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A Study of Different Frequencies of Repetitive Transcranial Magnetic Stimulation on Upper Extremity Muscle Activity and Hand Function in Chronic Stroke Patients

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The purpose of this study was to compare the use of different frequencies of repetitive transcranial magnetic stimulation (rTMS) on the upper extremity muscle activity and hand function of chronic stroke patients. The study subjects comprised 18 chronic stroke patients: the 5 Hz rTMS group (HFG), which included nine patients who received rTMS to the affected cerebral hemisphere, and the 1 Hz low-frequency group (LFG), which had nine patients who received rTMS to the nonaffected cerebral hemisphere. The intervention was conducted three times a week for four weeks. Electromyography was used to check muscle activity, and the stroke upper extremity function test (MFT) and grip strength test were performed to check hand function. Pre- and post-evaluations were performed for both groups. A comparison between the two groups showed a significant difference in the activity of the trapezius anterior and triceps brachii muscle for the muscle activities in the HFG group ($p < 0.05$) as well as a significant difference in the MFT results for hand function ($p < 0.05$). In the LFG group, a significant difference was noted in the triceps brachii muscle for muscle activity ($p < 0.05$), but no significant difference was evident in hand function ($p > 0.05$). The comparison of the two groups showed a significant difference in muscle activity in the triceps brachii muscle ($p < 0.05$) but no significant difference in hand function ($p > 0.05$). This study confirmed that high-frequency rTMS has a positive effect on upper extremity muscle activity and hand function in chronic stroke patients.

Keywords : high frequency repetitive transcranial magnetic stimulation, low frequency repetitive transcranial magnetic stimulation, stroke, muscle activity, hand function

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a representative non-invasive method for cerebral activation and can control brain excitability by adjusting the rTMS frequency [1]. The effect of rTMS can be directly confirmed by measuring the response of the stimulated cerebrum, mainly by focusing on the motor area that can be measured objectively [2]. A previous study reported that the excitability of the corticospinal tract can be temporarily changed when rTMS is applied to the primary motor region [3]. The value measured in the cortical motor area after rTMS is defined as the motor evoked potential (MEP), and the excitability of the cortex varies in line with the frequency of the rTMS [4]. In addition, it is known that the excitability of the cerebral cortex decreases when low-frequency stimulation of 1 Hz is applied and increases when high-frequency stimulation is given [5]. In a study by Higgins *et al.* (2013), task-oriented training combined with 1 Hz LF-rTMS was applied to the experimental group, and task-oriented training combined with sham LF-rTMS was applied to the control group in nine patients with chronic stroke. Significant improvements in upper extremity and hand function were subsequently reported in the 1 Hz LF-rTMS group [7].

Rose *et al*. (2014) investigated a functional task combined with 1 Hz LF-rTMS (experimental group) and a functional task combined with sham LF-rTMS (control group) among chronic stroke patients. They found significant improvements in the upper extremity and hand function in the experimental group [8]. In another study,

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the control group underwent forced exercise induced therapy combined with sham HF-rTMS, and the researchers noted a significant improvement in upper extremity function in the experimental group [9]. Khedr *et al.* (2010) investigated improvements in hand function after the application of 3 Hz, 10 Hz, and sham rTMS to 48 ischemic stroke patients and reported positive results for those who received 10 Hz rTMS [10]. It has recently been reported that intervention results vary depending on the frequency, stimulation time, intensity, number of treatments, and combined form with other treatments when rTMS is applied [11]. However, insufficient clinical studies have been conducted to compare the differences between the frequencies. Looking at previous studies on the stimulation frequency of rTMS, Kim (2014) applied rTMS at 1 Hz and 20 Hz to stroke patients and investigated the effect on upper extremity function. However, this study was conducted on patients in the acute phase and could not confirm the effect of upper extremity function according to the difference in rTMS frequency in patients with chronic stroke. In addition, there were limitations in confirming the results according to upper limb muscle activity and function [12]. The aim of the present study was therefore to compare upper extremity muscle activity and hand function in chronic stroke patients based on the application of different frequencies of rTMS.

