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Effects of High Frequency Repetitive Transcranial Magnetic Stimulation on Function in Subacute Stroke Patients

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The aim of the present study was to examine the effects of high and low frequency repetitive transcranial magnetic stimulation on motor cortical excitability and the balance function in subacute stroke patients. Twenty-four subjects were randomly assigned to either the high frequency (HF) rTMS group, or the low frequency (LF) rTMS group, with 12 subjects each. All subjects received routine physical therapy. In addition, both groups performed a total of 20 sessions of rTMS for 20 minutes, once a day, 5 times per week, for a 4-week period. In the HF rTMS group, 10 Hz rTMS was applied daily to the hotspot of the lesional hemisphere; and in the LF rTMS group, 1 Hz rTMS was applied daily to the hotspot of the nonlesional hemisphere. Motor cortex excitability was determined by motor evoked potentials, and the balance function was evaluated by use of the Balance Index (BI) and the Berg Balance Scale (BBS), before and after the intervention. The change rate in the value of each variable differed significantly between the two groups ($p<0.05$). Furthermore, significant differences were observed between all post-test variables of the two groups ($p<0.05$). In the HF rTMS, significant differences were found in all the pre- and post-test variables ($p<0.05$). On the other hand, in the LF rTMS, significant difference was observed only between the pre- and post-test results of BI and BBS ($p<0.05$). The findings demonstrate that HF rTMS can be more helpful in improving the motor cortical excitability and balance function of patients with subacute stroke treatment than LF rTMS, and that it may be used as a practical adjunct to routine rehabilitation.

Keywords : transcranial magnetic stimulation, motor cortical excitability, stroke

1. Introduction

Post-stroke functional recovery is related to various plastic processes leading to central nervous system reorganization. This has been particularly well demonstrated for motor strokes [1]. Post-stroke hemiparesis is characterized by decreased walking velocity with asymmetrical stride time and length, joint stiffness, and abnormal muscle tonus, as well as sensory and coordination impairment, mostly affecting the hemiparetic side. Patients with post-stroke hemiparesis have great problems in regulating physical movement and posture because of abnormal muscle tonus, body imbalance, decreased ability in weight shifting during walking, and reduced fine movement control, causing physical disability and difficulty in walking [2]. Balance impairment is considered the major problem in patients with post-stroke hemiparesis [3], and it may be one of the most difficult barriers to functional performance [4]. Furthermore, balance function is related to reduced functional mobility, which may result from fear or injury [4].

Repetitive Transcranial magnetic stimulation (rTMS) is a noninvasive technique used to assess corticospinal excitability and the plasticity of the central nervous system (CNS) [5]. rTMS is a series of magnetic pulses that temporarily summate and change neural activities to a greater degree than traditional single-pulse TMS. rTMS can modulate the excitability of the motor cortex beyond the period of stimulation [6]. rTMS has been used to measure CNS adaptation and its relationship to changes in neural control and function, primarily focusing on hand muscles in healthy subjects, and in patients with stroke

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[7]. The rationale for the application of rTMS in stroke patients is to modulate the stroke-induced imbalance of activity between both motor cortices. The first reported studies aimed at reducing the excitability of the unaffected hemisphere using low-frequency (LF) rTMS, or at increasing the excitability of the affected hemisphere using high-frequency (HF) rTMS [8, 9]. Other studies considered that stroke recovery might be enhanced by high-frequency stimulation applied at the lesion site. First, Khedr *et al.* [9] showed that 10 consecutive days of 3 Hz-rTMS sessions over the affected motor area improved the immediate clinical outcome in early stroke patients. The effects of rTMS were found to be significant on various disability scales of stroke (Scandinavian Stroke Scale, NIH Stroke Scale, and Barthel Index Scale). More recently, Kim *et al.* [10] observed in hemiplegics that 10 Hz-rTMS over the damaged M1 region could facilitate motor task learning by the paretic hand from 6 months to 3.5 years after stroke. Motor learning improvement was correlated with motor evoked potential (MEP) amplitude increase at the paretic hand.

rTMS has been used to measure CNS adaptation and its relationship to changes in neural control and function, primarily focusing on hand muscles in healthy subjects, and in patients with stroke. In addition, most studies of rTMS with chronic stroke patients have focused on the functional recovery of the upper extremity.

However, few reports have examined the relationship between motor cortical excitability of subacute stroke patients and the recovery of balance ability. The purpose of this study is to determine the effectiveness of HF and LF repetitive transcranial magnetic stimulation in subacute stroke patients.

2. Materials and Methods

24 subjects with subacute stroke hemiparesis volunteered in this study. They were randomly assigned to either an HF rTMS group of 12 subjects, or an LF rTMS group of 12 subjects. Inclusion criteria for the participation of this study were as follows: (1) first stroke within the last 6 months, (2) stroke onset duration of >6 months, (3) no neurological deficits in the cerebellum or the brainstem, and (4) no cognitive impairments (>25 in mini-mental function measure). Exclusion criteria were as follows: (1) patients with metal within the brain, such as clips for aneurysms, and (2) patients with a cardiac pacemaker, pregnant women, or a history of seizure. All subjects signed an informed consent document prior to participation in the study. The demographic information of the subjects is summarized in Table 1. There was no statistically significant difference in age ($t = 1.13$, $p = 0.27$) or onset time ($t = -1.45$, $p = 0.16$) between the two groups.

