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Original Article

The Effects of Transcranial Direct Current Stimulation on Depression, Anxiety, and Stress in Patients with Epilepsy: A Randomized Clinical Trial

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Abstract

Background: Epilepsy is a chronic disorder that affects both sexes and causes some physiological and psychological disabilities. The present study aimed to examine the effects of transcranial direct current stimulation (tDCS) on the psychological profile of patients with epilepsy.

Methods: The design of the present study was a randomized clinical trial with a pretest-posttest and a control group. The statistical population comprised patients with epilepsy, who were referred for treatment to a private health center in Urmia in 2019. The sample consisted of 30 patients with epilepsy selected via the convenience sampling method. Data collection was performed through the use of the Depression, Anxiety, and Stress Scale-21 (DASS-21) questionnaire. After the pretest, 15 subjects were randomly assigned to the intervention group, and 15 subjects were placed in the control group. The intervention was performed in 10 sessions, and the duration of stimulation was 20 minutes. The anode was placed in the F3 region (left hemisphere), the cathode in the F4 (right hemisphere), and the current intensity was 1.5 mA. After the intervention, the posttest was conducted for both groups, and the data were analyzed using a univariate covariance analysis in the SPSS software, version 23. A P value of less than 0.05 was considered statistically significant.

Results: The results of the ANCOVA analyses revealed significant differences between the intervention and control groups. The tDCS group represented a significant decrease in the scales of depression, anxiety, and stress in the posttest in comparison with the pretest ($P \leq 0.001$).

Conclusion: The results showed that tDCS could reduce depression, anxiety, and stress with the changes caused in the brain system.

Trial Registration Number: IRCT20190803044417N1.

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Keywords ● Anxiety ● Epilepsy ● Depression ● Transcranial direct current stimulation

What's Known

- Transcranial direct current stimulation is an effective intervention in treating the symptoms of depression, anxiety, and stress.
- This safe and efficient method can be used in patients with epilepsy for the reduction of seizures.

What's New

- For the first time, we evaluated the effects of transcranial direct current stimulation on the psychological profile of patients with temporal lobe epilepsy.
- The low current rate and the lack of sensitivity make this method a noninvasive technique; thus, its use in patients with epilepsy is unrestricted.

Introduction

According to the World Health Organization (WHO), neurological disorders affect the nervous system; cause some structural, biochemical, and electrical abnormalities in the central nervous

system; and produce a series of symptoms. Epilepsy is a chronic and neurological disease with its own features. Seizures are its main characteristic and can stem from systematic, metabolic, or toxic factors.[1] In addition to physical disabilities, this disorder causes some psychological problems. Elger and others demonstrated that psychological neuropathy had high comorbidity with chronic epilepsy.[2] These patients' psychological profiles should be examined to understand their psychological problems. The psychological profile is used for studying depression, anxiety, and stress.

Depression is one of the most common psychiatric disorders that affect individuals with epilepsy. Nonetheless, patients do not pay much attention to this disorder and usually do not receive treatment.[3] In these patients, failure to receive treatment or inappropriate treatment can result in suicide.[4] In recent years, numerous studies have reported a bidirectional relationship between depression and epilepsy. In other words, patients with epilepsy are more likely to be depressed. Likewise, the risk of epilepsy in depressed individuals is three to seven times higher than the normal population.[5] Thapar and colleagues indicated that, in the treatment of epilepsy, the management of depression was very important, since it controlled seizures, stress, and anxiety indirectly.[6]

Anxiety is one of the adjustment disorders experienced by patients upon diagnosis with depression. It is increased by the exacerbation of seizures.[4] The results of a study by Tellez-Zenteno and others showed that the risk of anxiety and depression (suicidal thoughts) in patients with epilepsy was 2.4 and 2.2 higher than that in healthy individuals.[7] The results of a meta-analysis performed by Scott and colleagues indicated that in patients with epilepsy, the prevalence of anxiety and depression was 20.2% and 22.9%, respectively.[8]