2. Materials and Methods

2.1. Subject

This study comprised chronic stroke patients who were admitted to the Department of Rehabilitation Medicine at B Hospital in Seongnam-si, Gyeonggi-do, from October to December 2021. Before the start of the study, the research procedure was explained to all the subjects, and only the subjects who agreed to participate in the study were included in the training. The inclusion criteria for this study were a stroke diagnosis six months previously or more, a score of 23 points on the Korean-Montreal cognitive assessment (K-MoCA), independent sitting, and a Brunstrom's upper extremity recovery stage of three or higher. The exclusion criteria were patients with metallic substances in the body, patients with convulsions or facemaker devices, and patients with unstable medical disorders, such as seizures, caused clinically by rTMS. Before conducting this study, a detailed explanation of the experiment was provided to the guardians and patients, and consent was confirmed through a written informed consent form. Subjects participating in this study were 10 experimental groups and 10 control groups based on previous studies, but a total of 18 completed the study due to exclusion criteria [13].

The final 18 subjects in this study were randomly divided into two groups of nine subjects each. The high-frequency rTMS group (HFG; experimental group) had high-frequency rTMS (HF-rTMS) applied to the cerebral hemisphere of the affected side, and the low-frequency rTMS group (LFG; control group) comprised nine people who received 1 Hz low-frequency rTMS applied to the non-affected cerebral hemisphere.

For the HFG, HF-rTMS was applied three times a week for four weeks to the cerebral hemisphere of the affected side. A stimulation frequency of 5 Hz was applied for six seconds, and 24 seconds of rest were provided thereafter. Nine hundred pulses were applied for 15 minutes. For the LFG, LF-rTMS was performed three times a week for four weeks on the non-affected cerebral hemisphere. Nine hundred pulses were applied for 15 minutes without a break at a stimulation frequency of 1 Hz.

As a result of looking at previous studies to set the number of treatments for optimal rTMS application, Kim (2013) said through a meta-analysis study on TMS that several studies generally preferred 10 to 15 treatment periods for rTMS[14]. Therefore, in this study, based on previous studies, the number of treatments was set to 12, which was applied equally to both HFrTMS and LFrTMS.

2.2. Assessment methods

2.2.1. Muscle activity

In this study, the compound action potentials from the muscle nerves and fibers were recorded and used as surface electromyography (EMG) to measure muscle activity. For the surface EMG, the signals between the muscle fibers and nerves were collected using QEMG-4 (LXM3204, LAXTHA, Korea) with an input impedance of 10^{12} ohm and a common mode rejection ratio of 90 dB at 20 Hz (Fig. 1).

The electrodes were placed at a distance of 25 mm from the centers of the electrodes, and two electrodes were attached to the belly muscle so that they were parallel to the muscle fiber direction. Thereafter, the muscles of the measurement site were maximally contracted at the same time and maintained for three seconds. A total of three measurements were recorded. The initial RMS value was obtained, the window was set as the operation unit, and the overlap ratio was obtained by setting it to 90 %. Afterward, the difference between the maximum value of the four channels was calculated. To consistently represent the difference in values for each muscle, the difference between the contraction values of both muscles was

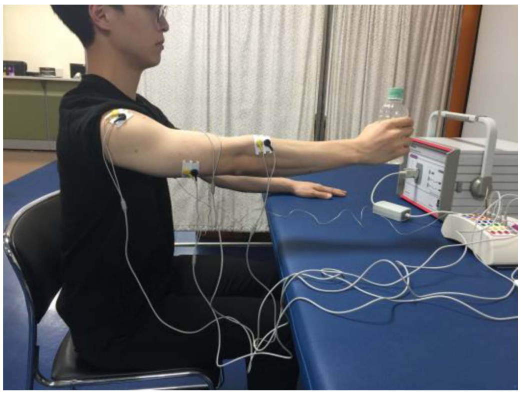

Fig. 1. (Color online) Surface electromyography to measure upper limb muscle activity after application of different frequencies of rTMS. EMG was measured by holding a water bottle with the paralyzed hand in an upright sitting posture and reaching forward.

converted into a ratio, and an absolute value was obtained. The posture for measuring muscle activity was for the patient to stretch a finger toward an object located 30 cm in front of the table while sitting on a chair. In accordance with the measurement procedure, the attachment sites for each muscle were the anterior deltoid, triceps brachii, biceps brachii, and extensor carpi radialis longus.

