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**Title:** Impact of Transcranial Direct Current Stimulation (tDCS) on Ultra Rapid Opioid Detoxification (UROD) Outcome

**Running Title:** A New Approach in Drug Abuse Therapy

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Highlights

- Patients did not report side effects of tDCS except for a tolerable tingling sensation under the electrodes reported by 5 patients.
- The results of the study support the hypothesis that tDCS reduces craving and withdrawal symptoms caused by treatment of opioid addiction by UROD.
- The results of this study deliver evidence that prefrontal tDCS may promote the tolerability and efficacy of treatment approaches for opioid addiction using UROD.
- tDCS reduced withdrawal symptoms for a relatively short time after anxiety-reducing and a possible dopamine-increasing effect, which were proposed in other studies.

Plain Language Summary

The study has provided to drug abuse practitioners. It has introduced an adjunctive treatment in drug abuse. Craving has a critical role in addiction. It is a powerful desire to consume drug abuse. Craving is a significant factor relapses or continues abuse after withdrawal from consuming. It is imprecisely defined. Craving is very difficult to measure. Different solutions are introduced to overcome craving. Transcranial direct current stimulation (tDCS) is one of them. It is a method to stimulate brain using constant and low direct current delivered via electrodes on the head. This study explores the adjunctive application of Transcranial direct current stimulation during treatment of opiate addiction with the ultra-rapid opioid detoxification approach. we found that tDCS may promote the tolerability and efficacy of treatment approaches for opioid addiction using Ultra Rapid Opioid Detoxification (UROD). It is very important because
Abstract

Background
Persistence of post-detoxification problems in drug addiction is one of the disadvantages of the ultra-rapid opioid detoxification (UROD) method. Transcranial direct current stimulation (tDCS) has been introduced in experimental addiction treatment for some years. Results of pilot studies suggest that it might be a promising method for addiction treatment.

Objectives
This study explores the adjunctive application of Transcranial direct current stimulation during treatment of opiate addiction with the ultra-rapid opioid detoxification approach.

Methods
This double blind sham-controlled clinical trial was carried out on patients with substance abuse admitted to the Bahman clinic of Yazd in Iran (March to September- 2014). Forty participants were randomly allocated to treatment and control groups. Two sessions of transcranial direct current stimulation (real or sham) over dorsolateral prefrontal cortices (DLPFC) were applied accompanied by ultra-rapid opioid detoxification. Withdrawal symptoms and craving were assessed by the Drug Desire Questionnaire (DDQ) and Objective Opiate withdrawal scale (OOWS) prior to ultra-rapid opioid detoxification as well as for the 24- hour interval after ultra-rapid opioid detoxification.

Results
Transcranial direct current stimulation optimized the opiate addiction treatment through craving and the withdrawal syndrome alleviation and.

Conclusions
The results of the study indicate that prefrontal transcranial direct current stimulation may promote the efficacy of the ultra-rapid opioid detoxification method in opioid addiction.

Key Words: Craving; Transcranial direct current stimulation; Substance withdrawal syndrome ; Opioid-related disorders
1. Background

Drug abuse highly threatens the health of societies. Addicts are prone to fatal infections and pregnancy complications, as well as other drug-related health problems (Mark, Woody, Juday, & Kleber, 2001). Regarding drug detoxification, different approaches do exist, however, their effectiveness is limited (Amato et al., 2008). One of the methods developed in the 1990s is ultra-rapid opiate detoxification. UROD includes the application of a large dosage of opiate antagonists under general anesthesia. Even though this method has numerous advocates, disadvantages are possible side effects after treatment, which can last from 3 to 10 weeks. Besides, a relatively high relapse rate limits the efficacy of this treatment (Safari, Mottaghi, Malek, & Salimi, 2010). Anxiety and mood disorders are relevant for this high relapse rate and further limit the applicability and value of UORD (Amato et al., 2008).

Hypo-function of the DLPFC with regard to its contribution to the reward system in addiction plays a critical role in craving for illicit drugs (P. S. Boggio et al., 2008). Stimulation of this area might thus be useful for the enhancement of dopamine-related physiological processes and alleviation of craving (Fregni et al., 2008). tDCS is a non-invasive brain stimulation procedure delivering a weak electrical direct current to the brain for several minutes. Anodal stimulation increases cortical excitability, while cathodal tDCS has antagonistic effects. Stimulation for some minutes results in likewise directed neuroplastic after-effects (Lupi et al.). Indeed, drug craving has been shown to be reduced by prefrontal tDCS in metamphetamine abuse, but also other drug addictions (Dastjerdi G, 2015; Sauvaget et al., 2015; Martinotti et al., 2019; Taremian et al., 2019).

