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The Role of Short-term Low-Dose Atorvastatin in Improving Endothelial Function in Normolipidemic Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) imposes a heavy burden on Iran's health system. Although therapeutics are prescribed for HFpEF, no evidence-based therapy has been generally accepted. Endothelial dysfunction is currently recognized as a promising therapeutic target for patients with HFpEF.

Methods: A total of 40 patients who referred to the echocardiography clinic of Imam Khomeini hospital in Ahvaz participated in this randomized clinical trial. Echocardiographic and clinical criteria for HFpEF and normal coronary angiography were recorded in all subjects. The patients did not have indications of statin therapy or a prior history of statin consumption. They were randomly assigned to the atorvastatin (20 mg once daily) and placebo groups ($n=20$ per group). Flow-mediated dilatation (FMD) of the brachial artery was measured in the two groups before the trial and after the two-month treatment period. Clinical trial registration is available from: https://irct.behdasht.gov.ir/, (identifier: IRCT2015010320538N1).

Results: The patients' mean age was 65 years, 40% were male, and 60% were female. There was a significant improvement in FMD only in the atorvastatin group (+41.5% in males and+18.25% in females) ($P<0.001$). The low-density lipoprotein (LDL) level significantly decreased after treatment in the atorvastatin group but not in the placebo group. The variation in FMD was not dramatically associated with the reduction in serum LDL in the two groups.

Conclusion: Atorvastatin has advantageous effects on the vascular endothelial function of HFpEF, and this effect is not associated with its lipid-lowering properties.

Keywords: HFpEF, Atorvastatin, Endothelial, Flow-mediated dilatation, Low-density lipoprotein

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Introduction

Heart failure (HF) is a vital public health issue that mainly affects the elderly. Its worldwide prevalence is over 23 million people, which accounts for remarkable morbidity and mortality rates (1,2). The occurrence of heart failure with preserved ejection fraction (HFpEF) has increased by about 48% to 57% in recent years. HFpEF is responsible for the deaths of approximately 1 in 8 individuals aged 65 and older (1). The heterogeneous and intricate nature of HFpEF is marked by cardiac remodeling, autonomic imbalance, and diastolic dysfunction. A significant aspect associated with HFpEF pathophysiology is the presence of both macrovascular and microvascular dysfunctions. However, vascular endothelial dysfunction is closely linked to the performance of cardiomyocytes, resulting in a reduced capacity for dilation and an increase in cellular rigidity (1,2). The flow-mediated dilation (FMD) method is a non-aggressive approach to analyzing vascular endothelial function, especially at the microcirculation level (3). Aging, body mass index, blood pressure, and smoking lower FMD while a healthy lifestyle changes and medical therapy improves it (4,5). FMD is a simple, accessible, and reliable tool for non-invasive assessment of vascular function. Although vascular dysfunction of the endothelium, assessed using FMD, is well established in patients with heart failure with reduced ejection fraction (HFrEF), HFrEF is independently considered a risk factor for a higher likelihood of clinical cardiac events and poor prognosis. In patients with HFpEF, much less is known about assessing the effects of different treatment protocols on vascular endothelial function using the FMD procedure (2). Despite the lack of evidence-based HFpEF therapy to improve mortality rates in HFpEF patients, the current treatments remain suboptimal (6,7). Recently, the

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role of endothelial dysfunction and atherosclerosis in HF as novel therapeutic targets has been examined (8,9). In addition to its ability to lower lipid levels, statin therapy shows desirable effects, such as anti-antithrombotic and inflammatory actions, and can improve endothelial function (10,11). Therefore, further studies are needed to reveal more details on the mechanisms of statins' effects on endothelial function. This clinical trial aimed to investigate the beneficial effects of atorvastatin on endothelial vascular function in HFpEF patients.

