Repetitive Transcranial Magnetic Stimulation (rTMS) in Fibromyalgia

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Objectives

Fibromyalgia syndrome (FMS) is a chronic pain condition characterized by widespread pain, stiffness, overwhelming fatigue, sleep disturbance, alteration in mood, cognitive dysfunction (fibrofog) and impaired quality of life and daily function (1,2). FMS is present in as much as 0.2% to 6.6% of the general population and is more common in women than in men (3). It has substantial impacts on quality of life, physical functioning and social-occupational productivity therefore financial costs are an economic burden to these patients (4). The pathophysiology of this syndrome is still unknown but genetic predisposition, hypothalamic-pituitary-adrenal axis dysfunction, environmental factors, autonomous dysfunction, metabolic factors, neuropathies and neuromodulation all being considered to be involved in the onset and course of the disease (2,5). As we know today, the most acceptable theory is the central sensitization that includes altered pain processing based on peripheral and central nervous system influences (5,6).

The purpose of FMS management is to reduce pain, improve sleep and restore physical, emotional and mental function, thereby improving overall quality of life but there is no gold standard treatment method due to the difficulty of the diagnosis of the disease as well as the unknown pathophysiology (2,7). High quality evidence are supporting multidisciplinary approach that include nonpharmacological therapies (education, exercise, cognitive behavioral therapy, physical-therapy agents, acupuncture, multicomponent treatments) and pharmacological therapies (tricyclics, serotonin norepinephrine reuptake inhibitors, and gabapentinoids) to achieve optimal management results (7-9). Recently, a growing number of studies are performed on modulation of

central pain pathways of FMS. The promising treatment option in this regard is seen as neuromodulation techniques such as transcranial magnetic stimulation (TMS) (10,11).

Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive method of stimulating neurons in the cerebral cortex. It is used to induce changes in brain activity that can produce after-effects on the brain (12,13). rTMS modulates cortical plasticity, which is called the functional rearrangement of connections between neurons and neuronal features (12,13). It is generally assumed that rTMS-induced effects may closely relate to synaptic plasticity, such as long-term potentiation (LTP) or depression (LTD) (13,14). An after-effect induced by rTMS depends on stimulation frequency. High-frequency rTMS at 5 Hz or higher transiently increases cortical excitability (i.e. LTP-like), while stimulation at 1 Hz decreases cortical excitability (LTD-like) (14). rTMS also affects brain activities related to pain modulation and processing. Therefore, its use in pain syndromes is increasing (15,16). Additionally, rTMS offers potential for clinical application in a variety of neurological, psychiatric diseases (e.g. stroke, Parkinson, dementia, depression) (16-18). Also recently, the success of these treatments is enhanced by using neuronavigation systems that accurately position the coil on a target and keep the coil in the correct place during the session (19).

Although there are many randomized clinical trials and meta-analysis revealing beneficial effects of rTMS in FMS, there is no consensus regarding the exact efficacy, neither on the optimal parameters of stimulation. Studies have generally focused on high frequency stimulation of the left primary motor cortex (M1) or left dorsolateral prefrontal cortex (DLPFC). In recent meta-analysis, few randomized controlled, double-blind studies were evaluated and these studies mainly investigated pain, quality of life, and mood in FMS. Klinck et al., reported that there was no significant difference between

sham or active rTMS for reducing pain or depression but active rTMS was associated with a significant improvement on quality of life (11). Saltychev et al. revealed moderate evidence that rTMS is not more effective than sham in reducing the severity of pain in FMS (20). Hou et al. suggested that M1 stimulation may be better in pain reduction and the DLPFC may be better in depression improvement (10). On contrary to this study, recently Lefaucheur et al. reported that high frequency-rTMS of the left DLPFC is more efficacious on pain, while high frequency -rTMS of the left M1 is more efficacious on the quality of life (21). In addition, there are very few studies investigating the effect of TMS treatment on cognitive dysfunction, which is an important problem in FMS (22). It is clear that there is still a need for further studies on the exact clinical effects of rTMS treatment in FMS.

Therefore, this study aimed to evaluate the effectiveness of 10 Hz neuronavigated rTMS to the left DLPFC on pain, stiffness, fatigue, depression/anxiety, quality of life and cognitive functions in FMS.

