

# The effects of additional electrical stimulation combined with repetitive transcranial magnetic stimulation and motor imagery on upper extremity motor recovery in the subacute period after stroke

## A preliminary study

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### Abstract

**Background:** To evaluate the therapeutic effects of additional electrical stimulation (ES) combined with low frequency (LF)-repetitive transcranial magnetic stimulation (rTMS) and motor imagery (MI) training on upper extremity (UE) motor function following stroke.

**Methods:** The participants with subacute stroke in the experimental group (n=8) received LF rTMS + MI + active ES interventions, and those in control group (n=9) received LF rTMS + MI + sham ES interventions. Interventions were performed 5 days a week for 2 weeks, for a total of 10 sessions. All participants were given the same dosage of conventional rehabilitation during the study period. The primary outcome measure was the UE Fugl-Meyer Assessment (FMA). The secondary outcome measures were the shoulder abduction and finger extension scores, modified Barthel Index, Purdue Pegboard Test, and finger tapping test. All scores were measured before and just after the intervention.

**Results:** After the 2-week intervention period, the FMA and modified Barthel Index scores were improved in both groups compared to baseline assessment ( $P < .001$  in the experimental group and  $P = .008$  in the control group). Of note, the change in FMA scores was significantly higher in the experimental group compared with that of the control group ( $P = .04$ ).

**Conclusion:** These results suggest that the use of LF rTMS + MI combined with additional ES lead to greater improvement of UE motor function after stroke. As such, this intervention may be a promising adjuvant therapy in UE motor training.

**Abbreviations:** ES = electrical stimulation, FMA = Fugl-Meyer Assessment, FTT = finger tapping test, LF = low frequency, MBI = modified Barthel Index, MEP = motor evoked potential, MI = motor imagery, OT = occupational therapy, rTMS = repetitive transcranial magnetic stimulation, UE = upper extremity.

**Keywords:** electrical stimulation, motor imagery, repetitive transcranial magnetic stimulation, stroke, upper extremity

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## 1. Introduction

Stroke remains a leading cause of long-term disability worldwide despite recent decreases in its mortality rate.<sup>[1]</sup> Hemiplegia of an upper extremity (UE) is one of the most common impairments after stroke, affecting more than 80% of patients in the acute stage and more than 40% of patients in the chronic stage of stroke.<sup>[2]</sup> UE motor deficits will affect a variety of activities of daily living, and can even limit participation in social activities.<sup>[3]</sup>

Since it is generally known that the recovery of UE motor function after stroke is often incomplete and its prognosis is poor,<sup>[4]</sup> therapeutic advancements to enhance UE motor recovery from an early stage after stroke have been made in recent decades.<sup>[5]</sup> Repetitive transcranial magnetic stimulation (rTMS) is a widely used, non-invasive brain stimulation technique.<sup>[6]</sup> Low frequency (LF)-rTMS, which uses frequency lower than 1 Hz to suppress the neuronal excitability of the brain, modulates stroke-induced dysbalanced inter-hemispheric interactions. A recent meta-analysis supported the therapeutic potential of LF-rTMS to facilitate UE functional improvement after stroke.<sup>[7]</sup> Furthermore, non-invasive neuromodulation combined with UE rehabilitation interventions can synergistically enhance UE movement function following stroke.<sup>[6,8]</sup> The techniques that can be applied

simultaneously with rTMS include motor imagery (MI) training, action observation, virtual reality, and electrical stimulation (ES). For example, MI training is a therapy modality during which the participant mentally rehearses movements without actually executing them.<sup>[5]</sup> It is effective in improving the quality and degree of movement of the hemiplegic UE when used in conjunction with arm rehabilitation by inducing neuronal activity and plasticity in the motor cortex.<sup>[9]</sup> In addition, ES has been used as a complementary therapeutic modality during neurorehabilitation.<sup>[10]</sup> Sensory-level ES increases corticomotoneuronal excitability and induces motor cortical plasticity, most likely by acting somatotopically in the motor cortex. Moreover, ES modulates GABAergic cortical function by decreasing cortical GABAergic inhibition.<sup>[11]</sup> A systematic review by Laufer and Elboim-Gabyzon<sup>[12]</sup> concluded that sensory transcutaneous ES may be helpful for motor recovery in stroke patients.

