Transcranial direct current stimulation reduces seizure frequency in patients with refractory focal epilepsy: A randomized, double-blind, sham-controlled, and three-arm parallel multicenter study

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been explored in epilepsy with limited samples, varied parameters, and inconclusive results. We aimed to study the efficacy of tDCS for patients with refractory focal epilepsy.
Method: We conducted a randomized, double-blind, sham-controlled, and three-arm (Group 1 (sham), Group 2 (20-min), and Group 3 (2×20-min)) tDCS parallel multicenter study. The primary outcome measurement was seizure frequencies (SFs). The study consisted of 28-days baseline, 14-days treatment, and 56-days follow-up. The cathode was placed over the epileptogenic focus, and the current intensity was 2 mA. The generalized estimating equations model, one-way analysis of variance, chi-square and Kruskal-Wallis test were used for analysis.
Results: Of the 82 enrolled patients, 70 patients were included for final analysis (Group 1, n = 21; Group 2, n = 24; and Group 3, n = 25). There was a significant reduction in SFs for both active tDCS groups compared with the sham group. Patients in Group 2 showed a significantly 50.73—21.91% greater reduction in SFs that lasted for 4 weeks (p = 0.008—0.060). Patients in Group 3 showed a significantly 63.19—49.79% greater reduction in SFs compared with the sham group that lasted for 5 weeks (p = 0.011 —0.045). Patients in Group 3 had a 64.98—66.32% greater reduction in SFs at W9—W10, when compared with Group 2 (p = 0.021—0.022).
Conclusion: Fourteen consecutive days tDCS significantly decreased SFs in patients with refractory focal epilepsy, with 2×20-min daily stimulation protocol being superior to 20-min daily stimulation protocol.
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Introduction

In epilepsy, 30% patients do not respond adequately to antiepileptic drugs (AEDs) [1]. Among these patients, neurosurgical treatment eliminates seizures in only approximately 50% of patients [2]. Neuromodulation offers a viable therapeutic option for patients who are not surgical candidates or who fail to benefit from surgical treatment.

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique. Generally, with the reference electrode frequently on the contralateral supraorbital region, anodal tDCS targeting motor cortex increases cortical excitability, while vise verse cathodal tDCS decreases it [3]. The primary action of tDCS during stimulation is a subthreshold shifting of the membrane potential, towards depolarization or hyperpolarization [4]. More importantly, the modulation of cortical excitability outlasts the stimulation duration. Although not fully illuminated, this mechanism includes synaptic plasticity changes of glutamatergic neurons with N-methyl-D-aspartate (NMDA) receptors [5] and even non-synaptic effects [6].

TDCS has been investigated in several neuropsychiatric diseases. Evidence-based guidelines on the therapeutic use of tDCS proposed a level B recommendation for fibromyalgia, depression, and alcohol/drugs/smoking craving [4]. However, the guidelines could not make any recommendation on the efficacy of tDCS for epilepsy because of limited evidence. Reported studies encompassing tDCS in epilepsy include five case (series) reports of 1–7 patients [7–11] and six controlled single center studies assessing 10–36 patients [12–17]. The stimulation parameters and effects varied among them. Clinical seizure frequencies (SFs) decreased in eight studies [8–11,14–17], showed a decreasing trend in one study [12], a clinically negligible reduction in one study [13], and was unreported in another study [7]. Interictal epileptic discharges (IEDs) were decreased in four [12–14,16], unchanged in three [7,10,15], and unreported in four [8,9,11,17] publications. The inconsistency of these results may be due to the variability of stimulation parameters, such as current intensity (1–2 mA), stimulation duration (20–60 min), repeated sessions (1–14), electrode area (needle to 35 cm^2 patch), and different reference electrode locations, even outside the head at the shoulder.

The main parameters of tDCS include intensity [18], duration, and interval [19]. Increasing the current intensity and duration is reported to enhance efficacy [20]; however, a partially non-linear relationship between the tDCS setting and the effects has also been reported [18]. Compared with the same total duration, repeating tDCS during the after-effect period of the first stimulation with a certain interval is reported to be more efficient [19,21].

Based on these previous studies, we hypothesized that a consecutive 14-days of active tDCS treatment (20-min daily) would reduce SFs for patients with epilepsy, and that an enhanced protocol (2 × 20-min daily) would induce a greater effect. Thus, we performed a study of tDCS in patients with refractory focal onset epilepsy.

Material and methods

Study design

A randomized, double-blind, sham-controlled, three-arm parallel group (Group 1: sham tDCS; Group 2: 20-min tDCS per day; and Group 3: 2 × 20-min tDCS per day) multicenter study was conducted at four hospitals in Beijing, including Xuanwu Hospital (coordinating research center), Beijing Tiantan Hospital, Beijing Luhe Hospital, and Beijing Children's Hospital.

Each study arm consisted of three basic phases with evaluation of eleven time periods: (a) a baseline seizure monitoring period of 28-days (Baseline); (b) a consecutive 14-days treatment period without weekend interruption (W1–W2), and (c) a follow-up period of 56-days (W3–W10) (Fig. 1).

