to promote brain plasticity. In recent functional neuroimaging studies, several reports of cortical reconstruction caused by physical intervention in stroke patients can be found. Task-oriented training (TOT) is one of the treatment methods for stroke patients. It refers to controlling movement required to perform a specific task as motor control and acquiring movement with repetitive exercises [12]. Several studies have demonstrated the effectiveness of TOT as a neuro-protective approach [13, 14].

Neuroimaging studies in animals and humans show a great deal of evidence for changes in various activation patterns that occur in damaged brain [15]. The transcranial magnetic stimulation, which is supported by these evidences, is a method of applying depolarization of neurons located in the cerebral cortex by applying micro-current directly to human brain cells using magnetic field waves generated by electromagnetic coils [16]. The application of this TMS repeatedly at regular intervals is called rTMS, it is suggested that noninvasive neuroimaging therapy can be applied to patients after stroke. Two protocols are used for rTMS: excitatory (high frequency) stimulation applied to the lesion hemisphere and inhibitory (low frequency) stimulation applied to the non-lesioned hemisphere [17]. Several randomized controlled trials have shown that low-frequency or high-frequency rTMS can improve the motor function of affected arms and that rTMS can be used in rehabilitation programs for acute stroke patients [18-20]. Despite the advantages of rTMS noninvasively stimulating specific brain regions, limited research has been done because of questions about the mechanism of action and difficulties in clarifying clinical effects. However, recent developments in brain science, such as functional brain imaging techniques, have solved these problems, and the grounds for their effectiveness have been established and are becoming increasingly of interest.

Nevertheless, there is a lack of rTMS studies as a practical therapy for stroke rehabilitation, and there is no systematic study of the effects of rTMS on recovery of upper limb function and HN in stroke patients. The purpose of this study was to investigate the effect of rTMS on upper extremity dysfunction and HN patients after stroke and to find out the most effective application method.

2. Materials and Methods

The subjects recruited those who agreed to participate in the study among the patients receiving outpatient treatment at the physical therapy room of Eulji University Hospital. All patients were diagnosed with stroke by computer tomography or magnetic resonance imaging and were less than 6 months. The exclusion criteria of the subjects were as follows: (1) Significant cognitive deficit (a score of > 25 points in the Mini-Mental Status exam) (2) Visual or hearing impairment (3) Previous cerebrovascular accident that left neurological disorder (5) A history of seizures (6) Other neurological and medical disorders Twenty-five subjects who met the criteria participated in the study. The Research Ethics Committee of Joongbu University approved the study, and all participants provided informed, written consent prior to involvement in the study. After the initial evaluation, the sealed envelope was drawn for randomization and 12 subjects in the experimental group and 13 subjects in the control group were assigned. In addition to randomization, all measurements before and after the subjects' treatment were assessed by a physical therapist 1 who was blind to treatment allocation. The intervention was performed by a physical therapist 2 who was blinded to the treatment allocation, not participating in the subject's assessment, and in a closed space. Both physical therapists were instructed not to talk to the subjects about the purpose and the evaluation items of the intervention.

Subjects participated in intervention for a total of 4 weeks, five times a week, all subjects receiving TOT 30 minutes in common, the experimental group receiving an additional 20 minutes of real rTMS, the control group receiving an additional 20 minutes of sham rTMS and a total of 50 minutes of treatment. The experimental group received real rTMS before the TOT session and while the control group received sham rTMS before the TOT session, providing the same sound and feel as the real rTMS, so that the patient did not know what group was assigned. The rTMS used a Magstim Rapid2 stimulator, targeting a first dorsal interosseous muscle that plays an important role in functional hand and arm movements such as grasp. A frameless stereotaxic system (Rogue Research, Canada) was used to accurately position the stimulus and apply it to the same site for all patients.

The center of the figure-8 coil was placed on the motor cortex of the unaffected hemisphere and placed perpendicular to the center sulcus. This was to stimulate the lower tissue efficiently. Low frequency stimulation was performed on the right P3 based on the EG 10/20 system. The motor performed a threshold intensity of 110 % for 5 minutes at a frequency of 1 Hz and rested for 1 minute. This process was performed four times, resulting in 1,200 pulses in total. The sham rTMS procedure was the same as real rTMS except that placebo coils were used [19].

The training consisted of goal-oriented tasks and activities carried out with the affected arms and hands selected for training according to the individual's potential. The goal-directed tasks and activities carried out the affected arms and hands. It was individually adjusted to the subject's goal and functional ability level. Activities included reaching, grasping, and pinching actions, such as cupping, bean podding, washing dishes and computer typing. Each task was performed for 10 minutes for each item, and 3 items were performed for a total of 30 minutes [19, 20].

