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Investigating the Synergistic Effects of Transcranial Direct Current Stimulation and Cranial Electrical Stimulation in Treatment of Major Depression in A Double Blinded Controlled Trial

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ABSTRACT

Despite recent advances in antidepressant medication as the main treatment option for severe depression, large portion of patients are drug resistant. The side effects of the drugs sometimes occur before the treatment effects which can terminate the treatment process. Therefore, developing new efficient and safe alternative treatment is the main focus of scientific societies. The present study aimed to comparatively investigate the synergistic therapeutic effects of transcranial direct current stimulation (tDCS) and cranial electrical stimulation (CES) in major depression in a double blinded randomized controlled trial. This was a double blinded randomized controlled trial conducted on 30 major depression patients diagnosed by semi-structured review of DSMiv-TR by a psychologist. The patients filled the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). The quantitative electroencephalograms of patients were recorded and analyzed with Neuroguide processing tool to determine the regions with abnormal function using the age and gender matched standard databases of quantitative electroencephalogram (QEEG0. Thirty patients were randomly divided into three groups: CES, combined CES-tDCS, and CES treatment. Each patient receive 6 sessions consisting of 3 consequtive days and 3 sessions on the every other day basis (3 sessions a week) of 20-min exposure. After the 6 treatment sessions the patients were asked to fill the BDI-II and BAI questionnaires. The combined treatment showed more response followed by CES and tDCS treatments ($P<0.01$). In addition, no significant difference was observed in the treatments' complications between the three groups ($P>0.01$). However, disease duration was significantly different between the three groups ($P<0.01$). Our findings showed that QEEG guided treatment with tDCS and CES can be effective in depression. It seems that tDCS acts through regulating the firing rate of cortical neurons and CEW through modulating the thalamus and limbic system in treatment of depression. Combined CES-tDCS can yield more efficient treatment.

Keywords: Cranial electrical Stimulation, Beck Depression Inventory, Beck Anxiety Inventory, Depression Treatment, transcranial Direct Current Stimulation, Combined treatment.

INTRODUCTION

Depression is one of the most common disorders worldwide and more than 350 million people suffer from various types of this disease[1]. Its symptoms include fatigue, sleeplessness, suicidal thoughts, suicide attempts, digestive problems, frustration, isolation, lack of concentration, memory loss, etc[2, 3]. In addition to these symptoms, brain imaging techniques show that different regions of the brain undergo significant physiological and functional changes[4-6]. In addition to the personal

and social aspects of human life, depression's symptoms adversely influence several physiological and psychological functions of the patient which make the treatment of depressive disorders as one of the world's most expensive medical treatment[1, 7-9]. American Psychiatric Association recognizes four main groups of treatments for depression which are drug therapy, psychotherapy, drug therapy plus psychotherapy, and electroconvulsive therapy (ECT)[7, 10]. Despite using of different antidepressants drugs, some portion of depressed patients are resistant to drug treatment[11]. Therefore, developing nonpharmacologic is necessary for depression treatment.

During the recent years, physical agents such as electrical and magnetic fields, sound waves and laser have been extensively used as alternative or adjunctive treatments for different disorders ranging from musculoskeletal, metabolic disorders, wounds, and neuropsychiatric disorders[12-17]. Despite recent advances in antidepressant medication as the main treatment option for severe depression, large portion of patients are drug resistant. The side effects of the drugs sometimes occur before the treatment effects which can terminate the treatment process. Therefore, developing new efficient and safe alternative treatment is the main focus of scientific societies. The present study aimed to comparatively investigate the synergistic therapeutic effects of transcranial direct current stimulation (tDCS) and cranial electrical stimulation (CES) in major depression in a double blinded randomized controlled trial.

