Original Article

Amantadine as Augmentation in Managing Opioid Withdrawal with Clonidine: a randomized controlled trial

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Objective: Withdrawal symptoms are a main reason of continuous use of opioid. This study compares the efficacy of augmentation of amantadine with clonidine in decreasing opioid withdrawal symptoms.
Methods: This double-blind randomized clinical trial was carried out in the detoxification and rehabilitation inpatient ward at Razi Hospital, Tabriz, Iran during 2012. The patients were randomly assigned to receive clonidine or clonidine plus amantadine; and withdrawal symptoms were evaluated in the admission day and 24, 48, and 72 hours later. Data were analyzed using SPSS by the 2*2 repeated analyses of variances (ANOVA).
Results: From the total of 69 participants, 30 patients completed the trial in each group. The severity of symptoms, however, had an increasing trend in both groups. Analysis of variance of the symptom severity score (by The Clinical Opiate Withdrawal Scale) revealed a significant group-time interaction, and the patients who were receiving amantadine experienced milder symptoms .
Conclusions: Treatment of opioid withdrawal symptoms with amantadine and clonidine would result in a better outcome compared with clonidine alone.
Keywords: *Amantadine, Clonidine, Withdrawal Syndrome*

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Addiction is accompanied by several physiological changes to human body as well as several social, economic and financial effects on body of the public. Detoxification is mostly the first step in the treatment of substance dependence and is a focus of research to find shortened cost-effective methods (1). Long-term opioid use increases the cyclic adenyl cyclase in noradrenergic system of the locus coeruleus. Hence, rapid opioid cessation after this compensatory change results in severe adrenergic symptoms (Ref.?) The therapeutic effects of some pharmacological agents (opioid agonist, opioid agonist-antagonist, opioid antagonists, and alpha-2 agonists) are well studied and confirmed for opioid detoxification (1). The effectiveness of clonidine as an alpha-2 agonist is established in randomized placebo controlled clinical trials as well (2). Three main mechanisms are responsible for the tolerance to and withdrawal of opioids including the up-regulation of adenyl cyclase, nitric oxide synthetase and activation of NMDA receptors. Consequently, the alpha-2 agonists (e.g., clonidine) and NMDA antagonists (e.g., dextromethamphetamine and ketamine) may minimize the tolerance phenomenon and could decrease the withdrawal symptoms (3). Bisaga et al. demonstrated that memantine, a non-competitive NMDA antagonist, would decrease the symptoms of naloxone withdrawal in heroin-addicted patients (4). However, the results are very limited for another NMDA antagonist, amantadine, which carries dopaminergic, noradrenergic and serotonergic properties all together (5). Despite the promising results for its effectiveness to treat cocaine dependent patients with withdrawal symptoms (6, 7), there are very few studies examining its efficacy in opioid withdrawal.

A successful detoxification as the first step of the treatment for opioid dependence may motivate these patients. Considering the fact that NMDA antagonists (such as amantadine) and alpha-2 adrenergic agonists (such as clonidine) might have unique contributions in this process. The current study aimed to evaluate the synergistic effects of these drugs in control and relief of opioid withdrawal symptoms.

Material and Methods

This double-blind randomized clinical trial was carried out in the detoxification and rehabilitation ward of Razi

Hospital, Tabriz, Iran. This trial is registered with the Iranian Clinical Trials Registry (IRCT 201207196972N2) and the procedure was approved by ethical committee of Tabriz University of medical sciences .

The patients who were admitted to the hospital and fulfilled the inclusion criteria were randomly assigned into two groups. Written consent was obtained from all the participants. The flow diagram of the process is provided in Figure 1.

