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RESEARCH ARTICLE

Transcranial direct current stimulation as an adjuvant in the improvement of symptoms of depression: A quasi-experimental design study.

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Aims

To evaluate the efficacy and tolerance of Transcranial Direct Current Stimulation (tDCS) in patients with major depression at the "Fray Bernardino Álvarez" Psychiatric Hospital.

Method

A pre/post intervention study, Patients attended in the outpatient clinic or continuous hospitalization with a diagnosis of major depression efficacy was measure with the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). The tDCS was applied in the region corresponding to the left lateral prefrontal cortex on the anode and the cathode on the right supraorbital region. Descriptive statistics were performed for continuous and discrete variables as appropriate, t-test, chi-square, significance $p<0.05$ was accepted.

Results

39 patients were included, 100% of patients reported symptom improvement, the mean initial versus final scores on the HDRS and BDI scales were 19.5±7.4 versus 9.9±6 and 25.4±8.8 versus 14.4±7.3, respectively with statistically significant differences ($p=<0.05$) for both scales.

Discussion

Transcranial direct current stimulation is an effective therapeutic option in the reduction of depressive symptoms as an adjunct to pharmacological treatment. The intervention did not cause adverse reactions requiring additional medication.

Introduction

According to data from the World Health Organization, depression affects 322 million people globally, particularly women, making it the main mental disorder affecting mankind.[1] The prevalence of depressive disorder is 20.3%, bipolar disorder 3.8%, anxiety disorder 21.2%, panic disorder 6.6%, compulsive disorders 12.2%, 8.0%, phobias 8.0% and psychotic disorders 4.5%.[2]

The latest National Health and Nutrition Survey of Mexico (ENSANUT 2018-2019) reported that symptomatology indicative of depression was 17.9% of Mexican adults, approximately 1.8 times higher in women than men.[3]

On other hand, depression is an important cause of disability and accounts for 5.45% of the years lost due to disability (YLDs) for all ages, especially for the 15-49 age group, YLDs represent 7.25%.[4]

A high percentage of patients with depression make a suicide attempt or die by suicide. In Mexico, suicidal behavior has progressively increased, during the last decade, the suicide rate increased from 7.1 to 8.8 per 100,000 inhabitants between 2008 and 2018.[5]

Due to the high prevalence of depressive disorders, it is necessary to use new therapeutic strategies for these patients; among them are non-invasive brain stimulation, which includes repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS).

These techniques follow the principles of electromagnetic induction stipulated by Michael Faraday; however, it was Anthony Baker and collaborators who managed to give them clinical utility, as they were able to stimulate neurons in the cerebral cortex and corticospinal pathways.[6] Both techniques are based on hormesis, i.e., the phenomenon that occurs when the response to a low stimulus is high and to a high stimulus the response is inhibitory. The mechanism of action of these techniques is unknown, however a study with brain stimulation techniques showed that it leads to an up-regulation of neurotrophins such as BDNF that facilitate neuroplasticity (synaptogenesis) and newly formed neurons (neurogenesis) by means of nerve growth factor (NGF), such is the case of transcranial infrared light therapy that has been used in patients with cognitive impairment, so it is possible that both tDCS and rTMS have a similar mechanism of action.[7]

A meta-analysis found that tDCS is a promising treatment that offers the opportunity for noninvasive modulation of cortical excitability and plasticity in psychiatric disorders and has a superior effect to placebo comparable to (B coefficient=0.35) rTMS and antidepressant drugs in primary care. The tDCS is indicated in mild and moderate depression with or without adjuvant antidepressant treatment, but not for treatment-resistant depression. After a systematized review, a group of experts from Europe gave a level of recommendation B, applying stimulation with the anode in the left lateral prefrontal cortex and the cathode in the right supraorbital region; the parameters of stimulation, the effect of the tasks and the medication remain undefined.[8]

