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Effectiveness of Transcranial Direct-Current Stimulation (tDCS) and Emotion Regulation Training in Reducing Current Drug Craving and Drug-Use Thoughts and Fantasies in Opioid-Dependent Patients: The Issue of Precedence

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Abstract

Background: Craving is an important factor in predicting relapse in opioid-dependent patients.
Objectives: The aim of the present study was to determine which combination therapy, including emotion regulation training followed by tDCS or tDCS followed by emotion regulation training, is more effective in reducing current drug craving and drug-use thoughts and fantasies in opioid-dependent patients in Zahedan, Iran.
Patient and Methods: A quasi-experimental study with a pretest-posttest design and two intervention groups was conducted. From eight randomly-selected centers, asample of 28 patients was selected based on the inclusion and exclusion criteria. They were randomly divided into two intervention groups. The first group received eight sessions of tDCS, followed by eight sessions of emotion regulation training. The second group received eight sessions of emotion regulation training followed by eight sessions of tDCS. The statistical population included all opioid-dependent patients at medium-term residential drug rehabilitation centers in Zahedan, Iran, in 2018 - 2019. The data were gathered using the personal drug use questionnaire, the desires for drug questionnaire (DDQ), and the drug use thoughts, fantasies, and temptations questionnaire. All analyses were performed using SPSS-16.
Results: The results of repeated measures ANOVA showed that both sequences had a significant, long-term effect on the reduction of current drug craving and drug-use thoughts and fantasies in opioid-dependent patients. In addition, emotion regulation training followed by tDCS was more effective in reducing current drug craving and drug-use thoughts and fantasies than tDCS followed by emotion regulation training.
Conclusions: Combination therapy can significantly reduce drug craving in opioid-dependent patients and starting treatment with emotion regulation training followed by tDCS can lead to better results.

Keywords: Transcranial Direct Current Stimulation, Emotion, Craving, Opioid-Related Disorders

1. Background

Substance use disorder is among the most important public health concerns around the world and in Iran, and is associated with significant impairment in functioning and high relapse and mortality rates (1,2). Craving is referred to as the psychological pain of addiction that has an important role in drug seeking and impulsive behaviors (3). Craving as a construct refers to continuing to use drugs despite its negative consequences (4, 5).

Behaviors indicating opioid addiction, such as craving, impaired self-control, and behavioral inflexibility, reflect dysregulation and impairment in specific neural circuits (6). Functional magnetic resonance imaging (fMRI) studies show that craving is related to the increased activity of the reward pathway (6).

Reward pathways consist of dopaminergic neurons that project from the ventral tegmental area (VTA) and the prefrontal cortex (PFC); the repeated activity of these neurons means the preference of craving-related rewarding

stimuli over neutral stimuli (7). The advancements in revealing the biological etiology of craving have been accompanied by advancements in neurological interventions including transcranial direct-current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) (6).

tDCS is a technique in which a continuous, low electric current is delivered to the scalp. It is a noninvasive method for brain stimulation that is useful in the modulation of cortical arousal and directing human behavior and perception (8, 9). The tDCS, in fact, leads to a reduction in drug craving through inducing changes in dopaminergic neurotransmission in the brain and reducing cortical arousal (10). In addition, tDCS reduces drug craving through influencing the DLPFC area of the prefrontal cortex (11).

Through the anodal stimulation of the right DLPFC (according to the international 10 - 20 system of electrode placement) and the cathodal stimulation of the left supraorbital area of the frontal lobe, tDCS reduces the skin conductance response (SCR) and emotional arousal that, in turn, leads to reduced craving (11).

Although the anodal stimulation of the DLPFC area leads to a significant reduction in craving, it should be noted that this reduction is only temporary. This can be due to the patients' lack of insight into or attentional biases toward the symptoms of craving that something can even worsen the symptoms of craving (12).

However, due to the lack of specific parameters in terms of therapeutic doses and the limited number of assumptions about the therapeutic mechanisms underlying electrical stimulation, it is not regarded as the first-line treatment of addiction (2). In addition, the future of neuromodulation for treating drug use and other psychiatric disorders requires more rigorous research. The current prominent theory maintains that combining brain stimulation with other therapies can increase the efficacy of treatment (11). In addition to tDCS, the efficacy of emotion regulation training and related techniques in reducing drug craving has been shown in different studies (4, 13-16).

Poor emotion regulation is regarded as an important factor in drug relapse (17-19). Therefore, emotion regulation training can lead to the higher use of reappraisal in overcoming drug abuse, which is more effective than the negative emotion regulation strategies, i.e. acceptance or suppression (4).

