Effects of transcranial direct current stimulation, associated with manual vagus nerve therapy, on pain in women with fibromyalgia: Study protocol for a double-blind, randomized, controlled clinical trial.

Aebe Alves Torres  
UFES: Universidade Federal do Espirito Santo

Bárbara Naeme Lima Cordeiro  
UFES: Universidade Federal do Espirito Santo

Samira Tatyiama Myiamoto  
UFES: Universidade Federal do Espirito Santo

Pablo Lucio Gava  
UFES: Universidade Federal do Espirito Santo

Andressa Braz Carlini Pestana  
UFES: Universidade Federal do Espirito Santo

Valéria Valim  
UFES: Universidade Federal do Espirito Santo

Gustavo Pinto de Oliveira Gomes  
UFES: Universidade Federal do Espirito Santo

Pamela Reis Vidal  
UFES: Universidade Federal do Espirito Santo

Elizangela Kuster  
UFES: Universidade Federal do Espirito Santo

Fernando Zanela da Silva Arêas  (fernandozanela@hotmail.com)  
Universidade Federal do Espirito Santo  https://orcid.org/0000-0002-2068-2606

Research Article

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Abstract

**Introduction:** Fibromyalgia (FM) is a condition of generalized musculoskeletal pain, associated with fatigue, autonomic dysfunction and sleep disorders.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique, tested in several diseases, including FM and depending on the parameters used, tDCS can reach several brain neural networks, including the central processing network of the pain. Another therapy that promotes analgesia is manual therapy (MT) which is defined as a set of techniques that uses the hands as the main therapeutic agents. Evidence indicates that MT, applied at points along the vagus nerve (VN), may improve pain in patients with chronic pain. This study will examine the immediate and late effects of tDCS associated with MT on the VN pathway in pain in women with FM.

**Methods:** This is a controlled, randomized, double-blind clinical trial with intention-to-treat analysis that will follow the guidelines of CONSORT (Consolidated Reporting Standards). The study will consist of thirty women diagnosed with FM who will be randomly allocated to the experimental group (tDCS 2 mA active for 20 minutes associated with MT) or to the control group (tDCS for 20 minutes associated with MT sham) and will receive daily sessions of treatment for five days. Outcome measures will occur at the beginning of the study, after the first visit, at the end of treatment and thirty days after the end of treatment.

**Discussion:** The search for therapies to improve pain in FM is quite challenging, mainly due to the lack of knowledge about its etiopathogenesis and the complexity of symptoms that are associated with it. Thus, the results of this clinical trial may result in an important advance for the rehabilitation of FM patients.

**Clinical trial registration:** U1111-1264-9863

**Introduction**

The term fibromyalgia, which is used today by most authors, was proposed in 1981 by Yunus et al¹. Currently, FM is recognized as a condition of generalized musculoskeletal pain² that is regularly accompanied by fatigue, memory impairment and sleep disorders³, in addition to autonomic dysfunction⁴.

FM expresses a high prevalence in today's society, as it affects from 0.2 to 6.6% of the general population, it affects women more than men in a proportion of 9:1, being more frequent in the age group between 40 and 55 years old⁵.

There are no specific laboratory tests capable of identifying the disease⁶, therefore, the diagnosis of FM is performed through a clinical assessment based on the diagnostic criteria established in 1990 by the American College of Rheumatology⁷. Over the years, other clinical aspects presented by FM patients were
taken into account and, today, we have an updated version of the assessment which is, indeed, more comprehensive than the initial one\textsuperscript{8}.

The etiology of FM remains unknown, however, some hypotheses such as pain processing disorders\textsuperscript{9}, neuroendocrine dysfunctions and inflammatory changes assume the appearance and maintenance of symptoms\textsuperscript{1011}.

Nonetheless, we must consider that autonomic dysfunction may play a relevant role in the pathophysiology of FM, although it is not clear whether this change is a cause or a consequence\textsuperscript{1213}. Evidence indicates that the pathways of pain control and autonomic control are related at various levels, from the periphery to the central nervous system (CNS)\textsuperscript{14}. The justification for this finding is anatomical, since areas of the CNS involved with the descending system of nociceptive inhibition overlap with areas that directly influence brainstem neurons. Therefore, in recent decades, interest in the use of therapeutic approaches through VN has grown, due to its role in the modulation of inflammation and pain\textsuperscript{1516}.

