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Adjuvant transcranial direct current stimulation in patients with chronic migraine: Protocol of a randomized controlled trial

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ABSTRACT

Introduction: Chronic migraine (CM) is a common neurological disorder with a global prevalence range of about 2%. There is evidence that anodal motor transcranial direct current stimulation (tDCS) might be a promising adjuvant intervention in CM. This randomized controlled trial (RCT) aims to evaluate the efficacy of tDCS in reducing migraine episodes in CM patients on standard prophylactic medication. **Research Hypothesis:** tDCS, as an add-on to standard treatment, might reduce the frequency of CM episodes in adults when compared to standard treatment alone. **Methods:** Adults with CM are included unless they meet the exclusion criteria (history of seizures; brain trauma or surgery; pregnancy; medication overuse; headache other than migraine; multiple or change of prophylactic medication in the last 3 months; metal prosthetics in the head or pacemaker). This trial is designed as a triple blind, parallel-group, multicenter (three centers in U.S. north-east geographical area), RCT, comparing an experimental group (tDCS + standard treatment) versus a control group (sham tDCS + standard treatment). According to a priori sample size calculation the inclusion of 100 subjects is estimated. The primary end point of the trial is the number of episodes during the 3 months study period. **Feasibility:** This trial includes patients regularly treated in specialized centers. Number of patients, limited complexity of the intervention setting and time frame of study period are strengths of the protocol. **Anticipated Results:** In the experimental group, a significant reduction of number of migraine episodes, compared to the control group, is expected.

KEY WORDS: Chronic pain, migraine, randomized controlled trial, transcranial direct current stimulation

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INTRODUCTION

Migraine is a common chronic neurological disorder characterized by recurrent headache attacks with different levels of pain intensity and duration. It has a significant negative impact on the quality of life of individuals because of its symptomatology and frequent comorbidities, representing a considerable burden to society due to its high medical and social costs. Migraine is recognized by the World Health Organization as a high-priority health condition [1,2]. Chronic migraine (CM) is defined by the presence of headache 15 or more days per month for at least 3 months, and its global prevalence ranges from 1.4% to 2.2%. The prevalence of CM in females is 3 times higher compared to males [3]. The management of CM can be extremely challenging due to the limited efficacy of available treatments and their side effects [4,5]. Therefore, there is a need for additional effective and tolerable options in order to improve the treatment of this highly debilitating disease.

Preliminary findings suggest that transcranial direct current stimulation (tDCS), a safe and non-invasive technique in which low-intensity electric current is applied to the scalp, may be safe and efficacious in migraine prophylaxis [6-9]. Besides it is known that neuronal cortical excitability is dysfunctional in migraine and reduced efficiency of inhibitory circuits is involved in the onset of a migraine episode [10]. Thus, the modulatory effect of anodal motor cortex tDCS would allow to target increased cortical inhibition preventing the episodes onset reflected by a reduction in their frequency over time.

Despite its limited efficacy, it is unethical to deprive subjects from standard prophylactic medication considering the severity of the condition. This randomized controlled clinical study aims to evaluate the efficacy of tDCS as an adjuvant treatment in reducing migraine episodes in patients who suffer from CM.

Research Hypothesis

tDCS as an adjuvant treatment is efficacious in reducing the frequency of migraine episodes in adults with CM as assessed by the number of episodes during the 3 months study period, measured as migraine attacks per patient per week.

METHODS

Study Population

Subjects between the ages of 18 and 59 years with headache 15 or more days per month for at least 3 months, having the features of migraine on at least 8 days per month will be considered for the study if they fulfill the criteria for diagnosis of CM according to the International Classification of Headache Disorders. All subjects will be admitted by the participating centers with a self-reported physician diagnosis of CM. The exclusion criteria are: History of seizures; brain trauma or brain surgery; medication overuse headache or any cause of headache other than migraine; pregnancy; use of more than one prophylactic medication; change of prophylactic medication in the last 3 months; contraindication to tDCS neurostimulation (metal prosthetics in the head or pacemaker). In order to represent CM population for every male subject enrolled, three females will be enrolled in the study.

Recruitment Plan

A target enrollment strategy will be adopted in this study and the recruitment will be performed in three quality treatment centers in the U.S. north-east geographical area (Massachusetts General Hospital, Boston-Coordinator Center; Johns Hopkins Hospital, Baltimore; New York-Presbyterian University Hospital of Columbia and Cornell, New York).

