Transcranial DC Stimulation in Patients with Migraine: a study protocol for a randomized clinical trial

Luana Dias Santiago Pimenta
UFPB: Universidade Federal da Paraiba
Elidianne Layanne Medeiros de Araújo
UFPB: Universidade Federal da Paraiba
Joyce Poláine dos Santos Silva
UFPB: Universidade Federal da Paraiba
Jamyson Júnior França
UFPB: Universidade Federal da Paraiba
Pedro Nascimento Araújo Brito
UFPB: Universidade Federal da Paraiba
Luiz Carlos Serramo Lopez
UFPB: Universidade Federal da Paraiba
Suellen Andrade (suellenandrade@gmail.com)
UFPB: Universidade Federal da Paraiba

Study protocol

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Abstract

Background

Chronic migraine is a disease with a difficult diagnosis and an as yet undefined pathophysiology. Its symptoms affect the quality of life and the daily activities of the individual, leading to momentary disability. This study is a controlled clinical trial of a randomized parallel group that will select patients aged between 18–65 years who are diagnosed with chronic migraine.

Methods / Design

This study will be held at the Aging Studies Laboratory and Neuroscience of the Federal University of Paraíba, where twelve sessions of transcranial direct current stimulation (tDCS) and associated with mindfulness practices will be applied over four weeks (one per week). Muse, a portable electroencephalogram (EEG), will be used to measure brain wave biomarkers before and after the intervention. We will use, at the beginning and end of treatment and one month after the completion of any intervention, the score on the Migraine Disability Assessment (MIDAS) questionnaire as the primary outcome and the scores on the HIT-6 (Headache Impact Test) questionnaire and on the Five Facet Mindfulness Questionnaire (FFMQ-BR) as the secondary outcomes.

Discussion

Based on the use of tDCS in patients with chronic pain, and in benefits of Mindfulness practice in these patients, the objective is to evaluate if the mindfulness-associated tD provides satisfactory results in the painful prophylaxis of patients with chronic migraine.

Trial registration

Clinicaltrials.gov, NCT04219345. Registered 16 September 2019. Retrospectively registered.

1 Background

Chronic migraine is a primary, common and disabling neurological disorder defined by the occurrence of a headache on 15 or more days per month, with 8 or more of these episodes with characteristics of migraine persisting for at least three months [1]. It has negative repercussions in the biopsychosocial sphere due to the frequent association with anxiety, depression, and decreased socialization [2, 3].

The main treatment for chronic migraine is drug therapy, although most drugs are not sufficiently specific and may trigger a series of side effects that are difficult to tolerate. In addition, the excessive use of some classes of drugs is a common factor causing chronic migraine. Approximately 50% of patients diagnosed with chronic migraine are subsequently diagnosed with episodic headache when drug weaning is successful [4].

In this context, nonpharmacological therapies could resulting in less frequent headaches have greater tolerability and safety than the current drug therapy [5].

Mindfulness is the intentional and nonjudgmental attention to the present moment. Interventions based on mindfulness produce effects similar to medication alone for chronic migraineurs with a history of overuse of pharmacological agentes [6].

According to electroencephalographic (EEG) and functional magnetic resonance imaging (fMRI) studies, the practice of mindfulness induces changes in the "state" of the brain, including the activation of the anterior cingulate cortex and the dorsomedial prefrontal córtex [7–9].

The administration of Transcranial Direct Current Stimulation (tDCS) in combination with an intervention based on mindfulness has recently been reported to improve cognitive and well-being parameters [10–12].

tDCS is a pure neuromodulatory strategy because anodic polarization increases the excitability of the cortical areas by depolarizing somatic neuronal stimulation in areas below the electrodes, whereas cathodic polarization typically decreases cortical excitability [13–15]. Stimulation of the dorsolateral prefrontal cortex may reduce the perception of pain because this area is involved in emotional regulation and pain control [16]. Clinical trials that administered tDCS to patients with migraine reported decreases in pain intensity, the frequency of seizures [17], duration of episodes, use of analgesics [18] and triptans [19]. These effects were achieved safely [20] and economically using a portable device [21] with minimal side effects in patients with chronic migraine [4].

