Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) of Primary Motor Cortex in Post-stroke Pain Patients

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex has been reported to be effective for the treatment of various types of neuropathic pain. However, the clinical effects of rTMS for the treatment of post-stroke pain are unclear. The present study investigated rTMS-induced analgesia in patients with post-stroke pain, and the clinical use of rTMS in the treatment of post-stroke pain is discussed. Changes in a visual analog scale (VAS) measuring pain following rTMS (sham and real) of the primary motor cortex (frequency 5Hz, at 100% resting motor threshold, 500 pulses per session) were examined in 20 post-stroke pain patients. No side effects related to rTMS were observed. The real rTMS significantly reduced the patients’ VAS scores immediately after rTMS, and the score reduction persisted for 300 min after rTMS ($p < 0.05$, ANOVA). These results indicate the usefulness of rTMS for the treatment of post-stroke pain with a high amount of safety.

Introduction

Post-stroke pain is a subset of neuropathic pain, and appears secondarily to the primary lesion of the central nervous system caused by the stroke. Dejerine and Roussy (1) first reported in 1906 that post-stroke pain is caused mainly by the thalamic lesion. However, other researchers contend that an extra-thalamic lesion can be the cause of post-stroke pain (2). It has been suggested that approx. 8% – 14% of post-stroke patients feel unpleasant or intractable pain (3, 4), and the persistence of this pain markedly decreases the affected patients’ quality of life. A mechanism of post-stroke pain has been proposed; it involves a complex group of factors such as changes in the plasticity of synaptic degeneration or conduction efficiency (5). Post-stroke pain has been described as one of the most difficult types of pain to treat, and the spontaneous remission of post-stroke pain is rare (6). Moreover, pharmacological therapy and relative nerve blocking have not induced a sufficient reduction of post-stroke pain (7, 8).

Neurostimulation techniques have been tested for severe medically refractory post-stroke pain. For example, chronic motor cortex stimulation (MCS) was first applied as a treatment for post-stroke pain (9) (Fig. 1). Several reports have indicated definite pain reduction following MCS treatment for post-stroke pain (10–12); however, the long-term follow-up results of MCS for post-stroke pain revealed a decrease in subjective pain scores of only approx. 50% (13). In addition, MCS requires a craniotomy under general anesthesia to place the electrode on the epidural space of the motor cortex. Thus, the identification of selection criteria for candidates for MCS therapy is important and may help to increase the effectiveness of chronic MCS.

Transcranial magnetic stimulation (TMS) has been developed and repetitive transcranial magnetic stimulation (rTMS) has been clinically applied for the treatment of neuropathic pain (14–17). The effectiveness of rTMS for the treatment of post-stroke pain has not yet been established. The present study examined rTMS-induced analgesia in post-stroke pain patients.

Materials and Methods

Patient Population

Twenty patients with post-stroke pain were tested (Table
12 males and 8 females, ranging in age from 54 to 85 years (mean, 63.6 ± 8.1). Patients were recruited from the outpatient clinic for neurosurgery at Nihon University Hospital between April 2010 and November 2011. The inclusion criteria were as follows: (1) history of stroke; (2) the patient had a cerebrovascular disorder corresponding to the origin of pain; (3) the pain had lasted more than 6 months; (4) pharmacological therapy and relative nerve blocking have not induced a sufficient reduction of pain. The exclusion criteria were as follows: (1) contraindications for rTMS (i.e., a history of epilepsy, cardiac pacemaker use, or treatment with a brain stimulation system); (2) nociceptive and peripheral neuropathic pain, especially post-stroke shoulder pain caused by contracture deformity; (3) serious psychiatric disorder, severe cognitive dysfunction, or neurodegenerative disorder.

The causes of post-stroke pain were thalamic hemorrhage (7 patients), putaminal hemorrhage (5 patients), brainstem hemorrhage (1 patient), thalamic infarct (4 patients), and brainstem infarct (3 patients). The durations between stroke onset and rTMS were from 6 to 180 months (mean ± SD, 38.2 ± 43.0). Informed consent was given by each patient, and an approval was obtained. This study was approved by the Committee for Clinical Trials and Research on Humans of Nihon University School of Medicine and conformed to the principles outlined in the Declaration of Helsinki.

rTMS

The patient’s head was registered with his or her MRI using a frameless stereotactic navigation system (Brainsight TMS, Rogue Research, Montreal, Quebec, Canada) to precisely localize the stimulation target (Fig. 2). The rTMS was delivered through a figure-eight coil (70-mm dia.) connected to a Magstim super-rapid stimulator (Magstim Co., Whitland, UK) (Fig. 3). The resting motor threshold (RMT) was measured from the unaffected primary motor hand area and was defined as the lowest intensity at which a motor-evoked potential ≥ 50μV was produced in the first dorsal interosseous (FDI) muscle at least five times after
the application of 10 stimuli.

