Effectiveness Of Atomoxetine For Cognitive Function In Methamphetamine Dependent Patients; A Randomized Controlled Trial

Ali Rabiey¹, Peyman Hassani-Abharina ², Ali Reza Moravveji³, Peyman Mamsharifi⁴, Amir Ghaderi¹,⁵, Hamid Reza Banafshe⁶,⁷*

¹ Department of addiction studies, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.
² Institute for Cognitive Science Studies (IRICSS), Brain and Cognition Clinic, Tehran, Iran.
³ Department of Community Medicine, Kashan University of Medical Sciences, Kashan, Iran.
⁴ Department of Psychology, Allameh Tabataba’i University, Tehran, Iran.
⁵ Clinical Research Development Unit-Matin/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran.
⁶ Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran.
⁷ Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

* Corresponding Author. E-mail addresses: Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran, banafshe57@hotmail.com (HR. Banafshe). Tel: +98-31-55463378; Fax: +98-31-55463377.

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Abstract

**Background:** A substantial body of evidences indicates that methamphetamine abuse can lead to persistent and serious cognitive dysfunction. Preclinical studies and early pilot clinical investigations have suggested that atomoxetine, a cognitive enhancer may be useful in improving of cognitive dysfunction. The present study evaluated whether atomoxetine would effect on cognitive dysfunction in methamphetamine dependent patients.
Methods: Participants with methamphetamine dependence (N = 86) which were on methadone maintenance therapy (MMT) were enrolled in a double-blind, placebo-controlled randomized clinical trial. This investigation was performed on 86 subjects to consume either 40 mg/day atomoxetine (n = 45) or placebo (n = 41) for 8 weeks. Between January 2016 and June 2017, volunteers were selected from methamphetamine abusers in MMT centers in Kashan, Iran. They completed at the first and each monthly visit the Cognitive Abilities Questionnaire for assessing the cognitive functions. The data were analyzed using Independent sample t test, Mann Whitney test and chi square with SPSS version 20.0.

Results: This study revealed that, atomoxetine treatment improved some of the cognitive dysfunctions in methamphetamine users including memory, inhibitory control, selective attention, decision making, planning, sustained attention, and cognitive flexibility in methamphetamine users (p<0.05), but the social cognition improvement was less than others (p=0.107). There were only mild side effects in placebo and atomoxetine groups.

Conclusions: The findings show the efficacy of atomoxetine for improving the cognitive dysfunction in methamphetamine users and suggest potential efficacy of atomoxetine for treating them.

Keywords: Atomoxetine, Methamphetamine, Dependent, Cognitive effects

1. Introduction

Methamphetamine is a psycho-stimulant drug, and its dependence causes many public health problems, and criminal justice cases (1). A substantial body of evidences indicates that methamphetamine abuse can lead to persistent and serious psychiatric, cognitive and neurological dysfunction (2, 3). Methamphetamine addiction may lead to profound cognitive
deficits (4), including deficits in executive functions, verbal memory, processing speed, response inhibition, and attention tasks (5, 6). Out of these cognitive impairments, executive functions are most commonly impaired in methamphetamine-addicted individuals (6). “Executive function” is a comprehensive term, including a wide range of cognitive processes and behavioral competencies. It also consists of verbal reasoning, problem solving, planning, sequencing, focusing, multitasking, cognitive flexibility, and dealing with novelty (7-10). Similarly, methamphetamine dependent individuals showed deficits in memory, attention, set shifting, response inhibition, and decision-making abilities (11-13). The severity of impairments in verbal memory and psychomotor function for methamphetamine users were correlated with loss of dopamine transporters in the striatum and nucleus accumbens (14, 15). Atomoxetine, a cognitive enhancer, is marketed for ADHD and has been shown to be a generally well-tolerated and efficacious treatment for ADHD across prolonged treatment (16, 17). In the study by Rabiey et al. (18), demonstrated that atomoxetine appropriate efficacy in suppressing methamphetamine craving and possible potential effects on its treatment. In addition, DeVito et al. (19), reported that 40 and 80 mg atomoxetine, over three sessions had only modest effects on mood and cognitive enhancement in abstinent cocaine users. Also, Weintraub et al. (20), demonstrated that atomoxetine treatment was not efficacious for the treatment of clinically significant depressive symptoms in Parkinson disease, but was associated with improvement in global cognitive performance and daytime sleepiness. In a randomized clinical trial (RCT) atomoxetine (80 mg daily) for 8 weeks in people with schizophrenia has limited benefit for improving cognition (21). Another study showed that a three doses of atomoxetine in smokers with schizophrenia no statistically significant improvement in performance on cognitive measures (22). It is a selective inhibitor of the norepinephrine transporter, which regulates norepinephrine neurotransmission by facilitating reuptake of norepinephrine into presynaptic nerve terminals. Inhibition of the norepinephrine
transporter with atomoxetine increases extracellular levels of norepinephrine and dopamine in the prefrontal cortex but not the striatum (23). In addition, atomoxetine inhibits serotonin reuptake to a very small extent (24). Therefore, it is important to assess its effects on cognitive domains in individuals with methamphetamine–dependent patients. We hypothesized that atomoxetine would improve performance in cognitive functions including memory, inhibitory control, selective attention, decision making, planning, sustain attention, social cognition and cognitive flexibility in methamphetamine users. A literature review revealed limited information about the effects of atomoxetine on cognitive functions in methamphetamine users. The current study was designed to evaluate the effects of 40 mg of atomoxetine on cognitive functions among methamphetamine users.

