BrJP
Brazilian Journal of Pain

ORIGINAL ARTICLE

Effect of transcranial direct current stimulation on pain and mood in end-stage renal disease patients: a randomized clinical trial

Efeito da estimulação transcraniana por corrente contínua na dor e humor de pacientes renais em estágio terminal: ensaio clínico randomizado

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Submitted on:
March 10, 2025.
Accepted for publication on:
May 9, 2025.
Conflict of interests:
none.
Sponsoring sources:
none.

Associate editor in charge:
Kátia Nunes Sá

ABSTRACT

BACKGROUND AND OBJECTIVES: Chronic kidney disease (CKD) is a significant public health concern. Patients affected by chronic kidney problems often experience symptoms, such as pain and mood disorders, while awaiting a transplant. Nonpharmacological interventions with no collateral effects are necessary for managing the symptoms. The objective of this study was to assess the effects of transcranial direct current stimulation (tDCS) on pain, anxiety, and depression in patients affected by CKD.

METHODS: This is a single-center, double-blinded, parallel, randomized sham-controlled clinical trial. The interventions consisted of ten non-consecutive sessions of anodal tDCS over the left dorsolateral prefrontal cortex and the cathode over the contralateral supraorbital region. Each session lasted 20 min with an intensity of 2 mA. This clinical trial included patients with CKD who experienced chronic pain and had been undergoing hemodialysis for more than three months. There were four assessments: at baseline, after the first and last intervention, and seven days after the last intervention (follow-up).

RESULTS: There was a significant interaction between group and time regarding pain (p=0.0005; partial η2 = 0.362) and a significant time interaction (p = 0.0005, partial η2 = 0.659) with significant differences between groups at day 10 (p= 0.004; partial η2 = 0.37) and follow-up (p= 0.03; partial η2 = 0.22). Additionally, there was a significant difference between groups for anxiety (p<0.02, partial η2= 0.258).

CONCLUSION: After ten sessions of tDCS, patients affected by chronic kidney disease showed a reduction in pain, anxiety, and depression.

KEYWORDS: Chronic pain, Hemodialysis, Neuromodulation, Noninvasive brain stimulation, Quality of life.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A doença renal crônica (DRC) é uma preocupação significativa de saúde pública. Pacientes com problemas renais crônicos frequentemente apresentam sintomas como dor e transtornos do humor enquanto aguardam um transplante. Intervenções não farmacológicas, sem efeitos adversos, são necessárias para o manejo desses sintomas. O objetivo deste estudo foi avaliar os efeitos da estimulação transcraniana por corrente contínua (ETCC) na dor, ansiedade e depressão em pacientes com DRC.

MÉTODOS: Trata-se de um ensaio clínico randomizado, controlado por placebo, paralelo, duplo-cego e conduzido em um único centro. As intervenções consistiram em 10 sessões não consecutivas de ETCC anódica sobre o córtex pré-frontal dorsolateral esquerdo, com o cátodo posicionado sobre a região supraorbital contralateral. Cada sessão teve duração de 20 minutos, com intensidade de 2 mA. O ensaio clínico incluiu pacientes com DRC que apresentavam dor crônica e estavam em hemodiálise há mais de três meses. Foram realizadas quatro avaliações: na linha de base, após a primeira e última intervenção e sete dias após a última intervenção (follow-up).

RESULTADOS: Houve interação significativa entre grupo e tempo em relação à dor (p=0,0005; η2 parcial=0,362) e interação significativa com o tempo (p=0,0005; η2 parcial=0,659), com diferenças significativas entre os grupos no dia 10 (p=0,004; η2 parcial=0,37) e no follow-up (p=0,03; η2 parcial=0,22). Além disso, foi observada diferença significativa entre os grupos quanto à ansiedade.

CONCLUSÃO: Após 10 sessões de ETCC, os pacientes com DRC apresentaram diminuição de dor, ansiedade e depressão.

