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ORIGINAL ARTICLE

Effect of High- and Low-Frequency Repetitive Transcranial Magnetic Stimulation on Visuospatial Neglect in Patients With Acute Stroke: A Double-Blind, Sham-Controlled Trial

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Abstract

Objective: To compare the therapeutic effect of low- and high-frequency repetitive transcranial magnetic stimulation (rTMS) of the posterior parietal cortex (PPC) in patients with acute stroke with visuospatial neglect.

Design: This study was a prospective, double-blind, sham-controlled trial. Data are presented from 27 patients (15 men, 12 women; mean age, 67.0y) randomly assigned to receive 10 sessions of low-frequency (1Hz) rTMS over the nonlesioned PPC, high-frequency (10Hz) rTMS over the lesioned PPC, or sham stimulation.

Setting: National university hospital.

Participants: Patients (N=27) diagnosed with visuospatial neglect after stroke.

Intervention: Ten sessions of rTMS over a 2-week period.

Main Outcome Measures: The severity of visuospatial neglect was assessed pre- and posttreatment using the Motor-Free Visual Perception Test, line bisection test, star cancellation test, and Catherine Bergego Scale.

Results: When comparing the differences in the Motor-Free Visual Perception Test, line bisection test, star cancellation test, Catherine Bergego Scale, and Korean-Modified Barthel Index (K-MBI) scores before and after treatment according to group, we found that changes in the line bisection test and K-MBI scores were significantly different between 3 groups. In the post hoc analysis, the improvement in the line bisection test score in the high-frequency rTMS group was statistically significant compared with that in the sham stimulation group (high vs sham $P=.03$, low vs sham $P=.09$, high vs low $P=.58$), and the improvements in the K-MBI scores of the 2 rTMS groups were statistically significant compared with those in the sham stimulation group (high vs sham $P<.01$, low vs sham $P=.02$, high vs low $P=.75$).

Conclusions: These results indicate that high-frequency rTMS is effective in the treatment of visuospatial neglect in patients with acute stroke. Archives of Physical Medicine and Rehabilitation 2013;94:803-7

Visuospatial neglect is defined as the failure "to attend, explore, and act upon the contralesional side of space,"[1(p499)] and cannot be explained by primary sensory loss or motor dysfunction.[1] It was traditionally considered a "parietal sign"[2(p209)] and arises most frequently after right hemispheric lesions of the middle cerebral artery that damage the parietal-frontal cortical-subcortical network that processes space representation and awareness.[2] The incidence of visuospatial neglect in acute stroke ranges from 30% to 81%,[3-5] and this disabling symptom is the main obstacle to effective rehabilitation during acute or subacute phases of stroke, eventually leading to poor cognitive and motor function and a poor prognosis.

Various therapeutic strategies, including visual scanning, central cueing, visually displacing prism adaptation, sensory stimulation, and pharmacologic treatments, have been attempted to treat visuospatial neglect.[3,6,7] Although these treatments may attenuate the severity of neglect, they are impractical as a basis for rehabilitation, particularly during acute or subacute phases of stroke, due to short duration of effects, patient discomfort, and poor patient cooperation.[8]

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Recently, repetitive transcranial magnetic stimulation (rTMS), a technique that is able to noninvasively modulate cortical activity, has gained increasing attention for the treatment of visuospatial neglect.[1] It is well known that high-frequency stimulation over the lesioned hemisphere increases cortical excitability, whereas low-frequency stimulation over the nonlesioned, intact hemisphere lowers cortical excitability. Although rare occurrence of seizures and syncope could be associated with high-frequency rTMS treatments, rTMS is regarded as reasonably safe. According to Kinsbourne's theory[9] that each hemisphere shifts attention toward the contralateral hemispace by inhibiting the other hemisphere, after a stroke, the nonlesioned, intact hemisphere experiences pathologic hyperactivity because of deficient transcallosal inhibition from the lesioned hemisphere. This interhemispheric rivalry is also considered the basic pathophysiologic mechanism underlying visuospatial neglect. Low-frequency rTMS over the nonlesioned hemisphere or high-frequency rTMS over the lesioned hemisphere would be expected to reduce the interhemispheric imbalance, thereby reducing visuospatial neglect.

