Epilepsia Open

FULL-LENGTH ORIGINAL RESEARCH

Cathodal transcranial direct-current stimulation for treatment of drug-resistant temporal lobe epilepsy: A pilot randomized controlled trial

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Summary

Objective: **To investigate the effect of cathodal transcranial direct-current stimulation (c-tDCS) on seizure frequency in patients with drug-resistant temporal lobe epilepsy (TLE).**

Method: **Twenty-nine patients with drug-resistant TLE participated in this study. They were randomized to experimental or sham group. Twenty participants (experimental group) received within-session repeated c-tDCS intervention over the affected temporal lobe, and nine (sham group) received sham tDCS. Paired-pulse transcranial magnetic stimulation was used to assess short interval intracortical inhibition (SICI) in primary motor cortex ipsilateral to the affected temporal lobe. SICI was measured from motor evoked potentials recorded from the contralateral first dorsal interosseous muscle. Adverse effects were monitored during and after each intervention in both groups. A seizure diary was given to each participant to complete for 4 weeks following the tDCS intervention. The mean response ratio was calculated from their seizure rates before and after the tDCS intervention.**

Results: **The experimental group showed a significant increase in SICI compared to the sham group ($F = 10.3$, $p = 0.005$). None of the participants reported side effects of moderate or severe degree. The mean response ratio in seizure frequency was −42.14% (standard deviation [SD] 35.93) for the experimental group and −16.98% (SD 52.41) for the sham group.**

Significance: **Results from this pilot study suggest that tDCS may be a safe and efficacious nonpharmacologic intervention for patients with drug-resistant TLE. Further evaluation in larger double-blind randomized controlled trials is warranted.**

KEY WORDS: **Cathodal transcranial direct-current stimulation, Drug resistant, Temporal lobe epilepsy.**

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Epilepsy impacts 50 million people (1% of the population) worldwide.[1] Management for patients with epilepsy includes antiepileptic drugs (AEDs), and for some patients with drug-resistant seizures, surgery. Temporal lobe epilepsy (TLE) is often resistant to AEDs,[2] and >40% of patients with epilepsy have adverse reactions to AEDs. Removing the epileptogenic regions surgically is not always feasible for patients, and the outcome is not ideal in 30–50% of cases.[3] Consequently, alternative methods of *seizure control* warrant more investigation.

The excitability of the γ-aminobutyric acid (GABA) ergic intracortical inhibitory circuits in primary motor

Key Points

- Within-session repeated (9-20-9 protocol) c-tDCS has shown no or minimal side effects in patients with drug-resistant temporal lobe epilepsy
- Cortical excitability was reduced, as measured by SICI, after one application of c-tDCS using the 9-20-9 protocol in patients with drug-resistant temporal lobe epilepsy
- Seizure rates reduced by 42% after one application of c-tDCS using the 9-20-9 protocol in patients with drug-resistant temporal lobe epilepsy

cortex (M1) can be assessed noninvasively in humans by paired-pulse transcranial magnetic stimulation (TMS). In this technique, two stimuli are delivered 1–5 msec apart through the same coil. The first stimulus is subthreshold for a motor response; however, it activates intracortical inhibition (ICI) circuits and reduces the size of the motor evoked potentials (MEPs) elicited by the second stimulus, which is supra-threshold for a motor response.[4] It has been shown that ICI measured using this method reflects the cortical activity of GABAergic interneurons in the M1 area.[5] This inhibition is termed short-interval intracortical inhibition or SICI.

ICI circuits have been assessed extensively with a paired-pulse paradigm in patients with epilepsy.[6–8] Several studies on drug-naive patients with focal epilepsy showed a decrease in SICI in the ipsilateral hemisphere.[9–15] Badawy et al. showed increased M1 excitability and decreased SICI in 35 patients with focal epilepsy 24 h before and after a seizure.

Transcranial direct current stimulation (tDCS) is a well-established cortical stimulation method that can be used noninvasively to modulate neuronal excitability in humans.[16] In this technique, a low intensity current (1–2 mA) is used that can affect the membrane potentials in two ways. Cathodal tDCS (c-tDCS) hyperpolarizes the resting membrane potentials, whereas anodal tDCS acts toward depolarization.[16] Modification of seizure network excitability by tDCS is a potentially valuable noninvasive alternative for reducing the excitability of this abnormal network in patients with epilepsy and thereby reducing the seizure rates in this population.