All subjects were randomly allocated to either the HF rTMs group, or the LF rTMs group. Each subject had an envelope with two cards, and they were instructed to blindly draw one of the cards on each occasion. Both groups received balance training based on the Bobath concept [11] for an hour per day, according to the routine schedule of the rehabilitation unit. In addition, both groups performed a total of 20 sessions of rTMS for 20 minutes, once a day, 5 times per week for a 4-week period.

A 70-mm figure 8 coil and a Magstim Rapid stimulator (Magstim Company, Dyfed, UK) was used for both groups. Before rTMS stimulation, the motor hotspot was determined, which is defined as the location where the stimulation evoked plantarflexion movement of the contralateral gastrocnemius, using a suprathreshold stimulus that was

Table 1. General and Medical Characteristics of Subjects (N=24).

	HF rTMS group (n=12)	LF rTMS group (n=12)	t	p
Age (years)	54.83±6.32	51.33±8.71	1.13	0.27
Height (cm)	163.33±6.43	166.08±6.93	−1.01	0.32
Weight (kg)	66.75±7.07	63.17±7.27	1.22	0.23
Onset time (months)	2.92±1.31	3.58±0.90	−1.45	0.16
Gender				
Male/female	6/6	7/4	0.39	0.70
Hemiparatic side				
Right/Left	8/4	6/6	−0.80	0.43
Stroke type				
Infarction/hemorrhage	5/7	4/8	−0.41	0.69
MMSE-K	26.00±1.91	24.92±1.44	1.57	0.13

Values are expressed as mean±SD
HF rTMS group, high frequency rTMS group; LF rTMS group, low frequency rTMS group; MMSE-K, mini mental state examination - Korea

most apparent over the central lobe zone. In both groups, all patients sat in a reclining wheelchair, and were asked to relax as much as possible, with their heads strapped to the head rest. For patients in the HF rTMS group, 10 Hz rTMS was applied daily to the hotspot of the lesional hemisphere in 10-second trains, with 50-second intervals between trains, for 20 minutes (total 2,000 pulses). For the LF rTMS group, 1 Hz rTMS was applied daily to the hotspot of the nonlesional hemisphere for 20 minutes (total 1,200 pulses). The intensity of rTMS was 90% of the resting motor threshold in each hotspot, in both the HF-rTMS and LF-rTMS groups.

MEPs were performed, using Magstim Rapid; and the balance function was evaluated by the balance index, and the Berg Balance Scale. We then recorded the MEPs, by adjusting the TMS intensity to achieve MEPs in the gastrocinumius muscle of about 1-mV peak-to-peak amplitude, and the intensity was maintained. The MEPs give a measure of global corticospinal excitability and inhibition [12]. The mechanism by which the motor cortex excitability appears is that the Ia afferent fiber is activated by the r-TMS application, and causes high excitation of the corticospinal tract. The latency and amplitude of the MEPs is related to the motor cortex excitability. Reduced latency and increased amplitude mean high motor cortex excitability [12]. Balance index (BI) scores were obtained by means of a balance measurement system (Biodex Balance Master, New York, USA). This system incorporates a specific monitor and a movable force platform, which provides up to 20° of surface tilt in a 360° range of motion, with a visual feedback system. BI refers to the subject's ability to maintain the vertical axis of the body within a suitable range of the balance center of the platform's angle of tilt. A low BI score implies excellent balance ability [13]. The BI has a strong internal consistency, and acceptable intrarater (r=0.82) and interrater (r=0.70) reliabilities [13]. The Berg Balance Scale (BBS) has been widely used to measure the quality of balance performance related to functional movement in clinical settings [14]. It consists of 14 items (9 balance and 5 motor activities), which assess static sitting and standing balance, as well as anticipatory balance during daily activities, such as turnings, transfers, reaching, and retrieving objects from the floor. The BBS has been shown to have excellent intrarater and interrater reliabilities (ICC = 0.99 and 0.98 respectively), and strong internal consistency (Cronbach alpha=0.96) [14].

Data collected from the subjects were analyzed by using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The values of the HF rTMS and LF rTMS groups were expressed in terms of the means and standard deviations. The independent t-test was used to compare demographic characteristics of the subjects between the two groups. In each group, differences between pre-test and post-test results were analyzed by using the paired t-test. Independent t-test was used to compare each variable between the groups. The significance level was set at 0.05 for all analyses.

Table 2. Comparison of the outcome measures within groups and between groups.