Both the patients and the investigators who evaluated the patients' SFs and quality of life scores were blinded to the group information. Only the technicians performing the tDCS procedure and the physician assigning the randomization without patient contact were aware of the group information. To maintain blindness, patients were kept not to communicate with other patients during their visits in any of the study phases.

Subjects were randomly assigned to the three groups in equal numbers, balanced at each center, using the random number table generated by SPSS v.20 before enrollment of the first patient.

The study protocol was approved by the central Ethics Committee at the coordinating center. All patients provided written informed consent for the research and publication of the data.

Participants

The inclusion criteria were as follows: (1) patients aged ≥18 years and ≤ 60 years; (2) proven focal-onset seizures, with or without focal onset bilateral tonic-clonic seizures (according to the ILAE 2017 operational classification of seizure types) [22]; (3) history of epilepsy for at least 2 years; (4) refractory to AEDs (defined as failure of adequate trials of two tolerated and appropriately chosen and used AEDs to achieve sustained seizure freedom); (5) the daily AEDs were unchanged for the last 4 weeks prior to the baseline period, and the participant agreed to keep the AEDs unchanged throughout the whole study; (6) one to five types of AEDs were used when enrolled; and (7) patient had two or more seizures during the 4-weeks baseline period.

The exclusion criteria were as follows: (1) presence of pseudo seizures; (2) evidence of progressive brain disorders or systemic diseases other than epilepsy; (3) breastfeeding or pregnancy; (4) drug addiction; (5) implanted with other electrical medical
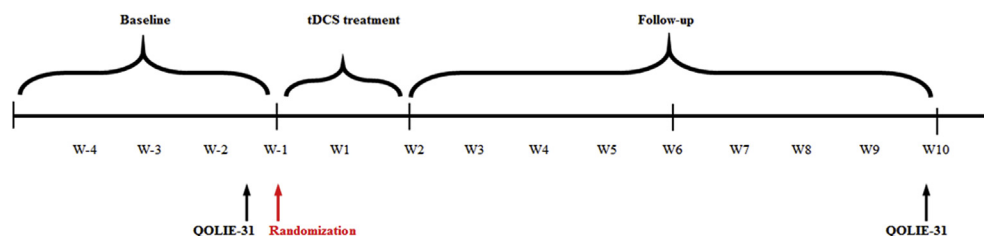
Fig. 1. Study timeline. There were 11 time periods for each patient: averaged weekly seizure frequency at baseline, 2 weeks during tDCS treatment (W1–W2) and 8 weeks during follow-up (W3–W10). Abbreviations: tDCS: transcranial direct current stimulation; QOLIE-31: quality of life in epilepsy - 31 inventory; W-4, W-3, W-2, W-1: 4-weeks baseline period; W1–W2: 2-weeks treatment period; W3–W10: 8-weeks follow-up period.

devices; (6) change of AEDs during the baseline, treatment, or follow-up periods.

EEG recordings and the localization of epileptogenic focus

Clinical semiology, EEG acquired at the end of baseline, and magnetic resonance imaging (MRI) were used for the localization of the epileptogenic focus. To maintain consistency, all patients from all centers went through the same pre-treatment evaluation for localization of the epileptogenic focus by the same team at the coordinating center.

Localization of tDCS electrodes

The cathode was placed generally in parallel over the epileptogenic focus using the EEG electrode 10–20 system. In case the epileptogenic focus involved more than one electrode position, the cathode was placed in the midpoint of the involving electrode positions. The reference electrode was placed over a contralateral, silent, and relatively far area to the cathode. The "silent area" was defined as area without or with minimal epileptogenic discharge in the EEG recorded at the end of baseline [12]. Increasing tDCS electrodes separation on the head generally increases the amount of current entering the brain [23]. Therefore "relatively far" was defined as follows: for cathodes assigned in the middle part of one hemisphere (e.g., T3/C3/C4/T4), any position in the contralateral hemisphere became the choice for the reference electrode. For cathodes assigned in the posterior/anterior part of one hemisphere, the contralateral anterior/posterior position became the choice. All three criteria: "contralateral", "silent", and "relatively far" had to be met for the selection of the position of reference electrode.