The aim of this study was to examine the effects of this noninvasive therapeutic approach on seizure frequency in this group of patients. We hypothesized that compared to sham tDCS, application of c-tDCS over the temporal lobe in patients with drug-resistant TLE, decreases seizure frequency and increases intracortical inhibition in the ipsilateral M1 area.

Method

Participants

We conducted a small pilot study in patients admitted to the video–electroencephalography (EEG) monitoring (VEM) unit at the Royal Melbourne Hospital or as outpatients at St Vincent's Hospital. Twenty-nine participants (11 male, 18 female) with drug-resistant TLE and mean age of 38 ± 13 (SD) participated in this study. All 24 participants from the Royal Melbourne Hospital were admitted as potential surgical candidates to the VEM unit. The etiology of the TLE varied between participants and included tumor, meningitis, infantile febrile, cortical dysplasia, and unknown reason. Inclusion criteria were the following: (1)≥18 years of age; (2) diagnosed with drug-resistant TLE, as defined by the International League Against Epilepsy (failure to become [and stay] seizure-free with adequate trials of two seizure medications); and (3) able to understand, speak, and write in English. Exclusion criteria were the following: (1) skin conditions (e.g., eczema, lesions) on scalp; (2) metal inside the head (outside the mouth) such as shrapnel, surgical clips; (3) any implanted devices such as cardiac pacemaker, cochlear implant, medical pump, or intracardiac line; (4) frequent or severe headaches; (5) previous head injury and any other brain-related disease; and (6) pregnancy and breastfeeding. All procedures used in this study conformed with the Declaration of Helsinki, and the protocol was approved by the Human Research Ethics Committees at The University of Melbourne and Melbourne Health. Written informed consent was obtained from each participant.

Intervention

One session of c-tDCS or sham tDCS (9-20-9 protocol) was applied in the last day of each participants' admission in the VEM unit at the Royal Melbourne Hospital (RMH) or in a quiet room at St Vincent's Hospital as an outpatient. Participants were randomly allocated to experimental or sham group. They were all blinded to the nature of the intervention (experimental vs. sham). This protocol involved a total of 18 min c-tDCS or sham tDCS, with 20 min rest after the first 9 min (Fig. 1). A DC-Stimulator (Chattanooga Intelect Advanced Combo) was used to deliver a 1 mA continuous galvanic current to the brain via two surface electrodes with surrounding saline-soaked sponges (0.9% NaCl). The active surface electrode (cathode, 3 × 4 cm) was placed over the affected temporal lobe, and the return electrode[17] (anode, 5 × 7 cm) was placed over the contralateral supraorbital area.

Assessment

Participants were asked to keep a record of their seizures in a daily seizure diary for 4 weeks after the intervention. The mean response ratio was calculated by the following

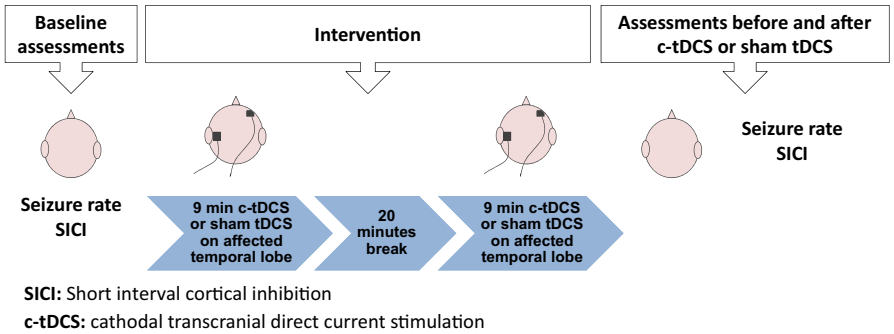

Figure 1.
Experimental set-up. All participants received one session of c-tDCS or sham tDCS paradigm (9-20-9 protocol). The active surface electrode (cathode) was placed over the temporal lobe in the affected hemisphere. The return (anode) electrode was placed over the supraorbital area contralateral to the stimulated hemisphere. SICI was assessed before and after tDCS intervention. Seizure rates were recorded for 4 weeks after tDCS intervention.

formula: $[(T-B)/(T+B)] \times 100$. In this formula, B is the patient's baseline seizure frequency over the 4 weeks prior to treatment, and T is the patient's seizure frequency in the 4 weeks after the treatment. In this study, the seizure rate prior the intervention for each participant was recorded based on participant's report. Negative response ratio values indicate reduced seizure rate from baseline. The response ratio allows for a normalized percentage change in seizure rate from baseline, with values within the range of −100 to +100. Zero value in this range indicates no change.[18]

