A Single-Center, Randomized, Double-Blind, Placebo-Controlled Study on the Efficacy of Clonidine in Detoxification of Opioid Dependency

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Abstract: Background: Clonidine is α² adrenergic receptor agonist with detrimental effect on locus coeruleus. It is considered as one of the detoxification drugs in order to reduce opiate withdrawal syndrome. We conducted this study in order to assess clonidine effect on withdrawal symptoms and signs. Materials and methods This double blind, clinical trial, single centered study was conducted among 104 male inpatient heroin dependent patients in Psychiatric Center. They were selected via convenient sampling method. Subsequently, they were divided randomly into two matched groups: trial–control (clonidine –placebo) groups. Withdrawal symptoms and signs based on DSM–5 were compared in groups. Results: In 14 day detoxification period (in 7th and 14th day examination), the effect of clonidine on craving and agitation (p < 0.01) was significant. With respect to other symptoms and signs, clonidine was not effective prominently. Discussion: Due to different results compared to previous studies in this area. Clonidine use with respect to opioid withdrawal syndrome needs further evaluation or may need to revise.

Keywords: Clonidine, Drug Dependency, Withdrawal Syndrome

1. Introduction

Heroin is an illegal, highly addictive drug derived from morphine, a naturally occurring substance extracted from the seed pod of certain varieties of poppy plants. It is typically sold as a white or brownish powder that is “cut” with sugars, starch, powdered milk, or quinine. Opium derivatives are one of the most prevalent abused substances in Iran. Some of dependent individuals tend to use this drug in order to reach euphoria and afterward they tend to repeat the act in order to re-experience the feeling. After the while, expenses of using a drug, adverse vocational of family problems caused by abuse, force individuals to ask for professional treatment. There are various drugs and therapeutic approaches with respect to dealing with opium derivatives. One the promising drugs worth mentioning is Clonidine. Clonidine is α² adrenergic receptor agonist, which was firstly administered in order to treat hypertension. Afterwards, it’s usage was extended in dealing with various problems such as alleviating withdrawal symptoms, sedative property, anti-anxiety and reducing stress level before surgery [1]. Other usage includes, alleviating symptoms induced by nicotine withdrawal [2], treating withdrawal syndrome of children of substance dependent mothers [3], soothing agitated children in ICU [4]. Clonidine appears to be efficient in detoxification, specifically regarding treating opium dependency treatment; this can be due higher tendency of opium dependent patients in comparing to heroin dependent patients [6, 7]. However, some studies have discussed tramadol as more efficient drug comparing to clonidine [7]. It appears plausible that clonidine specifically inhibits neuroimmune activities and consequently it enhances glial...
cells activities and finally it will elevate secretion of cytokine [8]. Reducing symptoms of withdrawal syndrome is due to partial inhibition of Adrenergic system; this effect is as same as prazosin and propranolol [9]. With respect to conspicuous contradictory results in various studies and in practice, regarding efficacy of clonidine in dealing with symptoms of withdrawal syndrome, we conducted this study in order to assess efficacy of clonidine in treatment of opioids withdrawal syndrome.

2. Materials and Methods

In order to assess efficacy of clonidine in treatment of opioids dependent individuals, we conducted this single-center, randomized, double-blind, placebo-controlled study on the efficacy of Clonidine in Detoxification of Opioid Dependency. We chose statistical sample via convenient sampling method. Opioids dependency was confirmed via criteria of DSM-V and patients’ declaration. Regarding confirmation of dependency, urinary test was conducted. Participants of the study included all opioids dependent men, between 20-50 year old, with history of 3-5 years dependency with daily abuse dosage of 2-5 grams. After explaining the study to participants, conducting motivational interview, acquiring written consent forms, necessity of staying two weeks hospitalization was explained to participants. Inclusion Criteria: Adults aged 15-18 year old; 2. Inpatients in Bandar-abbas psychiatric Hospital; 3. Meeting substance dependent criteria of DSM-5; Exclusion Criteria: 1. Having serious physical or psychiatric disease; 2. Using alcohol or other substances; 3. Patients who were under medical or psychotropic medications; 4. Patients, who were discharged from hospital sooner than 14 days period.

