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Modulation of Neural Excitability by Repetitive Transcranial Magnetic Stimulation: Effects on Dexterity and Motor Function in Subacute Stroke

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This study aimed to investigate the effects of low-frequency rTMS applied to the unaffected hemisphere on upper extremity motor function in stroke patients. This study employed a randomized, double-blind, controlled experimental design. A total of 20 participants were randomly assigned to either the experimental group (n = 10) or the control group (n = 10). The experimental group received 20 minutes of rTMS followed by 20 minutes of conventional physical therapy, whereas the control group received 20 minutes of sham stimulation followed by the same conventional physical therapy. Both interventions were structured as 40-minute sessions conducted five times per week for 4 weeks, totaling 20 sessions. In this study, the following clinical assessment tools were used to objectively evaluate upper extremity motor function and hand dexterity in the participants. The Box and Block Test (BBT) was used to assess hand dexterity. The Jebsen–Taylor Hand Function Test (JTHFT) was used to evaluate functional hand performance in activities of daily living. In addition, overall upper extremity motor recovery was assessed using the Fugl–Meyer Assessment for the Upper Extremity (FMA-UE), based on Brunnstrom's stages of motor recovery. Within-group analysis revealed that the experimental group showed significant improvements in BBT and JTHFT scores compared with baseline ($p<0.05$). In contrast, the control group showed no significant changes in any outcome measures ($p>0.05$). Between-group comparisons showed that the experimental group demonstrated significantly greater improvements in BBT and JTHFT scores than the control group ($p<0.05$). These findings suggest that rTMS may be an effective intervention for improving upper extremity function in patients with stroke.

Keywords : repetitive transcranial magnetic stimulation, hand dexterity, primary motor cortex, neuroplasticity

1. Introduction

Stroke is caused by sudden pathological damage to the central nervous system [1]. After stroke onset, patients may experience spasticity, cognitive decline, and motor and sensory impairments, which consequently lead to permanent limitations in performing activities of daily living (ADL) [1]. According to the World Health Organization (WHO), approximately 70% of stroke survivors experience motor dysfunction, and overcoming these impairments is an essential clinical goal for successful social reintegration and functional independence [2].

The most common motor deficit following stroke is hemiplegia, defined as the loss of motor control in the face and the upper and lower extremities contralateral to the brain lesion [3]. Patients with hemiplegia often present with neurological symptoms such as increased muscle tone and hyperactive deep tendon reflexes, which significantly impede their ability to perform independent movements [3]. Among affected body regions, recovery of motor function in the upper extremities is generally poorer than in the lower extremities. Previous studies report that 60–70% of stroke survivors experience upper extremity dysfunction, with more than 30% exhibiting severe motor paralysis [3]. These hemiplegic symptoms, which typically manifest early after onset, carry a high risk of becoming permanent disabilities if appropriate rehabilitation is not provided in a timely manner [4].

Impairment of fine motor performance in the hand is associated with damage to the primary motor cortex and the corticospinal tract [5]. The corticospinal tract is a major descending pathway originating in the primary motor cortex, decussating in the medulla oblongata, and controlling fine and fractionated movements of the contralateral upper limb [6]. However, in patients with extensive brain damage, motor-related neural activity in

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the unaffected hemisphere increases to compensate for functional deficits in the affected hemisphere during movement of the paretic upper limb [7]. Therefore, there is a need to develop effective rehabilitation strategies that minimize stroke sequelae and promote recovery of upper limb function. In this context, repetitive transcranial magnetic stimulation (rTMS) is attracting attention as a key intervention technique that non-invasively activates the patient's motor neural network. Clinically, rTMS promotes neuroplasticity in the affected hemisphere, thereby improving impaired upper limb motor function [8]. The mechanisms of rTMS that aid in the functional recovery of stroke patients are commonly explained by two main perspectives: the interhemispheric inhibition (IHI) model, which emphasizes on controlling the interaction between cerebral hemispheres through the corpus callosum [9], and the compensation model, in which neurons and astrocytes in the unaffected hemisphere build new neural networks to take over the role of the damaged regions [10]. In actual clinical application results, rTMS has induced improvement in upper limb function through the modulation of motor evoked potentials (MEP), and numerous studies have demonstrated that when low-frequency rTMS was applied to subacute stroke patients, hand function improved significantly [11].

