Original Article

Transcranial Direct Current Stimulation (tDCS): Pain Management in End-Stage Renal Disease - Report of an Early Randomized Controlled Trial

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Abstract

Context. Chronic pain in end-stage renal disease (ESRD) is an increasingly neglected clinical problem affecting more than 60% of patients. Long-term chronic pain could be associated with brain imbalance in circuits of pain matrix and is associated with poor quality of life (QoL) and mood disturbance.

Objectives. The aim of this study was evaluating the effects of transcranial direct current stimulation (tDCS) on pain, QoL, depression, anxiety and affectivity in ESRD patients undergoing hemodialysis (HD).

Methods. This double-blind, randomized, sham-controlled trial included 30 patients with chronic pain undergoing HD. Participants were allocated to Active tDCS and Sham tDCS and received ten non-consecutive sessions of anodal motor cortex stimulation (M1/Sp2 montage) at 2 mA intensity for 20 min. The primary outcome was pain assessed using numeric rating scale (NRS) and collected at baseline, immediately after the 10th day of intervention, one week, two weeks, and four weeks after the last stimulation. Secondary outcomes included QoL, depression, anxiety and affectivity collected before and after intervention.

Results. A mixed ANOVA model showed significant interaction between group and time on pain $F(4.112) = 3.106$, $P = 0.01$ with main effects of group ($P = 0.03$). Before and after intervention, a significant improvement was observed in QoL ($P = 0.009$), general health ($P = 0.03$), fatigue ($P = 0.05$), symptoms ($P = 0.05$) depression ($P = 0.01$) and anxiety ($P = 0.01$). No difference was found for affectivity.

Conclusion. Anodal tDCS over the motor cortex emerges as a potential therapeutic approach for improving pain, QoL, and mood in patients with ESRD. J Pain Symptom Manage 2022;64:234–243.

Key Words

Chronic pain, quality of life, neuromodulation, noninvasive brain stimulation, hemodialysis

Key Message

Ten non-consecutive sessions of anodal M1 tDCS improved pain, quality of life, and mood in patients with end-stage renal disease.

Introduction

Chronic pain is an important health problem in end-stage renal disease (ESRD), affecting up to 60% of the patients.[1] Several studies suggest that pain is one of

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the most common symptoms in ESRD and could be characterized as nociceptive, neuropathic or mixed.[2,3] Pain manifestation in patients with ESRD undergoing hemodialysis (HD) has different pathophysiological mechanisms that include osteodystrophy, osteoarthritis, calciphylaxis, peripheral neuropathy, critical limb ischemia, non-uremic peripheral neuropathy or osteoporosis, and has a negative impact on quality of life (QoL), social interaction, economic and psychological status.[2,4] Depression and anxiety are also common comorbidities of these patients and have been strongly correlated with worsening of QoL.[5]

Different factors including age, gender, body mass index, race/ethnicity, duration, place and type of HD contribute to increased pain.[6] The incidence of acute and chronic pain is a prevalent complaint in adults and elderly patients undergoing HD that negatively affect QoL, daily activities, mood, sleep and work.[7] Insufficient medical education, drug-related side effects and poor awareness of alternative treatment for pain control were important barriers for management of chronic pain in ESRD patients.[5] In addition to medical therapies, adjunctive non-pharmacologic interventions are considered whenever applicable.[8]

Several brain disorders have been shown in ESRD with impact in cognition, mood and pain control networks.[5] Patients with long period with chronic pain could present brain damage, and imbalance in circuits related of pain control.[9] Pain syndromes are associated with alterations in brain metabolism and functional connectivity in pain modulatory systems including emotional circuit.[5,9] These modulatory system regions are associated with the volume of pain perception, cognitive control of emotion, and self-referential processing.[4,10]

Ongoing clinical studies have indicated that noninvasive neuromodulating techniques can have pain-relieving effects on the treatment of chronic pain.[11,12] Transcranial direct current stimulation (tDCS) is especially deployable, well-tolerated, and safe alternative to improve pain.[11] The effects of anodal tDCS on the motor cortex (M1-SO montage) can modulate pain-related areas probably controlling pain through the restoration of cortical modulation of the pain network.[11] This effect was previously shown in several chronic pain syndromes.[11,13–15] M1 stimulation promote diffuse analgesic effect and may be used for treatment of diffuse chronic pain syndromes.[11,13–15] tDCS is commonly used to treat mood disturbance including depression and anxiety.[16,17] This neuromodulatory technique demonstrates greater clinical efficacy for major depression and for chronic pain syndromes associated with depressive symptoms.[18–20] tDCS has not been previously evaluated to treat chronic pain and mood disturbance in ESRD.