Although it is a common disorder, FM treatment is considered one of the most difficult for medicine\textsuperscript{17}. Pain is rarely successfully treated, just a small part of patients experience any clinically relevant benefit\textsuperscript{18}. Therefore, physical, psychological and pharmacological therapies can help to modulate the perception of pain in individuals affected by this condition\textsuperscript{19}. In an attempt to improve the results presented in the control of FM symptoms, several treatment interventions have emerged over the years and, among those with good efficacy for pain treatment, we can mention tDCS and MT\textsuperscript{2021}.

The first records of the use of electrical current for therapeutic purposes were made between 43 and 48 AD. Doctors at that time treated headaches using the electrical discharge of fish, which were rolled over patients' heads\textsuperscript{22}. From this experience onwards, several others have been tested and recorded over the years and have shown that the application of low-intensity continuous electrical current through electrodes located on the individual's skull is capable of inducing bidirectional changes in cortical polarity, where, during stimulation, the anode increases and the cathode decreases cortical excitability\textsuperscript{23}.

In recent decades, there has been a significant advance in research related to non-invasive brain stimulation, which has provided a deeper understanding of its physiological effects and, hence, new treatment possibilities have emerged. One of the pathological conditions that most received the attention of researchers was chronic pain\textsuperscript{24}. Recent studies show that the physiological effects produced by tDCS influence the central processing of pain, resulting in decreased pain and, consequently, improved function\textsuperscript{25}.

MT is another therapeutic option that has been used for many years in the treatment of several chronic pain conditions\textsuperscript{29}, including FM\textsuperscript{2627}, and it may be defined as a set of techniques which use the hands as the main therapeutic agent\textsuperscript{21}.
Experimental studies have shown that manipulations in the cervical and lumbar regions are capable of producing a sympathetic-excitatory effect that can be evidenced by changes in skin conductance and temperature\(^{28,27}\). In another study, it was found that cervical manipulation can acutely affect variability heart rate\(^{29}\).

In addition to the possible autonomic effect, manipulation may also promote an analgesic effect that can be explained in some ways. At the local level, the mechanical action of manipulation decreases the sensitivity of muscle spindles\(^{27}\). At the spinal level, it influences reflex neural outputs to muscles and viscera, affecting motoneuron excitability and, in the CNS, manipulation is able to decrease central sensitization by inhibiting the second pain\(^{30}\).

Considering the high prevalence of FM in the world context, the plurality of etiological possibilities, and the unsatisfactory results regarding the control of symptoms, especially pain, it is justified FM is the object of investigation in this study.

Therefore, we suggest a clinical trial, controlled, randomized, double-blind and with analysis by intention to treat, whose primary objective is to evaluate the effect of the association between tDCS and MT on the VN path, on pain in women with FM, and, as secondary objectives, trace the socio-demographic and clinical profile of the sample and identify the effects of tDCS and MT on VN, fatigue, quality of life (QL), quality of sleeping (QS) and heart rate variability (HRV) of women with FM.

**Methods**

**Study design:**

This is a clinical trial, controlled, randomized, double-blind and with analysis by intention to treat, which will follow the guidelines of the CONSORT (Consolidated Reporting Standards) and its guide for non-pharmacological interventions. Thirty women with FM will be part of the research, diagnosed by physicians from the rheumatology sector of Cassiano Antônio Moraes Hospital (HUCAM) with experience and trained to make differential diagnosis in FM. Participants will be randomly allocated to the intervention group (tDCS 2mA for 20 minutes + MT) or to the control group (tDCS 2mA for 20 minutes + MT SHAM). The treatment will be carried out in five sessions, which will take place on five consecutive days and, at each visit, the patients will receive both treatment protocols. Initially, they will be submitted to the tDCS protocol and then they will receive MT. Outcome measures will be collected by trained researchers before treatment, after the first visit, at the end of treatment and one month after the end. The analysis of the inclusion criteria, obtaining free and informed consent, data collection and statistical analysis will be carried out by researchers, who will not be aware of the allocation of groups. The study has received ethical approval from the Institution's Research Ethics Committee (CAAE: 34812120.9.0000.5060) of the Federal University of Espírito Santo, Vitória, Brazil. The trial was prospectively registered at ensaiosclinicos.gov.br. (Record: RBR-3xy4rxf).