The inclusion criteria were selected on previous evidences including the relation between gender and the response to detoxification (8), as well as previous studies with similar methodology (9) and those evaluating the effective factors in successful detoxification (10, 11). The inclusion criteria were male sex, age range of 20 to 40 years, a positive morphine test and the diagnosis of opioid dependence according to the DSM-IV-TR criteria. The criteria were evaluated by a psychiatric clinical interview, and patients with psychotic symptoms were excluded. History or current physical/general medical illness resulted in exclusion. Physical illness included all conditions requiring immediate treatment (e.g., trauma) or added risk for the patients who were supposed to tolerate adrenergic symptoms (e.g., diabetes mellitus, hepatic and renal insufficiency; creatinine ≥ 1.2 mg/dl and ALT≥ 40 IU).

The first group received clonidine tablet 0.4-1.2 mg per day in three divided doses (according to the patient's tolerance described later), Clonazepam tablet 1 mg each eight hours and acetaminophen tablet 500 mg each six hours. Acetaminophen was used as an analgesic drug and clonazepam was used as a sedative and anxiolytic agent according to the standard detoxification protocol. The second group received all of the medications described above plus amantadine capsule 100 mg each 12 hours.

The level of tolerance to possible side effects of clonidine was assessed according to a decrease in the systolic blood pressure. The dose was modified in a systolic blood pressure of less than 90 mmHg. All of the medications were selected from available preparations from the same company.

The severity of withdrawal symptoms was evaluated at the admission, and the measurements were repeated after 24, 48, and 72 hours. This evaluation was performed by the same blinded physician and according to the Clinical Opiate Withdrawal Scale (COWS).The Clinical Opiate Withdrawal Scale (COWS) is used by the American Association of Addiction Medicine measuring clinical severity of withdrawal symptoms (12). This questionnaire measures the severity of 11 types of opioid withdrawal symptoms: tremor, resting pulse rate, sweating, yawning, restlessness, pupil size, bone or joint aches, anxiety or irritability, rummy noise of tearing, gastrointestinal upset and gooseflesh skin. The total score indicates the severity of opioid withdrawal symptoms. The severity of symptoms may be subdivided into mild (5-12 scores), moderate (13-24 scores), relatively severe (25-36 scores) or very severe (more than 36 scores) according to the total score.

Two physicians were engaged in the process therefore the consequent inter-observer reliability was assessed in 18 patients. The Pearson correlation test showed a positive significant association ($P < 0.0001$) with a Cronbach's alpha to be 0.907 showing a high reliability .

The data were analyzed by SPSS ver.17 and included the patients who completed the study. Data were presented as Mean SD. The principal statistical analysis a 2 × 2 repeated analysis of variance (ANOVA) design with a group factor (clonidine vs. clonidine and amantadine) evaluated the severity of the withdrawal symptoms, and a repeated-measures factor (pre-treatment, 24, 48, and 72 hours after admission). The level of significance was set at $P < 0.05$.

Results

From the total of 69 participants, 30 patients completed the trial in each group. Basic characteristics including withdrawal symptoms at admission time had no significant difference between the two groups; all of the patients were male (Table 1). The mean dose of clonidine was 0.9±0.3 in patients receiving only clonidine and 0.8±0.4 in patients receiving added amantadine .

A significant group×time interaction ($F = 6.55$; $p=0.013$) was observed by the analysis of variance of the symptom severity score (by COWS), and patients receiving amantadine plus clonidine had milder symptoms during the three days. As described in Table 1 and illustrated in Figure 2, symptom severity in the two groups had a different pattern, and patients receiving amantadine experienced milder symptoms in each single measurement as well .

The severity of symptoms, however, had an increasing trend in both groups, with the greater intensity on day three.

Table 1: Age and symptom severity of the study sample

	Clonidine alone, n=30	Clonidine and Amantadine, n=30	P Value*
Age	28.9±4.3	28.1 ±3.9	0.673
Initial symptoms	2.67 ± 1.91	2.53 ± 2.11	0.814
Symptom at 24 hours	6.03 ± 2.87	4.50 ± 2.51	0.031
Symptom at 48 hours	8.06 ± 3.02	5.33 ± 3.13	0.001
Symptom at 72 hours	9.83 ± 5.19	6.27 ± 4.28	0.001

*P values are reported based on independent t tests.