We hypothesize that tDCS is thus a rational strategy for noninvasive and non-pharmacological treatment for chronic pain in ESRD. The present study uses tDCS to treat pain in patients with ESRD, a similar approach has not been tested before. Our aim is to evaluate the effects of anodal M1-SO tDCS on pain in ESRD patients undergoing HD, and further assess its impact on QoL, depression, anxiety, and affectivity.

Materials and Methods

Study Design and Participants

This study is a single-center, double (patient and evaluator) blinded, parallel, randomized, sham-controlled trial, in accordance with CONSORT/2010. This study was approved by the local institutional ethics committee under number 2.715.151. The study was conducted between August 2018 and February 2020 in Natal, Brazil, and registered with the Brazilian Clinical Trials Registry (RBR-46vhrkj).

Patients undergoing HD were recruited at the Kidney Institute by formal invitation. All participants were informed about the study objectives and provided a written informed consent, according to resolution No. 466/12 of the National Health Council and The Declaration of Helsinki.

No previous studies have reported results about tDCS in visual analog scale or numeric rating scale (NRS) in patients with chronic kidney disease (CKD). Sample size was estimated after we ran a pilot study with 10 patients allocated in two groups (active and sham). A large improvement of 79.09% was observed for active group, while 13.35% for sham. G-Power 3.1.9.2 (Franz Faul, Universitat Kiel, Germany) was used to calculate sample size. We used a significance level of 0.05, power of 90%, and an effect size of 0.25. With this methodology, the sample size resulted in 26 participants. We added four more patients to prevent any reduction of power in case of patient dropout. Thus, 30 patients were recruited and randomized in two groups.

Patients were included if they fulfilled the following inclusion criteria: 1) man or woman aged 18 to 75 years; 2) undergoing HD (CKD 5D) for >3 months, (four-hour session); 3) chronic pain (chronic musculoskeletal pain, chronic headache and/or chronic neuropathic pain) related with a score of more than 4 (range of scores from 1−10) in a visual analog scale (NRS) for >3 months[21]; 4) consenting to treatment and understanding study explanations and questionnaires. Patients with any of the following criteria were excluded from the study: 1) electrical implants in the body; 2) a history of epilepsy or convulsion; 3) clinically contraindicated to receive tDCS such as having metal embedded in their scalp or brain; 4) psychiatric illness; 5) pregnant women; and 6) signs of severe disease and/or indication of hospitalization including

