EPILEPSY

Transcranial Direct Current Stimulation for Treatment of Refractory Temporal Lobe Epilepsy: A Scoping Review

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ABSTRACT

Introduction: **Neuromodulation devices have emerged as an alternative treatment for drug-resistant epilepsy syndrome, especially for temporal lobe epilepsy (TLE). Transcranial direct current stimulation (tDCS) is one of neuromodulation techniques that shown promising results in refractory epilepsy. We aim to evaluate clinical efficacy of tDCS used in refractory TLE in clinical trial setting.**

Methods: **Six-stages Arksey and O'Malley's methodology framework were used to guide this scoping review. PubMed, SCOPUS, and Cochrane Library were searched for clinical trials involving tDCS in refractory TLE. We also examined the tDCS protocol used, clinical efficacy and its side effects.**

Results: **Five studies met the inclusion criteria. Three studies were randomized crossover studies, and the other two were randomized placebo-controlled double-blind study and pilot randomized control trial. A total of 85 subjects were involved with mean seizure frequency of 2.6 per week. TDCS protocols involved were 1 and 2 mA of direct current with varying frequency and duration. All studies showed improved seizure control in TDCS arm with minimal to zero side effects.**

Conclusion: **TDCS appears as a safe and better option. Despite the benefit seen among refractory TLE, future prospective studies should focus on standardization of tDCS application as well as a more homogenous patient selection.**

KEY WORDS

refractory epilepsy, temporal lobe epilepsy, tDCS, transcranial direct current stimulation

INTRODUCTION

Epilepsy is among the commonest and the third cause of worldwide burden of neurological diseases[1]. Approximately 50 millions people around the world are suffering from epilepsy and there are about of 2.4 million new cases of epilepsy each year[2]. Of these, only 50% achieve complete seizure control[3]. The primary treatment of epilepsy is the anti-epileptic drugs (AEDs), and currently there are more than 20 drugs available. However, about one-third of the patients are medically intractable as they failed to achieve seizure control, or suffered from unbearable side effects following AEDs[4-6]. Drug-resistant epilepsy is defined as a failure of at least two tolerated and appropriate AEDs to achieve good seizure freedom[6]. Typically, resistant epilepsy is treated by invasive surgery of removing the epileptogenic area in the brain, thus reducing the seizure frequency; however only selected patients are eligible[4,6]. Nevertheless, resective surgical treatment only resulted in 50%-67% of seizure-free rate[7]. On the other hand, patients for resective surgery are at risk to develop many complications[8-12]. Other than surgical, neurological and psychosocial complications, temporal resective surgeries impose the patients to neuropsychologic problems such as memory deficit, language abnormality, anxiety, depression and psychosis[9-12]. There are few options available other than surgery, namely dietary modifications, enrolled into clinical trials of new AEDs, and neurostimulation[4].

Recently, neurostimulation is increasingly recognized as an alternative option in refractory epilepsy[13]. TDCS is a modality of neurostimulation which has provided new opportunities for the treatment of drug-resistant epilepsy[14,10]. It is a simple and non-invasive device that delivers low intensity, direct current to cortical areas, facilitating or inhibiting spontaneous neuronal activity[16]. TDCS also offers several potential advantages over resective surgical approach as a classical treatment for refractory epilepsy[17]. In comparison to the non-invasive neuromodulation devices such as transcranial magnetic stimulation (TMS), tDCS can influence a larger region of the cortex than TMS[18].

Reports in animal studies have shown that cathodal tDCS reduce the epileptiform discharge[19,20], and the same finding shown in human studies where patients with refractory epilepsy who were stimulated by cathodal tDCS have shown reduction in epileptiform discharges measured by EEG.[15,16,21] TDCS has shown to improve psychological process, psychiatric, neurological conditions and alter performance across a range of cognitive tasks[22-25]. This neurostimulation device was applied and proven to improve depression, stroke and even altered states of consciousness[16,22,23,26]. This report aims to review clinical trials that apply tDCS as intervention onto patients with refractory TLE.

