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Effects of High Frequency Repetitive Transcranial Magnetic Stimulation with Physical Healthy Exercise in Stroke

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Abstract

It has been recently demonstrated high frequency repetitive transcranial magnetic stimulation (HF-rTMS) can improve motor function after stroke. However, there is no study that tested the synergetic effects of physical therapy to HF-rTMS in clinical settings. We therefore investigated the effect of physical healthy exercise (PHE) on paretic arm combined with HF-rTMS in stroke patients. All patients underwent HF-rTMS on contralesional hemisphere for 15 minutes and PHE on paretic arm. The cortical excitability by the amplitude and latency of motor evoked potential (MEP) were measured. We also evaluated arm function using Box and Block, arm reach, 9-hole pegboard, and grip force tests. We found for the first time significant differences of MEP between pre- and post-intervention. HF-rTMS with PHE had a tendency to induce a decrease in MEP amplitude on the non-paretic hand whereas it led to an increment in MEP amplitude in the paretic hand. In particular, the Box and Block, power grip, and arm reach tests showed improvement through every session. Furthermore, motor function and MEP were correlated especially on paretic side. These results indicate PHE with HF-rTMS partially improves arm function after stroke which may support additional effect to rehabilitation in stroke patients.

Keywords: High frequency repetitive transcranial magnetic stimulation, Physical healthy exercise, Stroke

Introduction

There has been increasing focus on transcranial magnetic stimulation (TMS) for last decade. In terms of the application of TMS into rehabilitation, the adjunction with additional therapeutic exercise has been highlighted to maximize the effect[1]. Still, it is unclear to prove the effect of TMS in clinical setting though there has been some effort to investigate the effect of TMS related to therapeutic exercise such as constraint-induced movement therapy (CIT) and intensive occupational therapy[2,3]. Patients after stroke commonly suffer from significant impairments including weakness, loss of voluntary motor control, and spasticity[4-8]. After completing standard rehabilitation, approximately 50-60% of stroke patients still experience some degree of motor impairment[9], and at least 20% are partially dependent in activities-of-daily-living (ADL)[10]. Physical therapy for stroke primarily concerns requisition of motor function to perform tasks and ADL such as grasping, reaching, and more physical demanding movements[6]. Previous report has seen a developing role for physical therapy assistants[11], and some studies have shown that physical therapy can increase upper extremity (UE) motor recovery[12,13]. In our previous study, we also investigated and proved the effect of range of motion exercise with low frequency repetitive TMS (LF-rTMS) in stroke patients[14]. Beside of our study, diverse therapeutic exercises, for example, simple movement exercise, sequential motor training, CIT, and occupational therapy, has been investigated with rTMS[1-3,15]. Including our previous work, all of them resulted in motor functional improvement after intervention. In terms of the mechanism of neuroplasticity induced by therapeutic exercise combined with rTMS is not clear and controversial as the other authors mentioned[16,17]. According to interhemispheric competition model, furthermore, both hemispheres inhibit each other in a competition in natural condition[18,19]. After brain injury, primary motor cortex (M1) of contralesional hemisphere inhibits M1 of ipsilesional hemisphere without competition, that results in abnormal increase of transcallosal inhibition (TCI) from contralesional hemisphere to ipsilesional one[18-20]. Previous studies reported that repetitive transcranial magnetic stimulation on contralesional M1 reduces TCI to disinhibit ipsilesional hemisphere, and it leads to enhance excitability of ipsilesional hemisphere[1,18-21]. rTMS can change excitability of human cortex for at least several minutes and influence to metabolic rate on stimulated cortex area and, therefore, may lead to functional change of paretic hand[1,20,22]. We were interested in UE motor function of chronic stroke patients after application of exercise with low frequency rTMS on unaffected hemisphere to downregulate TCI[14]. Regarding TCI, some brain system can work as an inhibitor to suppress the other, in other words, long term depression (LTD). Thus, in the previous work ours, LF-rTMS has been delivered to the contralesional hemisphere[14]. In the present study, we adapted high frequency repetitive TMS (HF-rTMS) stimulating the ipsilesional M1 for more direct access to the lesion site based on the opposite mechanism of LTD, so called, long term potentiation (LTP). These two mechanism explains the brain plasticity closely linked with cortical re-organization. However, TMS currently is not used directly with physical therapy[23], despite additional physical training can augment the effect of rTMS and it may contribute to functional recovery after stroke[1,24]. Moreover, it has been reported that there is a risk of occurring seizure during HF-rTMS. Due to this safety issue, main stream of rTMS study has been biased to LF-rTMS than HF-rTMS. Taken together, therefore, we hypothesized that physical healthy exercise (PHE) such as active-assisted, active, and resisted exercise on paretic UE combined with HF-rTMS on ipsilesional M1 changes cortical excitability. We examined to clarify whether PHE combined with HF-rTMS shows functional improvement on paretic UE and whether change of cortical excitability is correlated with improvement of UE activities in stroke patients.

