RESEARCH REPORT

The effects of repetitive transcranial magnetic stimulation on unilateral neglect of acute stroke patients: A randomised controlled trial

Hyun Gyu Cha, PT, PhD, Myoung Kwon Kim, PT, PhD*

a Department of Physical Therapy, Kyungbuk College, Hyucheon-dong, Yeongju, Gyeongbuk 750–050, Republic of Korea
b Department of Physical Therapy, College of Rehabilitation Sciences, Daegu University, Jillyang, Gyeongsan, Gyeongbuk 712–714, Republic of Korea

KEYWORDS
repetitive transcranial magnetic stimulation; stroke; unilateral neglect

Abstract Background: Rehabilitation of the unilateral neglect of acute stroke patients represents a major challenge.
Objectives: This study aimed to evaluate the effects of repetitive transcranial magnetic stimulation on the functional recovery of stroke patients with unilateral neglect.
Methods: Twenty patients with stroke were randomly assigned to two groups: a repetitive transcranial magnetic stimulation group (experimental) and a control group. The stroke patients in the experimental group underwent repetitive transcranial magnetic stimulation therapy and comprehensive rehabilitation therapy. The stroke patients in the control group underwent sham magnetic stimulation therapy and comprehensive rehabilitation therapy. The patients in both groups received therapy 5 days per week for 4 weeks. The Motor Free Visual Perception Test (MVPT), Line Bisection Test (LBT), Albert Test (AT), and Star Cancellation Test (SCT) were assessed before and after the 4-week therapy period.
Results: The experimental group showed a significant increase in the MVPT, LBT, AT, and SCT values compared with the preintervention values (p < 0.05). Furthermore, the control group showed a significant increase in the MVPT, LBT, and AT results compared with the preintervention results (p < 0.05). A significant difference in the post-training gains for the MVPT (8.9 ± 2.5 vs. 4.8 ± 3.0), LBT (−19.3 ± 7.5 vs. −6.5 ± 9.5), AT (13.1 ± 8.0 vs. 4.0 ± 1.9), and SCT (−13.6 ± 6.9 vs. −4.5 ± 6.9) 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 large in MVPT and AT (effect size = 3.25 and 2.90), respectively, and the effect size for gains in the experimental and control groups was small in LBT and SCT (effect size = 0.22 and 0.23, respectively).

* Corresponding author. Department of Physical Therapy, College of Rehabilitation Sciences, Daegu University, Jillyang, Gyeongsan, Gyeongbuk 712–714, Republic of Korea.
E-mail address: skybird-98@hanmail.net (M.K. Kim).

http://dx.doi.org/10.1016/j.hkpj.2015.04.001
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Introduction

Unilateral neglect refers to the inability to sense meaningful stimulation that is applied to the opposite side of a brain lesion [1]. Unilateral neglect can occur when either the left or right hemisphere is damaged, but generally occurs more frequently when the right hemisphere is damaged [2]. The continuance of this symptom in stroke patients leads to impaired ability to recognize objects placed in the space on the paralyzed side and difficulties carrying out daily activities independently [3]. In addition, it increases the incidence of other diseases and requires assistance or supervision during daily activities due to safety concerns [4]. Unilateral neglect can occur following lesions in various brain regions including the parietal lobe, frontal lobe, temporal lobe, basal ganglia, and thalamus, and patients with unilateral neglect are slower in functional recovery than patients without unilateral neglect [5]. Treatments for unilateral neglect determine the rehabilitation treatment period for acute stroke patients, and influence the level of their functional recovery [6]. Treatments that have been used to tackle unilateral neglect include constraint-induced therapy, mental imagery training, optokinetic stimulation, and trunk rotation therapy [7,8]. However, most of the treatment protocols used are labour intensive, which makes the provision of intensive treatment for all affected patients difficult.

Transcranial magnetic stimulation is a noninvasive technique, which delivers magnetic pulses reaching the cerebral cortex through the scalp. It is generally accepted that high frequency (>1 Hz) repetitive transcranial magnetic stimulation induces an increase in cortical excitability, whereas low frequency (<1 Hz) repetitive transcranial magnetic stimulation reduces it [9], although these assumptions have been challenged by recent neuroimaging studies in nonmotor areas investigating functional connectivity [10]. Previous studies have demonstrated that repetitive transcranial magnetic stimulation is able to modulate the activity of a particular cortical region, resulting in transynaptic effects on other distant areas [11]. Repetitive transcranial magnetic stimulation has been used to treat motor skills disorders such as stroke and Parkinson's disease [12]. Le et al [13] reported that repetitive transcranial magnetic stimulation has positive effects on the recovery of hand functions in stroke patients. They also reported that the application of transcranial magnetic stimulation to the right parietal lobe of normal individuals led to increased temporal and spatial attention to the left side [14]. However, studies have not yet been conducted on the effects of repetitive transcranial magnetic stimulation on the functional enhancement of poststroke patients experiencing unilateral neglect. In this regard, this study aimed to examine the effects of repetitive transcranial magnetic stimulation on the functional recovery of stroke patients with unilateral neglect.