Paired-pulse TMS (Magstim BiStim^2) was used to assess SICI before and after each intervention. Participants were seated with head and neck supported by a headrest. MEPs were recorded from the first dorsal interosseous (FDI) muscle before and after each intervention. Resting threshold (RT) for recording MEPs was defined as the lowest intensity to record three of five successive MEPs >50 μV (peak-to-peak amplitude) from FDI. The TMS intensity for the suprathreshold stimuli was adjusted to produce MEPs in FDI at rest of about 1 mV amplitude (test intensity). The TMS intensity for the sub-threshold stimuli was adjusted to $0.8 \times$ RT (conditioning intensity) with 3 msec interstimulus interval. Single or paired-pulse TMS was delivered in blocks of 20 stimuli (10 s interval between stimuli) at rest (40 trials at each session).

Adverse events related to the application of c-tDCS (e.g., itching, tingling, burning sensation; headache, neck pain, etc.) in this study were assessed using the Adverse Effects Questionnaire[19] during and after each session.

Results

All participants tolerated the intervention very well. None of the participants reported side effects of moderate or severe degree during or after the intervention. A few participants reported itching sensations (2/10) for few minutes under the anode electrode. Twenty-three participants returned their diaries (Table 1). The mean response ratio was calculated from their seizure rates before and after the tDCS intervention (Table 2). The mean response ratio was −42.14% (standard deviation [SD] 35.93) for the experimental group and −16.98% (SD 52.41) for the sham group. SICI was measured with paired-pulse TMS (Magstim BiStim^2) before and after the tDCS intervention in 17 participants (Table 1).

One-way analysis of variance (ANOVA) showed that SICI was increased significantly in the experimental group compared to the sham group ($F = 10.3$, $p = 0.005$) (Fig. 2). The individual SICI level before and after c-tDCS can be seen in Figure 3.

Discussion

This pilot study showed that c-tDCS using the 9-20-9 protocol could not only increase SICI, but also decrease seizure rates in patients with drug-resistant TLE. The results of this pilot study cannot be compared to those of previous studies, since no SICI data are available post c-tDCS and this new protocol (9-20-9) has not been applied previously to patients with drug-resistant epilepsy.

Regardless of the cause of epilepsy, it has been argued that seizure networks are highly excitable as a result of unbalanced neuronal excitatory/inhibitory networks within

Table 1. Distribution of collected data in participants

Group	Number of participants	TMS data collected	Seizure diary returned	No TMS data collected/no seizure diary returned
Experimental	20	12	16	3
Sham	9	5	7	2
Total	29	17	23	5

Table 2. Seizure rates in experimental group versus sham group before and after tDCS intervention and mean response ratio in both groups

Group	Seizure diary returned	Seizure rate before tDCS ± SD	Seizure rate after tDCS ± SD	Mean response ratio [(T−B)/(T + B)] × 100
Experimental	16	53 ± 78.95	17.18 ± 26.03	−42.14 ± 35.93
Sham	7	20.28 ± 33.69	13 ± 16.2	−16.98 ± 52.41

the affected region.[20] Therefore, the main aim in seizure control is manipulating these networks in such a way that the seizure networks remain in a "sub-threshold" condition and are not triggered. The excitatory/inhibitory networks can be manipulated by decreasing the excitability of the excitatory networks or increasing the function of inhibitory networks, or both at the same time.[21] Drugs that block voltage-dependent ion channels or excitatory *N*-methyl-D-aspartate (NMDA) receptors, or enhance GABAergic activity have been shown to have a profound ability to suppress the development of seizures.[21] Antiepileptic effects of c-tDCS can be expected due to the fact that c-tDCS decreases cortical excitability by hyperpolarizing the membrane potentials and subsequently altering synaptic efficacy.[22,23] Lang et al.[24] recorded corticospinal volleys evoked by single-pulse TMS of M1 before and after a 5-min period of c-tDCS in eight conscious patients who had electrodes implanted in the cervical epidural space. They showed that c-tDCS suppressed the excitability of cortical circuits generating later "indirect waves" (I waves) in the corticospinal system. They suggested that c-tDCS facilitates inhibitory connections or it produces dis-facilitation (e.g., hyperpolarization) of excitatory connections leading, to a selective suppression of later I waves.[24] In a recent study Dhamne et al.[25] reported that 1 mA c-tDCS for 20 min could reduce seizures, augment lorazepam efficacy, and enhance GABAergic cortical inhibition in kindled rats.