Through improving the ability to handle negative and positive emotions, emotion regulation training can control most triggers of drug craving and reduce the relapse (18). As a result, emotion regulation training can lead to the modification of maladaptive emotion regulation strategies and negative emotions, and provide an opportunity for direct or indirect reduction in drug craving through the effective management of emotions (14).

Although both emotion regulation training and tDCS can significantly reduce drug craving, research shows that addiction is very similar to other chronic disorders and that it is very difficult to change behaviors that force a patient to use drugs. Therefore, combination therapy is considered an important strategy for relapse prevention in drug abuse (15).

There are different factors involved in drug craving. Therefore, it is often difficult to overcome the powerful incentives related to drug use. Therefore, it is necessary to combine therapies to increase the success of treatment (20). In fact, combining tDCS with cognitive therapies leads to better therapeutic results than when each therapy is provided alone (21).

When there is a comorbidity of substance use disorder with other psychiatric disorders, starting the treatment process with psychotherapy followed by adding methadone maintenance treatment could be more effective than providing methadone maintenance treatment alone (22). At the same time, various studies have shown that patients with substance use disorder who had two or more therapeutic efforts gained better results (23-26).

2. Objectives

Based on what was said, the present study aimed at answering the following question: Is providing eight sessions of tDCS followed by eight sessions of emotion regulation training more effective than providing eight sessions of emotion regulation training followed by eight sessions of tDCS in reducing current drug craving and drug-use thoughts and fantasies among opioid-dependent patients in Zahedan.

3. Patients and Methods

According to the study objective, "examining the effectiveness of combined transcranial direct-current stimulation (tDCS) and emotion regulation training in reducing current drug craving and drug-use thoughts and fantasies in opioid-dependent patients," a quasi-experimental study with a pretest-posttest design and two intervention groups was used. The statistical population included all opioid-dependent patients at medium-term residential drug rehabilitation centers in Zahedan, Iran, in 2018 - 2019. The patents were under treatment in a two-month program. Eight centers were randomly selected among the rehabilitation centers. Then, a sample of 28 patients was selected from these centers using a purposeful sampling method concerning the inclusion and exclusion criteria. Then, they were randomly divided into two intervention groups.

In the first group, the participants first received eight sessions of tDCS in a group therapy format, followed by eight sessions of emotion regulation training in a group therapy format. In the second group, the patients first received eight sessions of emotion regulation training in a group therapy format, followed by eight sessions of tDCS.

The tDCS was applied using a battery-powered electrical stimulator and a pair of electrodes (5 × 7 cm) at a 2-mA intensity. In order to target the DLPFC, the anodal electrode was placed in the F4 region and the cathodal electrode in the F3 region (determined based on the 10 - 20 system of electrode placement). The stimulation was provided for 45 minutes with a 30-second rise and fall time with Neurostim-2. The devices were provided by Medina Teb Company (www.medinateb.com).

3.1. Tools of Study

3.1.1. The Desires for Drug Questionnaire (DDQ)

The desires for drug questionnaire (DDQ) was designed to assess current drug craving. It was first designed to assess heroin dependence, but was later used to additionally assess dependence on other drugs. The items of the DDQ are rated on a 7-point Likert-type scale ranging from 1 (totally disagree) to 7 (totally agree). Franken et al. reported a Cronbach's alpha value of 0.85 for the total questionnaire and alpha values of 0.77, 0.80, and 0.75 for its subscales (27). In the present study, an alpha of 0.73 was found for the total scale.

3.1.2. The Drug-Use Thoughts, Fantasies, and Temptations Questionnaire

This scale was developed by Ziaee et al. (28). It has 20 items designed to assess thoughts, fantasies, and temptations about drugs. The items are rated on a 6-point Likert-type scale ranging from 0 (totally true) to 5 (totally untrue). The reliability of the questionnaire using the Cronbach's alpha coefficient was found to be 0.94. The validity of the questionnaire was assessed by correlating it with the situational confidence questionnaire (SCQ) developed by Annis and Graham (1988) (r = 0.53, P = 0.001), the mental desire scale (r = 0.48, P = 0.001), and the positive and negative affect schedule (PANAS) developed by Watson et al. (1988); the direction and magnitude of correlations indicate the validity of the questionnaire (28). In the present study, a Cronbach's alpha of 0.80 was found for the total questionnaire.

At the beginning of the study, informed consent of all participants was obtained concerning the completion of the instruments and participation in the sessions.