Currently, few studies have investigated the association between mindfulness and tDCS in pain control. A double-blind clinical trial was conducted to evaluate the analgesic effects of these two therapies on patients with chronic pain. Individuals who received active tDCS and participated in more treatment sessions reported significantly higher rates of mindfulness and improvements in general health after participating in the mindfulness sessions [9].

Based on the beneficial effects of the combination of mindfulness and tDCS therapy on central nervous system diseases along with the theoretical gap in clinical trials investigating the use of these treatments in patients with chronic migraine, the present study aims to evaluate the short- and long-term effects of the combination of tDCS and mindfulness in this population and investigate which clinical variables (time of the migraine diagnosis, drug use, level of pain, and associated comorbidities) modulate the therapeutic response of patients. Our hypothesis is that the concomitant use of the therapies may improve the pain symptoms and quality of life of patients.

2 Methods

2.1 Research design

This randomized, double-blind, placebo-controlled clinical trial will analyze patients with a confirmed diagnosis of chronic migraine by a neurologist who were subjected to tDCS associated with mindfulness

practices.

Participants will be divided into two groups: Group A will be administered anodic tDCS and instructed in mindfulness practices, and Group B will be administered sham tDCS and instructed in mindfulness practices. Both groups will undergo the same protocol of twelve sessions of twenty minutes of tDCS associated with mindfulness, where only the type of received electric current is varied (active or simulated sham type). The twelve sessions will be performed in three sessions per week for four weeks, and mindfulness practice at home will be encouraged on days when the intervention is not administered. In the week preceding the beginning of treatment, the three assessment questionnaires, MIDAS, HIT-6 and FFMQ-BR, will be administered, and portable electroencephalography will be performed using the MuseTM device, manufactured in Toronto Canada. In an identical manner, electroencephalography will be performed using the Muse device within one week after the end of the intervention. We will administer the assessment instruments again one month after the end of the sessions (follow-up) to evaluate the long-term effect of the combination therapy (Fig. 1).

Patients will be allocated into the groups using a random number generator in an online randomization program (www.random.org). This allocation will be concealed, and opaque, sealed envelopes will be sequentially numbered to ensure that the person responsible for the group allocation does not have contact with the patients or the results collected by the other researchers involved in the project.

Figura 1: Description of the study design

All examiners will be blinded to the type of treatment the patient received (active current or sham type) and the other evaluations performed. Group A will receive the active current, and Group B will receive a simulated current of the sham type. At the end of the protocol, patients who were allocated to Group B will be invited to receive active stimulation using the same protocol applied to Group A.

Thus, an active current will be offered to all participants at the end of the study. Patients and outcome evaluators will be blinded to the type of treatment applied. The person responsible for administering the stimuli will also be blinded to the performance of the participants during the evaluations. At the end of the twelve sessions, patients will be questioned to assess their opinions on whether the system generating electrical current was on or off to ascertain whether the masking mechanism was actually efficient.

Using these criteria, the guidelines established by the Consolidated Standards of Reporting Trials [22] will be met by managing variables with the generation of a random sequence, concealment of allocation, blinding of the participating patients, members of the intervention team, and the outcome evaluators, and attrition bias.

2.2 Participants

The participants will be referred from the Clinical Neurology Outpatient Clinic of the Hospital Universitário Lauro Wanderley (Lauro Wanderley University Hospital; HULW) to the Laboratório de Estudos em Envelhecimento and Neurociências (Laboratory of Aging and Neuroscience Studies; LABEN) of the

Department of Physical Therapy of the Federal University of Paraíba (UFPB) after patient triage. Participants meeting the eligibility criteria of the study will be assessed by the service's neurologist.

Patient participation will be voluntary after agreement and signing the Informed Consent Form in accordance with Resolution No. 466/12 of the National Health Council (NHC). The study is predicted to be conducted with forty adult volunteers aged between eighteen and sixty-five years who will be randomly divided into Group A (tDCS with active current and mindfulness) and Group B (tDCS with simulated current of the sham type and mindfulness).

