



Effects of Hand Training During the Aftereffect Period of Low-Frequency rTMS in Subacute Stroke Patients

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Objective To investigate the effects of hand training using low-frequency repetitive transcranial magnetic stimulation (rTMS) within the aftereffect period on hand function in patients with subacute stroke.

Methods The subacute stroke patients with hand weaknesses were divided randomly into two groups. Patients in the intervention group underwent hand training within the aftereffect period, that is, immediately after receiving low-frequency rTMS treatment. Patients in the control group underwent hand training 2 hours after the low-frequency rTMS treatment. A manual function test (MFT) for 'grasp and pinch' and 'hand activities'; a manual muscle test (MMT) for 'grasp', 'release', and 'abductor pollicis brevis (APB)'; and the Modified Ashworth Scale for finger flexion were performed and measured before and immediately after combined therapy as well as 2 weeks after combined therapy.

Results Thirty-two patients with hand weakness were enrolled in this study. The intervention group patients showed more improvements in grasp MMT and MMT APB tested immediately after combined therapy. However, the changes in all measurements were not significantly different between the two groups 2 weeks after the combined therapy. In both groups, hand functions improved significantly immediately after combined therapy and 2 weeks after combined therapy.

Conclusion Hand training immediately after low-frequency rTMS showed more rapid improvement in the motor power of hands than hand training conducted 2 hours after low-frequency rTMS. Our results suggest that conducting hand training immediately after low-frequency rTMS could be an improved useful therapeutic option in subacute stroke patients.

Keywords Transcranial magnetic stimulation, Stroke, Functional recovery, Aftereffect

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INTRODUCTION

Post-stroke recovery of functions is associated with diverse neuroplastic processes that enable central nervous system reorganization [1-4]. Several approaches have been proposed to improve neuroplasticity and restore functions [3-5]. The recovery mechanism has been explained in terms of peri-infarction reorganization, activity in the ipsilesional or contralesional hemisphere, interhemispheric interactions, and diaschisis. Interhemispheric interaction, one of the well-known factors, refers to the inhibitory influences of transcallosal fibers on the homologous area of the opposite side.

Interhemispheric interaction can be induced by a few methods. Repetitive transcranial magnetic stimulation (rTMS) has been widely used for therapeutic purposes for various diseases since it was introduced in 1985 by Barker et al. [6] as a practical method. In rTMS, a strong magnetic field is applied to certain regions of the brain to induce changes in regional neural functions [6-8]. It is a noninvasive stimulation method that facilitates neurological recovery and neuroplasticity after a stroke.

Recent reports suggest that post-stroke low-frequency rTMS over the motor cortex of the unaffected hemisphere helps patients recover their affected hand motor functions [9-11]. In a recently published guideline, stimulating the unaffected motor cortex with low-frequency rTMS in the acute to chronic phase of stroke was methodologically sufficient to reach a Level B or 'probable efficacy' recommendation [12]. Though stimulating the affected motor cortex with high-frequency rTMS for patients in the acute or post-acute stage of stroke recovery was qualified enough to meet a Level C or 'possibly useful' recommendation [12]. A comparative study showed that contralesional low-frequency rTMS produced a better outcome in motor function recovery after ischemic stroke than ipsilesional high-frequency rTMS [13].

In a study of changes in motor-evoked potential after rTMS, applying low-frequency rTMS to the primary motor area inhibited corticospinal tract excitability, and this effect lasted for at least several minutes [14]. The duration of cortex excitability by rTMS depends on the intensity of and total number of stimulations. The resultant increase in motor cortex activity seems to decrease with time, though the exact relationship has not yet been determined. Some recent studies have reported that the

aftereffect-duration when low-frequency rTMS was applied in combination with electroencephalography lasted 15-70 minutes with a mean of 31 minutes [15].

In a study with stroke patients, routine rehabilitation with low-frequency rTMS showed more improved hand muscle force and function than routine rehabilitation with placebo magnetic stimulation [16]. Other studies have shown that rTMS was synergistic with motor training [17,18]. The therapeutic combination of intensive occupational therapy (OT) with low-frequency rTMS for 15 days was estimated to be a feasible, safe, and clinically useful neurorehabilitative therapy for post-stroke patients with upper limb weakness [19]. However, it has not been determined whether motor training applied within the aftereffect period after rTMS also contributes to motor improvement, and few studies have dealt with the temporal relationship between rTMS therapy and hand training. Thus, we hypothesized that hand training within this aftereffect period may have positive effects. The purpose of this study is to investigate the effects of hand training within the aftereffect period of low-frequency rTMS on hand function in patients with subacute stroke.

