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Repetitive Transcranial Magnetic Stimulation for Phantom Limb Pain in Land Mine Victims: A Double-Blinded, Randomized, Sham-Controlled Trial

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Abstract: **We evaluated the effects of repetitive transcranial magnetic stimulation (rTMS) in the treatment of phantom limb pain (PLP) in land mine victims. Fifty-four patients with PLP were enrolled in a randomized, double-blinded, placebo-controlled, parallel group single-center trial. The intervention consisted of real or sham rTMS of M1 contralateral to the amputated leg. rTMS was given in series of 20 trains of 6-second duration (54-second intertrain, intensity 90% of motor threshold) at a stimulation rate of 10 Hz (1,200 pulses), 20 minutes per day, during 10 days. For the control group, a sham coil was used. The administration of active rTMS induced a significantly greater reduction in pain intensity (visual analogue scale scores) 15 days after treatment compared with sham stimulation (−53.38 ± 53.12% vs −22.93 ± 57.16%; mean between-group difference = 30.44%, 95% confidence interval, .30–60.58; *P* = .03). This effect was not significant 30 days after treatment. In addition, 19 subjects (70.3%) attained a clinically significant pain reduction (>30%) in the active group compared with 11 in the sham group (40.7%) 15 days after treatment (*P* = .03). The administration of 10 Hz rTMS on the contralateral primary motor cortex for 2 weeks in traumatic amputees with PLP induced significant clinical improvement in pain.**

Perspective: ***High-frequency rTMS on the contralateral primary motor cortex of traumatic amputees induced a clinically significant pain reduction up to 15 days after treatment without any major secondary effect. These results indicate that rTMS is a safe and effective therapy in patients with PLP caused by land mine explosions.***

Key words: *Phantom limb pain, land mine victims, rTMS, neuropathic pain, noninvasive brain stimulation.*

Land mines are one of the world's most disabling public health hazards causing devastating injuries such as traumatic limb amputations and associated psychological disorders.[13,45] The exact number of worldwide land mine victims is currently unknown because there is no systematic collection of reliable data. However, it is widely estimated that land mines result in 15,000 to 25,000 victims each year.[43] After trauma-related limb amputation for land mine injury, one of the significant causes of disability is the presence of phantom limb pain (PLP).[38,42,48] PLP is a neuropathic syndrome characterized by pain felt in the patients' remaining perception of the amputated limb after partial or complete deafferentation. This pain is usually described as a stabbing, throbbing, burning, or cramping sensation.[14,24,33] PLP is present in up to 87% of all amputees[24] and is considered a challenging condition because of its negative effect on quality of life and lack of treatment response, particularly in patients with traumatic-related amputations.[1,15]

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Maladaptive plasticity seems to play a major role in the mechanisms of PLP. Reorganization of the primary sensorimotor cortex, including changes in motor cortex excitability and peripheral factors such as nociceptive inputs from the residual limb have been implicated in the development of this condition.[1,16,39] Additionally, psychological factors may affect pain duration and severity.[23] The high prevalence of PLP after amputation and its lack of treatment response have resulted in major efforts to develop interventions to decrease the pain in affected patients.[11] In light of PLP mechanisms, repetitive transcranial magnetic stimulation (rTMS) has been tested in this condition as a tool to block the maladaptive plasticity in the sensorimotor cortex.[1] rTMS applied daily over the primary motor cortex (M1) has shown pain relief effects in other neuropathic pain syndromes such as poststroke pain and spinal cord injury pain.[22,28,49] Some previous reports have also suggested analgesic effects of rTMS in subjects with PLP.[1,10] There have been only 3 trials testing rTMS in PLP—2 of them were small pilot studies[10,46] and the other was a randomized clinical trial (RCT) with 27 subjects.[1] The RCT showed that 5 consecutive sessions of rTMS induced a significant analgesic effect compared with sham rTMS, lasting up to 2 months in 39% of the subjects. However, a recent meta-analysis judged this trial as a high risk of bias study due to a deficient randomization method, which led to an unbalanced distribution between the intervention groups.[36] Furthermore, the conclusion of the cited meta-analysis, after including 56 trials using noninvasive brain stimulation techniques for chronic pain treatment, was that although single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain, these effects do not meet the predetermined threshold of minimal clinical significance, and there is therefore a need for larger, rigorously designed studies, particularly of longer courses of stimulation.

In light of these results, we aimed to assess in a larger sample size study and properly designed RCT, the immediate and sustained effects of a larger dose of real rTMS of M1—10 sessions—on PLP compared with sham rTMS in land mine victims. We hypothesized that 10 Hz rTMS for 2 weeks over M1 contralateral to the PLP could significantly decrease the level of pain compared with sham stimulation.

Methods

Study Design

This was a single-center, double-blinded, sham-controlled, randomized, parallel-group trial that consisted of 3 main phases: 1) a baseline evaluation consisting of a week period of observation to establish baseline measurements for pain levels, depression, and anxiety symptomatology, 2) a treatment phase consisting of daily sessions with active or sham rTMS for 5 days a week during 2 consecutive weeks, and 3) a follow-up evaluation after 15 and 30 days of treatment completion. In the baseline evaluation, we recorded demographic data, medical history, medications, and other therapies used for the treatment of PLP.

Study Population

Fifty-four patients (mean age, 33.9 ± 8.41 years; 4 female patients) were included in the study. The participants were prospectively selected from the rehabilitation department of the Regional Military Hospital and local nongovernmental organizations in Bucaramanga, Colombia. Patients were included if they fulfilled the following criteria: adults aged 18 years or older, who had amputation at any level of 1 lower limb by antipersonnel land mines with symptoms compatible with PLP. PLP was defined as a sensation of shooting, stabbing, boring, squeezing, throbbing, or burning or paresthesia or any other pain sensation in a limb that did not exist anymore.[34]

We excluded patients with a diagnosis of complex regional pain syndrome, any pathology that could alter the course of PLP (diagnosis of cancer, immunological disorders, renal insufficiency requiring dialysis treatment, etc), pregnancy, neuropsychiatric disorders that can affect the patient ability to consent to the study participation and contraindications to rTMS, such as cardiac pacemaker, medical pumps, or implanted metals in the scalp.[47] This study was performed in accordance with the Declaration of Helsinki (1964).[8] Written informed consent was obtained from each participant before inclusion in the study, which was approved by the local institutional review board.

Intervention: rTMS

Patients received rTMS on the primary motor cortex (M1) contralateral to the amputated leg using a figure-of-eight coil connected to a Magstim Rapid[2] magnetic stimulator, which provides a biphasic pulse (Magstim Company Ltd, Whitland, UK). The coil was positioned tangentially to the scalp, approximately at a 45° angle from the midline. The resting motor threshold (RMT) (of the first dorsal interosseous) was defined as the minimal intensity to induce motor evoked potentials of 50 μV peak-to-peak amplitude in at least 5 of 10 trials. Twenty trains of 6 seconds each (intertrain interval 54 seconds), using an intensity of 90% of RMT and 10 Hz frequency, were applied in each patient for 10 days during a 2-week period. For the sham treatment group, stimulation parameters were the same (location and duration), but a sham coil (Magstim Company Ltd) was used. This coil has similar appearance to the active coil in shape and weight, and produces a similar sound artifact but does not induce a scalp skin sensation nor emit a magnetic pulse within the cortex.[30] All sessions were administered by only 1 investigator who was not blinded to the intervention and did not participate in the outcome assessments. Participants and investigators who performed the pain assessments were blinded to treatment allocation.