The study enrollment will be held during a 6 months period. Assuming a sample size of 100, we expect to reach an average of 40 subjects (approximately 30 female and 10 male) at coordinator center and 30 in the other two centers (approximately 45 female and 15 male). This period of recruitment is expected to be satisfied due to the high prevalence of the disease in the population.

Primary care providers and neurologists of these centers will be reached by e-mail and letters with the explanation of the purpose and importance of the study, the methodology and eligibility criteria. We will send a personalized invitation letter to encourage them to refer the patients from their healthcare facilities. Physicians interested in the study will be invited to an information meeting in which the aims of the study, the intervention and the side effects of tDCS will be explained.

The recruitment will be reviewed every 15 days and in case of slow recruitment rate, a mixed recruitment strategy with an awareness campaign through the websites of Headache and Migraine Organizations will be held as a backup plan to increase study awareness among physicians and associated patient organizations of migraine. The strategy is shown in Figure 1.

Adherence Plan

After screening for eligibility, the protocol will be exhaustively reviewed with each subject in order to obtain the informed consent and screening for adherence will then be performed.

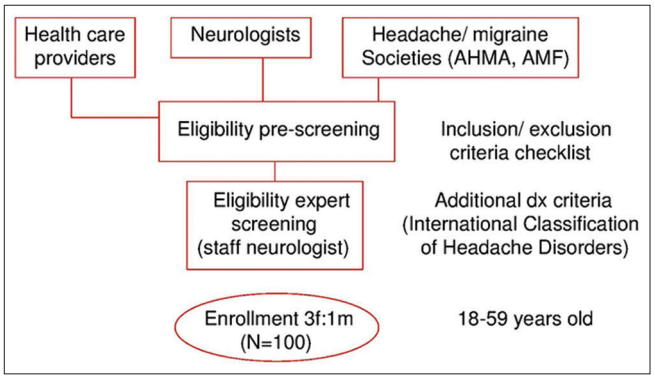

Figure 1: Study population and recruitment

The adherence to standard prophylactic treatment (that was initiated at least 3 months prior to the study enrollment) will be monitored through a device for counting pills. Besides the information obtained from the subjects, pill containers will be provided which have to be returned after 1 week. The pill containers will estimate the participants' compliance to the medication treatment plan and non-compliant participants will be removed from the trial. Compliant subjects will be enrolled in the study.

After enrollment and randomization, the subjects will be periodically monitored to assure patients' adherence to the protocol.

Throughout the study period, subjects will receive a controlled number of pills in a pill organizer to monitor the prophylactic pharmacologic treatment plan in accordance to the protocol. In their visits, they will be asked if they are taking the drug as prescribed and, if not, they will be encouraged to report the reasons. Subjects must perform a daily record of frequency, intensity and time of migraine episodes and abortive medication intake (for acute episodes) on the Headache Diary of the National Headache Foundation. This data, reported through a written diary or a smartphone application, will be also used to measure subjects' adherence. Subjects with written diaries will be recalled by phone calls and individuals with smartphone applications will be recalled through alarms and text messages to complete their diary.

During the visits, the investigator will always reinforce the importance of being compliant to the study protocol by:

- Incorporating effective communication and being always willing to promptly answer any question the participant might have
- Incorporating compensation for the visits as well as covering the expenses of transportation/meals
- Reinforcing motivations
- Supplying flexible hours for appointments.

When a participant is identified as non-compliant, the investigator should be able to recognize potential barriers faced by this participant and try to address those barriers using approaches to improve his/her adherence and reinforce his/her value in the study.

Primary and Secondary Endpoints

The number of episodes during the 3 months study period, measured as the number of migraine attacks per patient and week (Headache Diary-National Headache Foundation) is the primary endpoint.

Secondary endpoints include:

- Frequency of abortive migraine medication intake measured as doses per week
- Quality of life measure using a validated questionnaire (MIDAS - Migraine disability assessment test). Patients will complete the questionnaire before and after the study period
- Development over time of migraine episodes for every study week measured as number of migraine attacks per patient. For this variable, patients will be assessed on every prescheduled contact with the study team during the observation period
- All possible side effects of the tCDS (including serious adverse events). Adverse effects will be evaluated based on open questions on every contact with the study team
- Time required resuming everyday activities after an episode of migraine. Time will be calculated in minutes, based on patient surveys.

