ORIGINAL ARTICLE

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Randomized clinical trial on the efficacy of a new transcranial direct current stimulation (tDCS) device in the treatment of depression: a low-cost option for developing countries?

Ensaio clínico randomizado sobre a eficácia de novo equipamento de estimulação transcraniana por corrente contínua (ETCC) no tratamento da depressão: uma opção de baixo custo para países em desenvolvimento?

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ABSTRACT

Objective: Verify the clinical efficacy and safety of a low-cost tDCS device, in a clinical trial for major depressive disorder. **Methods:** 168 persons were recruited; 32 depressed individuals with moderate or severe depressive symptoms (HDRS17 scores higher than 18) were included and randomized for the trial (16 individuals in each group). The intervention consisted of 10 active anodal tDCS sessions at 2 mA for 30 minutes over the left dorsolateral prefrontal cortex; or sham. The main outcome was HDRS17; secondary outcomes included satisfaction (TSQM II) and quality of life (WHOQOL-BREF). Assessments at baseline, endpoint and at 30 days follow-up. **Results:** The sample was composed by a total of 11 men and 21 women, mean age of 42.75 years (95% CI: 38.10-47.40). Active treatment was superior than sham: There was a significant interaction between group and time regarding HDRS-17 scores (F = 4.089, df = 2, p = 0.029; partial Eta squared = 0. 239). Post hoc analyses exhibited a statistically significant difference between active and sham group symptoms after a 30 days follow-up (difference = -7.75, p = 0.008, Cohen's d = 1.069). There were 3 dropouts, all in the active group, due schedule issues. No severe adverse effects reported. **Conclusion:** The current active tDCS protocol was related with clinical improvement of depressive symptoms. Intervention was well-tolerated. Non-invasive brain stimulation techniques are still not routinely used, although a viable strategy for treatment-resistant patients, partial responders and people unable to use pharmacological treatment. We aim to increase knowledge and use of tDCS for the Brazilian population.

KEYWORDS

Neuromodulation, transcranial direct current stimulation, major depressive disorder.

RESUMO

Objetivo: Testar a eficácia clínica e a segurança de equipamento de estimulação elétrica transcraniana por corrente contínua (ETCC) de baixo custo em ensaio clínico para transtorno depressivo maior (TDM). **Métodos:** Foram recrutadas 168 pessoas e incluídos e randomizados 32 indivíduos com depressão moderada ou grave (escores na HDRS17 >18; 16 indivíduos em cada grupo). A intervenção consistiu de 10 sessões de ETCC ativa a 2 mA no córtex pré-frontal dorsolateral esquerdo por 30 minutos, ou *sham*. O desfecho principal foi HDRS17; os desfechos secundários foram satisfação (TSQM II) e qualidade de vida (WHOQOL-BREF). Avaliações no início, no final do tratamento e após 30 dias de seguimento. **Resultados:** A amostra foi composta de 11 homens e 21 mulheres, com idade média de 42,75 anos (IC 95%: 38,10 a 47,40). O tratamento ativo foi superior ao *sham*: houve interação significativa entre grupo e tempo em relação aos escores de HDRS17 na ANOVA (F = 4,089, df = 2, p = 0,029; *partial Eta squared* = 0,239). A análise *post hoc* mostrou diferença significativa na HDRS17 no *follow-up* após 30 dias (diferença = -7,75, p= 0,008, Cohen's d = 1,069). Houve 3 *dropouts*, todos no grupo ativo, devido a problemas de agenda. Não houve registro de efeitos adversos graves. **Conclusão:** O tratamento ativo teve relação com melhora clínica de sintomas depressivos. A intervenção foi bem tolerada. Técnicas de estimulação cerebral não invasivas ainda não são rotina na prática clínica, apesar de estratégias viáveis para pacientes resistentes a tratamento, respondedores parciais e pessoas com intolerância a medicamentos. Esperamos ampliar o conhecimento e o uso de protocolos de ETCC na população brasileira.

