Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex

YOUICHI SAITO, M.D., PH.D.,1 AZUMA HIRAYAMA, M.D.,1 HARUHIKO KISHIMA, M.D., PH.D.,1 TOSHI SHIMOKAWA, PH.D.,2 SATORU OSHINO, M.D., PH.D.,1 MASAYUKI HIRATA, M.D., PH.D.,1 NAOKI TANI, M.D.,1 AMAMI KATO, M.D., PH.D.,1 AND TOSHIKI YOSHIMINE, M.D., PH.D.1

1Department of Neurosurgery, Osaka University Graduate School of Medicine; and 2Graduate School of Medicine and Engineering, University of Yamanashi, and Medical Center for Translational Research, Osaka University Hospital, Osaka, Japan

Object. The authors previously reported that navigation-guided repetitive transcranial magnetic stimulation (rTMS) of the precentral gyrus relieves deafferentation pain. Stimulation parameters were 10 trains of 10-second 5-Hz TMS pulses at 50-second intervals. In the present study, they used various stimulation frequencies and compared efficacies between two types of lesions.

Methods. Patients were divided into two groups: those with a cerebral lesion and those with a noncerebral lesion. The rTMS was applied to all the patients at frequencies of 1, 5, and 10 Hz and as a sham procedure in random order. The effect of rTMS on pain was rated by patients using a visual analog scale.

Results. The rTMS at frequencies of 5 and 10 Hz, compared with sham stimulation, significantly reduced pain, and the pain reduction continued for 180 minutes. A stimulation frequency of 10 Hz may be more effective than 5 Hz, and at 1 Hz was ineffective. The effect of rTMS at frequencies of 5 and 10 Hz was greater in patients with a noncerebral lesion than those with a cerebral lesion.

Conclusions. High-frequency (5- or 10-Hz) rTMS of the precentral gyrus can reduce intractable deafferentation pain, but low-frequency stimulation (at 1 Hz) cannot. Patients with a noncerebral lesion are more suitable candidates for high-frequency rTMS of the precentral gyrus. (DOI: 10.3171/JNS-07/09/0555)

KEY WORDS • deafferentation pain • imaging-guided navigation • motor cortex • repetitive transcranial magnetic stimulation

DEAFFERENTATION or neuropathic pain caused by a cerebral, spinal cord, or peripheral lesion is one of the most difficult types of pain to treat, and most cases are refractory to medical treatment. Only MCS has been shown to provide relief in cases of such deafferentation pain, and relief is achieved in only 50 to 70% of patients.4,9,11,18 The mechanism underlying the effects of MCS in reducing pain remains controversial. However, the precentral gyrus is a common target for cortical stimulation in the treatment of medically intractable deafferentation pain.1,4,9,11,14,16–18 According to recent reports,3,7,8,13,21,22 rTMS of the precentral gyrus provides an effect similar to that of MCS in patients with medically intractable deafferentation pain. However, it can be difficult to stimulate the same cortical area repeatedly, and results tend to vary. In addition, the electric current evoked by rTMS is generally confined to the cortex.19 For these reasons, we have used navigation-guided rTMS in patients with intractable deafferentation pain to precisely stimulate specific cerebral cortical areas.

We have previously reported that navigation-guided 5-Hz rTMS of the precentral gyrus significantly reduced intractable neuropathic pain in 50% of patients.2 We selected four cortical targets for navigation-guided rTMS: the precentral gyrus, the postcentral gyrus, the premotor cortex, and the supplementary motor area. However, only stimulation of the precentral gyrus produced pain relief. In addition to the cortical target for rTMS, the stimulation parameters and the type of lesion are important. In the present study, we varied the stimulation frequency for navigation-guided rTMS of the precentral gyrus and compared the efficacies of the various frequencies, particularly between origins of pain.

Clinical Material and Methods

Patient Population

The patient population comprised 13 right-handed patients (seven men and six women; age range 29–76 years,
mean age 59.4 years) suffering from intractable deafferentation pain. Seven of the patients were suffering from poststroke pain due to thalamic hemorrhage or infarction (three), or putaminal hemorrhage (four). Two patients were suffering from deafferentation pain originating from a spinal cord lesion (ruptured arteriovenous malformation or infarction), and one patient each was suffering from pain due to brachial plexus injury, peripheral nerve injury, a cauda equina lesion, or a phantom limb. Patient characteristics are listed in Table 1. Patients were assigned to one of two groups according to the type of lesion: cerebral lesion, or spinal cord or peripheral lesion (noncerebral lesion). Patients were given anticonvulsants, nonsteroidal anti-inflammatory drugs, and antidepressants, as needed and also during the rTMS sessions. Patients also underwent psychological examination and electroencephalographic examination before rTMS to assess whether seizure development was likely. Patients who experienced pain reduction in response to 5-Hz stimulation were enrolled in this study. Informed consent was obtained from all study participants. The study was approved by the Ethics Committee of Osaka University Hospital, and all patients were blinded to the area being stimulated and to the expected effect.

