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Transcranial Direct Current Stimulation in Mesial Temporal Lobe Epilepsy and Hippocampal Sclerosis

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been evaluated in medication refractory epilepsy patients. The results have been inconclusive and protocols have varied between studies.
Objective: To evaluate the safety and efficacy of two protocols of tDCS in adult patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS).
Methods: This is a randomized placebo-controlled, double-blinded clinical trial, with 3 arms, 3 sessions, 5 sessions and placebo stimulation. Frequency of seizures (SZs), interictal epileptiform discharges (IEDs) and adverse effects (AEs) were registered before and after treatment, and at 30 and 60 days follow-up. Descriptive statistics, k-related samples, Friedman's test, and relative risk (RR) estimation were used for analysis.
Results: We included twenty-eight subjects (3d $n = 12$, 5d $n = 8$, placebo $n = 8$), 16/28 (57%) men, age 37.8(±10.9) years old. There was a significant reduction of the frequency of SZs at one ($p = 0.001$) and two ($p = 0.0001$) months following cathodal tDCS compared to baseline in the 3 arms ($p = 0.0001$). The mean reduction of SZ frequency at two months in both active groups was significantly higher than placebo (–48% vs. –6.25%, $p < 0.008$). At 3 days (–43.4% vs. –6.25%, $p < 0.007$) and 5 days (–54.6% vs. –6.25%, $p < 0.010$) individual groups showed a greater reduction of SZs. A significant IED reduction effect was found between baseline and immediately after interventions ($p = 0.041$) in all groups. Side effects were minor.
Conclusions: Cathodal tDCS technique of 3 and 5 sessions decreased the frequency of SZs and IEDs (between baseline and immediately post-tDCS) in adult patients with MTLE-HS compared to placebo tDCS.

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Daniel San-Juan, M.D., principal author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; also Daniel San-Juan, M.D. has full access to all of the data; and has the right to publish any and all data separate and apart from any sponsor.

Daniel San-Juan, M.D., principal author takes full responsibility for clinical trial data and the data results will be deposited in a clinical trials database (clinicaltrials.gov with the identifier NCT01763294).

We certify that the submission (aside from an abstract) is not under review at any other publication.

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Introduction

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is a well characterized electro-clinical epileptic syndrome. In adult patients MTLE-HS accounts for 80% of temporal lobe seizures (SZ) and is frequently refractory to antiepileptic drugs (AEDs) [1]. Resective surgical treatment results in approximately 50%–67% of patients becoming seizure-free, and surgical neurostimulation therapies (Vagal Nerve Stimulation [VNS] and Responsive Neurostimulation System [RNS]©) are FDA approved options that induce a seizure freedom rate of 7%. However, a substantial number of patients are not candidates for these invasive procedures, which have limited efficacy [2–4]. New therapies are needed.

Transcranial direct current stimulation (tDCS) is an emerging non-invasive technique for cortical excitability modulation by subthreshold membrane depolarization or hyperpolarization (cathodal stimulation decreases the cortical excitability while anodal stimulation increases it) which has been shown to be safe, economical, and easy to use [5,6]. TDCS has been tested in a limited number of pharmacoresistant epilepsy patients with heterogeneous etiologies using various parameters; 4 out of the 6 clinical studies reviewed showed an effective decrease in SZ frequency; and 5 out of 6 reported a 31.5–64.3% reduction of interictal epileptiform discharges (IEDs). All patients tolerated tDCS well [7]. However, some studies did not demonstrate a decrease in SZ frequency [8], were clinically irrelevant [9], include multiple epileptic etiologies, or used different stimulation parameters [7–13]. For example, current dosage, frequency and duration of tDCS sessions varied from 1 to 2 mA [7], 1–20 sessions (over 2 months) [8,10] and 20–60 minutes of stimulation, respectively [7,12]. Studies applying a 1 mA, 20 minute, single session stimulation reported a reduction of SZ frequency [8–10]. Conversely, clinical studies using 2 mA, 20–60 minute tDCS sessions daily for 3–5 consecutive days, reported significantly reducing SZ frequency [11,12]. These seemingly inconsistent results may be related to the short and long term effects dependent upon the duration of tDCS. Long-lasting after-effects in tDCS may reflect a change of NMDA receptor efficacy, which are involved in neuroplastic changes [7].