MATERIALS AND METHODS

This study is a randomized double-blind clinical trial. The study population consisted of 30 patients (three n=10 groups) of between 18 and 55 years, who have been diagnosed by psychiatrists to have major depressive disorder based on the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Having accepted and signed the written consent form, the patients with depressive disorder based on DSM-IV criteria were selected using the table of random numbers cooperated by a statistics consultant and were studied in three n=10 groups, Group A with tDCS On and CES off as sham, Group B with both tDCS and CES On (combined tDCS-CES), and Group C with CES On and TDCS off as sham. The devices were used separately and the excitement time was 20 minutes for each session. As the patients arrived, they were asked to fill 21-item Beck Depression Inventory (BDI) and 21-item Beck Anxiety Inventory (BAI). Electroencephalogram (EEG) and Quantitative Electroencephalogram (QEEG) were then used for the patients, and they were finally reassessed using Beck Anxiety Questionnaire and Depression Inventory, and the changes occurring using these scales were assessed. All of the patients were treated first within three successive days and then every other day (three sessions per week) for ten days in 6 twenty-minute sessions (for each device in each method). At the beginning of the sessions, the patients were tested using electrophysiological QEEG mapping and due to the primary electrophysiological disorders of electrodes, the devices were then installed in specific places in order to normalize the disrupted waves. At the end of the sixth session, the patients were assessed using BDI and BAI scales. After the data were collected, they were entered into SPSS 20 Software and were then analyzed using Chi-square Test, Paired T-test and Analysis of Variance (ANOVA) Test.

RESULTS

On the whole, 30 patients who were just treated using tDCS, CES, and combined tDCS-CES, and who had the required criteria were selected as the sample. The patients were divided into three n=10 groups, namely Group A, Group B and Group C. The patients of Group A were studied with CES on and tDCS off as (Sham), those of Group B were studied with tDCS on and CES off as (Sham) and Group three using both tDCS and CES on. The frequency distribution of the patients' gender and average age in three therapy groups is presented in Tables 1 and 2.

Based on the Table 1, the Chi-square Test and the P-value (0.33), it can be concluded that gender had no significant difference among the three intervention groups.

Based on the table above, the T-test and the P-value (0.86), it can be concluded that age had no significant difference among the three intervention groups. A comparison of the treatment complications in the three groups under study is presented in Table 3.

Based on the table above, the Chi-square Test and the P-value (0.83), it can be concluded that treatment complications have had no significant difference among the three intervention groups.

The disease duration in the three groups is compared and presented in Table 4.

Based on the Table 4, the T-test and the P-value < 0.1, it can be concluded that disease duration has had no significant difference among the three intervention groups.

The three groups of patients were examined and compared before and after the test in terms of anxiety and depression rate (Tables 5-6).

Table 1: The frequency distribution of the patients' gender in the three groups under study

Total	Male	Female	Group
10 (100%)	4 (40%)	6 (60%)	Group A
10 (100%)	4 (40%)	6 (60%)	Group B
10 (100%)	5 (50%)	5 (50%)	Group C
30 (100%)	13 (43.3%)	17 (56.7%)	total

Table 2. A comparison of the patients' age average in the three groups

Number	Mean ±Standard deviation (years)	variable
10	7.09± 30.1	Group A
10	7.17 ± 34.1	Group B
10	10.83 ± 30.2	Group C

Table 3: Frequency of the treatment complications among the three intervention groups

Percentage	Frequency	Group
10%	1	Group A
0%	0	Group B
10%	1	Group C

Table 4: Disease duration frequency among the three groups

> 5 years	2-5 years	<2 years	group
0	3	7	Group A
0	2	8	Group B
0	3	7	Group C

Table 5: Results of comparing the three groups in terms of depression and anxiety (before the test)

Significance	Group C	Group B	Group A	
0.47	7.6±26.2	6.1±28.2	6.7±25.7	depression
0.02	5.2 ±18.4	5.84 ±15.00	6.6 ±14.1	anxiety

Table 6: Results of comparing the three groups in terms of depression and anxiety (after the test)

Significance	Group C	Group B	Group A	
0.003	1.5 ± 8.90	4.93 ± 16.70	6.6± 10.00	depression
0.05	3.1 ± 7.0	5.3± 09.90	5.1± 2.2	anxiety

Based on the table above, the T-test and the P-value (0.47), it can be concluded that the depression test score has had no significant difference among the three intervention groups before the intervention, while there was a significant difference among them in terms of anxiety.

