

## Transcranial Direct Current Stimulation for Treatment of Refractory Childhood Focal Epilepsy

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### ABSTRACT

**Background:** Cathodal transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation method for suppressing regional cortical excitability. We examine the safety and antiepileptic efficacy of cathodal tDCS in children with refractory focal epilepsy. Although a prior cathodal tDCS trial in adults with epilepsy revealed EEG improvement, neither the antiepileptic potential nor the safety and tolerability of tDCS has been tested in children.

**Method:** The study consisted of three phases: 1) a 4-week pre-treatment monitoring period with vital sign measures, EEG, seizure diary, and baseline quality of life (QOL) questionnaire; 2) a single treatment with 1 mA cathodal tDCS for 20 min with cathode positioned over the seizure focus and anode on the contralateral shoulder; 3) follow-ups immediately after stimulation, and at 24, 48 h, and 4 weeks after tDCS with continued seizure diary and epileptic discharge counts on EEG; the QOL questionnaire was also repeated 4 weeks after stimulation. Patients were randomized to receive either single session active or sham tDCS 1 mA, 20 min.

**Results:** Thirty six children (6–15 years) with focal epilepsy were enrolled, 27 in active and 9 in sham group. All patients tolerated tDCS well. No serious adverse events occurred. Active tDCS treatment was associated with significant reductions in epileptic discharge frequency immediately and 24 and 48 h after tDCS. Four weeks after treatment, a small (clinically negligible but statistically significant) decrease in seizure frequency was also detected.

**Conclusion:** A single session of cathodal tDCS improves epileptic EEG abnormalities for 48 h and is well-tolerated in children.

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### Introduction

Epilepsy is one of the most common neurological conditions in children with prevalence of about 1% and incidence of approximately 40 cases in 100,000 person-years [1,2]. Yet, despite of more

than 30 antiepileptic drugs (AEDs) available, 10% of children with epilepsy remain intractable and half of all cases of intractable epilepsy occur in children with non-idiopathic localization-related epilepsy syndromes [3]. Epilepsy surgery is often an option for focal pharmacoresistant epilepsy, but many patients do not have access to medical centers that perform resective epilepsy surgery [4], while others have a seizure focus located in eloquent cortex where resection is likely to cause deficit [5]; and in the best circumstances the overall freedom from seizures in children approximates 59–70% [6]. Thus, there is an unmet need for adjunctive antiepileptic therapy, and this need drives research into methods for antiepileptic focal noninvasive brain stimulation.

Transcranial direct current stimulation (tDCS) is a painless and safe method for focal brain stimulation [7]. tDCS is based on decades-old observations that neuronal firing is modulated by low

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amplitude electrical direct current [8]. Specifically, when applied to the cerebral cortex, cathodal tDCS inhibits neuronal firing and leads to a durable reduction in cortical excitability. The mechanisms by which cathodal tDCS reduces neuronal firing are not completely understood, but may be related to hyper-polarization of the cell membrane which occurs when the vector of a propagating action potential is oriented toward the cathode in a constant electric field [9].

The practical application of cathodal tDCS is simple: low amplitude direct current is administered via broad scalp electrodes (typically saline-saturated sponges) such that the cerebral cortex is exposed to cathodal direct current beneath one of the electrodes – a second (anodal) electrode can be placed anywhere else on the body. tDCS units are inexpensive and light-weight. The electrical supply can be derived from conventional 9-V chemical batteries. The scalp electrodes can be fastened in seconds. tDCS can be combined easily with other therapies, such as those that may be required for treatment of a patient with resistant seizures. Thus for treatment of seizures, tDCS may offer a practical therapeutic option with the benefit of easy, rapid and focal application, even in children where the technique also appears well-tolerated [10].

Recent published reports suggest that cathodal tDCS may be useful in suppressing seizures. A preclinical trial of tDCS in a rodent model of focal epilepsy showed a significant elevation of the seizure threshold [11]. A single clinical trial of cathodal tDCS in 19 adult patients with refractory epilepsy and malformations of cortical development also showed promising results with suppression of epileptiform discharges on EEG, but only a trend toward clinical improvement [12]. However, neither the antiepileptic potential nor the safety and tolerability of tDCS has been tested in children with epilepsy. Therefore, the objective of our study was to obtain initial data on the safety and efficacy of tDCS in the pediatric focal epilepsy population.