Pan et al.<sup>[13]</sup> found that the combination of LF-rTMS with an MI protocol followed by conventional rehabilitation was more effective for recovery of UE motor function compared with LF-rTMS with conventional rehabilitation alone in patients with chronic stroke. To facilitate MI, it is important that participants receive accurate feedback regarding their current performance.<sup>[14]</sup> Somatosensory afferent input, such as vibrotactile stimulation and neuromuscular ES, are intrinsically linked to motor learning and play important roles in building the internal body representation necessary for MI.<sup>[15]</sup> For example, Corbet et al.<sup>[16]</sup> demonstrated that ES can foster MI performance by providing vital feedback information.

Given these data, we hypothesized that additional ES during LF-rTMS + MI would be more beneficial for hemiplegic UE motor recovery following stroke when compared with LF-rTMS + MI alone. Therefore, we aimed to investigate the additional effect of ES treatment during LF-rTMS with MI on the recovery of poststroke hemiplegic UEs in the subacute period after stroke.

## 2. Methods

### 2.1. Participants

Participants were prospectively recruited from the rehabilitation department between October 2019 and July 2020. The inclusion criteria were as follows: first-ever stroke diagnosed by computed tomography or magnetic resonance imaging; the period of 1 week to 3 months from stroke onset (the subacute stroke phase); age 20 years or older; absence of previous known UE functional impairments; Mini Mental State Examination score 20 or more<sup>[17]</sup>; and signed written informed consent. The exclusion criteria were as follows: medically unstable conditions (cardio-pulmonary disorders or severe liver or kidney insufficiency); stroke lesion in the parietal lobe; aphasia, severe cognitive impairment, or history of mental illness; history of seizures in the last month; pregnant; severe visual or hearing impairment; and presence of pacemaker, internal electrode, or metal implants. Study approval was obtained from our Institutional Review Board (IRB No: OC19DESI0115). Written consent forms were obtained from all participants before enrollment in the study. This study was registered with the Clinical Research Information Service (CRIS) of South Korea. (CRIS No: PRE20200910-003)

### 2.2. Study design

This study was a single-blind randomized controlled trial with 2 arms. Block randomization with 2 or more block sizes was

performed by generating random numbers. If eligible participants agreed to participate in the study, they were randomly assigned to 1 of 2 groups: the experimental group: rTMS + audio-based MI + active ES or the control group: rTMS + audio-based MI + sham ES. The intervention was performed 5 days a week for 2 weeks for a total of 10 sessions, and was immediately followed by occupational therapy (OT) for UE motor function training in both groups. All participants underwent the same dosage and standardized program of conventional rehabilitation for an hour twice a day during the study period. Conventional rehabilitation is defined as the physical therapy and OT training typically undergone by patients with stroke in the hospital. Any particular treatment related to MI training was not included in physical therapy or OT.

### 2.3. LF-rTMS

LF-rTMS was applied using a MagPro X100 with a MagOption stimulator (MagVenture, Farum, Denmark) with a standard 8-shaped coil. Participants were seated in a comfortable chair. Each rTMS session consisted of 1200 pulses over 20 minutes. The 1 Hz rTMS was applied over the contralesional hemispheric primary motor cortex (M1) where the largest motor evoked potential (MEP) amplitude in the abductor pollicis brevis muscle was elicited. For the proper stimulation intensity, the resting motor threshold,<sup>[18]</sup> which was the minimum stimulus intensity produced the minimal MEP response of the muscle at rest, was estimated. Then, the intensity of rTMS was set to 90% of the resting motor threshold of the abductor pollicis brevis muscle.

### 2.4. Audio-based MI

Modified audio-based MI training, which was originally designed by Pan et al.,<sup>[13]</sup> consisted of a 20-minute structured session. For the audio-based MI, participants followed audio-recorded instructions telling them to imagine UE motions and daily movements. MI training was simultaneously performed with rTMS in a quiet environment. Prior to MI training, an occupational therapist explained the contents of the MI training until all participants fully understood the training.

The contents of the MI instruction were divided into 4 parts, as follows.