Sample Size Calculation

To calculate the sample size, we reviewed previous studies that investigated tDCS for the treatment of central pain in spinal cord injury [11] and for migraine prophylaxis [9]. In the migraine tDCS study, sample size calculation was not reported, and 37 of 59 patients recruited were included in the statistical analysis. Among study results, migraine episodes frequency was compared in experimental and sham groups at 4, 8 and 12 weeks of follow-up after 20 days double-blind treatment sessions. Considering the mean of migraine episodes of the placebo group (3.82) at week 12, which was consistent across time (at weeks 4 and 8), and the standard deviations of active and placebo group (0.86 and 0.79, respectively) at week 12, we calculated a difference between means of 0.533 needed to obtain an effect size of 0.65. In addition, assuming a power of 80% and a critical alpha of 0.05 and considering an equal randomization, according to sample size calculation, we would need 38 patients in each group ($n = 76$). Taking into consideration that our study design differs from the Auvichayapat's study in which patients did not take any other standard prophylactic treatment and that we must consider possible dropouts [12] in a multicenter setting, the sample size was adjusted to 50 in each group (12 additional subjects in each group). A total of 100 subjects will be included.

Randomization Plan

A sealed envelope system will be used in order to randomly generate treatment allocation. A simple randomization will be performed. Subjects will be randomized into two study groups and documented using an identification number. In order to secure allocation concealment, all analyzes will be performed using a blind database containing the group variable with an unlabeled "A" and "B." Consequently, all analyzes will be done without any possible presumptions related to the intervention.

Blinding

A triple blind design will be performed. The subjects, the investigators delivering the treatment and the assessors will be blinded to the treatment administered (real or sham tDCS). All subjects will feel a sudden tingling in the scalp when the tDCS

device will be turned on and in all subjects this feeling will disappear after a few seconds. During real tDCS the tingling is brief and stops because of the usual habituation mechanism and during sham tDCS the tingling stops as the device is turned off automatically.

A blinded database (unlabeled "A" and "B") will be used to perform statistical analysis. Subjects will be debriefed and asked whether or not they received active tDCS in order to assess if blinding is successful.

Intervention Process

tDCS

tDCS requires to place two saline-soaked pair of surface sponge-based electrodes (20-35 cm^2) on the scalp to apply a low-amplitude electric current (2 mA of constant current flow) held in place by a non-conducting rubber montage affixed around the head. There is sufficient current to penetrate the brain and modify the transmembrane neuronal potential, but without substantial shunting of current at the scalp. The effects of tDCS depend on electrode montage, on the intensity and duration of stimulation. On all subjects, the anode electrode will be placed over the motor cortex (M1) contralateral to the most predominant painful side, and the cathode electrode will be placed over the contralateral supraorbital area. The material needed and tDCS electrode montage is shown in Figure 2.

Therefore, the montage will be the same for both arms (intervention and sham) and the session duration will be 20 min (for either real or sham stimulation). As described before, in the sham stimulation the current will ramp-up, and, after 30 s, the current will ramp down, and the patient will not receive real stimulation.

The intervention will be performed 3 times a week during 4 weeks; the tDCS group will receive 2 mA current stimulation during 20 min while the sham group will receive only 30 s.

A 3 months will be completed for each subject.

Standard Prophylactic Treatment

All subjects will be on standard prophylactic treatment for at least 3 months before study enrollment. The available pharmacologic treatments have similar efficacy and type of medication is chosen according to patient clinical features. The most commonly prescribed prophylactic drugs in CM are anti-epilepsy drugs, beta-blockers, tricyclic antidepressants and calcium-channel blockers [4].

