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Comparison of the Effect of Repetitive Transcranial Magnetic Stimulation by Frequency on Upper Limb Function in Acute Stroke Patients: A Randomized Controlled Trial

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This study was conducted to compare the effects of low frequency repetitive transcranial magnetic stimulation (LF-rTMS) and high frequency repetitive transcranial magnetic stimulation (HF-rTMS) on upper limb function in stroke patients with acute stage. A total of 40 subjects were randomly assigned 20 each to the LF(1Hz)-rTMS group and the HF(10Hz)-rTMS group, and all subjects received intervention for 20 minutes a day, 5 times a week, for 2 consecutive weeks. The subjects' upper limb function was evaluated using the Wolf Motor Function Test (WMFT), Fugl-Meyer Assessment (FMA), Box and Block Test (BBT), and Jebsen-Taylor Hand Function Test (JTHFT). As a result of this study, there were significant differences between before and after intervention in WMFT and FMA in the LF-rTMS group ($p < 0.05$). In the HF-rTMS group, there was a significant difference between before and after the intervention in FMA, and there was also a significant difference between before intervention and follow up test ($p < 0.01$). There were no significant differences between groups in all dependent variables ($p > 0.05$). These suggest that LF-rTMS and HF-rTMS applied to the primary motor cortex had a positive effect on upper limb function in stroke patients with acute stage, but there was no significant difference in the effect between the two.

Keywords : low frequency repetitive transcranial magnetic stimulation, high frequency repetitive transcranial magnetic stimulation, magnetic field, stroke, upper limb function, primary motor cortex, magnetic stimulator

1. Introduction

Stroke is a leading adult disease that causes long-term disability. Various kinematic defects appear after stroke, especially in more than two-thirds of patients with impaired upper limb function. Impairment of upper limb function due to muscle weakness, abnormal muscle tone, and sensory impairment causes many obstacles in the performance of activities of daily living and becomes a major factor that makes independent daily living difficult [1]. Rehabilitation of the upper limb remains an important task for post-stroke survivors, as only 20 % of patients with hemiplegia after stroke have recovery of normal hand function [2]. The recovery of a stroke depends on the location and severity of the injury, but the appropriate treatment for the first 3 months after the stroke has a great influence on the recovery, and the recovery becomes slower over time. Therefore, it can be seen that the management of the early acute phase of stroke is the most important factor determining the recovery of upper limb function [3].

Several disorders that appear after stroke are associated with metabolic and electrophysiological changes in cells and neural networks [4]. There is also a change in the balance between inhibition and excitement in the affected and opposite hemispheres, as well as both the subcortical and vertebral regions [5]. The affected hemisphere has decreased cortical excitability, causing a decrease in the excitability of that muscle, and the unaffected hemisphere increases cortical excitability. One of the most important processes in the recovery of motor function after stroke is cortical reorganization by neuroplasticity. In particular, many previous studies have suggested that the initial stage after stroke is important for improving neuroplasticity [6, 7].

There are a number of methods applied to accelerate recovery after a stroke. In recent years, research on the application of repetitive transcranial magnetic stimulation

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(rTMS) to functional recovery and brain reconstruction has been actively conducted [8]. rTMS is a non-invasive brain stimulation method that regulates cortical excitability in areas functionally connected to the stimulation site. High frequency (HF) rTMS (≥ 5 Hz) increases cortical excitability, while low frequency (LF) rTMS (≤ 1 Hz) acts to reduce cortical excitability [9].

Previous studies reported that stimulation of rTMS in a specific brain area of a stroke patient had a positive effect on various symptoms that appear after stroke, such as motor dysfunction and pain. In particular, it is considered to be a very effective intervention method for recovery of upper limb motor function after stroke [10, 11]. In particular, it has been reported that rTMS combined with rehabilitation therapy in the acute stage after stroke significantly contributes to the improvement of upper limb function in stroke patients [12]. According to the latest International Federation of Clinical Neurophysiology (IFCN) guidelines describing the therapeutic use of rTMS for motor symptoms after stroke, LF-rTMS has significant effects in the contralesional motor cortex and HF-rTMS has significant effects in the ipsilesional motor cortex [13]. In order to apply non-invasive brain stimulation such as rTMS, the interhemispheric inhibition (IHI) model should be considered. The IHI model explains that excitability in one cerebral hemisphere leads to an inhibitory effect in the other cerebral hemisphere, which can balance the hemispheres [14]. The effect of rTMS, including duration, is primarily determined by the frequency of stimulation or the target area. In particular, the primary motor cortex (M1) forms a major part of the motor cortex and is known to have many functions in motor control, so most of the previous studies on the application of rTMS to motor function recovery after stroke were applied to M1 [15, 16].