Patients of both genders aged between eighteen and sixty-five years who have been clinically diagnosed with chronic migraine according to the third edition of the International Classification of Headache Disorders (ICHD-3) will be selected. Only patients who are able to complete treatment in the twelve sessions of four preprogrammed consecutive weeks will be accepted.

Exclusion criteria will be the presence of headache attributed to another neurological or associated neuropsychiatric pathology, the use of central nervous system (CNS) - modulating drugs, the diagnosis of a severe, distinct neurological or psychiatric disease, the use of another nondrug therapy for migraine or other CNS pathologies concurrent with or immediately before the intervention, the presence of metallic implants located in the cephalic region and the implantation of cardiac pacemakers.

2.3 Attrition and adhenrence

Attrition will be considered under the following conditions: two consecutive or three alternate absences during treatment sessions; inability to complete the post-test and follow-up; development of any disabling condition for participation in the study.

Regarding adherence strategies, up to three alternating absences or two excused absences are tolerated. Absent days will be replaced with follow-up on the next working day to minimize dropouts and promote adherence to treatment. Flextime will be provided to participants who receive the therapy, as well as direct contact by calling participants by phone to confirm the evaluation dates and reinforce adherence to treatment. For the mindfulness practices, a table containing the days equivalent to the four weeks of intervention will be provided to increase adherence to home exercises and to enable better control of their performance Additional measures to prevent dropouts will also be applied, such as periodic evaluations (during the outcome analyses) on satisfaction with therapy, discussion of difficulties in continuing with treatment (for example, transport logistics to the laboratory), and attempts to resolve and prevent possible problems that may interfere with adherence and continued participation in the study.

2.4 Procedures

2.4.1 tDCS

The tDCS research instrument developed by Trans Cranial Technologies and 5 x 7 cm electrodes will be used. These electrodes will be wrapped in sponges moistened with a 0.9% saline solution to reduce direct contact with the patient's skin. For Group A, which will receive active stimulation, a 2 mA current with a

density equivalent to 0.05 A/m2 will be applied for twenty minutes while the anode electrode is positioned above the left dorsolateral prefrontal cortex (considered the main locus of pain control) and the cathodic reference electrode is placed above the right supraorbital region. Three sessions per week will be conducted for a total of four weeks, i.e., twelve sessions.

Group B, which will receive the sham-type current, will be subjected to an identical protocol; however, the device will only emit current during the initial 30 seconds of stimulation. Thus, the sensations of active stimulation, such as mild tingling and local pruritus, are simulated, but clinical effects are not induced due to the short period of stimulation. A posteriori, the group receiving the sham-type simulated current will be invited to receive the active current in the next cycle of interventions to ensure that all study participants have the opportunity to receive the active current.

At the end of each session, the patient will be asked whether they experienced adverse effects, such as dizziness, tingling, burning, headache, drowsiness and others, to describe the intensity of this sensation (1 - none, 2 - mild, 3 - moderate, and 4 - strong) and if this effect might be related to neurostimulation on a Likert scale ranging from 1 (no relation) to 5 (strongly related) [23].

2.4.2 Mindfulness practice

Concomitant with the tDCS intervention, an audio recording containing the mindfulness practices will be played for twenty minutes, i.e., the same duration as the electrostimulation session. This same audio recording will be made available by e-mail and/or WhatsApp for patients who will be encouraged to listen to it at home or another place of the individual's choice to obtain better results from this formal mindfulness practice. Four audio recordings with different practices will be provided, which is equivalent to one audio recording for each week of treatment.

With the help of the provided tables, the participants will be encouraged to take notes of the time at which they listened to the audio recording and if they listened to it in its entirety without interruptions (for twenty minutes). At the end of each week, the participant will deliver the completed table to a member of the project performing the intervention; this team member will provide another blank table for the next week, and this practice will continue until the end of the four week intervention period.

2.5 Assessment instruments

2.5.1 Portable electroencephalogram– Muse

As a biomarker to evaluate the brain wave patterns, we will record two electroencephalograms: one before treatment and the other at the end of the twelve sessions.