## Methods and materials

Criteria for refractory childhood focal epilepsy were defined according to Berg et al., 2013, and patients were recruited by advertisement at the Pediatric Outpatient Department, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. The inclusion criteria were (a) diagnosis of simple partial or complex partial, with and without secondary generalization, confirmed by EEG; (b) diagnosis of refractory epilepsy, defined as failure of more than two first-line AEDs to control seizures; (c) average seizure frequency of more than one per month for 18 months and no more than three consecutive seizure-free months during that interval; (d) age between 6 and 15 years. The exclusion criteria were (a) developmental delay, drug addiction, pregnancy, skull defects or prior cranial surgery, and other serious neurological diseases; and (b) change in dosage of antiepileptic drugs or use of herbal remedies and other alternative therapies. Per subject, focal epilepsy was diagnosed by the pediatric neurologist (N.A.) by interpretation of history, physical examination, and EEG.

All patients' guardians gave their written informed consent. The study conformed to the declaration of Helsinki and was approved by the Ethics Committee of Khon Kaen University (Identifier number: HE 531237).

### Experimental design

This study contained following three phases: 1) a 4-week period of observation to assess the baseline seizure frequency, baseline vital signs, and EEG to confirm seizure focus; 2) a single-dose treatment by 1 mA cathodal tDCS for 20 min; 3) EEG follow-up immediately post-treatment and at 24 h, 48 h and 4 weeks after treatment, with continued seizure diary for the 4-week follow-up

period. After the baseline period, the patients' guardians were given an open end list of possible adverse events and were advised to continue their routine antiepileptic medication regimens for the duration of the trial.

After the baseline-monitoring period, the patients were randomized in a 3:1 verum: sham ratio to receive either active or sham tDCS correspondingly. Given the limited resources in our medical center we chose that the 3:1 ratio to increase the number of patient to whom a potentially beneficial therapy would be made available, and to increase the number of subjects for purposes of assessing safety in the pediatric epilepsy population [13]. We note that in analogous published clinical trials, such asymmetric subject distribution has been useful in such cases [14].

All the patients and parents were informed about all possible adverse events and were blinded for the randomization.

### Transcranial direct current stimulation

Direct current was transferred using a saline-soaked pair of surface sponge electrodes (35 cm<sup>2</sup>) and delivered through battery-driven power supply. Constant current stimulator with a maximum output of 10 mA (Soterixmedical, Model 1224-B, New York, USA). The cathodal electrode was placed over the epileptogenic focus, centered on the electrode with the international 10–20 EEG electrode placement system location where spikes of sharp waves were greatest in amplitude, and the anodal electrode was placed over the contralateral shoulder area.

The tDCS device was designed to mask sham or verum stimulation. The control switch was in front of the instrument which was covered by opaque adhesive during stimulation. The power indicator was on the front of the machine, which lit up during the time of stimulation both in real and sham. However, in sham stimulation, the current was discontinued after 30 s while the power indicator remained.

The staff who analyzed the data was unaware of device setting (active or sham mode), and thus was blinded to the treatment condition.

### Epileptic discharges

Epileptic discharges were recorded by trained staff. EEG was acquired from all patients using a 32-channel, international 10–20 system of electrode placement (Neuvo, Compumedics, Australia with PerFusion EEG software). It has been reported that sleep increases the frequency of epileptiform discharges on EEG so the awake state during EEG recording have been controlled in this study by collected for 30 min in the awake state only. EEG with band pass filtered 0.5–70 Hz was recorded as a single session at baseline, immediately, 24 h, 48 h and 4 weeks follow-ups. EEG data were analyzed by visual inspection. The number of epileptic discharges (spikes and sharp waves) in the 30-min recording, and their locations were assessed by a practicing pediatric neurologist and clinical neurophysiologist (N.A.) who was blinded to the treatment condition.

