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Neuromodulatory effects of Transcranial Pulsed Current Stimulation (tPCS) in Fibromyalgia: protocol for a double-blinded, sham-controlled, randomized clinical trial

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Abstract:
Fibromyalgia (FM) is a functional syndrome characterized by musculoskeletal, diffuse and persistent (> 3 months) chronic pain, that is also characterized by sleep disturbances, fatigue, humor changes and cognitive and psychological changes. Transcranial Pulsed Current Stimulation (tPCS) is a new Transcranial Electrical Stimulation (tES) that has been studied as a treatment option for chronic pain and neurological conditions . Studies have shown that tPCS is capable of pain and cognitive modulation; however, there are not enough studies with evidence of its efficacy.Therefore, the primary aim of this study is to evaluate the effects of tPCS in pain, evaluated through Visual Analogue Scale (VAS) in FM patients; besides that, it is aimed to evaluate the effects of tPCS on quality of life, cognitive impairments, pain pressure threshold, descending inhibitory system of pain, and serum levels of Brain Derived Neurotrophic Factor (BDNF) and S100 Calcium-Binding Protein B (S100B). A randomized, double-blinded, controlled with sham clinical trial will be conducted with 70 (Critical f: 2.003; ES: 0.76; alpha: 0.05; power: 0.80) women with Fibromyalgia, from 30 to 65 years with pain on the Visual Analogue Scale (VAS) higher than 6 in the last 3 months. All patients will read and sign an Informed Consent Form (ICF). Each patient will be randomized to either 1+4 sessions of tPCS (2mA, 6-10Hz, 1-20ms, 20-25 minutes) or Sham. Patients will complete the following questionnaires/tests: Visual Analogue Scale (VAS), Pittsburgh Sleep Quality Index (PSQI), Fibromyalgia Impact Questionnaire (FIQ), Pain Catastrophizing Scale (PCS), Profile of Chronic Pain (PCP), Conditioned Pain Modulation Task (CPM-T), Pain Pressure Threshold Task (PPT-T), Rey Auditory-Verbal Learning Test (RAVLT), Controlled Oral Word Association Test (COWAT) and blood collection for serum levels of BDNF and S100B. For the main outcome, comparison between variables during time will be made through linear regression, with an adjustment for baseline levels and possible confounders.

Keywords: *Fibromyalgia, Transcranial Pulsed Current Stimulation, Chronic Pain, Randomized Clinical Trial, Double-Blinded*

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INTRODUCTION

Fibromyalgia (FM) is a chronic musculoskeletal diffuse andgeneralized pain condition without grounded cause (Üçeyler et al., 2013). Chronic pain can manifest through a nervous system maladaptive mechanism; this system responds with a painful experience to innocuous stimuli. Hyperalgesia and allodynia are two important signals present in this condition, representing the peripheral and central nervous system impairment, respectively (Staud & Smitherman, 2002). According to the diagnosis criteria, FM prevalence represents two percent of the world's population, regardless of culture and region. Peak age range of the syndrome is from 30 to 50 years, being progressive with age (Queiroz, 2013).

Abbreviations:
FM: Fibromyalgia
CNS: Central Nervous System
PNS: Peripheral Nervous System
tPCS: Transcranial Pulsed Current Stimulation
VAS: Visual Analogue Scale
PSQI: Pittsburgh Sleep Quality Index
FIQ: Fibromyalgia Impact Questionnaire
PCS: Pain Catastrophizing Scale
PCP: Profile of Chronic Pain
CPM: Conditioned Pain Modulation
PPT: Pain Pressure Threshold
RAVLT: Rey Auditory-Verbal Learning Test
COWAT: Controlled Oral Word Association Test

FM affects females on a higher scale (1:2-3) (Wolfe, Brähler, Hinz & Häuser, 2013).

