ISSN (Print) 1226-1750
ISSN (Online) 2233-6656
Journal of Magnetics 28(4), 514-520 (2023) https://doi.org/10.4283/JMAG.2023.28.4.514

Effects of 1 Hz Low-Frequency Repetitive Transcranial Magnetic Stimulation Combined with Upper Limb Robotic Therapy on Upper Limb Function and Activities of Daily Living in Stroke Patients

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(Received 18 October 2023, Received in final form 15 December 2023, Accepted 15 December 2023)

This study demonstrated that upper limb robotic therapy (ULRT) combined with 1 Hz low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) improved upper limb (UL) function and activities of daily living (ADLs) in stroke patients. 16 stroke patients were treated with 1 Hz LF-rTMS on non-affected cerebral hemisphere, 8 in ULRT group, and 8 in the UL combined with traditional occupational therapy (ULTOT) group. Assessment include fugl-meyer assessment (FMA), modified ashworth scale (MAS), and modified barthel index (MBI). As a result, ULRT group showed significant differences in FMA, MAS, and MBI ($p<0.05$), and ULTOT group showed significant differences in FMA and MBI in two groups ($p<0.05$). There were significant differences in FMA, MAS, and MBI between two groups ($p<0.05$) ($p<0.001$). Through this, ULTOT group and ULRT group with 1 Hz LF-rTMS helped UL function and ADLs. In particular, ULRT with 1 Hz LF-rTMS helped improve UL function and ADLs.

Keywords : 1 Hz low-frequency repetitive transcranial magnetic stimulation, stroke, robotic therapy, upper limb function, activities of daily living

1. Introduction

Upper limb (UL) and hand dysfunction occur in 80 % of patients with early hemiplegia after stroke and have a negative effect on activity function [1]. UL dysfunction includes muscle weakness, difficulty in shoulder movement, and decreased sensation. Thus, patients with stroke are either unable to perform physical activities effectively or have limited ability to participate in activities of daily living (ADLs) and social activities [2]. Therefore, the recovery of UL function is an important factor in ensuring that patients with stroke can participate in various functional activities, and the goal of rehabilitation is to improve functional activities by improving physical ability [3]. The rehabilitation of UL function in patients with stroke is important for improving motor function and daily living performance. Interventions to restore UL function are integrated to prevent contractures and deformities, reduce pain, and promote functional activity in patients. Therefore, a proactive approach is required [4]. Transcranial magnetic stimulation (TMS), which stimulates the cerebral cortex noninvasively, is being applied as a treatment for recovering UL function in patients with stroke [5]. TMS enhances or suppresses cerebral activity by projecting an electric current onto the cerebral cortex using a magnetic field formed by a coil. A previous study reported that frequencies above 5 Hz increase cerebral activity, whereas frequencies below 1 Hz suppress cerebral activity [6]. Notably, 1 Hz low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) inhibits the cerebral cortex on the uninjured side based on transcallosal inhibition (TCI) [7]. The cerebrum has mechanisms in both cerebral hemispheres that compete with or regulate the opposite cerebral hemisphere. Based on this mechanism, disinhibition can occur by suppressing the undamaged cerebral hemisphere using a magnetic field that increases the activity of the damaged cerebral hemisphere [8]. In a previous study, LF-rTMS and occupational therapy (OT) were combined