Fugl-Meyer assessment (FMA) - upper limb is the most common and standardized assessment tool used to assess sensorimotor recovery after stroke. There are 33 items, 21 are proximal items, and 12 are distal items. This is a three-point scale, with a total of 66 points. The higher the UE-FMA score, the better the motor function. The range of the minimal clinically important difference (MCID) of UE-FMA in stroke patients is 4.25 to 7.25. Therefore, if the UE-FMA changes more than 5 points ($\Delta FMA \geq 5$), it can be regarded as a clinical improvement for the intervention [21].

In this study, the tools used for Box and Block Test (BBT) consist of a box with two spaces separated by a wooden partition and 152 wooden cubes measuring 2.54 cm. The test was used to modify the method used by Mathivoetz to evaluate dexterity. Each participant sat comfortably in his chair and performed a BBT test on the table for 1 minute using the affected upper limb [22].

The Albert test (AT) uses A4 paper with 40 lines of 2.5 cm drawn in different directions. The patient's task is to line a line perpendicular to their line of sight, and there is no limit to the movement of the head. The score is recorded as the degree of deviation (number of neglected lines / total number of lines) × 100 or the number of lines indicated by the patient [23].

The grip strength of the subject's hand was measured by a muscle strength measuring system (JAMAR hand dynamometer, Sammons Preston Rolyan, Illinois, USA). The subjects were sitting on a chair without armrests, and their grip was measured with the elbow flexed 90 degrees and the wrist joint kept in neutral position. After 3 measurements, the mean value was calculated and recorded. Reliability of grip strength measurement r = 0.99, which means that it has very high reliability [20].

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. Table 1 pro-

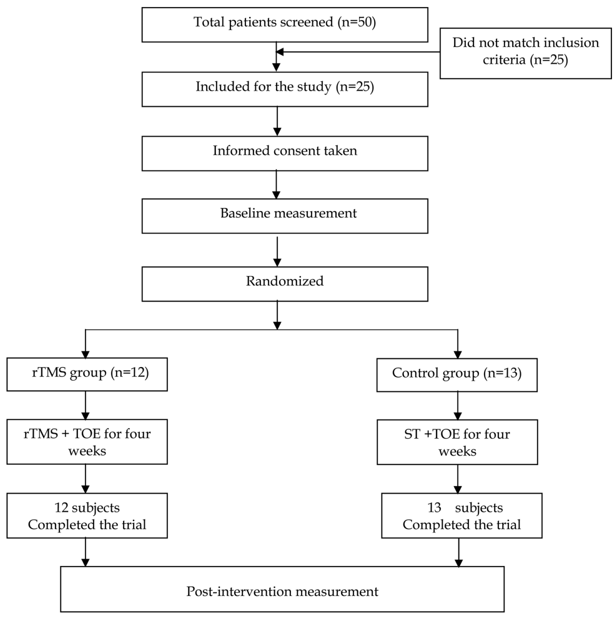

Fig. 1. Study flowchart. rTMS, repetitive transcranial magnetic stimulation; TOE, task oriented exercise. ST, sham therapy

Table 1. General characteristics of the subjects (n = 25).

Characteristic	EG (n = 12)	CG (n = 13)
Age (years)	63.92 ± 8.56	62.00 ± 8.28
Height (cm)	169.25 ± 7.03	167.23 ± 6.93
Weight (kg)	63.42 ± 8.46	67.00 ± 5.79
Time since onset (month)	2.50 ± 1.51	1.77 ± 1.17
MMSE (score)	25.14 ± 3.54	26.23 ± 2.16
Gender (male/female)	7/5	6/7
Type of stroke (Ischemia/Hemorrhage)	8/4	8/5

EG, experimental group; CG, control group
Values are expressed as mean ± SD.
MMSE, Mini-Mental State Examination

Table 2. Comparison of change in characteristics of the experimental group and control group with values presented as mean ± standard deviation.