1. Imagination preparation (1 minute): participants were encouraged to immerse themselves in an imaginary state. The recorded instructions told participants to close their eyes and breathe deeply to fall into a state of relaxation, and then gradually immerse themselves into a state of imagination.
2. MI warm up (10 minutes): participants spent time imagining performing several joint relaxation activities with their hemiplegic UE (e.g., arm raising, elbow flexion and extension, wrist turning, fist opening and closing, etc).
3. Imagining activities of daily living (10 minutes): participants simulated movements of daily life in their minds (e.g., washing their hands, eating, drinking water, brushing their teeth, buttoning up clothes, etc).
4. Cool down (30 seconds): participants were guided through returning to the real world from the imaginary state.

### 2.5. ES

Active ES in the experimental group and sham ES in the control group was administered during the rTMS + MI sessions. ES was

applied using a Novastim CU-FS1 system (CU Medical Systems, South Korea). The surface electrodes ( $5 \times 5 \text{ cm}^2$ ) were attached on 4 sites on the hemiplegic UE, as shown in Figure 1.<sup>[19]</sup> The pulse length and frequency were set to 1ms and 10Hz, respectively. The intensity of the electrical current was set at an intensity that felt most comfortable to the patient without eliciting visible muscle contractions or pain, and was adjusted according to the sensation reported by each individual participant as to their highest tolerable sensory stimulation. In the experimental group, the stimulus continued throughout the entire intervention time. On the other hand, during sham ES, the stimulus was given only at the first and final 10seconds of treatment to make participants believe that they underwent ES, but for the rest of the time the current intensity was kept at zero.

## 2.6. Outcome measurements

We collected the demographic information and medical history of all participants. Baseline (the day before the first treatment session) and postintervention (immediately after the 2-week intervention period) assessments were conducted by an occupational therapist who was blinded to group allocations. The primary outcome measure was the Fugl-Meyer Assessment (FMA) of the UE (FMA-UE).<sup>[20]</sup> The FMA-UE has a maximum score of 66 and 4 subsections, as follows: shoulder/elbow/forearm; wrist; hand/finger; and coordination. Secondary outcome measures were as follows: hemiplegic shoulder abduction and finger extension score, which is the sum of the Medical Research Council scoring system<sup>[21]</sup>; the modified Barthel Index (MBI)<sup>[22]</sup> for evaluating the activities of daily living; the Purdue Pegboard Test,<sup>[23]</sup> which measures hand dexterity; and the finger tapping test (FTT),<sup>[24]</sup> which measures the motor performance of the UE. Although the Purdue Pegboard Test consists of 4 subtests,

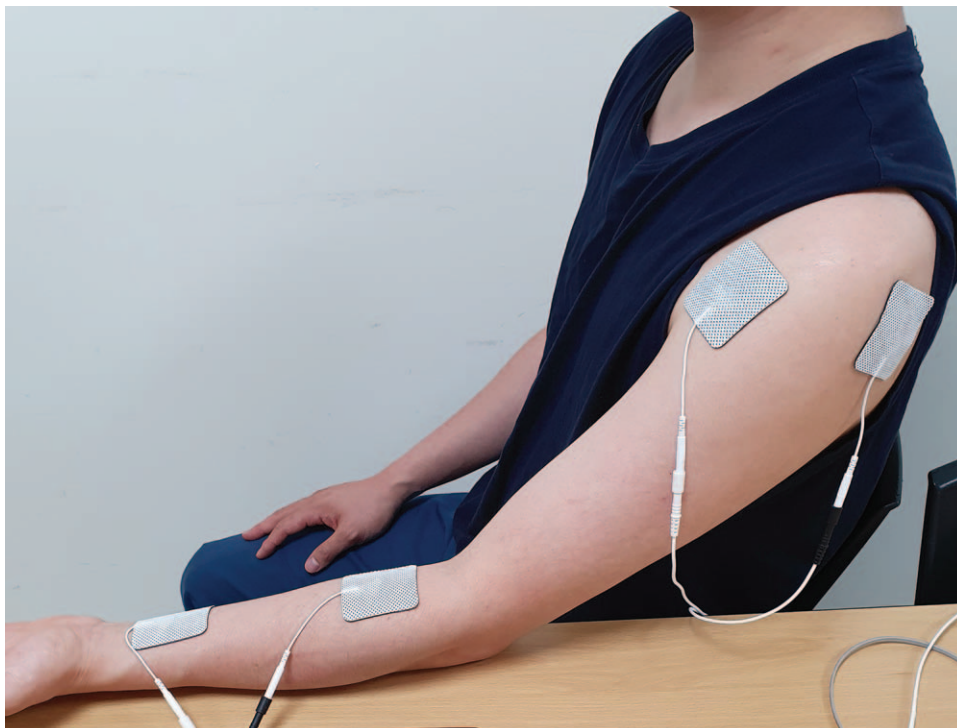
the first 2 subtests are the same task performed first with the dominant and then with the non-dominant hand. Subjects fill holes with pegs initially with their dominant hand for 30seconds, then with their non-dominant hand for 30seconds. Each subtest was repeated 3 times to obtain an average. The test scores equaled the number of filled holes or pieces assembled for each dominant and non-dominant hand. For the modified single-FTT, patients were asked to tap the table with the index fingers of their affected and unaffected hand as fast as possible for a period of 30seconds. FTT scores equaled the number of taps over those 30seconds.