Intervention

TDCS was applied through a constant-current investigational stimulator (Yunshen tech, China). An indication light on the panel of the stimulator turned on with stimulation onset and turned off with simulation offset, regardless of active or sham stimulation. The current intensity was 2 mA with 30-s fade-in and fade-off at the beginning and end of stimulation, respectively. A sponge saturated with 0.9% sodium chloride solution was used beneath the tDCS electrodes to facilitate current flow. The surface area of the oval sponge was 11.9 cm^2, (length of the long and short axes: 4.2 and 3.6 cm, respectively).
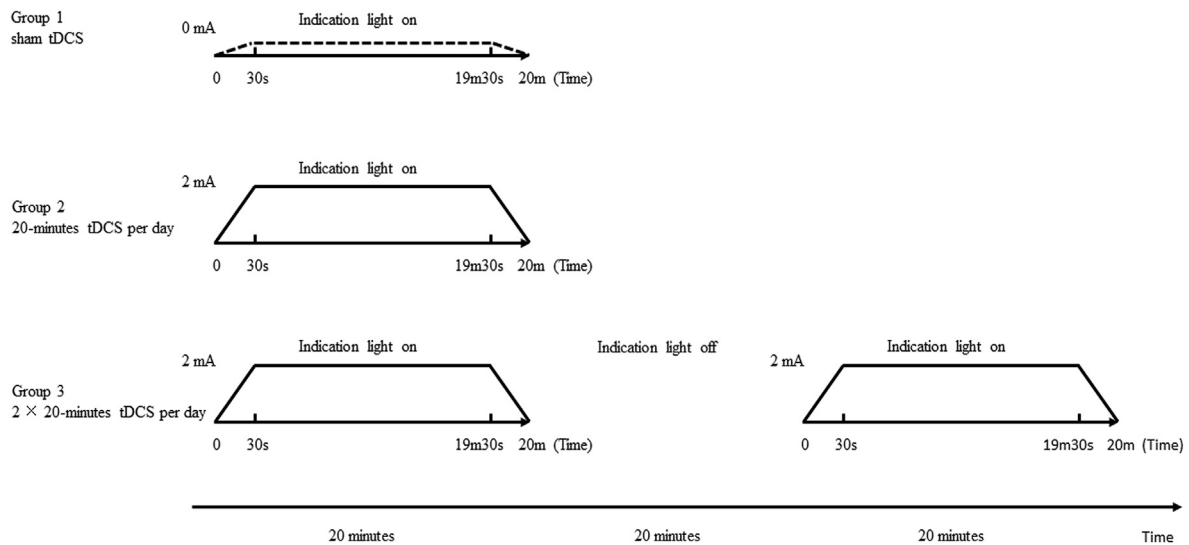
Patients in Group 2 received a 20-min stimulation per day (Fig. 2). Patients in the sham group (Group 1) received no stimulation but went through the same stimulation procedure as those in Group 2, being attached with two electrodes for 20 min. For Group 3, patients received a total of 40 min stimulation per day, which was equally separated by a 20-min interval. All participants were stimulated separately to maintain study blindness.

Measurements

The primary outcome measurement was SFs. The patients' caregivers were asked to update their individual seizure diary every day throughout the study. The secondary measurement was the Quality of Life in Epilepsy-31 Inventory (QOLIE-31 Chinese version [24,25]), measured at the end of baseline and follow-up; And the number of seizures occurred during the 20-min tDCS stimulation period, which was recorded separately.

Statistical analysis

Statistical analysis was performed with SPSS v.20 software. We compared the SFs per week for eleven periods: the averaged baseline (Baseline), 2 weeks during the tDCS treatment period (W1–W2), and 8 weeks during the follow-up period (W3–10) (Fig. 1). The generalized estimating equations (GEE) model [26] for repeated measures, based on a Poisson log-linear distribution, was performed to compare the eleven weekly SFs and estimate the group effect separately for each time period. The GEE model, conceptually similar to an analysis of variance study with repeated measures, has been used for the analysis of sequential epilepsy frequency [27,28]. The GEE model included intercept, group effects, time, group-by-time interaction, log of the averaged weekly baseline seizure counts, log of age, and baseline covariates. Least significant difference (LSD) was used to estimate adjusted treatment differences.

Fig. 2. The illustration of tDCS in three groups. Group 1: Sham group. Patients received 20-min sham stimulation, with the indication light on the panel of the stimulator turned on during the stimulation period. Group 2: Active group. Patients received 20-min active stimulation. And the indication light on the panel is also turned on during these 20-min. Group 3: Active group. Patients received 2 × 20-min active stimulation, however equally separated by 20-min interval. And the indication light on the panel is also turned on during these 40-min stimulation and turned off during the 20-min interval. Abbreviations: tDCS: transcranial direct current stimulation.

A one-way analysis of variance (ANOVA) was used to compare the difference of age and baseline QOLIE-31 sub-scores among the three groups. The chi-square test was used to compare the difference among the three groups in gender, epileptogenic focus classification, proportion of temporal and extratemporal seizures, seizure type classification, MRI lesion classification, AEDs amount, and the number of seizures occurred during the 20-min tDCS. The Kruskal-Wallis test was used for comparing averaged weekly baseline SFs. A repeated measure ANOVA was used to analyze QOLIE-31 scores among groups for the comparison of baseline follow-up data. A two independent samples Mann-Whitney test was used to compare SFs reduction between subgroups of patients with and without lesions. LSD corrections for multiple comparisons were performed for *post hoc* analyses. Differences with p-values <0.05 (two-sided) were considered significant.

Results

Subjects

Of the 82 enrolled patients at four centers in Beijing, 78 patients completed the 4-weeks baseline and 70 were randomized. Seventy patients finished the 2-weeks treatment period. Regarding follow-up, 65 patients finished the entire 8-weeks follow-up; two patients finished only 4-weeks of follow-up; and three patients finished 0 week of follow-up (Fig. 3). Only one patient from the sham group increased one tablet of AED per day during the follow-up (W7–10), and the change of drug was not to accommodate an increase of SFs. Only data from four time periods for this patient were excluded due to the medication change.