However, there are few previous studies comparing the effect of LF-rTMS and HF-rTMS applied to M1. Therefore, the purpose of this study was to investigate the safety and efficacy of LF-rTMS and HF-rTMS in the acute phase of patients with upper limb hemiplegia after stroke.

2. Materials and Methods

2.1. Participants

A priori sample size calculation [α level (.05), power (.80), and effect size (.92)] calculated a total number of 40 participants. With an anticipated dropout rate of 20 %, the recruitment aimed for 52 participants. The G-power version 3.1.2 software was used for the power analyzes (Franz Faul, University of Kiel, Kiel, Germany). Thus, a total of 40 hospitalized patients after stroke who met the inclusion criteria participated in this study.

The inclusion criteria for selection are as follows: (1) hemiplegic patients with upper limb dysfunction between 50-70 years old, (2) left cerebral hemisphere injuries and whose dominant hand is the right hand, and (3) stroke confirmed using computed tomography or magnetic resonance imaging.

The exclusion criteria for selection are as follows: (1) metallic implants in the head, (2) cardiac pacemaker, (3) history of seizure, and (4) severe cognitive dysfunction.

This study was performed according to the Declaration of Helsinki. All patients gave informed consent prior to taking part in any procedure in this study.

2.2. Study design

Subjects were randomly divided into LF-rTMS group (n = 20) and HF-rTMS group (n = 20) using a random number table. All subjects were blinded to their group until the study was completed. Two clinicians were involved in the study, randomization of group and application of LF- and HF-rTMS were performed by clinician 1. And all assessments of upper limb function were performed by clinicians 2 blinded to group assignment.

The subjects received rTMS before rehabilitation therapy. All subjects were treated 20 minutes a day, 5 days a week, for 2 consecutive weeks.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation (rTMS)

Subjects received LF- or HF-rTMS using a magnetic stimulator ALTMS (Remed, Korea) connected to an 88mm diameter 8-shaped coil while sitting comfortably. All subjects received conventional rehabilitation treatment, including occupational therapy, for 30 minutes after rTMS intervention. The LF-rTMS group was stimulated with 1 Hz at 90 % of the resting motor threshold (RMT) at the hot spot in the primary cerebral cortex of the contralateral cerebral hemisphere, that is, the M1 region. The HF-rTMS group was stimulated with 10 Hz at 90 % of the RMT at the hot spot in the M1 region of the ipsilateral cerebral hemisphere. The rTMS was applied based on the vertex position of the International 10-20 EEG system to stimulate the M1. The hot spot for stimulation of all subjects was defined as the place that caused the maximum MEP amplitude in the contralateral abductor pollicis brevis [17] (see Fig. 1). In the HF-rTMS group, 10 Hz stimulation was repeated 90 times for 1.5 seconds with a 10 second rest interval, and a total of 1350

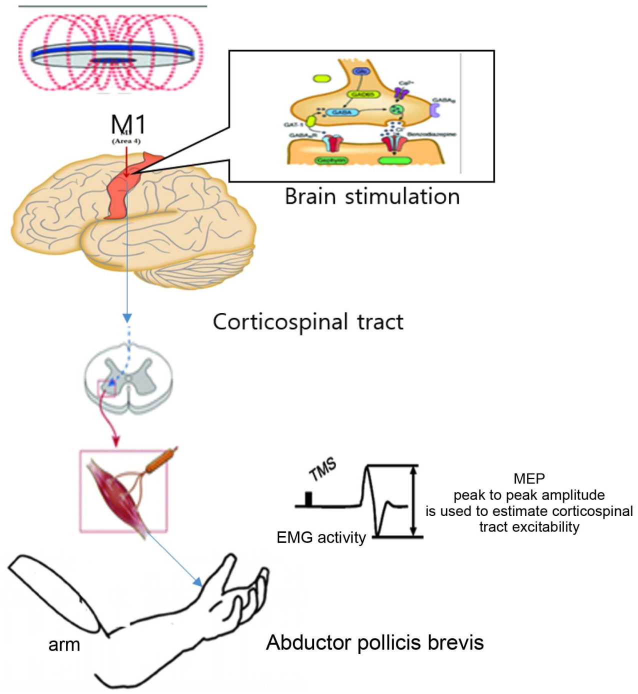

Fig. 1. (Color online) The mechanism of rTMS.

pulses were applied. In the LF-rTMS group, 1 Hz stimulation was repeated 100 times for 10 seconds with a 2-second rest interval, and a total of 1000 pulses were applied.

