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Effects of 10 Hz High Frequency Repetitive Transcranial Magnetic Stimulation Combined with Somatosensory Training for Recovery of Upper Limb Motor and Hand Function in Chronic Stroke Patients

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The paper was to investigate the effects of a combination of 10-Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) and somatosensory training (SST) on upper limb motor and hand function in chronic stroke patients. Upper limb motor and hand function were evaluated using Fugl-Meyer assessment (FMA), manual functions test (MFT), and pinch, grasping strength. The results revealed that there was a significant difference in FMA and MFT before and after the SST after 10-Hz high-frequency rTMS ($p<0.05$). The experimental group showed a significant improvement in FMA and pinch strength compared to the control group ($p<0.05$). There was no significant improvement between MFT and grasping strength between the groups ($p>0.05$). Thus, 10-Hz high-frequency rTMS, combined with SST, can be considered to be an effective treatment for the recovery of upper limb motor and hand function in chronic stroke patients.

Keywords : high frequency repetitive transcranial magnetic stimulation, stroke, somatosensory, upper limb motor function. hand

1. Introduction

Various approaches such as somatosensory training, imagination training, mirror therapy, forced suppression induction therapy, task-oriented training, virtual reality therapy, and robot therapy are being studied to restore the upper limb function of stroke patients in neurorehabilitation [1]. In addition, non-invasive electrical stimulation methods such as repetitive transcranial magnetic stimulation (rTMS) that promote neuromodulation by safely stimulating specific areas of the brain using magnetism or electricity, have been recently developed [2]. Non-invasive brain stimulation began in 1980 when Merton and Morton used transdermal electrical stimulation to measure the locomotor potential of the scalp corresponding to the motor cortex [3]. However, transcutaneous electrical nerve stimulation (TENS) was not widely used in clinical practice because of the pain and discomfort associated with electrical stimulation. Hence, transcranial magnetic stimulation (TMS) was developed and applied to reduce discomfort from stimulation by generating a magnetic field pulse on the scalp to generate an induced current in the cells for depolarization [4]. The induced current reaches a maximum level at the surface and drops exponentially as the distance increases [5]. TMS changes to an electric field in the tissue when the magnetic field formed through the coil reaches an appropriate strength over time. Like general electrical stimulation, TMS causes nerve depolarization [6]. In particular, the 8-shaped TMS coil can maximize the efficiency of the local stimulation of the cerebral cortex by creating a space of ~1 cm^2 at the site of stimulation [7]. Local stimulation of the cerebral cortex through TMS is used as a therapy in neurorehabilitation programs that improve sensory, cognitive, and motor functions of various neuropsychiatric diseases and stroke. With recent advances in science and technology, the limitations of these clinical applications have been gradually overcome, and the recovery mechanism has been elucidated in various studies. Locally, low blood flow and low metabolism in the left prefrontal cortex

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have been confirmed via rTMS in patients with depressive disorder, in whom it was used to activate the left anterior cortex [8]. In a high frequency rTMS study conducted in 20 normal adults, when a total of 1,000 10 Hz rTMS was performed at an intensity of 80 % of the motor threshold, the excitability of the corticospinal pathway and motor cortex activity increased. In addition, it was confirmed that the excitability of the inhibitory pathway in the cortex was reduced, and the changed excitability was found to appear continuously for up to 10 minutes after rTMS was applied [9]. In addition, it was reported that high frequency rTMS plays an important role in exerting effect of the treatment period, and in general, 10 to 15 times were the most effective [10]. Thus, various studies have shown that the cerebral cortex can be activated or inhibited according to the characteristics of the rTMS frequency. Specifically, rTMS ≥ 5 Hz has the effect of promoting excitability of the cerebral cortex, whereas rTMS with a low frequency of 1 Hz suppresses excitability of the cerebral cortex and selectively activates GABAergic neurons. [11, 12]. The effects of different frequencies of rTMS have been explained using the hemodynamic method: high-frequency rTMS increases regional cerebral blood flow, whereas low-frequency rTMS decreases this blood flow [13]. However, although several studies on rTMS have been reported, few studies have compared the effects of rTMS with neurorehabilitation in stroke patients. Therefore, this study aimed to examine the effects of rTMS combined with somatosensory training on the recovery of upper limb function in chronic stroke patients. Through this study, we sought to investigate the effectiveness of various approaches of neurorehabilitation.