## 2.7. Statistical analysis

Statistical analyses were performed by an independent statistician who was blinded to group assignment. Results were presented as means  $\pm$  standard deviations. For continuous variables, the Wilcoxon rank sum test was used to evaluate differences between groups, while the Chi-square test was used for categorical variables. Differences in mean differences within each group were compared using Wilcoxon signed rank sum test. The Wilcoxon rank sum test was used to test for differences between pre- and postintervention. Statistical analyses were conducted using SAS ver.9.4 for Microsoft Windows (SAS Institute Inc., Cary, NC).  $P \leq .05$  was considered statistically significant.

## 3. Results

Among 21 participants, 20 participants were enrolled after excluding 1 patient who declined to participate in the study. All 20 participants were randomly assigned to 1 of 2 groups. During the intervention period, 3 participants (2 participants in the experimental group and 1 participant in the control group) dropped out due to personal reasons, such as early discharge



**Figure 1.** The placement of electrodes on the upper extremity.

from the hospital. Finally, a total of 17 participants completed the intervention (rTMS+MI+active ES group,  $n=8$ ; rTMS+MI+sham ES group,  $n=9$ ) (Fig. 2). None of the participants experienced any adverse effects during the intervention. The demographic and baseline characteristics of the participants are summarized in Table 1, and there were no significant differences in these data between the experimental and the control groups. Data from the pre- and postintervention assessments are presented in Table 2.

### 3.1. Primary outcome

In both experimental and control groups, postintervention FMA scores were increased compared with those at baseline. The FMA scores of the experimental group changed from  $28.13 \pm 22.69$  to  $39.88 \pm 23.31$  ( $P < .001$ ), while the FMA scores of the control group changed from  $29.78 \pm 20.20$  to  $33.44 \pm 21.68$  ( $P = .008$ ). When comparing the 2 groups, the difference in the pre- and postintervention FMA scores was greater in the experimental group when compared to the control group ( $11.75 \pm 9.11$  vs  $3.67 \pm 3.67$ , respectively;  $P = .04$ ). Among the subcategories of the FMA, the shoulder/elbow/forearm and hand/finger scores were significantly increased after 2 weeks of intervention compared with the baseline scores in both groups ( $P = .019$  and  $P = .004$ ,

respectively) (Table 3). However, only the change in pre- and postintervention FMA scores for the shoulder/elbow/forearm was significantly higher in the experimental group compared to those in the control group ( $P = .03$ ).

### 3.2. Secondary outcome

The postintervention shoulder abduction and finger extension scores increased from baseline only in the experimental group (from  $4.50 \pm 2.07$  to  $5.63 \pm 1.92$ ;  $P = .007$ ). However, there were no significant differences between the 2 groups in terms of the degree of change between pre- and postintervention scores. After the intervention period, we observed a significant increase in MBI scores in both groups when compared to those at the baseline; scores increased from  $55.38 \pm 14.78$  to  $70.25 \pm 16.25$  ( $P = .001$ ) in the experimental group and from  $49.22 \pm 20.28$  to  $61.22 \pm 18.13$  ( $P < .001$ ) in the control group. However, comparison of the differences in pre- and postintervention MBI scores between 2 groups showed no significant difference. The results of the Purdue Pegboard Test and FTT after the 2-week intervention period were not significantly changed compared to those at baseline in both groups. Furthermore, there were no significant differences in Purdue Pegboard Test scores and FTT scores, or changes in scores after intervention, between the 2 groups.