Beyond its presumed effect on craving, anodal stimulation of the prefrontal cortex might be useful to reduce mood and anxiety problems (Borckardt et al., 2013). tDCS might furthermore be useful
for the reduction of detoxification-related pain symptoms. It has been used as an auxiliary treatment for the reduction of post-operative pain, and indeed reduced opioid consumption in these patients (Bashir & Yoo, 2016). Improving cognitive performance due to tDCS may be another aspect useful for the treatment of these patients (Conti & Nakamura-Palacios).

Because of these features of tDCS, we aimed to explore its putative effect for the treatment of opioid addiction via the UROD method.

2. Patients and Methods

2.1 Participants

This double blinded sham-controlled clinical trial was conducted in 40 opiate-dependent male patients, as defined by the Diagnostic and Statistical Manual of Mental Disorders (4th edition). The sample size was determined based on similar previously conducted studies (Gandiga, Hummel, & Cohen, 2006).

Inclusion criteria were age between 18 and 40 years, first attempt for treatment, the abuse of Heroin, Opium, Opium extract (Shire) or Opium and Shire combination via inhalation. Subjects who had a history of current or past physical, neurological, or psychiatric disorders or contraindications for tDCS or anesthesia were excluded from the study. Patients were randomly allocated to the experimental or control group (20 subjects in each group, mean age 25±2.11 and 26±1.71 years with a mean history of abuse of 8.37±2.4 and 7.37±2.2 years in the experimental and control groups respectively).

Subjects were required to refrain from opiate abuse for at least 12 h prior to UROD.
2.2 Transcranial direct current stimulation

The participants received three consecutive sessions of anodal tDCS over the right combined with cathodal tDCS over the left DLPFC with a 24-h inter-session interval. This montage was successful for addiction treatment in previous trials (Lupi et al.).

Two sessions of tDCS were performed prior to UROD, the third one was conducted one day after therapy.

The electrode locations (F3 and F4) were identified according to the 10/20 international system for EEG electrode placement. tDCS was delivered by a battery-driven stimulator (Activa Dose II, Taiwan) with two rubber electrodes covered by 5cm × 7cm saline-soaked sponges. tDCS intensity was 2 mA, and stimulation duration 20 minutes in the real tDCS group. In the control group, the electrodes were placed at identical locations, but the current flow was ramped down after 30s of stimulation (Kaye et al., 2003).

The evaluation of symptoms was conducted by a researcher who was blinded with regard to the stimulation protocol.

Participants were ignorant of the tDCS condition. The UROD lasted for 4 hrs. In UROD, a large dosage of an opiate antagonist (Naloxone 0.01 mg/kg) is applied under general anesthesia to detoxify the patients from opioid addiction. Anesthesia was initiated with a short-acting intravenous agent (propofol 1.5mg/kg) and a muscle relaxant (atracurium 0.5mg/kg) followed by a maintenance dose of the anesthetic propofol and the muscle relaxant (Shahbabaie et al., 2014).
2.3 Evaluations

Craving and withdrawal symptoms were assessed before and after each tDCS session. The results were analyzed via SPSS version 16. Additional assessments were selected for further evaluation as shown in tables 1 and 2.

Table 1: Results of t-tests comparing average craving between the two groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>Evaluation period</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Experiment</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>Before the 1st intervention</td>
<td>34.05</td>
<td>32.3</td>
<td>15.16</td>
</tr>
<tr>
<td>2</td>
<td>After the 1st intervention</td>
<td>24.35</td>
<td>22.6</td>
<td>13.40</td>
</tr>
<tr>
<td>3</td>
<td>Night</td>
<td>61.15</td>
<td>41.5</td>
<td>10.55</td>
</tr>
<tr>
<td>4</td>
<td>Before the 2nd intervention</td>
<td>48.05</td>
<td>32.9</td>
<td>14.74</td>
</tr>
<tr>
<td>5</td>
<td>After the 2nd intervention</td>
<td>30.95</td>
<td>22.2</td>
<td>11.67</td>
</tr>
<tr>
<td>6</td>
<td>After awakening</td>
<td>39.8</td>
<td>26.05</td>
<td>12.14</td>
</tr>
<tr>
<td>7</td>
<td>Before the 3rd intervention</td>
<td>33.45</td>
<td>21.05</td>
<td>11.33</td>
</tr>
<tr>
<td>8</td>
<td>After the 3rd intervention</td>
<td>27</td>
<td>11.45</td>
<td>11.02</td>
</tr>
<tr>
<td>9</td>
<td>2 weeks after treatment</td>
<td>29.36</td>
<td>29.72</td>
<td>16.81</td>
</tr>
<tr>
<td>10</td>
<td>1 month after treatment</td>
<td>13.37</td>
<td>14.7</td>
<td>3.40</td>
</tr>
<tr>
<td>11</td>
<td>3 months after treatment</td>
<td>15.8</td>
<td>20</td>
<td>9.73</td>
</tr>
</tbody>
</table>
Table 2: Results of the t-tests comparing withdrawal symptoms between the two groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>Evaluation period</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Experiment</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>Before the 1st intervention</td>
<td>1.3</td>
<td>1.25</td>
<td>1.03</td>
</tr>
<tr>
<td>2</td>
<td>After the 1st intervention</td>
<td>1.15</td>
<td>0.3</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>Night</td>
<td>5.6</td>
<td>4.55</td>
<td>1.60</td>
</tr>
<tr>
<td>4</td>
<td>Before the 2nd intervention</td>
<td>2.6</td>
<td>3.15</td>
<td>0.94</td>
</tr>
<tr>
<td>5</td>
<td>After the 2nd intervention</td>
<td>2.5</td>
<td>1.15</td>
<td>0.83</td>
</tr>
<tr>
<td>6</td>
<td>1 hour after the operation</td>
<td>5.1</td>
<td>2.55</td>
<td>1.71</td>
</tr>
<tr>
<td>7</td>
<td>3 hours after the operation</td>
<td>2.950</td>
<td>1.45</td>
<td>1.61</td>
</tr>
<tr>
<td>8</td>
<td>12 hours after the operation</td>
<td>2.2</td>
<td>0.7</td>
<td>1.06</td>
</tr>
<tr>
<td>9</td>
<td>Before the 3rd intervention</td>
<td>2.8</td>
<td>0.8</td>
<td>1.40</td>
</tr>
</tbody>
</table>
2.4 Craving

