Synergistic efficacy of repetitive peripheral magnetic stimulation on central intermittent theta burst stimulation for upper limb function in patients with chronic stroke: a double-blinded, randomized controlled trial

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Research Article

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Abstract

Background: Non-invasive techniques such as central intermittent theta burst stimulation (iTBS) and repetitive peripheral magnetic stimulation (rPMS) have shown promise to improve motor function for stroke patients. However, the combined efficacy of rPMS and central iTBS has not been extensively studied. This randomized controlled trial aimed to investigate the synergistic effects of rPMS on central iTBS in patients with stroke.

Method: In this study, 28 stroke patients were randomly allocated to receive either 1200 pulses of real or sham rPMS on the radial nerve of the affected limb, followed by 1200 pulses of central iTBS on the ipsilesional hemisphere. The patients received the intervention for 10 sessions over two weeks. The primary outcome measures were the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) and the Action Research Arm Test (ARAT). Secondary outcomes for activities and participation included the Functional Independence Measure-Self care (FIM-Self care) and the Stroke Impact Scale (SIS). The outcome measures were assessed before and after the intervention.

Results: Both groups showed significant improvement in FMA-UE and FIM-Self care after the intervention, \( p < 0.05 \). Only the rPMS + iTBS group had significant improvement in ARAT-Grasp, SIS-Strength and SIS-ADL \( p < 0.05 \). However, the change scores in all outcome measures did not differ between two groups.

Conclusions: Overall, the study's findings support that rPMS may have synergistic effects on central iTBS to improve grasp function and participation. In conclusion, these findings highlight the potential of rPMS as an adjuvant therapy for central iTBS in stroke rehabilitation. Further long-term studies are needed to fully investigate the synergistic effects of rPMS on central iTBS.

Trial registration: This trial was registered under ClinicalTrials.gov ID No. NCT04265365, retrospectively registered, on February 11, 2020.

Background

Stroke is a leading cause of death and disability worldwide, with impaired upper limb motor function being a common outcome for stroke survivors. According to the Global Burden of stroke 2013, stroke had become the second most common causes of death (11.8% of all deaths [95% UI, 10.9–13.0%]) and the third most common causes of disability (4.5% of DALYs from all causes [95% UI, 4.1–5.2]) in the world [1]. In 70% of stroke patients, upper limb involvement was responsible for long-term impairment of daily function and activities [5, 6]. The inability to use their affected upper limb for stroke survivors would hinder their independence [3] and limit their participation [4], which led to decreased quality of lives.

Even with traditional neurorehabilitation programs, approximately 50–60% of stroke patients still experience chronic motor limitations [7]. To address this, non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) and central theta burst stimulation (TBS), have been used to treat these patients [8]. Central TBS has been found to have persistent effects on motor evoked potentials (MEPs) [9, 10]. The bimodal balance-recovery model has been proposed as the underlying mechanism for rTMS and TBS [11]. This model combined the concepts of interhemispheric competition and vicariation effects of the intact hemisphere in patients with stroke [11]. The hypothesis posited that there was a reduction in cortical excitability within the impaired hemisphere, accompanied by an increase in transcallosal inhibitory signals originating from the intact
hemisphere [11]. To facilitate cortical excitability in the impaired hemisphere, intermittent TBS (iTBS) is applied, while continuous TBS (cTBS) is utilized to reduce transcallosal inhibitory signals in the intact hemisphere [12]. However, the effects of cTBS on transcallosal inhibitory signals diminish over time, limiting its effectiveness [2]. Therefore, iTBS was selected for central stimulation in this study.

Repetitive peripheral magnetic stimulation (rPMS) is another non-invasive brain stimulation technique that targets the peripheral motor nerve through both direct and indirect activation [13–15]. The transmission of direct activation occurred through the sensorimotor nerve, whereas indirect activation was facilitated by the mechanoreceptor nerve [13–15]. Previous studies have shown elevated motor evoked potential amplitudes of the upper limb after rPMS administration [16–19]. Accordingly, rPMS was proved to induce neuroplasticity and cortical reorganization [13–15]. However, more studies are needed to elucidate its therapeutic effects [20–23].

