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Effects of High-Frequency Repetitive Transcranial Magnetic Stimulation on Motor Functions in Patients with Subcortical Stroke

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ABSTRACT

Background: Motor function impairment occurs in approximately two-thirds of patients with subcortical stroke. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique for modulating cortical excitability.
Objectives: The present study was designed for assessing the efficacy of high-frequency rTMS (5 Hz) on ipsilesional primary motor cortex in patients with subcortical stroke.
Materials and Methods: Thirty participants who had subcortical stroke in the previous four weeks to four months were enrolled in this randomized double blinded clinical trial. Participants were divided into experimental and control groups and their motor ability of both upper and lower extremities were assessed using Fugl-Meyer assessment of motor recovery after stroke (FMA) before and after intervention. The study intervention rTMS (5 Hz) was administered in six 10-minute sessions on the ipsilesional primary motor cortex in the experimental group and on the vertex in the control group.
Results: Mean change in FMA score after rTMS sessions was significantly higher in the experimental group than in the control group ($p = 0.00$). Mean time interval between the stroke and rTMS intervention had a weak and insignificant ($\rho = 0.097$; $p = 0.61$) correlation with changes of FMA score.
Conclusions: High-frequency (5 Hz) rTMS effectively improved motor function in patients with subcortical stroke.

Keywords: Transcranial Magnetic Stimulation; Stroke

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Introduction

Stroke is the third leading cause of death in the world, as well as the most common cause of long-term neurological impairment (1-3). Following stroke, approximately two-thirds of patients experience motor function impairment (4). Previous studies reported that decreased upper extremity function in patients with subcortical stroke may lead to significant functional disability and to an increase in caregiving responsibilities (5, 6). Different patterns of neural reorganization occur in patients with stroke; neuroplasticity plays a major role in the improvement of these individuals (7, 8).

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that can modulate cortical excitability. Low-frequency rTMS decreases cortical excitability of the stimulated hemisphere and increases the cortical excitability of the non-stimulated hemisphere (9-12).

Different studies have assessed the impact of rTMS on upper extremity function in patients following subcortical stroke. The results are inconsistent, and there is a lack of consensus on the effectiveness of rTMS. Some studies have reported that rTMS has beneficial impact on the unaffected hemisphere, on hand dexterity, pinch acceleration, grip force and finger tapping (13-18). However, other studies did not report significant therapeutic impacts of rTMS on the motor function of patients with stroke (19-21). The aim of the present study was to determine the motor effect of administering six 10-min sessions of high-frequency (5 Hz) rTMS on ipsilesional primary motor cortex functioning following a subcortical stroke above the brainstem.

Materials and Methods

Study participants:

In the present randomized double blinded study, we enrolled 30 patients with subcortical stroke (higher than brainstem) occurring one to four months before the study began. Clinical features confirmed by computerized tomography (CT) scan and/or magnetic resonance imaging (MRI) identified eligible participants. We excluded patients with severe motor deficits (muscle force $^{2}/_{5}$ or less) or any other clinically significant medical comorbidity, history of seizure, head trauma in the previous 30 days, pregnancy, stent or coil in cerebral vascular system, artificial heart valves or pace maker, and use of antipsychotics. None of the participants had prior experience with rTMS.

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study protocol. All study participants or their legal representative provided informed consent.

Study design:

We entered the participants every other one into experimental and control groups. We used the Fugl-Meyer assessment of motor recovery after stroke (FMA) to evaluate the motor functioning of both upper and lower extremities of all participants. FMA is a 126-point scoring system that includes a range of motion, pain, sensation, upper- and lower-extremity motor function and balance. The sensory component of the test comprises 26 points and the motor component 100 points (22). FMA provides a reliable and valid measure of the specific motor function that is sensitive to change (22-24).

Every other day, we administered six 10-min sessions of ipsilesional rTMS (5 Hz) to every participant in both the experimental and control groups. In the experimental group, the treatment was administered to each subject’s primary motor cortex, whereas in the control group, treatment was administered to each subject’s vertex. Following rTMS sessions, we used FMA to assess the subject’s motor activity in all four extremities and recorded each score. All participants were blind to rTMS conditions, and the study examiner did not know the group to which the participants were assigned. We evaluated the motor situation in participants who had been assessed before and after rTMS sessions.

Statistical analysis:

In this study, student paired t-test was used for analyzing quantitative data between study patients before and after rTMS sessions. Standard student t-test was used for comparing other quantitative variables between patients of experimental and control groups. All *p values* < 0.05 were assumed significant. Non-parametric statistical test (Mann–Whitney U) was used for some variables without normal distribution.

Results

Twenty-three male and seven female patients were included in the present study. Male to female ratio between patients of experimental and control groups was not significantly different (p = 0.66). Mean age of patients in experimental and control groups was not significantly different (59.4 ± 13.8 years vs. 61.3 ± 6.9 years; p = 0.65).

Changes in FMA score after rTMS sessions in patients of the experimental group was significantly higher than that of patients in the control group (7.9 ± 2.6 vs. 0.26 ± 1.2; p = 0.00).