### Number of seizures

Patients' guardians recorded seizure frequency in a diary for 4 weeks prior to treatment to assess baseline and for 4 weeks after treatment to follow-up.

### Vital signs and oxygen saturation monitoring

Patients were closely observed by physicians during and post-treatment. Vital signs and oxygen saturation were monitored for

30 min prior to and during the treatment period, as well as 30 min after treatment and 48 h after the treatment period. Blood pressure (mm Hg) was measured by automatic sphygmomanometer (Ua-767 Plus, UK) in supine position with pediatric-size cuff wrapped around the left upper arm. Pulse rate was measured by automatic sphygmomanometer (Ua-767 Plus, UK) in supine position. Body temperature was measured by an axillary electronic thermometer. Respiratory rate was measured by visual inspection, by counting chest risings for 60 s. Pulse oximeter was placed on right index finger to monitor oxygen saturation throughout the procedure.

#### Adverse events

Patients' guardians were asked to report adverse events as well as other signs and symptoms every day after treatment. Patients were also observed closely by physicians during the stimulation. The self-recording terminated at four weeks after stimulation.

#### Quality of life (QOL) assessment

Patients and their parents were asked to answer the shortened and translated to Thai questionnaire adapted from "Quality of Life in Childhood Epilepsy Questionnaire" (QOLCE) [15] to assess the quality of life before and 4 weeks after treatment. The questionnaires were answered at the hospital. The current QOLCE is a 47-item parent rating instrument containing 10 subscales covering 4 domains of life function: physical function, social function, emotional well-being and cognition [15]. Items are rated on a 5-point scale, which are used to calculate the 10 subscale scores ranging from 0 (low functioning) to 100 (high functioning).

#### Statistical analysis

Results are presented as means  $\pm$  SEM. The outcome of epileptic discharges frequency, seizure frequency, vital signs, oxygen saturation and QOL questionnaire were compared by repeated-measures analysis of variance (ANOVA) followed by Fisher's least significant difference post-hoc. Analyses were done with Statistica 8.0 A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

The demographic data and baseline patient characteristics are described in Table 1. A total of 36 patients with intractable focal epilepsy were enrolled between August 2010 and September 2012. All patients completed the entire protocol and tolerated the tDCS well, without serious adverse events (please see below for a description of a single mild adverse event).

#### Epileptiform discharges

The EDs were localized to the right hemisphere in 15 cases and to the left hemisphere in 21 cases. The seizure foci in our cohort are shown in Table 1.

Repeated-measure ANOVA with group as a between-subjects factor and time as a within-subjects factor revealed a significant main effect of group ( $F(1, 34) = 7.9$ ;  $P = 0.008$ ), time ( $F(4, 34) = 15.1$ ;  $P < 0.0001$ ) and interaction between the two factors ( $F(4, 34) = 13.0$ ;  $P < 0.0001$ ) (Fig. 1). Post-hoc analysis showed that subjects epileptiform discharges frequency was not different between the groups before the treatment, however it significantly decreased to 45.3% of baseline immediately after tDCS ( $P = 0.0002$ ), and remained lower in treatment group in both 24

**Table 1**  
Demographic data and baseline characteristics ( $n = 36$ ).

	Cathodal tDCS	Sham
No. of subjects	27	9
Sex (male/female)	20/7	6/3
Age		
Mean $\pm$ SD	11.80 $\pm$ 2.10	11.12 $\pm$ 1.61
Range (years)	7–15	6–14
Diagnosis		
Partial seizures without secondary generalization	22	7
Partial seizures with secondary generalization	5	2
Etiologies of epilepsy:		
Idiopathic	18	8
Mesial temporal sclerosis	4	–
Focal cortical dysplasia	2	1
Generalized brain atrophy following encephalitis	1	–
Cerebral infarction due to moyamoya disease	1	–
Cerebral infarction due to protein S deficiency	1	–
Seizure focus		
C3–F3	8	2
C3–T3	5	1
C3	1	1
C4	2	1
C4–F4	2	2
C4–T4	1	–
P8	2	1
P7	1	–
T7–P7	1	–
P4	1	–
P4–P8	1	1
T7–F7	1	–
T8–P8	1	–
Baseline seizure frequency per month (mean $\pm$ SD)	11.67 $\pm$ 4.63	10.22 $\pm$ 1.72
Baseline epileptic discharges per 30 min (mean $\pm$ SD)	538.44 $\pm$ 279.25	582.00 $\pm$ 244.19
Age at onset of seizures (years)	7.3 $\pm$ 1.2	6.8 $\pm$ 2.3
Number of antiepileptic drugs used		
2	6	3
3	13	3
4	5	1
5	3	2