To date, the majority of studies have focused on examining the effects of integrating rPMS with rehabilitation programs for patients with stroke [22–25]. However, there is a gap in the literature regarding the effects of rPMS on central iTBS in motor function, activities, and participation. Prior research has showed that central iTBS may have more enduring effects than the rTMS in stroke patients [26, 27]. Meanwhile, rPMS has the ability to modulate motor cortical excitability in both the brain and spinal cord [13–15]. The radial nerve was chosen for rPMS administration due to its importance in wrist extension, which is essential for the recovery of skilled hand prehension [45]. Our hypothesis is that radial nerve rPMS has potential synergistic effects on central iTBS over the primary motor cortex to enhance motor function, activities, and participation in patients with upper limb dysfunction following a stroke. This is the first randomized controlled trial investigating the synergistic efficacy of rPMS on central iTBS to treat upper limb dysfunction in stroke survivors.

Method

Participants

Between 2019 and 2021, we recruited 28 stroke patients from the rehabilitation department of Chang Gung Memorial Hospital. We screened 557 patients, but excluded 525 patients. Four patients declined to participate, leaving us with a total of 28 participants. We randomly assigned them to either the rPMS + iTBS group (n = 14) or the sham rPMS + iTBS group (n = 14). The inclusion criteria for the study were as follows: (1) aged between 20 and 80 years; (2) ischemic or hemorrhagic stroke for the first time; and (3) unilateral cerebral stroke with hemiplegia or hemiparesis. The exclusion criteria were as follows: (1) stroke at brainstem or cerebellum; (2) progressive neurodegenerative diseases; (3) history of epilepsy; (4) medical histories of aneurysm and cerebral arteriovenous malformation; (5) patients with active medical problems; (6) active psychiatric disorders; (7) severe cognitive and language impairment; (8) metal implants such as pacemakers, head metal implants, and aneurysm clips; (9) Botox injections in six months; and (10) patients who are pregnant or who are probable pregnant. All patients signed the informed consent prior to the enrollment. The study protocol was executed in accordance with the Declaration of Helsinki and was approved by Chang Gung medical foundation institutional review board. This trial is registered under ClinicalTrials.gov ID No. NCT04265365.

Study design
The study was a prospective double-blinded, randomized, controlled trial. The severity of stroke was stratified according to Brunnström stage [28, 29] before randomly allocating the twenty-eight patients into two groups on the website (https://www.randomizer.org/). Figures 1 and 2 demonstrated the randomized allocation and experimental design, respectively. The patients were asked to relax 5 minutes before, during, and 5 minutes after the stimulation to avoid the effects of physical activities on central iTBS. The patients received 10 courses of central iTBS with real or sham rPMS on consecutive working days for 2 weeks. The rPMS was delivered before central iTBS. Outcome measures were performed 3 days before intervention and after intervention. Patients with any other treatment outside the project should also be documented for variables control. The raters were well trained to administer outcome measures prior to the project after passing competency and reliability test. At least two professional raters blinded to the group assignment performed the outcome measures. The intra-rater and inter-rater reliability were measured by a 10-patient reliability test at 7-day intervals. The intra-rater/inter-rater reliability of the ARAT and FMA-UE was by intra-class correlation (0.986/0.998, 0.984/0.992). The intra-rater reliability of the FIM-Self care and SIS were by intra-class correlation (0.993, 0.956).

[Insert Fig. 1]

[Insert Fig. 2]

**Determination of AMT and RMT**

The study used the TMS protocol to evaluate the AMT (Active Motor Threshold) and RMT (Resting Motor Threshold). The MagPro X100 package (Magventure, USA) was used for magnetic stimulation with a figure-of-eight coil (outer diameter of each wing 7.5cm). Silver/silver chloride (Ag/AgCl) disc electrodes were attached to the FDI (first dorsal interosseous muscles) of the affected limb. The coil was positioned tangentially to the scalp over the motor area of the affected limb in the optimal position to activate the FDI. The handle was held pointing backward and laterally at an angle of 45° to the sagittal plane to generate a posterior-to-anterior current flow in the brain. The point at the scalp that induced the maximum MEP (Motor Evoked Potential) was identified as the motor hot spot [30]. In cases where motor evoked potentials (MEPs) could not be induced, we would identify the motor hot spot by using the mirror site from the unaffected hemisphere [30]. The MEP was recorded using a Multifunctional Response and Stimulus Device (BioPAC Inc, USA). The patients were seated in a comfortable chair with their forearm in a pronated position on the desk. They were instructed to remain relaxed throughout the procedure. The RMT was defined as the minimal intensity of TMS that induced an MEP equal to the 50 uV peak-to-peak amplitude when the FDI was relaxed in at least 5 of 10 consecutive trials. The AMT was defined as the intensity of TMS that induced an MEP equal to the 200 uV peak-to-peak amplitude when the FDI slightly contracted in at least 5 of 10 consecutive trials (10–20% of maximum contraction).

