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Immediate Effects of Low-Frequency Repetitive Transcranial Magnetic Stimulation to Augment Task-Specific Training in Sub-acute Stroke

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Abstract

The current study examined the immediate effects of a single session low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) with task-specific training in sub-acute stroke. Sixteen participants were randomly received either active LF-rTMS (experimental group) over the non-lesioned hemisphere or sham stimulation (control group). Consequently, both groups underwent task-specific training with the paretic hand and constrained the non-paretic hand by a mitt for 1 hour. The authors evaluated the corticospinal excitability of the non-lesioned hemisphere (evaluated by motor evoked potential (MEP) amplitude) and the behavioral outcomes of both hands (evaluated by total movement time (TMT) of the Wolf Motor Function Test). There were significant differences between the two groups in the MEP amplitude of the non-lesioned hemisphere at post LF-rTMS and post motor training. Comparing to that of the baseline, the experimental group showed a greater decrease in TMT of the paretic hand immediately after active LF-rTMS than the control group. Additionally, the TMT of experimental group further decreased after the motor training and it was significantly less than that of the control group. Therefore, the task-specific training effect was augmented by LF-rTMS to improve the performance of paretic hand in sub-acute stroke.

Keywords : *Non-invasive Brain stimulation, Neural plasticity, Task-specific training, Stroke,*

1. Introduction

Stroke is a common disease that leads to a prolonged neurological disability in adults worldwide including Thailand [1, 2]. In 2012, the Ministry of Public health in Thailand reported that the prevalence of in-patients with cerebral vascular disease was 227,848 cases [3] and the estimated cost for medical care and rehabilitation was 1 million baht per person [1]. Therefore, the appropriate rehabilitation would reduce the burden on relatives and society.

After stroke, motor deficit of the upper extremity (UE) was reported to be more severe than the lower extremity (LE) [4, 5]. Approximately 55% of stroke survivors had no UE movement following initial rehabilitation[5] and only 12% could be completely recovered without receiving a rehabilitative treatment [6, 7]. Therefore, the statistics lead us to concentrate on the UE training. In general, the functional impairments of the UE were reaching and grasping which were essential components of daily life activities [8]. The impairment of reaching was greater recovered than grasping [8]. Therefore, it is essential to identify the optimal treatment for grasping. Additionally, period of the treatment is one of the influential factors for stroke recovery. A previous study reported that the recovery of motor function occurred over the first six months [13]. Thus, giving the intervention during the six months period would maximize the effectiveness of the training.

Functional recovery after stroke is related to various plastic processes. In the healthy brains, the activities of neurons in the motor areas, so called "Primary motor cortex or M1", of both hemispheres were cooperated and balanced in the sense of inhibitory control [9-11]. Interhemispheric inhibition between motor areas was transferred via transcallosal connection. The interhemisheric communication imbalance in individuals with stroke had been measured by the TMS. For instance, within four months after stroke, non-lesioned hemisphere had more corticospinal excitability than the lesioned hemisphere [9, 11, 12]. Moreover, there was an irregular increase interhemispheric inhibition from the non-lesioned hemisphere onto the lesioned hemisphere. This increased inhibition suppressing the recovery of the lesioned hemisphere led to remaining functional impairment [9-11, 13, 14]. There fore, the reduction of the corticospinal excitability of the non-lesioned may represent a procedure to support recovery. There were body of evidence reporting the application of low-frequency repetitive TMS (LF-rTMS) to decrease the corticospinal excitability in the non-lesioned hemisphere [e.g.(13-18)].

The LF-rTMS is a non-invasive technique that modulates excitability in the cerebral cortex by the stimulation through the coil [9, 10]. To best of our knowledge, there were only two studies examined the effects of a single session of LF-rTMS combined with motor training [16, 18]In 2008, Takeuchi and co-workers studied the combined effects of LF-rTMS with 15 minutes pinch training in individuals with chronic stroke. They reported the improvement of acceleration of pinch and pinch force in rTMS group [16]. In 2014, Vongvaivanichakul and co-workers investigated the effects of LF-rTMS on reach-to-grasp (RTG) training in chronic stroke. They found the improvement of total movement time of Wolf Motor Function Test and time of RTG actions in only in the experimental group [18]. Both studies suggested that the improvement of motor performance was depending on the combination of LF-rTMS and motor training. Based on the framework of Williams and co-worker, the motor training in individuals with stroke was an indirect rehabilitation of the paretic limb, which could be called “Bottom up approach”. This approach required a long period of treatment [19]. Later on, there was the direct brain stimulation which using rTMS. The rTMS approach was termed “Top down approach” that reduced the duration of treatment compared with the former approach[19]. Therefore, if both approaches are combined, they most likely lead to a better motor performance as demonstrated in the study by Takeuchi and Vongvaivanichakul [16, 18]. However, Takeuchi and co-worker applied the simple pinch task, not a real-world activity. Therefore, it is equivocal to identify the specific type of motor training which includes daily activity task, thereby causes the neural plasticity and the changes of the behavior. Additionally, both studies [16, 18] investigated the effects of training in chronic stroke. Based on the notion of “early is better, the current study therefore applied the intervention in sub-acute stroke [20].

