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Effect of 1 Hz Low Frequency Repetitive Transcranial Magnetic Stimulation on Cerebral Activity and Recovery on Upper Limb Motor Function in Chronic Stroke Patients

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The purpose of this study was to evaluate the effect of 1 Hz low frequency repetitive transcranial magnetic stimulation (rTMS) on cerebral cortex activity and recovery of hand function in chronic stroke patients. It was evaluated by motor evoked potentials (MEPs) amplitude, latency, and MFT. In Results, rTMS group and neurorehabilitation training (NRT) group showed differences in MEPs amplitude, latency, and MFT before and after intervention ($p < 0.05$). and rTMS group showed significant differences in MEPs amplitude and MEPs latency compared to NRT group ($p < 0.05$), but both groups did not show significant differences ($p < 0.05$). These results suggest that rTMS and NRT in chronic stroke patients have positive changes in cerebral cortex activity, but 1 Hz rTMS is more effective in cerebral cortex activity than in NRT. However, for recovery of hand function in chronic stroke patients, motor learning considering neurophysiology and biomechanics as well as cerebral cortex activity is required.

Keywords : 1 Hz low frequency repetitive transcranial magnetic stimulation, motor evoked potentials, motor evoked potentials latency, neurorehabilitation, hand function

1. Introduction

Various neurorehabilitation approaches have been suggested for restoring upper limb (U/L) function in stroke patients. In particular, physical and occupational therapy in stroke patients could apply Bobath approach based on a neurophysiology or constraint-induced movement therapy (CIMT) based on learned nonuse for recovery of U/L function. However, most of these neurorehabilitation do not directly alter the damaged brain, but rather enhance their function by promoting neuroplasticity through external stimuli and environmental changes [1]. Recently, to improve these limitations, repetitive transcranial magnetic stimulation (rTMS) has been proposed to enhance the central nervous system by non-invasively magnetically stimulating a specific area of the brain. Such non-invasive stimulation is recognized as another approach in terms of direct control of neurorehabilitation of stroke patients. However, Results of rTMS may differ depending on the individuals of the patient, such as the location, size, age, and gender of the brain injury lesion, and the effects may depending on the genetic characteristics [2]. And it is not clear when appropriate stroke stimulation criteria or noninvasive brain stimulation can be applied after stroke [3]. And the application of non-invasive rTMS of stroke patients should be based on many research results. Previous studies have reported the effects of rTMS on the U/L motor function of stroke patients, Based on this evidence, rTMS in the primary motor cortex (M1) responsible for recovery of U/L motor function. In previous study, short-term application of low-frequency rTMS in the M1 of chronic stroke patients improved the functional recovery of U/L. So the short-term application of rTMS was understood as a therapeutic approach to help restore U/L function in chronic stroke patients [4, 5]. Therefore, the purpose of this study is to investigate the changes and

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differences in cerebral cortical activity and hand function between low-frequency rTMS and neurorehabilitation training (NRT) applied to chronic stroke patients and to investigate the effects of various interventions for stroke patients.

2. Theoretical Background

2.1.Principles and effects of rTMS

rTMS is safe and effective in noninvasive stimulation of cerebral cortex, because it does not weaken strength by high resistance object such as skull or scalp and does not form strong current density in scalp. The effect of rTMS depends on the mode of stimulation. Single pulse rTMS depolarizes and discharges cerebral cortex under the stimulus point. For example, stimulation of the M1 can lead to muscle activity on the motor evoked potentials (MEPs), recorded by electromyography (EMG) [6]. rTMS that repeats a stimulus rather than a single stimulus results in a long lasting effect beyond the initial stimulus period. rTMS can increase or decrease the excitability to the corticospinal pathway depending on the strength of the stimulus, the direction of the coil, and the frequency. The mechanism of this effect is not clear, but it is thought to cause changes in synaptic efficacy similar to long-term potential and long-term depression. rTMS stimulates the high frequency at 5-20 Hz depending on the frequency of the stimulus and increases the response of the cerebral cortex, which can be seen as a decrease in the MEPs threshold. Low frequency rTMS below 1 Hz or the same frequency, causing inhibition on response of cerebral cortex [7]. A study on the duration of rTMS effects reported that the average effect duration of stimulation was 31 minutes with an average stimulus intensity of 101 % motor threshold (MT) (80-110 % MT) at low frequency rTMS [8].

