

Original Article

The Effect of transcranial Direct Current Stimulation (tDCS) on Opioid Craving

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Abstract

Introduction: Nowadays, substance use disorder is one of the most serious health problems in the world. Craving is one of the leading causes of substance use relapse. The purpose of this study was to evaluate the effect of transcranial Direct Current Stimulation (tDCS) on participants with opioid substance use disorder.

Materials and Methods: A randomized, sham-controlled trial was carried out to evaluate the effect of dorsolateral prefrontal cortex stimulation (right anodal and left cathodal) on craving among participants with opioid use disorder. Eighteen men were categorized into sham tDCS and active tDCS groups. Interventions were performed for seven consecutive days. In both groups, the instantaneous and periodic craving was evaluated by the Desire for Drug Questionnaire (DDQ) and Obsessive Compulsive Drug Use Scale (OCDUS) before and a week after the interventions. The differences between the two groups were evaluated by paired samples t-test and student's t-test.

Results: The results indicated that tDCS significantly reduced the scores on DDQ and OCDUS in the active tDCS group compared to the sham tDCS group ($P < .05$).

Conclusions: Our findings provide support for applying tDCS in controlling opioid craving. Therefore, this method can be considered to be a new therapeutic approach in treatment of opioid use disorder.

Keywords: transcranial Direct Current Stimulation, opioid use disorder, opioid craving, Obsessive Compulsive Drug Use Scale, Desire for Drug Questionnaire.

1. Introduction

Nowadays, addiction is one of the most serious health problems in the world. In fact, along with environmental, population-related, and nuclear issues, substance use is one of the four life-threatening human crises in the current century [1]. According to the data from the United Nations Office on Drugs and Crime (UNODC) in 2017, a quarter of a billion people experimented with substances worldwide, and 29.5 million people were diagnosed with substance use disorders in 2015 [2]. According to the published reports by the UNODC in 2003, about 2 million people in Iran were addicted [1]. In 2017, the anti-narcotics headquarters spokesman officially announced that there were 2,808,000 addicts in Iran [3]. In 2019, the secretary-general of the anti-narcotics headquarters announced the same statistics [4]. Such statistics necessitate applying newly discovered therapeutic approaches to treatment of substance use disorders.

Addiction influences different aspects of life including physical, psychological, social, and financial issues [5]. Long-term and successful management of addiction requires discovering new and effective treatments. The most important challenge of addiction treatment is relapse. The main cause of relapse is craving or desire to consume, which can continue for months or even several years after abstinence of substance use [5, 6].

Craving covers a wide range of phenomena, including anticipation of substance, reinforcement effects, and a strong desire for substances use [7]. Generally, craving is a crucial feature in contributing to relapse [8, 9]. Therefore craving control leads to less consumption and desirable outcomes in subjects with substance use disorders [6].

Transcranial Direct Current Stimulation (tDCS) is a new neural technique that has been investigated in several studies regarding its role in treatment of a wide

range of diseases such as anxiety, depression, cognitive disorders, food craving, and substance craving [10-13]. In this non-invasive and safe method, a weak continuous electrical current stimulates the brain's target cells. tDCS act on alternation of neural membrane polarization and may affect neurons' firing and conductance by either lowering or raising the threshold of activation [13].

There are no major contraindications to this method except precautions for pregnant women and people with a history of seizure. According to the previous researches, the reported common side effects of tDCS are tingling, local itching, restlessness, and pain under the electrodes, which are all mild and transient [12, 13]. Some researchers suggest that tDCS is an acceptable tool for raising brain processing capacity, and this feature makes other concomitant therapies more effective in the treatment of substance use disorders [10,11].

The research results by da Silva et al. in 2014 showed that tDCS reduced depressive symptoms and alcohol craving by reducing neuronal activity [14]. The efficacy of tDCS on alcohol craving was also shown in several studies [15-17]. Shahbabaei et al. indicated that stimulation of the dorsolateral prefrontal cortex reduced craving in methamphetamine users [18]. Batista et al. reported that tDCS reduced cocaine craving, depressive and anxiety symptoms [19]. The analysis of results on patients addicted to alcohol, cocaine, crack, or cigarettes showed the useful effectiveness of tDCS on craving scores [20].

Taremain in 2019 found that tDCS lowered craving, depressive and anxiety symptoms in opioid substance users [21]. Reviewing the related literature demonstrates that tDCS has been effective in reducing craving, but from the temporal point of view, few studies have evaluated both instantaneous and periodic craving. Additionally, previous research on opioid craving is limited. In

this study, we evaluated the effect of tDCS on opium craving in patients referring to an addiction treatment clinic.