MATERIALS AND METHODS

Subjects

This study was conducted from March 2014 to December 2016. The inclusion criteria for the trial were: (1) primary diagnosis of unilateral cerebral hemorrhage or infarction with computerized tomography or magnetic resonance imaging scan; (2) subacute stroke patients, onset less than 3 months ago; and (3) patients who could grasp a hand but could not perform finger counting and opposition. The exclusion criteria for the trial were: (1) patients with previous history of seizure; (2) patients who could not cooperate owing to cognitive impairment; (3) patients whose previous medical history indicated stroke or any nervous system disease; and (4) patients with a medical history of any injury in an upper extremity or the upper chest area or surgery in such areas.

Study design

Enrolled patients who met the inclusion criteria were randomly selected and assigned to the two groups. Randomization was done according to a table of random numbers; odd numbers went to the intervention group

and even numbers went to the control group. The subjects in both study groups received OT from a skilled therapist who was blind to the nature of the study during the 4-week treatment period. Patients in the intervention group underwent hand training within the aftereffect period, that is, immediately after receiving low-frequency rTMS treatment. Patients in the control group underwent hand training 2 hours after low-frequency rTMS treatment. In both groups, hand training was done in the morning session, and the group of OT without hand training was performed in the afternoon session. Hand training consisted of gross motor training, motor training of hand dexterity, and training of coordinated movement. After 2 weeks of combined therapy, both groups received 2 weeks of conventional OT two times a day, 5 days a week.

All groups received combined therapy of hand training, OT, and low-frequency rTMS for 2 weeks. Before performing rTMS, we evaluated the motor-evoked potential using MagPro (MagVenture Inc., Farum, Denmark) and a double remote control coil. Then rTMS was applied to stimulate the primary motor cortex of the unaffected hemisphere; the motor evoked potential was obtained from the abductor pollicis brevis (APB) muscle. The potential in the APB muscle were recorded using the Nicolet EDX electromyography device (Natus Medical Inc., Middleton, WI, USA). The magnetic stimulation was repeated with a change in intensity. The minimum intensity was 100 mV or more amplitude in 3 out of 5 consecutive stimulations was determined to be the resting motor threshold [20]. The location yielding the largest response amplitude in the APB motor cortex of the contralesional hemisphere was determined as the hot spot. For the treatment, magnetic stimulation of 1 Hz at 110% intensity of the resting motor threshold at the hot spot was applied for 20 minutes each (total of 1,200 pulses a day).

Evaluation

Upper extremity motor functions were evaluated using the manual function test (MFT) [21]. MFTs for 'total', 'grasp and pinch', and 'hand activities' were performed and measured by an occupational therapist. This test scores the upper extremity exercise, grip strength, and finger manipulation abilities for a possible total of 32 points. The MFT for 'grasp and pinch' was from 0 to 6 points, and that for 'hand activities' was from 0 to 10

points. A manual muscle test (MMT) was used to measure the muscle strength. MMTs for grasp, release, and APB were performed and measured. The spasticity was evaluated using the Modified Ashworth Scale (MAS) [22]. These were measured before and immediately after combined therapy as well as two weeks after therapy. The Institutional Review Board of Dong-A University Hospital (No. 17-191) approved the study.

Analysis methods

The changes in the evaluation parameters from before to immediately after combined therapy and 2 weeks after therapy were analyzed. Statistical analyses were conducted using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The Wilcoxon signed-rank test was used to evaluate the outcome measurements before and after treatment in each group. For comparing the two groups, statistical processing was conducted using the Mann-Whitney U test. Friedman tests were used for the changes in MMT and MFT according to the intra-group. Statistical significance was set at $p < 0.05$.

RESULTS

During the study period, 34 patients were enrolled. Seventeen patients were randomly assigned to each of two groups. Two patients dropped out owing to a decline in medical condition and an early discharge from the hospital. Finally, 32 patients with hand weakness completed the study. The average age of the intervention group ($n=16$) was 60.6 ± 11.5 years, and that of the control group ($n=16$) was 68.1 ± 17.9 years. Basic information was not statistically different between the two groups. National Institutes of Health Stroke Scale, MFT, MMT, MAS, Korean version of Mini-Mental State Examination, Korean version of Modified Barthel Index and day from stroke onset were not significantly different between the two groups (Table 1).

In both groups, changes in grasp MMT, release MMT, APB MMT, and MFT for 'grasp and pinch' and 'hand activities' improved until 2 weeks after combined therapy and the changes were statistically significant. The intra-group difference in the mean of the parameters showed statistically significant improvement over time (Table 2).