Results

The amplitude of the MEP was significantly increased in the non-paretic side compared with the paretic side in stroke patients. The latency of the MEP was greater in the paretic hand compared with the non-paretic hand (Figure 1). PHE combinded with HF-rTMS had a tendency to induce a decrease in MEP amplitude on the non-paretic hand whereas it led to an increment in MEP amplitude in the paretic hand of hemiplegic stroke patients (Figure 1). As shown in Figure 2, the representative results in the 3rd, 5th, and 6th session indicate that MEP amplitude was significantly decreased by HF-rTMS with PHE in stroke patients. Furthermore, compared with the non-paretic side, the paretic side showed a clear trend of continuous motor function improvement. In particular, the Box and Block, 9-hole pegboard, power grip, pinch grip, and arm reach tests on the paretic side showed improvement at post-intervention compared with pre-intervention (Table 1). Using Pearson's correlation, the study analyzed the correlation between motor function and MEP parameters. Most of the motor function tests and MEP parameters correlated with each other (Table 2).

Discussion

This study provides the first direct demonstration that PHE combined with HF-rTMS for stroke patients can facilitate cortical excitability and motor recovery. This study was based on the hypotheses that HF-rTMS would result in an increase in cortical excitability on the ipsilesional hemisphere and that PHE added to HF-rTMS would accelerate the increases in cortical excitability, which would ultimately translate into motor improvement. We found a clear increase of MEP amplitude in the paretic side whereas the non-paretic side showed a decrease in MEP. Results showing the change of MEP amplitude between pre-intervention and post-intervention on both first dorsal interosseous (FDI) muscles are in agreement with previous studies[1,20,21,24]. This indicates that HF-rTMS at 10 Hz over the ipsilesional hemisphere leads to an increase of cortical excitability on the ipsilesional hemisphere of stroke patients. In the previous study, the MEP amplitude of the paretic FDI muscle at post-rTMS + exercise significantly increased to a greater extent than at post-rTMS, and the greatest increase was at post-rTMS + exercise at the sixth session[14]. This finding suggests that physical therapy combined with rTMS may be more beneficial than lower frequency rTMS (LF-rTMS) alone and the effect may be cumulative over long term treatment. In this study, the results appear consistent with the previous work because they show continuous MEP changes through all sessions. One of the limitations of the previous study was that it was relatively time-consuming, taking approximately 90 minutes. That length could possibly cause fatigue and lack of attention during treatment. As a result, it couldn't be determined with certainty what results would be possible if the treatment time was modified. Considering this, there was an emphasis on time management to optimize the design of the present study. It took around 45 minutes in total, including motor function tests, at each session. Motor function tests were found to be consistent with the previous study. In the previous work, motor improvement between post-rTMS and post-rTMS + exercise on paretic UE function in the 9-hole pegboard test was demonstrated throughout the overall procedure whereas the nonparetic UE showed no continuous changes[14]. In this study, motor functions improved continuously on