Some important recommendations and procedures will be previously provided to participants, such as not ingesting caffeine (coffee, black tea, or soda) and chocolate, refraining from using facial cream, sunscreen and beauty products, such as a liquid foundation in the frontal region, and maintaining normal medications before the test.

Portable EEG recordings will be performed in a quiet environment while the patient is comfortably seated, and the patient will be instructed to remain relaxed but awake at the three time points of data collection: baseline, closed eyes and open eyes. Thus, recordings of at least two minutes will be obtained during each phase. A Muse system with 7 sensors in its hardware will be used, and an Fpz sensor placed over the central prefrontal lobe will serve as the reference. The tiara of the Muse device is placed on the head and measures the electrical brain signals using several finely calibrated sensors located on the forehead, behind the ears and a reference sensor with response at a frequency of 1 to 60 Hz. The tiara uses information from these EEG sensors to measure the state of mind of the individual, i.e., whether he/she is calm and focused or active and errant [24]. The aforementioned equipment measures the delta, theta, beta and alpha waves to interact with the brain-computer interface application in iOS devices, thus ensuring the acquisition of wireless data; thus, the device will be positioned in the frontal region of the patient and adjusted according to the patient's cranial diameter.

2.5.2 Migraine disablIity assessment questionnaire – MIDAS

The Migraine Disability Assessment Questionnaire (MIDAS) will be used in this evaluation. Its aim is to evaluate the inability of patients with migraine to perform daily and professional tasks. This instrument contains five questions that must be completed with the number of days that the patient failed to perform the specified activity because he or she was currently experiencing a migraine episode; this assessment is a useful tool to identify the severity of this condition.

This questionnaire was validated in the Portuguese language and can be applied to people of different educational levels and social backgrounds because it is considered easy to answer [25]. We will administer this questionnaire to participants from both groups before starting the intervention and after the end of the twelve sessions to assess whether the symptoms of chronic migraine improved.

2.5.3 Headache impact test - HIT-6

HIT-6 is a highly reliable questionnaire that had been validated in Portuguese. It assesses the frequency of the impact of headache on the quality of life of patients with chronic and episodic migraine and discriminates the types of migraine presented by the patient (episodic, chronic or nonmigrainous types). It is simple and easy to apply [26].

This questionnaire is composed of six questions assessing these parameters through the following options: never, rarely, sometimes, very frequently and always. A predetermined value is associated with each of these frequency parameters (for example, the score is rarely 8 points and usually 13 points), which will be added to the final score to determine the score equivalent to the headache impact. This score will be compared before and after the completion of all intervention sessions between both groups to assess whether a decrease in the frequency of headache impacted the participants' quality of life.

2.5.4 Five facets of mindfulness questionnaire (FFMQ-BR)

The FFMQ-BR is an instrument for assessing mindfulness characteristics that was validated in Brazil in 2014. It is subdivided into five main evaluation factors (observing, describing, nonjudging, nonreactivity,

and acting with awareness) that are appreciated in situations addressed in each item – for example, "in difficult situations, I can pause without reacting immediately". This scenario is classified by the participant through a scale ranging from 1 to 5 points, where 1 represents "never or almost never" and 5 represents "always or almost always". [27] The total score of the questionnaire will be calculated, and this score will be compared before and after all intervention sessions are completed between both groups to assess whether the participants' level of mindfulness increased.

2.6 Ethical aspects

Based on the tenets of the Declaration of Helsinki of the World Medical Association (WMA), the participation of the patient will be voluntary after agreement and signing the Informed Consent Form. This document will contain information about the possibility of discomfort and benefits, the lack of costs, and the use of the resulting data obtained from the questionnaires and EEGs in the study. It will also describe that the data can be removed from the study at any time without any penalty.

Detailed information about the clinical trial will be provided, such as the duration of the study and the protocol used. The participants will be informed about the possibility of being randomly allocated to the sham type current group and the opportunity of participating in the active current group in the next cycle; however, they will only know to which group they were allocated at the end of the intervention and the completion of questionnaires/EEG.

Confidentiality regarding the identity of the participants will be ensured according to Resolution NHC 466/12.