DESCRITORES: Dor crônica, Estimulação cerebral não invasiva, Hemodiálise, Neuromodulação, Qualidade de vida.

HIGHLIGHTS

- Patients affected by chronic kidney disease often suffer from pain and mood disorders
- The study involved ten non-consecutive sessions of anodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex, with each session lasting 20 minutes at 2 mA
- tDCS provided significant reductions in pain and anxiety, with notable differences between groups at day 10 and follow-up assessments

INTRODUCTION

Chronic kidney disease (CKD) is a global public health challenge, often requiring hemodialysis or peritoneal dialysis for management[1]. It is estimated that CKD affects approximately 10% of the world's population[2]. The progression of CKD leads to end-stage renal disease, resulting in a significant decline in quality of life, and physical function[2], along with a high prevalence of chronic pain (CP)[3].

Patients undergoing hemodialysis for end-stage renal disease experience a high prevalence of CP, ranging from 50% to 80%[3]. CP in these patients is linked to several negative outcomes, including poor adherence to treatment, social isolation[4], as well as symptoms of depression and anxiety[3]. Additionally, CP is associated with functional and structural changes in brain regions involved in pain processing and nociception control[5] This suggests that patients with end-stage renal disease and CP may have alterations in pain modulation systems, including deficits in cognitive control of emotions and self-referential processing[6-8].

Transcranial direct current stimulation (tDCS) has emerged as a cost-effective, user-friendly, and safe strategy for managing pain and cognitive dysfunction in patients affected by CKD[8]. Various stimulation sites have been explored to identify the optimal target for neuromodulating pain. While the primary motor cortex is typically considered the most effective target for inducing neuroplasticity in CP patients, the evidence supporting it, is still limited[9]. As emotion and pain regulation are disrupted in patients with CP[10], and the dorsolateral prefrontal cortex is widely studied as a key target for modulating cognitive control of emotion[11], stimulating the dorsolateral prefrontal cortex could potentially lead to improvements in patients with CKD and CP.

The mechanisms underlying brain neuroplasticity induced by tDCS are intrinsically linked to factors, such as electrode positioning, polarity, duration, and intensity. It's important to note that the effects of tDCS on pain are not confined to specific electrode sites, as the pain neuromatrix within the central nervous system (CNS) is multifaceted and involves various regions[12]. According to the somatic doctrine theory, tDCS elicits changes in neurotransmitters, gate channels, soma, axons, and receptors distributed throughout the CNS[12]. Consequently, the tDCS application involves a complex interplay of physiological mechanisms.

The use of tDCS targeting the dorsolateral prefrontal cortex has been linked to the behavioral and affective control of pain. Additionally, tDCS is known to neuromodulate brain circuits involved in emotional pain regulation[11]. Given that CP in end-stage renal disease is often overlooked clinically, strategies that enhance pain management and mood are highly recommended[13]. Therefore, utilizing tDCS as a low-cost adjuvant therapy with minimal adverse effects could be beneficial for patients with end-stage renal disease undergoing hemodialysis and experiencing CP[8]. The present study's objective was to assess the effects of tDCS on pain, anxiety, and depression in end-stage renal patients.

METHODS

Study design and participants

This is a single-center, double-blinded, parallel, randomized-sham-controlled clinical trial, elaborated in accordance with CONSORT/2010 statement[14]. This study received approval from the local Ethics Committee at the Federal University of Rio Grande do Norte, Faculty of Health Science of Trairí, under opinion number 2.715.151. Registration was completed on the Brazilian Clinical Trials Platform with the identifier RBR-6fgnsqr. This study was carried out between August 2018 and November 2022 at the Santa Rita Clinic and the Kidney Institute in Rio Grande do Norte, Brazil. Due to the outbreak of Coronavirus Disease in 2019, this study was temporarily paused in 2021 in compliance with the Brazilian Health Ministry regulations.