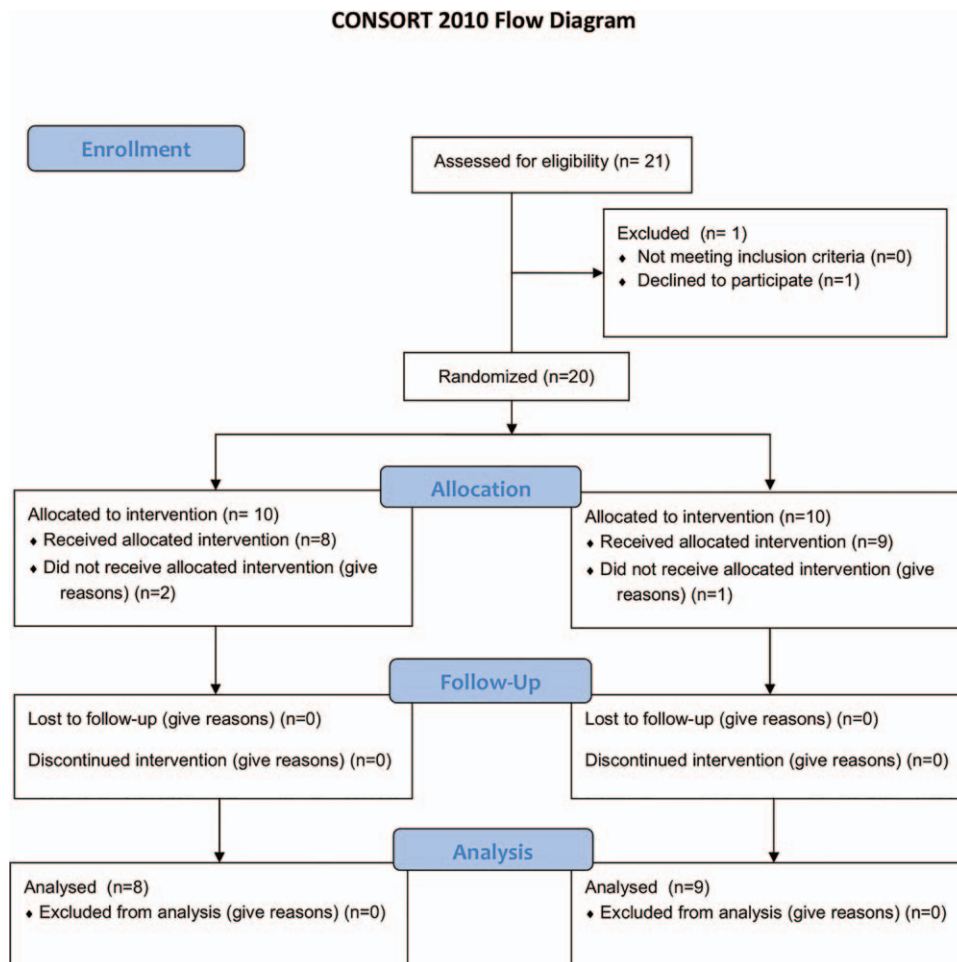


Figure 2. Flow diagram of the trial.