The effects of tDCS are strongly dependent on electrode montage and parameters of stimulation. It has been shown that the induced excitability changes and the length of the lasting effect depend on two parameters of direct currents: *intensity* and *duration of application.*[26,27] The effects of modifications of these parameters have been tested in a few clinical applications.[28–30]

Fregni et al.[31] studied the effects of c-tDCS (one session, 20 min, 1 mA) in patients with drug-resistant epilepsy and malformations of cortical development as indicated by seizure frequency and epileptiform EEG discharges. They applied the c-tDCS over the epileptogenic focus, and showed that c-tDCS could decrease cortical excitability in the epileptogenic focus of these patients. They also reported a trend ($p = 0.06$) for decrease in seizure frequency after active c-tDCS compared with sham treatment (mean seizure frequency decrease of −44.0% for the active treatment group and −11.1% for the sham treatment group). The seizure reduction rate was similar to that of the present study (−42.14% in experimental group and −16.98% in sham group).

Auvichayapat et al.[32] assessed the antiepileptic efficacy of c-tDCS in 36 children (6- to –15-years-old) with drug-resistant epilepsy. Twenty-seven children in the active group received a single session c-tDCS (1 mA) for 20 min, whereas the remainder were in a sham group. In the active group, c-tDCS suppressed epileptiform discharges for 48 h, with a small (clinically negligible but statistically significant) decrease in seizure frequency. Faria et al.[33] applied c-tDCS for 30 min with the same intensity in two children with drug-resistant continuous spike-wave discharges during slow sleep. They reported similar results in terms of safety and the efficacy of c-tDCS in reduction of the interictal epileptiform EEG discharges. Varga et al.,[34] however, applied c-tDCS before sleep on five patients with focal, drug-resistant continuous spikes and waves during slow sleep with no effects on the spikes. The c-tDCS parameters used were similar to those used in the Faria et al. study except that the duration of treatment was 10 min shorter.[34]

Yook et al.[35] reported the results of c-tDCS application in an 11-year-old girl with focal cortical dysplasia. This patient received c-tDCS over the site where the abnormal

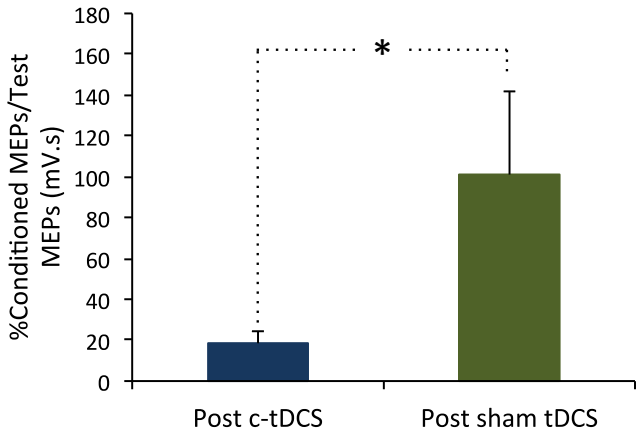

Figure 2.
Mean SICI changes post c-tDCS versus sham tDCS. The MEPs were recorded from the first dorsal interosseous (FDI) muscle. The area of the conditioned and unconditioned MEPs were measured from the averaged rectified MEPs obtained in each trial. The size of the conditioned MEPs was expressed as a percentage of the unconditioned test MEPs in order to assess the effectiveness of SICI. SICI was increased significantly in the experimental group compared to the sham group ($F = 10.3$, $p = 0.005$).
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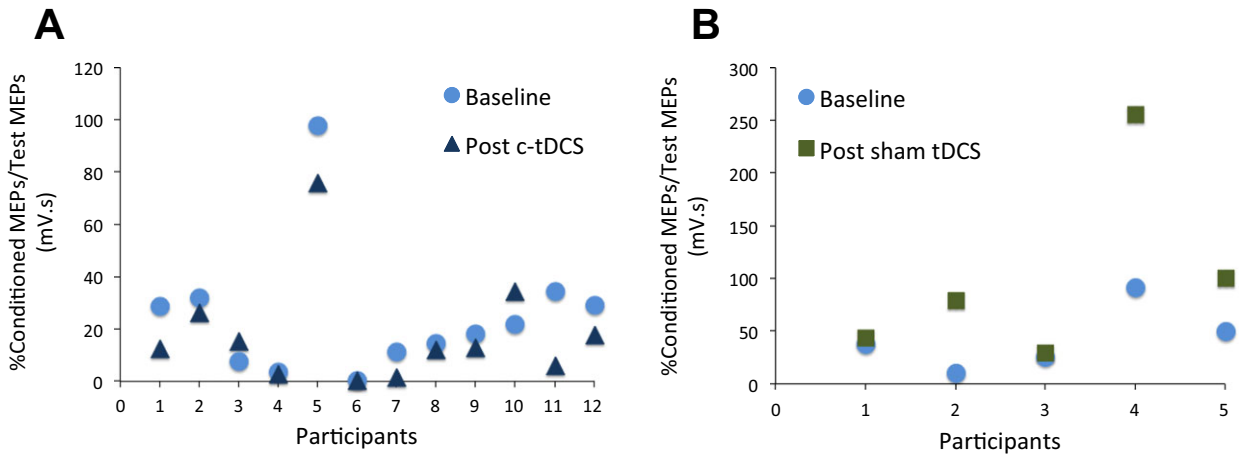

