Comparison of the Effects of High- and Low-frequency Repetitive Transcranial Magnetic Stimulation on Upper Limb Hemiparesis in the Early Phase of Stroke

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Background: Recently, high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) and low-frequency rTMS (LF-rTMS) are reported to improve motor function significantly in chronic hemiparetic stroke patients. However, few studies have investigated the safety and efficacy of these rTMS modalities introduced during the early phase of stroke. The purpose of this study was to clarify the rTMS modality that is more beneficial for upper limb hemiparesis in the early phase of stroke using a randomized controlled trial. Methods: Twenty-nine patients with a hemispheric stroke lesion in the early phase of stroke were examined. Patients were randomly assigned into 3 groups: the HF-rTMS group (10 Hz rTMS to the lesional hemisphere [n = 9]), the LF-rTMS group (1 Hz rTMS to the nonlesional hemisphere [n = 9]), and the sham stimulation group [n = 9]). Patients received sessions for 5 consecutive days. Grip strength and tapping frequency were assessed before and after the intervention. Motor improvement of the affected upper limb after intervention was compared among the 3 groups. Results: All patients completed the 5-day protocol. Both the HF-rTMS and LF-rTMS groups had significant increases in both grip strength and tapping frequency. Comparison of the extent of improvement showed a more significant increase in grip strength and tapping frequency in the HF-rTMS group compared to the sham stimulation group (each P < .05), and no difference between the LF-rTMS group and the sham stimulation group. Conclusions: HF-rTMS applied to the lesional hemisphere in the early phase of stroke was more beneficial for motor improvement of the affected upper limb than LF-rTMS. Key Words: Early phase—rehabilitation—stroke—transcranial magnetic stimulation—upper limb hemiparesis.

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Stroke is a common disabling neurologic disease in many countries, and upper limb hemiparesis is observed frequently in stroke patients. It has been reported that 55% to 75% of poststroke patients have functional motor limitations of the affected upper limb, even at 3 to 6 months after onset.1 This is an important concern, because functional limitation of the upper limb is associated with a diminished health-related quality of life.2

The local application of repetitive transcranial magnetic stimulation (rTMS) influences neural excitability of selected brain areas. It has been reported that low-frequency rTMS (LF-rTMS) of ≤1 Hz suppresses local neural activities, while high-frequency rTMS (HF-rTMS) of ≥5 Hz activates local neural activities.3-6 Recently, both HF-rTMS applied to the lesional hemisphere7-8 and LF-rTMS applied to the nonlesional hemisphere9-11 have been introduced clinically in some institutions as a therapeutic tool for upper limb hemiparesis in chronic stroke patients. The application of
these 2 rTMS modalities has been shown to be beneficial for upper limb hemiparesis when introduced in the chronic phase of stroke. However, only a few researchers have introduced therapeutic rTMS in the early phase of stroke.\textsuperscript{12-14} Although it might be reasonable to avoid stimulation of the brain in the acute phase of stroke (eg, within a week after onset) because of high-risk deteriorations related to recurrence and general complications, therapeutic rTMS may cause some adverse events if introduced in the early phase of stroke. We hypothesize that the introduction of therapeutic rTMS in the early phase of stroke can be performed with acceptable safety and feasibility, and that this therapy may facilitate motor functional recovery of the affected upper limb.

The purpose of this study was to investigate the safety and feasibility of rTMS introduced in the early phase of stroke, and to clarify which rTMS modality—HF-rTMS over the lesional hemisphere or LF-rTMS over the nonlesional hemisphere—is more beneficial for upper limb hemiparesis when applied using a randomized controlled trial.