Methods

Participants

Participants were recruited from Physical Medicine and Rehabilitation (PMR) outpatient clinics of a university hospital. Twenty patients (mean ages: 45.25 ± 9.08 years, range 29 to 64 years; 20 females) with FMS who met the following inclusion criteria were included in the study: (1) adults (age between 18-65 years); (2) diagnosis of FMS according to 2016 Fibromyalgia diagnostic criteria; (3) the mean pain intensity is VAS ≥4 /10; (4) stable treatment for at least last 3 months. Patients were excluded: if they had a clinical condition to be contraindicated for TMS (e.g. metallic implant, cardiac pace, pregnancy, lactation, epilepsy, head trauma, history of cranial operation); significant medical or psychiatric illness including malignancy, major depression, personality disorder, history of substance or alcohol abuse; major orthopedic/ neurological problems that limit daily life activities; pregnancy/breastfeeding; concomitant inflammatory rheumatic diseases, autoimmune diseases or other painful disorders and patients who have received TMS treatment before.

Study design and ethics

This is a single-center, prospective, randomized, double-blind, sham-controlled study in two-arm parallel-group design. Participants were informed about the study and provided written informed consents. The protocol was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by the local Research Ethics Committee (Approval number: 14.03.2019/25). This study was registered on www.clinicaltrials.gov with ID NCT03909009.

Demographics

At baseline, demographic information including age, gender, weight, height, body mass index (BMI), dominant side, marital status, education level, occupation, disease duration, additional diseases, smoking and alcohol use, drugs used for FMS treatment were questioned.

Randomization and blinding

Randomization was performed using computer-generated block randomization with 1:1 allocation between the active rTMS group (Group A) and the sham-control group (Group B) by an independent researcher not involved in the rTMS treatment sessions, patient selection or clinical evaluations. Two different researchers conducted other parts of this double-blind study. One of the researchers performed patient selection and interventions. The second researcher was blinded about the distribution of groups, patient selection and interventions. The blind investigator performed patient evaluations at the beginning of treatment, at the end of the 2nd and 6th weeks. The patients did not know which group they were in during the study.

Outcome assessment and data collection

After recording general demographic data clinical assessments were performed. All clinical outcome measures were assessed by an experienced researcher who was familiarized with the scales and tests used in this study and who was blinded of the group assignment. The clinical assessments consisted of six main sections: (1) Pain severity (VAS-pain) (2) Stiffness severity (VAS-stiffness) (3) Fibromyalgia Impact Questionnaire (FIQ) (4) Fatigue Severity Scale (FSS) (5) Hospital Depression Anxiety Scale (HADS) (6) Addenbrook Cognitive Examination - revised version (ACE-R)

Primary clinical outcome measure included VAS-pain (at the end of the 2nd week) whereas secondary outcome measures included FIQ and VAS-pain scores at the end of the 6th week.

Visual analog scale: Pain severity and stiffness severity were evaluated with VAS. VAS is a psychometric measuring instrument designed to document the severity of disease-related symptoms. In this study, the severity of the pain and stiffness experienced at rest were assessed on a 10cm VAS (Total score: 0-10)(Higher scores mean a worse outcome) (0=no pain/stiffness, 10=severe pain/stiffness) at baseline, at 2nd week and at the end of treatment (6th week) (23).

Fibromyalgia Impact Questionnaire (FIQ): Functional health status and quality of life of the participants were assessed with the FIQ, which measures 10 different features (physical functioning, missed days of work, depression, anxiety, feeling good, morning tiredness, pain, stiffness, fatigue, and well-being over the past week). The total FIQ score is 0-80 points. High scores indicate low functionality level. In our study, FIQ was evaluated at baseline, at the end of the 2nd and 6th week (24).

Fatigue Severity Scale (FSS): Severity of fatigue was evaluated with FSS, a 9-item self-report questionnaire scale. Each item of this scale consists of statements that are scored on a seven-point Likert type scale ranging from 1 to 7. Total FSS score is calculated as mean value of the nine items. Higher scores indicate higher fatigue severity (Total score range: 1-7). FSS was assessed at baseline, at the end of the 2nd and 6th week (25).

Hospital Anxiety and Depression Scale (HADS): HADS is an assessment tool developed to identify the risk of anxiety and depression and measure its level and change of severity. Its subscales are anxiety and depression. It contains 14 questions in total, including 7 (odd numbers) measuring anxiety and 7 (even numbers) measuring

depression. The lowest and highest total score that a person can obtain from this scale are 0 and 42, respectively. High scores are associated with a worse psychiatric condition. HADS was evaluated at baseline and 6th week of study (26).

