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Repetitive Transcranial Magnetic Stimulation Is Efficacious as an Add-On to Pharmacological Therapy in Complex Regional Pain Syndrome (CRPS) Type I

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Abstract: **Single-session repetitive transcranial magnetic stimulation (rTMS) of the motor cortex (M1) is effective in the treatment of chronic pain patients, but the analgesic effect of repeated sessions is still unknown. We evaluated the effects of rTMS in patients with refractory pain due to complex regional pain syndrome (CRPS) type I. Twenty-three patients presenting CRPS type I of 1 upper limb were treated with the best medical treatment (analgesics and adjuvant medications, physical therapy) plus 10 daily sessions of either real (r-) or sham (s-) 10Hz rTMS to the motor cortex (M1). Patients were assessed daily and after 1 week and 3 months after the last session using the Visual Analogical Scale (VAS), the McGill Pain Questionnaire (MPQ), the Health Survey-36 (SF-36), and the Hamilton Depression (HDRS). During treatment there was a significant reduction in the VAS scores favoring the r-rTMS group, mean reduction of 4.65 cm (50.9%) against 2.18 cm (24.7%) in the s-rTMS group. The highest reduction occurred at the tenth session and correlated to improvement in the affective and emotional subscores of the MPQ and SF-36. Real rTMS to the M1 produced analgesic effects and positive changes in affective aspects of pain in CRPS patients during the period of stimulation.**

Perspective: ***This study shows an efficacy of repetitive sessions of high-frequency rTMS as an add-on therapy to refractory CRPS type I patients. It had a positive effect in different aspects of pain (sensory-discriminative and emotional-affective). It opens the perspective for the clinical use of this technique.***

Key words: *Transcranial magnetic stimulation, noninvasive cortical stimulation, analgesia, motor cortex, complex regional pain syndromes, causalgia, reflex sympathetic dystrophy, quality of life, pain.*

The results of chronic pain treatment may be poor in spite of newer analgesic drugs and specialized pain centers. Refractory patients maintain high pain levels despite the use of modern pharmacological treatment.[9] Since the first use of motor cortex stimulation to treat neuropathic pain patients in the early 90s by Tsubokawa et al,[29] attention has been drawn to techniques that can modulate cortical excitability to treat chronic pain conditions.[19] In particular, noninvasive techniques, such as high-frequency repetitive transcranial magnetic stimulation (rTMS), have been applied to different cortical areas, especially the precentral gyrus to treat neuropathic pain.[14,26] To date, more than 20 double-blind sham controlled studies have been published indicating an overall positive effect of high-frequency rTMS in neuropathic pain.[15-17] However, the great majority of these studies were on neuropathic pain. Only a few were dedicated to nociceptive pain,[4] fibromyalgia,[22] low-back pain,[12] and complex regional pain syndrome (CRPS) patients.[24]

A large amount of evidence has now been accumulated on the specific effects of rTMS in chronic pain.

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However, its clinical use is still hampered by 2 facts. First, the majority of the studies evaluated the effects of a single session of rTMS in pain intensity, with some few exceptions.[11,13,22] Despite important mechanistic information provided by such single-session studies, the effects of a single session last for a few days at best[1,17] and are unlikely to change the long-term quality of life (QOL) of chronic pain patients. Second, all patients included in rTMS trials for chronic pain were refractory and were all under different pharmacological treatments, which were not controlled for in these studies. Since psychotropic medications used for chronic pain treatment can change cortical excitability and probably the individual response to rTMS,[17,31] this may have influenced the results of some studies, especially those with a small number of patients.[25] In order to overcome these limitations, we performed, for the first time, a sham-controlled study composed of successive sessions of rTMS in patients who were previously under the same evidence-based pharmacological treatment (ie, best medical treatment).[8,27,30]

Methods

We performed a double-blind, placebo-controlled, 2-arm, randomized trial comprising 3 phases: 1) Baseline best medical treatment (BMT) for 30 days; 2) BMT + rTMS sessions for 10 days; and 3) 1-week and 3-month follow-up evaluations (BMT only). Only patients who were able to complete phase 1 were included in phase 2.