2. Material and methods

2.1. Participants

The study design was a double-blind, placebo-controlled and randomized clinical trial and its protocol was reviewed and approved by the Kashan University of Medical Sciences (KAUMS/94126) Research Ethics Committee in accordance with the Declaration of Helsinki and registered in the Iranian website for registration of clinical trials at http://www.irct.ir: IRCT (IRCT2016041627413N1) and all participants provided written informed consent (Ethical Code: IR.KAUMS.REC.1394.127).

The patients included those who had been treated with methadone for a long time. Then, methamphetamine was used to reduce methadone complications, but after a while they were addicted to methamphetamine during their MMT. We examined in this trial the potentially beneficial effects of atomoxetine in improving cognitive dysfunctions in methamphetamine abusers which are on methadone maintenance therapy. The study enrolled treatment-seeking volunteers from methadone maintenance therapy centers in Kashan, Iran, meeting DSM-IV-
TR criteria for methamphetamine dependence to study admission. They had methamphetamine and methadone positive and opioid negative urine toxicology test results at study enrolment. All participants were screened for medical and neuropsychiatric disorders by the Structured Clinical Interview which previously designed in Iranian National Center for Addiction Studies (INCAS), Physical examination and laboratory testing were used for medical disorders screening too by a study physician. History of drug abuse and economic and social status evaluated by the same Structured Clinical Interview of INCAS (25).

Participants included men, aged 18-50 years old who met the following inclusion criteria. The treatment-seeking volunteers on methadone maintenance therapy meeting DSM-IV-TR criteria for methamphetamine dependence who reported methamphetamine use on two or more days per week in the month prior and methamphetamine and methadone-positive urine toxicology test results at the beginning of the study and no other current dependence or abuse of other drugs or alcohol (except tobacco) and exclusion criteria included severe cardiovascular disorder as history of myocardial infarction (MI), cerebrovascular accident (CVA), congestive heart failure (CHF) or an unstable medical condition (e.g., untreated bacterial infection), hypertension, liver enzymes greater than 3 times the upper limit of normal, liver failure or acute hepatitis, current psychiatric disorders as bipolar disorder or schizophrenia or major depression, taking a mood stabilizer, antidepressant or antipsychotic medication (including using a (MAOI) within the preceding 2 weeks), Suicide attempts or suicidal ideations, narrow angle glaucoma, pheochromocytoma and history of hypersensitivity to atomoxetine.

We assessed for eligibility 143 patients and Excluded 32 persons for different reasons of exclusion criteria. Then other subjects were randomized in two groups. During the treatment, 25 patients could not complete the trial (9 patients from treatment group and 16 patients from control group). Finally, the samples included 45 patients in atomoxetine group and 41 subjects in placebo group and they completed the intervention.
2.2. Randomization and blinding

Randomization assignment was conducted using computer-generated random numbers. Allocation and randomization were concealed from the researchers and participants until the final analyses were completed. The randomized allocation sequence, enrolling participants and allocating them to interventions, were conducted by a trained staff at the clinic. For proper
blinding, the atomoxetine and placebo were prepared in precisely the same size, color, and packaging. Also, numbered drug containers were used to conceal random allocation.

2.3. Assessment of outcomes
Memory, inhibitory control or selective attention, decision making, planning, sustain attention, social cognition and cognitive flexibility were considered as the primary outcomes.