Methods

Participants

Patients (n = 50) with stroke were screened for this study from March 2014 to September 2014. The inclusion criteria were: (1) no significant cognitive deficit (a score of >25 points in the Mini-Mental Status exam) [15]; (2) significant unilateral neglect (a score of <16 points in the Motor-Free Visual Perception Test (MVPT) [16]; (3) no eyesight or hearing problems; and (4) no psychological or emotional problems. Twenty-two patients with stroke met the criteria. They all showed left unilateral neglect symptoms. The Research Ethics Committee of Eulji University Hospital approved the study, and all participants provided informed, written consent prior to involvement in the study. All experiments were conducted in accordance with the Declaration of Helsinki. After the completion of the initial assessment, participants were randomly assigned to an experimental group (n = 11) or a control group (n = 11). For randomisation, sealed envelopes were prepared in advance and marked inside with A or B, indicating the experimental group and the control group respectively.

The randomisation was done by a third party that was totally unaware of the study content. The participant characteristics and all outcome measures before and after the treatment were assessed by Physician 1 who was blinded to the treatment allocation. The repetitive transcranial magnetic stimulation and sham treatments were conducted in a closed room by Physician 2 who was not involved in the assessment of patients. Both physicians were instructed not to communicate with the study participants about the possible goals or the rationale of either treatment.

Intervention

The patients in the experimental group received repetitive transcranial magnetic stimulation and conventional rehabilitation therapy for a total of 40 minutes (repetitive transcranial magnetic stimulation: 10 minutes; conventional rehabilitation therapy: 30 minutes) per day, with a 10-minute rest period halfway through the session. The patients in the experimental group received training 5 days per week for 4 weeks. Conventional rehabilitation therapy consisted of neurodevelopmental facilitation techniques. The patients in the control group received sham transcranial magnetic stimulation therapy and conventional rehabilitation therapy for a total of 40 minutes per day on the same day.

Conclusion: The current study findings indicated that repetitive transcranial magnetic stimulation may be beneficial in decreasing the unilateral neglect of stroke patients.
Magstim Rapid2 (Magstim co., Ltd, Wales, UK) was used for repetitive transcranial magnetic stimulation, 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 belly, specifically to the first dorsal interosseous muscle on the right side, and attaching standard electrodes to the tendon. After the region causing the largest motor evoked potential at the lowest intensity was found, the region was stimulated 10 times and the minimal intensity of stimulation exhibiting 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 right posterior parietal areas at locations P3 and P4 based on the electroencephalogram 10/20 system at a frequency of 1 Hz for 5 minutes with 90% of the motor threshold during rest, a 1-minute break was given [17]. The group performed repetitive transcranial magnetic stimulation for 4 weeks, five times each week and 10 minutes each day. The control group was led to hear sounds using a sham stimulator coil without knowing that the sounds were due to sham stimulation.

Outcome measurement

Motor Free Visual Perception Test
The Motor Free Visual Perception Test (MVPT) consists of 36 questions with a total score of 36 points, and is divided into five subcategories, including visual discrimination, figure ground, visual memory, visual closure, and spatial relationship. Unilateral neglect was determined based on whether the questions answered by a patient show a significant imbalance toward one side by calculating the number of questions with left-side or right-side answers, regardless of the number of correct answers. In the MVPT, the criteria to determine unilateral neglect are that response scores within the evaluation tool are 17 points or below for those aged 18 to 69 years, and 16 points or below for those aged 70 to 80 years. The MVPT’s test–retest reliability is 0.77 to 0.83 [16].

Line Bisection Test
The Line Bisection Test (LBT) is an instrument used to evaluate unilateral neglect. In this test, six of 20 lines of various lengths are arranged at the centre, left side, and right side on a 21.5 cm × 28 cm sheet of A4 paper. The test was performed by placing the test sheet at the front and centre of each patient and instructing him/her to indicate the midpoint of each line using a pencil. Scores were obtained by measuring the distance between each line’s actual midpoint and the midpoint indicated by the patient, adding those values, and then dividing the sum by the number of lines. Test results were interpreted as normal when the average length deviated from the midpoints was less than 6.3 mm, mild-unilateral neglect when the respective length was 6.3 mm or above, and severe-unilateral neglect when the respective length was 12.5 mm or above. The intertester reliability of the LBT is 0.82 [16].