Thus, 70 patients were included in the final statistical analysis, as follows: Group 1 (n = 21), Group 2 (n = 24), and Group 3 (n = 25). The patient distribution is summarized in Fig. 3. The primary analysis sample of SFs includes original data from 11 time periods (Baseline, W1–10) for 65 patients, 7 time periods for 2 patients, and 3 time periods for 3 patients. The intent-to-treatment (ITT) last-observation-carried-forward sample of SFs includes data from 11 time periods for 70 patients.

The main clinical profiles of the 70 participants are shown in Table 1. The statistical analysis showed that there was no significant difference among the three groups in terms of age, gender, epileptogenic focus classification, proportion of temporal and extratemporal seizures, baseline SFs, seizure type classification, MRI lesions, and AEDs amount (p > 0.05).

Effect of tDCS on SFs: active groups compared with sham group

The study showed a significant effect of stimulation for both Group 2 and Group 3 compared with the sham group (Fig. 4). The GEE model included a group-by-time interaction, so no single consistent estimate of group effect across the entire period was possible. The model-estimated differences between Group 2 versus sham and between Group 3 versus sham for mean SFs, expressed as a percentage of the mean SFs in the sham group, are shown in Table 2 [27]. The GEE estimated differences for the primary analysis sample showed that Group 2 compared with the sham group had a significantly 50.73–21.91% greater reduction in SFs at the period of tDCS treatment and the first 2 weeks of follow-up (W1–W4, p = 0.008–0.060) (Table 2). Group 3, compared with the sham group, had a significantly 63.19–49.79% greater reduction in SFs at
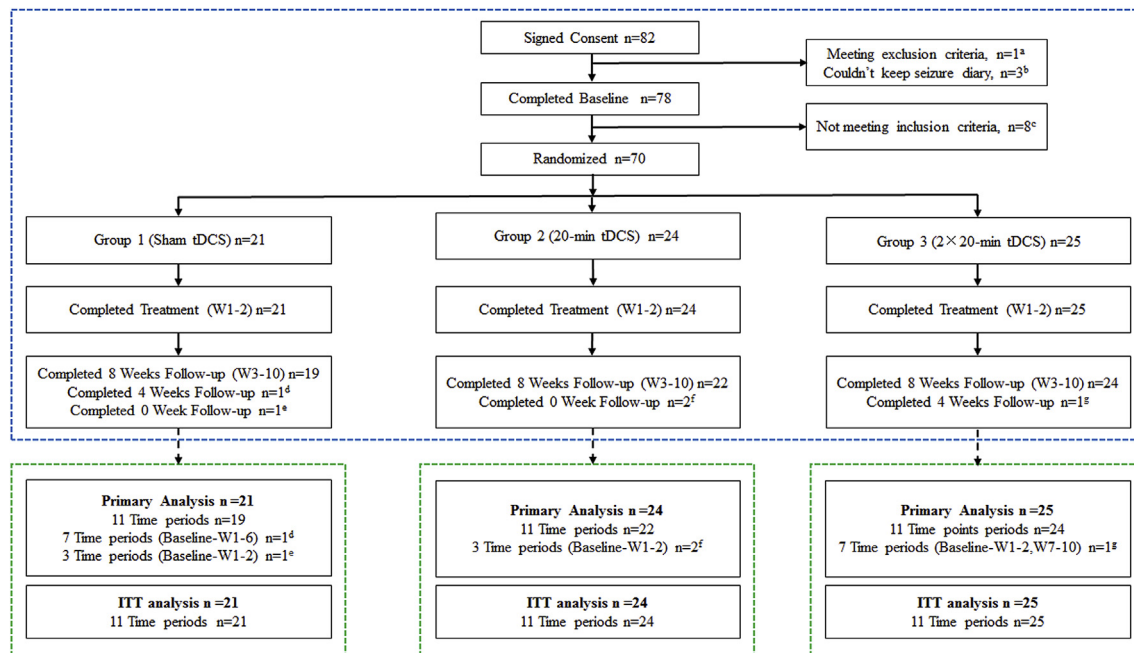

Fig. 3. Patient flowchart. Eighty-two patients were enrolled. [a] There was 1 patient excluded before the baseline period because of meeting exclusion criteria of pseudo seizures (n = 1). [b] There were 3 excluded during the baseline period because of being unable to keep seizure diary (n = 3). Seventy-eight patients completed 4-weeks baseline period. [c] Eight patients were excluded because of not meeting inclusion criteria at the end of baseline (the seventh inclusion criterion was as follows: patient had two or more seizures during the 4-weeks baseline period; however, 7 patients had only 1 seizure and 1 patient had no seizure during the 4-weeks-baseline). Seventy patients were randomized and finished 2-weeks treatment period. Sixty-five patients finished the whole 8-weeks follow-up; 2 patients finished only 4-weeks follow-up ([d], patient change AED for W7-10, n = 1; the change of AEDs was not to accommodate increased seizure frequency), ([g], patient did not keep seizure diary for W3-6, n = 1); 2 patients were lost at the begin of the follow-up ([f], patient loss for W3-10, n = 2); and 1 patient did not keep seizure diary at the follow-up ([e], patient did not keep seizure diary for W3-10, n = 1). Seventy patients were included for final analysis. The primary analysis sample of seizure frequency included original data from 11 time periods (Baseline, W1–10) for 65 patients, 7 time periods for 2 patients and 3 time periods for 3 patients. The intent-to-treatment (ITT) last-observation-carried-forward sample of seizure frequency included data form 11 time periods for 70 patients. Abbreviations: tDCS: transcranial direct current stimulation; AEDs: antiepileptic drugs; ITT: intent to treat.