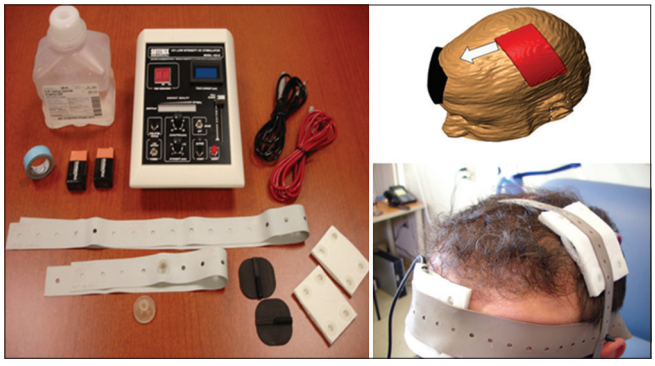

Figure 2: Transcranial direct current stimulation material and electrode montage

Statistical Analysis Plan

All patients will be randomized using 1:1 group allocation and will be documented including a study pseudonym. Patients will be allocated into a sham tDCS treatment group serving as controls and will be compared with patients in the intervention tDCS group.

For the persistence of allocation concealment, all analyzes will be performed using a blinded database containing the group variable with an unlabeled "A" and "B." Consequently, all analyzes will be done without any possible presumptions regarding treatment form.

Statistical analysis will be based on all patients randomized (intention-to-treat analysis [ITT]). A per-protocol analysis will be also conducted in order to allow a better understanding of the relationship between adherence and results.

First, baseline characteristics are analyzed. This includes the following variables:

- Age in years
- Number of migraine attacks per week at baseline
- Number of acute migraine medication intakes at baseline
- Quality of life measure using a validated questionnaire (MIDAS)
- Gender
- Comorbidity classified as chronic renal, hepatic, pulmonary (e.g. chronic obstructive pulmonary disease), heart disease (New York Heart Association)
- Co-medication and type of agent
- Type of migraine - with or without aura.

The continuous primary endpoint variable is defined as number of episodes during the 3 months study period measured by the number of migraine attacks per patient per week. For this variable, documentation of the validated patients' diary (Headache Diary of the National Headache Foundation; http://www.headaches.org/For_professionals/headache_diary) is used.

Secondary Endpoints

Frequency of acute migraine medication intake measured as doses per week, quality of life measured using a validated questionnaire (MIDAS), development over time of migraine episodes for every study week measured by the number of migraine attacks per patient and time required to resume everyday activities after a crisis of migraine, are continuous measurements. Furthermore, side effects of tDCS (including serious adverse events and adverse events) will be documented.

All continuous variables will be evaluated regarding distribution using graphical methods (histograms) as well as the Shapiro–

Wilk test to assess the presumption of normality. In normally distributed variables, descriptive statistics uses the mean as measure of central tendency including the standard deviation as a measure for variability. For testing differences between groups, a *t*-test is performed.

In the case of missing normal distribution, descriptive statistics uses the median as measure of central tendency including the 25 and 75% quartiles as measure for variability. For testing differences between groups a Mann–Whitney *U*-test is performed.

All categorical data will be expressed descriptively using absolute numbers and percentages of patients, when appropriate. Statistical significance tests for differences between groups will be performed using Chi-square tests or Fisher's exact test in case of small numbers of observations.

All adverse events that occur during treatment or during follow-up will be compared using descriptive statistics and evaluated by the study team as possibly related to the intervention or independent from the intervention. All reported adverse reactions will be compared using Fisher's exact test for categorical data due to the expected small numbers of observations.

Development over time of migraine episodes for every study week measured as number of migraine attacks per patient will be compared between groups using a two-way ANOVA including interaction of factors to evaluate a decline in symptomatic episodes over the study time. In this model, group allocation and mean numbers of episodes for every study week are introduced into the ANOVA model. The interesting evaluation in this analysis is the interaction between study group and time points giving a possible effect of the intervention on migraine episodes during study time. For descriptive analysis of this factor, an error bar diagram is built giving mean (including 95% confidence intervals) for evolution of episodes over time.

This pivotal randomized controlled trial (RCT) is planned using a 1:1 random allocation of patients. Despite these efforts, baseline characteristics will be evaluated to assess possible confounders to the primary end point. In the case of significant differences between groups regarding baseline characteristics, the primary endpoint will be reevaluated using multivariate regression analysis. In this model, group allocation and these specific baseline variables are integrated. In multivariable regression analyzes model quality is assessed using the Hosmer–Lemeshow test with a Type I error of $P = 0.05$. No subgroup analyzes are planned a priori for this study.