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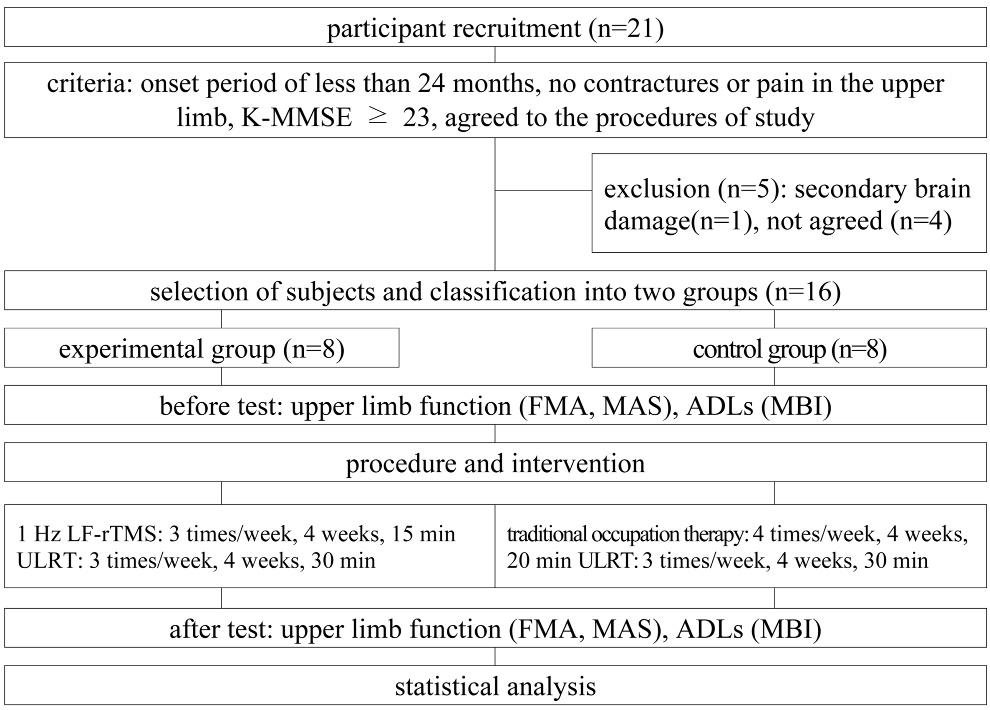
in patients with chronic stroke, which was evaluated using functional magnetic resonance imaging (fMRI) to confirm functional improvement in the motor cortex area [9]. Recovery of UL function for daily living performance is being approached in a variety of ways owing to improvements in technology using robot-assisted therapy. Robotic therapy supports three-dimensional movements with a computer-controlled device so that tasks based on upper-limb movements can be performed [10]. Although robotic therapy (RT) can be applied to improve the movement and motion of the UL, it does not significantly affect the performance of functional activities in connection with the patient's desired task performance [11]. UL robotic therapy applied to patients with stroke still lacks therapeutic evidence to explain changes in the central nervous system (CNS) and has limitations in linking with functional activities, such as those performed in daily life. The combination of upper limb robotic therapy (ULRT) with UL interventions to maximize the effect of the intervention could be a new alternative [12]. Therefore, in this study, we combined ULRT and 1 Hz LF-rTMS to determine how this combination can help UL function and ADLs of patients with stroke by increasing the activity of the cerebral cortex and promoting UL motor functions.

2. Materials and Methods

2.1. Participants

Participants were selected through a recruitment and selection process targeting patients with stroke hospitalized at C Hospital in Seoul. And participants included only patients who voluntarily agreed to participate in this study, and the number of subjects was selected using the G-power program. Sixteen people were selected based on the following selection criteria. Patients who had been diagnosed with stroke by a neurologist or rehabilitation medicine specialist, an onset period of less than 24 months, no contractures or pain in the upper limb, a score of 23 or higher on the Korean version mini-mental state examination (K-MMSE), no communication limitations, and agreed to the procedures of this study were selected. This study excluded patients who may have had seizures while undergoing 1 Hz LF-rTMS or who had metal objects surgically inserted into the brain. Additionally, this study excluded patients who did not voluntarily participate in the study. The participants were randomly divided into two groups of 8 each through drawing lots. The experimental group (EG) was treated with ULRT in combination with 1 Hz LF-rTMS on the uninjured cerebral hemisphere, and the control group (CG) received traditional OT and ULRT in parallel (Fig. 1).



Abbreviations are as follows. K-MMSE:korean version mini-mental state examination, FMA: fugl-meyer assessment, MAS: modified ashworth scale, MBI: modified barthel index, ADLs: activities of daily living, LF-rTMS: low-frequency repetitive transcranial magnetic stimulation, ULRT: upper limb robotic therapy

Fig. 1. The process of this study is briefly summarized in a schematic diagram.

2.2. Assessment methods

2.2.1. Upper limb function

2.2.1.1 Fugl-Meyer assessment (FMA)

The FMA was developed by Fugl-Meyer *et al.* in 1975 as a tool to evaluate motor, balance, sensory, and joint functions in patients with stroke [13]. UL motor function items of the FMA include 18 questions for the shoulder, elbow, and forearm; 5 questions for the wrist; 7 questions for the hand; and 3 questions for coordination. A total of 33 questions were tested with a maximum total score of 66 points; the higher the score, the higher the level of exercise recovery. The intra-examiner and inter-examiner reliability of UL motor function items were 0.99 and 0.98, respectively, and the test-retest reliability was 0.94-0.99 [14].