2.4. Outcome measure

Wolf Motor Function Test (WMFT), Fugl-Meyer Assessment (FMA), Box and Block test (BBT), and Jebsen-Taylor Hand Function Test (JTHFT) were used to evaluate the changes in the function of the subjects' upper limbs. All evaluations were followed before and after intervention and 2 weeks after completion of the interventions.

2.4.1. Wolf Motor Function Test (WMFT)

WMFT includes a wide range of functional tasks from simple to complex tasks, and is preferred as a functional test of the upper limb because it evaluates both the execution time and the quality of movement. It is divided into 6 grades (0-5), with the highest score of 18. The higher the score indicates the better the upper limb function. Inter-rater reliability of WMFT has been reported .99 [18].

2.4.2. Fugl-Meyer Assessment (FMA)

FMA consisting of 9 categories and 33 items was used to evaluate the motor function of the subjects' upper limbs. FMA is the most common outcome measure used in about 40 % of studies related to hand function recovery. FMA assesses range of motion, quality of movement, sensation, and pain while a subject performs movement patterns. It is on a 3-point scale (0-2), and the maximum score is 66, and the higher the score indicates the better the upper limb function. The reliability of the Fugl-Meyer Assessment was found to be excellent (r = .98) [19].

2.4.3. Box and Block test (BBT)

BBT is a widely used outcome measure to quantify gross manual dexterity. For the BBT, a 290 mm wide wooden box and 150 wooden cubes are used. The box is divided into two compartments by a 10 mm high partition. The subject is asked to sit in front of the box and move the wooden cube in one compartment to the other, and the total number of cubes moved in one minute is recorded. Excellent test-retest reliability when tested on more affected (r = .98) and less affected hand (r = .93) was found [20].

2.4.4. Jebsen-Taylor Hand Function Test (JTHFT)

JTHFT consists of 7 items including writing sentences, flipping cards, picking up small objects, simulated feeding using a teaspoon, stacking checkers, picking up large and light cans, and picking up large and heavy cans. In this study, all items except for sentence writing were tested, and the time taken to complete each item was summed and recorded. Excellent test-retest reliability was reported in all subtests for dominant hand except writing (r = .91-.99) [21].

In each group, repeated analysis of variance was performed to compare the measured values of the follow-up test before, after and 2 weeks after the intervention. If there is a significant difference, the Bonferroni method was used for the post-hoc. In addition, an independent-t test was conducted to compare the significance between the two groups at each measurement point in time. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and for all analyses, p values < 0.05 were considered significant.

3. Results and Discussions

The general characteristics of the subjects are summarized in Table 1, and there were no statistically significant differences in the characteristics of the subjects between the two groups. The WMFT, FMA, BBT, and JTHFT were used to evaluate the upper limb function, and the values for the measurements in the LF-rTMS group and the HF-rTMS group are summarized in Table 2. As a result of this study, there were significant differ-

Table 1. Baseline subject data.

	LF-rTMS (n = 20)	HF-rTMS (n = 20)	*p*
Age (years)	67.64 ± 7.16[a]	69.09 ± 6.04	0.612
Sex (male/female)	13/7	12/8	0.867
Type of stroke (Ischemia/Hemorrhage)	16/4	17/3	0.631
Interval from stroke onset (month)	3.82 ± 0.98	4.27 ± 0.90	0.272

[a]Mean ± SD, LF-rTMS: Low-frequency repetitive transcranial magnetic stimulation; HF-rTMS: high-frequency repetitive transcranial, magnetic stimulation.

Table 2. Upper limb function in the two groups post and follow-up test.