Nowadays, studies corroborate a physiopathology model that explains that FM happens through an increase of the sensorial input mediated by the Central Nervous System (CNS) (Üçeyler et al., 2013). Along with CNS dysfunctions, the Peripheral Nervous System (PNS) is changed in this condition. Findings show that patients with the syndrome, when compared to the control group, present a lower pain threshold to temperature stimuli and lower pain threshold to pressure, characterizing a functional impairment in A delta and C fibers (Üçeyler et al., 2013).

The need for a trial in treatment of this syndrome arises from the evidence that shows current treatments for Fibromyalgia are not used alone and the patient becomes dependent of the treatment (Chinn et al., 2016). Therefore, some Transcranial Electrical Stimulations (tES) have been investigated for FM treatment. A tES that has been studied over the past years is Transcranial Pulsed Current Stimulation (tPCS), which involves applying surface electrodes on the scalp and application of low amplitude current (2mA) with a pulsed current that acts randomly within a predetermined pulse range (Thibaut et al., 2017). tPCS is capable of modulating cortical activity, as well as cognitive performance, through its effects on synchrony of neuronal oscillations and the evident ability to increase the interhemispheric coherence of the low-frequency band that is modulated according to the frequency of stimulation (Morales-Quezada et al., 2015). It is known that this technique, when applied to auricular areas, is capable of modulating electrical activity in cortical and subcortical areas (Vasquez, Thibaut, Morales-Quezada, Leite & Fregni, 2017). In addition, , according to other studies, adverse effects of the technique are minimal and do not demonstrate significant differences compared to sham groups, which proves that it is a tolerable , safe and easily managed stimulation (Morales-Quezada, Saavedra, Rozisky, Hadlington & Fregni, 2014).

In general, tPCS has been shown to elicit neurological effects, which seems to be a potential route for treating pain in FM (Morales-Quezada et al., 2015). However, there is no previous trial using tPCS for this specific condition. To fill this gap of knowledge, this trial aims primarily to study the effects of five consecutive sessions of tPCS, compared to five consecutive sessions of sham stimulation, on FM pain, in women 30 to 65 years old, assessed by the Visual Analogue Scale for Pain (VAS). Secondary aims will evaluate the effects of tPCS on quality of life, pain catastrophizing thought, depression, anxiety, cognitive impairments, pain pressure threshold, descending inhibitory system of pain, and serum levels Brain Derived Neurotrophic Factor (BDNF) and S100 Calcium-Binding Protein B (S100B).

The null hypothesis of this trial maintains that there is no difference from tPCS to sham stimulation on pain levels in patients with FM. However, the alternative hypothesis asserts that tPCS is superior to sham stimulation when yielding analgesia in patients with FM. If the alternative hypothesis is confirmed, patients with FM may find a new potential treatment for their condition.

MATERIALS AND METHODS

Trial Design

This is a single-center, randomized, double-blinded, parallel-group, sham-controlled trial to evaluate the superiority of tPCS in pain reduction in women with FM.

Eligibility Criteria

Recruitment: The study will be held in a clinical center at Novo Hamburgo (RS) – Brazil. Data collection will begin in December 2021, and it will end when sample size is achieved. A targeted approach will be used: recruiting referrals from clinics in the region of the study setting, along with patients from the clinical center where the trial will be conducted. Besides that, posters will be placed in common areas and posted on social media.

Inclusion Criteria: women from 30 to 65 years old; FM diagnosis according to ACR criteria (2016); pain on VAS equal to or higher than 6 in the last 3 months; chronic stable treatment over the past 3 months.

Exclusion Criteria: pregnancy or lack of contraceptive use; history of alcohol or drug abuse in the last 6 months, neurological disorders, cardiac arrhythmia; use of drugs that change vascular response; history of head trauma, mild or severe, neurosurgery; decompensated systemic diseases; current diagnosis or history of cancer.

Risks and Benefits

Possible Benefits: possible increase in pain threshold may influence the quality of life and psychological and behavioral aspects.