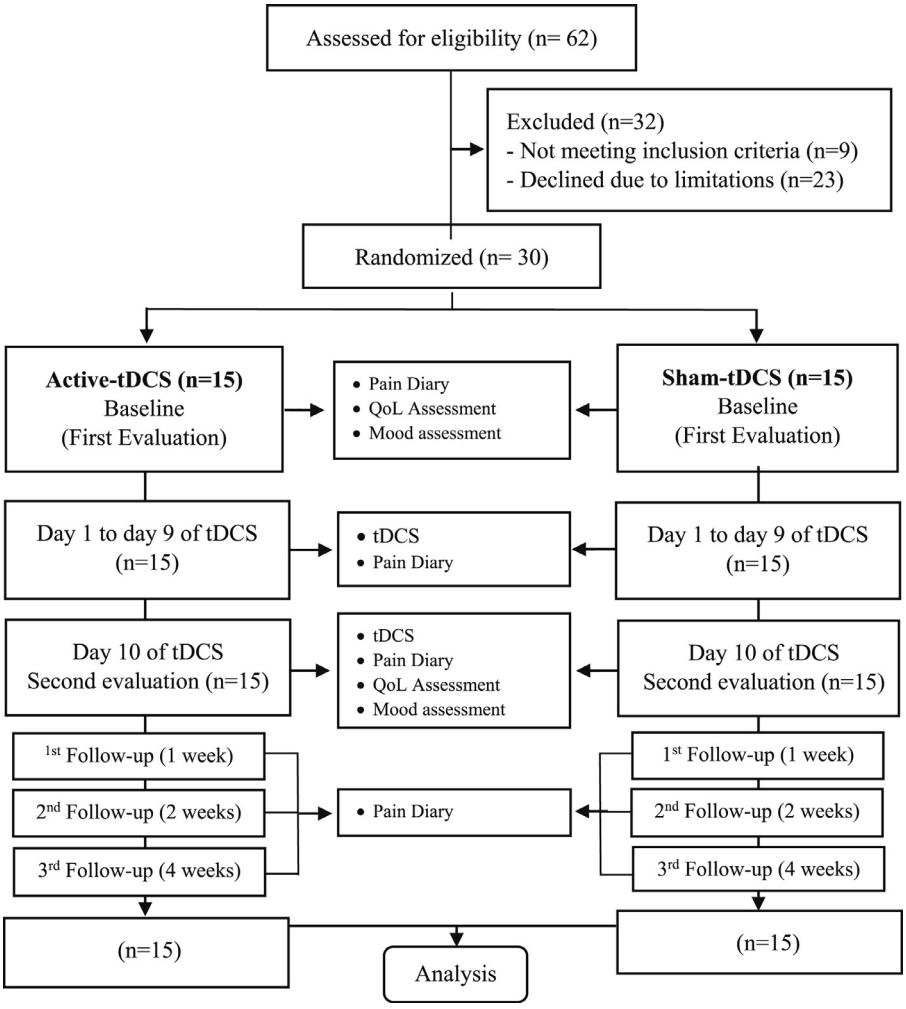

Fig. 1. Flowchart of the study. Follow-up was conducted on one week, two weeks, and four weeks after the last day of intervention.

hemodynamic instability, infection, acute myocardial infarction, and stroke.

Patients were randomized at a ratio of 1:1 to receive sham tDCS (sham group), or active tDCS (Active group) (Fig. 1). Randomization used the order of entry into the study and a previous computer-generated randomization list. A research assistant external to the study generated the allocation sequence. Each participant was equally likely to belong to one of the groups. Participants and researchers involved in the assessments and interventions were blinded to group allocation throughout the trial.

Intervention

A total of 10 sessions were administered to participants over Monday/Wednesday/Friday or Tuesday/Thursday/Saturday (three sessions per week) by a trained nurse at the Kidney Institute. tDCS used a monophasic continuous current with an intensity of 2 mA for 20 minutes. Each patient was awake and rested in a comfortable chair with back and arm support during the tDCS intervention. tDCS was performed during the usual session of HD. tDCS was carried out with anode electrode on the left primary motor cortex (C3) and the cathode electrode on the right supraorbital region (Fp2), according to the international 10−20 electroencephalography (EEG) system ("M1-SO" assembly). The electrodes were placed into a 35 cm^2 sponge hydrated with saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, a gradual current ramp-up and ramp-down with 30-s duration was used. The same protocol was applied in the sham group, but a gradual current ramp-up and ramp-down of 30 s was used. This method of sham intervention is therefore designed to provide an initial period of tingling so similar sensations are perceived during active tDCS with no modulatory effect.[22,23] Electrodes were attached to the scalp supported by an elastic band. The electrodes (anode and cathode) were connected to a custom battery-powered stimulator with

current verified by a precision digital multimeter (DT832, WeiHua Electronic Co., Ltd, China) with standard error of ±1.5%.[17,18] The device displays are identical in active and sham settings.

For ethical reasons, no changes were made to HD routines (days and place of sessions), clinical care (medicines, imaging or blood exams), and previous prescription of analgesics or other medications.

Outcome Measures

All evaluations were performed by an experienced physician blinded to group assignments. Socio-demographic and clinical characteristics were collected from the participants at baseline and contained age, gender, marital status, level of education, time of HD, medication profile, and comorbidities. Analgesic drug (dipyrone) prescriptions were analysed for prescribing patterns in terms of dosing and frequency of administration. Dipyrone was measured throughout intervention (baseline and 3rd follow-up) according to the number of prescription (one tablet of 500 mg). Baseline evaluation was assessed one week before the first day of tDCS in both groups.

Primary outcome was pain using the Numeric Rating Scale (NRS). The primary outcome was collected at baseline, immediately after the 10th day of intervention, one week after the last stimulation (1st follow-up), two weeks after the last stimulation (2nd follow-up) and four weeks after the last stimulation (3rd follow-up). An additional diary of pain was used 30 days before tDCS, during tDCS and 30 days after tDCS, with a total of 82 days. For diary of pain, participants were asked: how intense is your pain today?

The NRS is a unidimensional single 11-point numeric scale that measure pain intensity in adults[24]. The format consist in a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0−10 integers) that best reflects the intensity of their pain.[24] Participant was asked to indicate their worst pain intensity in the last 24 hours.

Secondary outcomes were collected at two times, on baseline and after intervention (day 10) (Fig. 1) and include QoL, depression, anxiety and affectivity.