METHODOLOGY

This review is triggered by a raise of acceptance in the application of neuromodulation as an alternative treatment for refractory epilepsy patients. Although not yet approved by FDA, tDCS offered great potential to be widely used as a treatment for drug-resistant epilepsy. We considered many systematic approaches but decided to do a six stages frame methodology of scoping review[27] as it will be an appropriate strategy to review and summarize a range of evidence in order to study

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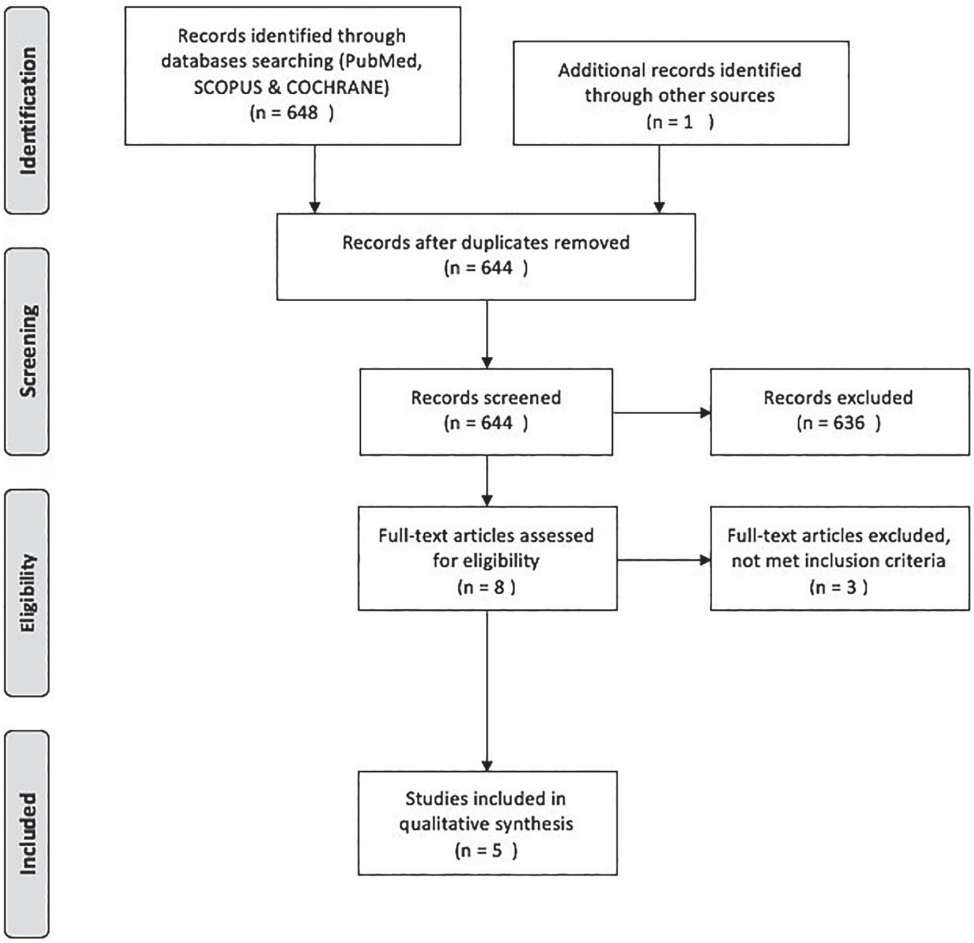

Figure 1: Six-stages Arksey and O'Malley's methodology framework[27].

the depth and range of literature available of this less attentive treatment option.

Stage 1: Identifying the Research Question

The research question is defined as: What are the different protocols, safety profiles and outcome results of tDCS as a treatment in refractory temporal lobe epilepsy patients?