2.2.1.2 Modified Ashworth scale (MAS)

The MAS is classified into 6 levels: where 0 is s very low or normal muscle tone, and 4 is a state in which manual stretching is almost impossible. This test is a popular measurement method, and its validity has been verified as a subjective method for measuring stiffness [15]. The inter-rater reliability of this test was r = 0.84, and the intra-rater reliability was r = 0.83. In this study, the biceps brachii muscle of the patient was measured, and the test was performed with the patient posture sitting upright three times. Repeated measurements were performed, and the average value was presented [16].

2.2.3. Activities of daily living (ADLs)

2.2.3.1 Modified Barthel index (MBI)

MBI was developed to evaluate a patient's independence in ADLs and identify changes in daily living. It consists of 10 daily living activity items, including 7 self-care index items and 3 mobility index items. For each criterion, there are 5 levels and a total score out of 100 scores. A total of 0-24 points indicates complete dependence, 25-49 points indicates maximum dependence, 50-74 points indicates partial dependence, 75-90 points indicates slight dependence, and 91-99 points indicates minimal dependence. A score of 100 indicated complete independence. The MBI has a test-retest reliability of r=0.89 and an inter-examiner reliability of r=0.95 [17].

2.3. Procedure

2.3.1. 1 Hz low-frequency repetitive transcranial magnetic stimulation (LF-rTMS)

The MagPro R30 (Medtronic Inc., Skovlunde, Denmark) was used in this study. A B65 butterfly coil stimulator with a diameter of 70 cm was connected to the MagPro R30 to stimulate the participant's cerebral cortex on the uninjured side with noninvasive magnetic stimulation. The maximum magnetic field was 2.0 Tesla (Fig. 2). To measure the motor threshold, a bandanna with coordinates to easily locate the stimulus coordinates was drawn on the participant's head and worn on the scalp. The coordinates of the hood were based on the intersection of the midsagittal line from the nasion to the inion and the interaural line, with the center point (Cz) at 1-cm intervals. It was marked by crossing lines in a checkerboard pattern. The coil stimulator was placed tangentially to the scalp on the damaged side of the cerebral hemisphere, with the handle facing backward and positioned at an angle of 45 °from the centerline. In this study, 900 pulses were applied for 15 minutes at a frequency of 1 Hz, 3 times a week, for a total of 12 times over 4 weeks.

Fig. 2. (Color online) Appearance of the rTMS equipment used in this study (MagPro R30, Medtronic Inc., Skovlunde, Denmark).

Additionally, the 1Hz LF-rTMS procedure and intervention are schematically presented in Fig. 1.

2.3.2. Upper limb robotic therapy (ULRT)

The InMotion® ARM (Interactive Motion Technologies, USA), which induces complex movements of the two-dimensional shoulder and elbow joints, was applied. UL rehabilitation robot used in this study is an InMotion® ARM robot, which is used as a motor evaluation and UL exercise assistance rehabilitation robot for stroke patients, and helps restore damaged UL function by providing damaged normal sensory feedback and inducing normal motion patterns through robots. The subjects who participated in this study set initial values by analyzing the normal movement trajectory of the patient by analyzing the joint motion range and muscle tension of the initial patient and abnormal UL movement patterns through the InMotion® UL rehabilitation robot. After that,

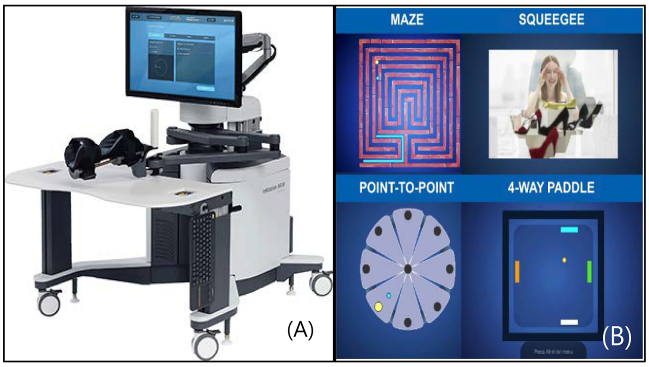


Fig. 3. (Color online) Appearance of the upper limb robotic therapy equipment (A) and In this study, a task-oriented approach program was used (B). (InMotion® ARM, Interactive Motion Technologies, USA).

based on the initial set values for each subject, UL exercise rehabilitation program suitable for each individual was presented by inducing a normal movement such as accurate joint motion range setting, direction, exercise assistance, strength, and resistance. InMotion® ARM included various programs in UL exercise rehabilitation training that can immediately check feedback on qualitative movements such as the trajectory of individual patient movements, the amount of power, and accuracy through a monitor (Fig. 3). This study used InMotion® ARM in both groups to improve UL motor performance in neurorehabilitation and used information exchange between the robot and participants to provide ULRT (Fig. 3). ULRT was performed for 30 minutes per session, 3 times a week, for a total of 12 times over 4 weeks.