Based on previous studies [7–13], we hypothesized that active tDCS protocols (30 minute sessions for 3 or 5 consecutive days) will produce a clinically meaningful reduction of SZ frequency and IEDS in patients with MTLE-HS refractory to AEDs compared with placebo tDCS. The present study compared two active tDCS protocols against placebo tDCS to evaluate safety and efficacy in the reduction of SZs and IEDs in patients with MTLE-HS refractory to AEDs.

Methods

Trial design

A randomized, double-blinded, placebo-controlled, 3-arm parallel-group (placebo, 30 min/2 mA daily sessions for 3 days, and 30 min/2 mA daily sessions for 5 days) clinical trial was conducted at the National Institute of Neurology and Neurosurgery in Mexico City.

Participants

Study subjects were recruited from the epilepsy clinic. Eligibility criteria for inclusion were (1) adults aged ≥18 years old; (2) proven MTLE-HS (defined as clinical seizures, the presence of unilateral HS on MRI, and interictal EEG findings according to the ILAE Commission on Neurosurgery of Epilepsy [14]); (3) MTLE-HS refractory to AEDs (defined as failure of adequate trials of two tolerated and appropriately chosen and used AEDs to achieve sustained seizure freedom); (4) antiepileptic treatment during the 12 months prior to inclusion; (5) patients who refused epilepsy surgery or are at least 6 months down the waiting list.

All participants signed informed consent and had a Mini-Mental Status score >23. Exclusion criteria were presence of pseudoseizures; idiopathic focal or generalized epilepsy; previous epilepsy surgery or craniotomy; history of recent stupor or coma; active intracranial infection; breastfeeding or pregnancy; or neurodegenerative diseases. Participants were required to stay on a stable AED regimen during the treatment and follow-up periods.

Intervention

Stimulation was applied with the Transcranial Direct Current 1ch Stimulator® and its electrodes (TCT Research Limited, TST Kowloon, Hong Kong). This tDCS device is a battery-powered investigational device. Thirty-five square centimeter sponge electrodes (anodal and cathodal) were saturated with 0.9% sodium chloride solution, to facilitate current flow, and placed over the scalp. The cathode was positioned over the most active IED area (defined as the zone [electrodes] with the highest discharge amplitude and/or frequency, located with the 10/20 system) as observed on the scalp EEG immediately before applying the tDCS. The anode electrode was placed over a silent supraorbital area (i.e. without epileptogenic activity) contralateral to the stimulated MTLE-HS side. The applied bipolar stimulation had a 2 mA current and lasted 30 minutes. In order to maintain the blind, placebo arm patients followed the exact same protocol (3 or 5 consecutive days of treatment) as active arms patients. The placebo arm patients were actively stimulated for the first 60 seconds of each of their sessions with the purpose of creating an initial stimulus. The latter procedure has been used before in tDCS placebo-controlled clinical trials and is described as effective for keeping subjects blind to treatments [15]. The participants were not permitted to interact with each other during their visits in any of the study phases. IEDs and monthly SZ frequency were evaluated at baseline, post stimulation (only IEDs) and at one and two month follow-ups. Data were recorded in individual SZ diaries, given 1 month prior to the first intervention, and during follow-up visits. AEs were evaluated at post-stimulation and at the follow-up visits using the AE questionnaire developed by Brunoni et al. [16]. AEs were defined according to the Medical Dictionary for Regulatory Activities (MedDRA©).

Awake 30 minute EEGs were performed prior to and immediately after treatment (at the end of 3 or 5 sessions), and at follow-up (after one and two months). These were conducted and analyzed according to the American Clinical Neurophysiology Society recommendations using the 10/20 international system [17]. All IEDs were analyzed and accounted for visually by two board certified clinical neurophysiologists blinded to the treatments (D.S. and D.E.L.).

Outcome measures

The primary outcome measure was a decrease in SZ frequency of at least 50% at 1 and 2 months compared to the baseline frequency. Secondary outcome measures were number of IEDs in EEGs; number of AEs reported by the patient during therapy and follow-up; and mean reduction of SZ monthly frequency.

Sampling and blinding

Individuals were randomly assigned to the intervention groups in equal numbers using SPSS v. 18. The group assignment was blinded for all patients. The evaluating physician (D.E.L.) was blinded and independent from the principal investigator assessing the patients. The researcher applying the tDCS therapy was not blinded