The Kidney Disease Quality of Life - Short Form (KDQOL-SF) was used to assess the QoL. This questionnaire is one of the most widely used generic and disease-specific component measures for CKD.[25] This questionnaire is a specific instrument to evaluate patients on HD and has been used to compare treatment modalities, longitudinal trends, and the impact of QoL according to introduction of new therapies.[25] It was assessed all dimensions of KDQOL-SF that include: physical functioning, role limitations caused by physical problems, role limitations caused by emotional problems, pain, general health perceptions, social functioning, emotional well-being, fatigue, symptoms, effects of kidney disease, burden of CKD, cognitive function, quality of social interaction, sexual function, sleep, social support, work status, overall health rating, patient satisfaction and dialysis staff encouragement.[25]

Depression levels were assessed using the Beck Depression Inventory (BDI), a self-reporting tool of 21 questions relating to cognitive symptoms and attitudes.[26] For each question, patients chose one or more phrases that best described how they felt in the previous week. The maximum score is 63 points, and high scores indicate severe depression Beck et al. suggest the following quantification scores for depression: a score of less than 10 signifies minimal or no depression; 10−18 mild to moderate depression, 19−29 moderate to severe depression, and 30−63 severe depression.[26]

The severity of anxiety symptoms was measured using the Hamilton Anxiety Scale (HAS).[27] The HAS was administered by an interviewer who asked a series of semi-structured questions related to symptoms of anxiety. The interviewer then rated the individuals on a 5-point scale for each of the 14 items. The values on the scale range from 0 to 4 (0 means there is no anxiety, 1 mild anxiety, 2 moderate anxiety, 3 severe anxiety, and 4 very severe or grossly disabling anxiety).[27] The total anxiety score ranges from 0 to 56. High levels are indicative of high anxiety.

Positive and Negative Affect Schedule (PANAS) was used to assess affectivity.[28] Patients were asked to indicate, on a 5-point scale (from 1 = very slight or not at all to 5 = extreme), the extent to which they had experienced each of 10 positive and 10 negative affects at the moment of the interview. PANAS have two independent factors, positive and negative affect.[28]

Statistical Analyses

Analyses were performed using the IBM SPSS Statistics for Windows (Version 19.0, IBM Corp, Armonk, NY). Quantitative variables were expressed as means and standard deviations. The Shapiro-Wilk and Levene's test assessed the normality of the distribution and homogeneity of variance of the data, respectively. The baseline demographic characteristics and clinical scores were compared between the sham and active groups using Student's t-test (or Mann-Whitney) for continuous variables and chi-square test for categorical variables.

The change from baseline in NRS was evaluated using a mixed ANOVA, in which the dependent variable was the pain and the independent fixed variables were the time of evaluation (baseline, day 10, 1st follow-up, 2nd follow-up, and 3rd follow-up), the group of stimulation (active and sham) and the hypothesis of interest that tends to be the time-by-group interaction. Mauchly's test of sphericity was used to validate the correlation of the repeated measures, and if the

assumption of sphericity was violated, the Greenhouse-Geisser correction was applied. When appropriate, post-hoc comparisons were carried out using Bonferroni correction for multiple comparisons. Partial η^2 were calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η^2 was used to calculate the effect size, where $\eta^2 = 0.01$ was considered small, $\eta^2 = 0.06$ moderate and $\eta^2 = 0.14$ large effect.

To calculate the mean difference between groups in each phase of the 82 days of pain diary and secondary outcomes, Student's t-test was used. For KDQOL-SF (and domains), depression, anxiety, affectivity and analgesic consumption an ANCOVA was used to determine the effect of tDCS on post-intervention after controlling for pre-intervention. Post-hoc analysis used a Bonferroni adjustment. Statistical significance was set at $P \leq 0.05$.

Results

A total of 62 individuals were screened for eligibility. Thirty-two individuals were excluded for not meeting the inclusion criteria. Fifteen patients with CKD undergoing HD were randomized to each group (active or sham), and all patients completed the entire experimental procedure. No complications were observed during the study period among patients who completed the treatment protocols, and patients tolerated the tDCS treatments well. Adverse events were minimal and consistent with prior tDCS trials, limited to transient skin irritation. Cardiovascular and renal parameters did not show clinically significant changes. This is important to mention because it is the first time that 10 sessions of tDCS was conducted during HD. No significant difference was found for socio-demographic and clinical variables at baseline between groups (Table 1). Patients were treated according to the guideline's recommendations for management of CKD and medication intake remained constant throughout the trial.