One of the major factors hindering recovery of upper extremity function after stroke is interhemispheric imbalance caused by the phenomenon of interhemispheric inhibition (IHI). Excessive activation of the unaffected hemisphere leads to abnormal inhibition of the affected hemisphere, thereby delaying functional recovery. Low-frequency (≤1 Hz) rTMS applied to the unaffected hemisphere can reduce this excessive inhibition and facilitate neuroplasticity, highlighting its clinical relevance as a rehabilitation intervention to improve upper extremity motor function [11]. Therefore, this study aimed to investigate the effects of low-frequency rTMS applied to the unaffected hemisphere on upper extremity motor function in stroke patients. Through this, we aim to maximize hand function in stroke patients and provide evidence for a safe and effective neurorehabilitation protocol applicable in clinical practice.

2. Materials and Methods

2.1. Participants

This study included 20 stroke patients with upper extremity dysfunction. The inclusion criteria were as follows: (1) patients with a lesion in the middle cerebral artery (MCA) territory, (2) those within 1–3 months of stroke onset, (3) those without cognitive impairment, defined as a Mini-Mental State Examination–Korea (MMSE-K) score ≥24.

The exclusion criteria included patients with apraxia, neglect, visual field deficits, or contraindications to TMS (e.g., pacemakers, intracranial metallic implants, or a history of epilepsy). The required sample size was calculated using G*Power version 3.1.9. Based on an independent samples t-test with a significance level (α) of 0.05, statistical power ($1-\beta$) of 0.95, and an effect size of 0.66, a minimum of 16 participants was required. Considering a 25% dropout rate, Twenty participants were recruited and randomly allocated to either the experimental group (n = 10) or the control group (n = 10). Selection bias was minimized using a computer-generated randomization table to assign participants to each group. In addition, neither the participants nor the evaluators were aware of the group assignments, thereby preventing expectation effects or observer bias from influencing the study results. The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

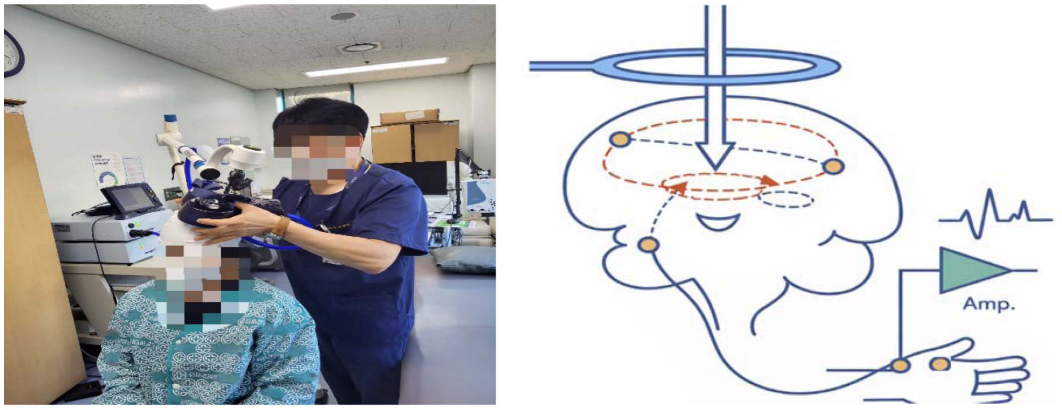
2.2. Study design

This study employed a randomized, double-blind, controlled experimental design. A total of 20 participants were randomly assigned to either the experimental group (n = 10) or the control group (n = 10). The experimental group received 20 minutes of rTMS followed by 20 minutes of conventional physical therapy, whereas the control group received 20 minutes of sham stimulation followed by the same conventional physical therapy. Both interventions were structured as 40-minute sessions conducted five times per week for 4 weeks, totaling 20 sessions.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation (rTMS)

rTMS was delivered using a figure-of-eight coil with a diameter of 70 mm (Magstim Super Rapid Transcranial Magnetic Stimulator, Magstim Company Ltd., Whitland, UK). Participants wore a standard EEG cap, and stimulation was applied to the same cortical region across sessions according to the International 10–20 system [12]. The resting motor threshold (RMT) was defined as the minimum stimulation intensity required to elicit motor evoked potentials (MEPs) of ≥50 μV in at least 5 out of 10 trials while the target muscle was at fully relaxed. MEPs were recorded using surface electrodes placed over the first dorsal interosseous muscle contralateral to the stimulated hemisphere. Stimulation was applied to the primary motor cortex (M1) at 110% of the RMT. Low-



rTMS intervention Mechanism of magnetic stimulation

Fig. 1. Description of rTMS intervention procedures and equipment.

frequency stimulation (1 Hz) was applied to the M1 of the unaffected hemisphere (Fig. 1). Each train consisted of 10 seconds of stimulation followed by a 2-second inter-train interval. A total of 1,000 pulses were delivered per session. The total stimulation time per session was 20 minutes, including the inter-train intervals [13]. Sham stimulation was administered to the control group. To minimize visual perception, participants were instructed to close their eyes, and then device noise identical to that produced during actual rTMS application was provided. In addition, the direction of the stimulation coil was rotated 90° from the scalp surface, designed so that the magnetic field stimulation would not substantially reach the cerebral cortex.