2.4. Procedures and variables assessment
The first group received atomoxetine capsules (Tadbir Kalaye Jam Co, Iran) 40 mg/day and the other group received the placebo capsules in the same form and packages as atomoxetine. Participants were treated as outpatients for 8 weeks. At each visit, participants received one-week supply of medication in blister packages and instructed in how to self-use the medication at home. To monitor the adherence, they were required to bring the drug packets to the clinic at the next visit for capsule counts. They completed at the first and at each monthly visit Cognitive Abilities Questionnaire (26) for assessing the performance in cognitive functions including memory, inhibitory control, selective attention, decision making, planning, sustain attention, social cognition and cognitive flexibility.

The Cognitive Ability Questionnaire (CAQ) has been prepared on a five-part Likert scale. Includes 30 items. This questionnaire was used to evaluate seven cognitive abilities Including memory, control and selective attention, decision making, planning, sustained attention, social recognition and cognitive flexibility. This questionnaire is in Persian language. Internal correlation (Cronbach’s alpha) was 0.834 and test reliability was P <0.01 (26).

2.5. Sample size
The main focus of present study was evaluation the effects of atomoxetine on cognitive function in methamphetamine dependence. To estimate the sample size, we used a randomized clinical trial sample size formula where type one (α) and type two errors (β) were 0.05 and 0.20 (power=80%), respectively. Based on a previous study (18), we used a standard deviation (SD)
of 20.07 and 13.1 for intervention and placebo groups, and a difference in mean (d) of 9.5, considering craving (Desire for Drug Questionnaire) as the key variable. The calculation shown 50 persons were needed in each group. Assuming a dropout of 5 persons per group, the final sample size was determined to be 55 persons per group.

2.6. Statistical analysis

Before performing t test, we used the Kolmogorov-Smirnov test to evaluate the normality of the data. Statistical significance was set at two-tailed P<0.05. The data were analyzed with SPSS version 20.0 statistical software. Data are presented as mean ± standard deviation (SD). The demographic and cognitive function variables were compared between atomoxetine and placebo groups using the chi-square test, independent t test, and Man-Whitney.

3. Results

3.1 Baseline Demographics

86 patients completed the study. These subjects all had the normal range of EKG, liver function tests (i.e., AST\(^1\) and ALT\(^2\)) and physical examination at the beginning. The mean (SD) Age in atomoxetine group was 32.60 (7.958) years, and in Placebo group was 33.58 (6.445) years. There was not any significant differences between two groups in demographic information (e.g., age, marital and educational status), duration of methamphetamine abuse and history of other important substance abuse (Table 1). Fig. 1 shows the enrollment, randomization and follow-up of study participants.

Table 1. General characteristics of the study participants.

<table>
<thead>
<tr>
<th>Character</th>
<th>Atomoxetine group (n=45)</th>
<th>Placebo group (n=41)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>7.958±32.60</td>
<td>33.58±6.445</td>
<td>0.540*</td>
</tr>
</tbody>
</table>

\(^1\) Aspartate aminotransferase (AST)

\(^2\) Alanine aminotransferase (ALT)
### Marital status

<table>
<thead>
<tr>
<th>Status</th>
<th>Before</th>
<th>After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent marriage</td>
<td>19(42.22%)</td>
<td>24(58%)</td>
<td>0.301b</td>
</tr>
<tr>
<td>Single/ Never married</td>
<td>18(40%)</td>
<td>9(22%)</td>
<td></td>
</tr>
<tr>
<td>Separated/but not divorce</td>
<td>5(11.11%)</td>
<td>4(10%)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>3(6.66%)</td>
<td>4(10%)</td>
<td></td>
</tr>
</tbody>
</table>

### Educational Status

<table>
<thead>
<tr>
<th>Level</th>
<th>Before</th>
<th>After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illiterate</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0.672b</td>
</tr>
<tr>
<td>Elementary</td>
<td>8(17.77%)</td>
<td>9(22%)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>10(22.22%)</td>
<td>5(12%)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>13(28.88%)</td>
<td>18(44%)</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>12(26.66%)</td>
<td>9(22%)</td>
<td></td>
</tr>
<tr>
<td>BSc</td>
<td>2(4.44%)</td>
<td>0(0%)</td>
<td></td>
</tr>
</tbody>
</table>

### Age of first heroin use

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean Differences (Mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After intervention</td>
<td>22.2±4.4</td>
<td>0.35*</td>
</tr>
<tr>
<td>Before intervention</td>
<td>21.2±4.9</td>
<td></td>
</tr>
</tbody>
</table>