Methods

The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, approved the study protocol, and written informed consent was obtained from all patients. Forty patients with HFpEF participated in the current triple-blinded, randomized, and placebo-controlled clinical trial (identifier: IRCT2015010320538N1) at the cardiology outpatient clinic of Imam Khomeini Hospital from March 2014 to January 2015. A self-determining researcher provided computer-generated random allocation cards. The person responsible for randomizing and allocating groups was blinded to the patients' condition and the study procedure. The data analyst and all patients were blinded to group allocation, ensuring a triple-blinded research. Independent pharmacists dispensed active or placebo tablets based on a computer-generated randomization list. Triple blinding refers to a protocol in which the participants, the clinicians, and the data analysts are unaware of which intervention patients are receiving throughout the entire clinical trial. Inclusion criteria were as follows: diagnosis of HFpEF confirmed based on the current clinical and echocardiographic criteria (12), not taking any statins, and having a normal coronary angiography (within the last two years). Exclusion criteria were as follows: indication of using statin according to the 2013 AHA guideline (based on medical history, diabetes profile, and ASCVD [atherosclerotic cardiovascular disease] score) and the presence of any contraindication to atorvastatin use (e.g., breastfeeding, pregnancy, increased liver enzymes, hypersensitivity, or hepatic failure) (13).

This trial was carried out based on the principles outlined in the Declaration of Helsinki. The participants were randomly assigned to one of the groups using the simple randomization method (computerized random numbers). The patients were assigned to two groups (n = 20), using the stratified block randomization method (blocks of four), to receive either 20 mg atorvastatin (Tehran Darou, Tehran, Iran) along with standard HFpEF therapies (atorvastatin group), or to receive placebo tablets along with standard HFpEF therapies (placebo group). The placebo tablets, filled with starch, were similar to the atorvastatin tablets in appearance. The placebo tablets were produced by the placebo production department of the Faculty of Pharmacology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Placebo and atorvastatin tablets were labeled as A and B, respectively, and an independent researcher performed randomization. The patients were treated for eight weeks. Moreover, blood samples were collected to check for liver enzymes and lipid profile variations. Echocardiography and FMD measurement were performed by a cardiologist using VIVID 3n GM (GE, USA) with a special transducer for cardiac and vascular examinations under standard conditions at the echocardiography cardiology outpatient clinic of Imam Khomeini Hospital. To evaluate diastolic ventricular function and classify diastolic dysfunction, left atrial (LA) size, left ventricular (LV) size, ejection fraction (EF), wall thickness, transmittal flow, myocardial tissue velocity, and pulmonary venous inflow patterns were checked (14).

Imaging was done by a cardiologist blinded to the study design. At each visit, prior to the FMD, supine resting diastolic and systolic arterial blood pressures were measured using an automated blood pressure monitor (OMRON automatic blood pressure monitoring, Japan). Heart rate monitoring was done using a standard three-lead ECG during the procedures (Fukuda, C110, Japan). According to current guidelines, all FMD procedures were performed in the outpatient echocardiography clinic of Imam Khomeini Hospital. After 20 minutes of supine rest, baseline brachial artery diameter and blood velocity measurements were recorded for one minute. Then, high-resolution ultrasound was used to take the basic images of the left brachial artery at five cm above the antecubital fossa to determine the basal diameter of the artery. Immediately following baseline measurements, a blood pressure cuff was placed on the forearm and inflated to a pressure of 50 mmHg above the patient's systolic blood pressure for four minutes to induce reactive hyperemia. Subsequently, it was deflated, and the right brachial artery images were recorded for two minutes after deflating the cuff. The brachial artery diameter images were taken using ECG gating at the end of the diastole (simultaneously with the R wave in the ECG). Blood velocity and vessel diameter were assessed with a vascular transducer of the Vivid 3n Doppler system operating in duplex mode. The sample volume was corrected in relation to the vessel diameter and centered within the vessel lumen. An angle of $\leq 60°$ was achieved for all calculations of blood velocity. FMD is defined as the percentage of variations in diameter from baseline using the following formula:

$$\text{FMD} = (\text{maximum diameter} - \text{baseline diameter}) / (\text{baseline diameter}) \times 100$$

The participants underwent FMD assessment of the brachial artery before and after the two-month treatment

period. Based on these digital images (between the media adventitia of one side and the media adventitia of the other side of the artery), the baseline and maximum diameters were determined (15).