**Participants and therapists: inclusion and exclusion criteria**
Participants will be women with FM, who will be eligible if they have a diagnosis of FM, according to the criteria of the American College of Rheumatology (ACR) – 2010, complaint of pain for more than three months and are between 21 and 65 years old.

However, they will be excluded if they present neurological diseases, rheumatic diseases in the acute phase, cancer, epilepsy, fractures of the skull, cervical or rib cage, severe osteoporosis, if they have a pacemaker or implantable cardioverter, patients who have undergone surgery in less than one year, and are pregnant or breastfeeding women.

Therapists who will perform the interventions will receive training from the research leaders. Those who are going to apply the MT will not be blinded due to the characteristics inherent to the intervention. However, the other participants will be blinded.

Research participants will be recruited at the Rheumatology Outpatient Clinic of HUCAM, in Vitória – ES, Brazil. Those who meet the eligibility criteria and sign the Free and Informed Consent Term, accepting to participate in the study, will be evaluated and will receive interventions on the premises of the Clinical School Interprofessional in Health of the Federal University of Espírito Santo - UFES in Vitória -ES, Brazil.

**Intervention:**

For the tDCS protocol, participants will be seated and will receive stimulation for twenty minutes, with an intensity of 2mA, according to the safety protocol. The stimulator (DC stimulator – Plus. Neurocon, Ilmenau, Germany) will supply a direct current through a pair of surface sponge electrodes, measuring 35 cm², soaked in saline substance, which will be placed on the patient's scalp. This is going to be the electrode placement: the anode, placed over the left primary motor area (C3) and the cathode, over the right supraorbital region.

For the MT protocol, a sequence of techniques will follow the path of the VN from the skull to the upper abdomen. The maneuvers will be applied bilaterally according to the following order:

1. Patient in lateral decubitus (LD), the physiotherapist, will make contact with temporal and occipital bones, and will perform, with her hands, three consecutive impulses in opposite directions.

2. Patient in supine and physiotherapist seated. At first, the physiotherapist will rest her left thumb on the sternocleidomastoid muscle. The remaining fingers will be in contact with the patient’s back of the neck. The maneuver will consist of exerting a force in a posterior direction along the muscle. Then the physiotherapist’s right hand will rest on the right side of the patient's head. The left hand, with the distal phalanges of the last four fingers flexed, will make contact with the left temporalis. The maneuver will consist of passively mobilizing the cervical spine, in lateral tilt and left rotation. Upon encountering restriction, the physiotherapist will ask the patient to take deep breaths. Finally, maintaining the final range of motion, the physiotherapist will perform rhythmic movements of cervical traction.
3. The physiotherapist, seated, will stabilize the patient's head, who will be in supine, with one hand and with the third finger of the opposite hand will locate, in the posterior part of the carotid artery, the point where the pulse will be weaker or absent. At this location, tension in an anterior direction must be imposed and maintained on the tissue. The technique will be completed when the artery pulse normalizes.

4. The physiotherapist, seated, will stabilize the patient's head, who will be in supine, and, with the second finger of the opposite hand flexed, will make contact through the middle phalanx over the costal insertion of the anterior and middle scalenes. The technique will consist of friction movements in the upper and lower directions until the tissue gets heated.

5. Patient in supine, head tilted, and the physiotherapist seated, with her cranial hand in supination will take a contact through the distal phalanges of the last four fingers on the side of the neck, between the trachea and esophagus and, with her caudal hand, will keep the sternum fixed. The technique will consist of performing friction movements in the upper and lower directions.

6. Patient in supine while the physiotherapist will be seated with caudal hand over sternum. Using her cranial hand, the physiotherapist will assess the direction of tissue restriction over the trachea. The technique will consist of keeping the caudal hand fixed and performing a high-speed, low-amplitude movement in the direction of restriction. The maneuver is going to be repeated three times.

7. Patient will be seated with trunk and head flexed, hands placed on thighs and shoulders relaxed. The physiotherapist, behind the patient, with one of her legs bent and resting on the stretcher, will make contact with the patient's trunk. Her arms will pass between the patient's arms and torso and, gently, using the digital pulp of her fingers, will make contact over the region of the cardia. During the patient's exhalation, the physiotherapist will slide her fingers in cranial direction and, at the same time, will passively extend the patient's torso. The maneuver will be repeated for ten respiratory cycles.