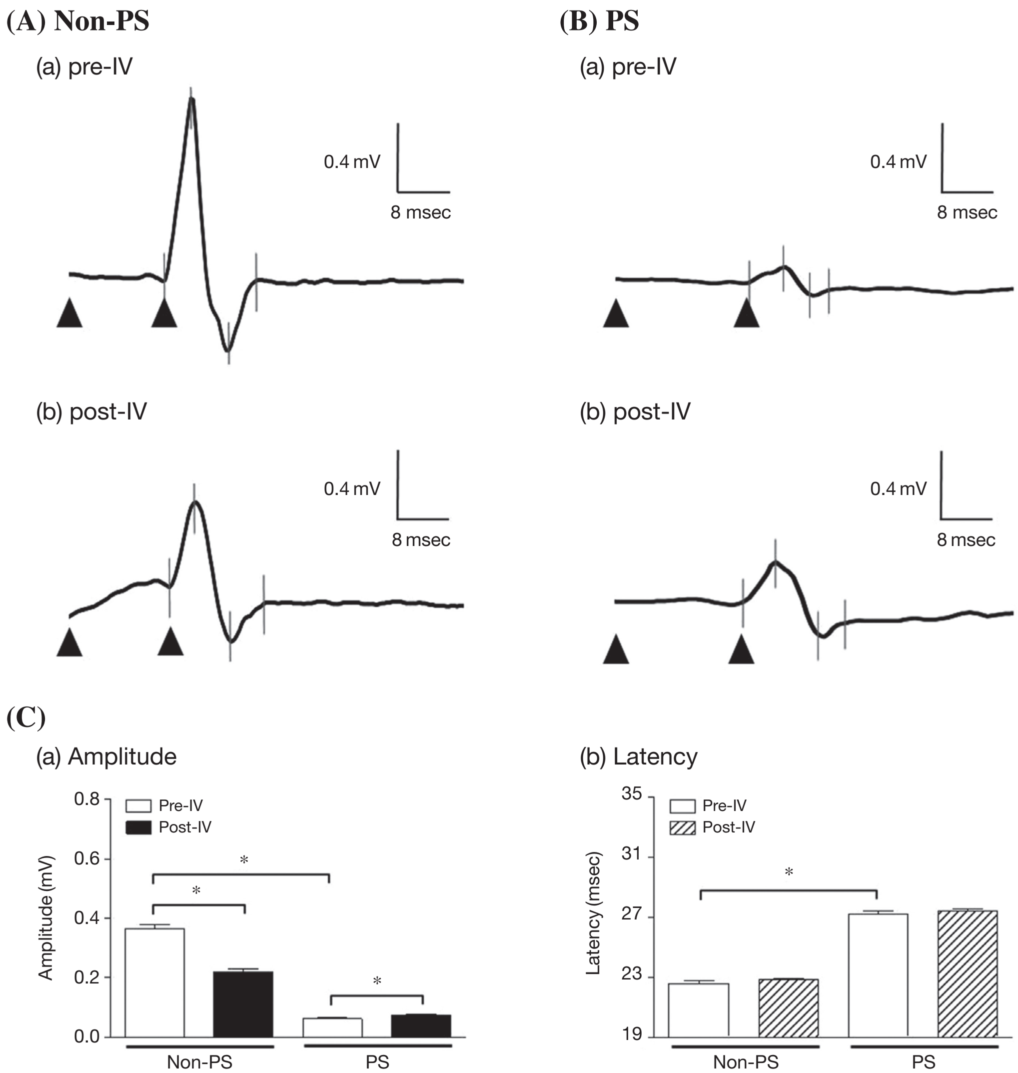

Figure 1. Diagram of MEP amplitude and latency from both first dorsal interosseous muscles. MEP amplitude and latency were determined, as described in the Materials and Methods. The paretic side showed increased motor evoked potential (MEP) amplitude whereas the non-paretic side showed decreased amplitude after intervention. However, there is no clear pattern of change in MEP latency. PS, paretic side; Non-PS, non-paretic side; pre-IV, pre-intervention, post-IV, post-intervention. *: $p < 0.05$.

the paretic hand with the Box and Block, power grip force, and arm reach tests. The 9-hole pegboard test also showed continuous improvement except at the fifth session. These improvements are greater than the previous results, which may suggest HF-rTMS has a stronger effect then LF-rTMS. Alternatively, the finding may be due to the unique design of the PHE intervention that is guided appropriately by a physical therapist. Previous studies combining motor function with rTMS used repetitions of simple movements[1,25]. UE movement is complex and needs coordinated activation of variable muscles[26]. In the results of this study, motor improvement in the paretic UE did not sharply correspond with an increase in MEP amplitude on the ipsilesional M1. This is not consistent with the previous study. It may be due to the temporary inhibitory effect seen right after HF-rTMS for homeostasis of brain activity[23,27,28]. To confirm that this phenomenon was occurring only temporarily and later resolved, the study should have measured the cortical excitability again after a suitable time interval. However, this would affect the original goal of controlling the overall time required for the intervention. Furthermore, the MEP in the next session showed a tendency to return to its level before the previous stimulation. Taken together, it could be proposed that MEP data at post-intervention might