Figure 3.
Individual SICI changes post c-tDCS or sham tDCS. SICI changes post c-tDCS (**A**) or sham tDCS (**B**) for each participant. Blue circles show SICI level at baseline. Full triangles or rectangles show SICI level post tDCS. In **A**, most participants show a trend of increased SICI post c-tDCS. In **B**, no trend of increased SICI is seen in any participant.

wave was observed (through EEG recordings) for 20 min with 2 mA, 5 days per week for 2 weeks. During the 2-month monitoring period after this treatment they reported that not only was the duration of the seizures decreased but also the frequency of her seizures reduced from eight seizures per month to three seizures per month. This protocol was reapplied for another 2 weeks, with only one seizure reported in the following 2 months.

Although all the tDCS protocols that have been used in the above-mentioned clinical studies are well within safety limits,[36] it is a general goal to keep current exposure as low as possible. High-intensity stimulation can not only be painful,[37] it also can affect different neuronal populations compared with low intensity stimulation. By increasing the intensity, the current may reach deeper sites that might not be the intended target.

One way to prolong the after-effects of tDCS might be the repetition of tDCS sessions. Monte-Silva et al.[38] showed that application of c-tDCS for 18 min with a 20 min break after the first 9 min will increase the inhibitory effects of this technique for up to 2 h (9-20-9 protocol). This protocol was used in this pilot study in one session on patients with drug-resistant TLE.

We had an opportunity to apply c-tDCS with (9-20-9) protocol on two consecutive days in a 48-year-old woman with drug-resistant TLE while she was admitted to VEM unit at RMH.[39] She had a right frontotemporal pleomorphic astrocytoma for 10 years with 5–10 seizures per day. After receiving the c-tDCS on the last 2 days of her admission, she reported a seizure reduction of 0–3 seizures per day over a 4 month period. These observations suggest that c-tDCS might have accumulative inhibitory effects on the abnormal epileptic networks.

A recent review of the effect of c-tDCS on epilepsy assessed nine original studies (three animal, six human) up to 2014.[40] In these studies, 109 animals and 65 humans received c-tDCS with different parameters (including electrode montage, size of the electrodes, and duration and intensity of the applied c-tDCS). Because of the different methods of c-tDCS application, and the lack of long-term follow-up, only preliminary evidence of the safety and efficacy of this technique in controlling seizures in animals and patients with epilepsy could be concluded.[40]

Limitations

We acknowledge the limitations of this pilot study (open label, unequal groups). However, the results are encouraging. The results of this pilot study should be interpreted with caution. Even though all participants were diagnosed with drug-resistant TLE, they were not homogenous in regards to the etiology, onset of their epilepsy, or the seizure rates. The seizure rate changes were measured based on baseline seizure rates that were reported by patients. TMS assessment could not be done on all participants due to unforeseen reasons (e.g., time constraint due to being scheduled for other assessments before they were discharged, unavailability of the device and so on).

Future directions

This novel technique (tDCS) has, to date, shown no or minimal side effects, and it can be applied by an inexpensive battery-operated device. This new technique should be assessed in a large randomized double-blind controlled trial. If successful, it has the potential to be readily translated into clinical practice as a safe and well-tolerated non-medical treatment option for epilepsy management. In this way,

patients may be able to control their seizures without the side effects associated with taking additional AEDs.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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