3 Safety

Safety criteria will be employed to assess possible adverse effects. The patient will be asked if he/she experienced sensations such as tingling, burning, headache, sleepiness, and pruritus at the stimulation site, among others, to evaluate the occurrence of adverse effects. Then, the patient will be asked to describe the intensity of this sensation (1 - none, 2 - mild, 3 - moderate, and 4 - strong) and whether this effect was related to the stimulation on a Likert scale ranging from 1 (no relation) to 5 (strongly related) points [28].

Patients will be monitored by the neurologist at the HULW Migraine Outpatient Clinic throughout the study to ensure compliance with all ethical requirements for providing therapeutic care to the participant, regardless of the group to which he/she is allocated, without any burden or cost to the participant.

4 Statistical Analysis

As observed in previous studies using tDCS to treat migraine for 4 weeks, the mean score recorded by the patients ranges between 2.2 and 8.3 points, with a standard deviation of 0.3 to 1.6 points [18]. Based on these criteria and considering 90% power and possible dropouts, we calculated a final sample size of 60 participants. A significance level of $p < 0.05$ will be considered.

We will analyze the results using an intent-to-treat analysis based on the last observation (for patients who started treatment and received at least 1 session).

We will use a mixed linear model to analyze the primary outcome. We will use the change in the inability to perform daily life activities resulting from migraine, according to MIDAS, using the time covariates at three levels (preintervention, postintervention and follow-up), group covariates at two levels (active and placebo) and the interaction covariates between treatment and time. The same design will be applied to the secondary outcomes. If necessary, post hoc comparisons using the Bonferroni correction will be performed. Deleterious and adverse cognitive effects will be calculated in terms of the proportion detected in each group during each period and will be analyzed using the Fisher exact test. Effect sizes will be calculated using the eta-squared test.

In parallel, the effect of the treatment on the neurophysiological measures (brain waves detected using Muse) will be analyzed. A comparative study will be performed using two methods of artifact rejection to reduce the artifacts generated during the Muse assessment: Filter-Bank Artifact Rejection (FBAR) and the Fully Automated Statistical Thresholding (FASTER) for EEG Artifact Rejection. The FBAR is a highly accurate EEG artifact detection algorithm for instruments such as Muse, is able to generalize data in all channels, has a low false-negative rate, and is more successful in detecting artifacts with a small amplitude [29]. Thus, FBAR will be used for Muse EEG applications due to its precise detection of artifacts.

5 Discussion

The main objective of this clinical trial is to evaluate the therapeutic effects of transcranial direct current stimulation associated with the practice of mindfulness in the prophylaxis of the painful symptomatology of chronic migraine because previous studies have shown that the administration of tDCS with concomitant development of tasks can improve behavioral results [30].

In the current scientific literature, favorable results have been reported in previous clinical trials administering tDCS to patients with migraine, as an improvement in pain intensity, a decrease in the occurrence and duration of new crises, and a decrease in the need for drugs was observed. This technique modulates the excitability and excessive cortical-neural overresponsiveness inherent to this pathology and has been used as an abortive or prophylactic treatment, enabling the use of lower amounts of acute drugs [19].

The use of mindfulness as a therapeutic practice was also shown to be safe and viable in adults with chronic migraine [31], revealing a reduction in functional disability and suffering related to migraine [32] and promoting greater awareness, disidentification with self, greater optimism related to sensations and feelings [33], reducing relapses by minimizing factors that trigger seizures such as anxiety and stress, increasing resilience to stress and effective regulation of the heart rate [34] and improving the perception of pain intensity and quality [35]. In addition, this therapy produces similar results to conventional pharmacological prophylaxis, thereby reducing the consumption of acute medications and the levels of inflammatory biomarkers [6].

The aim of this study is to analyze and compare the degree of disability in chronic migraineurs while performing daily life activities, the impact of daily headaches, and participants' levels of attention in the pre- and postintervention periods (immediately after the end of the sessions and one month after the conclusion of the sessions) as a method to assess the prophylactic effect of the two strategies administered simultaneously in this clinical context. The pathophysiological mechanism of this disease remains unclear, although the main current explanation for this disease is attributed to typical neurological changes [36].