Table 1
Demographics and clinical features.

	Group 1 (n = 21)	Group 2 (n = 24)	Group 3 (n = 25)	P-value
Age, years, mean ± SD	30.19 ± 13.03	30.58 ± 10.45	31.80 ± 9.25	0.870
Gender, male, n (%)	12 (57.14)	12 (50.00)	18 (72.00)	0.276
Epileptogenic focus classification, n (%)				0.444
Mesial temporal lobe epilepsy	3 (14.29)	7 (29.17)	7 (28.00)	
Neocortical temporal lobe epilepsy	7 (33.33)	3 (12.50)	8 (32.00)	
Frontal lobe epilepsy	4 (19.05)	5 (20.83)	4 (16.00)	
Parietal lobe epilepsy	5 (23.81)	8 (33.33)	3 (12.00)	
Occipital lobe epilepsy	1 (4.76)	0	0	
Others	1 (4.76)	1 (4.17)	3 (12.00)	
Epileptogenic focus classification, n (%)				0.424
Temporal	10 (47.62)	10 (41.67)	15 (60.00)	
Extratemporal	11 (52.38)	14 (58.33)	10 (40.00)	
Baseline seizure frequency/week, median	2.00	2.00	2.00	0.503
Seizure type classification, n (%)				0.143
Focal onset aware seizures (ASs) only	0 (0)	1 (4.17)	3 (12.00)	
Focal onset impaired awareness seizures (IASs) only	5 (23.81)	2 (8.33)	7 (28.00)	
Focal to bilateral tonic–clonic seizures (BTCs)	16 (76.19)	21 (87.50)	15 (60.00)	
MRI lesion, n (%)				0.868
Normal	7 (33.33)	9 (37.50)	10 (40.00)	
Hippocampus sclerosis	3 (14.29)	5 (20.82)	7 (28.00)	
Focal Cortical dysplasia	1 (4.76)	1 (4.17)	1 (4.00)	
Cerebromalacia	5 (23.81)	6 (25.00)	4 (16.00)	
Arachnoid cyst	1 (4.76)	0	0	
Tuber	0	1 (4.17)	0	
Severe brain malformation [a]	3 (14.29)	1 (4.17)	3 (12.00)	
Postoperative changes	1 (4.76)	1 (4.17)	0	
AEDs amount, n (%)				0.953
1 AED	3 (14.29)	3 (12.50)	3 (12.00)	
2 AEDs	8 (38.10)	12 (50.00)	11 (44.00)	
≥3 AEDs	10 (47.61)	9 (37.50)	11 (44.00)	

[a] Severe brain malformation included: Porencephaly for one patient, and schizencephaly with heterotopic grey matter for two other patients from Group 1; Partial dysplasia of corpus callosum for one patient from Group 2; Porencephaly for one patient, subcortical band heterotopia for one patient, and periventricular heterotopia for another patient from Group 3.
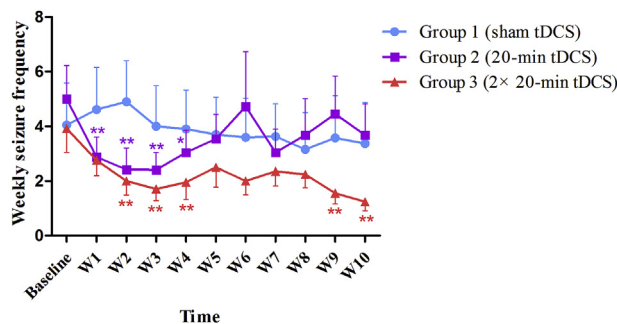
Fig. 4. The GEE model estimated mean weekly seizure frequency of three groups through the whole study based on primary analysis sample. Y axis: mean weekly seizure frequency estimated by GEE model for three groups at different time periods. X axis: the time periods of the study. Baseline: averaged baseline; W1–W2: treatment period of 2-weeks. W3–W10: follow-up period of 8-weeks ** indicates that seizure frequency at the time periods is significantly different from that of the sham group, $p < 0.05$. * marks the time point at which seizure frequency is marginally significant different from the sham group, $p = 0.06$. For Group 2 and Group 3, there were 4 and 5 time periods that significantly differed from the sham group, respectively. Bar represented standard error of the mean. Abbreviations: GEE: Generalized estimating equations. W: week. min: minutes.

the period of treatment, and at four weeks in follow-up (W2–W4, W9–W10, $p = 0.011$–0.045, Table 2). The GEE estimated differences for the ITT sample showed a significantly 50.73–31.94% greater reduction in SFs for three weeks, comparing Group 2 with sham (W1–W3, $p = 0.008$–0.071). The ITT sample-based GEE analysis showed a similar result of a significantly 59.94–48.96% greater reduction in SFs for five weeks when comparing Group 3 with the sham group (W2–W4, W9–W10, $p = 0.016$–0.063) (Table S1).