**TBS protocol**

During the study, we administered iTBS to either the affected primary motor cortex as central iTBS or to the radial nerve as rPMS. To deliver central iTBS, we used a hand-held figure-of-eight coil at the motor hot spot of the FDI, while for rPMS, we applied the coil at the radial groove. The true stimulation was given at 80% of active motor threshold (AMT) or 70% of resting motor threshold (RMT). During sham stimulation, we delivered the coil to the same site, but flipped it over and applied it at 60% of AMT. Previous research has shown that TBS with the
intensity lower than 70% of AMT has no effect on MEPs [32]. It is worth noting that approximately 78% of output was elicited by the non-flip side [31], meaning that the sham stimulation delivered approximately 46.8% of AMT.

Each session of iTBS comprised 20 rounds of stimulation. Each round consisted of a 2-second burst at 5 Hz followed by an 8-second period of rest. Each burst contained 3 pulses at 50 Hz, resulting in a total of 600 pulses per session. One session lasted 200 seconds. We administered 2 sessions of iTBS for central iTBS and rPMS with a 10-minute break between sessions. The stimulation was conducted at the same time for five consecutive days per week for two weeks.

### Outcome Measures

The primary outcomes were the improvement in motor function, as reflected by the scores on the upper extremity portion of the Fugl-Meyer Assessment (FMA-UE) and the Action Research Arm Test (ARAT). The FMA-UE is a performance-based scale used to evaluate motor function of upper limbs in patients with stroke [33]. In contrast, the ARAT is composed of 19 items divided into four subsections, including grasp, grip, pinch, and gross movement [34].

The secondary outcomes focused on improvement in activities and participation. Activities were assessed using the self care domain of the Functional Independence Measure (FIM). The self care domain was selected for this study because it comprises six items specifically associated with activities of the upper limb [35].

Participation was evaluated using the Stroke Impact Scale (SIS), a self-report assessment of disability for stroke patients [36]. The SIS includes eight domains: Strength, Hand Function, Activities of Daily Living (ADL), Mobility, Communication, Emotion, Memory and Thinking, and Participation. The scale comprises 59 items that are rated on a 5-point scale, with a score of 5 representing the best performance in participation.

### Statistical analysis

The data were processed by SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Shapiro–Wilk tests were adopted to confirm the assumptions of normal distribution. Due to the lack of normal distribution in some data, we adopted nonparametric methods for data analysis. The demographic and clinical characteristics were analyzed using Chi-square tests for categorical variables and Mann-Whitney U tests for continuous variables. The baseline of outcomes were analyzed using Mann–Whitney U tests. Wilcoxon signed-rank tests were applied to determine whether each group had significant improvement after the intervention. Mann-Whitney U tests were utilized to compare changes between groups (posttest scores - pretest scores) and determine if the rPMS + iTBS intervention yielded better therapeutic effects than the sham rPMS + iTBS group. The significance was pinpointed at 0.05 (one-tailed) and, we adopted T-distribution to determine a 95% confidence interval for small sample size (n < 30).