Possible Risks: patients may feel uncomfortable or shy when answering questionnaires, therefore a psychologist will be provided from the clinic if the patient feels the need for it. In the descending inhibitory system of pain test, the patient may feel a local discomfort while immersing the hand in cold water, after the procedure, the investigator will provide a warm cloth. Discomfort may be felt when collecting blood. During the intervention, patients may present phosphine in the retina, this effect was related to the frequency of pulse generated by the current. If some adverse effect alters the daily life of patients, the investigator may consider unblinding and stopping the intervention.

Randomization

A randomization table will be generated on a website (www.sealedenvelope.com), creating a randomization list. The random number codes will be placed in sealed brown envelopes. The system will use blocked randomization (blocks of 4 and 6), enrolling patients on a 1:1 allocation based into the two cohorts:

- Active tPCS
- Sham tPCS

Blinding and Adherence

Based on the nature of the intervention, participants and physicians (health care providers/investigators) shall be blinded. Only one investigator will have access to the randomization list and will program the stimulation according to the list. The device comes programmed to perform the task input by the investigator, which will be trained by previous enrollment to the study on how to perform the intervention. Sham stimulation occurs only for the initial 30 seconds, after which the patient should feel that the body adjusts to the stimuli. After the 5 sessions, patients will be questioned about which intervention they think they received (active or sham). If over the course of the trail, it is medically imperative to know which intervention the patient is receiving, treatment will be discontinued if the investigator considers that it can negatively affect the subject. The reason for the blinding break should be clearly documented. Unblinding may happen when the coordinator concludes that the experiment is providing some risk to the patient, such as health-related risks.

In order to increase adherence, patients from both groups will be observed and called one time in each day during the treatment period (2 weeks).

Intervention

tPCS

The procedure will begin with placement of bilateral circular electrodes in the inferior ear lobe (ECG position A1) fixed by an ear clip. The electrode's radius will be approximately 0.785cm2. Current has a peak pulse amplitude of 2mA, with a frequency range from 6 to 10 Hz. A battery-powered current stimulator will be used. This device provides stimulation through biphasic and alternating square wave pulse, with random pulse width range from 1 to 20 ms (as previously described by Vasquez et al., 2017). tPCS sessions will last 20 minutes plus 5 minutes for setting up, meanwhile when questionnaires and tests are applied, sessions can last 1 to 2 hours. Sessions will be made in a 1+4 way, in which outcomes will be evaluated before and after the first session and after the last session. Studies display evidence of clinical improvement after 5 sessions of transcranial electrical stimulation in FM (Fregni et al., 2006). A standardized questionnaire will be performed in order to observe adverse effects immediately after the intervention.

Sham tPCS

The current will only be applied for the first 30 seconds. Patients may notice the same sensation of initial stimulation but will not receive the current for the remaining time. Analogue to tPCS, 5 sessions will be performed (Morales-Quezada et al., 2015).

Outcomes

A different investigator from intervention and randomization will be collecting the outcomes. This investigator will be trained before the beginning of the study.

Primary Outcome

Pain on Visual Analogue Scale (VAS) pain, a continuous scale from 0-100mm, considering 60mm as the minimum for chronic pain.

Secondary Outcomes

- Quality of Sleep - Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman & Kupfer, 1989).
- Quality of Life - Fibromyalgia Impact Questionnaire (FIQ), subdivided into overall impact, symptoms and function (Bennett et al., 2009).
- Pain Catastrophizing - Pain Catastrophizing Scale (PCS), subdivided into magnification, rumination, and hopelessness (Sullivan, Bishop & Pivik, 1995).
- Profile of Pain - Profile of Chronic Pain (PCP), subdivided into pain intensity and frequency, the impact of pain in activities, and impact of pain in emotions (Ruehlman, Karoly, Newton & Aiken, 2005).
- Descending Inhibitory System - Conditioned Pain Modulation task: evaluate the descending inhibitory system of pain, measured by the difference of pain (VAS) between two painful stimuli (pressure threshold and cold water) (Nir & Yarnitsky, 2015).
- Pain Pressure Threshold task: an electronic algometer will be placed in the forearm, patient will report first pain sensation and maximum pain.
- Serum levels of BDNF, S100B, and estradiol.
- Cognitive - Rey Auditory-Verbal Learning Test (RAVLT) for cognitive evaluation (Schmidt, 1996).
- Cognitive - Controlled Oral Word Association Test (COWAT) for cognitive evaluation (Silverberg, Hanks, Buchanan, Fichtenberg & Milles, 2008).