Participants: inclusion and exclusion criteria, sample size, and randomization

Patients were recruited voluntarily through formal invitations extended by the researchers. Prior to participation, all patients signed the Free Informed Consent Term (FICT) in accordance with resolution No. 466/12 of the National Health Council and The Declaration of Helsinki. Eligible participants were those with end-stage renal disease undergoing hemodialysis who had previously been diagnosed with CP, as defined by the International Association for the Study of Pain[15,16].

Patients were included if they fulfilled the following inclusion criteria: 1) man or woman aged 18 to 75 years; 2) underwent hemodialysis (CKD 5D)[15] for >3 months (four-hour session); 3) experiencing CP (chronic musculoskeletal pain, chronic headache and/or chronic neuropathic pain) with a visual analog scale (VAS) score of more than 4 (on a scale of 1 to 10) for at least three months[16]; 4) be able to provide consent for treatment and understand study explanations and questionnaires. Patients were excluded if they had: 1) clinical contraindications to receive tDCS, such as having metal embedded in their scalp or brain; 2) a history of epilepsy or convulsions; 3) electrical implants in the body; 4) were pregnant; or 5) showed signs of severe disease and/or required hospitalization (hemodynamic instability, infection, acute myocardial infarction, or stroke).

The G-Power software 3.1.9.2 (Franz Faul, Universitat Kiel, Germany) calculated the sample size. A previous study with tDCS for pain in end-stage renal disease undergoing hemodialysis reported an effect size of 0.33 (according to Partial η2)[8]. A significance level of 0.05, a power of 90%, and an effect size of 0.33 was assumed. This calculation resulted in a total sample size of 18 participants. To account for potential dropouts without compromising statistical power, two additional patients were included, bringing the total recruitment to twenty patients. These patients were then randomly assigned to either the active tDCS (Active-G) or the sham tDCS (Sham-G) in a 1:1 ratio, as illustrated in Figure 1. Stratified randomization was performed according to the order of entry into the study to ensure balanced allocation over time. The website (www.random.org) assigned

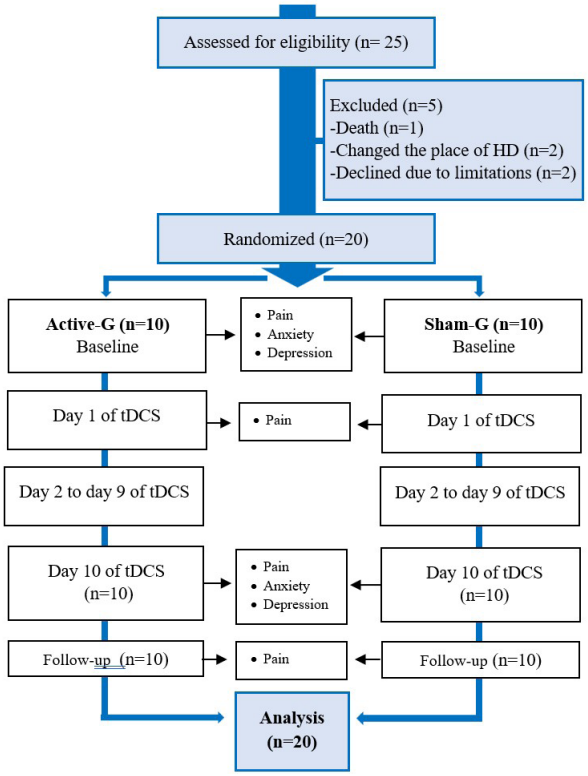

Figure 1. Flowchart of the study. Follow-up was conducted 1 week after the last day of intervention. HD = hemodialysis; tDCS = transcranial direct current stimulation; Active-G = active group; Sham-G = sham group.

each participant to the groups. An external assistant researcher, who was not involved in the data collection or analysis, was responsible for generating the random allocation sequence. To maintain allocation concealment, the assignments were placed in sequentially numbered, opaque, sealed envelopes. These envelopes were opened only after participant enrollment.