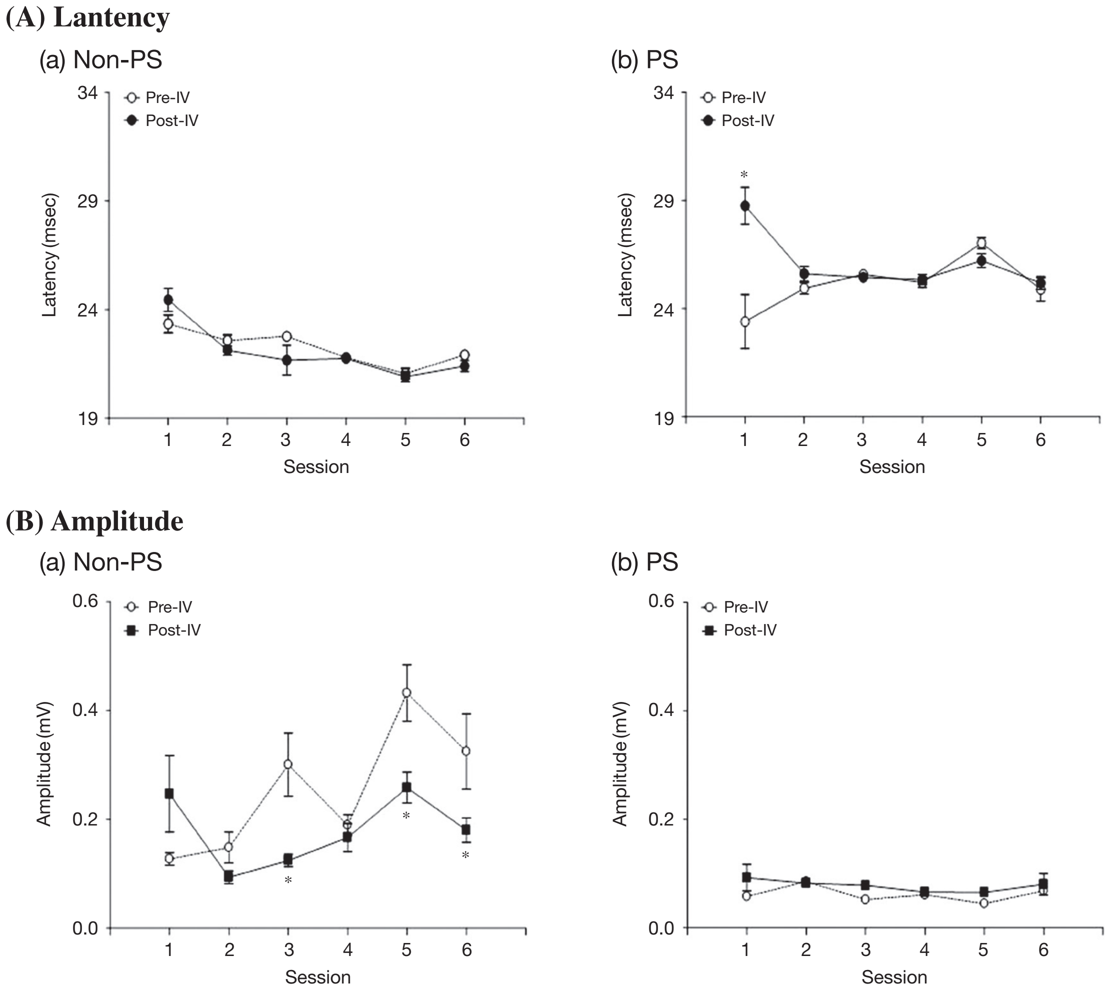

Figure 2. MEP amplitude and latency from both first dorsal interosseous muscles. A and B motor evoked potential (MEP) changes over six sessions. For each measurement, 25 data points were recorded and analyzed at pre-HFrTMS + PHE (pre-IV) and post-rTMS + PHE (post-IV) (n = 100). PS, paretic side; Non-PS, non-paretic side; HFrTMS, high frequency repetitive transcranial magnetic stimulation; MEP, motor evoked potential; PHE, physical healthy exercise; pre-IV, pre-intervention, post-IV, post-intervention. *: $p < 0.05$.

be the homeostatic reaction after HF-rTMS. In a previous study, the relationship between MEP amplitude and motor function was investigated by Kim *et al*. The study found a significant correlation between MEP amplitude and motor accuracy[25]. Takeuchi and colleagues reported that both pinch grip force and MEP amplitude were increased after application of rTMS and motor training[1,20]. In particular, Khedr and colleagues investigated the effect of 10 Hz rTMS and a significantly greater motor improvement, as well as changes in cortical excitability, was found after up to one year[28]. According to the current results, significant correlations between MEP and motor function were found. Therefore, the motor evaluation tool can be considered appropriate to measure motor recovery followed by changes of cortical excitability. The present study has two principal advantages. It is the first study to adopt PHE combined with HF-rTMS for stroke patients. As previous studies have reported, additional physical training may facilitate the effect of rTMS and lead to functional recovery after a stroke[1,24]. Thus, PHE guided by an experienced physical therapist after application of rTMS is appropriate in this respect. The previous study also showed greater excitation of the ipsilesional M1 after rTMS + exercise than after rTMS only. This implies that PHE can augment the effect of rTMS and can contribute to motor recovery. Though there has been no previous study that applied physical therapy with rTMS, some studies have been conducted with simple motor training and rTMS[1,20,25]. According to the

Table 1. Motor function of the upper extremities in hemiplegic stroke patients.