The median unadjusted weekly SFs percentage change from baseline for the primary analysis sample also favored the active groups, with greater seizure reduction compared to the sham group (Tables S2 and S3). A [median (Q1, Q3)] −50.00% (−62.50%, −8.33%) and −50.00% (−73.96%, −25.00%) change from baseline in weekly SFs in the first 4-weeks follow-up was observed in Group 2 and Group 3, respectively, as compared to a −25.00% (−50.00%, 28.75%) change in the sham group. A −25.00% (−57.44%, 5.56%) and −45.00% (−78.13%, 0) change from baseline in the second 4-weeks follow-up was observed in Group 2 and Group 3, respectively, as compared to a −12.50% (−57.50%, 12.50%) change in the sham group (Table S3).

Effect of tDCS on SFs: Group 3 compared with group 2

The primary sample-based GEE analysis showed that Group 3 had a 64.98–66.32% greater reduction in SFs at W9–W10, compared with Group 2 ($p = 0.021$–0.022) (Table 2, Fig. 4). The ITT sample-based GEE analysis showed a similar result that Group 3 had a 65.33–67.30% greater reduction in SFs at W9–W10, compared with Group 2 ($p = 0.018$–0.016) (Table S1).

Response to tDCS for patients with or without lesion on MRI

Patients with and without MRI lesion in Group 2 showed a [median (Q1, Q3)] −50.00% (−57.26%, 0) and −54.17% (−75.00%, −11.70%) reduction in weekly SFs in the first 4-weeks follow-up, as well as a −22.62% (−61.14%, 6.25%) and −45.83% (−58.04%, 16.67%) reduction in the second 4-weeks follow-up. As for patients with and without lesion in Group 3, the median SFs reduction for the first 4-weeks follow-up was −37.50% (−82.26%, −12.50%) and −50.00% (−71.88%, −29.69%), as well as −25.00% (−91.67%, 25.00%) and −56.25% (−73.44%, −31.25%) in the second 4-weeks follow-up.

Table 2
GEE model adjusted mean percent difference in seizure frequency in three groups based on the primary analysis sample.

Adjusted diff (%)	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10
G2 vs G1[a]	−37.76**	−50.73**	−39.77**	−21.91*	−4.18	31.31	−16.14	16.59	24.47	9.30
p-value	0.033	0.008	0.029	0.060	0.389	0.896	0.226	0.859	0.981	0.696
G3 vs G1[a]	−40.25	−59.22**	−57.29**	−49.79**	−32.43	−44.44	−35.01	−29.07	−56.41**	−63.19**
p-value	0.154	0.016	0.016	0.045	0.373	0.184	0.305	0.382	0.040	0.011
G3 vs G2[b]	−4.00	−17.24	−29.09	−35.70	−29.49	−57.69	−22.51	−39.16	−64.98**	−66.32**
p-value	0.617	0.905	0.771	0.475	0.758	0.182	0.967	0.477	0.021	0.022

The primary analysis sample included original data from 11 time periods (Baseline, W1-10) for 65 patients, 7 time periods for 2 patients and 3 time periods for 3 patients.
**: Significant difference (Estimated by GEE) (p < 0.05).
*: Marginally significant difference (Estimated by GEE).
Abbreviation: diff: difference; G1: Group 1; G2: Group 2; G3: Group 3; W1–W2: Treatment period; W3–W10: Follow-up period.
[a] Adjusted percent difference is calculated by [(Estimated active group mean − Estimated control group mean)/Estimated control group mean] * 100 (%).
[b] Adjusted percent difference is calculated by [(Estimated Group 3 mean − Estimated Group 2 mean)/Estimated Group 2 mean] * 100 (%).

The Mann-Whitney test revealed no significant difference in the reduction of SFs for patients with and without lesions from Group 2 or Group 3 in the first (p = 0.570, p = 0.886) or second (p = 0.664, p = 0.338) 4-weeks follow-up periods, respectively (Table S3).

Changes in psychological states

QOLIE-31 was evaluated at the end of baseline and follow-up. There was no significant difference in the sub-scales of QOLIE-31 among the three groups at baseline. A repeated measures ANOVA revealed no significant difference among groups, and only the sub-scores for energy/fatigue (p = 0.015) and emotional well-being (p = 0.039) showed a significant within-group time effect, with no significant time and group interaction effect noted.