Among the psychological problems experienced by these patients, stress is a vague factor, because it still is not clear whether stress is the cause or the effect of the disease. Since stress is an integral part of everyday life, its examination as a trigger for seizure attacks is important. Gelisse and colleagues demonstrated that in some patients with epilepsy (5 in 1000), seizures began after stressful events.[9]

It is clear that in these patients, the psychological profile undergoes some changes; interventions are, thus, required to improve it in patients, who suffer from epilepsy. In the present study, transcranial direct current stimulation (tDCS) was selected from among various interventions. San-Juan and others in a meta-analysis demonstrated that this method was safe and efficient in patients and animals with epilepsy.[10] Narita and Yokoi examined the effects of tDCS on cognition and depression among individuals with Alzheimer's disease. They placed the anode in the left dorsolateral prefrontal cortex (DLPFC) and the cathode in the F3 and FP2 regions. Individuals received 2 mA for 30 minutes. The findings represented an improvement in the quality of life.[11] Liu and colleagues studied patients with temporal lobe epilepsy and demonstrated that the tDCS intervention with 2 mA and for 20 minutes improved depression.[12] Brunoni and others used tDCS to improve emotional processing in the DLPFC of patients with major depressive disorders. They found that even one session of tDCS might cause potential changes in emotional processing.[13] Ironside and others used the tDCS method to treat anxiety. They placed the anode in the left DLPFC and the cathode in the right DLPFC. The results indicated a reduction in vigilance against threats.[14] Bishop and colleagues concluded that the activity of the DLPFC was negatively correlated with trait anxiety. The result of their study highlighted the fact that working in the DLPFC area could be useful and practical.[15] Brunoni and others showed that tDCS could lower cortisol levels and augment vagal activation through anodal stimulation, leading to the management of stress.[16] Moradi Kelardeh and colleagues investigated the effects of DLPFC stimulation on cigarette craving and stress and found tDCS useful in reducing cigarette cravings and stress.[17]

These studies highlight the gap in research, especially in the field of anxiety and stress. The aforementioned studies have not examined epileptic patients. Consequently, the present study endeavored to survey the effects of tDCS on depression, anxiety, and stress in patients with epilepsy.

Patients and Methods

The present study was a randomized clinical trial with a pretest-posttest and a control group. It was conducted in the private clinic of Dr. Hasani Kia in Urmia in 2019. The first step was participant selection. The target population consisted of 30 participants, who suffered from temporal lobe epilepsy. Delavar stated that in intervention studies and controlled conditions, researchers could accommodate 15 individuals in each group.[18] In the current investigation, the participants were selected by convenience sampling and were divided by simple randomizatoion into an intervention group and a

control group by using a random number table. The reason for using convenience sampling and 15 participants in each group was the limited availability of these patients.

The inclusion criteria encompassed willingness to participate, having temporal lobe epilepsy according to the medical record, age range between 15 and 50 years, a minimum mid-school qualification, not being pregnant, not being in the menstrual period, having a shower before the intervention so that the electrical current was not interrupted by greasy hair, having any prosthesis in the skull, having no battery in the heart, having received no psychological treatment in the past year, and having no other medical illnesses. The exclusion criteria were comprised of non-cooperation during the intervention and research, the decision to discontinue participation, any sensitivity to tDCS, and receiving any psychological interventions or psychiatric drugs.

In the second step, the participants completed the Depression, Anxiety, and Stress Scale-21 (DASS-21) questionnaire. After the administration of the pretest, tDCS was applied, followed by the posttest. In this technique, electrodes are placed in sponge pads, which are soaked in a conductive solution. The current passes through different areas, before it reaches the surface of the cerebral cortex. The current that reaches this area causes neurons to have an electric charge and creates positive and negative poles, leading to a change in the activity of that area. In the current research, during the intervention, a total of 15 patients, who were in the intervention group received 1.5 mA for 20 minutes over the left DLPFC. The anode was placed in the left hemisphere over the F3 region, while the cathode was placed over the F4 region in the right hemisphere. The intervention was implemented for 10 sessions. The first five sessions were held consecutively, and the last five sessions were held every other day. The control group did not receive any stimulation despite the placement of electrodes.