A mixed ANOVA model showed significant interaction between group and time on pain evaluated using NRS: F(4.112) = 3.106, *PP*= 0.01, partial $\eta^2 = 0.1$. Similarly, there were significant main effects of group F (1.28) = 4.881, $P = 0.03$, partial $\eta^2 = 0.14$ and time, F (4.112) = 6.339, $P = 0.0001$, partial $\eta^2 = 0.18$. Bonferroni showed a significant difference between groups in day 10 (mean difference: 3.13; $P = 0.001$) and 3rd follow-up (mean difference: 2.6; $P = 0.01$) (Fig. 2a). Sham group did not show significant differences in intragroup analyses. On the other hand, baseline NRS of active group differed significantly when compared with day 10 (mean difference: 3.55; $P = 0.0001$), 2nd follow-up (mean difference: 2.62; $P = 0.001$), and 3rd follow-up (mean difference: 3.69; $P = 0.0001$). When we compared baseline to 3rd follow-up, NRS in active group had a large reduction of 63.4% (sham reduction was 18.3%).

Table 1
Baseline Socio-Demographic and Clinical Characteristics Assessed one Week Before the First day of tDCS

Outcomes	Active-tDCS	Sham-tDCS	*P*value
Sex (female %)	86%	60%	0.10
Age	51.53 ± 12.03	56.67 ± 13.56	0.14
BMI	24.24 ± 5.10	25.14 ± 3.43	0.55
NRS	5.82 ± 2.29	5.79 ± 2.11	0.97
KQDOL-SF	11.91 ± 2.62	12.55 ± 2.43	0.49
HAS	16.13 ± 8.14	17.53 ± 7.42	0.62
BDI	9.73 ± 4.55	12.93 ± 6.84	0.14
Positive affect	21.67 ± 7.09	24.53 ± 11.64	0.42
Negative affect	18.67 ± 8.06	20.67 ± 10.30	0.55
Time of dialysis (month)	85.80 ± 66.63	51.53 ± 41.33	0.10
Numbers of catheters	2.13 ± 1.18	2 ± 1.25	0.76
Arteriovenous fistula (n)	2 ± 0.65	1.60 ± 0.98	0.18
Transplants	no	no	-
Comorbidities			
Hypertension	60%	80%	0.33
DM	26.7%	46.7%	0.3
Obesity	20%	20%	1.00
Fractures	46.7%	33.3%	0.49
MBD	73.3%	73.3%	1.00
Marital status			
Married	40%	40%	-
Never married	40%	26.7%	0.43
Widowed	0	26.7%	
Divorced	20%	6.7%	0.33
Education			
Elementary (incomplete)	13.3%	13.3%	-
Elementary	66.7%	66.7%	-
Secondary	20%	20%	-
University	0%	0%	-

Data described in mean and standard deviation. BMI = body mass index; NRS = numeric rating scale; KQDOL-SP = kidney disease quality of life short form; HAS = hamilton anxiety scale; BDI = beck depression inventory; DM = diabetes mellitus; MBD = mineral and bone disorder.

Diary of pain was assessed using mean difference between groups and calculated according to different periods of study (Fig. 2b). No difference was found between groups during 30 days before tDCS (mean difference: −0.02 ± 0.8; $P = 0.97$). Diary of pain showed significantly different pain perception between groups during the period of tDCS treatment (mean difference: 1.44 ± 0.5; $P = 0.02$), also after tDCS (1.81 ± 0.88; $P = 0.04$).

Fig. 2c shows total score of KQDOL-SF, and a significant difference in post-intervention was found for active group F(1, 27) = 4.153, $P = 0.05$, partial $\eta^2 = .013$. In addition, several KQDOL-SF domains including general health ($P = 0.03$), fatigue ($P = 0.05$) and symptoms ($P = 0.05$) significantly improved only for active group (Fig. 3). A significant difference between groups was found for analgesic (dipyrone) use after tDCS protocol with an improvement in active group (F[1.27] = 8.350, $P = 0.008$, partial $\eta^2 = 0.23$) (Fig. 3).