**Table 1****Demographic and baseline characteristics of participants.**

|                              | rTMS + MI + ES<br>(N=8) | rTMS + MI<br>(Control) (N=9) | P value* |
|------------------------------|-------------------------|------------------------------|----------|
| Age                          | 68.50 ± 9.80            | 61.78 ± 9.02                 | .16      |
| Sex (male:female)            | 6:2                     | 4:5                          | .33      |
| Time since stroke (days)     | 24.13 ± 12.46           | 27.89 ± 19.26                | 1.0      |
| Hemiplegic side (right:left) | 6:2                     | 3:6                          | .15      |
| Ischemic vs hemorrhagic      | 8:0                     | 7:2                          | .47      |
| Comorbidities                |                         |                              |          |
| Hypertension N (percentage)  | 7 (87.5)                | 5 (55.6)                     | .29      |
| Diabetes                     | 1 (12.5)                | 5 (55.6)                     | .13      |
| Dyslipidemia                 | 3 (37.5)                | 3 (33.3)                     | 1.0      |
| Atrial fibrillation          | 1 (12.5)                | 0 (0)                        | .47      |
| MMSE                         | 25 ± 2                  | 26.89 ± 1.96                 | .07      |
| FMA                          | 28.13 ± 22.69           | 29.78 ± 20.20                | .88      |
| SAFE MMT                     | 4.50 ± 2.07             | 4.44 ± 1.59                  | .95      |
| MBI                          | 55.38 ± 14.78           | 49.22 ± 20.28                | .49      |
| Purdue Pegboard              | 1.13 ± 1.89             | 1.00 ± 2.12                  | .68      |
| Finger tapping test          | 8.25 ± 10.04            | 7.11 ± 13.07                 | .80      |

ES = electrical stimulation, FMA = Fugl-Meyer Assessment, MBI = modified Barthel index, MI = motor imagery, MMSE = Mini Mental State Examination, rTMS = repetitive transcranial magnetic stimulation, SAFE = sum of the shoulder abduction and finger extension Medical Research Council muscle grades.

\* P value (rTMS + MI + ES group compared with rTMS + MI group).

**4. Discussion**

We performed a preliminary study to investigate if LF-rTMS + MI + ES is more effective for recovery of UE motor function in

**Table 2****Clinical assessments at pre- and postintervention.**

|                     | rTMS + MI + ES (N=8) | rTMS + MI (N=9) | P value* |
|---------------------|----------------------|-----------------|----------|
| FMA                 |                      |                 |          |
| Baseline            | 28.13 ± 22.69        | 29.78 ± 20.20   | .88      |
| Week 2              | 39.88 ± 23.31        | 33.44 ± 21.68   | .56      |
| Change              | 11.75 ± 9.11         | 3.67 ± 3.67     | .04*     |
| P value†            | .009†                | .017†           |          |
| SAFE                |                      |                 |          |
| Baseline            | 4.50 ± 2.07          | 4.44 ± 1.59     | .95      |
| Week 2 MBI          | 5.63 ± 1.92          | 4.89 ± 1.90     | .44      |
| Change              | 1.13 ± 0.83          | 0.44 ± 0.73     | .10      |
| P value†            | .007†                | .25             |          |
| MBI                 |                      |                 |          |
| Baseline            | 55.38 ± 14.78        | 49.22 ± 20.28   | .49      |
| Week 2              | 70.25 ± 16.25        | 61.22 ± 18.13†  | .30      |
| Change              | 14.88 ± 8.01         | 12 ± 6.18       | .42      |
| P value†            | .001†                | <.001†          |          |
| Purdue Pegboard     |                      |                 |          |
| Baseline            | 1.13 ± 1.89          | 1.00 ± 2.12     | .68      |
| Week 2              | 2.75 ± 3.15          | 1.22 ± 2.54     | .16      |
| Change              | 1.63 ± 2.20          | 0.22 ± 0.44     | .16      |
| P value†            | .125                 | .5              |          |
| Finger tapping test |                      |                 |          |
| Baseline            | 8.25 ± 10.04         | 7.11 ± 13.07    | .80      |
| Week 2              | 14 ± 12.57           | 12.11 ± 15.66   | .56      |
| Change              | 5.75 ± 6.63          | 5 ± 4.87        | .76      |
| P value†            | .062                 | .062            |          |

ES = electrical stimulation, FMA = upper extremity Fugl-Meyer Assessment, MBI = modified Barthel index, MI = motor imagery, rTMS = repetitive transcranial magnetic stimulation, SAFE = sum of the shoulder abduction and finger extension Medical Research Council muscle grades.

\* P < .05 (compared with rTMS + MI group).

† P < .05 (compared with baseline).

