Effects of repetitive transcranial magnetic stimulation on arm function and decreasing unilateral spatial neglect in subacute stroke: A randomized controlled trial

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Abstract
Objective: The objective of this study is to investigate the effect of repetitive transcranial magnetic stimulation (rTMS) on the functional recovery of stroke patients with unilateral neglect.
Design: Randomized controlled experimental study.
Setting: Outpatient rehabilitation hospital.
Subjects: Thirty patients with stroke were randomly assigned to two groups: an rTMS group (experimental) and a control group.
Interventions: Stroke patients in the experimental group underwent comprehensive rehabilitation therapy and rTMS. Stroke patients in the control group underwent sham therapy and comprehensive rehabilitation therapy. Participants in both groups received therapy 5 days per week for 4 weeks.
Main measures: Line bisection, Albert, Box and block and Grip strength tests were assessed before and after the four-week therapy period.
Results: A significant difference in the post-training gains in Line bisection (16.53 SD 9.78 vs. 3.60 SD 5.02), Albert (14.13 SD 4.92 vs. 3.26 SD 2.01), Box and block (15.06 SD 9.68 vs. 6.93 SD 7.52), and Grip strength tests (3.60 SD 2.66 vs. 0.80 SD 1.26) was 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 AT, BBT (effect size=2.15, 0.77 respectively).
Conclusion: We conclude that rTMS might be effective in improvement in reduction of the unilateral neglect and motor function.

Keywords
Repetitive transcranial magnetic stimulation, unilateral spatial neglect, stroke

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Introduction

Unilateral neglect can occur when either the left or right hemisphere is damaged, more frequently when the right hemisphere is damaged. In stroke patients, the persistence of this symptom leads to the inability to recognize objects placed in a space on the paralyzed side, as well as to difficulties in carrying out daily activities independently.

Unilateral neglect occurs in various brain regions, including the parietal lobe, frontal lobe, temporal lobe, basal ganglia, and thalamus. Functional recovery is slower in patients with unilateral neglect than patients without unilateral neglect.

A number of published studies have evaluated the effects of various rehabilitation methods, such as constraint-induced movement therapy, mental practice therapy, and mirror therapy, on decreasing unilateral neglect and improving upper extremity function. However, because most treatment protocols are labor intensive, provision of intensive treatment for all patients is difficult.

Because of its simplicity, transcranial magnetic stimulation (TMS) might be an appropriate alternative treatment. Single TMS pulses have been used as a noninvasive and painless method for stimulating the brain of intact conscious human subjects through the scalp. Repeated application of single TMS pulses (rTMS) can sometimes elicit long-lasting changes in the excitability of the corticospinal tract, M1, and spinal cord structures, resulting in significant improvements in the aspects of sensory and motor function in patients with motor disorders.

Q et al. reported that rTMS has positive effects on the recovery of hand functions in stroke patients, and that application of rTMS to the right parietal lobe in normal individuals led to increased temporal and spatial attention to the left side. Chieffo et al. reported that rTMS had a positive influence on the recovery of lower limb motor activity in chronic stroke patients. However, research is lacking on the effects of rTMS on subacute stroke patients with unilateral neglect and arm function weakness. The reason is that the majority of existing stroke interventions focus on the indirect activation of the cerebral cortex. Recently, the efficiency of non-invasive treatment methods has been emphasized, particularly the direct and selective activation of the cerebral cortex in damaged areas of the brain.

Based on the previous research, this study investigates the effects of rTMS on the functional recovery of stroke patients with unilateral neglect.

Methods

Patients were recruited from the neurological physical therapy outpatient clinic of the Faculty of Physical Therapy, Eulji University, after agreeing to participate in the study. All patients were diagnosed with stroke, confirmed with computed tomography or magnetic resonance imaging. Patients who met the following criteria were enrolled: (1) no significant cognitive deficit (a score of > 25 points on the Mini-Mental Status exam), (2) significant unilateral neglect (a score of < 16 points on the motor-free visual perception test (MVPT)), (3) no eyesight or hearing problems; and (4) no psychological or emotional problems.