Sample size

It was estimated that 40 patients with HFpEF would be needed to detect a 15% whole decrease in the mixed outcome measure between the groups, with a two-tailed $\alpha = 0.05$ and a $\beta = 0.1$, in an assessment of the difference between the two independent correlations. The sample size was determined according to previous studies (14) and consultation with a statistician, using the following formula:

$$n = \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 \times \left(\left(S_1^2 + S_2^2 \right) \right) / \left(\mu_1 - \mu_2 \right)^2$$

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as frequency (%). Qualitative information was evaluated using the chi-square test. Parametric tests were used to compare the quantitative factors, as all variables were normally distributed according to the Kolmogorov-Smirnov test. An independent samples *t*-test was applied to compare the baseline values of the lipid profile between the placebo and the intervention groups. Moreover, the analysis of covariance (ANCOVA) test was applied for baseline variable adjustment. In the present research, a significance level of $P < 0.05$ was established. All statistical analyses were performed using *Statistical Package for the Social Sciences* (SPSS) software version 18.

Results

This study included 40 patients with HFpEF who were randomly assigned to the atorvastatin (n = 20) or placebo (n = 20) groups. Figure 1 presents the study's CONSORT flowchart. The patients' mean age was 65 years old, and there were 16 (40%) men and 24 (60%) women (Table 1). There was no significant difference regarding gender, serum lipid level, age, and diastolic dysfunction grading between the two groups (Table 2). After eight weeks of therapy, total cholesterol, low-density lipoprotein (LDL), and triglyceride levels decreased notably in the atorvastatin group. However, variations in the high-density lipoprotein (HDL) levels were not significant (Table 2). On the other hand, variations in total cholesterol, LDL,