2.4. Outcome measure

In this study, the following clinical assessment tools were used to objectively evaluate upper extremity motor function and hand dexterity in the participants. The Box and Block Test (BBT) was used to assess hand dexterity. The Jebsen–Taylor Hand Function Test (JTHFT) was used to evaluate functional hand performance in activities of daily living. In addition, overall upper extremity motor recovery was assessed using the Fugl–Meyer Assessment for the Upper Extremity (FMA-UE), based on Brunnstrom's stages of motor recovery.

2.4.1. Box and Block Test (BBT)

The Box and Block Test (BBT) is a standardized assessment used to evaluate hand dexterity. It is widely used to assess manual dexterity in individuals with stroke or other neurological conditions. The test consists of a wooden box (290 mm in length) divided into two compartments by a partition and 150 wooden blocks. Hand performance is quantified by counting the number of blocks transferred from one compartment to the other within 1 minute. The test–retest reliability of the BBT is high (r = 0.98) [14].

2.4.2. Jebsen–Taylor Hand Function Test

The JTHFT evaluates hand function by measuring the time required to perform standardized tasks and is useful for assessing hand dexterity and functional use. This test consists of seven tasks: writing a sentence, turning over cards, picking up small objects (e.g., paper clips, bottle caps, coins), simulated feeding, stacking checkers, and moving large light and heavy objects. In this study, the time required to complete each task, except for the writing task, was recorded in seconds. The total time was calculated by summing the performance times across tasks, with shorter times indicating better hand function. The test–retest reliability is high (r = 0.99) [15].

2.4.3. Fugl-Meyer Motor Assessment Upper Extremity (FMA-UE)

The FMA-UE is based on Brunnstrom's stages of motor recovery and assesses motor function by evaluating movement patterns and the ability to perform isolated movements outside of abnormal synergies. The FMA-UE motor domain has a maximum score of 66 points, consisting of subscales for the shoulder/elbow/forearm (36 points), wrist (10 points), hand (14 points), and coordination/speed (6 points). Higher scores indicate better upper extremity motor function and greater neurological recovery. The FMA-UE demonstrates high inter-rater reliability (r = 0.95) [16].

All data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess the normality of the data. An independent samples t-test was used to compare

post-intervention differences between groups, and a paired samples t-test was used to assess within-group changes before and after the intervention. Descriptive statistics are presented as mean ± standard deviation (SD). The significance level (α) was set at 0.05.

3. Results and Discussions

A baseline homogeneity test showed no significant differences in general characteristics between the experimental and control groups ($p>0.05$) (Table 1). Within-group and between-group analyses were conducted to evaluate changes in upper extremity function following the intervention. Within-group analysis revealed that the experimental group showed significant improvements in BBT and JTHFT scores compared with baseline ($p<0.05$). In contrast, the control group showed no significant changes in any outcome measures ($p>0.05$). Between-group comparisons showed that the experimental group demonstrated significantly greater improvements in BBT and JTHFT scores than the control group ($p<0.05$). In addition, there was no significant difference in FMA-UE scores between the two groups ($p>0.05$) (Table 2). Post-stroke interhemispheric imbalance contributes to impaired upper limb and hand function, which in turn reduces independence in activities of daily living and quality of life. To address these deficits, rTMS has been widely used as a non-invasive neuromodulation technique that enhances cortical plasticity by regulating motor cortex excitability.

The effects of rTMS are commonly explained by the interhemispheric inhibition (IHI) model, which describes abnormal inhibitory interactions between the affected and unaffected hemispheres after stroke. According to this mechanism, two main strategies are applied to restore the neurological balance of the brain [17]. First, applying low-frequency (1 Hz) stimulation to the unaffected cerebral hemisphere to down-regulate excessive excitability blocks abnormal inhibitory signals directed toward the affected side, resulting in a disinhibition effect that increases the activity of the affected cerebral hemisphere [17]. Second, applying high-frequency (10 Hz) stimulation to the affected cerebral hemisphere to promote motor cortex excitability restores the inhibitory capacity of the affected cerebral hemisphere, allowing normal inhibitory signals to be transmitted toward the unaffected side, thereby reducing pathological hyperexcitability of the unaffected side [18].

The improvements in upper limb function observed in this study may be attributed to the rebalancing of cortical excitability induced by low-frequency rTMS. These findings suggest that rTMS may facilitate functional recovery by restoring interhemispheric balance.