Ethical Approval

The present study was approved by Urmia University of Medical Sciences (Ethical Code: IR.UMSU.REC.1398.140 and was registered with the Clinical Trials Code of: IRCT20190803044417N1). The researchers explained the process of the study to the participants, who completed the written informed consent under reassurance that they were free to leave the study at any time.

Measurement Instrument

The depression, anxiety, and stress scale consisted of 21 items and was the short version of the questionnaire developed by Lovibond and Lovibond.[19] Each subscale (depression, anxiety, and stress) was measured through seven items. The participants expressed agreement or disagreement on a four-point Likert-type scale, ranging from zero (i.e., Never) to three (i.e., Often). Items 3, 5, 10, 13, 16, 17, and 21 were related to depression. Items 2, 4, 7, 9, 15, 19, and 20 were related to anxiety. Finally, items 1, 6, 8, 11, 12, 14, and 18 were linked to the stress subscale. Lovibond calculated the Cronbach's alpha coefficients of reliability for the three mentioned subscales and reported 0.91, 0.84, and 0.9 for depression, anxiety, and stress, respectively.[19] Sahebi and colleagues reported that the Cronbach's alpha coefficients of reliability for depression, anxiety, and stress were 0.77, 0.79, and 0.78, respectively.[20] In the present study, the reliability index was 0.69 for depression, 0.64 for anxiety, and 0.71 for stress.

Statistical Analysis

The SPSS software, version 23, was used to analyze the data from the perspective of descriptive and inferential statistics. The comparisons of the DASS-21 scores before and after the intervention were done using the analysis of covariance (ANCOVA), which is a general method best suited to examine the between-group differences of pretest to posttest. Nonetheless, prior to the analysis, the hypotheses of ANCOVA were examined. The Levene's test was utilized to investigate the equality of variance between the two groups, and the Kolmogorov–Smirnov test was employed to check the distribution. A P value of less than 0.05 was considered statistically significant.

Results

The present study initially selected 52 patients, of whom 22 were excluded. Ultimately, 30 participants were assigned to intervention and control groups (figure 1). The demographic characteristics of the participants in both groups are compared in table 1 (P≤0.001).

The comparisons of the mean values of the DASS-21 components between the intervention and control groups of patients in the pretest and posttest are demonstrated in table 2. The comparisons of the mean values and P values of the intervention and control groups in the pretest showed no significant differences between them. In other words, the mean values of the two groups in all the components were almost equal. As is shown in table 2, the mean of depression, anxiety, and stress was significantly lower in the patients receiving tDCS (P≤0.001).