The Accelerated Skill Acquisition Program (ASAP) and Constraint Induced Movement Therapy (CIMT) are types of task-specific training that relate to the real object and real situation [21-23]. The ASAP is a restoration of the paretic limb in real world context which reduces motor impairments and compensatory strategies [21, 24]. Additionally, the CIMT is an adaptive behavior developed to overcome a phenomenon of “learned nonuse”, which is similar to the mechanism of LF-rTMS [21-23].

Taken together, the purpose of this study was to examine the immediate effects of single session of LF-rTMS with task-specific training that based on the CIMT and ASAP principles on the performance of paretic hand in individuals with sub-acute stroke.

2. Materials and methods

2.1 Participants

The recruitment process and group allocation is illustrated in figure 1. Thirty-five participants were screened by the telephone or face-to-face interview by the researcher. They were recruited from clinical services at the Faculty of Physical Therapy Mahidol University, Siriraj Hospital, and Golden Jubilee Medical Center Mahidol University (in-patient and out-patient clinic). There were sixteen participants who passed the inclusion and exclusion criteria (Figure 1). Sixteen individuals with a first-time sub-acute stroke participated in this study. The inclusion criteria were as follows: (1) subcortical ischemic or hemorrhage unilateral stroke with onset from 1-6 months were verified by medical record or CT/MRI, (2) age range 20 -79 years (±5 years), (3) right handedness evaluating by Edinburgh Inventory Test, (4) mild to moderate impairment level of upper extremity on the Fugl-Meyer Assessment (FMA), (5) able to understand and follow simple command were evaluated by Mini mental state examination (MMSE) Thai version 2002 (Cutoff > 23), (6) able to finger mass extension (FMA of hand section at least 1), (7) able to sit independently at more than one hour, (8) normal or corrected hearing system and visual system, (9) no unilateral visual neglect (Star cancellation test > 44 points) , (10) intact ideomotor apraxia (imitation meaningless of gesture; error score ≤ 3), and (11) no motor aphasia, sensory aphasia, and global aphasia. The exclusion were as follows: (1) positive screening for contraindication of rTMS which is confirmed by TMS screening questionnaire such as seizure and an intracranial metallic implant etc, (2) other neurological and musculoskeletal problems affecting arm, hand, or trunk which may interfere with task achievement such as at least 3 of 5 joints(of upper extremities) on the joint pain domain of FMA (FMA pain equal to zero), and (3) undergoing task-specific training elsewhere during the time of a participating this study. All participants were given a written informed consent and assessed before admittance into this study. The study was approved by the Mahidol University Institutional Review Board (MU-IRB 2012/064.0304) and Siriraj Institutional Review Board (SIRB SI134/2013).