2.2.2. Hand function

2.2.2.1 Manual function test

The stroke manual function test (MFT), which was developed by Northeast University Medical School, is a tool for measuring upper extremity function and movement ability among stroke patients with hemiplegia (Fig. 2). It consists of upper extremity exercises (four items), grasping (two items), and hand manipulation (two items). The MFT is designed to reflect the recovery process of upper extremity function and practical levels of movement in activities of daily living and to be objectively easy to implement [15]. In a study of stroke patients, the test-retest reliability and inter-inspector reliability were as high as 0.95 [15].

Fig. 2. (Color online) MFT used to evaluate upper extremity function in patients with chronic stroke after application of different frequencies of rTMS. MFT is a widely used assessment tool to evaluate upper extremity function in stroke patients.

2.2.2. Grip strength test

In this study, a dynamometer (Jamar Dynamometer, Sammons Preston, Bolingbrook, USA) was used to evaluate hand grip. For the measurement, the subject was positioned in a comfortable sitting position with their shoulders inward, the elbow joint bent 90°, the lower arm in a neutral position, and the feet placed on the floor. The maximum isometric contraction was measured, and the value was assessed three times and calculated as an average value [16].

2.3. Procedure

2.3.1. 5 Hz high frequency rTMS

HF-rTMS HF-rTMS is a stimulation method that induces cerebral excitability through stimulation with 5 Hz or more. This increases the excitability of the damaged cerebral cortex and increases the neural dominance. This procedure quickly restores damaged nerve function and induces neuroplasticity [17]. HF-rTMS was applied to the subjects in this study using an ALTMS® (Remed, Korea, 2018) device with a 70 mm 8-character coil. To confirm the target point, an imaginary line was connected from the nasion to the inion and then across the mid-sagittal line and the inter-aural line to mark the intersection point. The coil stimulator was placed on the head of the injured cerebral hemisphere at an angle of 45° from the midline. Before performing the rTMS, the subject was seated comfortably in a relaxed state in a chair. After fixing their head on the headrest of the device, the subject's arms and elbow joints were extended, the wrist joints were kept in a neutral position, the forearms were propped up, and the fingers were lightly extended. When measuring the MEP, the first dorsal interosseous muscle (FDI) was measured in the hand, which was in line with previous studies. The largest MEP value of the muscle was set as the motor cortex area. The resting motor threshold was set as the minimum stimulus intensity at which an MEP of 50 μV or more was recorded in at least five or more out of 10 stimuli. At 900 pulses, a frequency of 5 Hz was applied to activate the cerebral cortex on the injured side at an intensity of 120 % MT [18]. A total of 12 sessions were conducted for 15 minutes each three times a week for four weeks. The application of LF-rTMS is based on the theory of transcallosal inhibition. In this study, the same equipment and environment were used for LF-rTMS as for HF-rTMS. For LF-rTMS, a total of 900 pulses were applied 12 times at a frequency of 1 Hz for 15 minutes three times a week for four weeks.

2.3.2. 1 Hz low frequency rTMS

The application of LF-rTMS is based on the theory of transcallosal inhibition [19]. During activities such as writing, both cerebral hemispheres compete or regulate the contralateral cerebral hemispheres, which is described as interhemispheric inhibition [20]. In this study, the same equipment and environment were used for LF-rTMS as for HF-rTMS. For LF-rTMS, a total of 900 pulses were applied 12 times at a frequency of 1 Hz for 15 minutes three times a week for four weeks.

2.3.3. Data Analysis

The statistical analysis of the data was performed using SPSS 18.0 for Windows. The descriptive statistics and frequency analysis were used to present the general characteristics of the subjects. The Wilcoxon signed-rank test was used to determine the changes in muscle activity and hand function before and after the intervention in the two groups. The Mann–Whitney *U* test was used to compare the mean value differences before and after training for the two groups. All the statistical analyses were set at a significance level of 0.05.