	LF-rTMS (n = 20)	HF-rTMS (n = 20)	t	*p*
WMFT scale (score)				
Pre-test	6.18 ± 2.04[a]	6.45 ± 1.63	-0.346	0.733
Post-test	8.27 ± 1.01[b]	7.91 ± 1.81	0.581	0.568
follow-up test	7.09 ± 1.51	6.82 ± 1.99	0.362	0.721
F	4.790	2.361		
p	0.020	0.120		
FMA scale (score)				
Pre-test	28.64 ± 8.08	27.64 ± 5.63	0.337	0.740
Post-test	42.55 ± 7.23[b]	43.55 ± 8.43[b]	-0.299	0.768
follow-up test	38.45 ± 9.60	39.09 ± 11.12[c]	-0.144	0.887
F	6.086	16.500		
p	0.009	0.000		
BBT (unit)				
Pre-test	23.18 ± 3.31	24.55 ± 3.83	-0.893	0.382
Post-test	27.55 ± 6.06	27.09 ± 3.18	0.220	0.828
follow-up test	25.73 ± 4.45	25.82 ± 5.19	-0.044	0.965
F	9.000	1.325		
p	0.177	0.288		
JTHFT (s)				
Pre-test	44.55 ± 3.67	46.09 ± 3.42	-1.022	0.319
Post-test	40.45 ± 6.46	43.55 ± 3.50	-1.396	0.178
follow-up test	42.73 ± 6.00	45.09 ± 4.09	-1.080	0.293
F	2.561	2.970		
p	0.102	0.074		

[a]Mean ± SD; [b]Significant difference in gains between pre and post test, $p < 0.05$; [c]Significant difference in gains between pre and follow-up test, $p < 0.05$.
LF-rTMS: Low-frequency repetitive transcranial magnetic stimulation; HF-rTMS: high-frequency repetitive transcranial magnetic stimulation; FMA: Fugl-Meyer assessment; WMFT: Wolf Motor Function Test; BBT: Box and Block Test; JTHFT: Jebsen–Taylor Hand Function Test

ences between before and after intervention in WMFT and FMA in the LF-rTMS group ($p < 0.05$). In the HF-rTMS group, there was a significant difference between before and after the intervention in FMA, and there was also a significant difference between before intervention and follow up test ($p < 0.01$). There was no significant difference BBT and JTHFT between before and after intervention in both the LF-rTMS group and the HF-rTMS group, and there were no significant differences between groups in all dependent variables ($p > 0.05$) (see Figs. 2, 3, 4, 5).

rTMS became a major basis for establishing neuroplasticity because it can easily record changes in motor potential through electromyography. Therefore, it is widely used in neurorehabilitation to explain the plasticity of brain injury patients [22].

After a stroke, there are two periods during which the reorganization of the brain can be amplified. The first is