PALAVRAS-CHAVE

Neuromodulação, estimulação elétrica transcraniana por corrente contínua, transtorno depressivo maior.

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INTRODUCTION

Mood disorders are the leading causes of disability and morbidity worldwide, constituting the third main cause of the total world burden of diseases[1,2]. Prevalence of major depressive disorder (MDD) in 12 months varies across countries, being estimated to be around 6%, and a lifelong risk for the disorder ranging from 15% to 18%[1]. Although there were important advancements in treatment options, we still face high rates of treatment-resistant patients (25%-30%) and partial responders, who keep significant symptoms[3,4].

Since 1938, brain stimulation, represented by electroconvulsive therapy (ECT), is used as routine psychiatric treatment[5,6]. Less invasive and more accessible options began to flourish in both research and clinical practice after the 1980s, like transcranial magnetic stimulation (TMS) in 1985 by Barker and cols.[7]. More recently, since 1998, a new modality of brain stimulation, using low intensity direct currents (1-4 mA), has emerged[6,8]. Transcranial direct current stimulation (tDCS) is a simple noninvasive method in which a weak electrical current is applied to the cerebral cortex, resulting in short-term changes in membrane potential and lasting changes in neuronal excitability in the underlying cortical regions[6,8].

In contrast to TMS, tDCS is not capable of eliciting an action potential *per se*, but increases the chances of spontaneous ones[6,9-12]. The constant electric field produced by tDCS therapy displaces all polar molecules and could have the same effect over most of the neurotransmitters and receptors in the brain, which have electrical polarity, resulting in neurochemical and functional changes[6]. In major depressive disorder, neuroimaging and neurophysiology studies suggest relative hypoactivity of the left dorsolateral prefrontal cortex (LDLPFC) and hyperactivity of this same region on the right side; therefore, the most common treatment scheme for these patients is 2 mA of anodal stimulation over the LDLPFC and cathodal over the right dorsolateral prefrontal cortex (RDLPFC) or the right supraorbital area for 30 minutes[13,14]. In a recent meta-analysis on tDCS for depression, Wang assessed clinical trials from 2012 to 2018, and in a pooled analysis of 623 subjects found positive results in Montgomery-Asberg Depression scale (Z test global effect = 4.75, Hedges' g = 0.61, ($p < 0.00001$), and for the Hamilton Depression Scale (HDRS17, Z test global effect = 5.20, Hedges' g = 0.58, ($p < 0.00001$)[15].

Based on previous results and experience in the field, this study aimed to test clinically a Brazilian transcranial direct current stimulation device (tDCS), developed by the researchers[2]. Our main goals were to check the safety and effectiveness of the tDCS device. There are currently six devices cleared for market by the Brazilian Health Regulatory Agency (Anvisa): Soterix®, Neuroconn®, Neurostim®, MicroEstim®, Quark® and the Flow Headset®.

METHODS

Overview

The study was conducted at Faculty of Medical Sciences of Santa Casa de Sao Paulo, São Paulo, Brazil from July 2017 to April 2018 and July 2019 to March 2020. Device design and assembling of the first functional prototypes were conducted in 2016 and 2017 and clinical approval was granted in 2018[2]. The novel device was designed and assembled following Brazilian standards for medical electrical equipment: ABNT NBR IEC 60601-2-10:2014. A prototype was developed based on micro controlled circuit[16-19]. The first prototype, although simple, was 100% digitally controlled, and could stimulate at 1 or 2 mA for 20 or 30 minutes[2] (Figure 1). Lacking features were incorporated in a second phase of development, in partnership with a medical industry (Medsupply, Brazil), resulting in a new device, tested and approved by Anvisa for clinical use. This final version can deliver up to 3 mA, reads and displays in real time dynamic impedance and current in mA, and has a totally blind sham mode (Figure 1).

The study was approved by the Institutional Review Board of the Faculty of Medical Sciences of Santa Casa de Sao Paulo and by the National Commission on Ethics in Research (CAAE no 53160116.2.0000.5479), all procedures were conducted in accordance with the Declaration of Helsinki and reported according to CONSORT/2010 guidelines (Table 1). The clinical trial has the universal register UTT U1111-1197-0629 and was submitted to the German Clinical Trials Register/DRKS – Deutsches Register Klinischer Studien under register DRKS00012525. Written informed consent was obtained from all participants.