Missing data will be replaced using methods of multiple imputations. The number of imputations "m" will be chosen so that the relative efficiency compared to the maximum efficiency is $(1/[1 + \lambda/m]) \geq 0.98$. This means that when $\lambda = 0.2$ (20% missing data) m should be ≥ 10. All statistical analysis will be performed using these completed data sets.

A second and third approach, the direct likelihood method based on mixed models, and last observation carried forward, will be applied and compared by means of sensitivity analysis.

For all tests for group differences, a two side Type I error of $P = 0.05$ or less is assumed statistical significant. All analyzes are performed using STATA 13, 1996-2013 StataCorp LP College Station, Texas, USA.

Feasibility

This trial includes patients regularly treated in all participating specialized centers. Number of patients, limited complexity of the intervention setting and time frame of study period are strengths of the protocol. However, potential pitfalls are anticipated for this trial.

The recruitment can be compromised if health care providers do not refer patients despite receiving email and invitation letters in which all research procedures and goals will be explained. That is why a broader recruitment strategy is planned and will be adopted if needed.

Adherence can be an issue as well considering that frequent visits will be required during the 1st month in order to receive the treatment and a 3 months follow-up will be needed to assess endpoints. No change in clinical status related to either non-response to tDCS or to sham tDCS can also generate significant losses for the study, although real tDCS will be offered to patients of the control group if the intervention is proven to be efficacious after study completion. If tDCS is efficacious reducing frequency and intensity of migraine episodes, the volunteers might also abandon the study because the initial complaint is handled. For this reason, both an ITT (multiple imputation method) and per-protocol analysis will be conducted.

Besides the dependence on the patient feedback regarding the number of migraine attacks and drug dosage during the week may introduce a bias in the research since inaccurate responses might be obtained.

The questionnaires of quality of life should be properly explained, and guidance by assessors is important in order to obtain answers as reliable as possible.

Altogether, 100 individuals will be involved in this multicenter study. The procedures and protocols used will be strictly applied, with only a center responsible for data analysis in order to avoid bias. However, the study protocol assumes no differences in efficacy between centers. In the given sample size, possible center effect can only be evaluated roughly. On the other hand, including analyzes on center effects would require an increased numbers of subjects, which is not justifiable for both ethical and financial reasons in the context of current evidence.

ANTICIPATED RESULTS

In the intervention group, a significant reduction of the number of migraine episodes is anticipated. Based on previous studies assessing tDCS for migraine [7-9], an approximate reduction of up to 30% in migraine frequency could be expected when

compared to the control group. Furthermore, subjects included in the intervention arm are expected to experience less intense migraine episodes, require a reduced amount of medication (for acute episodes), have an improved quality of life according to the MIDAS and need less time to resume everyday activities without almost any adverse effects, compared to the control group.

DISCUSSION

CM leads to significantly impaired quality of life, and prophylactic therapeutic interventions are needed to reduce episodes frequency and pain intensity. Against the background of limited data regarding the efficacy of tDCS in CM this study protocol allows to gain evidence on the clinical benefit of a safe and non-invasive therapeutic tool in a multicenter RCT design.

This promising non-pharmacological intervention for patients suffering from a chronic condition could either be tested as an alternative or adjuvant treatment to standard prophylactic medication. The main limitation of testing tDCS as an add-on intervention is that the treatment effects cannot be isolated. Furthermore, there might be an interaction between tDCS and standard prophylactic pharmacologic treatment that may be variable depending on the specific type of prophylactic migraine medication. Despite this important drawback, it was considered that the potential benefit of tDCS in the most severe migraine population has to be determined prior to include a placebo group in a future study design. A factorial design (tDCS vs. standard treatment vs. tDCS + standard treatment vs. placebo) would allow a differentiation of treatment effects but would also deprive subjects with CM from standard available treatments proven to have a mild to moderate preventive efficacy, which would be unethical.

It is also important to remind that CM patients are a heterogeneous population and disease severity is one major determinant of trial inclusion. Consequently, results of this study will only be generalizable to patients who have severe migraine defined by chronic episodes associated with significantly impaired quality of life. However, on the other hand, this targeted population is expected to profit most from tDCS as an adjuvant intervention. This trial is designed with maximized precautions against bias focusing on internal validity. The authors hope to support future interventions in pain management improving life quality especially in chronically ill patients.

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