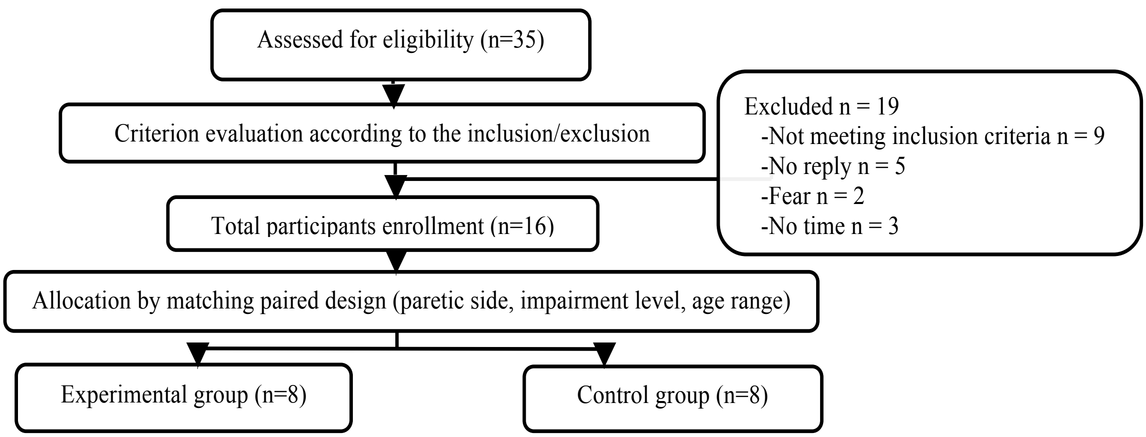

Figure 1. Recruitment process and group allocation

This study was a single blinded clinical trial. The participants were randomly allocated into two groups; the experimental and control groups by convenience sampling method and the both groups were matched their level impairment, paretic side and age range (±5 years). The experimental group received active rTMS with task-specific training while the control group received sham rTMS with task-specific training. In addition, participants in both groups were assessed as follows behavioral outcome and corticospinal excitability at Baseline (Pre); Post immediate after-r TMS (Post1) and Post after motor training (1 hr-Post training or post 2) (Figure2) by a blinded evaluator.

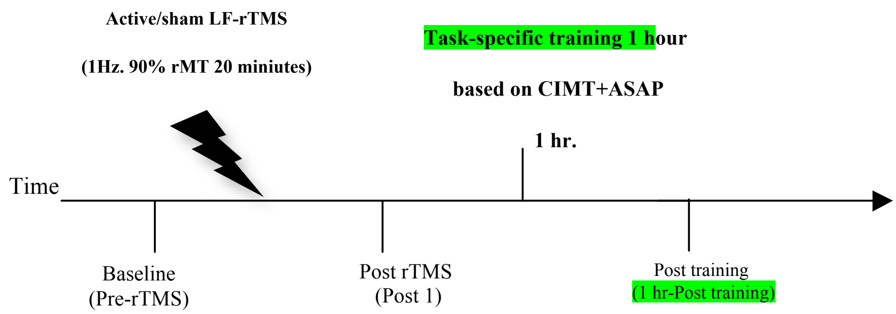

Figure 2. Time course and experimental design of the study

2.2 Task-specific training

The task-specific training of the paretic hand was modified from the principles which based on CIMT and ASAP. The principle of CIMT was restraint of the non-paretic hand by a mitt. The principle of ASAP included task-specificity, impairment mitigation, and motivation [21]. The ASAP protocol were as follows: (1) participants participated in collaboration of task selection which was real-world task, aiming to improve strength and fine motor control (selected each two task). The protocol did not aim to improve bimanual task because it was contrary to the principle of CIMT, (2) participants assigned a priority of the task which selected one from the four tasks they listed in the above. This task should be the key that they wanted to really do. If they were not able to do it, they would live everyday with great difficulty, (3) participants performed the priority of the task. At the same time, the researcher analyzed functional performance and interacted with the participant in problem analysis. Moreover, self-directed assessment was obtained from each participant after task analysis, (4) participants interacted with the researcher to solve the most important problems which designed the strategy of practice and the number of sessions, (5) before and after the training, they were encouraged confidence through self-efficacy assessment, (6) task completion was enhanced to increase motivation of the participants [24]. Specific tasks were chosen by the participants, which were grasping a glass with handle or without handle, manipulation of pen during writing, manipulation of spoon or fork during eating, and carrying a pot with five cans of rice during cooking.

2.3 Behavioral outcomes assessment

Behavioral outcomes of the paretic hand were measured by Wolf Motor Function Test (WMFT), hand-items (i.e. a can lifting, a pencil lifting, a picking up paper clip, stacking checkers, turning the key in lock, and folding towel). During the test, participants comfortably seated on the chair and were instructed to perform the functional test. The researcher demonstrated how to do each task and participants had a maximum of two minutes to fail the task. The movement time of each task was recorded by a stopwatch. Later on, behavior outcome of the non-paretic hand was measured similar to the paretic hand. The maximum time of performance was set at 120 seconds. If it was more than 120 seconds, it was marked as unsuccessful trial [21, 25].