Safety evaluation

Nineteen patients in Group 2 (79%), 21 patients in Group 3 (84%), and 2 patients in Group 1 (9%) reported a mild itching sensation beneath the electrodes during tDCS. During the 20-min stimulation, 2 out of 21 (9%) patients in the sham group, and 3 out of 25 (12%) patients in Group 3, experienced a focal onset impaired awareness seizure. Two seizures occurred in two patients from the sham group on the third and fifth day (the 3rd and 2nd minute), respectively. Three seizures occurred in three patients from Group 3 on the fourteenth, twelfth, and tenth day (the 2nd and 13th minute of the first 20-min tDCS, and 17th minute of the second 20-min tDCS), respectively. There was no change in seizure semiology compared with seizures at baseline. TDCS treatment was stopped immediately after the onset of seizures; patients were under close observation and protection by doctors and these seizures ended spontaneously and quickly without drug invention. TDCS was continued in the following days without further seizure during the 20-min tDCS for each patient. These five patients had 16, 12, 12, 4, and 12 seizures during the 4-weeks baseline, respectively. There was no significant difference between the three groups in the number of seizures occurred during the 20-min tDCS (p = 0.233). Two patients with prior cranial surgery were enrolled. One patient received arachnoid cyst resection 16 years before enrollment and was randomized to Group 2. Another patient received temporal lobe lesion resection 14 years before enrollment and was randomized to the sham group. No artificial material was implanted in the skull for either patient. These two patients tolerated tDCS well and reported no side effect, except for the itching sensation.

Discussion

TDCS has been successfully explored in some neurological diseases, such as pain [29], depression [30], and craving [31]; however studies in epilepsy are limited, with various parameters and generally small sample sizes. We designed and conducted our randomized, double-blind, sham-controlled, and three-arm parallel multicenter study based on reported studies. Our study found active tDCS, compared with sham tDCS, produced a significant reduction in SFs in patients with refractory focal epilepsy. The protocol using 2 × 20-min stimulation per day was superior to the protocol using 20-min stimulation only.

Epilepsy is associated with increased cortical excitability, synchronization, and defective inhibition [32–34]. Conventionally, cathodal tDCS decreases cortical excitability [3] and was theoretically expected to suppress seizures in patients with epilepsy. A reduction in spontaneous neuron spiking [35] and an increase in the threshold of convulsive activity for rat model of epilepsy following cathodal tDCS was reported [36]. Downregulation of synaptic strength, mediated by reduced presynaptic input to NMDA-receptors after cathodal tDCS, has been suggested as the mechanism underlying the anti-epileptic effect of tDCS for epilepsy [36]. Besides, a reduction in epileptic discharge on EEG [37] and suppression of convulsions by tDCS [38] have also been reported in animal models of epilepsy.

Reduction of SFs

Consistent with our result, eight of 11 clinical studies reported a positive result as significant reduction in SFs [8–11,14–17]. Seven of the eight positive studies used repeated sessions (3–14) [8–11,14,16,17], whereas all three non-positive studies used a single session [7,12,13].

A comparison to the results of other controlled studies with focal epilepsy was made, leaving out case reports and studies with epileptic syndrome. First, repeated tDCS sessions were explored in two studies: (a) A −43.4% and −54.5% reduction in SFs, lasting 2 months, was reported for patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS) (3/5-days, 30-min tDCS/day, n = 28) [14]; (b) A reduction of mean SFs from 10.58 ± 9.91 to 1.67 ± 2.50, lasting only one month of the 2-months follow-up, was reported by Tekturk et al. for patients with MTLE-HS (3-days, 30-min 12 Hz sinusoidal tDCS/day, n = 12) [17]. The median SFs reduction of −50.00% and −50.00% (the first 4-weeks of follow-up), as well as −25.00% and −45.00% (the second 4-weeks of follow-up), respectively, for patients from Group 2 and Group 3 in our study, was similar to the results of these two studies [14,17]. However, the effect lasted, at least in Group 3, longer in our study than in the study by Tekturk et al. [17]. Importantly, some differences should be mentioned viewing this comparison: (a) brain lesions: diverse in our study vs. uniform in the other two studies; (b) sample size: n = 70 vs. n = 28/12; (c) daily stimulation duration: 20/2 × 20-min vs. 30-min; (d) tDCS treatment: 14-days vs. 3/5-days; and (e) current style: traditional tDCS vs. sinusoidal tDCS in Tekturk et al.'s report. These differences might influence the results.

Second, three other studies, adopting single 20-min tDCS, reported a −4.8%, −44.0%, and −71.0% reduction in SFs for patients with diverse lesions (n = 36) [13], uniform lesion (n = 19) [12], and temporal lobe epilepsy (n = 10) [15], respectively. In conclusion, the studies in the literature differed in many aspects. Our study observed similar anti-epileptic effect, which lasted longer compared to those studies adopting repeated sessions. Although this study may provide more evidence, particularly exploring long sessions as 14-days tDCS for epilepsy, it remains to be evaluated whether even longer stimulation, as used in the treatment of depression [39,40] or epileptic spasm [11], may yield better results.