**Subjects and Methods**

Twenty-nine consecutive poststroke patients who met all of the inclusion criteria for this study were examined. The inclusion criteria for this study were as follows: (1) a clinical diagnosis of supratentorial intracerebral hemorrhage (ICH) without invasion into the cerebral cortex or cerebral subcortical infarction (CI) in the territory of the middle cerebral artery confirmed with noncontrast computed tomographic (CT) or magnetic resonance imaging (MRI) scans of the brain; (2) emergently admitted to our hospital within 6 hours of stroke onset; (3) age at the intervention was between 45 and 80 years; (4) no surgical management including intravascular surgery or no administration of tissue plasminogen activator; (5) no disturbance of consciousness (a score of eye opening of 4 and best verbal response of 5 on the Glasgow Coma Scale); (6) no apparent cognitive deficit (ability to understand and follow verbal commands of the doctors appropriately); (7) no serious general complications requiring intensive medical management (eg, pneumonia, heart failure, urinary tract infection, or malnutritional state); (8) the possibility to begin the study intervention within 30 days of admission; and (9) no pathologic conditions referred to as contraindications for rTMS in the guidelines (eg, patients with metal within the brain, such as clips for aneurysms, patients with a cardiac pacemaker, pregnant women, or a history of seizure).\textsuperscript{15,16}

In the 29 patients in this study, the age at admission was between 45 and 80 years (mean 65 ± 10 years), and the time between onset and the first session of rTMS or sham stimulation ranged from 6 to 29 days (mean 17.4 ± 5.4 days). The clinical diagnosis of underlying stroke was ICH in 16 patients and CI in the middle cerebral artery territory in 13 patients, respectively. Study patients were randomly assigned to 2 real rTMS groups, the HF-rTMS group (n = 9) and the LF-rTMS group (n = 11), and a sham stimulation group (n = 9). All patients received rTMS or sham stimulation for 5 consecutive days, and changes in motor function of the affected upper limb after intervention were assessed and compared among the groups. The ethics committee of our hospital approved the study protocol, and written informed consent was obtained from all patients or their family members before entry to the study.

**Application of Therapeutic rTMS and Sham Stimulation**

For the delivery of real rTMS and sham stimulation, a 70-mm figure 8 coil and a Magstim Rapid stimulator (Magstim Company, Dyfed, UK) was used. Before rTMS and sham stimulation, the motor hotspot, defined as the location where the stimulation evoked flexion movement of a contralateral index finger using suprathreshold stimulus most apparently over the primary motor cortex, was determined. If a motor response was not elicited by maximum stimulation over the hemisphere, a symmetric position (mirror region) of the motor hotspot of the contralateral hemisphere was defined as an alternate motor hotspot for the hemisphere. A resting motor threshold (RMT) was defined as the minimal output of stimulation that evoked target movement of the finger.

During rTMS or sham stimulation, all patients sat in a reclining wheelchair and were asked to relax as much as possible, with their heads strapped to the head rest. For patients in the HF-rTMS group, 10 Hz rTMS was applied daily to the hotspot of the lesional hemisphere in 10-second trains with 50-second intervals between trains for 10 minutes (total 1000 pulses). Patients in the LF-rTMS group received 1 Hz rTMS daily to the hotspot of the nonlesional hemisphere for 30 minutes (total 1800 pulses). The intensity of rTMS was 90% of RMT in the each hotspot of hemisphere in both the HF-rTMS and LF-rTMS groups. Sham stimulation was performed with the coil held at an angle of 90° to the scalp to reproduce the noise of 1-Hz stimulus for 10 minutes.

None of the patients were able to recognize which stimulation modality they were receiving during the session, because they had never experienced real rTMS before entry to the study and had no detailed knowledge of rTMS. Patients were scheduled to receive 1 session of rTMS or sham stimulation per day for 5 consecutive days. In terms of safety, patients were monitored clinically through medical and neurologic examination during the study period. Vital signs including blood pressure, heart rate, and consciousness level were assessed before and after each rTMS or sham stimulation session. During the study period, all patients received the same conventional rehabilitation, such as range of motion training, muscle exercise, fitness training, gait training, and
activities of daily living training, for 40 to 80 minutes each day from 3 days on average after onset. All of the patients also received conventional medical treatment, such as management of blood pressure, inhibiting oxidative injury by antioxidative radical scavengers, and anticoagulant or antiplatelet therapy (in the case of CI).