Regarding safety, a report showed that in 33,000 sessions, applied to 1000 subjects, there was no evidence of prolonged and irreversible lesions at conventional doses, with a wide range of stimulation parameters and duration (<40 mA-7.2 mA). Special care should be taken in patients with epilepsy and cases have been reported of turning to mania in patients with unipolar depression, so it is important to rule out a history of manic episodes, bipolar family history, although in all cases the symptoms have been controlled with conventional treatment.[9]

It has been shown that various drugs interfere with tDCS, such as calcium channel blockers, benzodiazepines, amphetamines, dopamine and dopamine receptor blockers, while SSRIs such as citalopram increase and prolong excitability.[10] There is controversy about the superiority of tDCS over treatment with antidepressants; for example, a randomized double-blind study did not find significant superiority of tDCS over escitalopram, although it did find superiority over placebo.[11] Another randomized double-blind clinical trial that measured the effect of sertraline and tDCS found both to have superior effect to placebo, concluding that the combination of sertraline and tDCS is safe.[12]

Our objectives were to evaluate the efficacy of Transcranial Direct Current Stimulation (tDCS) as an improvement of symptoms in the Hamilton and Beck scale in two stages, at three weeks and at three months in the maintenance phase. In addition, the tolerance of tDCS was measured. The hypothesis was that, the intervention with Transcranial Direct Current Stimulation improved > 30 percentage the baseline measurement in the Hamilton and Beck scales after three weeks of treatment.

Methods

A pre/post intervention study was designed at the "Fray Bernardino Álvarez" Psychiatric Hospital. The Research Ethics Committee approved the research on December 22, 2022. The non-probabilistic sample was made up of patients with a diagnosis of major depression collected consecutively in the outpatient clinic or continuous hospitalization. The diagnosis of major depression according to the diagnostic criteria of the DSM-V, made by board-certified physicians specializing in psychiatry.

The sample consisted of 41 patients of both sexes, aged between 18 and 65 years. Treated with monotherapy with selective serotonin reuptake inhibitors (fluoxetine, sertraline, citalopram or paroxetine) during the last eight weeks. Patients treated with benzodiazepines, with a history of placement of metal plates in the skull, pacemaker or diagnosis of epilepsy or previous episodes of hypomania or mania were excluded. Patients who did not complete the 15 sessions or the maintenance session and patients who reported adverse effects were eliminated.

All participants underwent a clinical performed clinical interview to confirm the diagnosis. After which the following ancillary diagnostic studies were performed: computed tomography, blood biometry, lipid profile, blood chemistry, electroencephalogram, and electrocardiogram; the following diagnostic tests were performed the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI).

A Sooma transcranial direct current stimulation equipment was used to apply tDCS; in each session, a 2mA stimulus was applied in the region corresponding to the left lateral prefrontal cortex, the anode and the cathode on the right

Table 1. Sociodemographic and clinical variables by sex.

Variable	Women	Men	χ^2 (*p*)	Shapiro Wilk test (*p*)
	n=31 (%)	n=8 (%)		
Age	42 (24 - 51)	42 (25 - 57)	-0.5 (>0.05)	
Degree of education			2.7 (>0.05)	
Primary	2 (7)	-		
Secondary	5 (16)	-		
High School	7 (23)	2 (25)		
Technical career	1 (3)	6 (75)		
Bachelor's Degree	16 (52)	-		
Occupation			7.5 (>0.05)	
Household chores	9 (29)	-		
Student	9 (29)	1 (12.5)		
Unemployed	2 (6.5)	2 (25)		
Employee	11 (35.5)	5 (62.5)		
Marital status			1.8 (>0.05)	
Single	21 (67)	4 (50)		
Married	10 (33)	4 (50)		
Beck Depression Inventory				
Basal*	28 (20 - 28)	21 (15 - 29)	1.6 (>0.05)	.968 (>0.05)
Final**	15 (11 - 21)	10 (4 - 19)	1.6 (>0.05)	.967(>0.05)
Delta	12 (5 - 18)	10 (1 - 16)	0.5 (>0.05)	
Hamilton Depression Scale				
Basal+	21 (14 - 28)	19 (11 - 23)	0.9 (>0.05)	.976 (>0.05)
Final++	10 (5 - 14)	10 (4 - 11)	0.8 (>0.05)	.963 (>0.05)
Delta	9 (5 - 13)	9 (7 - 13)	-0.1 (>0.05)	

supraorbital region; subsequently, one tDCS session per month was applied as maintenance. Daily sessions of 30 minutes were applied during five continuous days and two days of rest until 15 sessions were completed. The tDCS was applied by medical personnel trained by a certified professional.