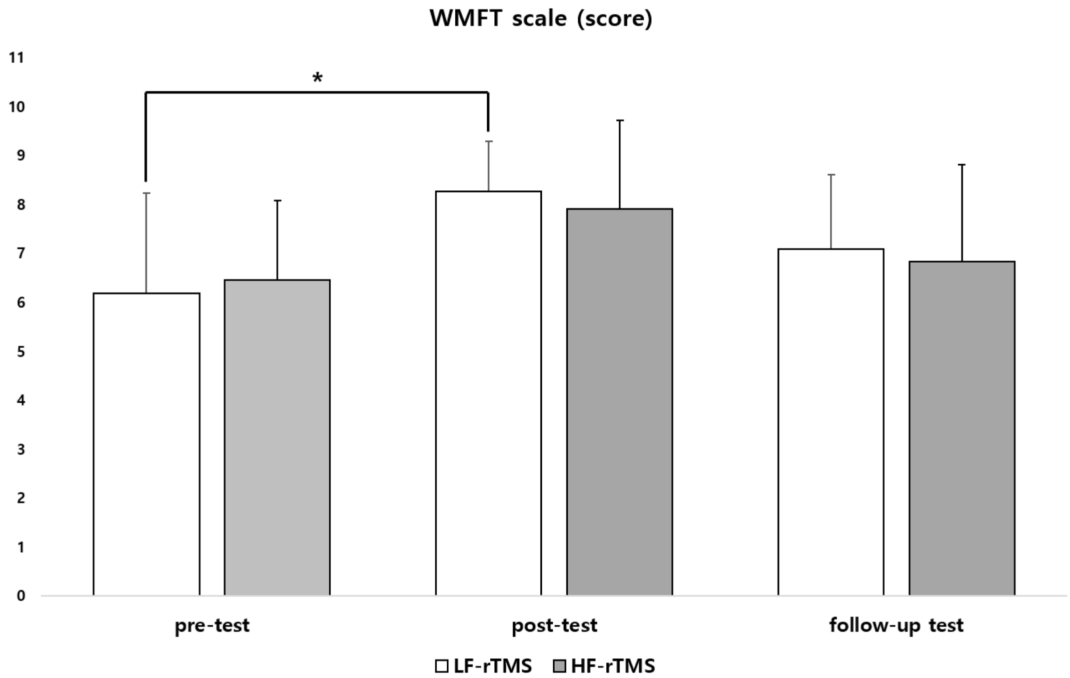

Fig. 2. Comparison of change in WMFT of the LF-rTMS group and HF-rTMS group.

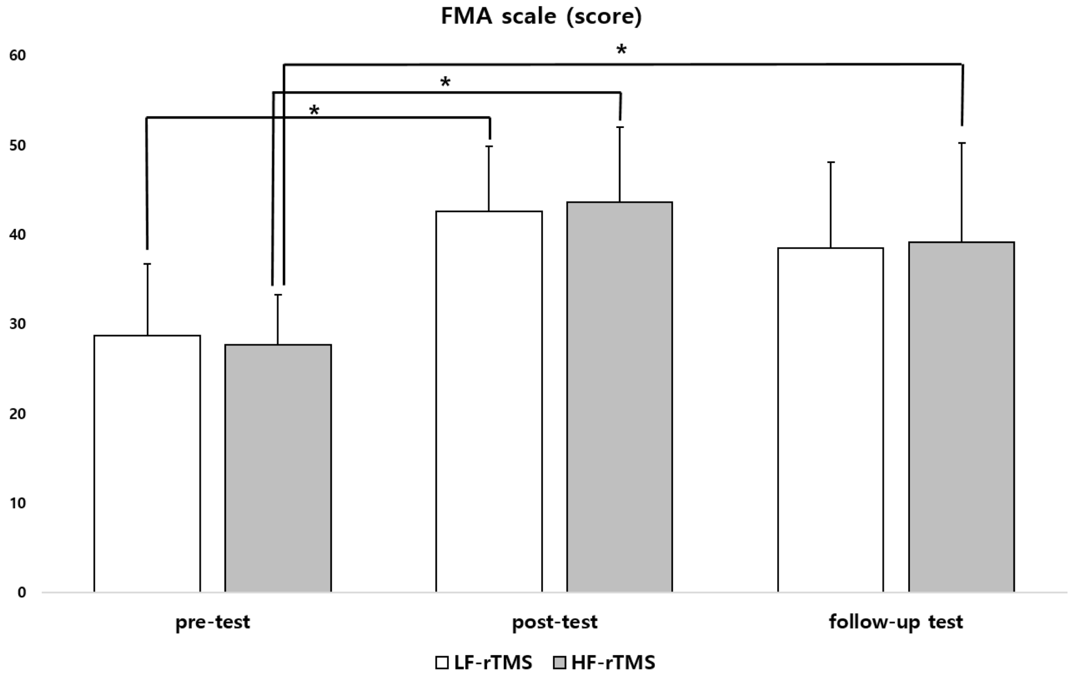

Fig. 3. Comparison of change in FMA of the LF-rTMS group and HF-rTMS group.

the acute phase in which the maximal plasticity change occurs, usually until 45 days after the stroke, and the second is an additional 45 days after the acute phase, called the recovery phase [23]. In the clinical setting, these two periods, i.e. up to 3 months after onset, are commonly referred to as the acute phase.

Although rTMS studies in stroke patients with chronic or subacute phage have confirmed the potential for promoting neuroplasticity, studies in stroke patients with acute phage have been rarely performed. Since the interhemispheric imbalance due to stroke increases most significantly in the acute phase, it is necessary to determine the efficacy of LF-rTMS and HF-rTMS in stroke patients with acute phase. For this reason, this study