For the rTMS, the subject sat relaxed on a stimulation chair while a total of 500 stimuli at 5Hz were delivered to the motor cortex, which corresponded to the site of the most severe pain on the lesion side. The stimulation intensity was 100% of the RMT of the unaffected motor hand area with 50 pulses per train at 25-sec intertrain intervals.

The protocols used in this study were in accord with Wassermann’s safety guidelines for rTMS of the primary motor cortex (18). According to those guidelines, the single trains of 5-Hz rTMS at 100% RMT of stimulation intensity are applied for up to 10 sec in one session, and a total of 500

<table>
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<th>Case</th>
<th>Age/ Sex</th>
<th>Cause of pain</th>
<th>Pain area</th>
<th>Pain duration (months)</th>
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<th>Maximum VAS Reduction (%)</th>
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M: male; F: female; Lt: left; Rt: right; PGIC: Patients Global Impression of Change (1 very much improved; 2 much improved; 3 minimally improved; 4 no change).

Fig. 2 The target point, which was identified using the MRI-guided navigation system and located on the hand area of the motor cortex, indicates the stimulation point of rTMS.
stimuli were applied to the motor cortex. Sham rTMS and real rTMS were performed on each patient to test for a placebo effect, and the two sessions were separated by 48 hrs. Sham rTMS was performed under the same conditions, but the stimulation coils were elevated at an angle of 45° from the skull as reported in this study (16). A co-worker neurosurgeon performed all of the healthcare interventions, and the author examined the curative effect.

To evaluate the effects of rTMS, a visual analog scale (VAS) for pain was used pre-rTMS, immediately after rTMS (0 min), and six times (at 60 min, 120 min, 180 min, 240 min, 300 min, and 24 hrs) with sham and real rTMS in each patient. Each of the averaged VAS scores at 0, 60, 120, 180, 240, and 300 min and 24 hrs after rTMS were compared with the VAS scores at pre-rTMS. We also calculated the maximum VAS score reduction rate, in which the maximum reduced VAS score among the time points 0, 60, 120, 180, 240, and 300 min and 24 hrs after rTMS were compared with the VAS score at pre-rTMS. Patients with a VAS score reduction of more than 30% compared to that before rTMS were considered sensitive to rTMS (15, 19). In addition, the Patient Global Impression of Change (PGIC) scale was assessed at after sham and real rTMS. The PGIC scale indicates overall improvement according to a 7-point categorical scale: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse. The ratings 2 and 1 were considered to be a clinically significant improvement (20).

**Statistical Analyses**

The intensities of pain as evaluated by the subjects’ VAS scores before and after (at 0, 60, 120, 180, 240, and 300 min and 24 hours) rTMS (sham and real) were compared. The average and maximum VAS score reduction rates in sham rTMS, compared to those in real rTMS, were examined by a paired t-test. In addition, the two groups of patients with facial pain (n = 10) and limb pain (n = 10), in response to the analgesic effect of real rTMS, were examined by an unpaired t-test. The analgesic effect of rTMS was analyzed with a one-way analysis of variance (ANOVA). A post hoc of ANOVA test was then conducted with Bonferroni correction for multiple comparisons. All of the statistical tests were conducted at the \( p = 0.05 \) significance level, and were performed using SPSS® Statistics 20 for Windows (International Business Machines Corp., New York USA).

**Results**

The average reduction rate of the VAS score induced by sham rTMS was 3.1% in all patients; the real rTMS induced
an average reduction rate of a 17.4% VAS score. The maximum reduction rate of the VAS score was 19.4% in sham rTMS and 35.8% in real rTMS. Both the averaged and maximum reduction rates of the VAS score in real rTMS showed significant differences from those in sham rTMS (* p < 0.05, paired t-test) (Fig.4). The one-way ANOVA demonstrated that the subjects' VAS score decreased significantly immediately after rTMS and had continued at 300 min post-rTMS (* p < 0.05, ANOVA) (Fig.5).