	HF rTMS group (n=12)	LF rTMS group (n=12)	t
Latency			
Pre-test	35.20±2.95	36.12±3.83	−0.65
Post-test	32.50±3.32	37.17±1.27	−4.55**
t	2.47*	−0.96	
change value	−2.70±3.79	1.05±3.78	−2.43*
Amplitude			
Pre-test	0.46±0.34	0.60±0.26	−1.15
Post-test	0.76±0.16	0.48±0.21	3.71**
t	−3.71**	1.82	
change value	0.28±0.25	−0.13±0.24	4.08**
Balance index			
Overall			
Pre-test	5.93±0.57	5.67±0.62	1.10
Post-test	3.98±0.96	5.37±0.56	−4.30**
t	6.46**	2.94*	
change value	−1.95±1.05	−0.28±0.37	−5.20**
Anterior-posterior			
Pre-test	4.12±0.69	4.23±0.86	−0.35
Post-test	3.25±0.81	4.03±0.60	−2.66*
t	4.03**	1.19	
change value	−0.87±0.75	−0.17±0.64	−2.46*
Medial-Lateral			
Pre-test	4.32±0.71	4.43±0.69	−0.38
Post-test	3.37±0.43	4.17±0.47	−4.35**
t	4.58**	2.14	
change value	−0.95±0.72	−0.26±0.42	−2.87*
Berg balance scale			
Pre-test	35.50±8.95	33.83±3.21	0.61
Post-test	58.00±10.99	46.00±7.52	3.12*
t	−6.32**	−5.80**	
change value	22.50±12.33	12.17±7.26	2.50*

Values are expressed as mean ± SD, *p < 0.05, **p < 0.01

3. Results

The values of the MEPs, the Balance Index and the Berg Balance Scale of the HF rTMS and LF rTMS groups are summarized in Table 2. The change rate in the value of each variable differed significantly between the two groups ($p<0.05$). Furthermore, significant differences were observed between the post-test results of all the variables of the two groups ($p<0.05$). In the HF rTMS group, significant differences were found in the pre- and post-test results of all variables ($p<0.05$); whereas, in the LF rTMS group, a significant difference was observed only between the pre- and post-test results of BI and BBS ($p<0.05$).

4. Discussion

This study was performed to identify the effects of HF rTMS and LF rTMS in sub acute stroke patients. The improvement of the MEPs of the affected lower limb, and of the BI and BBS in the sub acute phase of stroke, was significantly larger in patients treated with HF-rTMS, than those treated with LF rTMS.

rTMS of the brain is a non-invasive method, which allows a study of both the conductivity of descending motor pathways, and the excitability of the motor cortex in normal subjects, as well as in patients with motor disturbances. The recording of MEPs by TMS in the target muscles has been used in the evaluation of patients with brain injuries due to stroke [6]. In normal subjects, high-frequency rTMS (more than 5 Hz) increases cortical excitability beyond the time of stimulation [6]; whereas, low-frequency rTMS (1 Hz or less) leads to a long lasting decrease in cortical excitability [15]. These changes were thought to correspond to long-term synaptic potentiation (LTP) and depression (LTD) processes, respectively. Optimal recovery after stroke is thought to occur through the recruitment of pathways that are normally used in healthy subjects. Thus to ensure a good outcome, it is required that the functional capacity of the affected brain region should be restored [16].

The result is that the subjects the HF rTMS group significantly decreased latency and increased amplitude, compared to those in the LF rTMS group. Similarly, the present study found that improvement of motor function of the affected upper limb in the early phase of stroke was significantly larger in patients treated with HF-rTMS, than in those treated with LF rTMS [17]. Recently, Gao *et al.* [18] reported that infarct volumes of an acute stroke rat model were reduced significantly after 7 days of HF-rTMS (20 Hz on the lesional hemisphere). They concluded from the results of their micro positron emission tomographic studies that the phenomenon was caused by inhibiting neuronal apoptosis, and maintaining glucose use in the lesional hemisphere. The results of these studies show that HF-rTMS activated the motor cortical excitability of subacute stroke patients, and provided a positive influence to support reorganization in the brain. The results of the BI and the BBS showed that the HF rTMS group had significantly higher post-intervention values than the LF rTMS group did, which suggests that HF rTMS applied to the sub acute stroke patients was helpful in enhancing the balance function. Balance ability in the primary sensorimotor cortext plays an important role. The cerebrum and cerebellum, which are responsible for the activation of the ability to balance the visual, vestibular, and proprioceptive sensory abilities to affect dynamic balance, seem to be improved. HF rTMS in this study was used to increase brain neuroplasticity, and it was helpful in improving the balance ability of stroke patients

There are limitations to this study. The number of patients was relatively small, although this study was a randomized controlled study. Second, we did not use any functional neuroimaging studies such as fMRI or positron emission tomography. Third, we didn't confirm the continuity of the effects through follow-up.

5. Conclusion

The improvement in the MEPs, BI, and BBS of the affected lower limb in the subacute phase of stroke was significantly facilitated in post stroke patients treated with HF rTMS applied to the lesional hemisphere, compared to those treated with LF rTMS. HF-rTMS applied to the lesional hemisphere may be a useful neurorehabilitative approach with low-risk symptomatic deterioration, for subacute phase hemiparetic stroke patients.

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