**Table 3****Changes in FMA subscale scores.**

| FMA subscale              | rTMS + MI + ES (N=8) | rTMS + MI (N=9) | P value* |
|---------------------------|----------------------|-----------------|----------|
| A. Shoulder/elbow/forearm |                      |                 |          |
| Baseline                  | 19.38 ± 13.29        | 20.44 ± 12.70   | .81      |
| Week 2                    | 25.25 ± 12.60        | 21.33 ± 12.85   | .33      |
| Change                    | 5.88 ± 5.49          | 0.89 ± 0.93     | .03*     |
| P value†                  | 0.019†               | 0.062           |          |
| B. Wrist                  |                      |                 |          |
| Baseline                  | 2.50 ± 3.78          | 3.00 ± 3.04     | .71      |
| Week 2                    | 4.38 ± 4.34          | 3.44 ± 3.47     | .55      |
| Change                    | 1.88 ± 2.85          | 0.44 ± 0.88     | .24      |
| P value†                  | 0.125                | 0.500           |          |
| C. Hand/finger            |                      |                 |          |
| Baseline                  | 4.50 ± 5.42          | 4.78 ± 4.71     | .91      |
| Week 2                    | 7.63 ± 5.34          | 6.78 ± 4.94     | .74      |
| Change                    | 3.13 ± 3.44          | 2.00 ± 2.65     | .68      |
| P value†                  | 0.004†               | 0.125           |          |
| D. Coordination           |                      |                 |          |
| Baseline                  | 1.75 ± 1.75          | 1.33 ± 1.41     | .62      |
| Week 2                    | 2.63 ± 2.26          | 1.67 ± 1.41     | .27      |
| Change                    | 0.88 ± 1.36          | 0.33 ± 0.71     | .31      |
| P value†                  | 0.125                | 0.5             |          |

ES = electrical stimulation, FMA = upper extremity Fugl-Meyer Assessment, MI = motor imagery, rTMS = repetitive transcranial magnetic stimulation.

\* P < .05 (compared with rTMS + MI group).

† P < .05 (compared with baseline).

patients with subacute stroke compared to LF-rTMS + MI. Our results showed a significantly greater increase in overall FMA scores after treatment in the experimental group when compared to the control group, indicating the benefit of additional ES when combined with rTMS + MI. To the best of our knowledge, this is the first study to show the positive effects of ES application during rTMS and MI for arm rehabilitation in the subacute period after stroke.

To enhance the effects of the motor learning after stroke, numerous studies have combined rTMS with other therapeutic modalities. Pan et al<sup>[13]</sup> demonstrated combined rTMS and MI facilitate poststroke UE motor recovery. Consistent with those results, we found that the changes in FMA scores between the baseline and postintervention periods were statistically significant in both the experimental group (LF-rTMS + MI + ES) and control group (rTMS + MI). However, when comparing the 2 groups, the change in overall FMA score from baseline to postintervention was significantly higher in the experimental group than in the control group. This result suggests that poststroke UE motor recovery could be enhanced by providing afferent input to the peripheral nerves of the affected UE during MI using ES. Furthermore, given that the minimal clinically important difference value for the FMA in subacute stroke patients is known to range from 9 to 10,<sup>[25]</sup> the changes we observed in FMA scores in the experimental group (11.75 ± 9.11) have clinical significance in the context of stroke UE rehabilitation. In the subcategories of the FMA, both shoulder/elbow/forearm scores and hand/finger scores were significantly improved after 2 weeks of intervention in the experimental group, indicating both proximal and distal motor function had improved. However, the improvement in the shoulder/elbow/forearm FMA subscore seen after the intervention was significantly higher in the experimental group than in the control group. This result reflects that recovery of the proximal UE was

more pronounced in the experimental group than in the control group, and may explain why there were no significant changes between the 2 groups in secondary outcomes requiring not only proximal UE function but also distal hand function.

The importance of intensive OT has been well documented by previous studies.<sup>[26]</sup> In the acute-subacute period after stroke, if actual performance is difficult due to the presence of a not fully recovered hemiplegic UE, neuro-rehabilitation treatment based on the hypothesis of the benefit of activation of neural systems, such as movement observation, mirror therapy, and mental practice with MI, can be an alternative therapy to active range of motion exercise and activities of daily living training.<sup>[27]</sup> Nilsen et al<sup>[28]</sup> and Liu et al<sup>[29]</sup> demonstrated that MI training is beneficial for improving the quality and amount of movement in paretic UEs following stroke when combined with conventional rehabilitation. They concluded that this benefit was achieved via activation of the supplementary and pre-motor areas in control of motor function which are related to the actual movement of the imagined body segment. Furthermore, these treatments have the advantage that they can be administered simultaneously with rTMS, and MI can be applied without any restrictions regardless of the degree of limb function. Noh et al<sup>[30]</sup> reported that rTMS combined with movement observation helps to improve the affected UE's motor function. Similarly, Pan et al<sup>[13]</sup> showed the positive effect of additional MI combined with LF-rTMS on UE function and daily activities. In line with these previous studies, the FMA-UE scores in our study were significantly improved in both groups after completion of a 2-week intervention period.