The intervention group patients showed more improvements in grasp MMT and APB MMT for therapies at im-

Table 1. Baseline characteristics of both groups

	Intervention group (n=16)	Control group (n=16)	p-value
Age (yr)	64.64±11.47	68.09±10.95	0.223
Sex (male:female)	9:7	9:7	
Lesion			
Ischemic:hemorrhagic	7:9	8:8	
Cortical:subcortical	13:3	12:4	
Paretic side (right:left)	9:7	10:6	
Onset from stroke (day)	29.73±19.93	31.00±21.06	0.717
NIHSS	11.76±4.74	11.04±5.67	0.423
K-MBI	47.65±8.76 (45, 34-62)	43.63±11.76 (43, 28-62)	0.632
K-MMSE	25.18±4.24 (25, 17-29)	20.09±7.15 (19, 13-27)	0.075
MMT			
Grasp	2.55±0.82 (3, 1-3.5)	2.64±0.50 (2.5, 1-3.5)	0.768
Release	2.00±0.89 (2, 1-3)	2.18±0.60 (2, 1-3)	0.621
APB	1.55±1.21 (1, 1-3)	2.00±0.63 (2, 1-3)	0.288
MFT			
Total	13.36±8.69 (9, 4-29)	12.55±5.48 (13, 4-18)	0.895
Grasp and pinch	2.64±1.43 (3, 1-5)	2.36±1.03 (2, 1-4)	0.386
Hand activities	3.82±2.64 (4, 1-6)	3.55±1.37 (4, 1-6)	0.268
MAS of finger flexor	0.27±0.65 (0, 0-2)	0.09±0.60 (0, 0-1)	0.509

Values are presented as mean±standard deviation (median, range).

NIHSS, National Institutes of Health Stroke Scale; K-MBI, Korean version of Modified Barthel Index; K-MMSE, Korean version of Mini-Mental State Examination; MMT, manual muscle test; APB, abductor pollicis brevis; MFT, manual function test; MAS, Modified Ashworth Scale.

Table 2 . Change in MMT and MFT on both groups during 4-week treatments

	Intervention group (n=16)				Control group (n=16)			
	Before	After	2 weeks later	p-value	Before	After	2 weeks later	p-value
MMT								
Grasp	2.55±0.82	3.37±0.88 ^{a)}	3.45±0.94 ^{b)}	0.000*	2.64±0.50	2.94±0.48 ^{a)}	3.37±0.48 ^{b,c)}	0.000*
Release	2.00±0.89	2.73±0.92 ^{a)}	3.09±0.96 ^{b,c)}	0.000*	2.18±0.60	2.63±0.54 ^{a)}	3.09±0.57 ^{b,c)}	0.000*
APB	1.55±1.21	2.61±1.16 ^{a)}	2.63±1.12 ^{b)}	0.000*	2.00±0.63	2.36±0.58 ^{a)}	2.82±0.62 ^{b,c)}	0.000*
MFT								
Total	13.36±8.69	19.18±6.52 ^{a)}	22.09±7.94 ^{b,c)}	0.000*	12.55±5.48	18.00±5.12 ^{a)}	21.10±5.34 ^{b,c)}	0.000*
Grasp and pinch	2.64±1.43	4.09±1.23 ^{a)}	4.46±1.28 ^{b,c)}	0.000*	2.36±1.03	3.54±0.82 ^{a)}	3.81±0.84 ^{b,c)}	0.000*
Hand activities	3.82±2.64	5.09±1.88 ^{a)}	5.46±1.46 ^{b,c)}	0.000*	3.55±1.37	4.64±1.01 ^{a)}	4.91±0.96 ^{b,c)}	0.000*

Values are presented as mean±standard deviation.

MMT, manual muscle test; APB, abductor pollicis brevis; MFT, manual function test.

^{a)}p<0.017 significant difference between before and immediately after combined therapy.

^{b)}p<0.017 significant difference between immediately after combined therapy and 2 weeks after combined therapy.

^{c)}p<0.017 significant difference between before and 2 weeks after combined therapy.

*p<0.05 by Friedman test, post-hoc test.

Table 3. Comparisons of the change of hand motor function between both groups

	Intervention group (n=16)	Control group (n=16)	p-value
Before and after			
Δ MMT			
Grasp	0.82±0.60	0.30±0.48	0.047*
Release	0.73±0.65	0.45±0.52	0.316
APB	1.06±0.94	0.36±0.50	0.045*
Δ MFT			
Total	5.82±4.90	5.45±4.13	0.949
Grasp and pinch	1.45±0.69	1.18±0.41	0.386
Hand activities	1.27±0.65	1.09±0.54	0.268
Δ MAS	0.00±0.00	0.00±0.00	1.000
Before and 2 weeks after			
Δ MMT			
Grasp	0.90±0.70	0.73±0.47	0.537
Release	1.09±0.83	0.91±0.54	0.537
APB	1.18±0.87	0.82±0.60	0.316
Δ MFT			
Total	8.73±7.56	8.55±5.15	0.797
Grasp and pinch	1.82±0.75	1.45±0.52	0.672
Hand activities	1.64±0.55	1.36±0.51	0.605
Δ MAS	0.00±0.00	0.00±0.00	1.000

Values are presented as mean±standard deviation.