(50.3%;  $P = 0.0004$ ) and 48 (57.6%;  $P = 0.0014$ ) hours after the treatment. Four weeks after treatment ED frequency increased back to pretreatment levels and there was no difference between tDCS and sham treated groups.

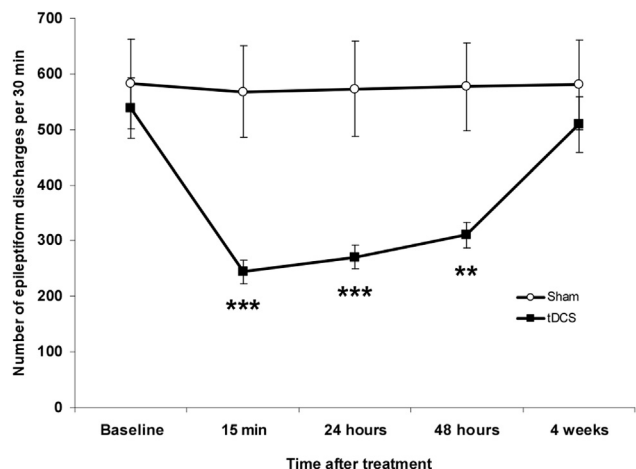
#### Clinical seizure frequency reduction after tDCS

The seizure frequency was recorded by patients' guardians in a diary for 4 weeks prior to treatment and continue recording for 4 weeks after treatment.

Repeated-measures ANOVA with group as a between-subjects factor and time as a within-subjects factor revealed no main effect of group ( $F(1, 34) = 0.4$ ; NS) or time ( $F(1, 34) = 0.4$ ; NS), however interaction between the two factors was significant ( $F(1, 34) = 6.3$ ;  $P = 0.0168$ ). Post-hoc analysis showed that clinical seizure frequency decreased 4.8% in tDCS group ( $P = 0.0035$ ) with no difference in sham treated group.

#### Vital signs and oxygen saturation

There was no clinically relevant difference between baseline and post-treatment vital signs and oxygen saturation in either group, and all recorded values were in the normal range for age.



**Figure 1.** Effect of tDCS on epileptiform discharge frequency. Data are presented as mean  $\pm$  SEM of number epileptiform discharges per 30 min of EEG recording at baseline, and various time points after treatment: 15 min, 24 h, 48 h and 4 weeks. \*\* $P < 0.01$ , \*\*\* $P < 0.001$  as compared to sham tDCS condition.

### Quality of life evaluation

Randomization (likely the small sample size resulted in significant baseline differences between the groups, and thus prevented conclusion as to whether changes attributable to tDCS (all improvements in the active cathodal tDCS group) were statistically significant. However in no subject did we observe a reduction in the in QOL score relative to baseline.

### Adverse events

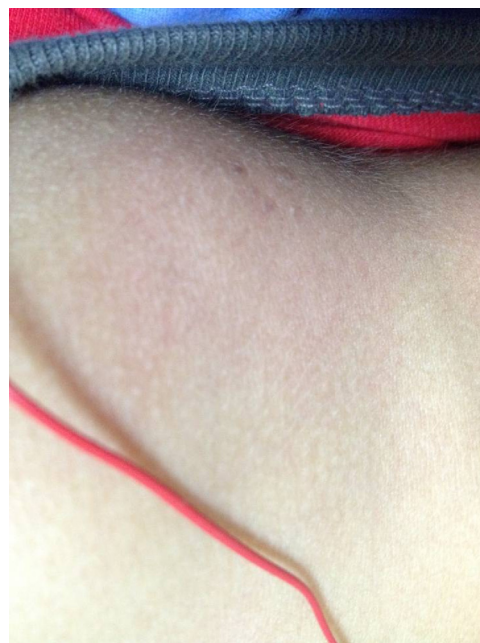
One patient (2.70%) in active group developed a transient erythematous rash with no pruritus or pain under the reference electrode, which resolved within 2 h (Fig. 2). No other adverse events were reported by the subjects or observed by the investigators.