3. Materials and Methods

3.1. Subject

This study was conducted with a randomized control design. The patient was diagnosed with a stroke on cerebral hemorrhage and cerebral infarction using computed tomography (CT) or magnetic resonance imaging (MRI). Twelve patients with chronic stroke who understood and agreed with the purpose of this study were selected. Prior to evaluation and intervention, patients were randomly divided into 1 Hz low-frequency rTMS groups (n = 6) and neurorehabilitation training (NRT) groups (n = 6). To prevent complications in patients with low-frequency rTMS, patients with cardiac pacemakers, patients with metallic material in the head, and patients with a history of seizure were excluded [9]. We also excluded patients with aphasia, cognitive impairment, unilateral neglect, visual field deficits, psychiatric or orthopedic disease. rTMS group performed NRT 5 times for 3 weeks and 15 times for 40 minutes per session, and at the same time, 1 Hz low frequency rTMS was performed 9 times for 3 minutes per week for 20 minutes. NRT group, such as the Bobath approach and task training was performed five times over three weeks and 15 times per 40 minutes per session.

3.2. Measurement

3.2.1. Motor evoked potentials (MEPs) measurement and manual function test (MFT)

This study measured MEPs of the cerebral cortex by connecting a 70 cm diameter B65 butterfly coil stimulator to MagPro R30 equipment, a low frequency rTMS application. In order to evaluate the MEPs threshold in the supine position, the cerebral corticomotor threshold was measured after wearing a hood with coordinates on the patient's head. The cerebral cortex threshold was tangential to the subject's cerebral hemisphere injury scalp using a B65 butterfly coil stimulator. In order to measure MEPs of each subject, a silver tender-silver chloride electrode (Ag/AgCl) was applied to the first dorsal interosseous (FDI). EMG values were measured by attaching a montage and attaching the ground electrode to the front of the forearm. EMG values were recorded using the mobile KEY POINT.NET® software. The signals were amplified at 100 mV/div and filtered at 2 Hz to 10 KHz. In order to find the exact location of the motor cortical region of the FDI, a single stimulus was applied using the B65 butterfly coil stimulator by moving the position slightly from the center of the brain of the subject. The location of the largest MEPs in the recording potential of FDI was determined as the motor cortical area of the muscle. The resting motor threshold is defined as the minimum stimulus intensity at which 50 μV or more MEPs are recorded for at least five of the ten stimulus, and the stimulus intensity is the amplitude of the MEPs stimulated at 120 % of the kinetics. The average value was determined by measuring 15 times and latent values [10]. MFT is an evaluation tool for objectively measuring motor function recovery of the upper limb in stroke patients. And its consists of 8 items such as U/L motion, grasping, manipulation. Specifically, the muscle strength of the shoulder, movement of hand, grasping, and carrying of the evaluation task are evaluated. According to the degree of evaluation, 0-4 points were given, and total score is 32 points in this study, scores were evaluated for hand function on the damaged side [11].

Fig. 1. (Color online) MagPro R30, Medtronic Inc., Skovlunde, Denmark.

3.3. Procedure

3.3.1. 1 Hz Low frequency rTMS and neurorehabilitation training (NRT)

1 Hz Low-frequency rTMS was performed using the same MagPro R30 (Fig. 1), where the largest MEPs was found at the recording potentials of FDI. The resting motor threshold is defined as the minimum stimulus intensity at which at least 5 of 10 stimuli are recorded at least 50 μV of MEPs, and the Bison with 120 % of MT at 1200 pulses. A frequency of 1 Hz was applied to the intact cerebral hemisphere for 20 minutes to suppress the cerebral motor cortex of U/L area [12]. The NRT used in the control group was applied to the Bobath approach based on the body mechanics and neuroscience, and the task training including approachs of the injured side and the cup, the small ball, the keyboard, and the finger joint movement.

3.4. Statistical analysis

Statistical analyses of the collected data was were performed using the SPSS 18.0 program for Windows.