Craving is a main psychological withdrawal symptom in drug addicts, which enhances relevantly the probability for relapse (P. S. Boggio et al., 2008). In this study craving was monitored via the 14-item Desires for Drugs Questionnaire (DDQ). This questionnaire assesses instantaneous craving at the time of assessment. Each scale comprises of three subdivisions, including Desire and Intention, Negative Reinforcement and Inhibition (Ekhtiari et al., 2008).

2.5 Withdrawal syndrome

Abstinence from opioid consumption results in physically observable withdrawal symptoms in drug addicts. These may vary in their intensity depending on the previous level of opioid consumption as well as other factors, such as context and environment (Segrave, Arnold, Hoy, & Fitzgerald, 2014). The OOWS is an interview and observation tool for assessing opioid withdrawal signs and symptoms. It contains 13 physically observable signs, rated as present or absent, based on observation of the patient by a rater for five minutes (Safari et al., 2010). Validity and reliability of this questionnaire have been demonstrated in Iran and other countries (Ekhtiari et al., 2008).
3. Results

3.1 Demographic Factors

Four subjects from the real tDCS and two from the control group left the study within one month after the treatment due to unknown reasons. For statistical analyses, we treated missing values by the missing completely at random (MCAR) mechanism followed by mean imputation of missing data. The demographic characteristics in the study groups did not show any significant discrepancies between groups (Table 3).

Table 3: Demographic characteristics of the study groups

<table>
<thead>
<tr>
<th>Demographic condition</th>
<th>Real tDCS group</th>
<th>Sham tDCS group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (percentage) /mean (+/- sd)</td>
<td>Number (percentage) /mean (+/- sd)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>25.3 ±1.29</td>
<td>26.25± 1.04</td>
<td>0.571</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>19 (47.5)</td>
<td>17 (42.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Single</td>
<td>1 (2.5)</td>
<td>3 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower than diploma</td>
<td>15 (37.5)</td>
<td>15 (37.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>License</td>
<td>4 (10.0)</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Higher than license</td>
<td>1 (2.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Below 5 years</td>
<td>7 (17.5)</td>
<td>8 (20.0)</td>
<td>0.87</td>
</tr>
</tbody>
</table>
### 3.2 Craving

We used a 2-factorial ANOVA model to perform an analysis of variance and test for group and time effects of the intervention on each primary outcome measure. For craving, the interaction of time and group was significant (p-value=0.0001) and both main effects of group and time were significant (p-value=0.0001 and p-value=0.0001 respectively).

Prior to and immediately after the first tDCS session, the craving was identical between groups. Craving was however reduced in the study group, as compared to the control group, from the night after the first intervention up to the craving measure after the third intervention (respective one tailed p-values < 0.05, table 1). However, this inter-group difference was not present any longer two weeks after therapy (post hoc t-test, P-value= 0.947), which indicates a limited duration of tDCS effects on craving.

According to the results of the t-tests, furthermore craving increased for both groups at the night before detoxification and after waking up from anesthesia, which was more intense in the control group (stages 3 & 6 in Diagram 1).
We also assessed the ratio of mean changes of craving by the \( R = \frac{E - B}{B} \) formula (\( E \) indicates craving after and \( B \) craving before tDCS). The value of \( R \) comparing craving before the first tDCS and 1 month after treatment was -0.4 in the sham and -0.5 in the real group, thus craving was more prominently reduced after intervention in the real tDCS group.