In the experimental group, mean of FMA score after intervention was significantly higher than that before intervention (78.47 ± 8.01 vs. 70.53 ± 7.13; p = 0.00). FMA mean score was not significantly different between patients of control group after and before rTMS intervention (70.27 ± 7.66 vs. 70.0 ± 8.08; p = 0.41). Interval mean between stroke and rTMS sessions was not significantly different between experimental and control groups (62.53 ± 21.87 vs. 52.27 ± 22.89; p = 0.22). Interval mean between stroke event and rTMS intervention had a weak and insignificant correlation with changes of FMA score (ρ = 0.097; p = 0.61). Patient age had a weak negative and insignificant association with changes of FMA score (ρ = 0.12; p = 0.53). Mean change in FMA motor function scores before and after rTMS was insignificantly different between male and female patients (3.65 ± 4.59 vs. 4.43 ± 5.06; p = 0.70).

Table 1. Demographic Features of Participants

	Control Group	Interventional Group	*p*
Sex (%)			
M	12(80)	11(73.3)	
F	3(20)	42(26.7)	-
Total	15(100)	15(100)	
Age: Mean(SD)	61.33(6.9)	59.47(13.88)	0.034
Mean F-M Score(SD)			
Pretest	70.27(7.66)	70.53(7.13)	-
Posttest	70.00(8.08)	78.47(8.01)	-
Mean change	-0.266(1.2)	7.9(2.6)	<0.001*

M: Male, F: Female, SD: Standard deviation , F-M: Fugl-Meyer.*p < 0.05 significant

Discussion

The results of the present study showed that FMA scores in the experimental group significantly increased compared with the control group's scores. This finding confirmed the effectiveness of six sessions (held every other day) of 10-min ipsilesional 5 Hz rTMS on the primary motor cortex as a therapeutic modality in patients following subcortical stroke.

These findings are compatible with Kheder et al. whose study found that motor function in stroke patients significantly improved after ipsilesional rTMS (at frequencies of 3 Hz and 10 Hz) when compared with patients in the control group. Although their report confirmed the effectiveness of rTMS on motor weakness and dysphagia in patients with stroke, their findings did not recommend a specific appropriate session frequency or interval between the stroke occurrence and the onset of rTMS treatment (25). Emara et al. reported that motor function in 60 patients following the brain infarction improved after 10 daily sessions of ipsilesional 5 Hz rTMS compared with control patients. Although the number, duration and interval between rTMS sessions differed from those in the present study (26). Chang et al. and Kakuda also confirmed the effectiveness of rTMS to improve motor function in patients with stroke (27–31). To develop a treatment protocol designed to achieve an optimal response in each patient, further studies are necessary to determine the specific characteristics used during rTMS, including frequency, duration and timing of onset following the stroke event. In a recent meta-analysis of the impact of rTMS on upper extremity function among patients with stroke, investigators reported that motor improvement was more pronounced in protocols that applied low-frequency rTMS to the unaffected hemisphere (32). Previous studies reported that interhemispheric competition altered after stroke (13, 33). Hemispheric imbalances may be compensated by a decrease in cortical excitability in the unaffected hemispheres (14, 26). Only Kheder et al. reported that stronger effects of low-frequency rTMS (1 Hz) resulted in improved motor function after stroke (34). Generally, literature has confirmed the effective therapeutic role of rTMS in motor recovery following stroke. Nevertheless, further studies are required to compare the efficacy and side effects between low and high-frequency rTMS protocols.

In the present study, FMA scores did not have significant association with the time interval between stroke and when rTMS treatment was initiated. From these data, one could argue that the interval used in this study (4 weeks to 4 months after the stroke event) was ideal for initiating rTMS. However, further properly designed studies are required to confirm or rule out this hypothesis.

Moreover, previous studies reported that rTMS had a clinically significant effect on motor function for each stage of stroke event. All such findings must be viewed with caution because few studies specifically recruited patients according to the duration between the stroke and rTMS therapy (32). As expected, rTMS effectiveness in the present study was not associated with the gender of patients. This is an expected finding because possible effective mechanisms of rTMS could not be related to the gender of patients. There is little evidence for assessment of relationship between rTMS effectiveness and age of patients. We believe that neuroplasticity is one possible rTMS mechanisms of effectiveness and older patients had lower plasticity in their neural system. Future studies should target the relationship between patients' age and rTMS effectiveness.

In the present study, none of the patients experienced seizure during rTMS sessions. This observation may be due to lower rTMS frequency and the subcortical site of the lesions in the participants. This finding suggests that six 10-min rTMS sessions at 5 Hz can be considered to be a safe protocol in patients with subcortical stroke.

The present study had some limitations. First, our study was performed in one medical center; future multi-center studies should focus on investigating additional treatment variables. Second, we assessed motor function among patients according to the FMA scale. Assessment of motor function in patients with stroke using other techniques, preferably quantitative tests, may help to determine the treatment role of rTMS and its effectiveness in rehabilitation of patients following subcortical stroke.

Future studies investigating the use of therapeutic rTMS with different frequency and time intervals between the stroke event and treatment are recommended for more accurate assessment of the effectiveness of this method.

Conclusion

High frequency (5 Hz) rTMS was effective in causing motor improvement in patients following stroke.

Conflict of Interest

No conflict of interest.

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