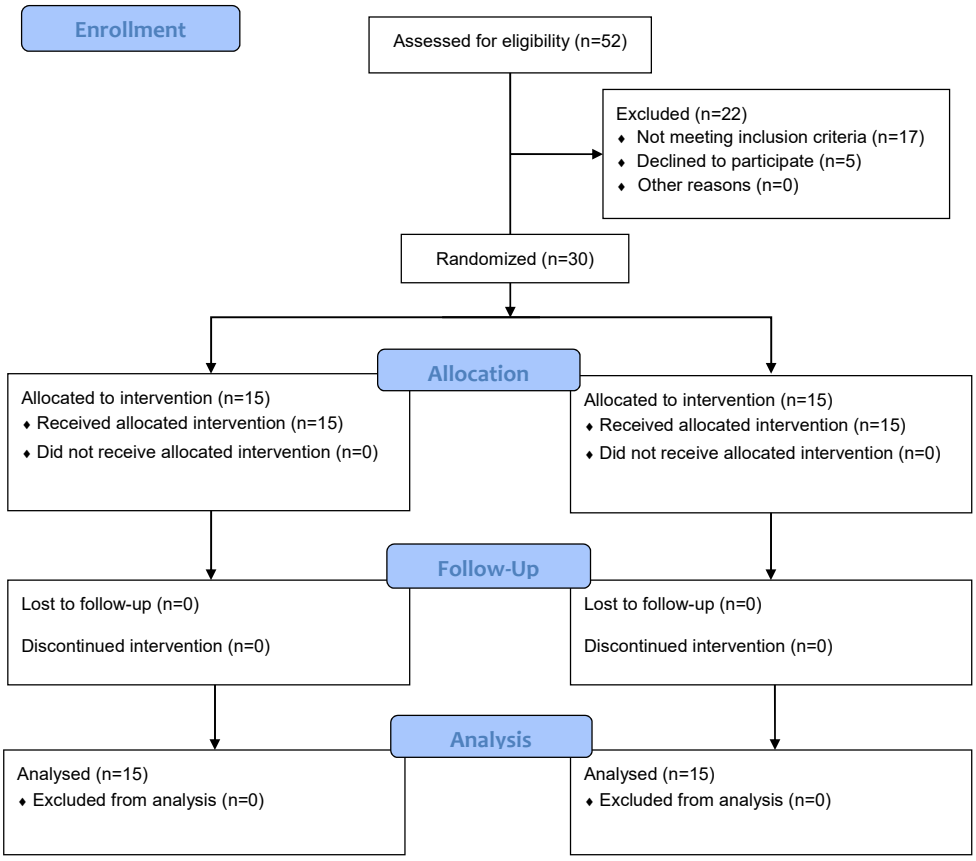

Figure 1: CONSORT diagram shows the flow of the participants through each stage of this randomized clinical trial.

Table 1: Demographic characteristics of the participants in the intervention group and the control group

Variables		Intervention Group (n, %) (n=15)	Control Group (n, %) (n=15)	P value
Marital Status	Single	4 (26.60%)	3 (20%)	>0.999
	Married	7 (46.70%)	7 (46.70%)	
	Divorced	4 (26.70%)	5 (33.30%)	
Education	High school	3 (20%)	2 (13.30%)	>0.999
	Bachelor	5 (33.30%)	7 (46.70%)	
	Master	7 (46.70%)	6 (40%)	
Sex	Male	8 (53.30%)	8 (53.30%)	0.839
	Female	7 (46.70%)	7 (46.70%)	
Age (Mean±SD)	15–50 (y)	38.13±9.14	34.73±9.26	0.320

P values were calculated for the unpaired *t* test (P≤0.001). Unpaired *t* test were applied and P values of less than 0.001 were considered significant.

Table 2: Descriptive indicators of depression, anxiety, and stress in the intervention and control groups

Variables	Pretest			Posttest		
	tDCS Mean±SD	Control Mean±SD	P value	tDCS Mean±SD	Control Mean±SD	P value
Depression	21.93±2.49	21.80±3.42	0.904	14.46±2.19	21.40±1.80	<0.001
Anxiety	21.20±2.36	21.73±1.62	0.478	13.80±2.56	20.86±2.03	<0.001
Stress	21.73±2.01	21.66±2.41	0.935	13.60±1.68	21.26±1.62	<0.001

tDCS: Transcranial direct current stimulation; P values were calculated for the *t* test (P≤0.001). Unpaired *t* test were applied and P values of less than 0.001 were considered significant.

As was stated above, conducting ANCOVA requires some assumptions. First of all, the measurement scales of the variables should be either a ratio or an ordinal and their distribution should be normal. The other important assumption is related to the equality of variances, which means that the population variance, for one thing, is the same as the population variance for some other thing or things. The homogeneity of variances was determined using the Levene test.

Table 3: Summary of the analysis of covariance of the DASS-21 scores

Source	Dependent Variables	SS	df	MS	F	P	Eta
DASS-21	Depression	366.971	1	366.971	175.812	<0.001	0.867
	Anxiety	330.663	1	330.663	93.068	<0.001	0.775
	Stress	442.655	1	442.655	176.257	<0.001	0.868

DASS-21: Depression, Anxiety, and Stress Scale-21; SS: Sum of the square; df: Degrees of freedom; MS: Mean square; F: Fisher; P: Probability; Eta: Euskadi Ta Askatasuna; The ANCOVA test was used to compare the variables between the experimental and control groups.