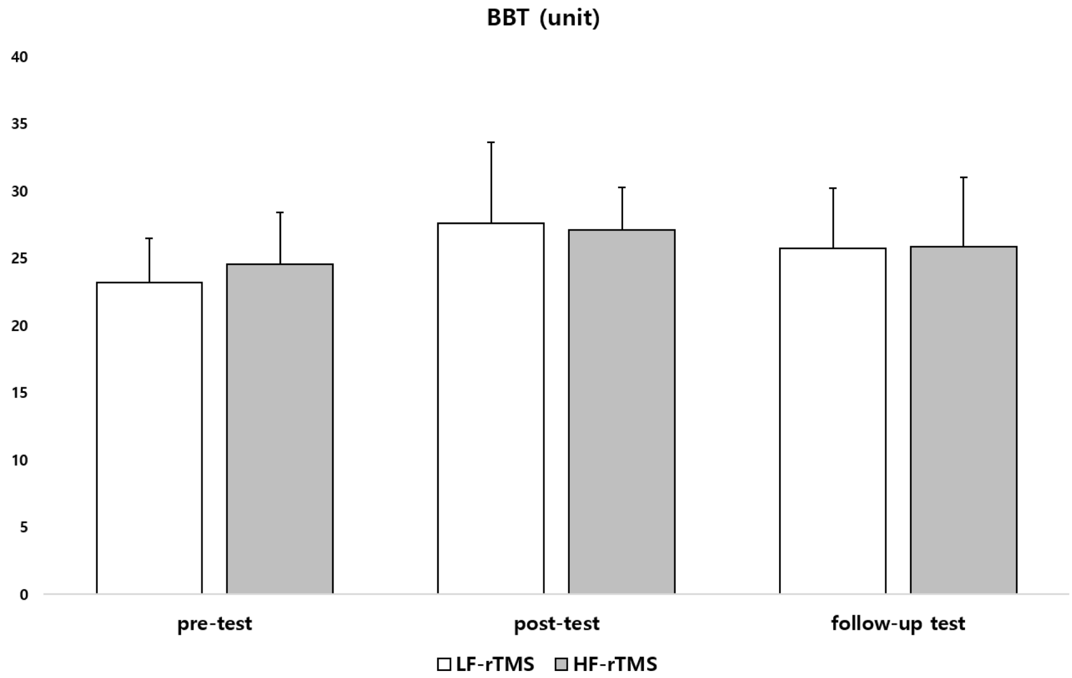

Fig. 4. Comparison of change in BBT of the LF-rTMS group and HF-rTMS group.

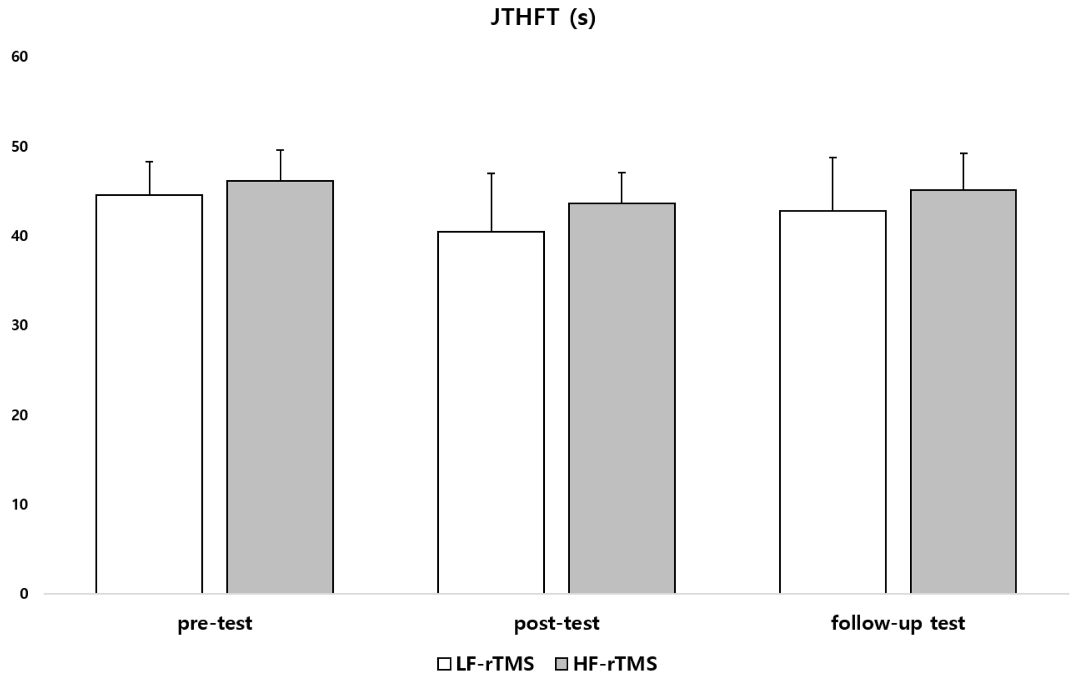

Fig. 5. Comparison of change in JTHFT of the LF-rTMS group and HF-rTMS group.

compared the effects of LF-rTMS and HF-rTMS on upper limb function in stroke patients with acute phase.