2.3.3. Traditional occupational therapy (TOT)

TOT applied in this study consisted of four detailed items: drinking water, using the phone, wiping the desk, and turning book shelves. Patients chose one of the four general occupational therapies and performed it for 20 minutes per session, 4 times a week, for a total of 16 times over 4 weeks (Fig. 1).

2.4. Data analysis

Statistical analyses were performed using WINDOW SPSS 18.0. Descriptive statistics and frequency analyses were conducted to determine participants' general characteristics. The Wilcoxon signed-rank test was used to compare UL function and ADLs before and after the intervention within the two groups, and the Mann–Whitney-U test was used to compare UL function and ADLs after the intervention between the two groups. All statistical analyses in this study were performed at the α = 0.05 significance level.

3. Results

3.1. General characteristics of subjects

The general characteristics of the participants were as follows: EG included 6 men and 2 women, with an average age of 73.13±13.92 years. Injury types is 2 cerebral hemorrhage, 6 cerebral infarctions, 5 right hemiparesis, and 3 left hemiparesis on the injured side. Average disease duration after onset and K-MMSE score were 2.50±1.41 months and 24.75±2.37 points, respectively (Table 1). CG included 3 men and 5 women, with an average age of 70.75±12.34 years. Brain injury types is 3 cerebral hemorrhage, 5 cerebral infarctions, 6 right hemiparesis, 2 left hemiplegia on the injured side. Average disease duration and K-MMSE score were 2.50±3.85 months and 27.00±2.77 points, respectively (Table 1).

Table 1. General characteristics of subjects.

Variables		EG (N=8)	CG (N=8)
Gender	Male	6(75%)	3(37.5%)
	Female	2(25%)	5(62.5%)
Age (years)		73.13±13.92	70.75±12.34
Side of stroke	Right	5(62.5%)	6(75%)
	Left	3(27.5%)	2(25%)
Type of stroke	Hemorrhage	2(25%)	3(37.5%)
	Infarction	6(75%)	5(62.5%)
Time from stroke to rehab (months)		2.50±1.41	2.5±3.85
K-MMSE (score)		24.75±2.37	27.±2.77

M±SD M: mean SD: standard deviation, EG: experimental group, CG: control group, K-MMSE: korean version mini-mental state examination

3.2. Comparison of changes upper limb function and activities of daily living before and after of intervention in two groups

3.2.1. Results of the FMA, MAS, and MBI in the two groups

Comparison of FMA before and after intervention within two groups revealed that EG changed from 61.75±9.40 to 88.88±5.38 points before and after intervention, respectively. MAS changed from 0.75 ± 0.46 to 0 ± 0 points before and after intervention, respectively. MBI changed from 53.75 ± 6.98 to 78.50±13.19 points before and after intervention, respectively. This difference was significant (p<0.05). In the CG, FMA increased to 74.13±12.14 and 76.87±13.46 points in pre and post intervention evaluation, respectively, MAS decreased to 0.38±0.51 and 0.25±0.46 points in pre and post intervention evaluation, respectively; MBI increased to 60.88±9.83 to 63.63±10.91 points in pre and post intervention evaluation, respectively. FMA and MBI both showed a significant difference (p<0.05), but MAS did not show a significant difference (p>0.05) (Table 2).

3.3. Comparison of changes upper limb function and activities of daily living after intervention between two groups

3.3.1. Comparison of the FMA, MAS, and MBI after intervention between two groups

Comparison of post intervention FMA, MAS, and MBI scores between two groups showed significant differences in all assessments (p<0.001, p<0.05, and p<0.001) (Table 3).

4. Discussion

The recovery of UL function after stroke is an important factor in returning to daily life, including productive and leisure activities. Approximately 70 % of patients with stroke experience a decline in their quality of life due to difficulties with independent ADLs and frustration with returning to daily life due to impaired UL function, which poses great difficulties in rehabilitation [18]. The independence and efficiency of daily tasks, such as washing the face, eating, and dressing, depends on the degree of recovery of UL function, which determine patient quality and level of life [19]. Pollock et al. (2014), examined UL interventions for patients with stroke, including neurodevelopmental treatment (NDT), non-invasive brain stimulation, and image training as treatments for UL functional recovery. Specifically, they analyzed robot therapy, constraint-induced movement therapy (CIMT), bilateral arm training, and mirror therapy were as interventions [20]. They divided 16 patients with stroke were randomly divided patients with stroke into experimental and control groups. In the EG, 1 Hz LF-rTMS and ULRT were combined, while TOT and ULRT were combined in the CG. After the intervention, changes in UL function and ADL were evaluated. UL function changed within two groups pre- and post-intervention. The FMA was different in both groups, while the MAS scores were only different in the EG. Differences in ADLs were confirmed before and after the intervention in both groups. Previous studies have reported improvements in UL motor function through robotic therapy. Rodgers et al.