MMT, manual muscle test; APB, abductor pollicis brevis; MFT, manual function test; MAS, Modified Ashworth Scale.

*p<0.05 by Mann-Whitney U test.

mediately after combined therapy. However, the changes in all measurements were not significantly different between the two groups at 2 weeks after combined therapy (Table 3). During the treatments, no other side-effects related to rTMS, such as seizure or headache, were found.

DISCUSSION

In this study, we investigated the positive effects of hand training within the aftereffect period of low-frequency rTMS on hand function in patients with subacute stroke. The hand training group within the aftereffect period of low-frequency rTMS in which the APB was targeted showed positive effects for the first 2 weeks. However, they did not show significant differences at 2 weeks after

combined therapy. The combined therapy of rTMS and hand training was effective in restoring the hand function of the subacute stroke patients without marked side-effects.

The intervention group who underwent hand training during the aftereffect period showed more improvement in grasp MMT and MMT APB immediately after combined therapy when compared to the control group. This indicated that hand training in the aftereffect period may induce earlier improvement in hand motor recovery. There was significant improvement in the hand function of both groups immediately after the combined therapy and at 2 weeks after combined therapy. This result was consistent with that of a previous study in which the grip strength of the affected hands was improved from the baseline only in the conventional therapy with real rTMS group compared to the conventional therapy with the sham rTMS group [23]. Our results could reinforce the evidence that low-frequency rTMS with hand training during the aftereffect period has positive effects on hand function.

The intervention group did not show additional improvement in terms of motor recovery when compared to the control group at 2 weeks after combined therapy. This may be because of the cumulative effects of 10 times of low frequency rTMS. A previous study presented a cumulative mechanism in which low-frequency rTMS effects induced several hours of long-term cortex excitability depression. Furthermore, the repeated stimulation caused a cumulative increase that reflected the responses of a neuronal network [24]. Another study of the upper limb function of stroke patients which conducted 5 days of low-frequency rTMS reported that the effects of rTMS were cumulative and lasted for at least 2 weeks [25]. These studies implied that the effects of rTMS were more localized to the specific area of stimulation. In our study, stimulation of APB in the affected hand was localized. In this respect, it is meaningful that the effects of 10 low-frequency rTMS treatments for 2 weeks on subacute stroke patients who had hand weakness were cumulative and continued for at least 2 weeks.

In this study, we investigated the subacute period after stroke. The period of around the first three months after stroke is considered a 'golden period' for exogenous restorative therapies because revitalizing endogenous recovery events, neuroplasticity, and functional reorgani-

zations are highly activated in the central nervous system during this period [26,27]. Studies have already shown that early rehabilitation induces better effects [28] and that most improvement is seen within the first 3 months after the onset of stroke [26]. There has been no case of serious adverse effects after rTMS in many previous studies on post-stroke patients [25,29,30], and no side-effects such as headache or seizure were observed in this study. Thus, for the combined therapy to produce maximal effects, low-frequency contralateral rTMS may have to be initiated within the initial 3-month period.

In this study, the stimulation intensity was set to be a supra threshold stimulation (110%) not only because many previous studies suggested that such stimulation induces more favorable results [13,31], but also because it was recommended in the guidelines on safety for rTMS [12]. A study recently reported that coupling inhibitory and facilitatory rTMS produced a more affirmative outcome than single-session rTMS alone [32]. Therefore, further studies may need to investigate the effects of hand training with combined inhibitory and facilitatory rTMS during the aftereffect period.

Our study has several potential limitations. First, the research period of 4 weeks was restricted. Further studies may be necessary to consider long-term evaluation in a longer follow-up period. Second, owing to the problems faced in selecting the control group, the subjects were not blinded and the study lacked a sham or high-frequency rTMS treatment group. Third, because of the difficulty in patient enrollment, the types and locations of stroke in each patient were not consistent. In addition, the number of subjects was small for subgroup analysis. Further studies should be performed as well-designed, large-scale cohort studies controlling for variables such as stroke location to clearly demonstrate the effects of low-frequency rTMS with hand training on stroke patients during the aftereffect period.

In conclusion, hand training immediately after low-frequency rTMS showed more rapid improvement in motor power of hand than training 2 hours after low-frequency rTMS. Our results suggest that conducting hand training immediately after low-frequency rTMS could be an important useful therapeutic option in subacute stroke patients. It could be proposed that when developing a protocol of combined therapy of hand training and rTMS, conducting hand training immediately after low-

frequency rTMS has more effective outcomes.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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