A previous study by Juan *et al.* that compared the effects of HF-rTMS and LF-rTMS showed a more significant improvement in HF-rTMS. In particular, activation of motor-related functional magnetic resonance imaging and improvement of FMA score were found, which is consistent with the result of significant improvement in FMA score of subjects applying HF-rTMS in this study. In addition, in this study, there was a significant difference in the FMA score between pre-test and follow-up test, and Juan *et al.* also reported that there was a significant difference at the follow-up test after 3 months [24]. These results suggest that HF-rTMS played an important role in exercise recovery by increasing the activity level of normal ipsilateral M1. Therefore, the application of HF-rTMS to ipsilateral M1 is considered to be a reasonable physiological target for rehabilitation in the acute phase of stroke [25].

There are several previous studies that reported improvement of function after stroke through the application of LF-rTMS. Conforto and colleagues reported that there was a significant improvement compared to the sham group in the evaluation of upper limb functions such as JTHFT and pinch force after applying LF-rTMS to contralesional M1 of acute stroke patients [26]. Khedr *et al.* reported that when LF-rTMS was applied to the contralesional hemisphere, the excitability of the affected hemisphere decreased and the excitability of the unaffected hemisphere increased [27]. According to previous meta-analysis, LF-rTMS induces a significant inhibitory effect of MEP in the contralesional hemisphere and a significant enhancement effect in the ipsilesional hemisphere [28]. In particular, in the case of severe motor impairment, abnormally high interhemispheric inhibition occurs in the ipsilateral hemisphere. Therefore, it has been reported that a decrease in the activation of the contralesional hemisphere can lead to an improvement in motor function. These findings support the evidence that excitability control in the motor region of the hemisphere can contribute to the improvement of motor function [29, 30].

There are advantages of rTMS useful in patients with neurological impairment such as stroke patients. rTMS can modulate the excitability of the corticospinal tract in response to stimulation. In addition, it is a great advantage that neuroplasticity changes not only in local areas under the magnetic coil to which stimulation is applied, but also in remote cortex and subcortical areas that are functionally connected [31]. In addition, there is an advantage that the effect persists even after stimulation is over. According to the rTMS study applied with electroencephalography, it was reported that the duration of the effect after rTMS stimulation lasted for an average of 31 minutes (15-70 minutes) [32]. This duration becomes longer as stimulation is repeated, and the results of FMA in this study show that the effect of rTMS persists even after the intervention is stopped.

Despite the various advantages of rTMS, in this study, it was not possible to clearly determine which of LF-rTMS and HF-rTMS has a beneficial effect on upper limb function in patients with acute stroke.

There are some limitations in this study. The duration of intervention in this study was not long. A significant difference was found between pre-intervention and follow-up in many previous studies that performed follow-up tests. In this study, the only significant difference in FMA is believed to be due to the difference in duration of intervention. Therefore, in future studies, it is necessary to clearly investigate whether there is a long-term effect according to the difference in intervention period. Because we focused on the comparison of the efficacy of LF-rTMS and HF-rTMS, we did not include a placebo control group in this study. This will require further evaluation in the future.

4. Conclusion

Because LF-rTMS decreases cortical excitability and HF-rTMS has an effect of increasing cortical excitability, a clinical intervention that is widely used for functional improvement of related sites through the control of cortical excitability in patients with brain lesions. In the results of this study to determine awhich frequencies are more effective for improving upper limb function in patients with acute stroke, both LF-rTMS and HF-rTMS showed significant improvement in execution time, the quality of movement, and range of motion related to upper limb function in acute stroke patients. However, the difference in efficacy between LF-rTMS and HF-rTMS was not clearly revealed. In order to derive more clear results, additional studies are required by supplementing the limitations of this study.

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