Interval between sessions

Increasing stimulation duration without interval is one option to enhance efficacy [19,20]. However, repeating cathodal stimulation with a short (3-min) and medium (20-min) interval, compared with the same total duration, showed advantages of prolongation and enhancement of efficacy [19]. Also, it was reported that repeating the second anodal stimulation with a medium interval (25-min), rather than a short one (5-min), enhanced efficacy [41]. Despite the inconsistency, these findings suggested repeating another stimulation with a certain interval probably improved efficacy. Our study also showed the protocol using 2 × 20-min-stimulation with a 20-min-interval prolonged the anti-epileptic efficacy, compared with 20-min-stimulation only. Although a group using 40-min-stimulation without interval as comparison was not set, our study indicates the worthiness of further exploring the optimal interval between repeated sessions.

Quality of life

A significant change of QOLIE-31 score at the end of the follow-up was not found, although there was a significant reduction in SFs. This may be due to the fact that for a significant improvement in quality of life to occur among patients with epilepsy, seizure freedom is imperative [42]. In our study, most patients were not seizure free for a long time. Besides, other factors, such as number of AEDs, also influence the QOLIE -31 score [43], which were kept unchanged.

Safety

TDCS has been proven to be a safe technique, according to an evidence based-update [44]. The increase in cortex excitability by the anode raised concern about its application in epilepsy. It was reported that no significant increase of IEDs was detected under the anode [12]. Placing the anode at the silent area, as our study also followed, is important in applying tDCS in epilepsy [12].

Five seizures occurred during the 20-min stimulation, 2 in the sham group and 3 in Group 3. These seizures had the same semiology with those at baseline, occurred in patients with frequent SFs at baseline, and occurred even in patients treated with sham tDCS. Similarly, San-Juan et al. reported two seizures during 30-min tDCS, in 2 patients (baseline SFs: 11 and 5/month) out of 8 patients with epilepsy on the first day of a 5-days active treatment [14]. In their report, no ictal EEG activity was found after the intervention [14]. To the best of our knowledge, no tDCS-induced seizure in patients without epilepsy has been reported. Considering the recurring nature of epilepsy [45] and the mechanism of subthreshold, rather than suprathreshold, shift of membrane potential of tDCS [4], we suggest these seizures might not be induced by tDCS. However, further studies are warranted to investigate this issue.

Two patients with prior cranial surgery, which occurred at least 14 years prior, were enrolled and tolerated tDCS well in this study.

Similarly, San-Juan et al. reported that two patients (two weeks after brain surgery for biopsy and electro-corticogram recording) tolerated and responded well to tDCS [9]. The electrical field is reported to be different inside the brain of patients with skull defects based on computational models [46]. However, the size, state of skull defects, and other factors influence the current in a comprehensive way [46]. Small defects in the skull, midway between two tDCS electrodes, and chronic defects shunt less current [46]. Further studies with animal, computational, and clinical evidence for this area are needed.

A few limitations of the present study should be reported. We did not analyze the change of IEDs after tDCS. Future studies should include IEDs and other neurophysiological parameters. Patients were taking AEDs during the study, and tDCS may interact with the drugs. Studies should investigate this in the future. Although we have verified the main study hypothesis that an enhanced protocol would induce a greater effect, the superiority of the anti-epileptic effect in Group 3 might also be caused by higher 'placebo-like' effect. Patients from Group 3 indeed received longer stimulation than patients in other groups. Further studies should rule out this issue.

Conclusions

In summary, our study shows the effectiveness of two active protocols of tDCS for the treatment of patients with refractory focal epilepsy. Moreover, the protocol using 2 × 20-min daily stimulation was superior to the protocol using 20-min stimulation only.

Author contributions statement

DY: Collected and followed up patients, evaluated the QOLIE score, wrote and revised the manuscript; QW: Collected patients; CX: Assigned randomization, localized epileptogenic foci and tDCS electrodes; FF: Collected patients; JF: Collected and followed up patients, evaluated the QOLIE score; LL: localized epileptogenic foci; QD: Collected and followed up patients, evaluated the QOLIE score; RZ: Collected and followed up patients; YeW: Collected and followed up patients, evaluated the QOLIE score; YL: Performed tDCS and revised the manuscript; ZH: Interpreted the results; HW: Collected and followed up patients; CC: Collected and followed up patients; QlX: Performed tDCS; YuW: Performed tDCS; YZ: Performed tDCS; ZZ: Performed tDCS; XiZ: Performed tDCS; XuZ: Performed tDCS; TL: Performed tDCS; CL: Collected and followed up patients, evaluated the QOLIE score; YN: Collected and followed up patients, evaluated the QOLIE score; QhZ: reviewed the literature; QlZ: Collected and followed up patients, evaluated the QOLIE score; YD: Collected and followed up patients, evaluated the QOLIE scores; XL: Performed tDCS; TY: Performed tDCS; QiX: Performed tDCS; JL: Acquired EEG; XD: reviewed the literature; JH: reviewed the literature; CR: Performed tDCS; HX: Performed tDCS; NL: Performed tDCS; JZ: evaluated the QOLIE score; NX: Performed tDCS; KY: interpreted the statistical results; YpW: designed the study, collected patients and revised the manuscript.

Declaration of interest

The authors declare no conflict of interest related to the submitted manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.09.006.

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