Figure 1. Display view of research prototype (left) and final version (right).

Study design

This is a double-blind, randomized, sham-controlled trial. Patients were randomized into two groups; active tDCS (LDLPFC anodic protocol) or sham tDCS. The chosen

randomization strategy was the block randomization method, designed to randomize participants into groups that result in equal sample. Randomization process was performed with a randomization generator (www.randomization.com). Randomized participants as well as the main evaluator were blinded.

Volunteers were recruited through press and social networks, internet, local flyers and medical referral. 168 individuals were assessed for eligibility. Were included volunteers between 18 and 69 years old with severe MDD, clinically assessed by a trained psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), additionally using the Mini Neuropsychiatric Interview (MINI 5.0.0 – Brazilian version) and the 17-item Hamilton Depression Rating Scale (HDRS-17)[20-22]. The cut-off on HDRS-17 for inclusion was defined as a score ≥ 19[20]. Patients could be on pharmacological treatment provided that on a steady dose for the last month before the first stimulation session and were asked to remain on the same dose until follow up evaluation.

Exclusion criteria were personality disorders; bipolar disorder; other types of depression; inability to consent; changes in medication within 30 days prior to assessment; brain stimulation within 6 months prior to assessment; imminent suicide risk; dementia; substance use disorders; unstable clinical illness; and a higher daily intake than an equivalent benzodiazepine dose of 10 mg of diazepam. For sample size prediction, we adopted an alpha level of 0.05, a power of 80%, and a minimal significant reduction of three points on the HDRS-17, based on the effect size of a previous work of one of the authors[23].

Assessment

Patients were assessed by a trained professional at three points; baseline, endpoint, 30 days after the first session (follow-up). Primary outcome was the mean difference in the 17-item investigator-rated HDRS-17 at endpoint and follow up. Response to treatment was defined as 50% decrease in HDRS17 from baseline and a remission threshold of 7 or less was adopted[20].

Secondary outcomes were satisfaction assessed by the *Treatment Satisfaction Questionnaire for Medication – version II* (TSQM II)[24], quality of life measured by the Brazilian version of the short version of the World Health Organization Quality of Life instrument (WHOQOL-BREF)[25,26]. Safety was assessed by a common side effects related to tDCS questionnaire (available as supplemental material) and by a cognitive function evaluation assessed by the Montreal Cognitive Assessment (MoCA)[27].

The number of failed previous treatments were assessed using an index proposed by the author, calculated as follows: 1 point for each treatment failure; 0.5 point for each potentiation tried; 3 points for ECT failure.

Intervention protocol

Experimental protocol was based on similar trials in the literature, consisted of a daily 30 minutes stimulation session[28]. Ten sessions were performed over the course of two weeks. Stimulation was delivered using 2 mA and with anodal placement over the LDLPFC (F3 position – 10-20 EEG standard) and cathode placement over the right supraorbital area Sponge electrodes measuring 25 cm^2 (5 x 5 cm) soaked in saline solution were used and held in position by an elastic headband.

For sham stimulation, the same montage was used and the device was turned off after 15 seconds of real stimulation, being set on again at the end of 30 minutes of silence, to allow a realistic experience for the sham group.

Statistical analysis

We analyzed data from the full intent-to-treat sample using repeated measures analysis of variance (ANOVA) with treatment as the between-subject factor and time as the within-subject factor.

Normal distribution of dependent variables was assessed before analysis using the Shapiro Wilk test. Changes in HDRS17 scores across groups over time (baseline, endpoint, and follow up) were analyzed using ANOVA. Categorical fixed effects were group assignment (active vs. sham stimulation). To analyze the mean differences for secondary endpoints, t-tests were applied. To analyze the distribution of categorical variables (response and remission rates), chi-squared tests (χ^2) were used. All tests were performed using SPSS®. The significance level was set at $p \leq 0.05$.