Thirty patients with stroke met the criteria. The Research Ethics Committee of Eulji University Hospital approved the study, and all participants provided informed, written consent prior to enrollment in the study. When the initial assessment was completed, the subjects were randomly assigned to an experimental group (n=15) or a control group (n=15). For randomization, sealed envelopes were prepared in advance and marked inside with A or B, indicating the experimental group or the control group. The randomization was done by a third party who was unaware of the study content. The subjects’ characteristics and all outcome measures before and after treatment were assessed by Physician 1, who was blinded to the treatment allocations. The rTMS and sham treatments were administered in a closed room by Physician 2, who was not involved in the assessment of the subjects. Both physicians were instructed not to communicate with the subjects about the possible goals or the rationale of either treatment.

Interventions

Subjects in the experimental group received rTMS and conventional rehabilitation therapy for a total of 50 min (rTMS: 20 min, conventional rehabilitation
therapy: 30 min) per day, with a 10 min rest period halfway through the session. Subjects in the experimental group received training five days per week for four weeks. Conventional rehabilitation therapy, consisting of neurodevelopmental facilitation techniques, was administered by therapists blinded to the study protocol and to subjects’ assignment to groups. The objectives of stroke rehabilitation were to improve patients’ functional abilities, such as dressing, transfer, ambulation and balance, and to provide education to the caregivers, so as to help patients achieve earlier and/or greater independence in activities of daily living.

Subjects in the control group received sham therapy and conventional rehabilitation therapy for a total of 50 min (sham therapy: 20 min, conventional rehabilitation therapy: 30 min) per day on the same day.

Magstim Rapid2 (Magstim co., Ltd, Wales, UK) was used for rTMS, and a figure-of-eight coil with a diameter of 80 mm was used. Motor evoked potentials were measured by attaching active electrodes to the muscle belly, specifically to the first dorsal interosseous muscle on the right side, and attaching reference electrodes to the tendon. Once the region causing the largest motor evoked potentials at the lowest intensity was located, it was stimulated ten times and the minimal intensity of stimulation showing a peak-to-peak amplitude of 50 µV or above at least five times was set as the resting motor threshold. Low-frequency stimulation was applied in P3 on the right side based on the EG 10/20 system at a frequency of 1 Hz for five minutes with 90% of the motor threshold during rest, and a one-minute break was given. This process was performed four times, resulting in a total of 1,200 stimulation events.14 Subjects in the test group performed rTMS for four weeks, five times each week and 10 minutes each day. Those in the control group were led to hear sounds using a sham stimulator coil without knowing that the sounds were due to sham stimulation.

**Outcome measures**

1) **Line Bisection Test (LBT).** The Line Bisection Test (LBT) is an instrument used for evaluation of unilateral neglect. In this test, six of 20 lines of various lengths are arranged at the center, left, and right of a 21.5 cm × 28 cm sheet of A4 paper. The test is performed by placing the test sheet at the front and center of each subject and instructing him/her to use the pencil provided to indicate the midpoint of each line. Scores are determined by measuring the distance between the actual midpoint of each line and the midpoint indicated by the subject, adding these values, and then dividing the sum by the number of lines. The results were interpreted as follows: normal when the deviation of the average length from the midpoint was less than 6.3 mm; mild-unilateral neglect when the respective length was 6.3 mm or greater; and severe-unilateral neglect when the respective length was 12.5 mm or greater. The intertester reliability was .82.15

2) **Albert Test (AT).** The Albert Test (AT) evaluation form, a 26 cm × 20 cm sheet, is an evaluation tool used to determine the degree of unilateral neglect. Forty lines, each 2.5 cm, are arranged in six rows (left two rows, middle two rows, right two rows) × six columns + one row (the center) × four columns. The evaluator demonstrates the test by drawing a line on the central column before the evaluation and instructs the subjects to draw on every line in the same manner. The evaluator then confirms the subjects’ response by asking, “Have you drawn through every line?” No limit is imposed on the subject’s head movement, and scores are measured by recording the degree of deviation (the number of ignored lines/the total number of lines) × 100, or by determining the number of indicated lines. The test-retest reliability was .99.16

3) **Box and Block Test (BBT).** This test measures the number of one-inch blocks moved by the subject from one box to another box in one minute. The subjects are motivated to move the blocks one by one as rapidly as possible, while being praised by the evaluator. They are cautioned not to throw the blocks because the number of hurled blocks will be subtracted from the total score. The test-retest reliability was very high: right hand at r = 1.00; left hand at r = 0.94.17
4) Grip Strength Test. A muscle-strength measurement system (JAMAR hand dynamometer, Sammons Preston Rolyan, Illinois, USA) was used to measure the grip strength of the subjects’ hands. Measurements were taken while the subjects were seated on an armless chair, with the arms placed against the body, the elbow joints flexed at 90 degrees, and the wrist joints in a neutral position. The average values of the three measurements were analyzed. The grip strength measurements showed very high reliability at $r = 0.99$.18

Data analysis
Before therapy, differences in the general characteristics of the experimental group and the control group were compared using independent $t$-tests and chi-square tests. Comparisons of variables before and after training within each group were made using paired samples $t$-tests. Comparisons of pre- and post-test differences in variables between the experimental group and the control group were performed using the independent $t$-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.