Session		B & B (No.)		9-hole PG (sec)		Power G (kg)		Pinch G (kg)		Arm R (cm)	
		Pre-rTMS	Post-rTMS + PHE	Pre-rTMS	Post-rTMS + PHE	Pre-rTMS	Post-rTMS + PHE	Pre-rTMS	Post-rTMS + PHE	Pre-rTMS	Post-rTMS + PHE
Non-paretic side	1st	60.8 ± 3.0	60.3 ± 5.0	18.5 ± 1.0	18.1 ± 1.4	32.6 ± 1.7	35.3 ± 2.4*	7.7 ± 0.6	8.0 ± 0.6	11.8 ± 0.3	12.1 ± 0.8
	2nd	61.8 ± 3.2	62.2 ± 4.0	18.8 ± 1.4	18.9 ± 1.2	33.3 ± 1.9	34.4 ± 2.0*	8.2 ± 0.6	7.8 ± 0.5	14.1 ± 0.6	14.6 ± 0.7
	3rd	65.4 ± 4.1	63.6 ± 2.0	17.9 ± 0.9	18.1 ± 1.0	34.2 ± 1.6	35.5 ± 1.9	7.8 ± 0.6	8.0 ± 0.5	13.4 ± 0.4	13.7 ± 0.6
	4th	64.0 ± 2.1	62.4 ± 3.5	17.7 ± 1.3	18.3 ± 1.3	35.2 ± 1.9	35.1 ± 2.0	8.1 ± 0.6	8.5 ± 0.6*	13.3 ± 0.8	13.2 ± 0.5
	5th	62.2 ± 2.9	61.2 ± 2.9	18.2 ± 1.6	18.6 ± 1.3	34.1 ± 1.8	33.1 ± 2.1	7.8 ± 0.5	8.3 ± 0.5*	13.5 ± 0.7	12.3 ± 0.6
	6th	63.8 ± 1.8	64.0 ± 2.7	17.7 ± 1.1	17.4 ± 1.3	34.3 ± 1.6	37.3 ± 1.5	8.2 ± 0.5	8.4 ± 0.6	12.0 ± 0.6	12.6 ± 0.4
Total		63.0 ± 1.3	59.8 ± 1.3	18.1 ± 0.5	18.2 ± 0.5	34.0 ± 0.7	35.0 ± 0.8*	7.9 ± 0.2	8.2 ± 0.2*	13.0 ± 0.3	13.1 ± 0.3
Paretic side	1st	19.4 ± 5.3	23.8 ± 7.4	205.5 ± 58.4	134.4 ± 60.0	12.6 ± 1.9	13.7 ± 1.5	3.5 ± 0.6	3.8 ± 0.5	9.0 ± 0.4	9.9 ± 0.4*
	2nd	19.4 ± 5.7	25.2 ± 6.7*	204.0 ± 55.9	172.2 ± 55.9	11.0 ± 1.5	12.6 ± 1.1*	4.0 ± 0.7	3.7 ± 0.4	11.3 ± 0.4	11.9 ± 0.5
	3rd	21.6 ± 6.0	24.8 ± 6.0*	173.2 ± 52.1	138.9 ± 45.9	11.7 ± 1.1	12.7 ± 0.9	3.9 ± 0.4	4.3 ± 0.4*	11.3 ± 0.5	12.5 ± 0.3*
	4th	19.8 ± 5.8	23.2 ± 5.8	164.7 ± 54.3	142.1 ± 47.2	11.3 ± 1.2	12.5 ± 0.9*	3.9 ± 0.5	4.4 ± 0.4*	12.1 ± 0.5	12.8 ± 0.6
	5th	21.2 ± 5.4	24.0 ± 6.1	154.7 ± 48.0	164.3 ± 57.5	11.0 ± 1.0	12.7 ± 1.0*	3.8 ± 0.4	4.3 ± 0.5*	11.6 ± 0.7	11.7 ± 0.4
	6th	27.4 ± 10.0	30.8 ± 9.0*	144.9 ± 44.2	124.2 ± 44.8	10.4 ± 1.4	11.2 ± 0.4*	4.8 ± 0.5	4.2 ± 0.4	11.5 ± 0.5	12.1 ± 0.4
Total		21.5 ± 2.5	25.3 ± 2.6*	174.5 ± 19.9	146.4 ± 19.5*	11.3 ± 0.5	12.6 ± 0.4*	4.0 ± 0.2	4.1 ± 0.2*	11.1 ± 0.2	11.9 ± 0.2*

rTMS, repetitive transcranial magnetic stimulation of high amplitude; PHE, physical healthy exercise; B & B, Box and Block test; 9-hole PG, 9-hole pegboard test; Power G, power grip; Pinch G, pinch grip; Arm R, arm reach. *$p < 0.05$

authors, motor functions were improved after motor training as well as after application of rTMS. Furthermore, PHE and evaluation tools in this study were designed by considering both complex actual UE movement such as reach and grasp[8] and overlapped brain mapping in the motor cortex[26]. Thereby, PHE was performed from the elbow to finger joints and used the Box and Block test and 9-hole pegboard test. Correlation analysis in this study also supports the consistency of the motor evaluation tool to changes of motor excitability. However, further systematic and scientific studies in the fields of neurorehabilitation and others are needed to confirm the effects of therapy[29-31]. In summary, cortical excitability on both hemispheres was changed continuously both after physical healthy exercise (PHE) combined rTMS. Furthermore, motor evaluation tests showed correlations with MEPs. These findings suggest that PHE with HF-rTMS facilitates motor recovery in hemiplegic stroke patients.

Methods

Subjects

We studied seven patients (five male, two female) aged 36 to 65 years (56.6 ± 3.9) who had suffered a stroke. The interval since their stroke ranged from 12 to 49 months (20.0 ± 4.9 months). They scored 29.7 ± 0.2 on the K-MMSE. Four of the subjects were right hemiplegic and three were left hemiplegic. Their lesion sites were all located in their subcortex, including basal ganglia, cerebrum, middle carotid artery, and medulla (Table 3). They were all patients of B Hospital in Korea, a specialized hospital with an intensive physical therapy unit for patients with neurological diseases such as stroke. Patients were regarded as suitable to participate if they fulfilled the following criteria:

(1) They had a single ischemic stroke with more than one year of duration.
(2) Their lesion site was located only in the subcortex as confirmed by computed tomography or magnetic resonance imaging.
(3) Their motor deficits of the paretic UE were improved to the extent that patients could perform grasp tasks.
(4) They scored in the normal range on the Korean Mini-Mental State Examination.

The exclusion criteria included the following:

(1) They had severe internal carotid artery stenosis.
(2) They had experienced a seizure.
(3) They had an intracranial metallic implant.

All participants provided their written informed con-

Table 2. Correlation between motor evoked potential and motor function in stroke patients.