The rTMS Procedure

The rTMS was applied through a figure-eight coil (MC B-70, Medtronic Functional Diagnostics A/S), which provides limited cortical stimulation. The coil was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnostics A/S). The resting motor threshold of the affected muscle area was determined by stimulation of the corresponding precentral gyrus area and electromyography in the affected area. The resting motor threshold at 90% intensity was used for treatment. Muscle twitches can be elicited in painful areas, if stimulated carefully according to somatotopy. This is possible even with trigeminal lesions and in the lower limbs. For patients in whom muscle twitches in painful areas were difficult to elicit due to severe damage of motor pathways, rTMS was applied with an intensity of 100 A/μsec. This was the maximum tolerable intensity for most patients in our study, with higher intensities resulting in scalp pain. A potential equivalent to 90% of the intensity of the resting motor threshold was used for treatment. Ten trains of 10-second 5-Hz TMS pulses with 50-second intervals between trains, five trains of 10-second 10-Hz TMS pulses with 50-second intervals between trains, continuous 1-Hz TMS pulses for 500 seconds, and sham 5-Hz TMS pulses were applied to the precentral gyrus in random order. A total of 500 stimulations were applied for each parameter, and there was an interval of about 48 hours before each new series of stimulations was performed. Sham stimulation was applied as described previously. In brief, the parameters were the same as for actual stimulations, but the coil was placed at a 45° angle to the skull, and synchronized electrical stimulations were delivered to the forehead. The protocol was in compliance with the Guidelines for the Safe Use of rTMS. The TMS coil was held and positioned by an articulated coil holder. The BrainInsight Frameless navigation system (Rogue Research Inc.) was used to monitor the position and direction of the coil and the position of the patient’s head, as described previously.

Evaluation of Pain Relief

Using a VAS and the SF-MPQ, the patients evaluated their own pain before and after (at 0, 15, 30, 60, 90, and 180 minutes) rTMS (at 1, 5, and 10 Hz) or sham stimulation. Statistical Analysis

We evaluated the effectiveness of stimulation for each patient according to the reduction rate of VAS scores (reduction rate = 1 - VASprestimulation/VASpoststimulation). We evaluated the influence of the various frequencies (sham, 1, 5, and 10 Hz) and lesion types by applying repeated-measures ANOVA to the reduction rate of VAS. To compare sham stimulation with rTMS (at 1, 5, and 10 Hz), we used the Dunnett multiple-comparisons at various points after stimulation (Fig. 1).

Results

All 13 patients participated in all planned sessions of navigation-guided rTMS, and no transient or lasting side effects, including convulsion, were observed. Patients were unable to distinguish sham stimulation from rTMS because the synchronized electrical stimulation applied to the forehead induced forehead spasms. All 13 patients underwent sham stimulation and 1-, 5-, and 10-Hz rTMS of the precentral gyrus. Repeated-measures ANOVA indicated that the frequency of stimulation (p = 0.03) and the presence or absence of a cerebral lesion (p = 0.04) contributed to pain reduction as judged by the reduction rate of VAS scores. Interaction between these factors was not significant (p = 0.80). The reduction rates of VAS scores for each frequency are shown in Fig. 1. Stimulation at 5 and 10 Hz, compared with sham stimulation, were effective in reducing pain for up to 180 minutes (p < 0.05, repeated-measures ANOVA). Stimulation at 1 Hz did not differ from sham stimulation. In the cerebral lesion group, 5- and 10-Hz