### Result

The demographic and clinical data did not differ in age, stroke side, stroke location, stroke type, aphasia, MMSE and NIHSS except sex (Table 1). The baseline of outcome measures did not differ between groups (Table 2). All patients well tolerated the intervention without significant adverse effects in the study.
<table>
<thead>
<tr>
<th></th>
<th>rPMS + iTBS</th>
<th>sham rPMS + iTBS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>51.4 ± 12.1</td>
<td>55.6 ± 10.3</td>
<td>0.326</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (28.6%)</td>
<td>11 (78.6%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Female</td>
<td>10 (71.4%)</td>
<td>3 (21.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke side</strong></td>
<td></td>
<td></td>
<td>0.500</td>
</tr>
<tr>
<td>Left</td>
<td>6 (42.9%)</td>
<td>7 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 (57.1%)</td>
<td>7 (50.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke location</strong></td>
<td></td>
<td></td>
<td>0.723</td>
</tr>
<tr>
<td>Subcortical</td>
<td>7 (50.0%)</td>
<td>9 (64.3%)</td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td>6 (42.9%)</td>
<td>4 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>1 (7.1%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke type</strong></td>
<td></td>
<td></td>
<td>0.347</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>8 (57.1%)</td>
<td>10 (71.4%)</td>
<td></td>
</tr>
<tr>
<td>Infarction</td>
<td>6 (42.9%)</td>
<td>4 (28.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aphasia</strong></td>
<td></td>
<td></td>
<td>0.702</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (14.2%)</td>
<td>2 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (85.7%)</td>
<td>12 (85.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>23.4 ± 8.5</td>
<td>27.8 ± 2.8</td>
<td>0.075</td>
</tr>
<tr>
<td><strong>NIHSS</strong></td>
<td>9.9 ± 6.5</td>
<td>8.6 ± 5.3</td>
<td>0.594</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or number (%)

*a* Mann-Whitney U tests; *b* Chi-square tests

**MMSE**: Mini-Mental State Exam; **NIHSS**: National Institutes of Health Stroke Scale
Table 2
Baseline of outcome measure

<table>
<thead>
<tr>
<th></th>
<th>rPMS + iTBS</th>
<th>Sham rPMS + iTBS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA-UE</td>
<td>28.6 ± 21.3</td>
<td>33.4 ± 19.7</td>
<td>0.542</td>
</tr>
<tr>
<td>FIM-Self care</td>
<td>4.2 ± 1.6</td>
<td>4.7 ± 1.4</td>
<td>0.407</td>
</tr>
<tr>
<td>ARAT</td>
<td>19.1 ± 20.9</td>
<td>21.8 ± 23.8</td>
<td>0.758</td>
</tr>
<tr>
<td>ARAT-GM</td>
<td>4.1 ± 2.9</td>
<td>5.0 ± 3.9</td>
<td>0.484</td>
</tr>
<tr>
<td>ARAT-Grasp</td>
<td>6.0 ± 7.3</td>
<td>6.6 ± 7.9</td>
<td>0.825</td>
</tr>
<tr>
<td>ARAT-Grip</td>
<td>4.3 ± 4.8</td>
<td>4.8 ± 5.6</td>
<td>0.801</td>
</tr>
<tr>
<td>ARAT-Pinch</td>
<td>4.8 ± 7.1</td>
<td>5.4 ± 7.6</td>
<td>0.838</td>
</tr>
<tr>
<td>SIS</td>
<td>53.2 ± 11.0</td>
<td>58.9 ± 14.7</td>
<td>0.252</td>
</tr>
<tr>
<td>SIS-S1</td>
<td>29.0 ± 13.8</td>
<td>33.0 ± 14.0</td>
<td>0.450</td>
</tr>
<tr>
<td>SIS-S2</td>
<td>82.7 ± 16.3</td>
<td>85.5 ± 19.0</td>
<td>0.678</td>
</tr>
<tr>
<td>SIS-S3</td>
<td>52.6 ± 12.0</td>
<td>55.0 ± 11.2</td>
<td>0.593</td>
</tr>
<tr>
<td>SIS-S4</td>
<td>83.4 ± 27.8</td>
<td>95.2 ± 7.9</td>
<td>0.150</td>
</tr>
<tr>
<td>SIS-S5</td>
<td>51.3 ± 12.2</td>
<td>54.6 ± 26.0</td>
<td>0.664</td>
</tr>
<tr>
<td>SIS-S6</td>
<td>50.2 ± 25.6</td>
<td>57.7 ± 30.7</td>
<td>0.487</td>
</tr>
<tr>
<td>SIS-S7</td>
<td>23.9 ± 27.8</td>
<td>26.4 ± 35.6</td>
<td>0.838</td>
</tr>
<tr>
<td>SIS-S8</td>
<td>37.7 ± 21.2</td>
<td>48.4 ± 19.8</td>
<td>0.179</td>
</tr>
<tr>
<td>Brunström-UEp</td>
<td>3.5 ± 1.1</td>
<td>3.5 ± 0.9</td>
<td>1.000</td>
</tr>
<tr>
<td>Brunström-UEd</td>
<td>3.3 ± 1.1</td>
<td>3.6 ± 1.4</td>
<td>0.474</td>
</tr>
</tbody>
</table>

Data are assessed by independent two-sample t tests

Data are presented as mean ± standard deviation


[Insert Table 1]

[Insert Table 2]

**Primary outcomes**

**Motor function**
In FMA-UE, both groups had significant improvement after the intervention (rPMS group: \( p = 0.019 \); sham group: \( p = 0.025 \)) (Table 3). However, the change scores did not differ in FMA-UE between groups (\( p = 1.000 \)).