2. Materials and Methods

This study is a randomized, sham-controlled trial that was performed in one addiction treatment clinics in Jiroft, Iran. 18 men who met the DSM-5 criteria for opioid use disorder participated in this study. They were under methadone maintenance treatment protocol and the dosage of methadone was stable before the study. Participants had positive opium test that showed lapse during methadone treatment. The inclusion criteria were: male addicts over the age of 18, stable medical condition, and reading and writing ability. Exclusion criteria included unstable medical or mental condition; substance use other than opioid except nicotine, history of epilepsy and contraindication for electrical brain stimulation techniques such as metal or electronic implants.

Written consent was obtained and the procedure and possible side effects were explained to all participants. Ethical approval was granted by the ethics committee of Jiroft University of Medical Sciences (ethics committee No. IR.JMU.REC.1394.11)

Demographic data including age, marital and employment status, and education were collected from all participants. They were randomly categorized into sham tDCS group and active tDCS group. For the active tDCS group, cathode electrode was placed on the left dorsolateral prefrontal cortex (F3 region) and anode electrode was placed on the right dorsolateral prefrontal cortex (F4 region). A constant current of 2 mA flowed for 20 minutes in each session.

The sham tDCS group was conducted in the active tDCS group arrangement, except that no electrical current was sent to electrodes. They underwent this process one session per day for seven consecutive days. In both

groups, the instantaneous and periodic craving was evaluated by the Desire for Drug Questionnaire (DDQ) and Obsessive-Compulsive Drug Use Scale (OCDUS) before and a week after the interventions.

The DDQ that investigates instantaneous craving includes 14 items that evaluate "negative reinforcement", "control", and "intention to use". Participants answer questions on a seven-point Likert-scale (1 = not at all, 7 = roughly complete) based on what they think or feel at the moment. Franken found the validity of the whole scale to be .79, using Cronbach's alpha. Also, the validity of the subscales of "intention to use," "negative reinforcement," and "control" was reported to be .77, .80, and .75, respectively [22]. The Persian version's validity and reliability have been approved in previous studies [23, 24].

The OCDUS that investigates periodic craving has 13 questions. This scale measures "thoughts and interference", "resistance against thoughts", and "Intention to use". Participants should select from a 5-point Likert scale (1= never, 5 = always) for each question in terms of their experiences in the week before. Hassani et al. showed that the Persian version of OCDUS has excellent validity and internal consistency [24].

Statistical analysis was done using SPSS software version 20. The probability value significance level was .05. The differences between the two groups were assessed by paired samples t-test and student's t-test.

3. Results

Demographic characteristics of the study population are shown in Table 1. There was no significant difference between the two groups in terms of age, marital status, education, and employment status. Mean and standard deviation of DDQ and OCDUS scores in the two groups are shown in Table 2. DDQ and OCDUS scores and their subscales did not differ significantly between the two groups in the pretest that shows homogeneity of the groups. The mean scores of DDQ and its subscales in the posttest were significantly different between the two groups except for the subscale of "control." These scores were lower in the active tDCS group compared to the sham tDCS group. The mean total scores of OCDUS and subscale of "thoughts and interference" in the posttest were significantly different between the two groups, and these scores were lower in the case group compared to the control group. However, there was no significant difference

4. Discussion

The aim of this study was to examine the effect of tDCS on opioid craving in men who referred to an addiction treatment clinic in Jiroft, Iran. As a general finding, present study showed that tDCS reduced instantaneous and periodic opioid craving based on DDQ and OCDUS, respectively. This has been shown about other types of substance use in previous studies [14-20].

Taremiyan et al. in 2019 studied opioid craving in sixty participants with opioid use disorder and concluded that tDCS significantly reduced the DDQ scores [21]. According to the findings of Dadashi et al., anodal tDCS on left dorsolateral prefrontal cortex (DLPFC) was effective in reducing drug craving and improving symptoms of attentional bias in opium addicts [25].

between the two groups for the other two subscales in the posttest. The scores of DDQ and its subscales in the posttest compared to the pretest in each group are shown in Table 3. The overall scores of the DDQ and its subscales, except for "control" in the posttest, were significantly lower than the pretest in the active tDCS group. There was no significant difference in DDQ scores and its subscales in the posttest compared to the pretest in the control group.

The scores of OCDUS and its subscales in the posttest compared to the pretest in both groups are shown in Table 4. In posttest, participants scored significantly lower in overall OCDUS score compared to pretest in the active tDCS group. Although the posttest OCDUS subscales scores were lower than the pretest in the active tDCS group, this difference was not statistically significant. OCDUS scores and its subscales in the sham tDCS group were not significantly different between the posttest and pretest.

Sharifi's evaluation of 40 addicts showed that applying tDCS on DLPFC of former crystalline-heroin users reduced craving [26].

The probable explanation of this finding is that anodic stimulation depolarizes resting membrane potential and increases excitability, and cathodal stimulation hyperpolarizes the resting membrane potential and reduces excitability. Thus, it is assumed that increased activity in DLPFC decreases craving [27].