RESULTS

One hundred sixty-eight volunteers were assessed and thirty-two participants were included. Most exclusions occurred due to overuse of benzodiazepines and recent changes in antidepressant doses (less than 4 weeks). The included sample consisted of 11 (34.4%) men and 21 (65.6%) women, with a mean age of 42,75 years old (95% CI: 38.10 to 47.40), most of them educated (93.75% had high school level and 62.5% with college education), 53% married and 75% self-declared white. There were no statistical differences between groups regarding these variables at baseline. There were 3 dropouts, all in the active group: 2 failed to comply with the schedule and one elderly was suspended due to risks related to SARS-CoV-2. Recruitment had to be halted in March 2020 due to

COVID-19 pandemic and our group decided to terminate the trial to ensure the safety of the volunteers. We followed CONSORT guidelines as presented in Table 1.

Regarding failure on previous treatments, the sample had a mean score of 1.95, with no differences between groups. However, we did not use a validated instrument to assess treatment-resistant depression, and this is just an indicative of treatment failures.

Primary outcome – HDRS17

The present study found an improvement in depressive symptoms over time, with differences between groups for HDRS17 scores favoring the active tDCS group. Multiple measures ANOVA has shown a significant interaction between group and time regarding HDRS17 scores (F = 4.089, df = 2, p = 0.029); partial Eta squared (η^2) was 0. 239, indicating a large effect size (small = 0.01; medium = 0.06; and large = 0.14)[29]. Mean differences between groups on baseline was -0.851 (95% CI: -3.07 to 1.36); after treatment was -5,163 (95% CI: -11.53 to 1.20); and on follow up was – 7.755 (95% CI: -13.31 to -2.19) – see Table 2 and Figure 2. The univariate F tests for each point of the measure in time, based on linearly independent pairwise comparisons among the estimated marginal means for HDRS17, found statistical significance only for follow up (F = 8.191, df = 1; p = 0.008, power = 0.788 - Table 3). Cohen's d for mean difference at follow up was 1.069. The rates of remission and response can be seen on Table 4.

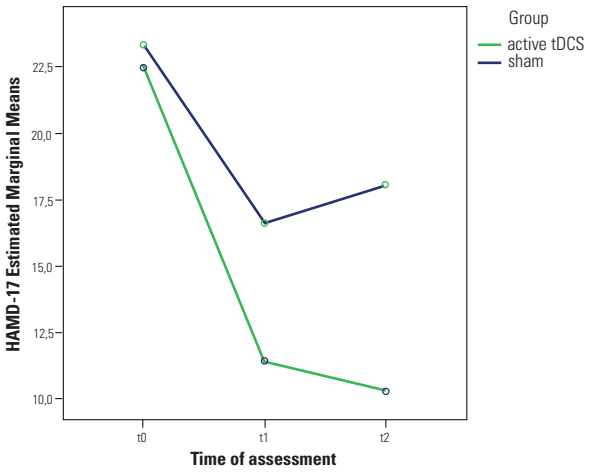

Figure 2. Hamilton Depression Scale (HDRS17) mean scores per group over time.