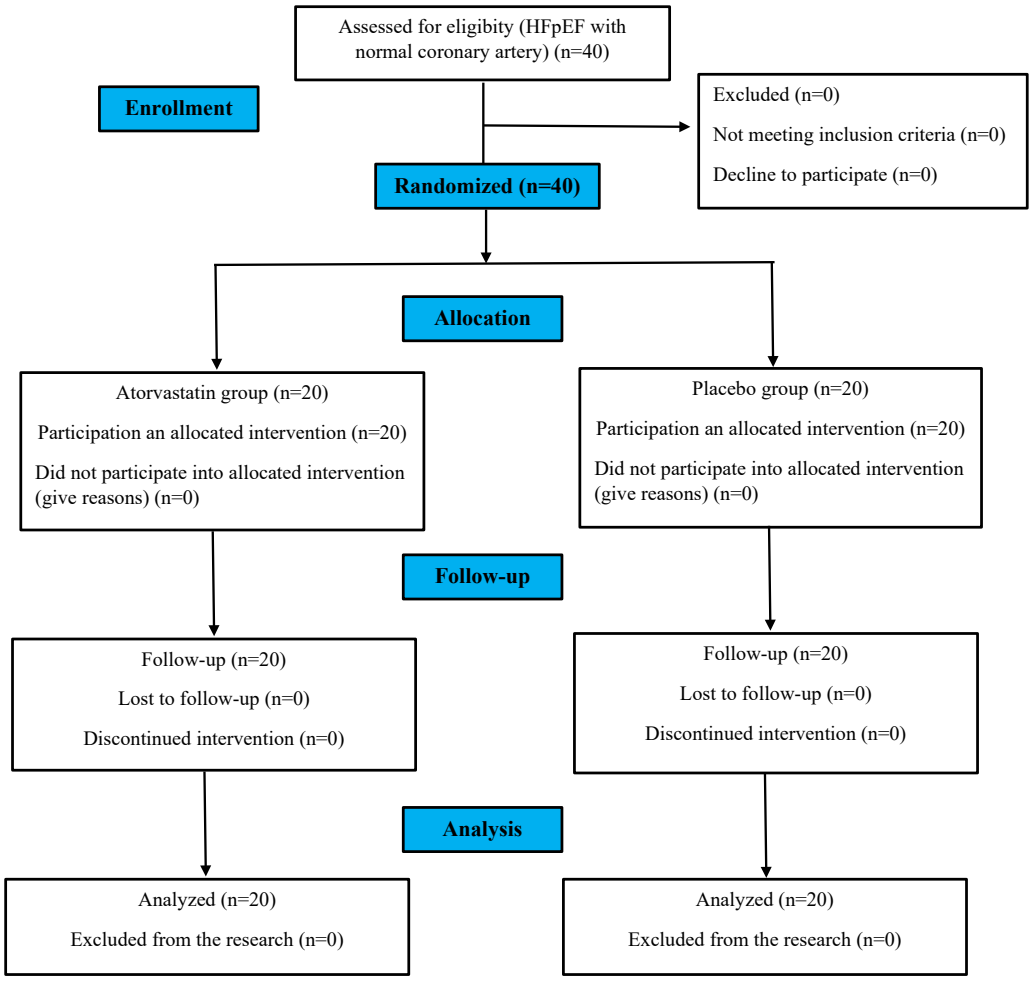

Figure 1. CONSORT flowchart of the present study

and triglyceride levels were not significant in the placebo group. Interestingly, no correlation was found between the lipid-lowering effect and the improvement of FMD in the atorvastatin group (Figure 2).

The two groups showed no significant variation in fasting blood sugar (FBS) and liver enzyme values (Figure 3). The mean FMD variations before and after treatment were +41.5% ± 7.62 in the atorvastatin group and +18.2% ± 2.11 in the placebo group. The statistical analysis revealed significant variations in FMD in the atorvastatin group compared to the placebo group ($P < 0.001$).

Discussion

Table 1. Baseline characteristics of heart failure patients

Characteristics	Atorvastatin group (n = 20)	Placebo group (n = 20)	*P* value
Initial NYHA			
Fc I	9 (45%)	12 (60%)	0.63
Fc II	8 (40%)	6 (30%)	0.77
Fc III	3 (15%)	2 (10%)	0.63
Comorbidity			
Hypertension	6 (30%)	5 (25%)	0.63
Diabetes mellitus	6 (30%)	8 (40%)	0.77
Smoking	8 (40%)	7 (35%)	0.63
Diastolic dysfunction grade			
Grade I	9 (45%)	12 (60%)	0.63
Grade II	8 (40%)	6 (30%)	0.63
Grade III	3 (15%)	2 (10%)	0.63
Cardiac medication			
ASA	12(60%)	9 (45%)	0.63
ACE I	11 (55%)	13 (65%)	0.74
ARB	9 (45%)	7 (35%)	0.74
BB	13 (65%)	11 (55%)	0.74
Diuretic	2 (10%)	3 (15%)	0.63

Abbreviations: Fc: Functional class, ASA: aspirin, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, and BB: beta blocker.
Qualitative data were evaluated using the chi-square test. In this test, $P < 0.05$ was set as the significance level.

As discussed earlier, HFpEF has remained one of the most challenging clinical syndromes. More importantly, its mortality and morbidity rates are the same as those of HFrEF. Of note, treatment with classic drugs for HF (i.e., diuretics, angiotensin-converting enzyme inhibitors [ACEIs], β-blockers, and cardiac glycosides) fails for most HFpEF patients. Although there has been clear success in treating HFrEF, no clinical trial has demonstrated that such standard therapies provide the same advantages for HFpEF. Furthermore, only a limited number of trials have shown symptomatic HFpEF improvement. Identifying the mechanisms, particularly those involving organs other than the heart, would help develop more efficient treatment strategies. HF is linked to endothelial dysfunction, which can arise from several factors. These include elevated cytokine levels, disrupted signaling pathways in endothelial receptors, and increased angiotensin-converting enzyme activity, leading to greater bradykinin breakdown. The elevated levels of endothelium-derived vasoconstrictors have been demonstrated in HF (15,16). Additionally, the heightened production of reactive oxygen species as well as oxidized LDL diminishes nitric oxide vasodilatory impacts (17,18).