Another objective is to evaluate changes in brain waves after joint treatment using the portable EEG.

Using the MIDAS questionnaire, we expect that the administration of the combination of tDCS and mindfulness interventions will promote a decrease in the degree of disability of patients with chronic migraine in the performance of activities of daily living (ability to perform household tasks, to have a healthy social life, to go to work without missing work days, etc.) because it prophylaxis for pain associated with new episodes of migraine. The data obtained from the HIT-6 are expected to reveal an improvement in the assessment of the impact of headache on the daily life of these patients. As another outcome, an increase in the level of mindfulness of these patients is expected before and after the intervention, as evidenced by the FFMQ-BR, thus reflecting a greater awareness of the present moment and the subsequent disidentification with painful symptoms, minimizing the suffering participants experience.

Regarding the electrophysiological data obtained in the present study, the brain wave patterns observed using the portable EEG are predicted to change, consistent with the results of the assessment instruments. Dynamic changes in the power and connectivity detected by the EEG have been observed in patients with migraine in previous studies supported by resting-state fMRI [37].

As main limiting factors, dropout or exclusion of participants may occur, as the required frequency of laboratory visits will be three times a week for four consecutive weeks, with a tolerance of two consecutive absences or three alterante absences with the necessary replacements, despite the provision of flexible schedules, direct contact and contact via telephone in an attempt to reinforce adherence of the participants.

Participants may also fail to perform or incompletely perform the domiciliary practices of mindfulness, despite the adoption of registration strategies (availability of a spreadsheet to record the time, date and if the practice was completely performed at home), the availability through a WhatsApp group of the audio recordings used in the intervention and the incentive to perform these personal practices.

Because a conventional pharmacological treatment only achieves favorable results in 50% of users and may cause side effects [18], more effective therapeutic alternatives with fewer adverse effects are necessary. The study of the concomitant administration of tDCS and mindfulness, both of which have already been established individually as treatments for chronic migraine, is unprecedented and may benefit patients with migraine by providing a low-cost, safe and effective treatment, in addition to enriching the scientific literature on this topic.

6 Trial Status

The protocol version number and date is TRLS-D-20-01370 in 11 January 2021. The recruitment of participants happened between September 2019 and February 2020. However, the current COVID-19 pandemic has already substantially delayed the intervention of this study. There is also an uncertainty around further development of the pandemic and its impact on clinical research in Brazil, and many other countries in the world. We are planning to continue, as soon as possible in this pandemic context, the sample screening and the intervention of participants already recruited.

7 Abbreviations

CNS: Central nervous system; EEG: Electroencephalographic; FASTER: Fully Automated Statistical Thresholding; FBAR: Filter-Bank Artifact Rejection; FFMQ-BR: Five facets of mindfulness questionnaire (validated in Brazil); fMRI: Functional magnetic resonance imaging; HIT-6: Headache impact test; HULW: Lauro Wanderley University Hospital; ICHD-3: International Classification of Headache Disorders (3rd edition); LABEN: Laboratory of Aging and Neuroscience Studies; MIDAS: Migraine Disability Assessment Questionnaire; NHC: National Health Council; TCT: Trans Cranial Technologies; tDCS: Transcranial Direct Current Stimulation; UFPB: Federal University of Paraíba; WMA: World Medical Association

8 Declarations

The financing statement is attached as additional material.

8.1 Ethics approval and consent to participate

The study protocol was performed in accordance with the Declaration of Helsinki and approved by the Federal University of Paraiba local ethics committee (CAAE: 97357518.1.0000.5188). Written informed consent will be obtained from all participants prior to participation.

8.2 Consent for publication

Not applicable.

8.3 Availability of data and materials

8he datasets generated during and analysed during the current study will be available from the corresponding author on reasonable request.

8.4 Competing interests

The authors declare no competing interests.

8.5 Funding

This study was supported by Coordination of Improvement of Higher Level Personnel (CAPES - Finance Code 001). The funder had no role in the design and conduct of the study, collection, management, and analysis of the data.