2.4 Corticospinal excitability assessment

Corticospinal excitability of the non-lesioned hemisphere, represented by the peak-to-peakd of Motor Evoked Potential (MEP) amplitude, was measured using single-pulse TMS (Magstim200, Magstim Co., Dyfed,UK) with figure of eight coil. The coil was placed tangentially of the non-lesioned M1 at the optimal site for the extensor digitorum (ED) area which was"the location where stimulation at slightly supra-threshold intensity elicited the largest MEP in the target muscle". Moreover, determining corticospinal excitability required electromyographic (Medelec Synergy, VIASYS Health Care Inc., Surrey, UK) recording which recorded from silver-silver-chloride electrodes positioned in a belly-tendon montage on the skin overlying the ED muscle. First, we measured the rMT of the non-lesioned hemisphere. The rMT referred to the lowest intensity that induces MEPs of 50 µv peak-to-peak amplitude in the target muscle in 50% of the trials given that TMS is applied to the "optimal site"[26]. Next, we calculated the 120% of rMT from the rMT value that was the point to find the peak-to-peak MEP amplitude. As for the peak-to-peak MEP amplitude, it was determined for ten times at 120% of rMT.

2.5 Procedure

After selection according to criteria, the participants participated in collaboration of task selection and followed as the process of ASAP in training session. Later on, all participants were randomly allocated into two groups; the experimental and control groups. After allocation, the participants received an assessment of behavioral outcomes (of both hands) and corticospinal excitability of the non-lesioned hemisphere. The experimental group then received active rTMS of the non-lesioned M1 at the optimal site for the ED area (1 Hz., 90% of rMT, Number of pulse = 10, Number of trains = 120, Total number of pulse = 1200 pulse, for 20 minutes). The stimulation was delivered via the figure of eight air-cooled coil with Magstim rapid2 (Magstim Co., Dyfed,UK). In contrast, the control group received sham stimulation which was given by the same coil placement, but the coil was tilted to 90 degrees (Figure3) [16, 27]. In addition, the control group received the same frequency and intensity as the experimental group. Immediately after rTMS, both groups were assessed for the corticospinal excitability and behavioral outcomes similar to the baseline (pre-rTMS) assessment.

Figure 3. Procedure of LF-rTMS (active stimulation (left) and sham stimulation (right))

After the application of rTMS, the participants in both groups underwent task-specific training with the paretic hand for one hour. The training was based on the principles of ASAP as described in experimental task section. During the training, the non-paretic hand was restrained by a mitt. After the training, both limbs of the participants were assessed for the immediate effects.

2.6 Data Analysis

The demographic data and clinical characteristics were analyzed by descriptive statistic. Moreover, two factors ANOVA (Group x Time) repeated measure (mixed model), repeated on time was used to compare behavioraloutcome (average total movement time (TMT) and movement time (MT) of each task) and corticospinal excitability (MEP amplitude of the non-lesioned hemisphere) of each time condition. Multiple comparisons were computed by Bonferroni. The Bonferroni test was used to analyze the differences of behavioral outcome and corticospinal excitability at each testing time between the experimental and control groups.

3. Results

During this study, participants did not report any adverse side effects and all of them completed the study. For the study, all participants had lesion locations as follows: internal capsule (2 persons from experimental group and 2 persons from control group), periventricular area (2 persons from experimental group and 3 persons from control group), and lacunar infarction (4 persons from experimental group and 3 persons from control group). Moreover, this study had only participants with right handedness. Characteristics of the sixteen participants are shown in Table 1. There were no difference of age, duration after stroke, and FMA between active rTMS and sham rTMS groups.

Table 1. Demographic and clinical characteristics comparing the experimental group (active-rTMS) and the control group (sham-rTMS)

Group	Active rTMS (n =8) Mean (SD)	Sham rTMS (n = 8) Mean (SD)
Age (years)	54.25 (9.07)	60.13 (11.58)
Post-stroke onset (months)	3.19 (2.14)	3.94 (1.37)
Fugl-Meyer Assessment score (maximum scores = 66 points)	47.00 (7.95)	46.5 (5.26)
Mini Mental State Examination (maximum scores = 30 points)	26.38 (1.85)	25.75 (1.75)
Star Cancellation Test score (maximum scores = 56 points)	53.13 (3.83)	53.25 (2.60)
Imitation of meaningless gesture (maximum scores = 6 points)	6.00 (0.00)	5.88 (0.35)

Table 2 shows the individual data of MEP amplitude of the non-lesioned hemisphere and total movement time in WMFT of the paretic hand at baseline (pre), immediately post LF-rTMS (post 1) and post training (1hr-post training) comparing between experimental (active-rTMS) and control group (sham-rTMS). To compare between and within group, the corticospinal excitability and behavioral data were normalized by conversion to percentage change from the mean values at baseline. As shown in figure 3 and 4, the positive quadrant represents an increase of the percent change and the negative quadrant represents a decrease of the percent change compared with the baseline.

