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Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: A randomized, multicenter, double-blind, crossover, sham-controlled trial

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ABSTRACT

There is little evidence for multisession repetitive transcranial magnetic stimulation (rTMS) on pain relief in patients with neuropathic pain (NP), although single-session rTMS was suggested to provide transient pain relief in NP patients. We aimed to assess the efficacy and safety of 10 daily rTMS in NP patients. We conducted a randomized, double-blind, sham-controlled, crossover study at 7 centers. Seventy NP patients were randomly assigned to 2 groups. A series of 10 daily 5-Hz rTMS (500 pulses/session) of primary motor cortex (M1) or sham stimulation was applied to each patient with a follow-up of 17 days. The primary outcome was short-term pain relief assessed using a visual analogue scale (VAS). The secondary outcomes were short-term change in the short form of the McGill pain questionnaire (SF-MPQ), cumulative changes in the following scores (VAS, SF-MPQ, the Patient Global Impression of Change scale [PGIC], and the Beck Depression Inventory [BDI]), and the incidence of adverse events. Analysis was by intention to treat. This trial is registered with the University hospital Medical Information Network Clinical Trials Registry. Sixty-four NP patients were included in the intention-to-treat analysis. The real rTMS, compared with the sham, showed significant short-term improvements in VAS and SF-MPQ scores without a carry-over effect. PGIC scores were significantly better in real rTMS compared with sham during the period with daily rTMS. There were no significant cumulative improvements in VAS, SF-MPQ, and BDI. No serious adverse events were observed. Our findings demonstrate that daily high-frequency rTMS of M1 is tolerable and transiently provides modest pain relief in NP patients.

1. Introduction

Neuropathic pain (NP) is one type of refractory chronic pain condition [6]. The annual incidence of NP has been reported to be 0.82% [8] and the prevalence of neuropathic characteristics with chronic pain has been reported as 6.9% in the general population [5]. The medical treatments for NP often fail to relieve the pain, and symptoms are persistent. These painful conditions often disturb the activities of daily living and reduce the quality of life for patients [6].

For these refractory disease conditions, electrical motor cortex stimulation (EMCS) targeting the primary motor cortex (M1) has provided pain relief in about half of patients [38]. However, EMCS requires an invasive implantation of intracranial electrodes and a pulse generator. According to recent reports, including ours, noninvasive high-frequency (HF) ($\geqslant$5 Hz) repetitive transcranial magnetic stimulation (rTMS) of M1 can have pain-relieving effects in NP patients [3,14,15,17,21–25,27,31,36]. Most previous reports

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have evaluated the short-term effects on pain after a single session of rTMS. The reported effect of a single-session of rTMS is transient, lasting from several hours up to a week [14,15,25,36]. Based on these results, repeated administration of rTMS, like daily stimulation, was expected to be suitable and practical in clinical use. A few multisession studies were reported. Five consecutive days of rTMS resulted in remarkable pain relief in NP patients, lasting over 2 weeks in a parallel study [17], although the Cochrane review suggested that this study had a high risk of bias in the randomization process [31]. Meanwhile, another blinded, randomized crossover study applying multisession rTMS to patients with spinal cord injury (SCI) did not demonstrate positive effects in the short or long term [16]. Of all the previous reports, adequate randomization and blinding of assessors were done in only 4 studies (3 single sessions evaluating a short-term effect [3,4,23] and one multisession [16]). To establish the further clinical use of HF-rTMS of M1 for NP, a well-designed, blinded, randomized controlled trial (RCT) of multisession rTMS is needed. In the current study, we aimed to assess the safety and efficacy of a daily 10-session of HF-rTMS targeting M1 in patients suffering from NP, assessing not only the short-term effects on pain, but also any cumulative effects.

2. Methods

2.1. Patients

This was a multicenter, randomized, double-blind, sham-controlled, crossover study conducted at 7 centers in Japan from August 2009 to December 2011. We enrolled patients aged 20 years or over who met the criteria for NP [29] and whose pain lasted 6 months or longer despite adequate treatments. Exclusion criteria were the inability to write the questionnaires, dementia, aphasia, major psychiatric disease, suicidal wish, pregnancy, and contraindications to TMS, like implantation of a cardiac pacemaker [39]. Enrollment of participants, interventions, and assessments were done in the study centers on an outpatient or inpatient basis. As we studied an add-on effect of rTMS, the patients were asked not to change their usual medications.