	EG (n = 12)		CWG	CG (n = 13)		CWG
	Pre-test	Post-test		Pre-test	Post-test	
FMA (score)[a,b]	37.33 ± 5.91	53.75 ± 5.99*	16.42 ± 8.02 (21.51 to 11.32)	35.54 ± 5.46	46.00 ± 9.26*	10.46 ± 5.85 (13.99 to 6.92)
BBT (%)	26.42 ± 6.65	42.67 ± 8.27*	16.25 ± 9.65 (22.38 to 10.12)	28.77 ± 10.43	40.92 ± 8.63*	12.15 ± 9.23 (17.72 to 6.57)
AT (%)[a,b]	11.42 ± 3.58	23.83 ± 4.63*	12.42 ± 5.32 (15.79 to 9.04)	9.15 ± 3.69	17.08 ± 4.23*	7.92 ± 5.95 (11.51 to 4.32)
Grip strength (kg)[a,b]	7.67 ± 3.03	13.75 ± 3.82*	6.08 ± 3.96 (8.60 to 3.56)	8.62 ± 2.87	10.08 ± 2.06	1.46 ± 2.50 (2.97 to 0.05)

EG, experimental group; CG, control group, CWG, changes within groups
Values are expressed as mean ± SD.
*Significant difference from pre-test, $p < 0.01$
[a]Significant difference in gains between two groups, $p < 0.05$
[b]Effect size greater than 0.70
FMA, fugl meyer assessment; BBT, box and block test; AT, albert test

vides a summary of the clinical and demographic features of the sample (n = 25). This table also shows that there were no significant differences in the baseline characteristics observed between the two groups (p > 0.05). Twenty-five subjects (experimental group = 12, control group = 13) completed this experiment. Table 2 shows the characteristics of the two groups before and after intervention.

The experimental group showed significant increments in FMA, BBT, AT, and grip strength test, compared to the pre-intervention results (p < 0.01). Furthermore, the control group showed significant increments in the FMA, BBT, AT, compared to the pre-intervention results (p < 0.05).

A significant difference in the post-training gains in FMA, AT, and grip strength test were observed between the experimental group and the control group (p < 0.05).

In addition, the effect size for gains in the experimental and control groups was very strong in FMA, AT, grip strength test (effect size = 1.29, 1.45, 0.96 respectively) and the effect size for gains in the experimental and control groups was very weak in BBT (effect size = 0.20).

4. Discussion

This study was conducted to compare real rTMS and sham rTMS to examine the effect of rTMS combined with TOT on patients with upper extremity dysfunction and HN after stroke.

To evaluate the effect, low frequency rTMS was applied to the unaffected hemisphere. As a result, there was a significant difference between before and after intervention in all items of real rTMS combined with TOT. In sham rTMS combined with TOT, there was a significant difference before and after intervention in other items except grip stregnth test. There was a significant difference between the experimental group and the control group except for the BBT. This suggests that rTMS affects the restoration of upper limb function and mitigation of HN symptoms after stroke. Previous studies have examined the effect of low-frequency rTMS (10 daily sessions of 1Hz rTMS) on contralesional motor cortex in mild-to-moderate symptoms in the early phase after stroke, Fugl-Meyer scores were significantly improved [24]. In a previous study, they also compared real rTMS and sham rTMS as in our study, showing that FMA and others were improved only in real rTMS [25]. This is the same as our study showing that rTMS contributed to the improvement of the affected hand function of the patient after stroke. There are several studies that improve the upper limb function by applying 1 Hz rTMS to unaffected hemispheres. This is based on the hypothesis that applying 1-Hz rTMS to unaffected motor cortex reduces transcallosal inhibition and increases the local excitability of the affected motor cortex and increases synaptic efficacy [26]. One study reported that the combination of rTMS and motor training can promote brain plasticity, also, in several studies, the combination of rTMS and upper limb training showed better results than upper limb training alone [25, 27]. Therefore, we suggest that rTMS combined with TOT may be an effective method for improving motor function in hemiplegic patients after stroke. Several studies have examined the effects of rTMS on HN. Kleinman *et al.* reported that HN in patients with damage to the right cortex is related to the dorsal visual pathway. The application of rTMS helps to improve spatial attention by activating the parietal lobe [28]. In the present study, rTMS also stimulated not only the cerebral cortex but also the Brodmann area 40, positively affecting motor activity as well as HN reduction. Several other studies have also shown that rTMS has been applied to unaffected hemispheres and has been shown to have an effect on HN, which is related to spatial attention being dependent on intact hemisphere activity due to loss of reciprocal inhibition in the affected hemisphere after stroke [29]. Although the results of this study are of clinical significance, there are some limitations. The sample size was small that it was difficult to generalize to all stroke patients and that the mediation period was short. And we did not confirm the effect on brain activity through the neuroimaging techniques such as MRI. Although based on previous studies, the frequency and dosage of rTMS may not be optimal for the patient's symptoms. Further studies should require longer intervention with larger sample sizes, and it is necessary to confirm with neuroimaging technology. This paper was supported by Joongbu University Research & Development Fund, in 2017.

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