Stage 2: Identifying Relevant Studies/Search Strategy

Identification of relevant studies to this review was obtained from PubMed, SCOPUS and COCHRANE Library online databases, grey literature sources and reference list of key studies. The main search keywords were obtained from the research title, defined as: 'transcranial direct current stimulation', 'drug-resistant epilepsy' and 'temporal lobe epilepsy' which were further expanded for their synonyms using medical subject headings to widen the capture of relevant published literature. For each database, 3 limiters were applied; clinical trials, human study and English language. Search was not limited by a certain date range to provide a rich data and literature. Search result was downloaded and imported into EndNote software for primary screening. Any duplicate papers were excluded prior to the screening process using this software.

Stage 3: Study Selection

The aim of this study is to review and summarize human clinical trials involving application of tDCS on patients with refractory TLE to study the different protocols, efficacies and its safety profile specific to temporal lobe epilepsy. Studies will be eligible if they address aspects of inclusion criteria as the following: published in the English language; adult or pediatric human cohort; clinical trials including randomized control trials; peer-reviewed primary research and the design or use of tDCS on patients with refractory temporal lobe epilepsy with specific intention to determine the effectiveness of the intervention to decrease the frequency of epileptic seizure and reduce inter-epileptic discharge on EEG. Exclusion criteria include non-human study, letter to editor, case reports, case study, review articles, unpublished paper or design or use of tDCS in clinical trials to study the effect towards other conditions or other types of epilepsy.

The review process involved two stages of screening: (1) Title, keyword and abstract screening; (2) Full text screening. In primary screening, two investigators screened the titles, keywords used and abstract of all the retrieved articles for inclusion against a set of minimum inclusion criteria. Article that does not meet the inclusion criteria were excluded. Any article that is relevant by the reviewers was included for full text review. In secondary screening level, two reviewers independently assessed and read-through the selected full text articles to determine if they really meet the inclusion/exclusion criteria to be included in the study. Any discordant in full-text articles or disagreements about study eligibility at this stage were resolved through discussion with the third party and face-to face discussion by the review team until a consensus was obtained. The selection, exclusion and screening process were organized and conducted using a PRISMA flow diagram.

Stage 4: Collecting the Data

Data extractions include publication year and author, publication type, study design, sample size, age, sex, and tDCS application's protocol. Two researchers reviewed all the studies independently and subsequently each set of data extracted were compared and any differences and discrepancies were discussed to ensure consistency between the reviewers.

Stage 5: Summarizing and Synthesizing the Results

The results were summarized according to the patients' characteristics and the tDCS protocols such as current tDCS applied, montage design, electrode sizes and types, duration and frequency of tDCS stim-

Table 1: Summary of studies included in this scoping review.

Author (year)	Article Design	Total sample	Age (year [mean ± SD or range])	I = current (mA)	Montage	Type of epilepsy	Electrode size	Frequency and duration of tDCS stimulation	Adverse effect	Result
Zoghi *et al.* (2016)[14]	Pilot Randomized control trials	29 Study group: 20 Sham group: 9	38 ± 13	I = 1 mA	Cathode position: Over the affected lobe. Anode position: Contralateral supraorbital area	RTLE with heterogenous aetiology	Cathode: 3 cm X 4 cm = 12 cm Anode: 5 cm X 7 cm = 35 cm	9-20-9 protocol. 9 min tDCS/sham – 20 min rest – 9 min tDCS/sham total tDCS: 18 min	Itching sensation	Significant increase SICI in tDCS group compared to the sham group 42.14% (SD - 35.93) reduced mean response ratio in seizure frequency
Tecchio *et al.* (2018)[15]	Randomized double-blind sham-controlled crossover trial	6	33.83	I = 1 mA	19 channel EEG Cathode position: Over epileptic foci predetermined clinically & by EEG. Anode position: Over opposite homologous region.	RTLE	5 cm X 7 cm = 35 cm^2	TDCS: 20 minutes Sham: not stated (1 month apart)	-	83% increased FC Reduced seizure frequency tDCS 74.1 ± 41.2% vs Sham 39.4 ± 45.6%
Assenza *et al.* (2016) [28]	Double-blind, randomized, sham-controlled, crossover, monocentric study	10	42 ± 15.7	I = 1 mA	Cathode position: Over the epileptic foci predetermined by EEG. Anode position: Over contralateral homologous region 19 electrode video EEG	RTLE	5 cm X 7 cm = 35 cm^2	Symmetric montage First session: tDCS 20 minutes or Sham 10 seconds on day 8 of seizure diary Second session: opposite stimulation on day 38	Skull itching	TDCS reduced the weekly percentage of seizure frequency in comparison to sham stimulation. tDCS 71 ± 33% vs sham 25 ± 125%; p = 0.028
Tekturk *et al.* (2016) [29]	Randomized crossover study	12	35.42 ± 6.96	I = 2 mA 12Hz peak to peak sinusoidal DC	Cathode position: At pathological affected side (temporal region, either T3 or T4) pre-determined by cranial MRI & ictal/interictal EEG	MTLE-HS	5 cm X 7 cm = 35 cm^2	TDCS: 30 minutes for 3 consecutive days or Sham stimulation. Second session: opposite stimulation after 2 months	Tingling sensation	> 50% reduced seizure frequency in 10 patients (83.33%) 6 patients (50%) seizure free