Clinical Measures for Motor Function of the Affected Upper Limb

The main outcome measures for this study were grip strength and tapping frequency. In some previous studies of rTMS, grip strength was used as a reasonable, simple, and easy test of muscle strength, and tapping frequency was used as an index of skilled movement or movement speed. Before the first application and after the last application of rTMS or sham stimulation, these evaluations were performed in a seated position by a medical doctor from our department. Using a standard Jamar dynamometer, grip strength was measured twice, and the higher value was recorded. In the evaluation of tapping frequency, the examiner put his hand on the knee of seated patients and set the patients’ paresis hand over the examiner’s hand, and the patients were asked to tap the examiner’s hand as fast as possible using their index finger. Involuntary movements of the other fingers by spasticity or synergy were permitted. Each tap was counted as 1 movement, and the frequency of tapping over 30 seconds was recorded. In addition, the National Institute of Health Stroke Scale (NIHSS) score and the finger-hand and upper-limb subitems of the Brunnstrom Recovery Stage (BRS) were also evaluated. These evaluations were serially performed by another neurologist who had no information about the group to which each patient belonged before the first session of rTMS or sham stimulation as preintervention data.

Statistical Analysis

Comparison of the clinical characteristics at preintervention and the baseline motor function among the 3 groups was tested by 1-way analysis of variance (for parametric data; ie, age, number of days between onset and rehabilitation or rTMS, grip strength, and tapping frequency), by the Kruskal–Wallis test (for nonparametric data; ie, NIHSS score and BRS), and by Chi-square test (for categorical data; ie, gender, subtype of stroke, and side of cerebral lesion). The significance of changes of grip strength and tapping frequency with the intervention in each patient group was analyzed with the paired Student t test, and the comparison of the extent of changes in these 2 measures with the intervention among the 3 groups was performed by unpaired Student t test. All statistical analyses were performed using IBM SPSS Statistics software (version 19; IBM, New York, NY). P < .05 was considered statistically significant.

Results

As shown in Table 1, there was no significant difference in the clinical characteristics at preintervention or the baseline motor function among the 3 groups. The protocol of this study was completed by all patients. No patient experienced any pathologic symptoms such as seizure or any deterioration of motor function in the affected upper limb during the study period. With the 5-day intervention, grip strength increased significantly in both the HF-rTMS and LF-rTMS groups (P < .05 in the HF-rTMS and LF-rTMS groups; Fig 1A). However, the sham stimulation group did not show a significant increase in grip strength after the intervention (P = .10). Similarly, both the HF-rTMS and LF-rTMS groups showed significant increase in tapping frequency after the 5-day intervention, and the increase in sham stimulation group was not

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**Table 1. Comparison of clinical characteristic among the 3 groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sham(n = 9)</th>
<th>HF-rTMS (n = 9)</th>
<th>LF-rTMS (n = 11)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission, y</td>
<td>63.0 (9.3)</td>
<td>65.7 (9.1)</td>
<td>68.6 (8.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Gender, M/F, n (%)</td>
<td>6 (67)/3 (33)</td>
<td>6 (67)/3 (33)</td>
<td>8 (73)/3 (27)</td>
<td>0.94</td>
</tr>
<tr>
<td>Subtype of stroke, CI/ICH, n (%)</td>
<td>4 (44)/5 (56)</td>
<td>4 (44)/5 (56)</td>
<td>5 (45)/6 (55)</td>
<td>1.00</td>
</tr>
<tr>
<td>Side of cerebral lesion, R/L, n (%)</td>
<td>6 (67)/3 (33)</td>
<td>4 (44)/5 (56)</td>
<td>3 (27)/8 (73)</td>
<td>0.21</td>
</tr>
<tr>
<td>No. of days between onset and rehabilitation</td>
<td>4.0 (2.2)</td>
<td>2.7 (1.0)</td>
<td>2.3 (1.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>No. of days between onset and rTMS</td>
<td>15.4 (4.3)</td>
<td>18.4 (5.8)</td>
<td>17.0 (6.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>NIHSS at the beginning of rTMS</td>
<td>7.0 (2.4)</td>
<td>5.8 (2.5)</td>
<td>6.1 (2.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hand-fingers of BRS at the beginning of rTMS</td>
<td>2.1 (1.2)</td>
<td>2.6 (1.5)</td>
<td>2.5 (1.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Upper limb of BRS at the beginning of rTMS</td>
<td>2.3 (1.5)</td>
<td>2.4 (1.6)</td>
<td>2.2 (1.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Grip strength at the beginning of rTMS, kg</td>
<td>7.9 (11.6)</td>
<td>4.4 (5.4)</td>
<td>4.9 (4.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Tapping frequency at the beginning of rTMS, times/30sec</td>
<td>20.6 (25.9)</td>
<td>31.7 (35.0)</td>
<td>20.8 (17.4)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Abbreviations: BRS, Brunnstrom Recovery Stage; CI, cerebral infarction; F, female; ICH, intracerebral hemorrhage; L, left; M, male; NIHSS, National Institute of Health Stroke Scale; R, right; rTMS, repetitive transcranial magnetic stimulation.