2. Materials and Methods

2.1. Subjects

This study was conducted on patients with chronic stroke who had an onset period of 6 months or longer and who were hospitalized in B Hospital from April to August 2020. As a selection criterion, a stroke was diagnosed by a neurologist, based on the impairment of the motor function of the hands and upper limbs and a score of ≥ 23 points according to the korean version of montreal cognitive assessment (K-MoCA). This study was conducted on 16 patients who did not have any contraindications to the application of rTMS, and the study was conducted after confirming their consent to the study. In this study, 16 subjects were randomly classified into two groups of 8 subjects each: the experimental group received 10-Hz high-frequency rTMS with somatosensory training, whereas the control group received 10-Hz false rTMS after which somatosensory training was conducted. Among the subjects who agreed with the purpose of the study, the subjects who first fulfilled the selection criteria were selected, after which subjects were randomly selected and assigned to the two groups before starting the study. For the experimental group that received somatosensory training along with 10-Hz high-frequency rTMS, rTMS was performed 5 times a week for 4 weeks. The stimulation frequency was 10 Hz, stimulation time 10 s, and rest time was 50 s. The number of times that stimulation was performed was set to 20, and 2,000 pulses were applied for a total of 20 min. In the control group, sham or false 10-Hz high-frequency rTMS was performed for 20 min, and then upper limb somatosensory training was performed for 30 min. The general characteristics of the subjects who participated in this study are shown in Table 1.

2.2. Assessment methods

2.2.1. Fugl-Meyer Assessment (FMA)

This study employed specific evaluation tools to confirm the recovery of upper limb motor function of the subjects. FMA evaluates motor function, balance, sensation, and joint function of stroke patients. It helps to evaluate the degree and level of motor recovery, which can help in establishing a treatment plan [14]. Evaluation items are assigned 0–2 points depending on the degree of performance: 0 points are classified as "not being performed", 1 point is "partially performed", and 2 points are "completely performed". The total score for items of motor functions is 100 points, the total score for items of upper limb motor functions is 66 points, and the total score for items of lower limb motor functions is 34 points. A motor

Table 1. General characteristics of subjects.

Variables		rTMS with SSTG (n=8)	Sham rTMS with SSTG (n=8)
Gender	Male	3	3
	Female	5	5
Age		54.25±5.47	55.23±6.02
Lesion type	Hemorrhage	4	3
	Infarction	4	5
Lesion side	Right	5	3
	Left	3	5
Duration (months)		18.45±3.78	19.26±4.12

Data are shown as M±SD where M: mean; SD: standard deviation; rTMS: repetitive transcranial magnetic stimulation, SSTG: somatosensory training group.

function score from 0 to 35 indicates very serious damage; if this score is 36 to 55, it indicates severe damage; and if it is 56 to 79, it can be classified as mild damage.

2.2.2. Manual function test (MFT)

MFT was developed to evaluate upper limb motor dysfunction in stroke patients and statistically analyze possible recovery processes after intervention [15]. MFT consists of 8 items that test upper limb motor function (4 items), grip (2 items), and finger manipulation (2 items). All subjects were evaluated before and after intervention.

2.2.3. Grasping and pinch strength measurement

Grasping strength was evaluated using a hydraulic hand dynamometer (JAMAR Hydraulic Hand Dynamometer, Sammons Preston, IL, USA). The measurement unit is in kg, and the distance of the grasping surface can be adjusted in 5 steps to measure even those subjects who cannot fully grasp due to finger construction. The measurement method required the subject to be in a seated position with internal rotation of the shoulder joint, 90° bending of the elbow joint from the neutral position of the lower arm, 0–30° extension of the wrist, and 0–15° radial deviation. The affected hand to be evaluated was measured three times, and the average value was used. In the evaluation process, a 30-s break was applied, and before the test, the subject was informed about the need to maintain an upright posture during the test to prevent compensatory movements from occurring. Pinch strength is measured using a Preston JAMAR hydraulic pinch gauge, and the unit of measurement is kg. The measurement posture comprised of sitting on a chair and of internal rotation of the shoulder joint and elbow joint flexion of 90°; the lower arm is maintained in a neutral position, the wrist is extended by 0–30°, and the radial deviation is maintained at 0–15°. The lateral pinch is a pinch pattern in which the side of the index finger and the thumb contact each other, whereas in the case of a tripod pinch, the maximum grip is measured by placing the index and middle fingers in contact with the thumb. In this study, the lateral pinch was measured three times, and the average value was used.