San-Juan *et al.* (2016)[30]	Randomized controlled, double-blinded clinical trial, 3 arm parallel group	28 5 days: 8 3 days: 12 Sham: 8	37.8 ± 10.9	I = 2 mA	Cathode: Over the most active IED area. Predetermined by EEGs (10/20 system) Anode: Over silent supraorbital area	MTLE-HS	5 cm X 7 cm = 35 cm^2	TDCS: 30 minutes (3 or 5 consecutive days) Sham: 60 seconds	Mild itching sensation & moderate headache post-stimulation	TDCS decreased 48% mean seizure frequency in 3-day and 5-day. Significant IED reduction in all groups comparing to baseline

TDCS, Transcranial direct current stimulation; EEG, Electroencephalography; RTLE, Refractory temporal lobe epilepsy; MTLE-HS, Mesial temporal lobe epilepsy with hippocampal sclerosis; SICI, short interval intracortical inhibition; SD, Standard deviation; FC, Functional connectivity; IED, inter epileptic discharges.

ulation, adverse effect and result. Data synthesis were presented as text and table.

RESULTS

A total of 648 publications were identified during the initial search and four duplicates articles were removed. After going through the inclusion and exclusion criteria, 636 articles were excluded. Eight full text articles were reviewed and assessed for eligibility in the second stage of screening. Three articles were subsequently excluded as they are not eligible for inclusion criteria, leaving 5 articles included in this study. (Figure 1) The summary of the included articles is presented in Table 1.

The Research Protocols

Among the five articles retrieved, three were randomized crossover studies[15,28,29]. Another two were randomized placebo-controlled double-blind study and pilot randomized control trial[14,30]. Two of the randomized crossover studies are sham-controlled[28,29]. A total of 85 subjects involved in these studies with 48.2% of them are males and mean of age is between 34 to 42 years old. However, all studies have small sample sizes.

Three of the clinical trials applied 1mA of direct current (DC) in their subjects[14,28,29] and another two studies used 2 mA of current as their stimulation protocol with one of them specify the frequency of stimulation at 12 Hz with peak to peak sinusoidal DC[15,30]. For stimulation montage, all five studies applied cathodal electrodes over the epileptic foci or areas with the most active inter-epileptiform discharge which were predetermined by electroencephalogram (EEG) recording. Only one study clearly stated the EEG montages used were international 10-20 system[30]. One study added cranial magnetic resonance imaging (MRI) as an additional supportive method to determine the epileptic foci[15]. Despite the homogeneity in cathode position, the anode positions are different across the studies. Two studies positioned the anode electrode over contralateral homologous region[29,30] and the other two studies, over the silent and contralateral supraorbital area[14,30]. All studies used the same 35 cm^2 saline-soaked sponge electrode for both anode and cathode (5 cm X 7 cm = 35 cm^2) except for a study by Zoghi M *et al*. (2016)[14] in which they applied a 12 cm^2 cathode (3 cm X 4 cm = 12 cm^2) and 35 cm^2 anode.