All steps of the randomization process including group assignment and envelope handling were performed by a blinded assistant researcher, ensuring that both participants and research team involved in the assessment process remained unaware of group allocation throughout the intervention period.

Assessment

An experienced physical therapist, blinded to the treatment allocation, conducted all evaluative procedures. The study comprised four phases: (1) one week before the first session (baseline assessment); (2) immediately after the first tDCS session (day 1); (3) immediately after the tenth tDCS session (day 10); and (4) one week after the final tDCS session (follow-up). At baseline, the clinical and sociodemographic information of the patients were assessed, including age, pain, anxiety, and depression levels, time of hemodialysis, gender comorbidities, marital status, and educational level.

The primary outcome, pain intensity, was assessed using VAS, a widely used tool for pain assessment across various populations[17]. VAS is a self-administered, unidimensional scale that measures pain intensity on a continuous line of 100mm, anchored by the verbal descriptors "no pain" (score of 0) and "worst imaginable pain" (score of 100)[17]. Participants were asked to indicate their current level of pain at four different time points: baseline, day 1 of tDCS, day 10 of tDCS, and seven days after the final tDCS session (follow-up).

The secondary outcomes included levels of anxiety and depression, which were assessed at baseline and on day 10 of the study. The Hamilton Anxiety Scale assessed anxiety. This scale is a self-scored questionnaire composed of 14 items divided into two groups of psychological and somatic symptoms[18]. Each item is scored on a numeric scoring of 0 (not present) to 4 (severe), with scores above 17 indicating mild anxiety and scores between 25 and 30 indicating moderate to severe anxiety[19]. Depression was assessed using the Beck Depression Inventory, which comprises 21 multiple-choice questions[20]. Scores on this inventory range from 0 to 63, with scores of 0-13 indicating minimal depression, 14-19 indicating mild depression, 20-28 indicating moderate depression, and scores above 29 indicating severe depression[20]. Participants were instructed to select the responses that best reflected their mood in the week leading up to the questionnaire administration.

The researchers conducted continuous evaluations of adverse events during and after tDCS interventions, in both groups. Itching, tingling, nausea, headache, and burning sensations under the electrode sites were monitored throughout the study. There were no changes in drug prescriptions, time of hemodialysis, or other clinical routine of the participants.

Intervention procedures

An experienced physical therapist administered ten non-consecutive sessions of tDCS, with three sessions per week (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday). The MicroEstim Genius stimulator (NKL, Santa Catarina, Brazil) delivered a monophasic continuous current at an intensity of 2 mA for 20 minutes per session. The anode electrode was positioned over the left dorsolateral prefrontal cortex (F3) and the cathode electrode over the contralateral supraorbital region (Fp2), according to international standards for the EEG 10–20 system. The electrodes were first placed into a 35cm2 sponge soaked in saline solution (154 mM NaCl, approximately 12 mL per sponge), and then attached to the scalp and secured with an elastic band. In the Active-G group, the stimulation began with a 30-second ramp-up, followed by 19 minutes of continuous stimulation, and concluded with a 30-second ramp-down. For the Sham-G group, the same parameters were used, but only the 30-second ramp-up and ramp-down were applied. This sham method creates a sensation similar to active stimulation and has been used in previous studies[8]. Throughout the study, patients remained blinded to their group allocation.