Timeline

The schedule and procedures of this protocol are presented in **Table 1**.

Description	1st Visit (Baseline)	2nd Visit	3rd and 4th Visit	5th Visit	6th Visit
	Monday (Outcomes before tPCS)	Tuesday (Outcomes before tPCS)	Wednesday and Thursday	Friday (Outcomes after tPCS)	One week after 5th visit
Screening (Inclusion/Exclusion Criteria)	X				
Informed Consent Form	X				
Demographic data collection	X				
tPCS (Active or *Sham*)	X	X	X	X	
Pain levels – VAS	X	X	X	X	X
Quality of Sleep – PSQI	X	X		X	X
Quality of Life – FIQ	X	X		X	X
Pain Catastrophizing – PCS	X	X		X	X
Profile of Chronic Pain – PCP	X	X		X	X
Conditioned Pain Modulation – CPM	X	X		X	X
Pain Pressure Threshold – PPT	X	X		X	X
Cognitive factors – RAVLT	X	X		X	X
Cognitive factors – COWAT	X	X		X	X
Blood Collection	X	X		X	X
Adverse Effects of tPCS	X	X	X	X	X
Blinding Questionnaire					X

Table 1. Timeline

Sample Size Calculation

Sample size calculation was made through GPower 3.1 and based on Fagerlund et al. (2015). The primary outcome used was the Numerical Pain Scale, evaluated by t-test: a two tailed test, alpha adjusted for 0.05 and power of 0.80. To achieve at least a critical f of 2.003, the effect size estimated was 0.76, the software showed that 29 participants in each group would be needed. Considering a drop-out rate of 20%, the total sample size was 70 (35 per group).

Statistical Analysis

Sociodemographic data is presented as continuous (i.e: years) or categorical (i.e.: sex); for continuous data a Shapiro-Wilk test will be performed to assess normality and, considering it a normal distribution, continuous data will be presented as mean + SD and as the score from each group and the total score, compared to each other with an independent samples t-test; for categorical data it will be presented as percentage (N) and it will show the results from each group and the total score, compared to each other with a Fisher's exact test or Chi-Square.

The VAS pain scale will be used as a continuous variable (mean + SD), with readings from 0-100mm. Shapiro-Wilk test will be used to assess normality, along with a visual comparison from a histogram; assuming a normal distribution, an independent samples t-test will be used to compare the baseline data for the primary outcome. Comparison between variables during time will be made through linear regression; a Bonferroni post-hoc test will be used for multiple comparisons to detect differences between groups at any moment, considering intervention group as a factor and time the repeated measure. Except for adverse effects, secondary outcomes are considered continuous (mean + SD) and will be analyzed the same way that VAS will. Adverse effects will be shown as percentage (N) and compared through Fisher's exact test or Chi-Square.

If data is not normally distributed, a Mann-Whitney test will be applied instead. A significant difference will be considered when $P<0.05$. No special subgroup analysis will be made. Analysis will be performed trough SPSS 26.0 (SPSS, Chicago, IL).

Ethical Considerations

All included participants must provide a signed Informed Consent Form. This study will be performed according to the Declaration of Helsinki, registered in the international platform for clinical trials (www.clinicaltrials.gov) and described according to CONSORT guidelines.

DISCUSSION

The need for a trial addressing tPCS in FM arises from clinical evidence that transcranial current stimulations have shown central analgesic effects and, therefore, could be a great treatment for women that suffer from Fibromyalgia. As far as we know, this is the first study to investigate the use of tPCS in patients with Fibromyalgia. Hopefully, tPCS will provide pain relief in patients with FM, given that it is still a disease without a defined cure and with drug-dependent treatments. Additionally, it is estimated that tPCS may improve psychosomatic and cognitive activities in women affected by the syndrome.