Based on the Table 6, the ANOVA Test and the P-Value<0.001, it can be concluded that the depression test score has had a significant difference among the three intervention groups after the intervention. As presented in Table 5, the difference among the groups in terms of anxiety after administration of the test has also been significant.

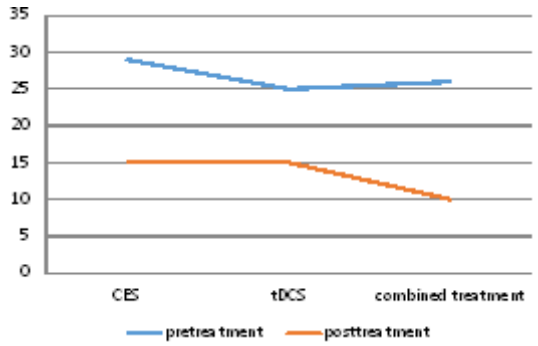

Fig. 1. A comparison of pre- and post-treatment depression scores between the three groups

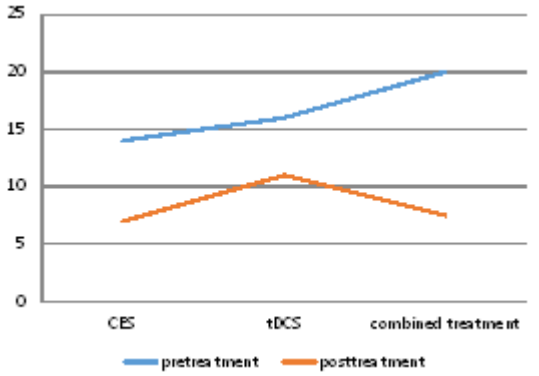

Fig. 2. A comparison of pre- and post-treatment anxiety scores between the three groups

The three groups' scores of depression and anxiety before and after the intervention were compared with and the results are shown in Figures 1 and 2.

DISCUSSION

We studied and compared the effect of tDCS, CES, and combined tDCS-CES in treating major depression. It was shown in this study that there was a significant difference among the patients who were placed in three different groups to be treated differently (Table 6). It was also shown that Group C, which had used the two therapies showed less rate of depression and anxiety than the other two groups that had used either tDCS or CES. The CES method was also shown to be more effective for treatment of depression and anxiety than the tDCS method. Due to the great effect of tDCS on depression and its reduction of negative feelings and enhancement of positive feelings, it can be concluded that tDCS adjusts the cerebral cortex waves which had been taken based on primary QEFG and patients' age. This result was in line with another research which showed that TDCS can affect the general arousal level and raise attention to the frontal lobe of the brain.

Depression causes a change or disorder in the balance and dynamics of the left hemisphere of the brain, and causes the two hemispheres of the brain to act differently in cognitive and emotional processes. However, tDCS can induce a balance between the two hemispheres and helps improve the depressive disorder in this way[18]. As different areas of the brain were recognized in this research and tDCS was placed in the hyperactive and inactive areas of the brain, it was shown that detecting the damaged area of the brain is very effective in the therapy process. This finding is in line with another study indicating that tDCS exerted its physiological effects within a few minutes to hours on the dorsolateral prefrontal cortex (Anode: right, cathode: left) the left hemisphere to the right hemisphere and thus affected the moods and reduced the depression and anxiety rate in the subjects. What attracted our attention was that the depression rate was also affected by the places of electrodes as well as by their diameter and stream[19].

