Exercise and Neuromodulation in Women with Fibromyalgia: Neurophysiological Adaptations and Clinical Effects

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INTRODUCTION

Fibromyalgia (FM) is the third most common musculoskeletal condition among unspecific chronic pain conditions with a prevalence of 2.7% worldwide[1] and a ratio female to male 3:1[2]. FM is characterized by three cardinal symptoms[1]: widespread pain (i.e. generalized head-to-toes [1] and neuropathic symptoms such as paraesthesia [3 4]), fatigue (physical and mental) and sleep disorders (insomnia, frequent awakening, non-restoring sleep) [1 5-7].

Several non-pharmacological treatments are available for managing FM symptoms such as (i) patient education, (ii) psychotherapy, (iii) neuromodulation (transcranial direct current stimulations: tDCS) and (iv) exercise [1]. The exercise has shown effective for reduce pain, fatigue and improves functionality in fibromyalgia[8]. The Ottawa expert panel recommends aerobic exercise as a treatment for individuals with fibromyalgia [9]. Similarly, the European League Against Rheumatism [10] exercise has strong recommendation as well; specifically, aerobic exercise has a moderate effect size to reduce pain and to improve physical function [11]. Bush et al. (2002) [12] was conducted to examine the effects of aerobic exercise training in FM, reporting reduction in pain levels (11.4%), pain pressure threshold (28.1%) and improves aerobic performance (17.1%) [12]. Despite the positive results of exercise interventions, the effect of moderate intensity exercise is small [13] and the adherence of these exercise programs is variable, with a treatment dropouts between 5%-34%[14].

Among the strategies to enhance these metrics, various components of physical training have been analyzed, including frequency, duration, type of exercise, and intensity. Interesting, the intensity can play an important role in modulating pain and fatigue [15]. In healthy subjects, has been reported high-intensity interval training (HIIT) generates positive effects in the physical performance, such as increase in maximum strength, muscle power and lean mass [16]. HIIT can modulate the corticospinal excitability, generates exercise enjoyment and increases opioids release in comparison to moderate intensity continuous aerobic exercise [17-19]. These three components can play an important role in increasing exercise adherence. Regarding FM, there are two studies that have shown HIIT decrease pain, anxiety, depression and improves functional capacity, sleep quality and QoL[15 20].

On the other hand, exercise has limitations such as muscle soreness and fatigue, which are described as common physiological effects of initial training in individuals who are deconditioned. Another alternative that has been shown to be effective for modulation of pain in FM, is neuromodulation through transcranial Direct Current Stimulation (tDCS). The tDCS has been shown to increase endogenous μ-opioids release in chronic pain [21] and in healthy subjects improves the muscle endurance [22]. The exercise and tDCS have shown effectiveness in management on pain, fatigue, sleep, anxiety, depression, and quality of life [15 20 23-26]. This suggests the tDCS effects are complementary to exercise [23]. However, further research is needed to confirm these findings, due to the lack of evidence about combined effects of HIIT and tDCS in FM. We hypothesized HIIT + tDCS will be more effective in

the modulating on clinical and neurophysiological variables in comparison than HIIT + sham and HIIT alone.

OBJECTIVES

Primary objective

The study aims to compare the effectiveness HIIT + tDCS, HIIT + sham tDCS and HIIT alone in reducing pain in women with FM.

Secondary objective

- To identify changes after training HIIT + tDCS, HIIT + sham tDCS and HIIT alone on pain, clinical and neurophysiological variables.
- To determine the association between pain, clinical and neurophysiological variables of HIIT + tDCS, HIIT + sham tDCS and HIIT alone.

MEHTODS AND ANALYSIS

Trial design

This protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials Guide[27]. This is a single centre, 3 arm factorial randomized clinical trial (RCT). The participants will be randomized by age and intensity of pain (moderate-severe) using a random blocked randomization sequence after pre intervention measurements. We will use a 1:1:1 allocation ratio to HIIT + tDCS, HIIT + sham tDCS and HIIT. Other investigator of staff will be carried out the randomization and sequentially numbered sealed envelopes process.

Only one investigator responsible for all assessments and training sessions will be blinded to tDCS intervention. The volunteers will not be blinded to tDCS.

Study setting

This is a single site study. All procedures will be carried out at the Musculoskeletal Laboratory, Andrés Bello University.

Eligibility criteria

Inclusion criteria: will include women between 18-65 years old with a diagnosis of Fibromyalgia by physician according to the criteria of the American College of Rheumatology (ACR) 2016. Stable medical treatment for symptoms for a least 4 weeks prior to participation, reported pain equal or higher than 4/10 on numeric rating pain scale (moderate or severe pain) for more than 3 months, body mass index (BMI) between 18.5 and 39.9 kg m^{-2}, stable doses medication for ≥4 weeks, Central Sensitization inventory ≥40 points, controlled high blood pressure.