### Duration of methamphetamine use

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean Differences (Mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After intervention</td>
<td>3.6±1.9</td>
<td>0.31*</td>
</tr>
<tr>
<td>Before intervention</td>
<td>3.2±1.7</td>
<td></td>
</tr>
</tbody>
</table>

### Days of methamphetamine use in the last month

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean Differences (Mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After intervention</td>
<td>19.4±6.5</td>
<td>0.29*</td>
</tr>
<tr>
<td>Before intervention</td>
<td>18.0±5.7</td>
<td></td>
</tr>
</tbody>
</table>

### Duration of methadone use

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean Differences (Mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After intervention</td>
<td>6.7±2.1</td>
<td>0.81*</td>
</tr>
<tr>
<td>Before intervention</td>
<td>6.8±2.1</td>
<td></td>
</tr>
</tbody>
</table>

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**3.2. The effects of atomoxetine on cognitive functions.**

As shown in table 2, atomoxetine significantly improved cognitive functions including memory, inhibitory control, selective attention, decision making, planning, sustain attention, social cognition and cognitive flexibility in methamphetamine use. P values show the differences between after and before the study in each group and are resulted from paired t-test and Man-Whitney.

**Table 2.** Means (± standard deviation) of cognitive functions including memory, inhibitory control, selective attention, decision making, planning, sustain attention, social cognition and cognitive flexibility in methamphetamine users after and before the study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Mean Differences (Mean ± SD)</th>
<th>P-value</th>
<th>Effect size</th>
<th>confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>Atomoxetine group</td>
<td>Placebo group</td>
<td>t-value</td>
<td>p-value</td>
<td>d-value</td>
<td>Lower CI</td>
<td>Upper CI</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------</td>
<td>---------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Memory</td>
<td>17.00±3.249</td>
<td>13.67±3.115</td>
<td>3.31±3.732</td>
<td>0.006</td>
<td>0.82</td>
<td>-1.41</td>
<td>-0.87</td>
</tr>
<tr>
<td>Inhibitory control</td>
<td>16.66±2.988</td>
<td>15.37±2.981</td>
<td>1.29±2.272</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or selective attention</td>
<td>17.68±3.429</td>
<td>14.65±3.169</td>
<td>2.64±3.207</td>
<td>0.028</td>
<td>0.51</td>
<td>-2.23</td>
<td>-0.19</td>
</tr>
<tr>
<td></td>
<td>17.27±3.033</td>
<td>16.29±3.487</td>
<td>1.20±2.676</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decision making</td>
<td>15.30±3.085</td>
<td>13.21±3.226</td>
<td>2.05±3.200</td>
<td>0.046</td>
<td>0.35</td>
<td>-1.77</td>
<td>-0.52</td>
</tr>
<tr>
<td></td>
<td>15.51±3.067</td>
<td>14.78±3.267</td>
<td>0.73±2.684</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planning</td>
<td>9.23±2.177</td>
<td>7.65±2.181</td>
<td>1.60±2.073</td>
<td>0.036</td>
<td>0.42</td>
<td>-0.75</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td>9.56±2.145</td>
<td>8.88±2.462</td>
<td>0.68±1.809</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustain attention</td>
<td>9.32±2.021</td>
<td>7.23±2.057</td>
<td>2.02±2.279</td>
<td>0.033</td>
<td>0.41</td>
<td>-1.94</td>
<td>-0.21</td>
</tr>
<tr>
<td></td>
<td>9.24±1.758</td>
<td>8.34±2.045</td>
<td>0.95±2.236</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social cognition</td>
<td>9.73±1.689</td>
<td>11.00±1.839</td>
<td>-1.36±1.859</td>
<td>0.107</td>
<td>0.12</td>
<td>1.32</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>9.22±1.509</td>
<td>9.88±1.847</td>
<td>-0.66±2.045</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>14.11±2.535</td>
<td>10.23±2.136</td>
<td>3.74±3.013</td>
<td>0.003</td>
<td>0.69</td>
<td>-1.70</td>
<td>-0.97</td>
</tr>
<tr>
<td></td>
<td>13.22±2.253</td>
<td>10.98±2.372</td>
<td>2.24±1.090</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a= Mann Whitney test\)

\(^d= independent sample t test\)

### 3.3. Safety

No significant adverse experiences were reported, but there were some mild side effects as headache and Dizziness, Insomnia, Abdominal pain, nausea, constipation, dry mouth, and Appetite loss.
4. Discussion

Our findings showed that, atomoxetine treatment at 40mg/day improved some of the cognitive functions in methamphetamine users. Atomoxetine significantly improved cognitive functions including memory, inhibitory control, selective attention, decision making, planning, sustain attention, and cognitive flexibility in methamphetamine users but the social cognition improvement was less than others.