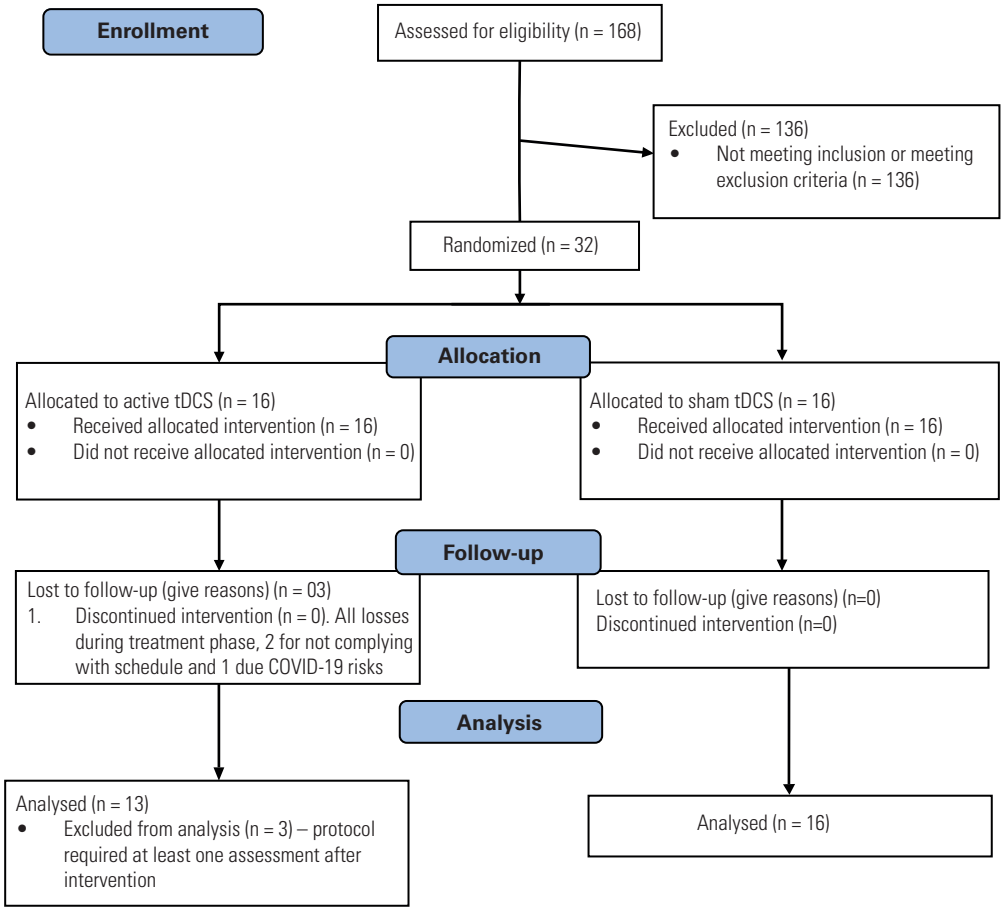

Table 1. CONSORT 2010 Flow Diagram[1].

[1] http://www.consort-statement.org/

Table 2. Means on Hamilton Depression Scale (HDRS17), by group at each assessment

Group	Time	Mean	95% confidence interval	
			Lower limit	Upper limit
Active tDCS	Baseline	22.462	20.813	24.110
	Endpoint	11.462	6.732	16.191
	Follow-up	10.308	6.178	14.437
Sham	Baseline	23.313	21.826	24.799
	Endpoint	16.625	12.362	20.888
	Follow-up	18.063	14.340	21.785

Table 3. Univariate F tests for each point of measure of Hamilton Depression Scale (HDRS17) in time based on the linearly independent pairwise comparisons among the estimated marginal means of each group (sham versus active tDCS)

Time	Mean difference between groups	Lower limit	Upper limit	Sum of squares	df	F	Sig.	Power
Baseline	-0.851	-3.07	1.36	5.194	1	0.619	0.438	0.118
Endpoint	-5.163	-11.53	1.20	191.226	1	2.768	0.108	0.361
Follow-up	-7.755	-13.31	-2.19	431.328	1	8.191	0.008	0.788

Table 4. Response (50% decrease from baseline) and remission (HDRS17<=7) rates for Hamilton Depression Scale (HDRS17) at the endpoint and 30 days follow-up

	Active tDCS (13 subjects)	Sham (16 subjects)	df	Pearson $\chi 2$	Sig. (2 tail)
Response at endpoint	69.2%	25.0%	1	5.673	0.017
Response at follow-up	61.5%	18.8%	1	3.908	0.048
Remission at endpoint	30.8%	25.0%	1	0.120	0.730
Remission at follow-up	30.8%	6.3%	1	3.022	0.082

Secondary outcomes

No statistically significant difference was found regarding side effects or treatment satisfaction between groups. A screening tool for common side effects was used, encompassing nine questions and a maximum score of 36 (available as supplemental material); at the endpoint, the active group scored 16.15 (±3.80) and control group scored 15.50 (±3.79), t-test = -0,368 p = 0.716. Side effects were mild, and the most common were itching on stimulation site, headache and local erythema. Treatment satisfaction and adverse reactions at endpoint were assessed using TSQM II scale, ranging from 0-100 possible points; active group scored 51.23 (±9.61) and control group scored 43.23 (±11.51), t-test = 0,461; p = 0.649.