There was a statistically significant difference in post-intervention depression score between groups (F[1, 27] = 7.241, $P = 0.01$, partial $\eta^2 = .211$) with a decrease

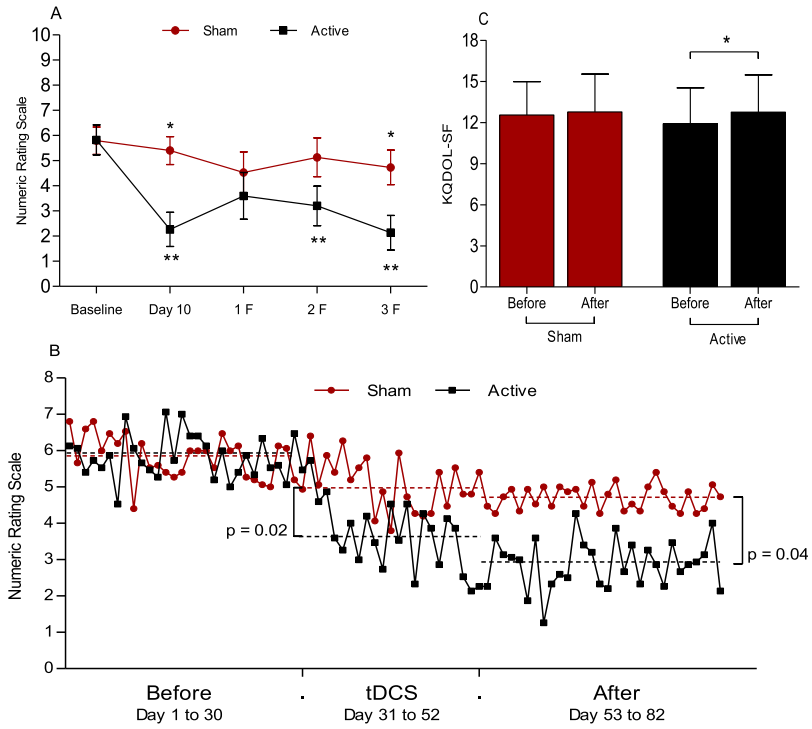

Fig. 2. a) Pain score using numeric rating scale (NRS). *Statistical analysis demonstrated significant result for day 10 ($P = 0.001$) and at F3 ($P = 0.01$) between tDCS group and sham group. **Denotes significant difference when compared with baseline only for active group. First follow-up (1F); Second follow-up (2F); Third follow-up. b) Total score of KQDOL-SP. *Significant difference in active group ($P = 0.009$). c) NRS diary with a total of 82 days. Dotted straight signifies means of each group. No difference between groups was found before tDCS ($P = 0.97$). The P value shows the difference between means in each different moment of the study.

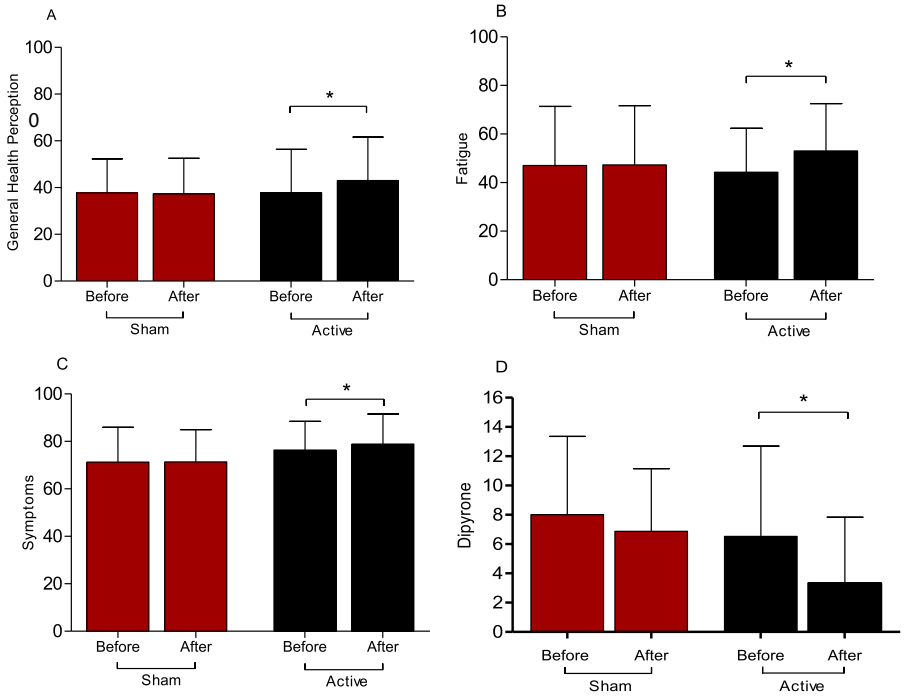

Fig. 3. KQDOL-SP domains. *Denotes significant results only in active group. a) General health perception ($P = 0.03$); b) fatigue (= 0.04); c) symptoms ($P = 0.03$); d) Dipyrone was measured throughout intervention in terms of dosing (1 tablet of 500 mg) and frequency of administration (baseline and on 3rd follow-up).