Table 1. General characteristics of subjects.

Variables		rTMSG (N=6)	NRTG (N=6)
Gender	Male	4	4
	Female	2	2
Age		45.17±6.17	46.00±6.32
Lesion type	Hemorrhage	3	4
	Infarction	3	2
Lesion side	Right	4	3
	Left	2	3
Time from onset stroke (months)		22.17±5.60	22.67±4.13

M±SD M: mean SD: standard deviation rTMSG: repetitive transcranial magnetic stimulation group, NRTG: neurorehabilitation training group

The general characteristics of subjects were descriptive statistics and frequency analysis. The Mann-Whitney U test was used to determine the difference the MEPs amplitude, MEPs latency and MFT before and after intervention in groups. Wilcoxon signed rank test was performed to determine the difference of MEPs amplitude, MEPs latency, and MFT between two groups. All statistical analyzes were performed at $\alpha = 0.05$ significance level.

4. Results

4.1. General characteristics of subjects

General characteristics of the participants in this study are shown in Table 1. rTMS group was 4 males, 2 females, and the mean age was 45.17 years. The causes were 3 hemorrhages and 3 cerebral infarctions. The injured side was 4 on the right and 2 on the left. The disease duration was 22.17 months. NRT group was 4 males and 2 females with an average age of 46.00. The cause of the disease was cerebral hemorrhage in 4 patients and cerebral infarction in 2 patients.

Table 2. Comparison of MEPs amplitude, MEPs latency and MFT before and after intervention in groups.

Variables			Pre-test	Post-test	*z*	*p*
			M±SD	M±SD		
rTMSG	MEPs	amplitude (mV)	0.13±0.00	0.34±0.01	-2.333	.02*
		latency (ms)	28.60±2.53	23.80±1.40	-2.201	.03*
	MFT (point)		17.00±1.78	19.83±1.94	-2.333	.02*
NRTG	MEPs	amplitude (mV)	0.12±0.00	0.29±0.01	-2.214	.03*
		latency (ms)	29.34±3.23	28.39±3.82	-2.201	.03*
	MFT (point)		17.50±1.04	18.67±1.21	-2.070	.04*

M±SD M: mean SD: standard deviation, *$p < .05$, rTMSG: repetitive transcranial magnetic stimulation group, NRTG: rehabilitation training group, MEPs: Motor evoked potentials, MFT: manual function test

Table 3. Comparison of MEP amplitude, latency and MFT between two groups.

Variables	rTMSG (N=6)	NRTG (N=6)	*z*	*p*
	M±SD	M±SD		
MEPs amplitude (mV)	0.21±0.01	0.17±0.01	-2.903	.002**
MEPs latency (ms)	-4.80±2.11	-0.95±0.68	-2.402	.015*
MFTs (point)	2.83±4.08	1.17±0.75	-1.069	.310

M±SD M: mean SD: standard deviation, $^{**}p < .01$, $^{*}p < .05$
rTMSG: repetitive transcranial magnetic stimulation group, NRTG: neurorehabilitation training group, MEPs: Motor evoked potentials, MFT: manual function test

4.2. Changes in MEPs amplitude and MEPs latency before and after intervention in both groups

MEPs amplitude of rTMS group increased from 0.131 mV before intervention to 0.34 mV after intervention, and MEPs latency increased from 28.60 ms before intervention to 23.80 ms after intervention, with statistically significant differences ($P < 0.05$) (Table 2). The MEPs amplitude of NRT group increased from 0.12 mV before intervention to 0.29 mV after intervention, and MEPs latency decreased from 29.34 ms before intervention to 28.39 ms after intervention, with statistically significant differences ($P < 0.05$) (Table 2).

4.3. Comparison of the difference MEPs amplitude MEPs latency and MFT between two groups

The difference in the MEPs amplitudes between the two groups was rTMS group 0.21 mV and NRT group 0.17 mV, and the MEPs latency was rTMS group -0.165 ms and NRT group -0.95 ms, which was statistically significant ($P < .05$) (Table 3).