Statistical analysis

For statistical analyses, the Statistical Package for the Social Sciences (SPSS) software version 19.0 (IBM Corp., Armonk, NY, USA) was used. Means, standard deviations, and frequency tables described

the clinical and sociodemographic characteristics. The baseline comparison between groups for quantitative and categorical data was performed by the t-test and Chi-squared, respectively. Shapiro–Wilk and Levene's test assessed the normality of the distribution and homogeneity of variance, respectively. Mauchly's test of sphericity validated the correlation of the repeated measures. The Greenhouse-Geisser correction would analyze the data if the sphericity assumption was violated. The mixed analysis of variance model analyzed the effect of stimulation on VAS. The score of VAS was the dependent variable. The time of treatment (baseline, day 1, day 10, and follow-up), groups (active and sham), and time versus group interaction were the independent fixed variables. When appropriate, Bonferroni correction for multiple comparisons calculated post hoc comparisons. For the Hamilton Anxiety Scale and Beck Depression Inventory, ANCOVA calculated the effect of tDCS on post-intervention after controlling for pre-intervention. Partial η2 determined the effect size: η2 = 0.01 small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Statistical significance was set at $p \leq 0.05$.

RESULTS

Initially, a total of 25 patients were evaluated. Five individuals were excluded: one death, two for changing the center of hemodialysis, and two for losing interest in participating in the study. Thus, 20 patients were selected and included. Table 1 presents the baseline clinical and sociodemographic characteristics of the participants. There were no significant differences between groups at baseline for any clinical variables.

Figure 2 shows a significant interaction between group and time on pain, F(3.54) = 10.220, p=0.0005, partial η2 = 0.362. Also, there is a significant time interaction, F(3.54) = 34.787, p=0.0005, partial η2 = 0.659. It is possible to identify a decrease in pain over time, however, in a different intensity between groups. When

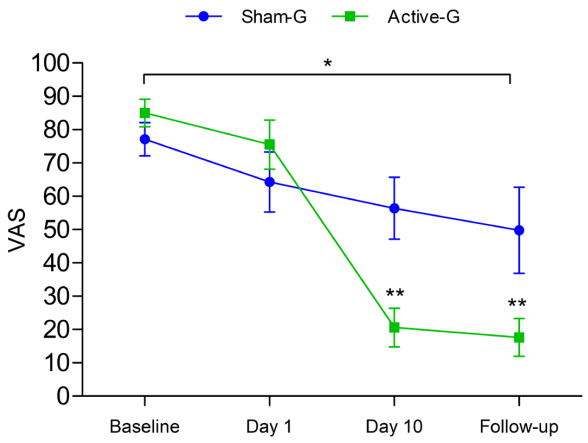

Figure 2. Visual Analog Scale, timeline between groups (Mean/SE). *Denotes significance time vs group interaction. **Denotes significant difference on the respective day between groups.

Table 1. Sociodemographic and clinical characteristics of the study groups.

Variables	Sham-G (n = 10)	Ative-G (n = 10)
Age (years)	55.20 ± 18.75	59.80 ± 8.31
VAS	77.1 ± 15.77	85 ± 13.01
HAS	16.1 ± 9.8	19.5 ± 7.35
BDI	12.1 ± 9.41	15.5 ± 6.24
Time of HD (month)	69 ± 75.73	80 ± 81.24
Gender (female %)	50%	50%
Comorbidities		
Hypertension	90%	100%
Diabetes	50%	70%
Obesity	10%	10%
Marital status		
Married	50%	30%
Single	20%	40%
Widowed	10%	10%
Divorced	20%	10%
Not respond	0%	10%
Education		
Elementary (incomplete)	40%	40%
Elementary	50%	30%
Secondary	10%	20%
University	0%	10%

VAS = Visual Analog Scale; HAS = Hamilton Anxiety Scale; BDI = Beck Depression Inventory; HD = hemodialysis.

comparing the VAS at baseline to follow-up, active-G decreased by 79.3% and Sham-G group by 35.4%.

Table 2 shows the Active-G intragroup analysis with Bonferroni adjustment. It shows a significant difference when comparing the visual analogue scale at baseline to day 10 (p = 0.0005) and follow-up (p = 0.0005). For Sham-G, there was a significant difference between the VAS at baseline and follow-up (p = 0.04).

Table 3 shows the intergroup analysis. It is possible to observe a significant difference between groups at day 10 (p = 0.004; partial η2 = 0.37) and follow-up (p = 0.03; partial η2 = 0.22).