Table 2. The individual data of MEP amplitude of the non-lesioned hemisphere and total movement time in WMFT of the paretic hand in baseline (pre), immediately post LF-rTMS (post 1) and post training (1hr-post training) in the experimental group (active-rTMS) and the control group (sham-rTMS)

Subject	Sham-rTMS						Active-rTMS					
	MEP amplitude			Total Movement time of WMFT			MEP amplitude			Total Movement time of WMFT		
	Baseline	**Post 1**	**1hr- Post training**	**Baseline**	**Post 1**	**1hr- Post training**	**Baseline**	**Post 1**	**1hr- Post training**	**Baseline**	**Post 1**	**1hr- Post training**
S01	107.64	221.36	167.36	32.32	25.87	24.98	281.35	202.2	256.51	12.71	10.91	9.74
S02	234.85	214.73	247.21	332.12	308.77	292.65	101.69	35.85	40.6	336.27	164.44	170.96
S03	247.58	187.94	185.86	142.34	139.73	138.19	590.59	257.2	436.44	139.97	137.18	134.89
S04	144.91	254.64	177.2	146.03	142.94	140.26	601.87	297.94	358.32	603.04	450.4	253.13
S05	96.52	134.49	113.47	154.42	148.66	143.69	196.66	148.72	156.61	79.9	72.11	47.25
S06	105.41	86.69	88.72	138.84	137.91	136.13	368.36	242.93	185.77	37.3	27.24	28.49
S07	126.25	163.97	116.13	186.6	165.97	154.75	438.35	242.33	169.32	21.26	22.62	22.75
S08	145.77	147.43	158.55	433.93	331.03	237.77	286.53	158.02	80.77	181.38	175.32	156.32
Mean	151.12	176.41	156.81	195.83	175.11	158.55	358.18	198.15	210.54	176.48	132.53	102.94
SD	58.51	54.17	50.31	126.71	99.21	78.91	178.42	82.65	134.12	202.99	144.18	88.49

3.1 Effects of LF-rTMS with task-specific training on corticospinal excitability: considering the MEP amplitude of the non-lesioned hemisphere at different testing times

Significant difference were detected in the main effects of group (p-value=0.016). There was significant difference between the two groups in the average MEP amplitude at post rTMS (post1) (p-value = 0.043) and post training (post2) (p-value = 0.047) (Figure 4). As for the within group, there was no significant difference in the average MEP amplitude of the non-lesioned hemisphere at any testing times compared with the baseline. However, the experimental group showed a greater decrease in the percent change of MEP amplitude of the non-lesioned hemisphere immediately after active LF-rTMS than the control group. Moreover, the reduction of percent change of average MEP amplitude of experimental group continued to decrease after the training (Figure 4).

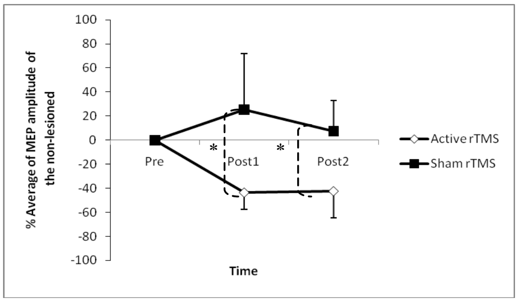

Figure 4. Percent change of average MEP amplitude of the non-lesioned hemisphere at baseline (pre), immediately post LF-rTMS (post1) and post training (post2) in the experimental group (active-rTMS) and the control group (sham-rTMS) (* = significant difference (p-value < 0.05))

3.2 Effects of LF-rTMS with task-specific training on behavioral outcomes: considering movement time (MT) of the paretic hand at different testing times

The result showed significant main effects of group (p-value=0.025). There was a significant difference between the two groups in the improvement of the total movement time (TMT) of the paretic hand at post the training (p-value = 0.023). However, there was no significant difference between the two groups in the average TMT of the paretic hand at post1 (p-value = 0.082) (Figure 5). As for the within group, there was no significant difference of the average TMT at each testing time. However, as for the raw data, comparing to that of the baseline, the experimental group showed a greater decrease in TMT of the paretic hand immediately after active LF-rTMS than the control group. Additionally, the TMT of experimental group further decreased after the training.

