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The effect of transcranial direct current stimulation on seizure frequency of patients with mesial temporal lobe epilepsy with hippocampal sclerosis☆

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ABSTRACT

Objectives: Transcranial direct current stimulation (tDCS) is a non-invasive and safe method tried in drug-resistant epilepsies, in recent years. Our aim was to evaluate the effect of tDCS in patients diagnosed with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) which is a well-known drug-resistant focal epilepsy syndrome.

Patients and methods: Twelve MTLE-HS patients diagnosed with their typical clinical, EEG and MRI findings fulfilling the criteria for drug-resistance as suggested by the ILAE commission were included after Ethics Committee approval and their signed consent. All patients received modulated cathodal stimulation; 2 mA for 30 min on 3 consecutive days. All patients also received sham stimulation with the same electrode positions; designed as 60 s stimulation gradually decreasing in 15 s with placement of the electrodes for 30 min over the stimulation side. They were followed up by standard seizure diaries and their medical treatment was not changed during the study period. Their seizure frequencies both before and after cathodal tDCS and sham stimulation were compared statistically. Adverse effects were also questioned.

Results: Mean age of our study group was 35.42 ± 6.96 (6 males; median: 35.50). The mean seizure frequency was 10.58 ± 9.91 (median = 8; min-max = 2-30) at the baseline and significantly decreased to 1.67 ± 2.50 (median = 0.5; min-max = 0-8) after cathodal tDCS application ($p = 0.003$). Ten patients (83.33%) had more than 50% decrease in their seizure frequencies after cathodal tDCS. Two patients (16.67%) also showed positive sham effect. Six patients (50%) were seizure-free in the post-cathodal tDCS period of one month. No adverse effect has been reported except tingling sensation during cathodal stimulation.

Conclusion: Our small series suggested that cathodal tDCS may be used as an additional treatment option in MTLE-HS. It may be tried in TLE-HS patients waiting for or rejecting epilepsy surgery or even with ineffective surgery results. More studies are needed with large series of patients to investigate the effects of tDCS in drug resistant epilepsies.

1. Introduction

About 20–30% of patients with epilepsy may continue to have seizures despite at least two appropriately chosen and adequate anti-epileptic drug (AED) treatments which make them labeled as drug resistant [1]. Since epileptic seizures are triggered by paroxysmal depolarization shift, non-invasive brain stimulation techniques

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such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have become popular research methods of changing cortical excitability. Furthermore, it has been shown that direct current stimulation of deep brain structures could suppress epileptiform activity [2]. Vagal nerve stimulation (VNS) is also a well-known invasive method for seizure control with clinically positive results on many focal and generalized epileptic syndromes [3].

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is the most common focal epilepsy syndrome that is usually associated with drug resistant seizures [4]. Epileptic focus is located deeply in the mesial temporal region including mainly hippocampus, parahippocampal gyrus and amygdala. Since most of the cases are drug resistant, epilepsy surgery is the current gold standard therapy option for cessation of seizures [5]. However, some MTLE-HS patients could not be convinced and reject the risks of brain operation. Besides, some others could not be operated due to bilateral onset of seizures or long waiting lists due to unavailability of invasive recordings in many parts of the world. Moreover, there is a substantial group of MTLE-HS patients who have undergone epilepsy surgery but continue to have seizures [6].

Recently, tDCS has been suggested and used as a promising and safe method which is effective in the improvement of neuroplasticity, cognition, motor activity and also for seizure control [7–14]. The low amplitude electrical currents can be conducted transcranially, where cathodal direct current stimulation has been reported to decrease seizures in both humans and animal models, including drug refractory ones [15,16]. It has been shown that both continuous direct current and sinusoidal alternative current waveforms could suppress epileptiform activity in in-vitro epilepsy models [2]. However, there is no study with a homogeneous group that used tDCS in a frequent specific focal epilepsy syndrome like MTLE-HS.

The aim of our study was to evaluate the effect of tDCS in patients with MTLE-HS, as a frequent focal epilepsy form with deeply located focus. Although we appreciate that surgery is the gold standard for the treatment of this syndrome, we wanted to try tDCS as a non-invasive and additional method and aimed to investigate its effect on seizure frequency in MTLE-HS group.