3. Results

3.1. General Characteristics of Subjects

The general characteristics of the subjects who participated in this study are presented in Table 1. The HFG comprised five males and four females with an average age of 52.222 ± 4.94 years, and the duration of illness was 11.666 ± 2.95 months since onset. Three subjects had a cerebral hemorrhage, six had cerebral infarction, three had right hemiplegia, and six had left hemiplegia. The K-MoCA average score for the HFG was 28.000 ± 1.93 (Table 1). The LFG included six males and three females with an average age of 51.222 ± 6.09 years and a duration of illness of 12.777 ± 2.53 months since onset. Five subjects had a cerebral hemorrhage, four had cerebral infarction, six had right hemiplegia, and three had left hemiplegia. The K-MoCA average score for this group was 27.444 ± 1.81 (Table 1).

3.2. Comparison of changes in muscle activity and hand function before and after intervention within the two groups.

An EMG test was performed to determine the changes in muscle activity in both groups. In the HFG, a statistically significant difference between the pre-intervention evaluation of 77.388 ± 8.01 in the deltoid muscle and 80.973 ± 8.98 in the post-intervention evaluation was noted ($p < 0.01$). No statistically significant difference was observed in the biceps brachii muscle (40.336 ± 4.76 pre-intervention evaluation vs. 40.535 ± 4.59 post-intervention evaluation; $p > 0.05$). However, a statistically significant difference was evident in the triceps brachii muscle (35.692 ± 3.77 before the intervention vs. 38.050 ± 3.66 after the intervention; $p<0.05$). There was no statistically significant difference in the extensor carpi radialis longus pre-intervention evaluation at 27.582 ± 4.81 compared to the post-intervention evaluation (28.112

Table 1. General characteristics of subjects in this study for rTMS application according to frequency. The following table presents the general characteristics of the subjects who participated in this study.

Variables		HFG (N=9)	LFG (N=9)	x^2/t	*p*
Gender	Male	5(55.6%)	6(66.7%)	0.234	0.629
	Female	4(44.4%)	3(33.3%)		
Age		54.222 ± 4.94	51.222 ± 6.09	8.667	0.564
Side of stroke	Right	3(66.7%)	6(33.3%)	2.000	0.157
	Left	6(33.3%)	3(66.7%)		
Type of stroke	Hemorrhage	3(33.3%)	5(55.6%)	0.900	0.343
	Infarction	6(66.6%)	4(44.4%)		
Time from stroke to rehab(months)		11.666 ± 2.95	12.777 ± 2.53	6.000	0.740
K-MoCA		28. ± 1.93	27.444 ± 1.81	1.867	0.867

M ± SD M: mean SD: standard deviation,
HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group, K-MoCA: korean-montreal cognitive assessment

± 5.28; p > 0.05) (Table 2).

In the LFG, no statistically significant difference was noted in the pre-intervention evaluation (75.615 ± 8.12) compared to the post-intervention evaluation (75.891 ± 7.94) for the deltoid muscle (p > 0.05). There was also no statistically significant difference in the biceps brachii muscle (40.366 ± 7.41 pre-intervention vs. 40.112 ± 7.51 post-intervention; p > 0.05). However, a statistically significant difference was noted for the triceps brachii muscle, which was 28.430 ± 4.83 before the intervention and 30.780 ± 4.06 in the post-intervention evaluation (p < 0.05). No statistically significant difference was found for the extensor carpi radialis longus muscle at 23.566 ± 3.61 in the pre-intervention evaluation and 23.787 ± 3.10 in the post-intervention evaluation (p > 0.05) (Table 2).

An MFT and grip strength test were performed to investigate changes in hand function in both groups. There was a statistically significant difference in the pre-intervention evaluation for the MFT in the HFG (13.777 ± 3.59 vs. 15.111 ± 3.14 post-intervention; p < 0.05). In the LFG, no statistically significant difference was evident (14.111 ± 3.75 pre-intervention and 14.333 ± 4.03 post-intervention; p > 0.05) (Table 2).