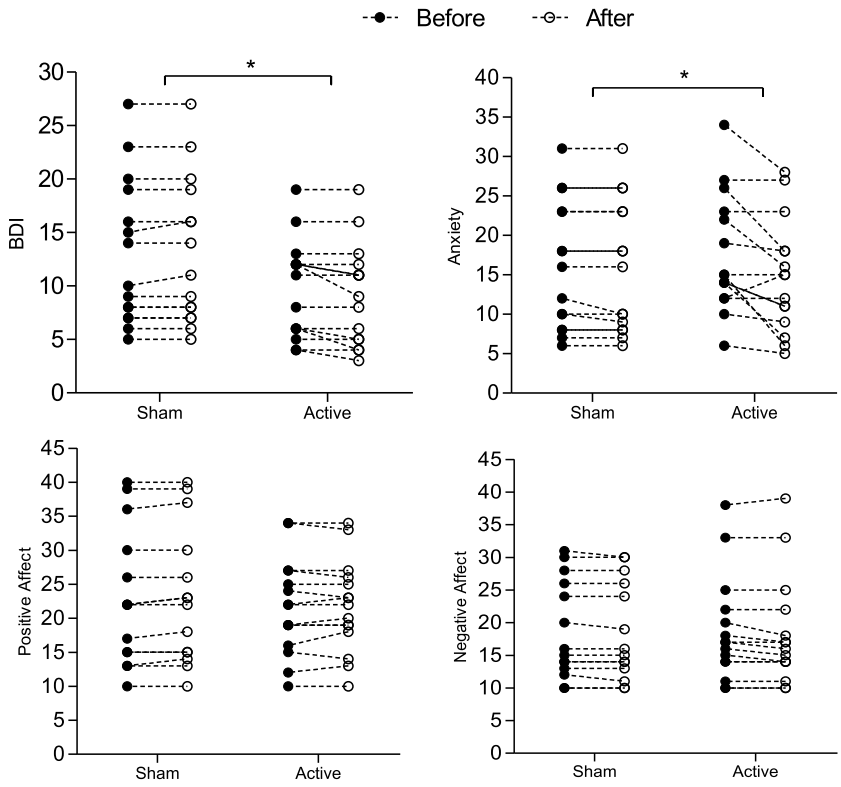

Fig. 4. Mood variables assessed before and after intervention. *Significance between groups (BDI: $P = 0.01$; Anxiety: $P = 0.01$). BDI: Beck Depression Inventory.

only in active group (mean difference: 0.72). Significant difference in post-intervention was found for anxiety (F[1, 27] = 7,198, $P = 0.01$, partial $\eta^2 = .21$) with a decrease only for active tDCS (mean difference: 2.51). No significant difference was found for positive affect F (1, 26) = 0.919, $P < 0.34$, partial $\eta^2 = .003$, and negative affect F(1, 26) = 1.591, $P < 0.21$, partial $\eta^2 = 0.005$ (Fig. 4).

Clinical biomarkers including hemoglobin (g/dL), Kt/V, potassium (meq/L), phosphorus (mg/dL), ferritin (ng/mL), calcium (mg/dL), and PTH (pg/mL) of the two groups of patients with CKD are shown in supplementary files (Tables A.1 and A.2). No differences were found for laboratorial parameters between groups.

Discussion

This is the first randomized controlled trial assessing the effects of tDCS on ESRD patients undergoing HD. It used a protocol of ten non-consecutive days of anodal tDCS over the M1 at 2 mA for 20 min. All baseline data were the same for both groups. Significant improvement in pain was found only in the active group which lasted for one month after tDCS, with a large reduction of 63.4%. QoL including general health, fatigue, symptoms, sleep quality, depression and anxiety improved after tDCS only in the active group. No significant difference in positive and negative affectivity was found for active group. These results suggest anodal M1-SO montage could be a good cost-effective approach for a non-pharmacological strategy to pain relief in ESRD.