2.3. Procedure

2.3.1. 10-Hz high-frequency rTMS

In this study, after maintaining the patient's arm on the armrest to maintain a comfortable posture, a 70-mm, 8-shaped coil stimulator (ALTMS®, Remed, Korea, 2018) was used to apply 10 Hz of high-frequency rTMS (Fig. 1). Before applying the 10-Hz high-frequency rTMS, a hood with a grid of 1-cm intervals was placed on the subject's head to perform the motor evoked potentials (MEPs) test according to the 10/20 International electroencephalogram (EEG) standard recording guidelines. The central lobe zone was set as the intersection of the median sagittal line and the bilateral trunk line, connecting the nasion to the inion. The intensity of the stimulation was 80 % of the resting motor threshold; the motor threshold was the minimum response intensity indicating the amplitude between the peaks of ≥ 50 μV for ≥ 5 out of 10 stimulations in the first dorsal interosseous muscle by performing an MEPs test [16]. The frequency of stimulation of high-frequency rTMS was set to 10 Hz, stimulation time to 10 s, rest time to 50 s, and stimulation frequency to 20; 2,000 pulses were applied for a total of 20 min, 5 times a week, for a total of 4 weeks [18].

Fig. 1. (Color online) ALTMS®, Remed, Korea. 10 Hz high frequency rTMS was applied using the figure-eight coil of this equipment in a sitting position for patients.

2.3.2. Somatosensory training (SST)

SST was performed by revising and supplementing the contents studied by Raine *et al.* [19]. The shoulder and upper arm area assisted the movement of the shoulder complex in the sitting position. The therapist gradually increased the mobile stability so that the scapular and upper trunk could move separately. While limiting the trunk, the activities of the scapular and humerus were used to increase proprioception of various muscles such as the rotator cuff, triceps, biceps, and deltoid muscle. In addition, SST connects with the activated shoulder complex to perform functional reaching using the hand grasp function. Securing the length of the extrinsic muscle of the hand promoted the contraction of the intrinsic muscle, and proprioception was stimulated to gradually increase the movement of the fingers and the hand.

2.4. Data Analysis

Statistical analysis of the data collected in this study was performed with SPSS 21.0 for Windows. Descriptive statistics and frequency analysis were used for analysis of the general characteristics of participants. Mann-Whitney *U*-test was used to determine the differences in upper limb motor function and hand function between the two groups before and after intervention. The differences in upper limb motor function and hand function before and after intervention within the group were measured using the Wilcoxon signed-rank test. The significance level of all statistical analyses was set to $\alpha = 0.05$.

3. Results and Discussion

3.1. General characteristics of subjects

As shown in Table 1, the experimental group consisted of 3 males and 5 females with an average age of 54.25 years. The causes of onset were bleeding in 4 patients and infarction in 4 patients. The paralytic side presented as right hemiplegia in 5 patients and left hemiplegia in 3 patients; the onset period was 21.45 months. The control group consisted of 3 males and 5 females with an average age of 55.23 years. The causes of onset were hemorrhage in 3 cases and infarction in 5 cases. The affected side was caused by right hemiplegia in 3 cases and left hemiplegia in 5 cases; the onset period was 22.26 months.

3.2. Changes in upper limb motor function and hand function before and after intervention in both groups

In the experimental group, FMA increased significantly from 36.37 points to 39.12, while the MFT increased from 17 points to 18.5 ($p < 0.05$) (Table 2).

3.3. Comparison of upper limb motor function and hand function between the two groups

There was a significant difference in FMA between the two groups: 2.75 points in the experimental group and 0.75 points in the control group ($p < 0.05$) (Table 3). Similarly, there was a significant difference in pinch strength between the two groups: 0.37 kg in the experimental group and -0.18 kg in the control group ($p < 0.05$) (Table 3).