An additional assessment for craving was accomplished 3 months after treatment.

\( R \) for craving before and after the first tDCS session was -0.3 in the sham and -0.33 in the real stimulation group, before and after 2rd tDCS was -0.33 in the sham and -0.35 in the real stimulation group, and finally \( R \) values before and after the 3rd tDCS session were -0.21 in the sham and -0.49 in the real stimulation group.

### 3.3 Withdrawal syndrome

The results of the 2-factorial ANOVA showed a significant interaction between time and group (\( P \)-value=0.0001). Both main effects of group and time were significant (\( p \)-value=0.0001 and \( p \)-value=0.0001 respectively).

Withdrawal symptoms were identical for both groups before the first tDCS session but differed significantly between groups after the first intervention and at night before UROD. Before and after the second tDCS session, withdrawal symptoms were identical in both groups. However, after UROD, withdrawal symptoms were significantly lower in the real as compared to the sham tDCS group up to the 3rd tDCS session, as shown by the respective post hoc tests (table 2).

In addition, the night before and one hour after UROD, the intensity of withdrawal symptoms increased in both groups, especially one hour after UROD (\( P \)-value =0.026 and 0.0001 respectively). This increase was related to baseline values. See diagram 2.
The ratio of the mean change of withdrawal symptoms comparing withdrawal before and 1 month after treatment was 0.71 in the sham and -0.64 in the real tDCS group. Withdrawal symptoms decreased after each intervention only in real tDCS group. R for withdrawal symptoms before and after the first tDCS session was -0.058 in the sham and -0.57 in the real stimulation group, before and after the 2nd tDCS it was 4.92 in the sham and -0.66 in the real stimulation group, and finally R before and after the 3rd tDCS session was -0.16 in the sham and -0.5 in the real stimulation group.

4. Discussion

Patients did not report side effects of tDCS except for a tolerable tingling sensation under the electrodes reported by 5 patients (three patients from the real tDCS and 2 from the sham stimulation group). This result is comparable with other studies in the field (Pedron, Monnin, Haffen, Sechter, & Van Waes, 2014).

The results of the study support the hypothesis that tDCS reduces craving and withdrawal symptoms caused by treatment of opioid addiction by UROD.

Lower levels of craving were observed in the real tDCS group from the night after the 1st session to the end of the 3rd session in agreement with the results of other tDCS studies in addiction (Lupi et al.), in further agreement with the role of the prefrontal cortex in urging and control of craving in humans (Fregni et al., 2008), and animal models of addiction (Goldstein & Volkow, 2011). In addition to deep brain structures involved in addiction, recent studies have revealed a relevant contribution of the prefrontal cortex (Fowler, Volkow, Kassed, & Chang, 2007). In accordance, prefrontal cortex and anterior cingulate activation are relevant for cognitive processes, especially drug craving, in cocaine addicts (Paulo Sergio Boggio et al., 2009).
The positive effect of tDCS on craving is in accordance with similar effects of this intervention on nicotine, marijuana and alcohol withdrawal, but this is the first study which showed such an effect in opioid addiction. However the effects were relatively short-lived. This might be caused by minor cumulative effects following three sessions of tDCS (Klauss et al., 2014). Interestingly, we saw slightly enhanced craving in the real stimulation group at the last timepoint obtained. This may be related to improved attention caused by tDCS, as described by previous anodal tDCS studies with the electrodes placed over prefrontal cortices (Borckardt et al., 2013).

Most studies on UROD describe a manifest withdrawal syndrome during treatment and in the weeks after treatment (Rostami, Hamidi Kenari, Mirzaieyan, & Rezaie kochaksaraie, 2013). In one study, symptoms of the drug withdrawal syndrome increased during UROD and 24 hours later (Safari et al., 2010). Other studies indicate sustained withdrawal symptoms for up to 10 weeks (Rostami et al., 2013). In the present study, tDCS reduced withdrawal symptoms for a relatively short time after anxiety-reducing and a possible dopamine-increasing effect, which were proposed in other studies (Klauss et al., 2014). One reason for the positive effects of tDCS on withdrawal may relate to more intensive protocols has to be explored in future studies.

Generally speaking, the results of this study deliver first evidence that prefrontal tDCS may promote the tolerability and efficacy of treatment approaches for opioid addiction using UROD.

5. Ethical Considerations

The study was approved by the ethics committee of Yazd University of Medical Sciences and registered at the Iranian registry of clinical trials (IRCT ID: 2015022821273N1).

Conflict of interest

The authors have no conflict of interest.
Acknowledgement

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