All subjects were diagnosed with refractory TLE. Two of the studies specified their subjects' aetiologies of epilepsy as mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS)[14,30]. One study included refractory TLE subjects with heterogeneous aetiology without specifications[9]. Another study mentioned and classified the diagnosis of their subjects as symptomatic and cryptogenic[29].

The frequency and duration of tDCS stimulation vary between studies. Two studies did crossover clinical trials of one-time tDCS stimulation for 20 minutes duration with 30 days interval of sham stimulation to every subject before or after the active stimulation[28,29]. Both studies used different current and frequency of stimulation. Another randomized crossover study, applied 30 minutes cathodal stimulation on three consecutive days with 60 seconds sham stimulation of 2 months interval[15]. One randomized placebo-controlled consisted of 3-arm study; placebo, 30 min/2 mA daily sessions for three days, and five days of cathodal stimulation were randomized between the subjects[30]. However, one study applied the stimulation protocol differently, which involved a total of 18 minutes 1 mA cathodal tDCS or sham tDCS with 20 minutes rest after the first 9 minutes[14].

Efficacy of Cathodal TDCS on Refractory Temporal Lobe Epilepsy

Due to the heterogeneity of study designs, different epilepsy aetiologies, small samples and the differences in the study protocols, the evidence data cannot be analyzed into a single summarized result and the evidence quality were judged independently for each study included. Overall, despite considerable variations in experimental design and conditions, all the included studies in this review documented a reduction in seizure frequency[14,15,28-30]. One study documented more than 50% seizure frequency reduction in 10 patients (83.33%) and 6 patients (50%) were seizure free in post study period of 1 month[29]. Assenza *et al*. reported reduced weekly percentage of seizure frequency in comparison to sham stimulation, (tDCS, 71 ± 33% vs sham, 25 ± 125%; p = 0.028)[28] San Juan *et al*. reported 48% of reduced seizure frequency seizure among tDCS groups in comparison to placebo group but they found no difference among 3-day and 5-day sessions[30]. They also noted improvement of inter-epileptic discharges (IED)[30] meanwhile, two studies revealed no significant changes of IED[15,28]. Study done by Tecchio *et al*. showed increased brain functional connectivity in five out of six subjects and reduced seizure frequency among tDCS group, although not statistically significant (tDCS, 74.1 ± 41.2% vs sham, 39.4 ± 45.6%; p = 0.068.)[15] Paired pulse transcranial magnetic stimulation (TMS) was used by Zoghi *et al*. to evaluate intracortical short interval inhibition (SICI) in the primary motor cortex ipsilateral to the temporal lobe epileptic foci. This research showed a significant increase in SICI relative to sham group, and the mean response ratio for experimental group seizure frequency was higher than the sham group[14].

Safety Profile

Three from five studies reported mild adverse effect of scalp itching sensation over the electrode stimulation site with one of them specifically stated the itching sensation under the anode electrode[14,28,30]. One study identified scalp tingling sensations, as experienced by most of their subjects[29]. San-Juan *et al*. reported moderate headache post stimulation which lasted for one hour with spontaneous resolution[30]. A randomized crossover study involving 6 subjects did not report any adverse effect in all their subjects[15].

DISCUSSION

All of the studies showed protocols heterogeneity in term of current intensity, anode position, electrode size, epilepsy aetiologies, frequency and duration of stimulation. Majority of the studies used 1 mA DC current, with 2 mA as an alternative protocol. Increasing intensity and duration of stimulation may enhance its efficacy but this cannot be accepted as a general rule[31]. Increasing tDCS current intensity might shift the direction of excitability changes. For instance, doubling intensity from 1 mA to 2 mA could lead to increase excitability from both stimulation polarities and even switch the inhibitory effect produced by cathodal tDCS into excitation[32]. The induced electrical field will extend deeper into the brain as the stimulation strength increases, allowing alteration of the recruited neural network and resulting in unexpected biological and clinical effects[33].