Albert Test
The Albert Test (AT) evaluation form, which is a 26 cm × 20 cm sheet, is an evaluation tool used to identify the degree of unilateral neglect [18]. A total of 40 lines, each with a length of 2.5 cm, are arranged in six rows (left 2 rows, middle 2 rows, right 2 rows) × six columns + one row (the centre) × four columns. The evaluator demonstrated the test by drawing a line on the central column before the evaluation and instructed the participants to draw on every line in the same manner. The evaluator then confirmed the participants work by asking “Have you drawn through every line?” There is no limit imposed on the participants head movement, and scores were generally measured by recording the degree of deviation as (the number of ignored lines/the total number of lines) × 100, or by identifying the number of indicated lines. This study identified the total number of indicated lines to detect the degree of deviation in an easy manner. The test–retest reliability is 0.99.

Statistical analysis
The sample size for this study was calculated using the G*power program 3.1.0 (G power program Version 3.1, Heinrich-Heine-University Dusseldorf, Germany). Based on the data from the pilot study, the estimated sample to obtain a power of minimum 80% at a significant alpha level of 95% was 20 participants. The statistical software SPSS 20.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The result of testing to identify the existence of a normal distribution revealed no normal distribution. Therefore, nonparametric statistics was used for analysis. Before therapy, differences in the general characteristics of the experimental group and the control group were compared using the Mann-Whitney U test and Chi-square test. Comparisons of gait before and after the training within each group were made using the Mann-Whitney U test. Comparisons of pre- and post-test differences in gait between the experimental group and the control group were done using the Wilcoxon signed rank test. The level of significance was set as $p = 0.05$ for all tests.

Results
A summary of the clinical and demographic features of the sample ($n = 20$) is shown in Table 1, which also shows that there were no significant differences in the baseline characteristics observed between the two groups ($p > 0.05$). Of the 22 participants included in this study, two participants [experimental group ($n = 1$) and control group ($n = 1$)] dropped out before the post-test due to extremely poor health. Therefore, 10 participants (experimental) and 10 participants (control) in each group completed this experiment. Figure 1 shows the flow chart of the study. Table 2 shows the characteristics of the two groups ($n = 20$) before and after transcranial magnetic stimulation.
Table 1. General characteristics of patients (n = 20).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EG (n = 10)</th>
<th>CG (n = 10)</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59.8 ± 9.9</td>
<td>56.7 ± 8.2</td>
<td>−0.644</td>
<td>0.516</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.5 ± 7.9</td>
<td>166.0 ± 4.1</td>
<td>−0.909</td>
<td>0.365</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.7 ± 5.6</td>
<td>63.0 ± 5.1</td>
<td>−0.763</td>
<td>0.443</td>
</tr>
<tr>
<td>Time since onset (wk)</td>
<td>4.4 ± 0.2</td>
<td>4.9 ± 0.3</td>
<td>−1.314</td>
<td>0.182</td>
</tr>
<tr>
<td>MMSE-K (score)</td>
<td>26.92 ± 1.79</td>
<td>26.89 ± 1.64</td>
<td>−1.364</td>
<td>0.203</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>5/5</td>
<td>6/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected side (left)</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of stroke (ischaemic/haemorrhagic)</td>
<td>3/7</td>
<td>4/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPT (score)</td>
<td>12.7 ± 2.2</td>
<td>12.1 ± 3.0</td>
<td>−0.608</td>
<td>0.543</td>
</tr>
<tr>
<td>LBT (cm)</td>
<td>37.0 ± 8.3</td>
<td>34.7 ± 6.0</td>
<td>−0.917</td>
<td>0.354</td>
</tr>
<tr>
<td>AT (%)</td>
<td>20.0 ± 3.2</td>
<td>22.0 ± 3.8</td>
<td>−1.251</td>
<td>0.213</td>
</tr>
<tr>
<td>SCT (%)</td>
<td>29.9 ± 4.9</td>
<td>27.9 ± 6.3</td>
<td>−0.720</td>
<td>0.472</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

AT = Albert Test; CG = control group; EG = experimental group; LBT = Line Bisection Test; MMSE-K = Mini-Mental State Examination; MVPT = Motor Free Visual Perception Test; SCT = Star Cancellation Test.