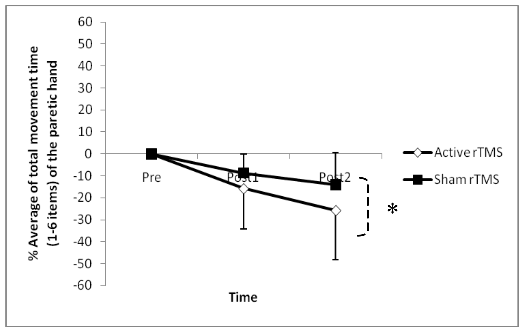

Figure 5. Percent change of average total movement time of the paretic hand at baseline (pre), immediately post LF-rTMS (post1) and post training (post2) in the experimental group (active-rTMS) and the control group (sham-rTMS) (* = significant difference between group (p-value < 0.05))

The Table 3 illustrates the raw data of within group for each item of the WMFT. Due to an unequal baseline performance of the two groups and to compare the outcome measures across groups and testing time, the authors computed the percent change using the following equation. From the percent change, the authors found that only a can lifting item showed nearly significant difference between the two groups in the movement time of paretic hand at post training (p-value = 0.091). For within group analysis, only a can lifting item showed a decrease in the percent change of movement time of the paretic hand immediately after active LF-rTMS when compared with the baseline (active-rTMS group = decreased 22.53% (p-value = 0.046). Additionally, it further decreased after the training (active-rTMS group = decreased 44.08 % (p-value = 0.000). In contrast, the sham group did not show significant difference in the movement time. Additionally, the authors did not observe the similar pattern of findings in other items of WMFT.

Table 3. The movement time [mean(SD)] of six items of the paretic hand at baseline (pre), immediately post LF-rTMS (post 1), and post training (1hr-post training) in the experimental group (active-rTMS) and the control group (sham-rTMS)

Task	Sham-rTMS			Active-rTMS		
	Baseline	Post 1	1hr- Post training	Baseline	Post1	1 hr-Post training
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
A can lifting	18.6(41.5)	18.1(41.6)	15.7(36.2)	33.9(54.0)	19.0(41.4)	6.1(8.3)
A pencil lifting	6.3(6.6)	5.8(6.2)	3.9(3.4)	5.3(4.4)	3.8(2.3)	3.3(3.5)
A picking up paper clip	20.5(40.8)	18.9(41.4)	3.5(2.2)	18.2(41.6)	17.9(41.7)	4.9(4.6)
Stacking checkers	24.3(37.3)	9.8(9.5)	14.9(16.6)	24.0(40.3)	10.8(13.3)	11.5(12.5)
Turning the key in lock	107.3(38.8)	107.4(38.6)	107(39.6)	68.8(57.2)	68.5(57.1)	65.6(59.5)
Folding tower	18.89(16.3)	15.1(15.5)	13.5(15.1)	26.1(35.7)	12.6(12.2)	11.6(13.8)

3.3 Effects of LF-rTMS with task-specific training on behavioral outcomes: considering movement time (MT) of the non-paretic hand at different testing times

For the non-paretic hand, no significant difference were found in the main effect of time (p-value = 0.929), main effect of group (p-value = 0.708), or interaction of time by group (p-value = 0.263) in total movement time. There were no significant differences of the TMT between the two groups at post1 (p-value = 0.373) and post2 (p-value = 0.337). For the multiple comparisons in each group, there were no significant differences of the average total movement time of non-paretic hand at each testing time.