Table 2. Comparison of upper limb function and activities of daily living in two groups.

Variables		Groups	Pre-test	Post-test	Z	p
Upper limb function	FMA (score)	EG	61.75±9.40	88.88±5.38	-2.524	0.012*
		CG	74.13±12.14	76.87±13.46	-2.226	0.026*
	MAS (score)	EG	0.75±0.46	0.±0.	-2.449	0.014*
		CG	0.38±0.51	0.25±0.46	-1.000	0.317
Activities of daily living	MBI (score)	EG	53.75±6.98	78.5±13.19	-2.524	0.012*
		CG	60.88±9.83	63.63±10.91	-2.070	0.038*

M±SD M: mean SD: standard deviation, $^{*}p$<.05
EG: experimental group, CG: control group, FMA: fugl-meyer assessment, MAS: modified ashworth scale, MBI: modified barthel index

Table 3. Comparison of upper limb function and activities of daily living between two groups.

Variables		EG (N=8)	CG (N=8)	Z	p
Upper limb function	FMA (score)	27.13±6.12	2.75±3.15	-3.376	0.000***
	MAS (score)	0.75±0.46	0.13±0.35	-2.440	0.038*
Activities of daily living	MBI (score)	23.75±8.41	2.75±3.37	-3.386	0.000***

M±SD M: mean SD: standard deviation, * p<.05, *** p<.001
EG: experimental group, CG: control group, FMA: fugl-meyer assessment, MAS: modified ashworth scale, MBI: modified barthel index

(2019) reported that robotic therapy was effective in improving UL function in patients with stroke in a randomized controlled study [21]. The results of this study were the same as those of previous studies for both groups particularly, the EG showed effects on more items. For this reason, it is concluded that ULRT is helpful in repeating simple movements but lacks elements in connecting and motivating the planning and execution of movements through active movement and sensory recognition of the subject's center. To maximize the shortcomings of robotic therapy, finding new methods or attempting approaches combined with other interventions is considered a particularly important factor in recovering a patient's UL function. Comparison of FMA, MAS, and MBI after the intervention between two groups revealed that the EG showed more effective results than did the CG. Based on these results, stimulation of the cerebral cortex through rTMS and ULRT may possibly be more helpful in recovering UL motor function and ADL. In a previous study, more positive functional recovery was expected when the residual effects after rTMS were combined with other UL intervention [22]. Based on these studies, stimulation of the cerebral cortex through rTMS may be more effective in connecting concurrent intervention, which agree with our results that showed changes in both groups. However, the effect on the than that of the CG. ULRT alone can affect UL motor function and ADLs. UL robot-assisted rehabilitation involves repetition of simple movements, in order to improve UL function and subsequently the performance of ADLs in patients with stroke, rendering it difficult to connect the movements with the ADLs desired by the patient [23]. Therefore, it is believed that ULRT with rTMS and various traditional UL intervention can effectively contribute not only to UL motor function but also to the functional activities required by the patient. Among them, it is believed that effectiveness can be improved if combined with noninvasive interventions, such as rTMS, which can directly stimulate the cerebral cortex. This study has few limitations. Generalizing the results was challenging, owing to the small number of subjects, so was controlling for other treatments during the intervention process. Future research should focus on clarifying the basis of these results by including a larger number of subjects and different treatments.

5. Conclusion

In this study, we investigated the effects of ULRT combined with 1 Hz LF-rTMS on UL function and ADLs in patients with stroke. Comparison of the results within two groups in this study revealed that significant differences of EG in FMA, MAS, and MBI ($p<0.05$), while CG showed significant differences in FMA and MBI ($p<0.05$). A comparison between two groups revealed significant differences in their FMA, MAS, and MBI scores ($p<0.05$) ($p<0.001$). These results confirm that ULRT combined with 1 Hz LF-rTMS can increase the positive effect on UL function and ADLs in patients with stroke, compared with ULRT combined with TOT.

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