### TABLE 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration (hrs)</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>59, M</td>
<td></td>
<td>rt putaminal hemorrhage</td>
<td>16</td>
<td>lt lower limb</td>
</tr>
<tr>
<td>2</td>
<td>57, F</td>
<td></td>
<td>lt putaminal hemorrhage</td>
<td>5</td>
<td>lt lower limb</td>
</tr>
<tr>
<td>3</td>
<td>62, M</td>
<td></td>
<td>lt thalamic hemorrhage</td>
<td>8.5</td>
<td>rt upper limb</td>
</tr>
<tr>
<td>4</td>
<td>70, M</td>
<td></td>
<td>lt thalamic infarction</td>
<td>2.2</td>
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</tr>
<tr>
<td>5</td>
<td>64, F</td>
<td></td>
<td>lt putaminal hemorrhage</td>
<td>6.9</td>
<td>rt lower limb</td>
</tr>
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<td>6</td>
<td>74, F</td>
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<td>35</td>
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<tr>
<td>7</td>
<td>76, F</td>
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<td>lt thalamic infarction</td>
<td>2</td>
<td>rt lower limb</td>
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<tr>
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<td>55, F</td>
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<td>ruptured spinal AVM</td>
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<tr>
<td>10</td>
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<td>phantom limb pain</td>
<td>7</td>
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<tr>
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<td></td>
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</tr>
<tr>
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<td></td>
<td>lt brachial plexus injury</td>
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<tr>
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<td></td>
<td>peripheral nerve injury</td>
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<td>lt lower limb</td>
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</table>

* AVM = arteriovenous malformation.
† The patients in Cases 1 to 7 experienced neuropathic pain due to a cerebral lesion, and those in Cases 8 to 13 had neuropathic pain due to a spinal cord or peripheral lesion.
Pain reduction with high-frequency rTMS of the precentral gyrus

rTMS, in comparison to sham stimulation, resulted in significant pain reduction just after rTMS (p < 0.05, according to Dunnett multiple-comparisons), and the mean reduction in VAS scores just after rTMS was greater than 30% (Fig. 2). In the noncerebral lesion group, 5-Hz rTMS resulted in significant pain reduction at 0, 30, and 90 minutes after rTMS (p < 0.05), and the mean reduction in VAS scores was greater than 30% for up to 30 minutes. The rTMS at 10 Hz, compared with sham stimulation, resulted in significant pain reduction for up to 90 minutes (p < 0.05), and the mean reduction in VAS scores was greater than 30% for up to 60 minutes (Fig. 3). The rTMS did not produce a consistent change in SF-MPQ scores. In patients with a high baseline SF-MPQ score (> 20), the VAS and SF-MPQ scores tended to be similar. In patients with a low baseline SF-MPQ score (< 10), the SF-MPQ score changed little, regardless of a reduction in the VAS score.

Discussion

In our previous study, only 5-Hz rTMS of the precentral gyrus, compared with rTMS of adjacent cortical areas (the postcentral gyrus, the premotor cortex, and the supplementary motor area), relieved pain. Appropriate stimulation parameters (for example, stimulation frequency) have remained uncertain. In the present study, 5- and 10-Hz rTMS of the precentral gyrus were significantly more effective than sham stimulation, but 1-Hz rTMS was not. The rTMS may be more effective at 10 Hz than at 5 Hz (Figs. 1–3). Correlation between the efficacy of rTMS and type of lesion was also investigated. Deafferentation pain caused by a cerebral lesion was more refractory to rTMS than that caused by a spinal cord or peripheral lesion (Figs. 2 and 3).

Pain reduction in response to rTMS of the precentral gyrus was likely due to modification of pain perception, as previously reported. The detailed mechanism underlying pain relief in response to MCS was examined by positron emission tomography activation studies.

Fig. 1. Graph showing the reduction rate of VAS in all 13 patients after sham stimulation and 1-, 5- and 10-Hz rTMS of the precentral gyrus. As a result of repeated-measures ANOVA, the frequency of stimulation and the presence or absence of a cerebral lesion contributed to pain reduction as determined by a decrease in the VAS. Patients exhibited significant pain reduction after 5- and 10-Hz rTMS (but not after 1-Hz rTMS) compared with sham stimulation until 180 minutes, as indicated by the VAS scores. The VAS scores are presented as the means ± standard error of the means (SEMs). *p < 0.05. Circles denote sham stimulation; squares, 1-Hz rTMS; diamonds, 5-Hz rTMS; and triangles, 10-Hz rTMS.

Fig. 2. Graph showing the reduction rate in VAS scores in the cerebral lesion group (seven patients). According to the Dunnett multiple-comparisons procedure, rTMS at 5 and 10 Hz, compared with sham stimulation, significantly reduced pain as determined by the reduction rate of VAS score only just after rTMS. The VAS scores are presented as the means ± SEMs. *p < 0.05.