Another reason is that tDCS adjusts the neuronal firing of different parts of cortex and this causes the cortex of the brain to adjust the neurons and thus affect the patient's mood and behavior. Another research also showed that tDCS causes long-term synapses, which in turn cause the neurotropic activity of the brain. The research showed that the type and degree of brain injury and the time when the illness starts also affect the therapy[20]. Another research showed that TDCS creates changes in the frontal lobe and the left frontal skull and thus creates antidepressant properties[21].

The mechanism of CES influence can also be explained in the following way: CES adjusts the blood flow between the two hemispheres of the brain and thus adjusts the limbic system, the thalamus, and the basal ganglia. Different studies have shown that CES has considerably helped CSF (cerebrospinal fluid) and plasma serotonin treatment-resistant depression[22]. Therefore, the basal ganglia and the thalamus help reduce the depression rate by adjusting the serotonin[23].

Another research also showed that CES influences the brain system by changing the level of hormones and neurotransmitters[24]. Another report about the clinical improvement in depression and anxiety showed that CES enhances monoamine oxidase activity and plasma concentration from Gamma-amino butyric acid [25]. Moreover, CES increases the levels of catecholamine in both males and females and increases the production of thyroxin in those males who receive CES for a long period of time[26]. A research which studied the changes of EEG showed that CES reduces the beta wave power and modifying the abnormality of these two waves helps create therapeutic effects[25].

The results of several studies show that CES influences different regions of the brain compared with the tDCS.

The influence of CES has been reported by different studies to be between 30 and 40 percent[26, 27], while that of tDCS has been shown to be between 35 and 40 percent[29, 18]. It was shown in this research that as the two methods have no serious and dangerous complications and the selection of patients was in such a way that it reduced the possibility of complications, and also because no research has argued against this combination, the two methods were combined in this research. This combination increased their effect up to 66 percent due to the simultaneous stimulation of different areas of the brain, which affects one's mood and behavior.

Considering what has been mentioned so far, we can come to the conclusion that the integration of the two therapies will help improve depression due to the effect of tDCS on cortex and that of CES on the limbic and the thalamus, which are parts of the brain that adjust one's mood.

Since depression paves the way for anxiety in an individual, it is expected that the reduction of depression will lead to the reduction of anxiety in the patient, which actually happened in the present research. About 85% of the patients with depressive disorder experience considerable symptoms of anxiety, and similarly, 90% of the patients with anxiety disorders become depressed too [30]. Anxiety was not followed as a main factor in the present research, but it was investigated as a peripheral factor. However, it was shown that the reduction of the patients' depression resulted in the significant reduction of their anxiety. It can thus be concluded that the CES and tDCS therapies are very effective in managing depression and anxiety.

It was shown in Table (4), related to the second hypothesis, that the mean score of depression with three methods of CES, tDCS, and both tDCS and CES has not been significant in terms of disease duration. The result of this research is in line with the conclusions made by Nilsson et al., and Bernini et al. The result of this research can be justified in that the depression duration among the sample subjects has been nearly similar, or the difference has not been significant. However, other studies have shown that the reason for the insignificant difference in terms of disease duration is due to the small number of the sample size. No definite conclusion can be made from this hypothesis and more extensive studies are actually needed for it.

In testing the third hypothesis, a comparison of the frequency distribution of the treatment complications using the three methods of CES, tDCS and both tDCS and CES showed no significant effect after the intervention. It is noteworthy that only two cases of headache were observed among the 30 subjects of the research, one in the group that had used the tDCS method and the other in the combination therapy group (Group C). The research results are in line with the research conducted by Nietzsche[36]. Similar studies have also shown that tDCS has had a few complications such as headache[32, 33, 34, 37, 39], but the studies have provided no reason for this problem. However, another research showed skin complications with greater erythema and browning of the skin[38]. However, the present research has showed no symptoms of erythema or browning of the skin, because the stimulation in this research was less than 2 mA and gel or pad soaked in a solution of salt was used and the stimulation was done twice a week. The stimulation in the research that was mentioned earlier[38] was, however, 2-3 mA and tDCS stimulation was done five times a week.

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