Exclusion criteria: Present pain unrelated to Fibromyalgia (isolated inflammatory joint, cancer, infectious, traumatic, localized neuropathic or degenerative joint pain), intense headache, cerebral surgery, seizure/epilepsy, cardiovascular, lung, metabolic (II diabetes mellitus), retinopathy or neurological diseases (i.e. stroke and traumatic brain injury antecedents), severe psychiatric disorders, medication contraindicated by TMS, have a cochlear-ferromagnetic and cardiac pacemaker, drugs and alcohol abuse. Are currently pregnant/breastfeeding, under physical therapy treatment or have participated in a designed

sports or exercise training in systematic programs previous 3 months. Are unable to speak or read Spanish fluently (inability to understand the pain scale and cooperate in testing).

INTERVENTION

Exercise

HIIT familiarization

The participants will perform a physical conditioning protocol that includes two weeks with three times per week [28] of HIIT 80%-95% of maximum heart rate (HR) [20] in the following way:

TIME	INTERVAL	PASSIVE RECOVERY	SESSIONS	maximum HR
15 s	2	2 min	2	80%-95%
30 s	3-5	2 min	2	80%-95%
45 s	5-7	2 min	2	80%-95%

Table 1. Description of HIIT familiarization.

HIIT training

From the seventh session to the eighteenth, the participants will perform a HIIT protocol that consists of 1 minute of active cycling at 80%-95% maximum HR [20], 2 minutes of passive recovery for 10 times (1x2x10). Moreover, during HIIT training, will be monitored the effort of HIIT session through RPE scale (6-20) [29] at 15-18 RPE [30 31] between 50-60 revolutions per minute ("workload it costs to pedal, neither light nor heavy"), HR and pain at the beginning and end of each cycle of HIIT. If the participant fails to recover within 2 minutes (>70% maximum heart rate), longer rest time will be allowed until ≤ 70% of maximum HR is achieved [28]. The maximum HR of each session will be considered the maximum HR for the HIIT prescription for the next session. In addition, the diet will be controlled with respect to the day before and the day of exercise session.

Transcranial direct current stimulation (tDCS)

Over the course of four weeks, the tDCS will be applied at the same time as the HIIT session (during exercise). The individual will receive a total of 12 tDCS sessions.

Active (anodal) tDCS

The anode will be placed on the left M1 and the cathode on contralateral supraorbital area before the exercise starts. The stimulation will start at the same time the start exercise intervention, with an intensity of 2mA for 20 minutes [32].

Sham tDCS

During exercise intervention, to replicate the feeling of current ramping up during active stimulation, the active anode placed on the left M1 will be activated for 30 seconds at the beginning and end of the procedure [33]. A period of 30 seconds of ramping is reliable for blinding [34]. Evidence shows that a time period of less than 3 minutes of tDCS intervention, does not generates cortical excitability changes [33].

Outcomes

Primary clinical outcome

The primary outcome is the Numeric rating scale (0-10). Commonly used to assess pain severity using a 0–10 scale, with zero meaning "no pain" and 10 meaning "the worst pain imaginable" [35].

Secondary clinical outcomes

The other cardinal symptoms in fibromyalgia are fatigue and sleep alterations. The fatigue will be assessed through the Multidimensional Fatigue Inventory (MFI)[36]. Sleep will be assessed through VAS (0-100mm)[37] and Pittsburgh Sleep Quality Index (PSQI)[38].

Also, women with fibromyalgia suffer in psychosocial features and will be evaluated catastrophizing of pain through Pain Catastrophizing Scale (PCS)[39], fear of movement through The Tampa Scale for Kinesiophobia (TSK)[40-42], anxiety through State Trait Anxiety Inventory (STAI)[43] and depression through Beck's Depression Inventory II (BDI-II)[44 45]. The cardinal symptoms and psychosocial features affect the QoL. Will be evaluated the QoL through Fibromyalgia Impact Questionnaire (FIQ)[46] and Short Form 36[47].

Regarding exercise, will be evaluated the Three-repetition sit-to-stand test (3R-STS) to quantify the muscle soreness before training sessions, the individuals will be asked to sit and stand 3 times with their legs shoulder width apart and bend their knees to 90° [48] by the VAS pain (0-100 mm). The VAS pain is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain" [49]. The volunteers must mark with a straight vertical line on the horizontal line. Moreover, will be assessed exercise adherence through Exercise Attitude Questionnaire-18 (EAQ-18) [50 51], exercise enjoyment through Physical Activity Enjoyment Scale (PACES)[52 53], physical level activity through International Physical Activity Questionnaire (IPAQ)[54] and cardiovascular risk through Physical Activity Readiness Questionnaire (PAR-Q)[55], the perception of effort during the exercise by Borg's Scale [56] and dyspnoea[57 58]. Finally, will be assessed the anthropometric characteristics through InBody 770 (Sout Korea) and the heigh by stadiometer.