The inclusion criteria were: 1) CRPS type I in upper limb according to the International Association for the Study of Pain (IASP) diagnostic criteria.[21] Specifically, all patients underwent nerve-conduction tests to exclude signs of nerve lesion or dysfunction, and care was taken to ascertain that the pain did not fit in the regional distribution of a nerve root or trunk; 2) Patients with chronic pain moderate to severe in intensity (VAS >4) despite optimized pharmacological (at least 2 first-line medications used at maximal tolerated doses, for at least 3 months) and physical therapy; and 3) pain lasting longer than 6 months. Patients presenting severe systemic or psychiatric disorders, prior history of epilepsy, intracranial metallic devices, pacemakers, intrathecal infusion pumps, or epidural electrodes over the brain or spinal cord were excluded. All participants signed a Term of Informed Consent to participate in the study, which had been approved by our Institution's Ethics Review Board.

Best Medical Treatment

All patients were washed out of their previous treatment and started on a standardized pharmacological treatment based on the best evidence available for 30 days (naproxen 250 mg bid, amitriptyline 50 mg qd, and carbamazepine 200 mg bid) and a physical therapy program (kinesiotherapy plus low impact, aerobic, relaxation and stretching exercises) which were continued throughout the study and follow-up (3 months).[8,27,30]

Repetitive Transcranial Magnetic Stimulation

Each participant received 10 consecutive rTMS sessions to the precentral gyrus (once a day with pauses on weekends) of either real (r)-rTMS or sham (s)-rTMS. Each stimulation session consisted of a total of 2,500 pulses delivered during 25, 10-second trains of 10 Hz rTMS (Dantec, MagPro, Minnesota, USA) with an intertrain interval of 60 seconds at an intensity of 100% of rest motor threshold (RMT). A figure-of-eight shaped coil (2 $\times$ 97 mm, MC-B70, MagVenture Tonika Elektronik, Farum, Denmark) was used. RMT was determined in all participants before each session, using single-pulse stimulation of the hand area on the precentral gyrus contralateral to the painful upper limb. Motor-evoked potentials were recorded from the left first dorsal interosseous muscle (FDI) with an EMG amplifier module (9016C070, MagVenture Tonika Elektronik) to the rTMS machine and surface electrodes (9013S0212, Alpine Biomed, Skovlunde, Denmark). RMT was defined as the lowest intensity required eliciting a motor-evoked potential of at least 50 μV in 5 out of 10 trials over the FDI representation on the motor cortex. During stimulation, the coil was oriented tangentially to the scalp and with the main component of the induced electrical current in the anterior-posterior direction. For s-rTMS sessions, an identical 8-shaped coil was used, which did not generate a magnetic field, but did emit a similar noise as the active coil (MC-P-B70, MagVenture Tonika Elektronik). Patients were sat in a comfortable reclining armchair with the head in a fixed position. The coil has held by a custom-made arm that could be adjusted in 3 dimensions and was attached to the chair and to the volunteers head with the use of a tape. After the end of the stimulation, the position of the coil was rechecked to inspect for possible deviations from the targeted scalp area.

Design and Time Course of the Experiment

Fig 1A shows the general outlook of the study according to the CONSORT guidelines and Fig 1B illustrates its design and time course.

1) Phase 1 (BMT) lasted 30 days, during which conventional treatment was standardized. T0 stands for the 30th day of this period.
2) Phase 2 (10 rTMS sessions + BMT) included 10 days, each designated from T1 (first day) to T10 (last day).
3) Phase 3 (follow-up period, under BMT) included an evaluation on the seventh day after the last TMS session (T11) and 3 months after the rTMS treatment (T12).

Pain and QOL Assessment Tools

Changes in pain level were assessed daily (from T0 to T10 and on T11 and T12) by the Visual Analogue Scale for Pain (VAS; 0–10 cm), where zero corresponded to no pain at all and 10 to the most severe pain.[25] The VAS was applied after each rTMS session treatment. The McGill Pain Questionnaire[20] and the Pain Impact