Fig. 3. Graph showing the reduction rate of VAS scores in the noncerebral lesion group (six patients). According to the Dunnett multiple-comparisons procedure, rTMS at 5 Hz significantly reduced pain as determined by the decrease in VAS score at 0, 30, and 90 minutes; rTMS at 10 Hz significantly reduced pain for up to 90 minutes. The reduction rate of the VAS score for 10 Hz was greater than that for 5 Hz at each time point after stimulation. The VAS scores are presented as the means ± SEMs. *p < 0.05.
pears to activate several brain areas involved in pain perception. A common finding in patients with poststroke pain was a relative decrease in thalamic regional cerebral blood flow during chronic pain. We previously reported activation of the anterior cingulate gyrus and left posterior thalamus in response to right MCS. Garcia-Larrea et al. reported that MCS may activate cingulate, orbitofrontal cortex, and upper brainstem regions. The mechanism underlying pain relief in response to high-frequency rTMS may be similar to that of MCS. Several brain regions associated with pain perception may be activated by subthreshold high-frequency rTMS of the precentral gyrus and may reduce deafferentation pain comprehensively. High-frequency rTMS enhances neuronal firing efficacy, and low-frequency rTMS has the opposite effect. The rTMS at 20 Hz significantly increased global blood flow, whereas rTMS at 1 Hz did not. Lefaucheur et al. evaluated the effect of rTMS at two frequencies (10 and 0.5 Hz) in 18 patients with intractable unilateral hand pain. The VAS score improved in response to 10-Hz stimulation but did not improve in response to 0.5-Hz stimulation. In addition, good pain control has been reported in response to high-frequency stimulation (10 or 20 Hz) in some rTMS studies. Effectiveness of low-frequency (1-Hz) rTMS was reported only in healthy individuals with acute pain caused by capsaicin. The findings are consistent with our results indicating that 5- and 10-Hz rTMS are effective but 1-Hz rTMS is not.

It is likely that the greater the stimulation frequency, the greater the effect of rTMS on pain reduction. Lefaucheur et al. used 80% of the resting motor threshold of the intact hand for rTMS treatment of deafferentation pain. We used 90% of the resting motor threshold of the affected limb, and our rTMS was of higher power than theirs. Our success rate seemed to be superior to theirs. However, suprathreshold rTMS of the precentral gyrus corresponding to the affected limb and stimulation at frequencies of greater than 10 Hz appear to increase the risk of seizure development in patients who have suffered stroke. Therefore, we did not evaluate these types of rTMS. In the future, subthreshold rTMS with 5 or 10 Hz may prove to be useful for clinical applications of rTMS.

We believe that it is very difficult to apply all rTMSs to the same cortical area. We therefore performed rTMS using a frameless magnetic resonance imaging–guided navigation system in accordance with each patient’s own cortical anatomy. The TMS coil was positioned by an articulated coil holder. Without a navigation system, identification of the precentral gyrus is difficult in patients with severe motor weakness whose motor evoked response is barely induced by a single TMS. The anatomical error of the navigation system is considered to be less than about 5 mm. This is based on the observation that muscle twitches did not occur if the coil was out of position by about 1 cm on the magnetic resonance imaging–guided navigation system. Experimental simulation showed that the electrical current induced with the figure-eight coil is considerably limited in the cortex. We consider a navigation system to be indispensable when performing rTMS.

We have reported that there is good correlation between the results of rTMS and those of MCS. Migita et al. reported on two patients with central pain who were evaluated using rTMS of precentral gyrus and then treated using MCS. We believe that high-frequency rTMS can predict the results of MCS.

Conclusions

Subthreshold high-frequency rTMS of the precentral gyrus significantly reduces intractable pain for up to 180 minutes. Low-frequency rTMS is ineffective. Treatment with the aid of rTMS appears to be more effective in patients with a spinal cord or peripheral lesion than in those with a cerebral lesion. Several brain regions associated with pain perception may be activated by subthreshold high-frequency rTMS of the precentral gyrus, and such stimulation may reduce deafferentation pain comprehensively. The rTMS may be a good predictor of MCS efficacy, and thus, we believe that MCS can be recommended to patients who have good results from rTMS.

References


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Address reprint requests to: Youichi Saitoh, M.D., Ph.D., Department of Neurosurgery, Osaka University Graduate School, 2-2 Yamadaoka, Suita-shi, Osaka, 565-0871, Japan. neurosaitoh@mbk.nifty.com.