3.4. Discussion

Almost 85 % of stroke patients develop upper limb dysfunction at the beginning of the onset, after which 55-75 % of patients continue to have upper limb dysfunction, making it difficult to perform activities of daily living (ADLs) [20]. In addition, impairment of motor function after a stroke leads to non-use of the affected upper limb, causing a deterioration of the quality of ADLs such as self-care. In neurorehabilitation of the upper limb of a stroke patient, somatosensory training helps to detect and

Table 3. Comparison of FMA, MFT, grasping and pinch strength between groups.

Variables	rTMS with SSTG (n=8)	Sham rTMS with SSTG (n=8)	*z*	*p*
	M±SD	M±SD		
FMA (points)	2.75±1.66	0.75±1.03	-2.292	0.02*
MFT (points)	1.75±1.03	0.75±1.48	-1.779	0.08
Grasping strength (kg)	1.25±0.70	1.00±0.75	-0.687	0.57
Pinch strength (kg)	0.37±0.23	-0.18±0.45	-2.598	0.01**

Data are shown as M ± SD where M: mean; SD: standard deviation, $^{**}p<0.01$ $^{*}p<0.05$

rTMS: repetitive transcranial magnetic stimulation; SSTG: somatosensory training group; FMA: Fugl-Meyer assessment; MFT: manual function test.

Table 2. Comparison of FMA, MFT, grasping and pinch strength before and after intervention in two groups

Variables		Pre-test	Post-test	*z*	*p*
		M±SD	M±SD		
rTMS with SSTG (n=8)	FMA (points)	36.37±5.28	39.12±4.73	-2.375	0.01**
	MFT (points)	17.00±2.92	18.50±2.32	-2.136	0.03*
	Grasping strength (kg)	8.62±1.68	9.87±2.1	-2.428	0.15
	Pinch strength (kg)	1.00±0.75	1.25±0.92	-1.633	0.10
Sham rTMS with SSTG (n=8)	FMA (points)	36.25±4.71	37.00±4.24	-1.730	0.08
	MFT (points)	16.87±3.22	17.62±3.58	-1.414	0.15
	Grasping strength (kg)	10.00±2.77	11.00±2.92	-2.271	0.23
	Pinch strength (kg)	3.00±1.37	3.00±1.18	-1.134	0.25

Data are shown as M±SD where M: mean; SD: standard deviation, $^{**}p<0.01$, $^{*}p<0.05$

rTMS: repetitive transcranial magnetic stimulation; SSTG: somatosensory training group; FMA: Fugl-Meyer assessment; MFT: manual function test.

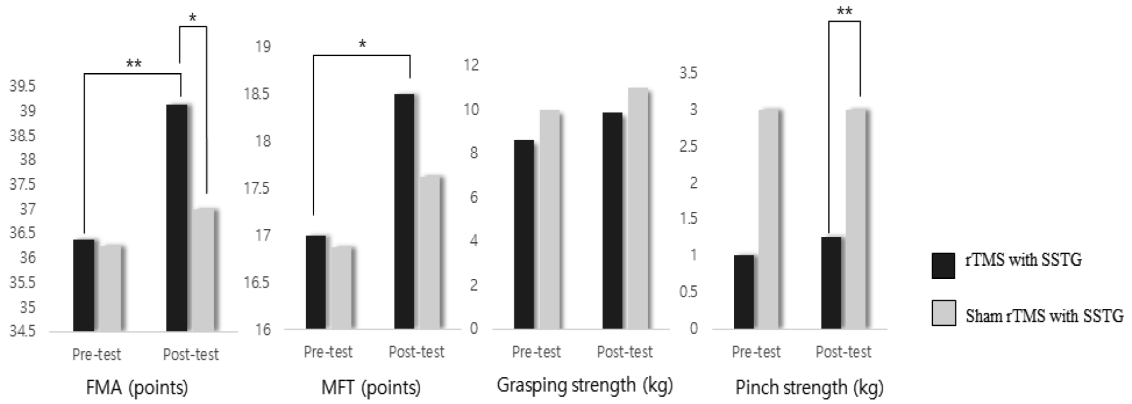

Fig. 2. Comparison of FMA, MFT, grasping and pinch strength before and after intervention in groups and between groups.