	Lat	Amp	B & B	9-hole PG	Power G	Pinch G	Arm R
Lat	1.00						
Amp	−0.42**	1.00					
B & B	−0.59**	0.50**	1.00				
9-hole PG	0.62**	−0.40**	−0.84**	1.00			
Power G	−0.65**	0.50**	0.93**	−0.70**	1.00		
Pinch G	−0.58**	0.36**	0.90**	−0.77**	0.89**	1.00	
Arm R	0.05	0.25*	0.31**	−0.21*	0.21*	0.17	1.00

PS, paretic side; NPS, non-paretic side; Amp, amplitude; Lat, latency; B & B, Box and Block test; 9-hole PG, 9-hole pegboard test; Power, power grip force; Pinch, pinch grip force; Power G, power grip; Pinch G, pinch grip; Amp, amplitude; Arm R, arm reach. *$p < 0.05$, **$p < 0.01$.

Table 3. Clinical characteristics of hemiplegic stroke patients.

Sex	Age (yr)	Time Post-Stroke (mo)	K-MMSE (P/NP)	rMT (P/NP) (%)	PS	Clinical Diagnosis	Power Grip (P/NP) (kg)	Pinch Grip (P/NP) (kg)
M	55	15	30/30	64/47	R	BG ICH	10/46	4.2/11.0
M	63	49	30/30	62/60	R	CbrI	24/26	7.0/6.2
M	51	17	30/30	75/50	L	BG ICH	10/37	3.2/8.6
M	62	13	30/30	66/42	R	BG ICH	12/34	1.7/6.0
F	65	12	29/30	60/50	L	MCAI	9/29	1.3/5.4
M	36	16	30/30	NT	R	BG ICH	11/32	3.0/10.5
F	64	18	29/30	NT	L	Lat. MI	18/20	5.5/5.5

K-MMSE, Korean version of mini mental status examination; No, number of patient; rMT, resting motor threshold; P and PS, paretic side; NP, non-paretic side; L, left side; R, right side; Lat, lateral side; M, male; F, female; ICH, intra-cerebral hemorrhage; BG, Basal ganglia; CbrI, Cerebrum infarct; MCAI, Middle cerebral artery infarct; MI, medullary infarct; NT, not tested.

sent for participation in this study.

Experimental Design

The study was designed as a single-blind trial. All participants had undergone a standard physical therapy and occupational therapy program on a regular basis in the hospital. In the study, they attended the TMS therapy unit on seven days and participated in rTMS treatment and additional PHE specially designed for the study (Figure 3). All participants underwent the following procedures:

(1) Familiarization with experimental procedures, including motor function evaluation tests and repetitive finger opposition movement.
(2) Motor cortex mapping of the hot spot of M1 representation corresponding to the FDI muscles of both hands.
(3) Determination of rMT and stimulation intensity of both hemispheres.
(4) Six sessions of HF-rTMS with finger opposition repetition and PHE intervention.
(5) Motor function evaluation tests and MEP measurements twice at pre- and post-intervention per each session (2×6, total 12 times).

On the first day, participants completed a practice session for familiarization with the overall procedures in the study after which the hot spots corresponding to both hands' FDI muscles and rMT were investigated. The participants with whom we couldn't find the hot spot were excluded. All remaining participants practiced finger opposition training following a therapist's positioning and guidance on their UE in a supine position. Next, they received motor function evaluation tests and practices for them. The practice time varied for motor function evaluations since they had different experience in performing the tests. The practice concluded when they showed a stable result in two consecutive trials or they reported that they understood well and felt comfortable with the tests. The practice time ranged from 10 to 20 minutes. From the second to seventh visit, participants underwent HF-rTMS and PHE treatment. Motor function and cortical excitability were evaluated in each session. Motor function was measured using the Box and Block test, 9-hole pegboard test, maximum protraction distance, power grip force, and lateral pinch grip force. We collected the data of cortical excitability by MEP amplitude and latency, which were measured using electromyographic signals of both FDI muscles. All patients were evaluated twice in every session. In total, motor function and MEP parameters were measured 12 times (Figure 3).