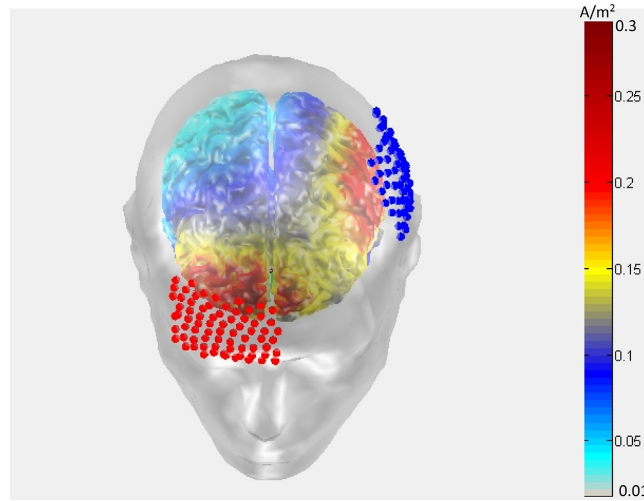

Fig 1. Computational head model of transcranial electrical currents.
Red dots represent location of anode electrode, blue dots represent location of cathode electrode on scalp (size of electrodes are $5 \times 7\ cm^2$). Cortical electrical current distribution is shown on head model. The colour scale on the right shows the current intensity changes between minimum 0.01 A/m^2 and maximum 0.3 A/m^2. The mean current intensity under anode electrode is measured as 0.35 A/m^2 (the mean of 3 selected points under the anode electrode)[18]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2. Methods

This is a randomized cross-over study evaluating 12 MTLE-HS patients diagnosed with their typical clinical, EEG and MRI findings. All the patients fulfilled the criteria for drug-resistance as suggested by the ILAE commission and all were included in the study after getting their signed informed consent [17]. The Ethics Committee of Istanbul University approved the study protocol (No: 2012/350-969). Exclusion criteria were previous surgery either for MTLE-HS or any intracranial lesion, cardiac electrical device, VNS and pregnancy. All the patients except three were candidates for epilepsy surgery waiting for the operation or for the video-EEG monitoring. One patient had refused surgery.

In the pre-stimulation phase, the patients were first trained for filling the seizure diaries accurately and then began to fill their seizure diaries one month before the tDCS trial. This formally recorded, basal seizure numbers for one month period was checked with the previous monthly seizure numbers in their files for one year and found consistent in all of the patients. No drug alterations were made during the entire study period including the two months period before tDCS. All patients had received both active and sham stimulations in a counterbalanced randomized order with a two-month interval. We used a randomization list with the order of entrance which was generated by a free software—Research Randomizer version 4.0 [18].

All patients, their relatives and the authors evaluating the seizure diaries (PT, BB) were blindfolded to the type of the applied stimuli. Adverse events were systematically questioned in every visit.

An experienced clinical neurophysiologist evaluated all EEGs and video-EEGs of the patients which were performed according to the international 10–20 system. All patients had EEGs at the start of the study and all their other previous EEGs were evaluated to find the focus in order to exclude other sources of epileptiform discharges, when present. We placed active electrode over the pathologically affected HS side (temporal region, either T3 or T4 electrode place) which was determined by both concordant cranial MRI and ictal or interictal EEG findings, depending on the availability of the seizure records, and reference electrode over the contralateral supraorbital region (Fig. 1) [19].

All patients received modulated cathodal stimulation (2 mA for 30 min on 3 consecutive days). In modulated tDCS, 2 mA, peak to peak sinusoidal direct current was applied using 7 cm × 5 cm, saline soaked sponge electrodes. Its frequency was chosen as 12 Hz which is in upper alpha range. Maximum current density was 500 mA/m^2 and maximum charge density was 900 C/m^2 for 30-min stimulation period. The calculated values were reported to be safe [20–22]. A 50% or more decrease in the seizure frequency compared to baseline was accepted as positive response to tDCS application.

For sham stimulations, electrodes were placed on same positions on the scalp and patient received stimulation for 60 s, but we waited for 30 min before removal of the electrodes. The current was ramp up in first 15 s and ramp down in last 15 s. Patients felt the initial itching sensation but received no current for the rest 29 min. All continued to fulfill their diaries for two months after tDCS trial. This range of time was determined according to experience of our physiology laboratory and literature [16]. Study design is summarized in Fig. 2.

Descriptive statistics were used for demographic characteristics. Non-parametric Wilcoxon signed rank test was used to compare seizure frequencies of pre- and post-stimulation periods. $P < 0.05$ was accepted as statistically significant.