Several studies have reported the beneficial effect of low-frequency rTMS over the nonlesioned hemisphere on visuospatial neglect in patients after stroke,[10-15] and 1 study has investigated the effect of high-frequency subthreshold rTMS on visuospatial attention for the contralateral hemifield in healthy subjects.[16] However, to our knowledge, there are no double-blind, sham-controlled trials that have compared the effect of both low- and high-frequency rTMS on visuospatial neglect in patients with acute stroke. Although 1 study[15] compared the effect of low- and high-frequency rTMS on visuospatial neglect in patients with stroke and low-frequency rTMS over left parietal cortex showed beneficial effects on visuospatial neglect, this study was a crossover design with only 1 session of rTMS and was performed in patients with chronic stroke.

Therefore, we performed a double-blind, sham-controlled study to compare the therapeutic effect of low- and high-frequency rTMS applied over the posterior parietal cortex (PPC) in patients with acute stroke with visuospatial neglect.

Methods

Subjects

This study was a prospective, double-blind, sham-controlled trial, and the control group was defined as the sham-stimulation group. Thirty-three participants were recruited from patients who were admitted to our hospital between September 2010 and April 2012 because of a first-time cerebral stroke in the cortical or subcortical area. Of those patients, 6 were lost to follow-up because of early discharge. Finally, the data from 27 patients with acute stroke (15 men and 12 women; average age, 67.0y; range, 62.8−71.2y) were analyzed for the study. To be eligible for participation, patients had to be diagnosed with right cerebral ischemic or hemorrhagic stroke and have visuospatial neglect (confirmed using the line bisection test[17]). The inclusion criterion for the bisection test was based on patients who scored a ≥15% deviation to the right from the center.[18] Patients were excluded if they had (1) severe cognitive impairment making them unable to understand the instructions given by therapists; (2) contraindications for TMS, such as a history of epileptic seizure, a history of major head trauma, the presence of metal in the skull, or a pacemaker; or (3) unstable medical or neurologic conditions. Thirty-three participants met these criteria and were enrolled in the study. All participants provided written informed consent, and our local Ethics Committee approved the study protocol.

Baseline demographic and stroke-related data are presented in table 1. Patients were randomly assigned to 1 of 3 treatment groups using a table of random numbers: low-frequency rTMS (n=9), high-frequency rTMS (n=9), or sham stimulation (n=9). The average ages of the low-, high-frequency, and sham groups were 68.6, 64.1, and 68.3 years, respectively. The average stroke duration from stroke onset to the time of initial evaluation was 14.2, 14.3, and 16.4 days, respectively. All patients were right-handed. No significant differences were observed in age, sex, duration from stroke onset to the time of initial evaluation, or lesion location between the 3 groups.

For the duration of the study, all participants received conventional rehabilitation treatment, including physical, occupational, and cognitive therapies of the same intensity and duration. In addition, all participants received conventional rehabilitation programs for visuospatial neglect, such as visual tracking, reading and writing, drawing and copying, and puzzles. There were no changes to medications that could affect attention.

All 27 participants completed the scheduled rTMS sessions without any adverse events.

rTMS protocol

A physiatrist performed rTMS using a Magstim Super Rapid Magnetic Stimulator[a] with a 70-millimeter, air-cooled coil in the shape of a figure 8. The coil was held with the handle posterior and oriented sagittally and positioned on the scalp according to the 10−20 system, which is an internationally recognized method to describe the relation between the location of scalp electrodes and underlying areas of the cerebral cortex. The rTMS stimulation site corresponded with position P3, which is localized over the left PPC, and position P4, which is localized over the right PPC. Subjects were seated in a comfortable chair with foam earplugs. We determined the motor threshold of the right first dorsal interossei muscle[12] as the stimulus intensity required to produce motor-evoked potentials of more than 100 microvolt peak-to-peak amplitude in 3 of 5 consecutive trials.

For low-frequency rTMS, 1-Hz stimulation at a 90% motor threshold was delivered over the left (nonlesioned) P3 in 4 trains of 5-minute duration, each separated by 1 minute. This resulted in a total stimulation period of 20 minutes and a total delivery of 1200 pulses. For high-frequency rTMS, 10-Hz stimulation at a 90% motor threshold was delivered over the right (lesioned) P4 in 20 trains of 5-second duration, each separated by 55 seconds. This resulted in a total stimulation period of 20 minutes and a total delivery of 1000 pulses. Sham stimulation was delivered as per the low-frequency stimulation protocol, except that the coil was oriented 90° perpendicular to the skull rather than tangential to it.

List of abbreviations:

ADL	**activities of daily living**
CBS	**Catherine Bergego Scale**
K-MBI	**Korean-Modified Barthel Index**
MVPT	**Motor-Free Visual Perception Test**
PPC	**posterior parietal cortex**
rTMS	**repetitive transcranial magnetic stimulation**