Addenbrook Cognitive Examination Revised (ACE-R): Addenbrook Cognitive Examination-Revised is a brief cognitive test that consists of 5 basic sections: attention and orientation, memory, verbal fluency, language and visual-spatial abilities. Total score that can be obtained is 0-100. Higher scores are associated with a better cognitive state. ACE-R is considered useful in discriminating cognitively normal subjects from patients with mild cognitive impairment. ACE-R was assessed at baseline and 6th week of our study (27).

Interventions

Twenty patients were randomized into two groups. After randomization, group A received total 14 sessions of rTMS, 10 sessions daily (5 days/week, 2 weeks) and 4 sessions weekly (1 day/week, 4 weeks). Group B received sham treatment in the same sessions and time.

Neuronavigated repetitive transcranial magnetic stimulation: Brain images for participants were performed on a 1.5T magnetic resonance scanner (GE Sigma HDxt, General Electric Medical Systems, Milwaukee, WI, USA) using an eight-channel head coil. Magnetic resonance imaging (MRI) scans of each participant's brain were imported to the 3D guided neuronavigation device (NeNa-Neural navigator, The BrainTRAK^{TM}, Brain Science Tools BV, Utrecht, Netherlands). Then, we performed brain segmentation and the creation of stimulation target. The location of the left DLPFC was determined by an experienced researcher in accordance with the literature (28). These information were saved and used to target the left-DLPFC in the future sessions. The position of the TMS

coil and the patient's head was tracked using the BrainTRAK^{TM}, a magnetic position tracking device built into the Neural Navigator.

A Neuro-MS/D TMS device (Neurosoft, Russia) with a figure-of eight coil was used for rTMS. The participants were seated in a comfortable chair with headrest and armrests, and were told to rest both hands and upper limbs on top of their thighs. At the beginning of each session, the resting motor threshold (RMT) of each participant was determined using Neuro-MEP-Micro 2-channel Electromyogram (EMG) (Neurosoft, Russia) device. RMT was defined as the minimum stimulation intensity to evoke an MEP greater than 50μV in at least 5 of 10 single-pulse TMS trials applied to the left primary motor cortex (M1). EMG signals were recorded from electrodes placed over the first dorsal interosseous muscle of the right hand, with a circular ground electrode placed over the wrist. rTMS therapy was applied under the guide of neuronavigation with the following parameters: target-left DLPFC, with the %90 of the RMT, 10 Hz stimulation for 5 seconds intervals (on) with 25 seconds inter-train intervals (off), 15 minutes, 1500 pulses. The stimulation parameters of the study protocol are within the safety limits recommended for rTMS (29). For sham stimulation, probe localization was performed as in the active group but probe reversely positioned and during sham stimulation, patients heard a sound similar to the sound heard by those receiving the active treatment. Moreover, all patients were rTMS-naive, so they could not recognize the sham or active treatment techniques.

Sample size

Sample size calculation was performed with G*Power software (G*Power, version 3.1.9.2, Germany). A priori sample size based on the work of Tekin et al. (30) was calculated on the basis of changes in pain scores (VAS) evaluated before and after the

treatment. It was determined that at least 5, total 10 patients in each group should be included in the study according to 80% power, 5% margin of error and 1.73 effect size. Considering the statistical methods and the drop of patients from the study, the sample size was planned as at least 10 patients in each group and at least 20 patients in total.

Statistical analysis

Database management and statistical analyses were performed by an independent researcher. The statistical analysis was performed by SPSS Statistics 22.0 (IBM Corp., Armonk, New York, ABD) software. As the descriptive statistics, the number of units (n), percent (%), mean ± standard deviation ($\bar{x} \pm ss$), median [IQR (interquartile range)] values were given. Distributions of continuous variables were evaluated using the Shapiro–Wilk test and Q-Q plots. Pearson chi-square test, Fisher's Exact test, and independent samples t-test were performed to determine differences between the demographic and clinical characteristic of the groups. Wilcoxon's signed-rank test and Mann-Whitney U-test were used to determine differences within and between the groups' baseline, 2nd or 6th week outcome parameters. If the two groups met the assumptions in terms of pain, stiffness, FIQ, and FSS variables measured at three different times, they were compared using bidirectional (treatment method x time) variance analysis in repeated measurements. The variables examined in the 95% confidence level and P values less than 0.05 were considered significant.

Ethics Committee Approval

Author declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

University local Research Ethics Committee Approval number: 14.03.2019/25

Informed Consent

Written informed consent was obtained from the patients who participated in this study

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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