Figure 1. Study flowchart. CRT = comprehensive rehabilitation therapy; rTMS = repetitive transcranial magnetic stimulation; ST = sham therapy.
The experimental group showed a significant increase in the MVPT, LBT, AT, and SCT values compared with pre-intervention results \( (p < 0.05) \). Similarly, the control group showed a significant increase in the MVPT, LBT, and AT values compared with the pre-intervention results \( (p < 0.05) \). A significant difference in the post-training gains for the MVPT \( (8.9 \pm 2.5 \text{ vs. } 4.8 \pm 3.0), \) LBT \( (19.3 \pm 7.5 \text{ vs. } -6.5 \pm 9.5), \) AT \( (13.1 \pm 8.0 \text{ vs. } 4.0 \pm 1.9), \) and SCT \( (13.6 \pm 6.9 \text{ vs. } -4.5 \pm 6.9) \) 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 large in MVPT and AT \( (effect \text{ size } = 3.25 \text{ and } 2.90, \) respectively) and the effect size for gains in the experimental and control groups was small in LBT and SCT \( (effect \text{ size } = 0.22 \text{ and } 0.23, \) respectively).

### Discussion

After 4 weeks of transcranial magnetic stimulation, a significant decrease in left unilateral neglect was observed between the experimental group and the control group. This result supports the primary hypothesis of the study that transcranial magnetic stimulation would decrease the unilateral neglect of stroke patients. Repetitive transcranial magnetic stimulation causes the depolarisation of nerve cells within the cerebral cortex by applying magnetic fields outside the cranium noninvasively, and an explanation of how to use this method on humans was introduced in detail. Later, the method of applying magnetic fields repeatedly was developed and revealed the fact that the excitability of the cerebral cortex changes for a certain period of time after repetitive magnetic stimulations. Recent studies have suggested that magnetic stimulation can be used as a therapeutic method for various types of brain diseases using the characteristic that repetitive transcranial magnetic stimulation changes the excitability of the cerebral cortex. Most studies reported that the application of repetitive transcranial magnetic stimulation in patients with mental diseases such as depression and stroke was effective in improving motor or language functions or reducing unilateral neglect \([20]\).

The main finding of the current study was that repetitive transcranial magnetic stimulation combined with conventional rehabilitation reduced unilateral neglect more effectively than the conventional rehabilitation alone, as measured by the MVPT, LBT, AT, and SCT of stroke patients. LBT, AT, and SCT are part of the Behavioral Inattention Test. These tests were used in the current study as they provided a simple and easy method of evaluating unilateral neglect. A study by Brighina et al \([21]\) reported that the application of repetitive transcranial magnetic stimulation at low frequencies in the left cerebral hemisphere of three patients with infarction in the right cerebral hemisphere improved hemispatial neglect on the affected side. This mechanism was explained by Kleinman et al \([17]\) when they reported that unilateral neglect in patients with damage in the right cerebral hemisphere was associated with the dorsal visual pathway, including Brodmann’s areas 40 and 44. In the present study, the regions where repetitive transcranial magnetic stimulation was performed were P3 and P4 based on the electroencephalogram 10/20 system, which applies to Brodmann’s area 40 that is related to unilateral neglect. The present study reported that after the application of high-frequency stimulation to the left and right parietal lobes of normal individuals, visuospatial attention to the opposite side of each stimulated parietal lobe increased, and its mechanism was the activation effects of high-frequency stimulation on the parietal lobe of the cerebral cortex. In the present study, participants were patients with unilateral neglect on the left side due to damage in the right brain lesions. The participants showed differences in the effects of magnetic stimulation due to large variations in their characteristics. It is possible that different individuals may require different stimulation protocols because of the heterogeneity in location and severity of stroke. Additional studies are required to investigate the effects of different magnetic stimulation frequencies \([14]\).

The present study has some limitations. First, the sample may not be representative of the overall acute stroke population as the size of the sample is small. Therefore, the results cannot be generalised to all acute stroke patients having unilateral neglect. Second, the absence of follow-up after the end of the repetitive transcranial magnetic stimulation does not allow for determination of the durability of the effect of this intervention. Third, functional measures were not undertaken to see whether or not the experimental treatment conferred any therapeutic effects.
on ability to perform functional activities. Further studies, including a long-term follow-up assessment, are needed to evaluate the long-term benefits of repetitive transcranial magnetic stimulation.

Conclusion

This study demonstrated that repetitive transcranial magnetic stimulation may be beneficial in decreasing the unilateral neglect of stroke patients.

Conflicts of interest

The authors declare no conflicts of interest.

Funding/support

The authors received no financial or grant support for the study.

References