Pain in ESRD patients has different origins ranging from direct result of an underlying kidney disease process and sequelae of pain associated with underlying systemic and comorbid diseases (peripheral vascular disease and musculoskeletal process).[29] No previously studies were found for tDCS in ESRD, but current evidence suggests tDCS for treatment of several chronic pain syndromes that include central neuropathic pain, peripheral neuropathic pain, and musculoskeletal pain.[13–15,20,22,30–32] Positive results were reported using anodal tDCS over M1 for migraine, fibromyalgia, and chronic chikungunya arthralgia, with pain relief usually defined by more than 30%–50%.[14,22] Different studies with tDCS in patients with osteoarthritis and spinal cord injury showed pain reduction with five and fifty daily sessions of stimulation respectively.[33,34] Our results find more than 50% of pain reduction, suggesting a strong clinical effect.[35] The results showed a mild placebo effect in sham group, but with no statistical

effect. This finding could be found in a several studies with this sham protocol.[13,14]

Anodal M1-SO tDCS may reduce pain by activating neural circuits present in the precentral gyrus involved in sensory or emotional components of pain processing.[36] Chronic pain in ESRD could be considered a neurological disturbance in the context of suffering for a long lifetime period with a possible adaptive neuroplasticity and functional reorganization of the pain neuromatrix.[37,38] Chronic pain in ESRD is an increasingly neglected clinical problem, and several studies have assessed adjunctive nonpharmacologic interventions including cryotherapy, transcutaneous electrical stimulation (TENS), and physical exercise.[2,38] However, cryotherapy and TENS seem to have only short-term effect on pain, and some ESRD patients do not have functional capacity to perform physical exercise.[37,39] In this context, tDCS could be applied during the HD session, with no treatment routine changes and with minimal adverse effects.

Other studies suggest a significant association between pain, depression, anxiety, poor QoL, and greater limitations in daily activities.[29,38,40] Our study showed a significant improvement in QoL and mood states assessed in the short-term effects of tDCS. Some authors suggest that the reduction in pain improves the functional activities of daily living, social interaction, and mood.[11,29,38,40] Studies reported that tDCS for chronic pain has a positive short-term effect on QoL and mood states including anxiety and depression.[11] Mu et al. showed an abnormal brain interaction between the affective and cognition control network in patients with ESRD.[41] tDCS could be a potential moderator of the affectivity network, depending on the site of stimulation.[42] Our study did not show significant effects on positive or negative affectivity in active tDCS group. Petrocchi et al. showed that the soothing positive affectivity was enhanced with a single session of anodal tDCS over the left temporal lobe (T3).[42] While the anodal M1-SO is the most common tDCS parameter for pain, other electrode montages including the stimulation of dorsolateral prefrontal cortex (DLPFC) or T3 was previously reported with significant effect on mood.[10,43] Thus, it was suggested that the improvement in depression and anxiety could be associated with pain reduction.[44] Future studies focused on mood disturbance in patients with ESRD could use other electrode montages targeting DLPFC. tDCS could be an important adjunctive nonpharmacologic intervention because the increase in drug use and the associated adverse effects may occur due to reduced renal clearance and accumulation of a toxic parent compound.[16] tDCS is a well tolerate therapy with mild adverse events (itching, tingling, skin redness, somnolence, concentration issues, headache, fatigue, light headedness).[45] Managing pain and mood in ESRD is often a challenge for all interdisciplinary teams that aim to promote better QoL and functionality for patients with ESRD.

Our study had limitations that need to be addressed in future studies. First, questionnaires were completed during the course of tDCS treatment (in three weeks and a half) and possibly a longer time of observation of QoL and mood states should be required. Second, the presence of medical staff and other patients may have influenced the questionnaire responses, but the patients' treatment routine prevented other approaches. Future research that includes ESRD patients not undergoing dialysis is required.

Conclusion

This preliminary study shows improvement in pain, QoL, depression and anxiety with 10 non-consecutive days of anodal M1-SO tDCS. These results encourage further clinical trials to access dose (montage, current, duration) optimization and long-term tDCS treatment (e.g., 15 or 20 sessions) not only for pain relief but also for cognitive function and physical performance. This novel approach brings new perspectives for an optimal, safe, and effective pain control in patients with ESRD undergoing HD.

Authors' contributions

AQ: conceptualization, planning, data collection, and writing of the manuscript. MB: writing of the manuscript and supporting data analysis. TO: planning, data collection. RP: data collection, conceptualization, planning, supporting data analysis and writing of the manuscript. GMK: conceptualization, planning and writing of the manuscript.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	3
	4b	Settings and locations where the data were collected	3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3,4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4,5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3,4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	3,4
	11b	If relevant, description of the similarity of interventions	3,4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	7,8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6,7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6,7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	6,7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10,11
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	https://ensaiosclinicos.gov.br/rg/RBR-7qk2cs
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.