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Repetitive Transcranial Magnetic Stimulation Increases the Corticospinal Inhibition and the Brain-Derived Neurotrophic Factor in Chronic Myofascial Pain Syndrome: An Explanatory Double-Blinded, Randomized, Sham-Controlled Trial

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Abstract: **Chronic myofascial pain syndrome has been related to defective descending inhibitory systems. Twenty-four females aged 19 to 65 years with chronic myofascial pain syndrome were randomized to receive 10 sessions of repetitive transcranial magnetic stimulation (rTMS) (n = 12) at 10 Hz or a sham intervention (n = 12). We tested if pain (quantitative sensory testing), descending inhibitory systems (conditioned pain modulation [quantitative sensory testing + conditioned pain modulation]), cortical excitability (TMS parameters), and the brain-derived neurotrophic factor (BDNF) would be modified. There was a significant interaction (time vs group) regarding the main outcomes of the pain scores as indexed by the visual analog scale on pain (analysis of variance, $P < .01$). Post hoc analysis showed that compared with placebo-sham, the treatment reduced daily pain scores by −30.21% (95% confidence interval = −39.23 to −21.20) and analgesic use by −44.56 (−57.46 to −31.67). Compared to sham, rTMS enhanced the corticospinal inhibitory system (41.74% reduction in quantitative sensory testing + conditioned pain modulation, $P < .05$), reduced the intracortical facilitation in 23.94% ($P = .03$), increased the motor evoked potential in 52.02% ($P = .02$), and presented 12.38 ng/mL higher serum BDNF (95% confidence interval = 2.32–22.38). No adverse events were observed. rTMS analgesic effects in chronic myofascial pain syndrome were mediated by top-down regulation mechanisms, enhancing the corticospinal inhibitory system possibly via BDNF secretion modulation.**

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Perspective: ***High-frequency rTMS analgesic effects were mediated by top-down regulation mechanisms enhancing the corticospinal inhibitory, and this effect involved an increase in BDNF secretion.***

Key words: *Myofascial pain syndrome, transcranial magnetic simulation, clinical trial, brain-derived neurotrophic factor, quantitative sensory testing.*

Myofascial pain syndrome (MPS) is considered a leading cause of musculoskeletal pain.[50] Epidemiologic studies have found that myofascial trigger points might be the source of nociceptive inputs in 30–85% of the patients with chronic pain who seek pain therapy.[49] Although the complete pathophysiology of MPS remains unknown, cumulative evidence suggests that in chronic pain there are defective inhibitory systems as indexed by motor cortex intracortical inhibition.[39,46] The intracortical inhibition is partially reverted by treatment with noninvasive brain stimulation techniques[3,31,32,38] such as repetitive transcranial magnetic stimulation (rTMS).[27]

Previous studies have shown positive therapeutic effects of rTMS in acute pain[41] and in some chronic pain conditions, such as migraine, central pain, fibromyalgia, trigeminal neuralgia, postherpetic neuralgia, and visceral pain.[29,30,33,42] However, results have been mixed. In a recent meta-analysis[43] that included 19 rTMS studies, multiple discrepancies were revealed such as size, sample characteristics, and rTMS parameters, including the site of stimulation and the number of stimulation sessions. In fact, the mechanisms of rTMS underlying its antinociception effects are not completely understood, even though cumulative evidence suggests that the initial effect of rTMS on neuronal depolarization or hyperpolarization[34] induces long-term potentiation or depression, which in turn produces lasting changes on neocortical excitability and synaptic connections[18] that secondarily modulate pain-related neural circuits.

As a neuronal modulator, the brain-derived neurotrophic factor (BDNF) appears to play a role in chronic pain and neuronal plasticity. The BDNF has shown to be an important upstream regulator of long-term potentiation in the hippocampus and neocortex during motor learning.[21] Clinical studies have found higher BDNF levels in blood and in the cerebrospinal fluid in patients with chronic pain conditions such as fibromyalgia and migraine when compared with healthy controls.[20] Additionally, the BDNF effects may be region-specific, as it is downregulated in the hippocampus but upregulated in the spinal dorsal horn in rats exposed to pain.[16] Notably, BDNF can also be regulated using therapeutic interventions. Healthy subjects receiving rTMS increase their plasma BDNF levels almost 3-fold compared to those receiving a sham intervention.[54] Additionally, depressed patients receiving multiple rTMS sessions increase their serum BDNF.[56] Thus, we hypothesize that chronic pain will behave similarly, and that rTMS may change the activity of the BDNF, which plays a role in chronic pain. Although rTMS has shown promising results, few studies have assessed simultaneously its effect on human behavior, neurophysiology, and biochemistry. Thus, besides pain, we assessed TMS-indexed cortical excitability and a neuroplasticity mediator, the BDNF, after either rTMS or a placebo-sham intervention in patients with chronic MPS.

We conducted an explanatory phase II clinical trial to understand the initial efficacy of rTMS in MPS and also the mechanisms underlying the therapeutic effects of rTMS. We tested the hypothesis that 10 sessions of rTMS in MPS as compared with placebo-sham intervention were associated with significant changes in pain score and quantitative sensory testing (QST) during cold water immersion (conditioned pain modulation [CPM]). In addition, we measured 2 biological markers of neuroplasticity: cortical excitability parameters and serum BDNF.

Methods

The methods and results sections are reported according to the CONSORT guidelines. In Fig 1, the flow chart of the study is presented.

Design Overview, Settings and Participants

All patients provided written informed consent before participating in this randomized, double-blinded, 2-group parallel clinical trial, which was approved by the research ethics committee at the Hospital de Clínicas de Porto Alegre (institutional review board 0000921) in accordance with the Declaration of Helsinki (resolution 196/96 of the National Health Council). We recruited 24 right-handed female patients aged 19 to 65 years with a diagnosis of MPS in an upper body segment for at least 3 months prior to enrollment; these patients were experiencing limitations in active and routine activities due to MPS several times a week. The last criterion was evaluated using a questionnaire that included 6 categorical questions (yes/no). These questions were asked by an independent examiner and were aimed at assessing interference with work, personal relationships, pleasure of activities, responsibilities at home, personal goals, and clear thinking (ie, problem solving, concentrating, and/or remembering) during the past 3 months. For enrollment, subjects needed a positive answer to 1 or more of these questions to ensure that chronic pain was lowering the patient's quality of life. Moreover, the diagnosis of MPS was confirmed by a second independent examiner (W.C.) with more than 10 years of clinical experience related to chronic pain. The MPS criteria were defined by regional pain, normal neurologic examination, decreased range of motion, stiffness in the target muscles, presence of trigger