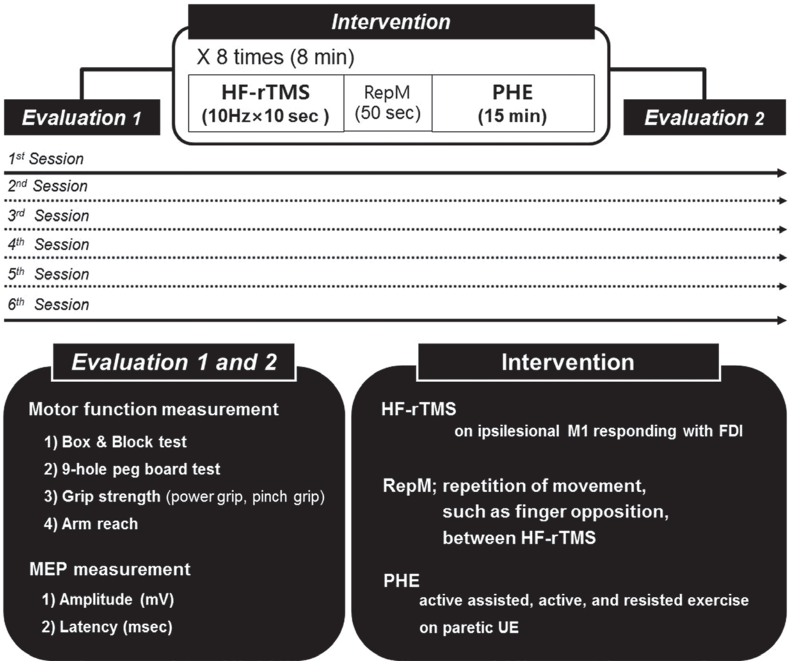

Figure 3. Schematic representation of the experimental procedure and time course. MEP amplitude and latency were determined, as described in the Methods. Stroke patients in their chronic stages received HF-rTMS (10 Hz, 8 minutes) on the ipsilesional M1 responding area with the paretic FDI muscles and then physical healthy exercise (15 min) on the paretic upper extremities. Their hand functions and cortical excitability were measured during six treatment sessions. HF-rTMS, high frequency repetitive transcranial magnetic stimulation; FDI, first dorsal interosseous muscles; M1, primary motor cortex; MEP, motor evoked potential; UE, upper extremity.

Determination of Resting Motor Threshold and HF-rTMS

A MAG PRO butterfly coil (MCF-B65) and MAG PRO R30 (Medtronic, Inc.) were used for determination of resting motor threshold and conduction of HF-rTMS for eight minutes. The coil was placed tangentially over the primary motor cortex in the optimal site corresponding with the FDI muscle during HF-rTMS application. The handle of the coil was pointed backward and laterally at 45 degrees to the sagittal plane. The optimal site was defined as the location where stimulation of a slightly suprathreshold intensity elicited the largest MEPs in the FDI muscle. The motor hot spot was investigated by moving the coil in 0.5 cm increments around the presumed primary hand motor area. This hot spot was marked on the scalp with a soft tip pen. EMG activity was recorded from silver-silver chloride electrodes positioned in a belly-tendon montage on skin overlying the FDI by software KEYPOINT®. NET. The rMT was defined as the lowest stimulator output that could activate MEPs with peak-to-peak amplitude of 50 V in at least half of 10 trials[32]. rMT of both FDI muscles was obtained separately at a baseline level. To set the rMT, stimulation was started at 40% of maximal intensity. If this didn't produce appropriate response of the MEPs, the intensity was increased or decreased until the rMT was found. The rMT could not be found in two participants, so they were excluded from the study. Participants received HF-rTMS with an intensity of 80% rMT on the hot spot in the ipsilesional M1. The handle of the coil was fixed to an integrated holder unit so that the positioning of the coil would not change. Coil positioning was continuously monitored throughout the stimulation period. Based on the previous study, the appropriate stimulation intensity was determined to be 80% of the rMT to reduce overall intensity and reduce the risk of evoking a seizure[33]. The HF-rTMS protocol consisted of a total of 800 pulses during eight minutes, administered as 10 trains of 100 stimuli, at 10 Hz (each train was 10 seconds duration, followed by a 50 second inter-train interval) for each session. A 50 second period of finger opposition motion was conducted immediately following cessation of each HF-rTMS train. Finger opposition motion was defined as the repetitive contact between the tip of the thumb and the tips of the other fingers in turn. During this motion, the participant's wrist was stabilized and motion was guided when needed based on the experienced physiotherapist's decision. The HF-rTMS protocols used were in accordance with the safety guidelines for rTMS to the M1 (Figure 3)[34,35].

Physical Healthy Exercise

Considering the lasting time of cortical excitability change in M1, physical healthy exercise (PHE) was performed for 15 minutes immediately following HF-rTMS on the paretic UE. In this study, PHE consisted of active assisted, active, and resisted exercises of joints and muscles in the UE. PHE mainly focused on stabilization of the proximal UE (shoulder, elbow, and wrist) and hand movements. PHE included:

(1) Shoulder active assisted exercise and active exercise into the neutral position between protraction/retraction, external rotation/internal rotation, and abduction/adduction.
(2) Elbow active assisted exercise and active exercise into extension.
(3) Forearm active assisted exercise and active exercise into supination.
(4) Wrist active assisted exercise and active exercise into slight extension.
(5) Finger active assisted exercise and active exercise into extension and abduction.
(6) Finger resisted exercise of opposition.

During PHE, the physiotherapist controlled the movement in the context of the individual's body functions and structural features.