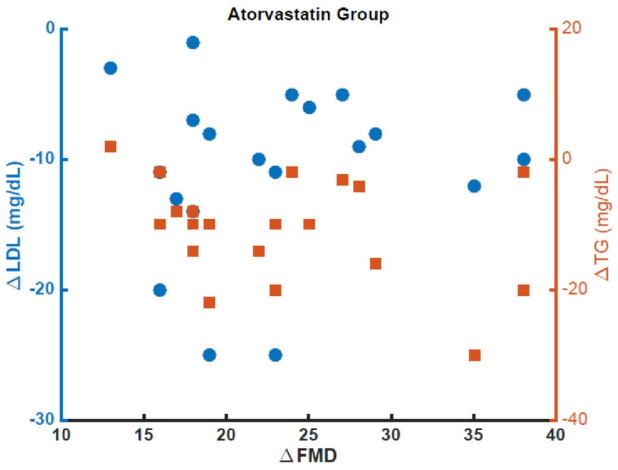

Figure 2. Correlation between variations in flow-mediated dilation (FMD) and variations in TG and LDL in the atorvastatin group. The X-axis indicates variations in FMD, the left Y-axis indicates variations in LDL (blue circles), and the right Y-axis indicates variations in TG (red squares). Each point represents data from one individual subject. Our results revealed no significant correlation between variations in FMD and those in LDL or TG

Table 2. Baseline and post-intervention values on lipid profile

Variable	Baseline value		Post-intervention values		*P* value*	*P* value**
	Atorvastatin group	Placebo group	Atorvastatin group	Placebo group		
LDLC	95.7 ± 13.28	96.7 ± 14.01	85.3 ± 10.41	98.25 ± 14.74	0.818	0.003*
HDLC	47.5 ± 6.95	44.75 ± 6.9	46.65 ± 6.82	45.95 ± 6.63	0.217	0.744
TG	123.2 ± 29.8	109.9 ± 25.66	112.55 ± 25.58	108.35 ± 26.64	0.068	< 0.001*
Total cholesterol	181.9 ± 15.21	187 ± 15.2	166.15 ± 12.43	184.7 ± 15.99	0.295	< 0.001*

Abbreviations: LDLC: low-density lipoprotein cholesterol, HDLC: high-density lipoprotein cholesterol, TG: triglyceride.
The analysis of covariance (ANCOVA) test was used to obtain the *P* value of triglyceride, and an independent samples *t* test was used to compare the baseline value of the lipid profile between the placebo and the intervention groups. In this study, $P < 0.05$ was set as the significance level.
* Baseline value between atorvastatin and placebo.
** ANCOVA test between the intervention and the placebo groups post-intervention, when adjusted for baseline values.