*Data are expressed as mean (SD) unless otherwise indicated.
significant ($P < .05$ in the HF-rTMS and LF-rTMS groups, $P = .23$ in the sham stimulation group; Fig 1B). The mean increase in grip strength was $4.2 \pm 2.8$ kg in the HF-rTMS group, $2.3 \pm 2.9$ kg in the LF-rTMS group, and $0.6 \pm 0.7$ kg in the sham stimulation group, respectively (Fig 2A). A significantly larger increase in grip strength was observed in the HF-rTMS group compared with the sham stimulation group ($P < .05$). However, the extent of increase in grip strength was not different between the HF-rTMS and LF-rTMS groups or between the LF-rTMS group and the sham stimulation group ($P = .28$ between the HF-rTMS and LF-rTMS groups; $P = .15$ between the LF-rTMS group and the sham stimulation group). The mean increase in tapping frequency was $12.3 \pm 8.7$ times per 30 seconds in the HF-rTMS group, $14.3 \pm 15.1$ times per 30 seconds in the LF-rTMS group, and $2.8 \pm 4.1$ times per 30 seconds in the sham stimulation group, respectively (Fig 2B). Statistically, the increase in tapping frequency was significantly larger in the HF-rTMS group than that in the sham stimulation group ($P < .05$), although there was no significant difference in the increase in tapping frequency between the HF-rTMS and LF-rTMS groups or between the LF-rTMS and the sham stimulation groups ($P = .81$ between the HF-rTMS and LF-rTMS groups; $P = .11$ between the LF-rTMS and the sham stimulation groups).

**Discussion**

The improvement of motor function of the affected upper limb in the early phase of stroke was significantly larger in patients treated with HF-rTMS than those treated with LF-rTMS or sham stimulation.
treated with sham stimulation, although the extent of the improvement did not differ between patients treated with HF-rTMS and those treated with LF-rTMS. In addition, all patients in whom real rTMS was applied completed the 5-day protocol without any adverse effect. To our knowledge, this is the first study to compare the clinical influence of consecutive application over several days in the early phase of stroke between HF-rTMS and LF-rTMS.

TMS has been developed not only as a safe, painless, and noninvasive strategy for mapping cortical motor representation but also as a therapeutic tool for the neurorehabilitation of stroke patients.2-6 rTMS is dependent on various factors, but the frequency of pulses is most important. Previous studies have shown that HF-rTMS of ≥5 Hz activates local neural excitability, whereas LF-rTMS of ≤1 Hz suppresses local neural excitability.4-6 Although there exists no confirmed criterion standard method of rTMS,18 LF-rTMS over the intact hemisphere at the chronic phase, which reduces interhemispheric inhibition (IHI)19,20 drive from the intact hemisphere to the lesional hemisphere, is more commonly applied as a therapeutic tool for poststroke patients. Kakuda et al19 revealed that a combined application of LF-rTMS over the intact hemisphere and a constraint intensive rehabilitation program significantly improved motor function of the affected upper limb in poststroke patients, and that the beneficial effects were maintained for 4 weeks after the intervention. Kirton et al11 showed that low-frequency rTMS over the intact hemisphere was effective, even in children with chronic stroke. However, only a few studies have introduced therapeutic rTMS in the early phase of stroke, and the appropriate method of stimulation remains uncertain.12-14