Previous studies have reported that combining 1 Hz rTMS with mental practice significantly improves upper limb function, as measured by BBT, FMA-UE, and WMFT [19]. Numerous prior studies consistently support the clinical efficacy of Low-Frequency rTMS improving upper limb function after stroke. Another study demonstrated that the application of LF-rTMS to the unaffected primary motor cortex (M1) of acute stroke patients resulted in significant functional improvements in JTHFT and Pinch grip indices compared to the control group [20]. These clinical improvements are explained by changes in neurophysiological mechanisms between the cerebral hemispheres. According to a meta-analysis of

Table 1. General characteristics of participants (N=20).

	EG (n=10)	CG (n=10)	*p*
Age (years)	67.10±4.41[a]	66.50±5.40	0.78
Sex (male/female)	5/5	6/4	0.67
Disease duration (month)	1.70±0.82	2.00±0.82	0.42
Type of stroke (Infarction/Hemorrhage)	6/4	6/4	1.00

[a]Mean±SD, EG: repetitive transcranial magnetic stimulation, CG: Sham Therapy

Table 2. Comparison of upper limb function between the two group. (N=20)

	EG(n=10)	CG(n=10)	t	*p*
Box and Block Test (Number of blocks)				
Pre-test	22.60±2.95	23.00±3.80	-0.26	0.79
Post-test	30.50±7.99	24.30±3.47	2.25	0.37*
Difference value	7.90±8.52	1.30±5.15	-6.07	0.00**
t	-4.25	-0.89		
p	0.00**	0.39		
Jebsen–Taylor Hand Function Test (Second)				
Pre-test	44.70±3.92	46.40±5.08	-0.83	0.41
Post-test	39.00±5.52	45.30±6.63	-2.30	0.03*
Difference value	5.70±6.77	1.10±8.35	-0.09	0.92
t	3.47	0.46		
p	0.00**	0.65		
Fugl-Meyer Motor Assessment Upper Extremity (Score)				
Pre-test	28.20±6.23	29.50±5.68	-0.48	0.63
Post-test	32.10±7.23	31.10±7.20	0.31	0.76
Difference value	3.90±9.54	1.60±9.17	-3.04	0.14
t	-1.66	-0.97		
p	0.13	0.35		

[a]Mean±SD, EG: repetitive transcranial magnetic stimulation CG: Sham Therapy, * $p < 0.05$, ** $p < 0.01$

prior studies on rTMS, LF-rTMS applied to the unaffected cerebral hemisphere was found to significantly inhibit MEP in that region while simultaneously promoting excitability in the affected cerebral hemisphere [21, 22, 24]. Additionally, neurophysiological studies using EEG have reported that the modulatory effects of rTMS persist beyond the stimulation period and may accumulate with repeated sessions [22, 23, 25].

The limitations of this study are as follows. First, although the improvement in upper extremity function was investigated through the mechanisms of IHI and cortical excitability rebalancing, objective neurophysiological evaluation indicators such as EEG or fMRI were not directly collected. Consequently, the causal relationship between clinical improvement and actual changes in brain plasticity could not be directly cross-verified. Second, only short-term effects after intervention were assessed, and long-term follow-up was not performed. Therefore, the results of this study alone have limitations in determining whether functional improvement following rTMS intervention is sustained over the long term. Third, subgroup analysis was not performed to subdivide various clinical characteristics, such as the duration of stroke onset and the location and type of lesion (infarction/hemorrhage). Fourth, the small sample size limits the generalizability of the findings to the broader population of stroke patients. Future studies should incorporate objective neurophysiological assessments and long-term follow-up designs to better elucidate the mechanisms underlying rTMS effects and their sustainability.

4. Conclusion

In the present study, the control group receiving conventional physical therapy alone showed no significant changes in the BBT or JTHFT, whereas the experimental group receiving rTMS demonstrated significant improvements in both outcomes. In particular, given that BBT and JTHFT are tests that verify improvements in actual upper limb functions such as hand dexterity, manipulation ability, and task execution speed, these findings suggest that the application of rTMS may observable functional improvements in clinical practice, rather than being limited to simple neurophysiological changes. This holds significant clinical value as it can be linked to the enhancement of daily living activities and functional independence, which are key goals in the rehabilitation of stroke patients. Furthermore, These findings suggest that rTMS may provide enhanced recovery opportunities for patients whose upper limb functional recovery is delayed or stagnant, and that it can be utilized as an adjunctive intervention to improve the efficiency of rehabilitation therapy. Therefore, in future clinical practice, the selective application of rTMS taking into account the patient's lesion location, degree of paralysis, and stage of recovery may contribute to the development of more individualized rehabilitation programs.

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