One hundred fourteen individuals were chosen via inclusion criteria and subsequently 36 patients were ruled out based on exclusion criteria. Finally, 102 individuals who maintained criteria of this study were chosen and they were randomly assigned into two groups of case group and control group. Regarding all patients, ECG, CBC, Sedimentation Rate Test, Fasting Blood Glucose, Liver Function Test(LFT) and Urine Test were done. Participants’ substance abuse was stopped from the first day of the study. Administered divided dosage of clonidine was administered orally between 0.6-0.8 mg/d; drug is produced by Tolid. Daroo Co. Regarding both groups Flurazepam capsule (40-60mg/d) and Tramadol (300-400mg/d) were administered; all drugs except clonidine in case group and placebo in control group were reduced gradually and stopped by the end of first week. In cases that experienced severe agitation or aggression, haloperidol (5-10mg) IM was administered. In case of diarrhea, nausea and vomiting symptoms based treatment was conducted. Participants of both groups were under same group-therapy treatment. Participants of both groups maintained physical examination, psychiatric interview every other day; probable side effects of clonidine and withdrawal symptoms (agitation, substance abuse tendency, aggression, insomnia, diarrhea, nausea and vomiting), were assessed based on DSM-5 criteria. Both medical doctor and patients were oblivious of administered substance (clonidine/placebo) and medical doctor assessed withdrawal symptoms independently. Data regarding withdrawal symptoms were recorded by day 7 and 14. Sample number was specified according to two sided alpha level of 0.05 and power of 0.80. After gathering data via T-test, data were analyzed via SPSS-19.

3. Results

In current study, firstly 140 individuals were chosen based on inclusion criteria. Afterwards, 36 individuals were ruled out according to exclusion criteria. One hundred four individuals were entered in this study; forty-two individuals were excluded from the study before ending 14 days period due to various reasons (Based on medical doctor comments or participants’ request). Number of individuals in case-group and control-group were 32 and 30 respectively. Mean ages of individuals were 28.6 and 29.7 in case and control group respectively (Table 1) and in both groups we didn’t notice meaningful difference with respect to level of significance. According to Table-No1, average dosage substance abuse in case and control groups were 2.9gr and 2.7gr respectively that maintained no significant difference. Average duration of substance abuse were 3.9(year) and 4.1(year) in case group and control group respectively that maintained no significant difference (Table 1). On 7th day assessment, substance abuse tendency and agitation were reduced in case group comparing to control group. However, with respect to aggression, insomnia, nausea and vomiting, diarrhea, muscle aching and lack of appetite, no significant difference was noticed between two groups. Thus, clonidine didn’t have significance impact on alleviating these symptoms (Table 2). On 14th day assessment, significance impact of clonidine on alleviating agitation and substance abuse tendency were noticed, however clonidine didn’t have any impact on alleviating other symptoms (Table 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Number</th>
<th>Number of Participants Who Finished the Study</th>
<th>Mean Age of Participants</th>
<th>Mean dosage of Substance Abuse</th>
<th>Mean Duration of Substance Abuse (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine(CaseGroup)</td>
<td>52</td>
<td>32</td>
<td>28.6</td>
<td>2.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Placebo(ControlGroup)</td>
<td>52</td>
<td>30</td>
<td>29.7</td>
<td>2.7</td>
<td>4.1</td>
</tr>
</tbody>
</table>
reducing withdrawal symptoms. However, in aforementioned and Colleagues (2009) postulate that clonidine is efficient in the current study. Broom and Colleagues (2011) and Alexander (2009) are partly consistent with the result of the efficiency of clonidine in the current study. Results of reducing withdrawal symptoms. With respect to partial that tramadol is more efficient than clonidine with respect to tolerance of withdrawal symptoms in former study can be noticed that in contrast to the current study, in aforementioned study, no specific screening was done in order to separate participants according to their type of substance abuse. In other study, alleviating withdrawal symptoms was not the first line medication for treatment and it was administered supplementary. Noticing this point is essential; there is no magical medication for treating substance abuse and behavioral modifications should be accompanied with drugs. According to the result of the current study, clonidine solely, is not ample treatment for substance abuse; hence future researches should aim to find other efficient drugs and approaches.

### 4. Discussion

According to the results of the current study, clonidine maintained positive effect on agitation and substance abuse tendency in both steps of assessment (7th, 14th day). However, clonidine didn’t have noticeable impact on other withdrawal symptoms (Aggression, Insomnia, Nausea and Vomiting, Diarrhea, Muscle Aching and Lack of Appetite). Ziaadinni and Colleagues assert that, clonidine is efficient in reducing tendency toward abuse and even fast substance withdrawal. Noticing that in contrast to current study, in aforementioned study, no specific screening was done in order to separate participants according to their type of substance abuse. In other study, alleviating withdrawal symptoms was not noticeable which is consistent with the result of the current study, clonidine solely, is not ample treatment for substance abuse; hence future researches should aim to find other efficient drugs and approaches.

### Authors’ Contribution

MBM conceived and designed the study, performed statistical analysis of the study. SMM interpreted clinical data, drafted the manuscript. All authors read and approved the manuscript.

### References