Based on the results of this study, HF-rTMS is more effective for upper limb hemiparesis in the early phase of stroke, although both HF-rTMS and LF-rTMS were beneficial. Regarding this difference between the 2 TMS modalities, we can speculate as to the underlying mechanism. Recently, Gao et al21 reported that infarct volumes of an acute stroke rat model were reduced significantly after 7 days of HF-rTMS (20 Hz on the lesional hemisphere). They concluded from the results of their micro–positron emission tomographic studies that the phenomenon was caused by inhibiting neuronal apoptosis and maintaining glucose use in the lesional hemisphere. This is the first report showing the neuroprotective effect of HF-rTMS, although no authors have shown this effect using LF-rTMS.22 In addition, HF-rTMS may be more appropriate than LF-rTMS in the early phase after stroke from a neuronal reorganization viewpoint. Marshall et al23 investigated the time course of cortical activation using functional magnetic resonance imaging (fMRI) after the onset of hemiparetic stroke, and revealed that activation of the contralesional primary sensorimotor cortex was increased from 3 to 6 months after onset. Murase et al19 reported abnormally high IHI driven from intact hemisphere in stroke patients with poorly recovered hand motor performance, although it is known that patients with good recovery after stroke were more likely to have “normal” brain activation.24 From these results, HF-rTMS over the lesional hemisphere may be reasonable in the early phase until the IHI has been increased. In addition, it is the more direct stimulation for stroke brain in which developmental proteins, not normally expressed in the adult brain, are reappearing only for the early phase.25

One debate remains regarding the nonresponder to single TMS over the lesional hemisphere for identifying the hotspot in the HF-rTMS group. We applied symmetric mirror position as the hotspot when the motor response was absent with maximum single TMS over the lesional hemisphere, and used the RMT of the nonlesional side, as mentioned above. The inability to respond to stimulation over the lesional hemisphere in the early phase after stroke is the predictor of poor recovery.26,27 This may result in underestimating the efficacy in the HF-rTMS group. Future studies should select only the patients who have clear hotspot.

The overall status of the patients is generally unstable during the acute phase of the stroke. In particular, HF-rTMS has been reported to be associated with a risk of seizure in poststroke patients,15 and the seizure may lead a recurrence of the stroke and general complications, such as hypoxic encephalopathy. Therefore, it may be reasonable to avoid HF-rTMS over the lesional hemisphere during the acute phase, such as within a week after onset. However, no adverse event was observed in our patients, or in the patients of recent previous studies (10 Hz rTMS for patients with postonset duration 6 ± 2.82 days,13 10 Hz rTMS for patients with postonset duration 12.9 ± 5.2 days14). We suggest that HF-rTMS over the lesional hemisphere is safe if applied by our protocol and criteria.

One of the most problematic questions regarding rTMS in the early phase concerns the duration of its effect, and a few studies have examined this question. Chang et al14 showed that efficacy continued over 3 months after stroke, and Khedr et al13 showed a long-lasting advantage even after 12 months. Whether or not the better improvement by rTMS seen in the early phase of stroke will last for a long amount of time, better improvement during the early phase is beneficial for both the patients and medical economy. However, it is necessary to investigate the most lasting effect by any type of stimulus.

There are limitations to this study. The number of patients was relatively small, although this study was a randomized controlled study. Therefore, the findings of this study should be confirmed in a larger number of patients. Second, we did not use any functional neuroimaging studies such as fMRI or positron emission tomography in this study. These studies should be serially applied to clarify the difference of functional neural reorganization with the intervention among the study groups. Third, no detailed evaluation of motor function of the
affected upper limb such Fugl–Mayer Assessment and Wolf Motor Function Test was applied in this study, although it might be difficult to serially introduce such evaluations clinically in the early phase of stroke. There may be some discrepancy between the score changes in the 2 measures applied in the study and the improvement of motor function of the affected upper limb during activities of daily living in the patients.

Improvement of motor function of the affected upper limb in the early phase of stroke was significantly facilitated in poststroke patients treated with HF-rTMS applied to the lesional hemisphere than those treated with sham stimulation. HF-rTMS applied to the lesional hemisphere may be a useful neurorehabilitative approach with low-risk symptomatic deterioration for early phase hemiparetic stroke patients, although the findings should be confirmed in a larger number of patients.

References