4. Results

The mean age of the participants was 30.42 ± 5.36 years. The youngest participant was 20-years-old and the oldest participant was 40-years-old. In terms of marital status, 15 participants (53.6%) were married and 13 (46.4%) were single. In terms of education, 19 participants (67.9%) had a high school diploma, 5 (17.9%) had an associate degree, and 4 (14.3%) had a bachelor's degree. In terms of the type of abused opioid, 4 participants (14.3%) used hashish, 12 (42.9%) opium, 1 (3.6%) heroin, 6 (21.4%) shire, and 5 (17.9%) a combination of opioids. In terms of the method of use, 15 participants (53.6%) smoked the drug, 2 (7.1%) injected the drug, 6 (21.4%) took the drug orally, and 5 (17.9%) used a combination of methods. In terms of the reason for drug use, 8 participants (28.6%) mentioned curiosity, 4 (14.3%) fatigue, 11 (39.3%) recreation, 2 (7.1%) life problems, and 3 (10.7%) psychological problems.

Table 2 presents the means and standard deviations of the pretest and stage-I and II posttest scores for current drug craving and drug-use thoughts and fantasies in patients dependent on opioids.

According to the results presented in Table 2, the pretest mean scores of current drug craving were 47.21 ± 10.72 and 46.64 ± 10.96 for the Tdcs + emotion regulation training group and emotion regulation training + tDCS group, respectively, while the posttest mean scores of current drug craving were 42.71 ± 14.43 and 36.42 ± 13.51 in the two groups, respectively.

In addition, according to Table 2, the decrease in current drug craving was higher at the stage II posttest (after adding the second intervention) than the stage I posttest. The mean ± scores at the posttest were 41.04 ± 13.79 for group 1 (tDCS followed by emotion regulation training) and 31.78 ± 14.02 for group 2 (emotion regulation training followed by tDCS). The results indicate that adding the second intervention to the initial intervention improved the therapeutic results, but the decrease in current drug craving was higher in the group that first received emotion regulation training followed by tDCS.

Table 3 shows the means and standard deviations of drug-use thoughts and fantasies scores at pretest and stage I and II posttest for patients dependent on opioids.

According to the results presented in Table 3, the pretest mean scores of drug-use thoughts and fantasies were 59.85 ± 13.21 and 65.64 ± 15.95 in the tDCS + emotion regulation training group and emotion regulation training + tDCS group, respectively, while the posttest mean scores of drug-use thoughts and fantasies were 48.14 ± 15.26 and 46.71 ± 12.03 in the two groups, respectively. Therefore, the combined emotion regulation training + tDCS group had a more decrease in the mean posttest score

Table 1. A Summary of the Contents of Cognitive Regulation Training Sessions Based on Berking Model (2014)

Sessions	Contents
Session 1	Importance of stress, painful emotions, and negative moods, and their role in creating a vicious cycle; introduction of ART skills: (1) emotional relaxation, (2) breathing exercises for relaxation, (3) nonjudgmental awareness, (4) acceptance and tolerance, (5) compassionate self-support, 6-analysis of emotions
Session 2	How to create emotion: the importance of brain structure in emotion, benefits of emotions, and identification of emotion regulation strategies
Session 3	Review of the vicious cycle of activation of the amygdala and muscle tension followed by the activation of the amygdala and respiratory tension; getting rid of the viscus cycles through muscle and breathing relaxation training
Session 4	The vicious cycle of the brain under the name of negative thoughts and activation of the amygdala: the role of thought suppression in the intensification of negative thoughts, techniques for experiencing emotions without judging or labeling them, nonjudgmental awareness
Session 5	Review of the chain of skills in relaxation: nonjudgmental awareness, the role of avoidance in the activation of the amygdala
Session 6	(1) Acceptance and tolerance as goals, (2) group members' reasons for acceptance and tolerance, (3) observation of emotions as the one's partner, (4) resilience in different situations, (5) temporary nature of emotions
Session 7	Review of emotional reframing, review of emotions: stress, anger, fear, guilt, sorrow, hopelessness, and depression; the value of each emotion; the good times-bad times technique to improve resilience in the client
Session 8	Review of the two essential parts of compassionate self-support, i.e. self-worth and involving with positive emotions, practicing self-compassion; these practices were repeated at the end of the session

Table 2. The Means and Standard Deviations of the Pretest and Posttest Scores for Current Drug Craving in the Two Study Groups

Group	Pretest		Posttest I		Posttest II	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
tDCS + emotion regualtion	14	47.21 ± 10.72	14	42.71 ± 14.43	14	41.07 ± 13.79
Emotion regulation training + tDCS	14	46.64 ± 10.96	14	36.42 ± 13.51	14	31.78 ± 14.02
Total	28	46.92 ± 10.64	43	39.57 ± 14.08	28	36.42 ± 14.44

Table 3. Means and Standard Deviations of Drug-use Thoughts and Fantasies Scores at Pretest and Posttest in the Two Study Groups

Group	Pretest		Posttest I		Posttest II	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
tDCS + emotion regualtion	14	59.85 ± 13.21	14	48.14 ± 15.26	14	44.21 ± 15.65
Emotion regulation training + tDCS	14	65.64 ± 15.95	14	46.71 ± 12.03	14	32.00 ± 19.91
Total	28	62.75 ± 14.67	43	47.42 ± 13.50	28	38.10 ± 18.64

of drug-use thoughts and fantasies than the other group.