In total ARAT, both groups did not achieve significant improvement after the intervention (Table 3). In Grasp domain of ARAT, only rPMS + iTBS group attained significant improvement. (Grasp domain: rPMS: \( p = 0.013 \); sham group: \( p = 0.107 \)). The change scores did not differ between groups in total ARAT and the four domains of ARAT.

<table>
<thead>
<tr>
<th>Variables</th>
<th>rPMS + central iTBS</th>
<th>sham rPMS + central iTBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Tx</td>
<td>Post-Tx</td>
<td>( p^a )</td>
</tr>
<tr>
<td>FMA-UE</td>
<td>mean ± SD</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>28.6 ± 21.2</td>
<td>~ 40.9</td>
</tr>
<tr>
<td>ARAT</td>
<td>19.1 ± 20.9</td>
<td>~ 31.2</td>
</tr>
<tr>
<td>GM</td>
<td>4.1 ± 2.9</td>
<td>~ 5.8</td>
</tr>
<tr>
<td>Grasp</td>
<td>6.0 ± 7.3</td>
<td>~ 10.2</td>
</tr>
<tr>
<td>Grip</td>
<td>4.3 ± 4.8</td>
<td>~ 7.0</td>
</tr>
<tr>
<td>Pinch</td>
<td>4.8 ± 7.1</td>
<td>~ 8.9</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation

\(^a\) Wilcoxon signed-rank tests; \(^b\) Mann-Whitney U tests

SD: standard deviation, CI: confidence interval

T-distribution was used to compute a 95% CI. Degrees of freedom = 27

FMA-UE: Fugl-Meyer Assessment-Upper Extremity, ARAT: Action Research Arm Test, GM: Gross Movement

\(* p < 0.05\)
Secondary outcomes

Activity

In FIM-Self care, both groups achieved significant improvement after the intervention (rPMS group: $p = 0.013$; sham group: $p = 0.011$). The change scores did not differ between groups ($p = 0.874$).

Participation

In total SIS, both groups did not attain significant improvement after the intervention (rPMS group: $p = 0.064$; sham group: $p = 0.352$). The rPMS + iTBS group had significant improvement in Strength and ADL. The rPMS + iTBS group had borderline improvement in Hand Function. The sham rPMS + iTBS group achieved significant improvement in Mobility. (rPMS group: Strength: $p = 0.019$; ADL: $p = 0.040$; Mobility: $p = 0.346$; Hand Function: $p = 0.050$; sham group: Strength: $p = 0.385$; ADL: $p = 0.430$; Mobility: $p = 0.034$; Hand Function: $p = 0.562$). The change scores did not differ in total SIS and the 8 domains of SIS between groups.

[Insert Table 4]
Table 4
Descriptive and inferential statistics of secondary outcome measures