This RCT was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and the Japanese ethical guidelines for clinical studies. The study protocol was thoroughly reviewed and approved by institutional review boards and the ethics committees of all the study institutions. All patients provided written informed consent and assent before enrollment.

2.2. Randomization and masking

Before the patient enrollment, the independent data center developed a randomization program to assign each patient to one of 2 treatment groups (1:1). A real rTMS period was followed by a sham period in group A, and a real rTMS period came after a sham period in group B. We used Pocock and Simon's minimization method to stratify treatment groups according to institution, age (<60 or $\geqslant 60$ years), sex, and underlying disease (a cerebral lesion or not), and the Mersenne twister for random number generation [34].

After confirmation of patient eligibility, the data center received a registration form from an assessor who collected questionnaires and assessed adverse events, and then sent an assignment notice to an investigator who conducted the rTMS intervention. Patients were identified by sequential numbers that were assigned by the data center. Patients and assessors were blind to group assignment until the study was completed. The data center was responsible for assigning patients to a treatment group, data management, central monitoring, and statistical analyses.

2.3. Procedures

A session of the stimulation was applied daily for 10 consecutive days, except for weekends, followed by a follow-up of at least 17 days. Typically, a stimulation period started on Monday (day 1) and ended on Friday (day 12), and the follow-up lasted up to Monday after 4 weeks (day 29). The same stimulation (real or sham) was applied daily over the stimulation period. Real and sham stimulation periods were separated by 17 days or longer. This interperiod interval was based on the fact that significant pain relief was no longer observed 2 weeks after a single 5-Hz rTMS session of 1500 pulses in 30 NP patients [15].

Fig. 1 shows the time schedule of the evaluations. Current pain intensity was examined every day in each patient using a visual analogue scale (VAS; scaled 0–100) and short-form McGill pain questionnaire (SF-MPQ; scaled 0–45) [30] from the day before intervention (day 0) to day 29. In the days with the intervention, these scores were obtained before the intervention, just after, and 60 min after the intervention. On the other days, patients were asked to record the scores once a day at approximately the same hour as the intervention. The Patient Global Impression of Change (PGIC) [9] uses a 7-point scale from "very much improved" to "very much worse." A PGIC score was obtained on days 5, 12, 15, 22, and 29. In addition, the severity of depressive symptoms was measured by the Beck Depression Inventory (BDI) on days 0, 1 (before the intervention), 5 (after the intervention), 12 (after the intervention), 22, and 29. All items were recorded in unified forms by patients. Blinded assessors rated these scales and recorded on case report forms with or without observed adverse events.

The rTMS was applied through a figure-8 coil connected to a magnetic stimulator, which provides a biphasic pulse (Magstim Rapid, Magstim Company, UK; or AAA- 81077, Nihon Kohden Corp, Tokyo, Japan). To keep the same conditions as sham stimulation, sham electrodes were fixed on the head during real stimulation. The center of the coil was placed on M1 corresponding to a painful region (face, hand, or foot). The optimal stimulus site, motor hot spot, was finally determined according to visual detection of muscle twitches, and a resting motor threshold was defined as the minimal intensity necessary to induce at least one visible muscle twitch [13]. A real rTMS session consisted of 10 trains at 90% intensity of resting motor threshold (one train, 50 pulses at 5 Hz; intertrain interval, 50 s). A total of 500 pulses were applied in a session. The detailed methods have been described in previous reports [14,36]. This protocol was developed in accordance with the guidelines for the safe use of rTMS [39].

Realistic sham stimulation [32] was implemented in this study. Ten trains of electrical stimuli at 2 times the intensity of the sensory threshold (one train, 50 stimuli at 5 Hz; intertrain interval, 50 s) were delivered with a conventional electrical stimulator through the electrodes fixed on the head. The cortical effect of the cutaneous electrical stimulation was considered to be negligible at this intensity because of the high electrical resistance of the skull and brief duration of the stimulation [32]. A figure-8 coil, which did not connect to a magnetic stimulator, was placed on the head in the same manner as a real rTMS session. Another coil, which discharged simultaneously with the electrical stimuli, was placed near the unconnected coil to produce the same sound as real rTMS, but not to stimulate the brain.

2.4. Statistical analysis

The primary outcome was a short-term change in the VAS, and the secondary outcomes were short-term change in SF-MPQ, cumulative changes in all the scores (VAS, SF-MPQ, PGIC, and BDI), and the incidence of adverse events.