The results also showed that at stage II posttest (after adding another intervention), the group receiving emotion regulation training followed by tDCS had more decreases in drug-use thoughts and fantasies than the group receiving tDCS followed by emotion regulation training. The means ± SD of drug-use thoughts and fantasies were 32 ± 19.91 in the group receiving emotion regulation training followed by tDCS and 44.21 ± 15.65 in the group receiving tDCS followed by emotion regulation training. In the following, the results of testing the second hypothesis are presented. The repeated measures ANOVA was used to examine the study hypotheses.

Table 4 shows the results of examining the effectiveness of emotion regulation training followed by tDCS in reducing current drug craving in opioid-dependent patients. According to the results, all the tests of repeated measures ANOVA were significant ($P \geq 0.01$). The Wilks' lambda had a higher value than the other tests (Wilks' Lambda = 0.676, $F(6.004) = 0.324$, $P \geq 0.01$). The effect size was found to be 0.324. The Bonferroni post hoc test was used to examine mean differences and the results are shown in Table 5.

According to the results of the Bonferroni post hoc test presented in Table 5, the participants had significantly different current drug craving scores at pretest (46.92), posttest I (39.57), and posttest II (36.42) ($P \geq 0.01$). This finding indicates that the therapeutic effects remained stable over time. Therefore, it can be said that the group receiving emotion regulation training followed by tDCS experienced more decreases in current drug craving than the group receiving tDCS followed by emotion regulation training.

Table 6 shows the results of examining the effectiveness of emotion regulation training followed by tDCS in reducing drug-use thoughts and fantasies in opioid-

Table 4. Results of Repeated Measures ANOVA for the Group Receiving Emotion Regulation Training Followed by tDCS

Test	Value	F	Mean Square	df	P Value	Partial Eta Squared
Pillai's trace	0.324	6.004	2	25	0.007	0.324
Wilks' lambda	0.676	6.004	2	25	0.007	0.324
Hotelling's trace	0.480	6.004	2	25	0.007	0.324
Roy's largest root	0.480	6.004	2	25	0.007	0.324

Table 5. Results of the Bonferroni Post Hoc Test for the Current Drug Craving Scores in the Group Receiving Emotion Regulation Training Followed by tDCS

Stage of Assessment	Mean Difference	Std. Error	P Value	Confidence Interval for Difference	
				Lower Bound	Upper Bound
Pretest					
Posttest I	7.357	2.863	0.049	0.032	14.68
Posttest II	10.500	2.997	0.005	2.832	18.168
Posttest I					
Pretest	-7.357	2.863	0.049	-14.683	-0.032
Posttest II	3.143	1.809	0.282	-1.468	7.772
Posttest II					
Pretest	-10.500	2.997	0.005	-18.168	-2.832
Posttest I	-3.809	1.809	0.282	-7.772	1.486

dependent patients. According to the results, all the tests of repeated measures ANOVA were significant ($P \geq 0.01$). The Wilks' Lambda test had a higher value than the other tests (Wilks' Lambda = 0.408, F (18.164) = 0.592, $P \geq 0.01$). The effect size was found to be 0.592. The Bonferroni post hoc test was used to examine mean differences and the results are presented in Table 7.

As shown in Table 7, according to the results of the Bonferroni post hoc test, the participants had significantly different drug-use thoughts and fantasies scores at pretest (62.75), posttest I (47.42), and posttest II (18.64) ($P \geq 0.01$). Therefore, the intervention effects remained stable over time and the group receiving emotion regulation training followed by tDCS had more decreases in drug-use thoughts and fantasies than in current drug craving.

5. Discussion

The present study aimed at determining which sequence of combination therapy, i.e. emotion regulation training followed by tDCS or tDCS followed by emotion regulation training, is more effective in reducing current drug craving and drug-use thoughts and fantasies in opioid-dependent patients in Zahedan (Iran). According to the study results, the combination therapy was effective in reducing current drug craving and drug-use thoughts and fantasies in the participants, and it seemed that the group who first received eight sessions of emotion regulation training followed by eight sessions of tDCS experienced more reductions in these variables. In addition, the results of stage II posttest showed that the reduction in current drug craving and drug-use thoughts and fantasies became more stable and that adding another intervention to the initial intervention led to more reductions.