perceive the external environment through the cutaneous sense in the skin and the proprioception in the muscles and joints on the upper limb and hand. Thus, afferent stimulation information and training can help to control body position and movement [21]. Winward *et al.* (2007) classified 18 stroke patients with somatosensory impairment into patients with an onset date of less than 1 month and patients with less than 6 months of onset and observed the recovery characteristics of somatosensory sensation. Although not shown, the recovery of proprioception and changes in M1 were observed [22]. To examine the effects of recovery of upper limb function in stroke patients, studies are being conducted to determine the basis of neurological changes through direct cerebral motor cortex stimulation. Recently, rTMS non-invasive and direct stimulation of the cerebral cortex—has been used to study neurological changes in stroke patients. Pascual-Leone *et al.* (1993) reported for the first time that rTMS can be used to control cortical activity in normal subjects [23]. In other studies, motor function and performance could be improved through the application of rTMS to stroke patients [24]. In particular, it was reported that high-frequency rTMS can induce changes in neurons after the development of neural connections in the central nervous system. In addition, high-frequency rTMS was considered as a method capable of promoting motor learning and activity of the motor cortex by increasing the activity in the cerebellum as well as in the cerebral cortex [25]. Higgins *et al.* (2013) reported that the application of low-frequency rTMS combined with task-oriented training resulted in significant differences in hand and MEP in chronic stroke patients with impaired hand function [26]. In a recent randomized controlled study (RCTs), it was confirmed that upper limb training e combined with low-frequency or high-frequency rTMS improved motor function of the injured upper limb. In Ryu *et al.* (2010), after a stroke, hemiplegic patients were subjected to high frequency r TMS followed by cup-carrying, and as a result, significant improved upper limb function compared to the control group who performed the same training after sham rTMS [27]. Task-oriented training in connection with direct brain stimulation through rTMS affects positively neuroplasticity and helps upper limb function. This enhance cortical activity of stroke patients through a therapeutic approach in the rehabilitation program combined with various rTMS approaches and is believed to improve hand function. In this study, a significant difference was observed in FMA and pinch strength between the two groups. This was consistent with the results of previous studies in which 10-Hz high-frequency rTMS in stroke patients increased the subjects' MEPs and recovered motor function of the hand [28]. In general, neurorehabilitation using rTMS mainly uses a method of increasing the excitability of the affected cerebral hemisphere or inhibiting the excitability of the unaffected cerebral hemisphere, which is consequently used to reduce the inhibitory effect on the affected cerebral hemisphere. [29]. In this study, after increasing the excitability of the affected cerebral hemisphere through 10-Hz high-frequency rTMS, the difference in upper limb and hand function between the two groups was confirmed by somatosensory training. Stimulation of M1 through rTMS and somatosensory feedback training through peripheral sensory stimulation were more effective in improving the upper limb and hand functions of the affected side. This study has some limitations: first, it is difficult to generalize the results due to the small number of subjects, and second, it is possible to evaluate only the motor function of the upper limb and hand and not functional activities such as ADLs of patients. In future studies, it will be necessary to confirm the effectiveness of this combination of rTMS and systematic somatosensory training with a larger number of study subjects to ensure the generalizability of the results.

4. Conclusion

The purpose of this study was to investigate the effects of high-frequency rTMS combined with somatosensory training on upper limb motor and hand function in 16 chronic stroke patients. The results of this study show significant differences in the FMA and MFT of the experimental group ($n = 8$) before and after the intervention ($p < 0.05$), but not in the control group ($n = 8$) ($p > 0.05$). Although there was a significant difference in FMA and pinch strength ($p < 0.05$) between the two groups, there was no significant difference in MFT and grasping strength ($p > 0.05$). These results confirmed that 10-Hz high-frequency rTMS combined with SST was a positive intervention for upper limb motor and hand function in chronic stroke patients. In conclusion, 10-Hz high-frequency rTMS combined with SST can be provided as a therapy for improving upper limb motor and hand function in stroke patients.

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