The DLPFC is responsible for determining actions, evaluating the consequences of current behavior, predicting the outcome and social control. Stimulation of this area improves social control and prediction of the

consequences of behavior; as a result, it can lower substance craving. Probably one mechanism by which DLPFC stimulation decreases craving is improving social control, and therefore individuals become more capable of suppressing their urges [28]. On the other hand, based on functional neuroimaging findings, the relationship between DLPFC and the limbic system plays a key role in craving control [29].

An alternative explanation is that stimulation of the prefrontal cortex stimulates dopaminergic pathways. This explanation is acceptable in both instantaneous and periodic craving [30].

Although tDCS lowered the overall scores of DDQ and OCDUS in our study, significant decrease in the "control" subscale of DDQ and "resistance against thoughts" and "Intention to use" subscales of OCDUS was not observed.

The lack of efficacy of tDCS on all subscales of craving is inconsistent with the findings of previous studies in that most of these studies showed tDCS significantly lowers all subscales of DDQ and OCDUS scores in patients with substance use disorders [14-20].

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Some psychological and social factors can influence craving. Relationships with friends who do not consider such treatments effective as well as past experiences and attitudes as a self-efficacy source may affect treatment outcome because people probably do not consider themselves successful enough to control craving. Therefore, we suggest that psychologists focus more on these factors [5-7].

5. Conclusion

The results of our study indicated that tDCS could reduce instantaneous and periodic craving. Given that, we can probably consider this method to reduce craving. Yet, these results need to be confirmed in future studies.

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Conflict of interest

The authors declare that they have no conflict of interests.

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Tables:

Variables		Active tDCS group	sham tDCS group	P-value
Age(year)		39.40±8.05	40.24±7.01	0.76
Marital status	single	2(22.2%)	1(11.1%)	0.85
	Married	7(77.8%)	8(88.9%)	0.91
Occupation	Employee	6(66.6%)	5(55.5%)	0.83
	Unemployed	3(33.4%)	4(44.5%)	0.87
Education(year)		8.70±2.30	9.30±2.20	0.77

Table1. Demographic characteristics of the study population

Variable	Test	Sham tDCS group Mean ± SD	Active tDCS group Mean ± SD	Df	T	P value
DDQ score	Pretest	39.66±28.44	52.11±30.30	16	0.89	0.38
	Posttest	42.66±28.11	20.66±7	8.98	-2.27	0.04
Intention to use	Pretest	9.77±9.20	13.88±10.06	16	0.90	0.37
	Posttest	11.11±10.24	1.77±1.71	8.44	-2.79	0.02
Negative reinforcement	Pretest	11.33±12.92	18.55±11.67	16	1.24	0.23
	Posttest	13.22±11.28	3.44±4.34	10.21	-2.43	0.03
Control	Pretest	18.55±8.44	19.66±9.75	16	0.25	0.79
	Posttest	17.77±7.93	15.44±5.93	16	-0.70	0.49
OCDUS score	Pretest	55.44±30.86	54.44±23.71	16	-0.07	0.94
	Posttest	60.88±29.35	34.11±15.21	12	-2.43	0.03
Thought and interference	Pretest	24.77±13.06	23.44±17.69	16	-0.18	0.85
	Posttest	24.55±12.11	11.88±10.75	16	-2.34	0.03
Intention to use	Pretest	17.88±10.56	17.33±7.14	16	-0.13	0.89
	Posttest	19.44±10.79	13.33±6.32	16	-1.46	0.16

Resistance against thought	Pretest	12.77±9.06	13.55±7.82	16	0.19	0.84
	Posttest	15.77±9.58	8.88±5.66	16	-1.85	0.08

Table 2. Mean and standard deviation of DDQ and OCDUS scores in two groups.

	Groups	Mean difference	T	P-value
Active tDCS group	pretest- posttest			
	DDQ	31.44	2.78	0.02
	Intention to use	12.11	3.42	0.009
	Negative reinforcement	15.11	3.79	0.005
	Control	4.22	0.93	0.37
Sham tDCS group	DDQ	-3	0.40	0.69
	Intention to use	-1.66	-1.54	0.16
	Negative reinforcement	-1.88	-0.46	0.65
	Control	0.77	0.29	0.77

Table 3. Scores of DDQ and its subscales in posttest compared to pretest in two groups

	groups	Mean difference	T	P-value
Active tDCS group	pretest- post test			
	OCDUS	20.33	2.95	0.01
	Thought and interference	11.55	1.93	0.09
	Intention to use	14	1.27	0.23
	Resistance against thought	4.66	1.37	0.20
sham tDCS group	OCDUS	-5.44	-2.23	0.05
	Thought and Interference	0.22	0.09	0.93
	Intention to use	-1.55	-0.64	0.53
	Resistance against thought	-3	-1.22	0.25

Table 4. OCDUS scores and its subscales in posttest compared to pretest in two groups