<table>
<thead>
<tr>
<th>Variables</th>
<th>rPMS + central iTBS</th>
<th>sham rPMS + central iTBS</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Tx</td>
<td>Post-Tx</td>
<td></td>
<td>Pre-Tx</td>
<td>Post-Tx</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>95% CI</td>
<td></td>
<td>mean ± SD</td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIM-Self care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.2 ± 1.6</td>
<td>3.3 ~ 5.1</td>
<td></td>
<td>5.1 ± 0.9</td>
<td>4.0 ~ 5.8</td>
<td></td>
<td>0.013*</td>
<td>4.7 ± 1.4</td>
</tr>
<tr>
<td>SIS</td>
<td>53.2 ± 11.0</td>
<td>46.8 ~ 59.5</td>
<td></td>
<td>66.3 ± 10.8</td>
<td>40.0 ~ 66.2</td>
<td></td>
<td>0.064</td>
<td>58.9 ± 14.7</td>
</tr>
<tr>
<td>SIS-S1</td>
<td>29.0 ± 13.8</td>
<td>21.1 ~ 38.0</td>
<td></td>
<td>44.2 ± 19.8</td>
<td>31.5 ~ 42.6</td>
<td></td>
<td>0.019*</td>
<td>33.0 ± 14.0</td>
</tr>
<tr>
<td>SIS-S2</td>
<td>82.7 ± 16.3</td>
<td>73.3 ~ 92.1</td>
<td></td>
<td>88.1 ± 14.1</td>
<td>68.1 ~ 92.2</td>
<td></td>
<td>0.357</td>
<td>85.5 ± 19.0</td>
</tr>
<tr>
<td>SIS-S3</td>
<td>52.6 ± 12.0</td>
<td>45.7 ~ 59.5</td>
<td></td>
<td>65.9 ± 15.8</td>
<td>50.6 ~ 66.0</td>
<td></td>
<td>0.218</td>
<td>55.0 ± 11.2</td>
</tr>
<tr>
<td>SIS-S4</td>
<td>83.4 ± 27.8</td>
<td>67.4 ~ 99.5</td>
<td></td>
<td>95.5 ± 10.2</td>
<td>63.5 ~ 99.8</td>
<td></td>
<td>0.246</td>
<td>95.2 ± 7.9</td>
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<tr>
<td>SIS-S5</td>
<td>51.3 ± 12.2</td>
<td>44.2 ~ 58.3</td>
<td></td>
<td>63.3 ± 16.4</td>
<td>48.8 ~ 70.2</td>
<td></td>
<td>0.040*</td>
<td>54.6 ± 26.0</td>
</tr>
<tr>
<td>SIS-S6</td>
<td>50.2 ± 25.6</td>
<td>35.4 ~ 65.0</td>
<td></td>
<td>66.1 ± 21.7</td>
<td>40.4 ~ 69.2</td>
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<td>0.346</td>
<td>57.7 ± 30.7</td>
</tr>
<tr>
<td>SIS-S7</td>
<td>23.9 ± 27.8</td>
<td>7.9 ~ 40.0</td>
<td></td>
<td>43.7 ± 33.1</td>
<td>14.9 ~ 56.6</td>
<td></td>
<td>0.050</td>
<td>26.4 ± 35.7</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation

a Wilcoxon signed-rank tests; b Mann-Whitney U tests

SD: standard deviation, CI: confidence interval

T-distribution was used to compute a 95% CI. Degrees of freedom = 27


*p < 0.05
Variables | rPMS + central iTBS | sham rPMS + central iTBS
--- | --- | ---
| Pre-Tx | Post-Tx | $p^a$ | Pre-Tx | Post-Tx | $p^a$ | $p^b$
| SIS-S8 | 37.7 $\pm$ 21.2 | 25.5 $\sim$ 50.0 | 32.0 $\sim$ 50.2 | 0.421 | 48.4 $\pm$ 19.8 | 37.0 $\sim$ 59.9 | 46.7 $\pm$ 25.3 | 32.1 $\sim$ 61.2 | 0.683 | 0.352

Data are presented as mean ± standard deviation

$^a$ Wilcoxon signed-rank tests; $^b$ Mann-Whitney U tests

SD: standard deviation, CI: confidence interval

T-distribution was used to compute a 95% CI. Degrees of freedom = 27


* $p < 0.05$

**Discussion**

This is the first study to investigate the synergistic efficacy of rPMS on central iTBS for enhancing UL function in stroke patients. Both the rPMS + iTBS group and the sham rPMS + iTBS group showed improvement in FMA and FIM after the treatment. However, only the rPMS + iTBS group exhibited additional improvement in the ARAT-Grasp and certain domains of SIS. Although there was no significant difference in the change scores of all outcome measures between the two groups, these findings suggested that rPMS might have potential synergistic effects on central iTBS, particularly in improving grasp function and participation, but not in the activities of self care.

This study showed that rPMS could enhance significant improvement on central iTBS in grasp domains of ARAT. The grasp movement involves the wrist/hand flexion and extension [45]. The extension of wrists and hands was innervated by the radial nerve, which was the target of the rPMS intervention. Although the mechanism of rPMS to facilitate motor function still remained controversial, there were emerging hypotheses believing that rPMS could change sensorimotor nerve and mechanoreceptor nerve [13–15]. The rPMS could directly stimulate the sensorimotor nerve, and the consequent muscle twitching could give another stimulation via mechanoreceptor [13–15]. The afferent proprioceptive inflow to the CNS induced by the rPMS could also stimulate the neuroplasticity in the primary motor cortex and the supplementary motor area [13]. Hence, rPMS may exhibit synergistic effects on central iTBS, enhancing cortical reorganization and consequently improving grasp function.