Results
A flow chart of the study is shown in Figure 1. Table 1 provides a summary of the clinical and demographic features of the sample ($n = 30$), which shows that no significant differences in the baseline characteristics were observed between the two groups ($P > 0.05$). Thirty subjects (experimental group = 15, control group = 15) completed this experiment. The characteristics of the two groups ($n = 30$) before and after intervention are shown in Table 2.

The experimental group showed significant increments in line bisection test, albert test, box and block test, and grip strength test, compared to the pre-intervention results ($P < 0.05$). In addition, the control group showed significant increments in the line bisection test, albert test, box and block test, and grip strength test, compared to the pre-intervention results ($P < 0.05$). Significant differences in the post-training gains in line bisection test, albert test, box and block test, and grip strength test were observed between the experimental group and the control group ($P < 0.05$).

The effect size for gains in the experimental and control groups was very strong in AT, BBT (effect size = 2.15, 0.77 respectively).

Discussion
After four weeks of rTMS therapy, significant improvements in upper extremity function and decreased unilateral spatial neglect were observed between the experimental group and the control group. These results supported the primary hypothesis that rTMS has positive effects on improving upper extremity function and decreasing unilateral spatial neglect in subacute stroke patients.

To the best of our knowledge, our study is the first to investigate the effects of rTMS on upper extremity function and unilateral spatial neglect. The results of line bisection, Albert, box and block, and grip strength tests showed significant improvements in the experimental group compared to the control group, indicating the augmented therapeutic effect of rTMS.

Several underlying mechanisms have been suggested to explain the effect of rTMS on motor recovery and decreasing unilateral spatial neglect after stroke. Martin et al.19 noted that rTMS was a non-invasive application of the electrical field outside the cranium, which triggered the depolarization of nerve cells within the cerebral cortex and changed the excitability of the cerebral cortex after repetitive magnetic stimulation.

Several studies investigating the effect of rTMS on brain activity and unilateral spatial neglect have been reported. Kleinman et al.20 reported that the symptom of unilateral neglect in a patient with damage to the right cerebral cortex was related to the dorsal visual pathway, including Brodmann areas 40 and 44.

Application of rTMS led to activation of the parietal lobe of the cerebral cortex, increasing visuospatial attention to spatial neglect. In the current study, application of rTMS stimulated the area corresponding with Brodmann area 40, as well as the cerebral
Included for the study (n=30)

Informed consent taken

Baseline measurement

Randomized

rTMS group (n=15)

rTMS + CRT for four weeks

15 subjects Completed the trial

rTMS, repetitive transcranial magnetic stimulation; CRT, comprehensive rehabilitation therapy. ST, sham therapy.

Figure 1. Study flowchart.

Table 1. General characteristics of the subjects (n =30).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EG  (n=15)</th>
<th>CG (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.07 (12.1)</td>
<td>63.33 (12.16)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.60 (8.54)</td>
<td>164.87 (7.32)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.67 (9.82)</td>
<td>62.07 (6.97)</td>
</tr>
<tr>
<td>Time since onset (month)</td>
<td>4.13 (1.13)</td>
<td>3.86 (0.83)</td>
</tr>
<tr>
<td>MMSE (score)</td>
<td>26.87 (1.64)</td>
<td>28.20 (1.97)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>7/8</td>
<td>9/6</td>
</tr>
<tr>
<td>Type of stroke (Ischemia/hemorrhage)</td>
<td>8/7</td>
<td>10/5</td>
</tr>
</tbody>
</table>

EG, experimental group; CG, control group. Values are expressed as mean (SD). MMSE, mini-mental state examination.
cortex area, evoking motor potentials and positively affecting alleviation of the unilateral neglect. Brighina et al.,21 who applied low-frequency rTMS to the right cerebrum of three stroke patients with left unilateral neglect and right brain damage, finding decreased unilateral neglect, explained that stimulation of the right cerebral cortex led to the disinhibition of excitability in the left cerebral cortex through the corpus callosum, thereby exciting the right cerebral cortex.