Several studies have demonstrated that ES helps to facilitate motor recovery following stroke. It has been reported that neuromuscular ES enhances neuroplasticity by activation of the primary motor and sensory cortices and the supplementary motor cortex, reduction of intra-cortical inhibition, and augmentation of MEPs amplitude.<sup>[31]</sup> ES can be used as an adjuvant therapy by providing afferent input to peripheral nerves to enhance the therapeutic effect of MI. For example, Okuyama et al<sup>[32]</sup> found that ES at the motor threshold combined with MI was effective for improving daily activities as well as upper limb motor recovery. They suggested that this MI+ES intervention might be effective on motor recovery by facilitating plastic changes in corticospinal excitability and spinal reciprocal inhibition. Furthermore, LF-rTMS combined with motor level ES yielded better results in improving UE motor function when compared with rTMS alone. ES is a treatment with no applicable restrictions with regards to the degree of paralysis, and has the same advantage as MI in that it can be applied simultaneously with rTMS. Therefore, we chose ES as an additional rehabilitation therapy in conjunction with rTMS+MI to enhance motor recovery and motor learning in the current study. Regarding the electrodes' positions, we attached electrodes to cover a large area of the UE in order to stimulate all somatosensory receptors, including the nerve trunks of the shoulder, elbow, and wrist. It is known that stimulation of a nerve trunk elicits synchronized afferent volleys in the corresponding stimulated body part representation of the primary somatosensory cortex.<sup>[33]</sup> For example, median nerve stimulation increases site-specific signals and representational reorganization in the motor cortex and part of the pre-motor cortex, as well as the primary somatosensory cortex.<sup>[34]</sup>

Functional recovery in most stroke patients is reported to take place in the first 3 months following stroke.<sup>[35]</sup> Considering the

non-linear, logarithmic pattern of the typical neurological recovery seen after stroke, the functional recovery in the chronic phase is limited.<sup>[36]</sup> Therefore, it is necessary to make an effort to maximize the recovery potential of upper limb function in the first 3 months. A meta-analysis investigating the effects of rTMS on poststroke motor function reported that the improvement in UE paralysis was higher in patients in the acute period following stroke rather than in the chronic period.<sup>[37]</sup> Furthermore, previous studies with subacute stroke patients reported that combination therapy of rTMS with action observation<sup>[30]</sup> or virtual reality<sup>[38]</sup> has a positive effect on motor function in the subacute period. Therefore, unlike Pan et al's study of patients with chronic stroke, we included participants with stroke in the subacute period, during which time participants were transferred to a rehabilitation ward in a medically stable state and began an intensive rehabilitation treatment regimen.

There are several limitations to this study. First, the small number of participants who were all enrolled from a single center may affect the statistical significance of our results. However, even with a small sample size, the primary outcome was significant in the present study. Second, because we intended to investigate the effect of additional ES, we did not design a control group with rTMS as the only intervention. Third, we compared only pre-intervention and immediate postintervention test scores; therefore, the long-term effect of intervention is unknown. Finally, we did not perform any neurophysiological studies which could reflect clinical improvement. Therefore, the clinical efficacy of the LF-rTMS+MI+ES intervention reported in the present study needs to be validated through randomized controlled trials with a larger sample size and long-term follow-up. Also, further neurophysiological studies are necessary for understanding the neural mechanisms of cortical plasticity induced by combination therapy.

In conclusion, our results showed that the addition of ES to LF-rTMS+MI treatment seems to improve recovery of motor performance in paretic UEs compared with LF-rTMS+MI alone. Therefore, the combination of LF-rTMS+MI+ES may be a feasible and synergistic rehabilitation strategy in UE motor training for stroke regardless of degree of UE paralysis.

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