For the application of the MT SHAM protocol, the order of execution of the techniques, the positioning of both the patient and the physiotherapist will follow the established for the active MT treatment, however, the physiotherapist will remain with her hands placed in the described places for two minutes without applying any force on the structures.

**Primary result:**

The primary result will be about intensity of pain, measured through a numerical scale, containing eleven points, where zero will represent no pain and ten will represent the worst possible pain. Patients will be instructed to indicate the intensity of pain felt at the time of all assessments.

**Secondary results:**

Secondary results will be about: feeling of fatigue, QL, QS and HRV.
The feeling of fatigue will be evaluated through the application of the Short Form-36 (SF-36) questionnaire, which presents at its 9th item, four sub-items (“a”, “e”, “g” and “i”) related to vitality. The score will range from zero to one hundred and the lower the score achieved, the higher the level of fatigue.

QL will be assessed by applying the FM Revised Impact Questionnaire (FRIQ) which contains twenty-one questions, divided into three domains, related to function, overall FM impact and symptom intensity. The questions will be answered based on the last seven days and through eleven numerical points, from zero to ten, being ten the worst evaluation. The sum of the three domains can reach a maximum score of one hundred points.

The QS will be assessed by applying the Pittsburgh Sleep Quality Index (PSQI) questionnaire, which will assess the sleep of patients in the past thirty days through nineteen items grouped into seven components: subjective sleep quality, subjective sleep latency, duration of sleep, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The grading of scores will range from zero, no difficulty, to three, severe difficulty. The total score will be the sum of the seven components, where we will have the following indication: zero to four points, good sleep quality, five to ten points, poor sleep quality and ten to twenty-one points, presence of sleep disorder.

The evaluation of the HRV will be carried out using the RS800CX device (Polar Electro Oy Inc., Finland). Participants will be informed in advance neither to practice physical activity nor to ingest caffeine in the 24 hours prior to the evaluation. Data collection will be carried out in a room with a temperature between 21 and 23°C and humidity between 40 and 60%. The evaluator will place the chest strap around the patients’ chest and the HR receiver on the patients’ wrist, who will be positioned in supine and should remain at rest for ten minutes. After collection, participants must stand. The HRV reading will be performed in supine and standing for five minutes.

The behavior pattern of variability will be recorded beat-to-beat, throughout the experimental protocol, with a sampling rate of 1000 Hz. For data analysis, a thousand consecutive RR intervals will be used and automatic low filtering will be performed through the software HRV Kubios HRV Standard version 3.1.0 (HRV analysis, University of Eastern Finland) and complemented by a manual for the elimination of premature ectopic beats and artifacts, and only series with over 95% of sinus beats will be included in the study.

Time and frequency domain variables will be analyzed. In the variability time domain, we will evaluate the SDNN = standard deviation indices of all RR intervals, expressed in m/s; rMSSD = square root of the average of the sums of squares of the frequencies between the RR intervals greater than 50m/s, expressed in m/s; pNN50 = percentage of successive cycles that present differences in duration above 50m/s, expressed as a percentage and the SD1 geometric indices - instantaneous recording index of the beat-to-beat variability and will represent the parasympathetic activity, while the SD2 index will represent the HRV, in long-term records, and will reflect global variability. The frequency domain will be evaluated.
according to the indices LF = low frequency; HF = high frequency; WF = strength of variability; VLF = very low frequency; LF/HF = low frequency/high frequency ratio\(^\text{38}\).

The clinical evaluation will be carried out in four moments: before treatment, after the first visit, at the end of the treatment and one month after the end.

**Sample size:**

Thirty women with FM will be recruited at the Rheumatology Outpatient Clinic of HUCAM, in Vitória – ES, Brazil. For the sample calculation, an effect size of 0.25 was used for the F test, and a value below than or equal to 0.10 is considered as low power, lower than or equal to 0.30, medium effect, and lower than or equal to 0.50, large effect.