In the current study, higher scores for the box and block and grip strength tests were observed in the experimental group than in the control group. Thus, the function of the upper extremity of the experimental group increased after rTMS intervention. Mally and Dinya22 applied rTMS to the area of the brain governing the upper extremities of patients with hemiplegia caused by a stroke. The results showed that Hoffman’s reflex latency increased, reaction intensity decreased, and upper extremity movement improved. Sasaki et al.,23 who stimulated the motor cortexes of acute-state stroke patients using rTMS at a frequency of 10 Hz for five days, reported that their grip strength increased and hand motor function improved. Pomeroy et al.,24 who applied rTMS to sub-acute stroke patients, found that muscle contraction of the brachial triceps increased. Dafotakis et al.25 reported that grip strength and motor function of the hands improved, finding that application of rTMS led to activation of the corticospinal tract from the cerebrum to the upper extremities, positively affecting the recovery of brain neural plasticity.

rTMS is a clinical intervention used for recovery of the motor function of stroke patients. It works non-invasively to stimulate the cerebral cortex, thus triggering depolarization of the brain’s nerve cells.26 rTMS may also change the excitability of the cerebral cortex and assist in the functional recovery of stroke patients.23 In addition, rTMS infiltrates the cerebral cortex without resistance by the skin and stimulates the damaged brain area without pain. It may be used selectively to stimulate damaged areas by freely moving the stimulation point without the need for direct contact with the cranium.27 The findings of the current study indicate that rTMS might be effective in improvement in reduction of the unilateral neglect and motor function.

The current study has some limitations. First, the small sample size may have influenced certain variables and influenced the results. Therefore, these results cannot be generalized to all stroke patients. Second, due to the absence of follow-up after completion of repetitive transcranial magnetic stimulation, the durability of the effect of this intervention could not be determined. Third, functional measurements were not performed to determine whether or not there would be a functional benefit in terms of activities of daily living. Hence, further studies, including a long-term follow-up assessment, are needed to evaluate the long-term benefits of repetitive transcranial magnetic stimulation.

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

<table>
<thead>
<tr>
<th></th>
<th>EG (n=15)</th>
<th></th>
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<th>CG (n=15)</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
<td>CWG</td>
<td>Pre-test</td>
<td>Post-test</td>
<td>CWG</td>
</tr>
<tr>
<td>LBT (cm)a</td>
<td>35.87 (8.08)</td>
<td>19.33 (6.87)</td>
<td>16.53 (11.11 to 21.95)</td>
<td>38.20 (4.72)</td>
<td>34.60 (4.00)</td>
<td>3.60 (0.81 to 6.38)</td>
</tr>
<tr>
<td>AT (%)a,b</td>
<td>21.40 (3.98)</td>
<td>35.33 (2.90)</td>
<td>14.13 (16.86 to 11.40)</td>
<td>24.07 (4.11)</td>
<td>27.33 (4.55)</td>
<td>3.26 (4.38 to 2.14)</td>
</tr>
<tr>
<td>BBT (%)a,b</td>
<td>21.73 (11.03)</td>
<td>36.80 (8.18)</td>
<td>15.06 (20.42 to 9.70)</td>
<td>24.13 (8.83)</td>
<td>31.07 (6.44)</td>
<td>6.93 (11.10 to 2.76)</td>
</tr>
<tr>
<td>Grip strength (kg)a</td>
<td>11.67 (4.73)</td>
<td>15.27 (4.82)</td>
<td>3.60 (5.07 to 2.12)</td>
<td>12.00 (3.30)</td>
<td>12.80 (3.03)</td>
<td>0.80 (1.50 to 0.09)</td>
</tr>
</tbody>
</table>

EG, experimental group; CG, control group; CWG, changes within groups.

aSignificant difference in gains between two groups, P<0.05; beffect size greater than 0.70.

LBT, line bisection test; AT, albert test; BBT, box and block test.
Clinical message

- Subacute stroke patients who received repetitive transcranial magnetic stimulation showed an improvement in reduction of the unilateral neglect and upper extremity function.

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Conflict of interest

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