Electrode montage is an important factor in tDCS protocol[34,35]. Even though cathode electrodes were positioned homogenously according to predetermined epileptic foci, differences in anode electrodes positioning would affect stimulation outcomes. Orientation of the electrical field would influence the stimulation effect[34,35]. The distance of the reference electrode to the active electrode as well as electrode size will change the focality of tDCS[36]. It is very important to consider that even little variations of electrode size area, shape, or montage can strongly influence the current diffusion and the geometry of the induced DC fields into the brain[37-40].

TDCS had consistently being reported to have very high safety profile with regard to the currently applied protocol and recent review, and studies confirmed the absence of evidence for serious adverse effects[41-43]. TDCS safety has been assessed in animal studies and in other numerous pathologies with a total of more than 1000 subjects, yet no unfavorable long-term adverse effects had been reported[44,45]. Adverse effects were only limited to mild headache to tolerable short-term local sensory discomfort, and in up to 10% related to mild and reversible skin irritation[46-48]. In fact, no abnormal variations in heart rate, blood pressure, or temperature noted during and 20 minutes after the stimulation[49]. In one study, magnetic resonance imaging (MRI) done before and after tDCS stimulation applied to prefrontal and motor cortex did not exhibit pathological signal changes thus, concluded that tDCS does not induce cerebral oedema or altering blood-brain barrier or brain tissue[50]. Immunohistochemical and morphological analyzes of microglial expression did not report any detrimental effects of tDCS and suggest that the stimulation is safe and did not cause any tissue damage[19]. One case however reported a seizure occurred during a tDCS protocol but this was justified to have occurred due to possible previous down-tempering of the antiepileptic drugs (AEDs) by the co-medication of escitalopram[51].

The antiepileptic effect of cathodal tDCS was reported in several studies. In animal studies, cathodal stimulation was shown to increase seizure threshold, reduce seizure frequency, and reduce epileptic slow-wave discharges[19,52-54]. The effect was depended on current strength and duration of stimulation[19]. In an animal study, tDCS also was demonstrated to reduce hippocampal cell loss together with improved cognitive performance[50]. It was postulated that refractory epilepsy originated from the effect of neuronal network damage affecting brain areas beyond the hippocampus, thus tDSC has a potential to prevent further progression of neuronal damage[52,56,57]. Furthermore, in a recent review, no evidence was found that tDCS in epilepsy may lead to an increase in seizures[41,42].

CONCLUSION

This review attempted to provide a comprehensive overview of transcranial direct current stimulation as an intervention towards patients with refractory TLE in clinical trial settings. The limited number of clinical trials and varying research protocol used made any reasonable conclusion regarding its definite efficacy and defining what best protocol was rendered difficult.

Although some clinical studies showed positive and promising results, there are still unclear path regarding the next steps of investigation in this field and presence of inter-individual variability in tDCS response[43,57,58]. TDCS still requires deeper analysis of the most beneficial protocols and elucidation of the underlying mechanism of action[59,60]. Few studies have suggested ways to improve its application in future researches. Additional methodological studies and clinical trials involving larger cohort of patients, further sham-controlled, larger double-blind and randomized studies based on methodological sound protocols, homogenous patient populations and epileptic conditions are required to investigate the effect of tDCS in refractory epilepsy[36,43,59,60]. Within the refractory epileptic patients, careful patient selection is recommended to create a homogenous group of the same epileptoid foci aetiology. Every study used different patient categories, stimulation protocols, electrode sites, and direct current strength, therefore comparison of these studies should be used to provide standardized measures with reproducible outcome. Eventually, it would be advantageous to establish international guidelines on the use of tDCS to expand its application among the physicians.

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