These findings are consistent with previous preclinical and clinical studies supporting the role of the noradrenergic system in mediating acute amphetamine responses. Mehmet Sofuoglu et al. reported that atomoxetine's capacity to attenuate some of the physiological and subjective responses to dextroamphetamine supports its potential use for stimulant addiction (27). In a previous clinical trial with cocaine users, was reported that atomoxetine may have a favorable tolerability and abuse potential profile in individuals with CUDs who are currently in early abstinence from cocaine but only showed very modest evidence of cognitive enhancing effects (28). Atomoxetine showed modest effects on improving performance on a measure of discriminability (IMT d'), which taps into processes of attention, response inhibition and memory, although this finding did not survive correction for multiple comparisons (28). In a previous study, with only male cocaine users in the medication condition, atomoxetine improved performance on the n-back, a task of working memory and sustained attention, and speeded corrected responses on a continuous performance task, without affecting the performance on other measures of cognitive control (Stroop test), psychomotor speed and cognitive flexibility/set-shifting (Trails) (29). Stoops et al. reported that atomoxetine treatment did not affect the subjective effects of intranasal cocaine in stimulant users (30). Based on the similarities between the actions of stimulants, one may expect atomoxetine to act similarly on cocaine and amphetamine responses. However, there are significant differences between the
pharmacological effects of cocaine and amphetamines. Most importantly, accumulating evidence indicates that norepinephrine contributes more to the effects of amphetamine than to the effects of cocaine. In a recent study, dextroamphetamine and methamphetamine were 5-9 times more potent at the norepinephrine transporter than the dopamine transporter (31). In contrast, cocaine was equally potent at norepinephrine transporter and dopamine transporter (31). In another study, the initiation of psychomotor sensitization to dextroamphetamine, but not to cocaine, was dose-dependently inhibited by an alphal-adrenergic blocker prazosin or by an α2-adrenergic agonist clonidine in rats (32). Our findings are consistent with these studies suggesting that norepinephrine contributes to acute amphetamine responses. As many preclinical and clinical studies indicate, norepinephrine transporter inhibitors acutely increase synaptic levels of norepinephrine. However, with prolonged treatment, norepinephrine response to pharmacological and behavioral challenges is attenuated while the tonic norepinephrine activity stays elevated. This is possibly due to neuroadaptation including both increased stimulation of inhibitory alpha2 adrenergic auto-receptors and down-regulation of the postsynaptic noradrenergic receptors (33).

In our study we used atomoxetine 40 mg/day but it is better that effects of atomoxetine evaluated in upper doses in the future. This may show that upper doses of drug can also be more effective.

This study had some limitations. The first limitation was the lack of female patients in the sample. This is because of the fewer proportions of females in meth users in our country. The second limitation was our evaluation of the compliance of patients to the atomoxetine regimen through patient reports and pill counts. This may be better evaluated and managed in future studies. Another limitation of the study is the small sample size. However, this result may warrant a replication with larger samples. Our findings suggest new avenues for future research, for example, to elucidate the brain mechanisms underlying the atomoxetine effects
on cognitive enhancing to methamphetamine using functional magnetic resonance imaging (fMRI). Hence, studies assessing the effects of chronic atomoxetine therapy to evaluate long-term changes in neurocognitive and behavioral outcome measures are warranted. Further studies are warranted to examine the therapeutic utility of atomoxetine for amphetamine addiction.

**Conclusion**

This study confirms the clinical and safety tolerance of atomoxetine, and its appropriate efficacy on cognitive dysfunction in methamphetamine users. Further evidence are needed to confirm our findings.

**Declarations:**

**Ethics approval and consent to participate**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

**Consent for publication**

Not applicable.

**Availability of data and material**

The primary data for this study is available from the authors on direct request.

**Competing interests**

The authors declare no conflict of interest.

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**Authors' contributions**

AR, PH-A, ARM and HRB contributed in conception, design, statistical analysis, drafting of the manuscript and supervised the study. AR, AGH and HRB contributed in data collection and manuscript drafting. AR, AGH and PM contributed in edit native manuscript drafting.
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Clinical trial registration number

www.irct.ir: IRCT2016041627413N1

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