This test is used to assess the equality of the variances of a variable in two or more groups. This test is a prerequisite for performing some statistical analyses. If the P value of the Levene test is less than some significance level (in this research 0.01), the null hypothesis of equal variances is rejected, and when the P value is more than 0.01, the variances are equal. The results of the Levene test showed no significant differences between the two groups in the scores of depression (P=0.623), anxiety (P=0.197), and stress (P=0.182). Based on these results, all the P values were more than 0.01. Hence, the homogeneity of the variances in the above variables was confirmed in the intervention and control groups. The results of this test showed that the assumptions of the parametric tests were fulfilled. Data distribution was also considered normal after the implementation of the Kolmogorov–Smirnov test, and the P values obtained for all the variables exceeded 0.01, justifying the use of parametric tests. Therefore, it could be acknowledged confidently that the homogeneity of the regression slope assumption was appropriate for performing the covariance analysis, because the interactions between the variables were not significant (P≥0.01).

Table 3 presents the results of the univariate analysis of covariance. This table shows that the tDCS group and the control group were significantly different regarding the scores of depression, anxiety, and stress in the posttest (P≤0.001). In simple terms, the depression, anxiety, and stress scores in the intervention group were significantly different from those, who received no intervention. More information can be found in the Euskadi Ta Askatasuna (Eta) column. The partial Eta-squared value indicates the effect size and should be compared with the Cohen guidelines (0.2: small effect; 0.5: moderate effect; and 0.8: large effect). It can be seen that for all the components, the effect size was large (depression=0.867, anxiety=0.775, and stress=0.868). This value was also used to describe how much of the variance in depression, anxiety, and stress was explained by the intervention (tDCS). It means that 86% of the variance of depression was explained by group; this amount was 77% for anxiety and 86% for stress. In other words, most of the changes in the scores were because of the therapeutic effects of the intervention.

Discussion

The results of the current investigation showed that tDCS could reduce depression, anxiety, and stress due to the changes that it caused in the brain system. From a neurobiological view, tDCS is used for neuromodulation, such that while the anode increases the rate of neural firing and depolarizes the membrane, the cathode causes hyperpolarization and inhibition.[21] We used tDCS because of its role in modulating cortical excitability and treating psychiatric disorders. First, the findings of the present study showed that the use of tDCS over the DLPFC decreased the depression scores of patients with epilepsy. These results are consistent with the results of studies by Narita and Yokoi, Liu and colleagues, and Brunoni and others.[11-13] Depression is a psychiatric disorder that has a high rate of comorbidity with epilepsy.[5] The fact that antidepressants have anticonvulsant properties demonstrates the linkage between depression and epilepsy.[22] It is known that in depression, the balance between hormones and neurotransmitters is upset; an intervention that causes changes in these elements may, therefore, be useful. In stressful situations, the corticotropin-releasing hormone is secreted by the hypothalamus to regulate the cortisol secretion of the adrenal gland.[23] Stressful life events are important factors in the occurrence and continuation of depression,[24] which renders cortisol regulation a significant component of the process of treatment. Brunoni stated that tDCS anodal stimulation over the left DLPFC caused a decrease in the level of cortisol and heart rate.[16] Surveying neurotransmitters highlights the role of serotonin in depression. Any abnormality in the central serotonergic system that causes problems in the synthesis of serotonin and decreases its secretion may increase the risk of depression.[25] In a review study, Belujon and Grace studied dopamine system dysregulation in major depressive disorders and demonstrated that in patients with depression, there were deficits in the dopaminergic system.[26] Therefore, the effects of

tDCS on the regulation of the dopamine rate may be another explanation for the present result. One of the pathomechanisms of depression involves the problems of neural plasticity.[27] Kim and Han used anodal tDCS to provoke neuroplasticity in rats with traumatic brain injury and demonstrated the capability of this tool to induce neural plasticity.[28] Villamar and colleagues revealed that noninvasive brain stimulation could prove useful in increasing neural plasticity in animals and humans.[29]