For the grip strength test, no statistically significant difference was recorded for the HFG (7.722 ± 2.50 before the intervention and 7.889 ± 2.42 after the intervention; p>0.05). Similarly, the LFG showed no statistically significant difference at 8.277 ± 1.80 in the pre-intervention evaluation and 8.500 ± 1.71 in the post-intervention evaluation (p > 0.05) (Table 2).

Table 2. Comparison of changes in muscle activity and hand function within groups after application of different frequencies of rTMS. The following table presents the before-and-after comparison values in the two groups.

Variables		Groups	Pre-test	Post-test	*Z*	*p*
Muscle activity (RMS)	AD	HFG	77.388 ± 8.01	80.973 ± 8.98	-2.666	0.008**
		LFG	75.615 ± 8.12	75.891 ± 7.94	-0.652	0.515
	BB	HFG	40.336 ± 4.76	40.535 ± 4.59	-0.296	0.767
		LFG	40.366 ± 7.41	40.112 ± 7.51	-0.178	0.859
	TB	HFG	35.692 ± 3.77	38.050 ± 3.66	-2.429	0.015*
		LFG	28.430 ± 4.83	30.780 ± 4.06	-2.666	0.008**
	EC	HFG	27.582 ± 4.81	28.112 ± 5.28	-0.889	0.374
		LFG	23.566 ± 3.61	23.787 ± 3.10	-0.652	0.515
Hand function	MFT(score)	HFG	13.777 ± 3.59	15.111 ± 3.14	-2.047	0.041*
		LFG	14.111 ± 3.75	14.333 ± 4.03	-1.000	0.317
	Grip strength(kg)	HFG	7.722 ± 2.50	7.889 ± 2.42	-1.342	0.180
		LFG	8.277 ± 1.80	8.500 ± 1.71	-1.265	0.206

M ± SD: mean±standard deviation
*p<0.05, statistical significance; **p<0.01, statistical significance
HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group, AD: anterior deltoid, BB: biceps brachii, TB: triceps brachii, EC: extensor carpi radialis longus, MFT: manual function test

Table 3. Comparison of changes in muscle activity and hand function between two groups after application of different frequencies of rTMS. The following table presents comparative values for the amount of change between the two groups.

Variables		HFG (N=9)	LFG (N=9)	*Z*	*p*
Muscle activity (RMS)	AD	2.781 ± 0.39	0.124 ± 0.01	-1.104	0.297
	BB	0.012 ± 0.01	0.024 ± 0.01	-0.397	0.730
	TB	3.016 ± 0.91	2.102 ± 0.52	-3.048	0.001**
	EC	0.512 ± 0.15	0.014 ± 0.01	-1.855	0.063
Hand function	MFT(score)	2.072 ± 0.15	0.201 ± 0.01	-0.666	0.505
	Grip strength(kg)	0.402 ± 0.01	0.360 ± 0.01	-0.710	0.489

M ± SD: mean ± standard deviation
*p<0.05, statistical significance; **p<0.01, statistical significance
HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimlation group, AD: anterior deltoid, BB: biceps brachii, TB: triceps brachii, EC: extensor carpi radialis longus, MFT: manual function test

3.3 Comparison of changes in muscle activity and hand function before and after between the two groups

A statistically significant difference was noted for the triceps brachii muscle when comparing the muscle activity between the HFG and LFG ($p < 0.01$). However, no statistically significant difference was evident when comparing the results of the MFT and grip strength test to determine the difference in hand function between the two groups ($p > 0.05$) (Table 3).

4. Discussion

rTMS is a treatment that modulates brain function through the application of local stimulation to a specific area of the cerebral cortex in a non-invasive way using an electromagnetic field formed by an electromagnetic coil [21]. When the magnetic field signal that has passed through the scalp and skull connects to the cranial nerve cells, it generates an electric current that can be stimulated to a depth of up to 5 cm [22].