Figure 3A illustrates the anxiety levels analysis. There was a significant difference between groups F (1, 17) = 5.915, p < 0.02, partial η2 = 0.258 with a 95% confidence interval of 0.400; 5.641.

Figure 3B shows the depression analysis. There was a tendency of decrease F (1, 17) = 4,426, p = 0.05, partial η2 = 0.207 with a 95% confidence interval 0.007-5.329. In Active-G, nine patients improved anxiety and five improved the depression symptoms. Also, in Sham-G, four people and one person improve anxiety and, depression, respectively.

During the research, there were no critical clinical problems related to hemodialysis. All the patients completed the treatment

Table 2. Comparison of visual analogue scale at baseline to day 1, day 10 and follow-up.

Groups	Time		Mean difference	SE	p-value	95% confidence interval	
						Lower bound	Upper bound
Sham-G	Baseline	Day 1	12.80	7.57	0.65	-9.64	35.24
		Day 10	20.70	7.02	0.052	-0.12	41.52
		Follow-up	27.30	9.08	0.046	0.37	54.22
Active-G	Baseline	Day 1	9.50	7.57	1.000	-12.94	31.94
		Day 10	64.40	7.02	0.0005	43.58	85.22
		Follow-up	67.40	9.08	0.0005	40.47	94.32

SE = Standard error.

Table 3. Between groups comparison of visual analogue scale at baseline, day 1, day 10 and follow-up.

Time	Mean difference	SE	p-value	95% confidence interval	
				Lower bound	Upper bound
Baseline	7.90	6.46	0.23	-5.68	21.48
Day 1	11.20	11.66	0.35	-13.30	35.70
Day 10	-35.80	10.95	0.004	-58.80	-12.79
Follow-up	-32.20	14.13	0.03	-61.88	-2.51

SE = Standard error.

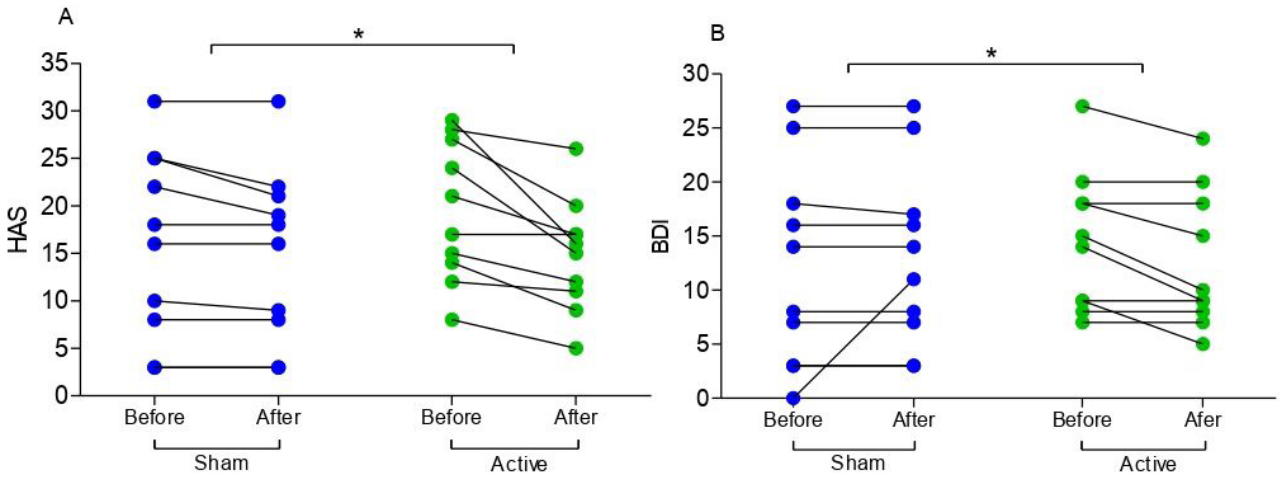

Figure 3. (A) Hamilton Anxiety Scale (HAS) showing statistical difference between groups. (B) Beck Depression Inventory (BDI). *Denotes p ≤ 0.05.