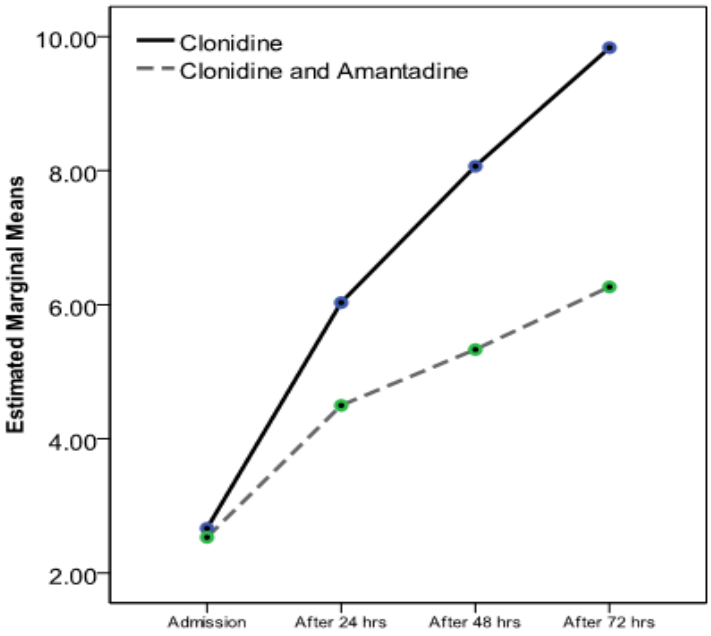

Figure 1: Flow diagram of opioid dependent patients admitted for detoxification

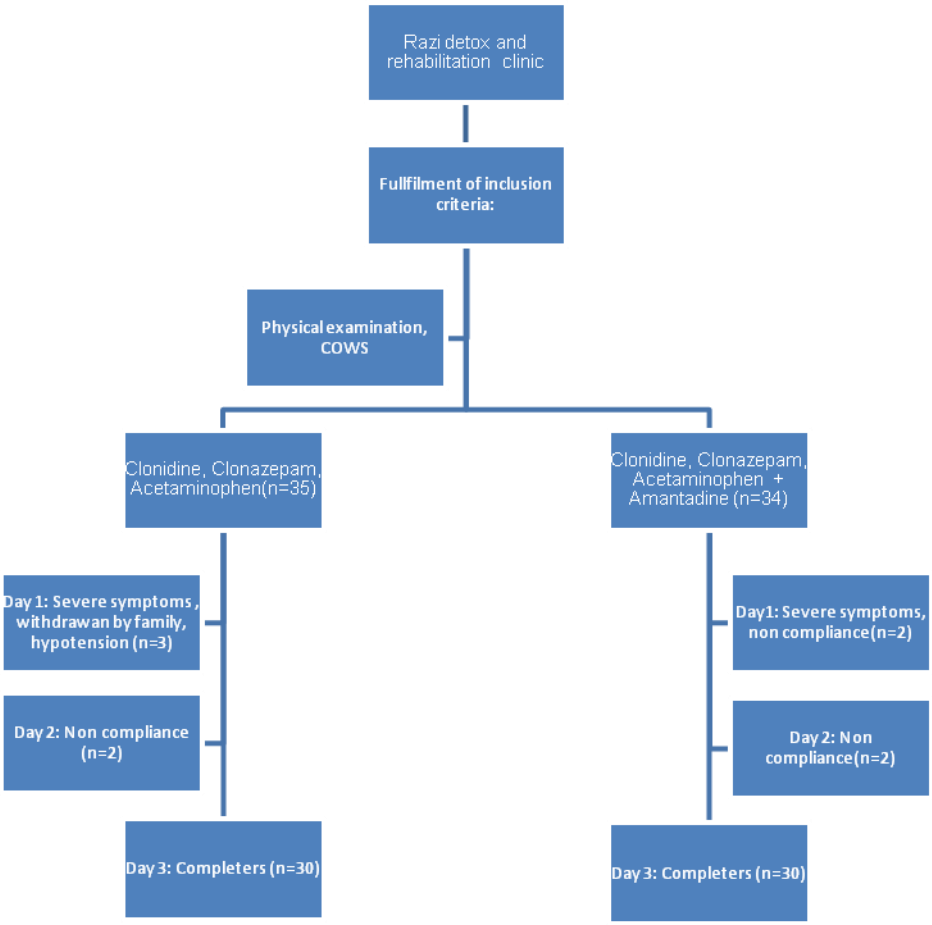

Figure 1: Withdrawal symptom score in two groups receiving Clonidine alone or clonidine and Amantadine in continuous measurements.

Discussion

The findings of this study revealed that amantadine added to clonidine has a better effect in controlling the opioid withdrawal symptoms compared to clonidine alone, and this superior effect lasts for the first three days .

Controlling the excess activity of the adrenergic system is the underlying mechanism for decreasing the opioid withdrawal symptoms by alpha-2 agonists such as clonidine (13). Ever since 1980 that clonidine was introduced for this purpose (14, 5, 15) it has been a part of detoxification regimen in the majority of approaches (16), but its efficacy may not be optimal when used alone. As shown in the result of the current study, amantadine augmentation improves the results.

N-methyl-D-Aspartate (NMDA) receptors are an important part of the glutaminergic neurotransmitter system which is an activator mediator of the central nervous system. Despite its critical role in synapses development, hyperstimulation of these receptors is neurotoxic as seen in strokes, convulsive attacks and head trauma (14). Functions of the glutaminergic and opioid neurotransmitter systems have several connections .

Memantine is a NMDA-antagonist which has been proposed as an effective agent in the treatment of opioid and cocaine withdrawal and dependence. Studies report that memantine is only effective in the reduction of subjective symptoms of withdrawal syndrome (17). Dextromethorphane is another antagonist of NMDA receptors that is used as an antitussive, adjuvant analgesic, alcohol and opioid withdrawal symptom reducer (18).

The results are not conclusive for amantadine. Kampman et al. demonstrated that amantadine is more effective than placebo to alleviate the cocaine withdrawal symptoms (19). Other studies showed the efficacy of amantadine in controlling withdrawal symptoms in cocaine-addicted patients as well as decreasing its use (20, 21). Amantadine was unable to have any additive effect on methadone tapering to detoxify heroin-dependent inpatients (22). Thought these studies have different methods, and further research is needed to make a conclusion.