This study demonstrated that rPMS led to significant improvement on central iTBS in SIS-Strength and SIS-ADL. The reasons may be that the rPMS has potential synergistic effects on central iTBS in grasp movement, which further enhanced participation in the Strength, and ADL domains. Moreover, a higher percentage of patients in the rPMS + iTBS group achieved the minimal clinically important difference (MCID) in SIS-Hand Function, Strength, and ADL, and the rPMS + iTBS group also had borderline improvement in Hand Function. For example, in SIS-Hand Function, 5 patients (35.7%) in the rPMS + iTBS group achieved MCID, while only 3 patients (21.4%) in the
In this study, both groups showed improvement in the FMA and FIM after the treatment, but the degree of improvement did not differ between the groups. The improvement in these two outcome measures was likely due to central iTBS. The bimodal balance-recovery model proposes that central iTBS helps to balance cortical hyperexcitability from the intact hemisphere. Furthermore, central iTBS has been shown to induce long-term potential-like (LTP-like) plasticity changes [10, 38, 39] and alter the balance of synaptic endogenous transmitters [40, 41]. Previous studies have also demonstrated that we could improve motor function and activities in chronic stroke patients by combining central iTBS with conventional neurorehabilitation programs [31, 42–44]. These findings showed that the improvement in FIM and FMA was primarily attributed to central iTBS rather than rPMS.

The study has some limitations that should be taken into consideration when interpreting the results. Firstly, the study recruited patients from a rehabilitation ward using convenience sampling, which may limit the generalizability of the findings to other populations. Secondly, the study did not evaluate the long-term effects of the treatment, which may provide important information about the durability of the treatment effects. Thirdly, the sex of the participants did not match between the two groups, which may have influenced the results. However, despite these limitations, the study findings provide valuable insights into the potential synergistic effects of rPMS on central iTBS in motor function, activities, and participation.

**Conclusion**

The rPMS may have synergistic efficacy on central iTBS for the grasp function and participation in patients with stroke. This study elucidates that the rPMS could be the adjuvant therapy for central iTBS in stroke rehabilitation. Future long-term studies are required for investigating the synergistic effects of rPMS on central iTBS.

**Abbreviations**

ADL  
Activities of Daily Living  
rPMS  
Repetitive peripheral magnetic stimulation  
AMT  
Active motor threshold  
MEPs  
Motor-evoked potentials  
RMT  
Resting motor threshold  
TMS  
Transcranial magnetic stimulation  
rTMS
Declarations

Ethics approval and consent to participate

All participants gave their written informed consent prior to participate in this study. Approval of this study was obtained from the Institutional Review Board of Chang Gung Memorial Hospital, Taiyuan, Taiwan.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.
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Authors’ contributions

CSC and CLC contributed equally to the manuscript. CSC and CLC analyzed and interpreted the data, and drafted the first manuscript. CLC contributed to the design of the study, project management, data collection, and revision of the manuscript. RSC instructed the TBS protocol, analyzed and interpreted the data. HCC contributed to software and hardware integration, and data analyses. CYW and KCL involved in the data collection, analysis and interpretation. All authors involved in the revision of the study and approved the final manuscript.

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Figures

Flow diagram of recruitment and randomized allocation

Figure 1

Screen for eligibility (n=557)

Excluded (n=529)
- Not meeting inclusion criteria (n=525)
- Declined to participate (n=4)

Randomized (n=28)

rPMS + iTBS

Allocated to intervention (n=14)
- Received allocated intervention (n=14)

- Received allocated evaluation (n=14)
- Lost to follow-up (n=0)

Sham rPMS +

Allocated to intervention (n=14)
- Received allocated intervention (n=14)

- Received allocated evaluation (n=14)
- Lost to follow-up (n=0)
Outcome Measures
- Body function
  - Fugl-Meyer Assessment Upper Extremity
  - Action Research Arm Test
- Activity
  - Functional Independence- Self care
- Participation
  - Stroke Impact Scale

Figure 2
Experimental protocol

Supplementary Files

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- CONSORT2010checklistofinformationtoincludewhenreportingarandomisedtrial.docx