and evaluation protocols. Only adverse effects of clinical routine related to hemodialysis were detected, such as hypoglycemia, hypotension, fatigue, cramps, headache, muscle pain, and hemodynamic instability. Patients tolerated tDCS well and reported a few adverse effects, such as itching and tingling. Any clinical intercurrences related to hemodialysis were treated according to the protocols of the clinic and by the evaluation of the medical team on duty.

DISCUSSION

This study aimed to evaluate the effect of 10 sessions of anodic tDCS over the dorsolateral prefrontal cortex on pain, anxiety, and depression in end-stage renal disease patients undergoing hemodialysis. The study showed significant improvement for all outcomes, suggesting that the tDCS montage chosen could be a promising strategy for the treatment of CP and mood disorders for this population. The use of non-invasive brain stimulation in patients with CKD is a new area of study. So, it is important to emphasize the promising initial findings of tDCS intervention. This is the second study elaborated by using tDCS in end-stage renal disease patients and the first with this electrode assembly[8].

The effects of anodal tDCS using the C3/Fp2 montage in patients with end-stage renal disease led to significant improvements in pain, quality of life, and mood. When targeting pain treatment, anodal stimulation over the primary motor cortex (M1) emerges as the optimal choice. However, determining the most effective treatment target should be based on individualized considerations[21]. The pathophysiology of painful syndromes and the prevalence of severe mood disorders are frequently linked in fibromyalgia patients[22], a perspective that applies similarly to those with end-stage renal disease. The association between CP and mood disorders also holds true in end-stage renal disease patients[23-26].

It is important to mention that the dorsolateral prefrontal cortex may be involved in the upregulation of negative emotional outcomes, commonly shown in end-stage renal disease patients[27]. Patients with end-stage renal disease undergoing hemodialysis have a high prevalence of CP (with moderate to severe intensity) and mood disorders, such as depression, anxiety, and loss of cognitive function[28,29]. Also, the dorsolateral prefrontal cortex is associated with the regulation of psychological symptoms and emotional pain through a top-down mechanism in brain circuits related to pain volume[30]. Neuroimaging studies suggest that the dorsolateral prefrontal cortex alters functional activation and connectivity of brain areas that include cortical-striatal and limbic circuits[27]. Thus, cortical neuromodulation could interfere with subcortical structures, including the amygdala, nucleus accumbens, and cingulate[27]. These brain areas are involved in the balance of the volume of pain and emotional processing[27,30].

The dialysis session could be a trigger to intensify pain because of the imbalance of electrolytes[26]. Specific pain-relief protocols during the dialysis session must be encouraged to improve the quality of the treatment and the global symptoms (fatigue, anxiety, nausea, and global distress)[26]. Therefore, tDCS emerged as an easy-to-use, safe, and low-cost adjuvant non-pharmacological intervention to treat pain and mood disturbance during hemodialysis.

Some limitations must be acknowledged and addressed in future clinical trials. First, this trial was conducted during the COVID-19 outbreak period. So, the data collected needed to stop according to Brazilian Health Minister law. Second, to reduce contact with participants, no physical tests were performed, but future studies could assess aerobic capacity, physical function, strength, and mobility. Third, the results of this trial might be biased due to the limited sample size, but the clinical findings and statistical tests demonstrate the effect of the interventions. Future work is required to determine the effect of anodal tDCS over the dorsolateral prefrontal cortex over a long follow-up (more than three months) and the optimal dose for pain improvement.

CONCLUSION

tDCS over the dorsolateral prefrontal cortex in patients affected by chronic CKD generated improvements in pain after ten sessions and the effects lasted for one week later (follow-up). Also, tDCS improved anxiety and depression symptoms after ten sessions.

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