Secondary neuro-physiological outcomes

The corticospinal excitability will be measured with transcranial magnetic stimulation using a Magstim 200[2] & a 7 mm double cone coil (Magstim, UK) in combination with surface electromyography (sEMG; Delsys Bagnoli 16 channels, USA) (supplementary information 10). The stimulation will be in left M1 cortex, and the EMG recordings will be gathered in right vastus lateralis muscle using Ag/AgCl electrodes. The specific variables that will be assessed are:

Motor Evoked Potential (MEP): is the response of the muscle to the stimulation of the corticomotor pathway and it is frequently used to estimate corticospinal excitability [59]. It can be measured as the peak-to-peak amplitude of the EMGs signal. The average of 15 MEPs peak-to-peak amplitudes using an intensity of 120% active motor threshold (aMT) will be collected to asses CSE [60 61].

Cortical Silent Period (CSP): The CSP is defined as the "temporary interruption of electromyographic signal from muscle following a MEP" [62]. It is considered a measure of the excitability mediated by gamma-aminobutyric acid ($GABA_B$) receptors ($GABA_BR$). The SP will be measured in milliseconds (ms) from the end of the MEP wave to the recovery EMG signal to the basal averaged amplitud [63 64].

Rest Motor Threshold (rMT, % output): rMT is defined as the lowest stimulus intensity to evoke MEPs with a peak-to-peak amplitude of 50μV in at least five out of 10 consecutive trials when the muscle at rest [65]. rMT will be expressed as percentage of the TMS output.

Active Motor Threshold (aMT, % output): it is the lowest intensity of the stimulator needed to evoke MEPs with a peak-to-peak amplitude of ≥200 μV in five out of 10 consecutive trials while maintaining an isometric contraction at 10% of the maximal voluntary contraction (MVC)[66]. aMT will be expressed as percentage of the TMS output.

Short Interval intracortical Inhibition (SICI) and Intracortical Facilitation (ICF): Both are transient phenomena that occur at the motor cortex, SICI is a suppression or reduction of the firing of cortical neurons - $GABA_A$ inhibitory circuits- [67-69] and ICF is an excitatory phenomenon mediated by N-methyl-D-aspartate receptors (NMDAR) [70]. Paired pulse paradigms will be used to assess both. These paradigms involve two consecutive stimulations, one conditioning stimulus that is below the threshold (80% rMT) followed by a test stimulus that is above the threshold (120% of the motor threshold) [32]. To assess short intracortical inhibition (SICI), the interstimulus interval will be set to 2 ms, while for intracortical facilitation (ICF), the interval will be set to 15 ms [32]. We will administer ten random stimuli at each interval and calculate the percentage of inhibition or facilitation before and after treatment [32].

Others neuro-physiological outcomes will be assessed are pain pressure threshold by algometer in bilateral supraspinatus muscle, lateral epicondyle, gluteus area and medial fat knee according ACR 1990 [71 72], aerobic capacity [73], quadriceps strength of dominant leg by maximal voluntary isometric contraction (MVIC) [74] and endurance muscle contraction by a time to exhaustion of knee extensors (20% MVIC) adding to High density electromyography (HD-sEMG) for motor units recruitment [75-77].

STATISTICAL ANALYSIS PLAN

Study sample

Will include women between 18-65 years old with a diagnosis of Fibromyalgia by physician according to the criteria of the American College of Rheumatology (ACR) 2016. We will enroll 40 volunteers divided into 3 groups.

Sample size calculation

The sample size was calculated using G*Power 3.1 (Germany), based on the variable pain measured by the Visual Analogue Scale (VAS) from the study by Kolak et al. (2022)[78] with a power of 0.80, an alpha level of 0.05, and accounting for a 20% dropout rate, the required sample size was determined a total of n=40.

Statistical Analysis

The distribution of the data for all variables will be corroborated with the Shapiro wilk normality test. Two-way ANOVA and Pearson correlation will be used if the data is normally distributed, considering a p value < 0.05. If no normal distribution is found the data will be transformed or nonparametric analysis will be used. The data will be presented as mean and standard deviation. Moreover, Two-way ANCOVA will be performed.

Ethics and dissemination

This protocol was approved by the scientific ethics committee (number: 33B2024) at the Faculty of Medicine, Andres Bello University. The results will be reported in congress and peer review journal.

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