Statistical analysis

Descriptive statistics were performed for continuous and discrete variables, t-test, and Pearson chi-square test. HDRS and BDI total scores were categorized into minimal, mild, moderate or severe depression, according to the scores established by them. The normality of scale scores with the Shapiro-Wilk test. Significance $p<0.05$ was accepted. All statistical analyses were carried out in IBM SPSS® version 26 software.

Results

In the final analysis, 39 patients were included, 31 women and 8 men. The most frequent schooling was high school; the main occupation was housework for women. All patients had previous treatment with SSRIs lasting more than eight weeks (17 fluoxetine, 9 sertraline, 11 citalopram and 1 paroxetine) and venlafaxine 1.

Table 2. Beck and Hamilton scales initial and final scores

Variable	Basal	Final	*t* (*p*)	χ2 (*p*)
	n=39 (%)	n=39 (%)		
Beck Depression Scale	25.4 ± 8.8	14.4 ± 7.3	5.9 (<0.05)	
Categorization				
Minimum / negative	2 (5)	10 (26)		
Mild	4 (10)	14 (36)		27.9 (<0.05)
Moderate	16 (41)	15 (39)		
Serious	17 (44)	-		
Hamilton Depression Scale	19.5 ± 7.4	9.9 ± 6	6.3 (<0.05)	
Categorization				
Minimum / negative	4 (10)	19 (49)		
Mild	11 (28)	16 (41)		25.4 (<0.05)
Moderate	20 (51)	4 (10)		
Serious	4 (10)	-		

Table 3. Comparison of the categorization of the score in HDRS and BDI

Variable	BDI	HDRS	*t* (*p*)
	n=39	n=39	
Decrease (delta)	12 (5 - 17)	9 (5 - 13)	0.7 (0.4)
Categorization			2.5 (0.3)
Increase	3 (8)	5 (13)	
No change	2 (5)	-	
Decrease	34 (87)	34 (87)	

BDI=Beck Depression Inventory, HDRS= Hamilton Depression Rating Scale

There were no differences between men and women when comparing sociodemographic variables. In the response to treatment, no differences were found between the two groups either, although lower scores were observed in the men's group, which may be due to the limited number of cases (n=8). The initial and final scores of both scales had normal distribution according to the Shapiro Wilk test. Table 1

Both the Beck and Hamilton scales showed a reduction in scores at the end of the 15 treatment sessions. Mean baseline BDI and HDRS scores corresponded to moderate and mild depression, respectively. After the 15 sessions of tDCS, the baseline scores on both scales decreased with statistically significant differences. Table 2

The decrease was evident both in the scores of the scales and in the severity when categorizing the scores, especially the decrease in symptoms was marked when HDRS was taken as a reference. Comparison of the initial score versus the final score on both scales showed no statistically significant differences. In this case, a greater decrease in BDI score was observed. As for the categorization of this change, with both instruments 87% of the intervened users showed improvement. Table 3.

Of the 41 patients, one dropped out of treatment due to an anxiety episode, and another withdrew his consent to participate. The patient who experienced an episode of anxiety was followed up and did not require additional medication. The most frequent adverse effects were three cases of headache (7.6%), two cases of redness in the stimulation area (5.1%), 100% reported pruritus in the electrode area, no patient required additional medication for adverse reactions.