Regarding quality of life, WHOQOL-BREF includes 4 domains: physical health, psychological, social relationships and environment. We found no differences between groups at any time (respective total scores for active and sham groups: baseline = 35.99/32.98; endpoint = 46.56/45.57; and follow-up = 49.51/43.86; F = 0.586, df = 2, p = 0.564.

DISCUSSION

Our novel low cost tDCS protocol was effective and safe on treating volunteers with MDD. The protocol was well tolerated and no severe adverse effects were reported.

The clinical trial consisted of treating at least moderate major depressive disorder, considering that there is sufficient literature supporting this use, allowing to compare results[13,30]. A recent guideline and secondary Meta-Analysis included 18 clinical trials on tDCS use for MDD; of those, half (9) had negative results for active stimulation. However, in most of these studies with negative results, both groups improved, probably due to an active control group, such as therapy, electroconvulsive therapy or a sham stimulation that was biologically active[28].

All parameters such as intensity of stimuli, length of stimulation, site of stimulation and number of sessions impact for optimal results, and still need to be well established for each clinical group[28]. Treatment resistant MDD appears to have less benefit with this technique[28].

Figure 2 shows a decrease of HDRS17 scores from baseline to endpoint in both groups, though more pronounced in the active group. After 30 days (follow up), the difference between groups increases due to additional improvement in the tDCS group and a discrete worsening in the sham group, and a statistically significant interaction of the group over time was found for HDRS17 (p = 0.029). Univariate analysis detected that the difference between groups was significant only at the endpoint (p = 0.008; Cohen's d = 1.069), and the statistical power reached 79%. The number of previous treatment failures did not predict tDCS response or remission rates. These results can be compared to a previous trial by the first author and to the already cited meta-analysis by Wang, although tending to be overestimated due to the sample size and power[15,23]. There were problems to carry on the research from March 2020 on due the outbreak of COVID 19 pandemic, requiring a full halt of the study, for safety reasons. From the originally included 32 individuals, 29 completed the trial.

As shown in Table 4, there were significant differences between groups both at endpoint and follow up for response. An additional improvement detected after 30 days could be a carry-on effect of stimulation mediated by neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and activation of glutamathergic pathways via N-methyl-D-aspartate receptors (NMDA)[6,31,32]. These effects could improve synapses, changing the expression of membrane receptors and long-term potentiation and depression in pathways related to depressive disorder, leading to lasting neuroplastic changes[31,33].

Regarding quality of life, we acknowledge that a short-term intervention may be unable to modify social, physical and environmental aspects of life. Perhaps WHOQOL-BREF is not the best instrument to measure improvement in short-term interventions, constituting just an illustration of quality of life status of this sample. In the literature, there are few clinical trials of MDD treatment using WHOQOL-BREF as an outcome measure. In a sample of patients with treatment-resistant depression, the mean score on this scale was 42.33; therefore greater than our baseline scores in active (35.99) and sham (32.98) groups. In the few studies found using WHOQOL-BREF after an intervention for MDD, follow up was longer, and quality of life increased over time for treated patients[34,35].

Non-invasive brain stimulation techniques are still not routine in clinical daily practice, maybe for lack of knowledge, lack of experience, and difficulties in access. They can be an option for non-responders, partial responders, persons sensitive to side effects and special populations, such as pregnant women[30,36-38]. The synergic use of tDCS with antidepressants could make a difference and reduce 50% of depressive symptoms in a short period with an easy to use technique. A recent meta-analysis by Fregni *et al.* concluded that "anodal left DLPFC tDCS is definitely effective for treatment of depression in MDD (Level A)", with pooled effect size of −0.36 (−0.66, −0.06)[28]. However, the variability of tDCS response should still be investigated.