As for limitations, generalizability of results may be a factor, since this study is a single center trial with a considerable small sample size. Application of questionnaires might present a subjectivity from patients.

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Conflict of Interest

None.

REFERENCES

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research, 28(2), 193-213.

Bennett, R. M., Friend, R., Jones, K. D., Ward, R., Han, B. K., & Ross, R. L. (2009). The revised fibromyalgia impact questionnaire (FIQR): validation and psychometric properties. Arthritis research & therapy, 11(4), 1-14.

Chinn, S., Caldwell, W., Gritsenko, K. (2016) Fibromyalgia pathogenesis and treatment options update. Current pain and headache sports, 20(4), 1-20

Fagerlund, A. J., Hansen, O. A., & Aslaksen, P. M. (2015). Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. Pain, 156(1), 62-71.

Fregni, F., Gimenes, R., Valle, A. C., Ferreira, M. J., Rocha, R. R., Natalle, L., ... & Boggio, P. S. (2006). A randomized, sham-controlled, proof of

principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 54(12), 3988-3998.

Morales-Quezada, L., Saavedra, L. C., Rozisky, J., Hadlington, L., & Fregni, F. (2014). Intensity-dependent effects of transcranial pulsed current stimulation on interhemispheric connectivity: a high-resolution qEEG, sham-controlled study. Neuroreport, 25(13), 1054-1058.

Morales-Quezada, L., Castillo-Saavedra, L., Cosmo, C., Doruk, D., Sharaf, I., Malavera, A., & Fregni, F. (2015). Optimal random frequency range in transcranial pulsed current stimulation indexed by quantitative electroencephalography. Neuroreport, 26(13), 747-752.

Nir, R. R., & Yarnitsky, D. (2015). Conditioned pain modulation. Current opinion in supportive and palliative care, 9(2), 131-137.

Queiroz, L. P. (2013). Worldwide epidemiology of fibromyalgia. Current pain and headache reports, 17(8), 356.

Ruehlman, L. S., Karoly, P., Newton, C., & Aiken, L. S. (2005). The development and preliminary validation of the profile of chronic pain: extended assessment battery. Pain, 118(3), 380-389.

Schmidt, M. (1996). Rey auditory verbal learning test: A handbook (p. 1996). Los Angeles, CA: Western Psychological Services.

Silverberg, N. D., Hanks, R. A., Buchanan, L., Fichtenberg, N., & Millis, S. R. (2008). Detecting response bias with performance patterns on an expanded version of the Controlled Oral Word Association Test. The Clinical Neuropsychologist, 22(1), 140-157.

Staud, R., & Smitherman, M. L. (2002). Peripheral and central sensitization in fibromyalgia: pathogenetic role. Current pain and headache reports, 6(4), 259-266.

Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The pain catastrophizing scale: development and validation. Psychological assessment, 7(4), 524.

Thibaut, A., Russo, C., Morales-Quezada, L., Hurtado-Puerto, A., Deitos, A., Freedman, S., ... & Fregni, F. (2017). Neural signature of tDCS, tPCS and their combination: comparing the effects on neural plasticity. Neuroscience letters, 637, 207-214.

Vasquez, A. C., Thibaut, A., Morales-Quezada, L., Leite, J., & Fregni, F. (2017). Patterns of brain oscillations across different electrode montages in transcranial pulsed current stimulation. Neuroreport, 28(8), 421.

Wolfe, F., Brähler, E., Hinz, A., & Häuser, W. (2013). Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. Arthritis care & research, 65(5), 777-785.

Üçeyler, N., Zeller, D., Kahn, A. K., Kewenig, S., Kittel-Schneider, S., Schmid, A., ... & Sommer, C. (2013). Small fibre pathology in patients with fibromyalgia syndrome. Brain, 136(6), 1857-1867.