**Randomization:**

Eligible participants who agree to participate in the study will be randomized into two groups: Experimental group: tDCS plus MT and Control group: tDCS plus MT SHAM. An independent researcher, who is not involved in the recruitment, intervention or data collection process, will randomize into two blocks. Another independent investigator will allocate participants through software and will notify the supervising investigator by email to ensure all information will be hidden from reviewers and participants. The randomization process is going to be conducted through the website www.randomization.com. To avoid bias, the evaluation of participants will be conducted by blind evaluators. In addition, participants will be instructed not to disclose details of their treatment.

**Data analysis:**

The results will be analyzed in the following aspects:

I. Comparison of the evaluation before and after the execution of the protocols in the two groups and between them.
II. Analysis of results after the first visit, at the end of treatment and one month after the end.
III. Correlation between all the variables described in the two groups, in the evaluations before and after treatment in the three moments: acute, at the end of treatment and one month later.

**Data monitoring:**

An independent researcher, who will not know the group allocations, will monitor any adverse effects and perform database management and statistical analyses. The therapists in charge for the treatment will be responsible for monitoring the doses and adherence of the participants.

**Study organization and funding:**

This study will be conducted in accordance with relevant ethical structure, it has received institutional ethics board approval and will be self-funded. The results will be submitted for publication in journals
related to the field of rehabilitation, and access to the final trial dataset may be the object of the authors based on a reasonable request.

**Discussion**

This clinical trial will examine the immediate and late effects of tDCS associated with MT on VN on pain, fatigue, QL and QS and HRV in women diagnosed with FM. Although tDCS is considered level B of evidence for pain management in patients with FM, no study has investigated the association of tDCS with MT on VN in clinical outcomes of women with FM.

In response to this challenge, a double-blind randomized clinical trial will be conducted, with expected high internal validity, due to randomization, concealed allocation, blinding of evaluators and participants, intention-to-treat analysis and adequate sample size.

Although the pathophysiology of FM is not fully understood, data reveal that this syndrome may be due to ANS dysfunction. In addition, sustained pain stimuli are capable of altering both pain processing and autonomic regulation over the body.

Thus, therapeutic interventions that result in autonomic changes can be effective in reducing pain levels. An intervention that has been increasingly investigated is MT, which, when applied to specific points in the VN path, can influence the parasympathetic function. A probable explanation for this is the anatomical relationship between the VN and the musculoskeletal structures through which it passes along its path. Therefore, our hypothesis is that MT, associated with tDCS, may promote additional benefits with regard to pain control, fatigue sensation, QL, QS and HRV in women with FM.

This trial, however, has some limitations, as the interventions will be applied for five consecutive days and, therefore, it depends on the motivation, adherence and commitment of the participants. In addition, one month after the intervention period, the participants will be re-evaluated, making it necessary to accompany them and motivate them to continue contributing to the study. Strategies such as contracts and phone calls will be adopted in order to encourage participants to comply with the protocol. And, finally, it will not be possible to blind the therapists due to the inherent characteristics of the interventions. However, evaluators and participants will be blinded and will be advised not to disclose details about treatment and evaluations.

Thus, it is concluded that, as it is a chronic condition, the treatment for FM is of great importance, as these patients make frequent and extensive use of health services, impacting high personal and social costs. However, the search for therapies to improve pain in FM is quite challenging, mainly due to the lack of knowledge about its etiopathogenesis and the complexity of associated symptoms. So, the results of this clinical trial may result in an important advance for the rehabilitation of women with FM.

**Study status:**
Recruitment of study participants it's happening

Declarations

Ethical approval and consent to participate:

The study received ethical approval from the Research Ethics Committee (CAAE: 34812120.9.0000.5060) of the Federal University of Espírito Santo, Vitória, Brazil, which means that all study procedures remain in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human beings. Informed consent will be obtained from all study participants.

Consent to publication: Not applicable.

Availability of data and materials: Study investigators have full access to study datasets. The datasets used and analyzed during the study are available from the corresponding author upon reasonable request; however, any information shared will be blinded to any participant identifying information. The test results will be communicated to the health professionals and other relevant groups through publications, reporting in outcome databases and presenting the data during medical congresses and conferences.

Conflicts of interest: The authors declare no conflicting interests.

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Author contributions: All authors contributed to the development of the study protocol and this manuscript. All authors read and approved the final version of the manuscript.

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References


**Figures**
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Figure 1

Example template of recommended content for the schedule of enrolment, interventions, and assessments.*

** Supplementary Files **

This is a list of supplementary files associated with this preprint. Click to download.

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