The objective to reduce tDCS devices costs was achieved. The Neurostim® and similar national devices cost less than $850,00 dollars – a fraction of imported devices, sold in Brazilian market for over $5000,00 dollars. Using a research grant from the Brazilian National Research Council, devices were produced and sent free of charge to research centers.

Comparatively, Transcranial Magnetic Stimulation or Electroconvulsive Therapy have a higher cost per treatment, requiring special infrastructure, larger and trained teams and more expensive devices. tDCS could be used in primary care and outpatient psychiatric clinics by trained doctors, nurses, physiotherapists or psychologists as a low cost, safe and simple intervention for depression and other neuropsychiatric conditions. One device has a potential to treat more than 10 patients a day, and could be an option for non-complicated cases or as a backup, considering the intermittent interruption of supply of antidepressant drugs for distribution in the Brazilian public health system. Assessment of cost-effectiveness and applicability of tDCS technique in the Brazilian public health system should be addressed by the National Committee for Health Technology Incorporation (Conitec – Ministry of Health), considering these remarks.

Limitations

We acknowledge the limitation of the sample size and that the 3 dropouts observed in the active group are also a source of bias for the sample. Additionally, in our study all subjects were under pharmacological treatment, and the results should be a combined effect in a "real world" approximation[39].

CONCLUSION

We found the current low-cost-tDCS device to be effective for ameliorating depressive symptoms. The device was safe, trustworthy, easy to use and well tolerated. Clinical utility of a new low-cost device was proven, with results in accordance with most previous clinical trials and meta-analysis[9-11,14,15,23,28,30,39].

We hope that our study helps to expand tDCS depression treatment protocols use within the Brazilian population.

INDIVIDUAL CONTRIBUTIONS

Rafael Bernardon Ribeiro – Conceptualization (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead).
Marcelo Bruno Generoso – Conceptualization (lead); investigation (equal); methodology (equal); writing-original draft (equal).
Ivan Trombino Taiar – Investigation (equal); project administration (equal); writing-original draft (equal).
Ana Elisa De Conti Lord – Investigation (equal).
Geraldo Teles Machado Netto – Investigation (equal).
July Silveira Gomes – Investigation (equal).
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Mara Fernandes Maranhão Girão – Investigation (equal).
Maria Augusta Azevedo de Araujo – Investigation (equal).
Samuel Araújo Leite da Silva – Investigation (equal); writing-original draft (equal).
Pedro Shiozawa – Conceptualization (equal); investigation (equal); methodology (equal); writing-original draft (equal).
Quirino Cordeiro – Conceptualization (supporting); methodology (supporting); project administration (lead); writing-review & editing (equal); formal analysis (lead); funding acquisition (lead).

CONFLICTS OF INTEREST

Rafael Bernardon Ribeiro has a partnership with MedSupply company (Santa Rita do Sapucaí, MG, Brazil) for the development of Neurostim tDCS device.
Marcelo Bruno Generoso reported no biomedical financial interests or potential conflicts of interest.
Ivan Trombino Taiar reported no biomedical financial interests or potential conflicts of interest.
Ana Elisa De Conti Lord reported no biomedical financial interests or potential conflicts of interest.
Geraldo Teles Machado Netto reported no biomedical financial interests or potential conflicts of interest.
July Silveira Gomes reported no biomedical financial interests or potential conflicts of interest.
Lucas Pagnan Garrocini reported no biomedical financial interests or potential conflicts of interest.
Mara Fernandes Maranhão Girão reported no biomedical financial interests or potential conflicts of interest.
Samuel Araújo Leite da Silva reported no biomedical financial interests or potential conflicts of interest.
Pedro Shiozawa reported no biomedical financial interests or potential conflicts of interest.
Quirino Cordeiro reported no biomedical financial interests or potential conflicts of interest.

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