Measurements of Motor Evoked Potential

There are several TMS parameters related to MEP, including amplitude and latency, cortical thresholds, cortical silent period (SP), central motor conduction time (CMCT), intercortical inhibition (ICI), size of the cortical area from where the potentials are evoked, and others[36]. MEP is the most frequently measured TMS parameter in stroke patients. As action potentials traverse neurons, MEPs can be detected by EMG in a contralateral target muscle, typically a finger muscle. TMS is usually done with the target muscle initially at rest. Therefore, TMS measurements are not dependent on subjects performing a particular movement. This feature makes TMS a tool amenable to studying motor cortex excitability in stroke patients, even those with hemiplegia. MEPs recorded in the early post-stroke period appear considerably more predictive than clinical examination for the recovery of motor function[9]. That is, the existence of MEP in the early stage suggests a good prognosis while no MEP suggests a poor prognosis[36,37]. The changes of cortical excitability after stroke are best demonstrated in the early stage and modify over time[36]. During the early stage, the changes are induced by pathophysiologic changes such as reversal of diaschisis and resolution of edema. In the chronic stage, the changes mainly originate from functional reorganization[38]. MEPs evaluate the integrity of the motor pathways and may generate meaningful prognostic information, as the recovery after stroke is influenced by a critical residual spared function[39]. Therefore, an increase of cortical excitability shown by average MEP may be interpreted as a positive sign of prognosis while a decrease of excitability may not. For example, when it comes to the interpretation of the MEP amplitude and latency in terms of the cortical excitability, the amplitude and cortical excitability are in a positive relationship, whereas the latency and cortical excitability are in the negative relationship[22].

Measurements of UE Motor Functions

Box and Block Test

The Box and Block test is a measure of manual dexterity that requires repeatedly moving 1-inch wooden blocks from one side of a box to another in 60 seconds. The number that can be moved from one compartment to the other in one minute is counted. Several studies have been completed on patient populations that established the validity of this test for use with various diagnoses[40]. It has been used to evaluate gross manual dexterity, not only for healthy individuals, but also for individuals with disorders such as cerebral palsy[41]. In this study, the individual patient tried the test for 15 seconds immediately prior to the actual test beginning. The patient placed his/her hands on the sides of the box. As the test begins, the patient picks up one block at a time with one hand, transports the block over the partition in the center, and releases it into the opposite compartment. The test was done with the non-paretic hand first and then repeated with the paretic hand. One physical therapist counted the blocks. If the patient transported two or more blocks at a time, the number was subtracted from the total. The score of the test is the number of blocks transported from one compartment to the other in one minute. Each hand was measured separately[14].

9-hole Pegboard Test

The 9-hole pegboard test is commonly used in the rehabilitation setting by therapists as a simple, quick assessment for finger dexterity. The 9-hole pegboard test is correlated with the Purdue pegboard test, indicating adequate concurrent validity of the measures[42]. The 9-hole pegboard test is a timed test in which nine pegs are inserted and removed from nine holes in the pegboard with each hand. The test should be conducted with the dominant arm first. In this study, the 9-hole pegboard test was conducted with the non-paretic arm first and repeated with the paretic side. One preparation trial for each arm was provided prior to the actual test. The time was recorded with a stopwatch in seconds. The record of time was started when the patient touched the first peg and stopped when the patient placed the last peg in the container[14].

Grip Force Test

Hand grip strength is widely used in adults and is seen as being representative of total body strength. This study measured the power and lateral pinch grip force using a JAMAR® Hand Evaluation Kit (a hydraulic dynamometer and a hydraulic pinch gauge) in kilograms-force on both the paretic and non-paretic hands. The evaluation kit has been examined regarding validity and reliability compared with other grip force measurement systems[43]. For each measurement, patients were seated with their shoulder adducted and neutrally rotated, elbow flexed at 90 degrees, forearm in neutral position, and wrist between 0 and 30 degrees dorsiflexion and between 0 and 15 degrees ulnar deviation[44]. During each trial, the patients were encouraged to put their maximal force to grip the equipment by the therapist's verbal cue. The scores of three successive trials were recorded and averaged[14].

Arm Reach Test

Arm reach is commonly defined as the motion that occurs when the humerus is flexed at 90 degrees and moved forward in the sagittal plane of the body[45]. Arm reach is a critical motion for hand activities such as reaching for an object or pushing an object away. Neurological disorders including stroke could limit shoulder protraction[46]. In this study, arm reach was measured using a modification of the functional reach test. The patients were in the supine position and raised their arms straight up at 90 degrees flexion, while making a fist, as the starting position. They were asked to reach their arms forward without lifting their scapulae off the surface. The therapist adjusted the patients into a neutral position and recorded the location of the end point of the third metacarpal bone in the starting position. The patients were instructed to reach as far as possible when their scapulae were allowed to leave the surface for maximal protraction of the shoulder without moving the thorax and the midline of the body. The therapist then recorded the ending point of the third metacarpal bone. Prior to the three repetitions of the actual test, all patients had two practice trials. The non-paretic side was measured first, followed by the paretic side. To collect the shoulder protraction data, the procedure measured the difference between the starting point and ending point of the location of the third metacarpal bone[14].

Statistical Analysis

Data were expressed by mean ± standard error (SE). Before and after the intervention, the statistical difference of MEP parameters and motor functions between the paretic and non-paretic sides was determined by analysis of variance for repeated measures (repeated ANOVA), analysis of covariance (ANCOVA), and paired t-test, depending on the variables. Any possible correlation between changes of various parameters was determined by using a Pearson correlation coefficient test.

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