### Discussion

This study, although limited in scope, provides further evidence that cathodal tDCS may be safe and well-tolerated in the specialized population of children with intractable epilepsy. We also show that, in the pediatric patients with focal seizures, cathodal tDCS can suppress epileptiform discharges for 48 h, but the effect of a single 20-min tDCS application on epileptic EEG abnormalities was not sustained for 4 weeks. We note that the frequency of epileptiform discharges on EEG were unlikely clinical relevance with seizure frequency.

Our data are consistent with the result of Fregni et al. [12], which revealed a significant reduction in the number of epileptiform discharges following cathodal tDCS over the seizure focus. However, the duration of the antiepileptic effect on the EEG in the Fregni et al., where spikes and sharp waves were suppressed for up to 4 weeks, study was longer than in ours. Among possible explanations for this discrepancy are: 1) our cohort age (pediatric vs. adult in the Fregni et al. study), 2) the disease severity in our cohort (11.7 seizures/month vs. 7.2 seizures/month in the prior publication), 3) a higher number of AEDs prescribed in our study, and 4) the etiologies of focal epilepsy of our patients which were heterogenous in our study while Fregni et al. enrolled only patients with malformation of cortical development.

Few additional recent publications support improved antiepileptic efficacy with repeated tDCS applications:



**Figure 2.** Image of a single adverse event. Erythematous rash under reference electrode in verum tDCS group, which resolved within 2 h.

Yook and colleagues used 2 mA, 20 min cathodal tDCS five consecutive days a week for 2 week in one epilepsy patient with focal cortical dysplasia to reveal 50% reduction in seizure frequency for up to two months after treatment [16]. This is consistent with data outside of epilepsy suggesting that regional cortical excitability is affected more profoundly by recurrent stimulation than by single sessions [17,18]. However, in contrast to the favorable anti-epileptic reports, Varga applied 1 mA, 20 min cathodal or sham tDCS to the five patients with continuous spike and wave during slow sleep. They revealed that cathodal tDCS did not reduce the spike index in any of patients. Here, the authors explained that the small surface of the cathode was unlikely to affect wide-spread epileptiform activity [19].

We applied electrodes with a surface area of 35 cm<sup>2</sup>. The current strength was 1 mA so the current densities produced was 0.029 mA/cm<sup>2</sup> at the skin surface. This current density is in range of previously-suggested safety limits (0.029–0.142 mA/cm<sup>2</sup>) [7] and in accordance with the absence of serious adverse events in our trial. The single minor adverse event, transient skin erythema in one patient, likely reflected vasodilation reluctant from skin conductance of electrical current [20].

### Limitation of this study

Since ours is the first controlled study of cathodal tDCS in children with focal epilepsy, aimed largely to investigate safety and tolerability in this fragile population, we performed only single stimulation. In future trials, investigations of a “dose–response” relationship between an EEG or clinical outcome and tDCS amplitude, session duration, and session number, is anticipated.

In addition, current randomization with limited sample size resulted in unequal randomization in QOL questionnaire responses which prevents to draw significant conclusions. However, for purposes of planning future trials it is important to mention that in no patient the QOL decreased following verum or sham tDCS which also supports tDCS safety. Even though we intended to employ a double-blinded study, however, an unpredictable proportion of

patients may have become aware of their treatment allocation because of a recognized complication.

In summary, our results show that a single session of cathodal tDCS was well-tolerated in children with epilepsy, and was associated with reduction in epileptic EEG abnormalities for the following 48 h. These findings encourage further study to explore the clinical effect of multiple session cathodal tDCS on epilepsy in children.

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