There were no significant differences between the facial pain group and the limb pain group, for both the averaged and maximum reduction rates of the VAS score in real rTMS. The real rTMS showed a >30% reduction of the VAS score in 11 (55%) of the 20 patients. Temporary or permanent side effects were not observed in any patients. On the PGIC scale, four patients reported a rating of 3 (minimally improved) and 16 patients reported a rating of 4 (no change) in sham rTMS. In addition, one patient reported a rating of 1 (very much improved), two patients reported a rating of 2 (much improved), 10 patients reported a rating of 3 (minimally improved) and seven patients reported a rating of 4 (no change) in real rTMS (Table 1). On the PGIC scale, 11 patients reported improvement of at least one rank in the comparison of real rTMS and sham rTMS. Among these results, the most

![Fig. 4](image-url)

![Fig. 5](image-url)
improvement of pain was observed in the facial pain patient.

**Discussion**

Tsubokawa et al. (9) were the first researchers to demonstrate the efficacy of the electrical stimulation of the motor cortex in post-stroke pain, and several studies conducted since that 1991 report have shown the effectiveness of MCS therapy (21-24). rTMS has been shown to induce persistent changes in the central nervous system, noninvasively (25). Based on the MCS studies’ findings, rTMS is currently being applied to neuropathic pain. High-frequency rTMS (≥ 1 Hz) enhances neuronal firing efficacy, and low-frequency rTMS (< 1 Hz) has an inhibition effect (26). Lefaucheur et al. (14) examined the effect of rTMS at two frequencies (0.5 and 10 Hz) in 18 patients with intractable unilateral upper limb pain. The VAS score was improved in response to stimulation at 10 Hz; stimulation at 0.5 Hz did not improve the VAS score. Analgesic effects of high-frequency rTMS have also been reported in neuropathic pain (27-29).

In the present study, a single session of 5-Hz rTMS was applied. As a result, the real rTMS led to a decrease in VAS pain scores and demonstrated an analgesic effect compared to the sham rTMS. No side effects related to the rTMS were observed, further confirming the safety of rTMS. In addition, no significant differences between the facial pain group and limb pain group were observed in this study. However, the PGIC scores showing the most improvement of pain were observed in the facial pain patients. In an analysis of 60 patients with neuropathic pain, it was reported that pain reduction was more effective against facial pain compared to limb pain (15). I suspect that this difference may have been caused by the number of investigated cases. I intend to increase the number of investigated cases in a continuation of the present study.

The mechanisms of analgesic effects in motor cortex stimulation have not been elucidated. According to a positron emission tomography (PET) study, MCS increases cerebral blood flow at the ventral-lateral thalamus, medial thalamus, anterior cingulate/orbitofrontal cortex, anterior insula, and upper brainstem (30). A functional magnetic resonance imaging (fMRI) study demonstrated that high-frequency rTMS changes the blood flow in brain regions apart from the stimulation site (31). A common finding is the relatively decreased thalamic regional cerebral blood flow in post-stroke pain patients. Andrade et al. (32) reported that naloxone injection significantly decreased the analgesic effect of rTMS in their study of the cold pain threshold in healthy volunteers, and they demonstrated the involvement of endogenous opioid systems in rTMS-induced analgesia. In addition, Maarrawi et al. (33) reported that MCS, using epidurally implanted electrodes, induced the release of endogenous opioids in brain structures involved in the processing of acute and chronic pain, and they proposed a role of the endogenous opioid system in pain control induced by MCS. Although the stimulation site is the same, it was reported that rTMS induces an electrical current in a direction horizontal to the cerebral cortex, whereas MCS, using epidurally implanted electrodes, induces a current in the vertical direction (34). Thus, we should consider slightly different mechanisms of pain reduction induced by rTMS and MCS.

Hirayama et al. (16) reported that navigation system-guided 5-Hz rTMS (total, 500 stimuli) provided significant and beneficial pain relief in 10 (50%) of 20 patients, and the effect lasted for 180 min. In addition, in a meta-analysis of motor cortex rTMS in 66 post-stroke pain patients, the VAS pain score decreased by 16.7% compared to sham rTMS (35). The present results indicate that rTMS significantly decreased the subjects’ VAS scores until 300 minutes after rTMS, indicating the effectiveness or rTMS treatment for post-stroke pain. However, only one session of motor cortex by rTMS is not sufficient for long-lasting pain reduction in post-stroke pain patients. Khedr et al. (27) reported that the analgesic effect continued at least two weeks after rTMS was performed every day for five days. In the present study, one session of rTMS for primary motor cortex-induced analgesia lasted for 300 min in subjects with post-stroke pain, suggesting that further, rigorously designed studies will be of merit. We strongly stress that rTMS can be adapted for post-stroke pain patients, and it may be useful to select candidates for chronic MCS with epidural electrodes, since it has been reported that the success rate of chronic MCS is about 50% (36).

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