Unfortunately, there is a dearth of evidence that shows the effect of tDCS on anxiety. In line with studies by Ironside and others and Bishop and colleagues, we found that the anxiety scores of participants decreased after the intervention.[14, 15] Alizadeh Goradel and others demonstrated that after 10 sessions of tDCS, anxiety symptoms decreased by 87.5% in patients with obsessive-compulsive disorder.[30] Patients with epilepsy may experience fear and threat, since seizure attacks are unpredictable and can happen in public places.

Yook and others used tDCS for 20 minutes and showed that, with an intensity of 2 mA, it reduced epileptic seizures.[31] Therefore, decreasing the frequency of seizures can be one of the reasons for the low scores of anxiety. Ironside and colleagues surveyed the effects of tDCS over the DLPFC in women, who experienced trait anxiety and found that the stimulation could diminish the influence of threat by reducing the activation of the amygdala and increasing cortical activation.[32] A review of the related literature provides some evidence that depression, anxiety, and fear are related to the right DLPFC.[33] As was mentioned earlier, we used the cathode electrode in the right DLPFC. As a result, decreasing the activation of this part can be effective in declining negative emotions. On the other side, we used an anode electrode in the left DLPFC. Boggio and others used an anode electrode in the left DLPFC and argued that this method could reduce unpleasant perceptions.[34] Moreover, Peña-Gómez and colleagues confirmed that applying anode tDCS in the left DLPFC could modulate the perception of negative emotions.[35] Consequently, in patients with epilepsy who experience negative emotions because of their chronic disorder and social stigmata, changes in perception that are caused by tDCS can be useful.

The last finding of the present study was linked to the scores of stress. The scores of this component decreased after the intervention. This result is consistent with the findings of studies by Brunoni and others, Bogdanov and Schwabe, and Hodges and colleagues.[16, 36, 37] In stress, the integration of body and brain plays a key role. Neurotransmitters such as acetylcholine, gamma-aminobutyric acid (GABA), dopamine, and glutamate are essential.[38] It is important to note that the sympathetic nervous system is involved in the stress process. Therefore, anything that decreases its activity can be effective in reducing stress. Jesus and Goncalves showed that the application of tDCS over the left DLPFC could increase the activity of the parasympathetic system and decrease the activity of the sympathetic nervous system.[39] Another feature of tDCS is the reduction of blood pressure. Knotkova and colleagues found that using anodal tDCS over the left DLPFC could reduce blood pressure.[40] It seems that this reduction pacifies individuals who feel the tension.

The fact that our study was done on patients suffering from epilepsy is its salient strength given the paucity of research on the effects of tDCS on this group of patients. As was mentioned before, the safety of this method has been confirmed, and San-Juan and others acknowledged its effect on reducing seizures.[10] The literature shows that the side effects of this method are not serious, although occasional itching, redness, and headache can happen. These side effects fade away shortly after the intervention. In the present study, no acute problems were reported. The potential limitations of the current study are convenience sampling, the limited number of participants, self-report questionnaires, and the absence of follow-up periods.

Conclusion

The findings of the present study demonstrated that tDCS as a neurostimulator device could cause changes in the brain structure and result in a reduction in depression, anxiety, and stress. To remove the limitations of the present study, we suggest that future studies use sophisticated brain imaging equipment along with questionnaires to better justify the changes in subjects' moods and have a follow-up period to determine the long-term effects of this intervention. Moreover, increasing the number of samples can lead to better results. According to the results of this study, it seems advisable that physicians and psychologists employ this intervention as a useful, practical, and inexpensive treatment, along with other therapies, to improve psychological profiles in patients with epilepsy.

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