8.6 Author's contributions

SA and LP designed the study and managed all stages of the design and writing process. LP performed the data analysis and wrote the first draft of the manuscript. LL contributed to the interpretation and review of the data. EA and PB operationalized portable electroencephalography. JS and JF operationalized tDCS. All authors contributed to the revision of the manuscript, read and approved the submitted version.

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Figures

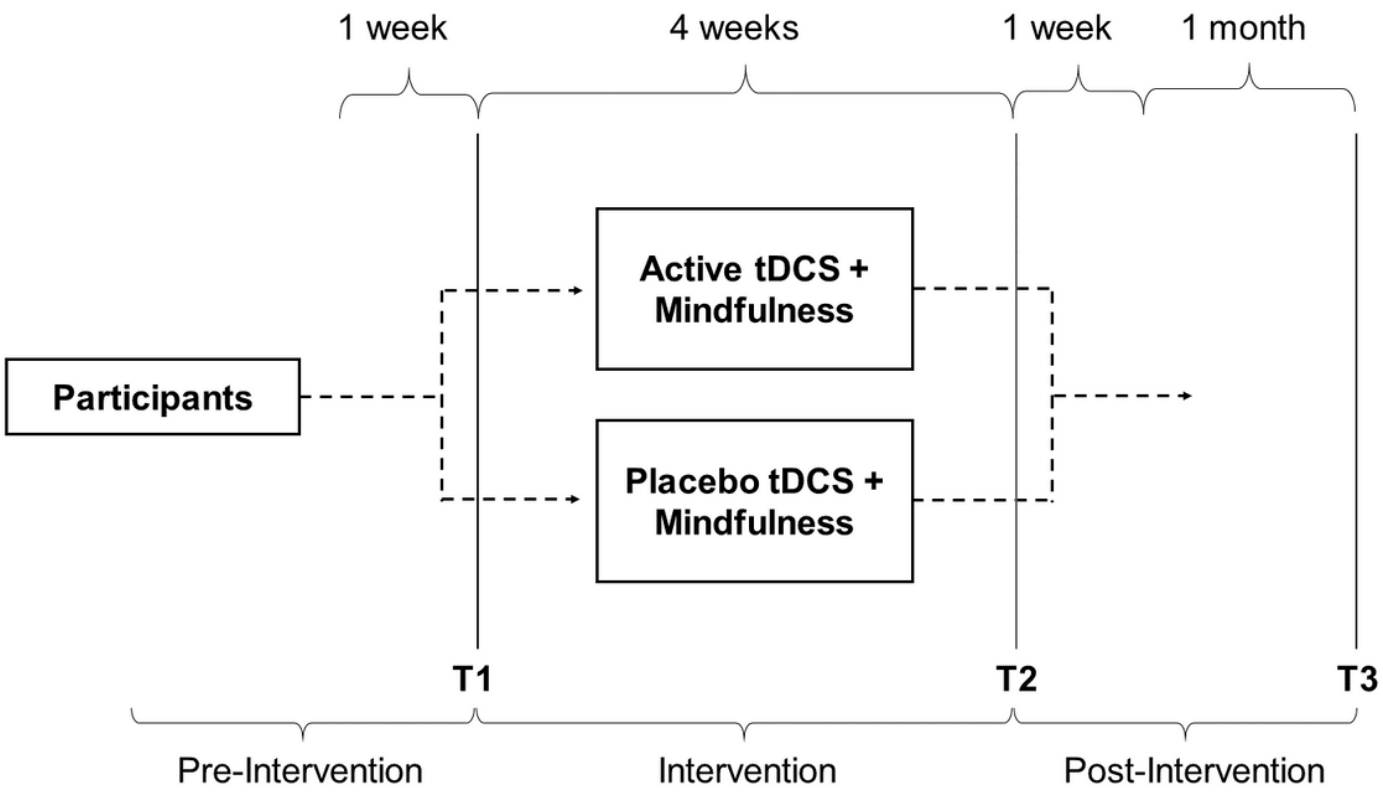

Figure 1

Study design for active tDCS versus placebo tDCS, both combined with mindfulness in the treatment of chronic migraine. Baseline (T1), end of intervention (T2) and postintervention (T3).

Supplementary Files

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- SPIRITChecklistVersion02.doc