It has been reported that the rTMS protocol can cause the excitation or inhibition of cortical activity depending on the frequency, intensity, period, and duration of stimulation [20]. In general, LF-rTMS below 1 Hz is inhibitory, and HF-rTMS above 5 Hz is excitatory. HF-rTMS and LF-rTMS provide evidence of long term depression and long term potentiation at the level of the neural synapses [23].

In this study, LF-rTMS and HF-rTMS were applied to chronic stroke patients to compare the effects on upper extremity muscle activity and hand function. Eighteen subjects who satisfied the selection criteria were assigned to the HFG (nine subjects) and LFG (nine subjects), and a total of 12 applications were applied three times a week for four weeks for both groups and then analyzed before and after the interventions.

First, EMG was performed to examine the changes in muscle activity. In the HFG, significant differences in the trapezius anterior and triceps brachii muscles were observed, and in the LFG, a significant difference was apparent in the triceps brachii muscle. In a comparison between the two groups, significant differences were confirmed with respect to the triceps brachii muscle.

Haghighi *et al.* (2021) reported a significant improvement in hand agility and grip following the application of 20 Hz HF-rTMS to subacute stroke patients [24]. Yozbatiran *et al.* (2009) showed through a single case study of HF-rTMS (20 Hz) that it had a positive effect on motor arm function in a subject in the chronic stage of stroke [25], while Kim *et al.* (2013) reported that the application of HF-rTMS (10 Hz) could improve motor learning and promote brain plasticity in chronic stroke patients [26].

Previous studies have confirmed that the application of HF-rTMS improves upper extremity function in stroke patients, and this result is consistent with the improvements in muscle activity in this study. Compared to LF-rTMS, the application of HF-rTMS produced a more significant improvement in muscle activity. These results are thought to be because LF-rTMS exerts an indirect effect on the non-injured cerebral hemisphere through inhibitory activity, while HF-rTMS activates the cerebral cortex through direct stimulation of the injured cerebral hemisphere.

In this study, the MFT and grip strength test were used to examine changes in hand function, and a significant difference was found in the MFT results for the HFG, but no significant difference was noted for the LFG. Kim *et al.* (2021) conducted a study to determine the optimal target point of rTMS for improving hand function and confirmed that the hand movement area showed the greatest improvement through MEP [27]. This study was conducted with the FDI area as the target, and significant improvements were shown in the MFT results. However, no significant improvement was apparent in the hand grip test. It is thought that a more positive effect could have been obtained after HF-rTMS stimulation if strength training and occupational therapy had been combined within the residual effect.

As a result of examining the upper limb function of chronic stroke patients through rTMS frequency differences through this study, more positive changes were confirmed in HFrTMS than in LFrTMS. Based on the results of this study, we propose the following rTMS utilization plan for the recovery of upper limb function in stroke patients. First, if there is no concern about the subject's underlying disease or side effects and if stability is secured, stimulation of the damaged cerebral hemisphere through H-rTMS will be effective in recovering upper limb function in stroke patients. Second, if the subject has anxiety or concerns about stability, LFrTMS will be a countermeasure for the recovery of upper limb function in stroke patients.

It is difficult to generalize the results of this study due to the small number of study subjects. Future studies should consider the application of different frequencies as well as the study of a variety of diseases.

5. Conclusion

The purpose of this study was to compare upper limb muscle activity and hand function in chronic stroke patients according to the different frequencies of rTMS. As a result of examining the changes in the two groups in this study, there were significant differences in the triceps anterior and triceps brachii muscle among the muscle activity in HFG ($p < 0.01$) ($p < 0.05$). There was a significant difference in MFT during hand function test ($p < 0.05$). In LFG, there was a significant difference in triceps brachii muscle among muscle activity ($p < 0.01$), and no significant difference in hand function ($p > 0.05$). As a result of examining the changes between the two groups, there was a significant difference in the triceps brachii muscle among muscle activity ($p < 0.05$). There was no significant difference in hand function ($p > 0.05$). These results suggest that HFrTMS is more effective than LFrTMS in improving upper limb muscle activity and hand function in chronic stroke patients.

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