4. Discussion

The purpose of this study was to examine the immediate effects of single session of LF-rTMS with task-specific training that based on CIMT and ASAP principles on the performance of the paretic hand in individuals with sub-acute stroke. The LF-rTMS reduced the MEP amplitude of the non-lesioned hemisphere, but not shown in sham LF-rTMS group. The findings supported that the LF-rTMS has an inhibitory effect on the over-excitability of the non-lesioned hemisphere [e.g.(14-18, 28-30)]. To the best of our knowledge, this is the first study till now to investigate the combined effects of one session LF-rTMS and task-specific training on corticospinal excitability in the sub-acute stroke. A previous study by Takeuchi et al.[16] and Vongvaivanichakul et al.[18] did not report the result of the corticospinal excitability after the motor training. We extended two studies by evaluating the result of the corticospinal excitability of the non-lesioned hemisphere after the task-specific training and trained in sub-acute stroke. In active rTMS group, the reduction of the MEP amplitude induced by the LF-rTMS was maintained immediately after the task-specific training while the reduction was not observed in the sham group. Therefore, these findings indicate that the effect of task-specific training alone was not enough to reduce corticospinal excitability of the non-lesioned hemisphere. The LF-rTMS induces the long-term depression (LTD-like mechanism) that leads to release gamma-butyric acid ($GABA_A$) neurotransmitter. This mechanism relates the inhibitory circuit that can be used to modify excitability within the human cortex. When the LF-rTMS was given before task-specific training that might provide functional networks for the training [27, 31, 32]. Additionally, the reduction of the MEP amplitude may be resulted from the inhibition activity of the non-paretic hand during the task-specific training. This result is consistent with previous studies and this mechanism helps to support the mechanism of LF-rTMS [21-23].

In addition, the benefits of adjunctive effects of LF-rTMS and task-specific training could result in the reduction of TMT of the paretic hand. Accordingly, our protocol of LF-rTMS was similar to the study of Takeuchi [16]; and further extended the protocol of motor training from Takeuchi's work to a more real-world task like reaching and grasping tasks. These findings indicate that the application of LF-rTMS or task-specific training alone could not induce the improvement of paretic hand performance. Additionally, the TMT was measured from the hand function of WMFT including six items. In each item showed no significant difference between the two groups and the within group at each testing time. However, only for a can lifting item, the authors observed that there was a decrease in the average of movement time (MT) of the paretic hand from the baseline immediately after active LF-rTMS and after the training. These findings were possibly due to the similarity of the can lifting item and the task-specific training chosen by most of the participants such as grasping a glass without handle. Moreover, the essential prime mover of can lifting item is the wrist extensor muscle which was the target muscle of the stimulation in the current study. As for the MT of the other items, they did not show the improvement. These results suggest that the task- specific training was not enough to transfer to the other tasks. One of the possible explanations is that the transfer learning requires more repetition of training [33].

For the non-paretic hand, the application of LF-rTMS did not deteriorate on the performance of non-paretic hand. Moreover, the both groups did not show the improvements of the TMT and MT in each task at after task-specific training. Thus, these results suggest that the adjunctive intervention did not affect on the performance of non-paretic hand. Additionally, during the task- specific training, the non-paretic hand was restrained by a mitt for one hour in order to inhibit activity of non-paretic hand and support the mechanism of LF-rTMS. Therefore, it did not worsen the performance of non-paretic hand.

Furthermore, this study confirmed that early phase of post stroke had an effect on the efficiency of intervention and the improvement of motor performance. There was a study by Higgins and colleges[34] applying the LF-rTMS and task-specific training by occupational therapist, and comparing the effects of sham stimulation and task-specific training in individuals with chronic stroke. They assigned 1200 pulses of LF-rTMS and 90-minutes training that based on activities daily (2 times per week, total 4 weeks). There were no significant improvements of the WMFT time task and grip strength between two groups at after intervention and after 4-week follow-up. With regard to the within each group, there were no significant differences of the WMFT time task and grip strength at after intervention and after 4-week follow-up. Therefore, it was suggested that the combined effects of LF-rTMS and task-specific training should be assigned to the early onset. Thus, our findings supported the principle of experience induced –plasticity, "early is better" (20).

Accordingly, our protocol is an indicative protocol to retrieve upper extremity function in individuals with sub-acute stroke who has mild to moderate severity. However, if this protocol is applied in severe stroke, the intensity may need to be more intensive than the one of the current study. The author investigated only the immediate effects of the combination of LF-rTMS and task- specific training. Furthermore, the results of TMT in the paretic hand tend to continuously decrease compared to the baseline. Therefore, we plan to investigate the persistent effects of LF-rTMS and task-specific training on the paretic hand dexterity.

5. Conclusion

These preliminary findings demonstrated that a single session of LF-rTMS of the non-lesioned hemisphere augmented the task-specific training thereby improved the paretic hand dexterity. The improvement was evidenced by the reduction of MEP amplitude of the non-lesioned hemisphere and TMT of the paretic hand performance.

6. Acknowledgement

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