Discussion

Our work demonstrated that transcranial direct current stimulation is an effective therapeutic option in the reduction of depressive symptoms as an adjuvant to pharmacological treatment. Both in the Beck depression inventory and in the Hamilton Depression Rating Scale, we observed a greater than 30% reduction of symptoms in 70% of the patients after three weeks of treatment with respect to the baseline level, with statistically significant differences.

The reduction of symptoms was maintained one month after the conclusion of the 15-programmed sessions, with statistically significant differences with respect to the first measurement. It is important to highlight that most of the patients qualified with mild to moderate depression at baseline level even with continuous pharmacological treatment for more than eight weeks; so that the additional improvement observed we consider can be attributed to the brain stimulation technique used. The intensity of the symptoms is an effect demonstrated in various clinical trials with depressed patients, even in special situations such as pregnancy. A study, which used the same technique as this work, reported a reduction in symptoms of up to 80% in pregnant patients with depression after four weeks of treatment with tDCS.[13]

As mentioned above, there are multiple reports that demonstrate the positive effect of tDCS however, it is still unknown whether this effect is due to an improvement in affective symptoms or to the effect on the cognitive symptoms of depression.[14] In this regard, one study reported that the reduction in HDRS scores after tDCS was strongly associated with baseline values of the factors "Cognitive Alterations" and "Delay", while the factor "Anxiety/Somatization" showed a slight association with response.[15] Another study reported that bifrontal tDCS rapidly reduced depressive symptoms and the effects persisted until the end of the trial, the improvement was most notable in cognitive performance, anxiety and psychosocial functioning.[16] The procognitive effect of the tDCS may be mediated by factors such as educational level, gender, and improvement in depression, a hypothesis described in a clinical trial that measured cognitive performance in a population aged 18-65, so that the tDCS does not it has neither beneficial nor harmful effects on cognition since the aforementioned factors influence its improvement.[17]

We believe that the decrease in cognitive symptoms after treatment with tDCS is due to the improvement in depression, since failures in memory, concentration, attention, among others, are typical of the spectrum of depressive symptoms. Perhaps for this reason, when measuring cognitive functions in elderly patients with depression, no improvement is observed; for example, one randomized trial found little improvement in executive functions after four weeks of treatment with deep transcranial magnetic stimulation.[18] In the same sense, a randomized study measured the effect of tDCS in a sample of the geriatric population, finding no improvement in working memory and global cognitive function compared to the placebo group at 14 and 90 days after the intervention.[19] But when measuring them associated with the affective state, an increase in cold working memory was found attributed to improvement in the inhibitory control of the dorsolateral prefrontal cortex (DLPFC), the authors of this study declare that it is necessary to correlate the findings with imaging studies.[20]

Conclusion

We conclude that tDCS proved to be effective as an adjunct to antidepressant treatment in reducing depressive symptoms after three weeks of treatment with 2mA stimulation in 30-minute daily sessions, effect maintained after one month of treatment. We believe that future studies should evaluate how long the effect is preserved, since it has been observed that at three months there are no differences between patients with antidepressant treatment alone versus patients with antidepressant plus tDCS.[21] This is a recent aspect for low- and middle-income countries, since the cost of the intervention may be an impediment for its implementation in regular clinical practice. It is also necessary to correlate the findings with imaging or laboratory studies to further support the findings.

Limitations

The main limitation of this study is that it was not possible to include a control or placebo group, because the depressive disorder associated with suicidal behavior is the second reason for seeking care at the hospital where the investigation was performed and that since there is sufficient evidence of the effectiveness of tDCS in improving the symptoms of depression, the researchers for ethical reasons, consider it necessary to benefit the largest possible number of patients during the limited time (five months) that we had available equipment.

Ethical considerations

In compliance with Mexican legislation, this research is considered minimum risk based on article 17, section II of the Regulations of the General Health Law on Research for Health. Approved by the Research and Research Ethics

Committee of the Psychiatric Hospital "Fray Bernardino Álvarez" on December 22, 2022. All participants signed informed consent before entering the study.

Declarations of interest

None

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