The study results are in line with those of Carvalho et al. (29), Witkiewitz et al. (30), and Conti et al. (31). In the study by Witkiewitz (30), a mindfulness-based intervention as a psychological intervention combined with tDCS significantly reduced symptoms in alcoholic patients after seven weeks of therapy and the reduction remained stable until two months after the end of therapy. It was found in the follow-up assessments that the combined therapy could increase the participants' capacity to pay attention to alcohol-use inhibitors and reduced their desire to use alcohol. In a study of the relationship between addiction relapse and non-invasive brain stimulation (NBS) following Ultra-rapid opiate detoxification (UROD), Nazari et al. (32) failed to show the long-term effects of tDCS on addiction relapse after UROD. However, combination therapy was very effective in reducing current drug craving and addiction relapse. The results of the study, also, shows that TENS (transcutaneouse electerical nerve stimulation) in combination with methadone could reduce severity of withdrawal symptoms 33.

Table 6. Results of Repeated Measures ANOVA for Drug-Use Thoughts and Fantasies Scores in the Group Receiving Emotion Regulation Training Followed by tDCS

Test	Value	F	Mean Square	df	P Value	Partial Eta squared
Pillai's trace	0.592	18.164	2	25	0.000	0.592
Wilks' lambda	0.408	18.164	2	25	0.000	0.592
Hotelling's trace	1.453	18.164	2	25	0.000	.592
Roy's largest root	1.453	18.164	2	25	0.000	.592

Table 7. Results of the Bonferroni Post Hoc Test for Drug-Use Thoughts and Fantasies Scores in the Group Receiving Emotion Regulation Training Followed by tDCS

Stage of Assessment	Mean Difference	Std. Error	P Value	Confidence Interval for Difference	
				Lower Bound	Upper Bound
Pretest					
Posttest I	15.321	3.940	0.002	5.238	25.405
Posttest II	24.643	4.058	0.000	14.258	35.028
Posttest 1					
Pretest	-15.321	3.940	0.002	-25.405	-5.238
Posttest II	9.321	2.857	0.009	2.010	16.633
Posttest 2					
Pretest	-24.643	4.058	0.000	-35.028	-14.258
Posttest I	-9.321	2.857	0.009	-16.633	-2.010

Combination therapy through combining psychological and neuroscience interventions can significantly improve emotion regulation skills and flexibility of patients dependent on drugs. In addition, this therapeutic approach can lead to greater recovery and fewer relapses in patients with substance abuse disorder (34).

Combination therapy approach to treating addiction considers addiction as a biological and behavioral disorder. On the other hand, it has been empirically shown that addiction results from an interaction between biological predisposition, life experiences, and environmental factors (35).

Combination therapy for addiction can improve interdisciplinary cooperation so that integrated therapies could be designed for addiction using knowledge from different domains of treating addiction and thus, craving could be reduced in patients more effectively. The present study provided a new model for treating addiction that emphasizes the importance of biopsychosocial models (36).

Although brain stimulation techniques are recommended for treating drug addiction and other mental disorders, the underlying mechanisms are not yet completely known (37). In addition, due to the specific nature of brain stimulation techniques, they should only be considered after a thorough examination of the pros and cons and therapeutic priorities (38).

The improvement of cognitive abilities is one of the main challenges in treating addiction that can reduce drug craving and relapse rate in patients (31). According to the World Health Organization (WHO), the most successful method of treating addiction is to combine interventions based on the biopsychosocial models. Given the specific cycle of addiction, psychological training such as emotion regulation training should be used to change the patients' attitudes toward using drugs in order to empower them to overcome addiction because people return to using drugs often due to psychological problems (39).

5.1. Conclusions

The study results can be explained by the fact that patients are often less familiar with brain stimulation methods. Therefore, it seems that the group receiving emotion regulation training followed by tDCS could better accept the treatment process, thus experiencing more reductions in drug craving. Some of the limitations of the present study were related to the fact that the majority of the patients were not familiar with tDCS because it is not a well-known technique in Iran.

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Footnotes

Authors' Contribution: Author contributions: Study concept and design: Behzad Rigi Kooteh, Behrooz Dolatshahi. Analysis and interpretation of data: Masoud Nosratabadi and Nour-Mohammad Bakhshani. Important intellectual content: Masoud Nosratabadi. Statistical analysis: Behzad Rigi Kooteh, Behrooz Dolatshahi, Masoud Nosratabadi, and Nour-Mohammad Bakhshani.

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