Amantadine was first used for treatment and prevention of influenza A. According to the review by Huber et al. this medication has valuable therapeutic effects in the treatment of Parkinson's disease, head trauma, dementia, multiple sclerosis and cocaine withdrawal syndrome (23). Amantadine has dopaminergic, noradrenergic and serotonergic properties. It inhibits the monoaminoxidase Type A as well as NMDA receptors resulting in increased beta-endorphin levels (22). Therefore, it seems a potential agent for managing withdrawal symptoms. The results of this study give a promising evidence for the therapeutic effect of amantadine in reducing withdrawal symptoms. Even though symptom severity had an increasing trend in the first three days of opioid abstinence, the results were superior compared to the effects of clonidine. Although most intense opioid withdrawal symptoms are demonstrated in the first 72 hours, further studies may observe patients for a longer period.

The results of this study are limited in part. The study sample consisted of patients volunteered for detoxification treatment. Their high motivation could influence their subjective complaints in part and may decrease the generalization of the results. However, the questionnaire measured several objective symptoms as well. The accuracy was increased due to the double blind setting. Similar to most of the studies in this field, we could not include a placebo group due to the ethical issues. A probable effect for the mean dose of clonidine was not evaluated in this study for patients received the medication based on their symptoms and the amount was only limited because of the side effects. Therefore, the results are more close to the outcome in practice.

Conclusion

Amantadine is effective in the relief of opioid withdrawal symptoms. This may result in increasing the efficacy of clonidine and reducing the need to opioid agonists.

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