5. Discussion

Impairment of U/L function in stroke patients is one of the most common symptoms, and many neurorehabilitation approaches have been proposed. recovery of U/L function is primarily based on neurophysiological and biomechanical aspects, and it is important to have an open view in determining the cause of impairment in U/L function and applying various interventions. In this respect, Bobath approach, which is based on biomechanics and neurophysiology and CIMT based on the learned-nonuse, is a systematic approach applied to restoring U/L function in stroke patients and is a universal approach in neurorehabilitation. At the same time it is described as a appropriate approach for restoring U/L in stroke patients. However, this approach has many difficulties in controlling external stimuli and environmental changes, limiting the effectiveness of treatment [1]. In restoring the U/L function of the stroke patient and objectively explaining the effect, the application of rTMS, which can safely activate specific parts of the brain by non-invasive method to the damaged the brain has attracted attention as another method for restoring the U/L function. TMS measures stroke-induced potentials in stroke patients and applies rTMS to the U/L motor function areas that constitute the M1 of the cerebral cortex, and restores U/L function of stroke patients through short-term rTMS treatment. It can have a positive impact. In particular, a single short-term application of 1 Hz low-frequency rTMS to M1 of chronic stroke patients reported recovery of impaired hand function after stimulation. In addition, rTMS was reported to be effective in restoring the motor function of the damaged U/L by performing low-frequency rTMS daily for 5 days [13, 14]. Based on these previous studies, this study also attempted to investigate the changes of U/L function recovery in chronic stroke patients through 1 Hz low-frequency rTMS and neurorehabilitation approaches. We divided the two groups at random and tried to find out the difference between before and after intervention. 1 Hz rTMS was used to identify changes in MEPs amplitude and latency in relation to recovery of U/L on chronic stroke. In particular, NRT group confirmed positive cerebral cortex activity. In a previous study, when the low frequency rTMS was applied to the unaffected intact cerebral motor area in stroke patients in 2005, the changes in hand function were reported to be higher in the pinch acceleration of the fingers than in the sham rTMS group. Eventually, the speed of finger movement is increased [15]. The results showed that cerebral cortex activity and recovery of U/L function were found in both groups with 1 Hz low-frequency rTMS and NRT. The difference in cerebral cortex activity between 1 Hz low-frequency rTMS and NRT. These results suggest that 1 Hz rTMS could be a new therapeutic field in improving the recovery of U/L function in chronic stroke patients. TMS has been widely used in neurology to test the conducting ability of the central and peripheral nervous systems. Recently, Neurorehabilitation has been used to explain the plasticity of brain injury patients based on TMS [7]. TMS can easily record to change motor potentials by EMG, which has become an important foundation for organizing and establishing neuroplasticity [16]. Therefore, in this study, the application of rTMS with NRT applied to the recovery of U/L function in stroke patients may be helpful in explaining the macroscopic level of neuroplasticity. Finally, the comparison between rTMS and NRT groups showed a difference in cerebral cortex activity but no improvement in U/L function. Indeed, normal hand function is composed of very complex components combining neurophysiological and biomechanical aspects and requires an integrated approach of postural control and sensorimotor components necessary to perform tasks to restore hand function of stroke patients [17, 18]. Therefore, in the recovery of U/L function of stroke patients, it is considered to be the key factor for recovery not only in cerebral cortex activity through rTMS but also in integrated approach of task-oriented sensorimotor component.

6. Conclusions

The purpose of this study was to evaluate the effects of 1 Hz rTMS and neurorehabilitation training on the recovery of cerebral cortex activity and U/L function in 12 patients with chronic stroke. In results, rTMS group ($n = 6$) and NRT group ($n = 6$) showed significantly differences in MEPs amplitude, MEPs latency, and MFT before and after intervention ($p < 0.05$). And rTMS group showed significant differences in MEPs amplitude and MEPs latency compared to NRT group ($p < 0.05$), but both groups did not show significant differences ($p < 0.05$). In this study, both rTMS and NRT were helpful in cerebral cortex activity of chronic stroke, but more significant differences were found in rTMS. It was also confirmed that recovery of U/L function in chronic stroke patients requires a systematic neurological rehabilitation approach based on motor learning as well as cerebral cortex activity.

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