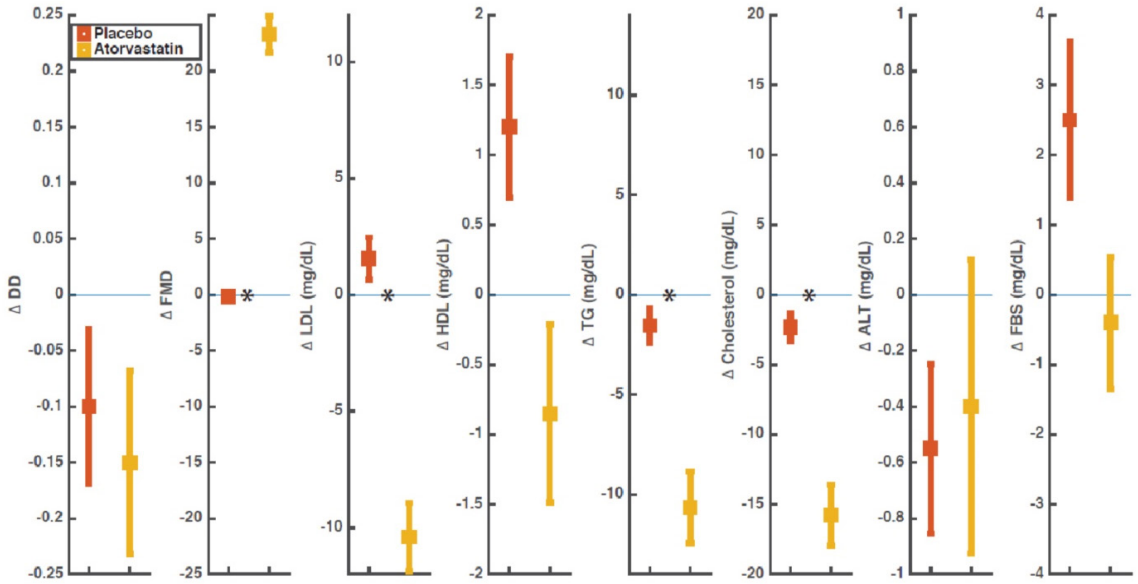

Figure 3. Effect of placebo and atorvastatin on diastolic dysfunction (DD), flow-mediated dilation (FMD), and biochemical lab results. Each panel represents the mean variations in one of the studied variables for the placebo (red) and atorvastatin (yellow) groups. Asterisks indicate statistically significant differences between the FMD, LDL, TG, and cholesterol groups. Error bars represent the standard error of the mean

There is ample experimental and clinical data suggesting that both peripheral and central endothelial dysfunction contribute to the pathogenesis of HF. However, a major proportion of this evidence is obtained from studies on HFpEF. Previous studies have extensively discussed the effect of statins on the primary and secondary prevention of cardiac events in patients with reduced EF with both ischemic and non-ischemic etiology. Observational studies on statin management in HFpEF have produced mixed results regarding its impact on diastolic parameters. Nonetheless, a meta-analysis of 11 studies, primarily retrospective in nature, indicated that statin therapy significantly influences survival rates (19-21). This is thought to be due to the pleomorphic anti-inflammatory impact. However, few trials have investigated the benefits of this class of drugs on patients with HFpEF, and further trials are necessary (20).

In the present study, the effect of low-dose atorvastatin on endothelial dysfunction in normolipidemic patients with HFpEF was examined in the short term. We chose normolipidemic patients with HFpEF to detect whether atorvastatin could benefit this group of patients, independent of its lipid-lowering effects. Moreover, the inclusion of only non-ischemic patients helped us assess the potential of this class of drugs in improving the FMD of the vessels, thereby ameliorating clinical HF syndrome in this group of patients. FMD has been widely used in many studies as a marker of vascular endothelial function. In HF, the impaired FMD of the brachial artery is common and, irrespective of etiology, is associated with poor outcomes (22).

In one comparable study, Strey et al. investigated short-term atorvastatin impact in subjects suffering from non-ischemic chronic HF and those with cholesterol levels within the population average. In this double-blinded, crossover trial, 24 patients with low EF (<40%) were treated with 80 mg atorvastatin daily for six weeks, and FMD was measured as an indicator of endothelial function. The results of this study indicated that FMD increased following the short-term atorvastatin treatment in patients with non-ischemic HF and low EF (20) levels. As in our research, this finding was independent of variations in LDL cholesterol.

Many researchers have evaluated the mechanisms underlying the impact of statins on endothelial function in patients with atherosclerosis, high risk for atherosclerosis, HFpEF, or hyperlipidemia. However, few studies have reported that statins can improve endothelial dysfunction in patients without ischemic heart diseases or hyperlipidemia. Nevertheless, the effect of statins should be examined in trials with larger populations of HFpEF patients.

In the present clinical trial, the effect of atorvastatin on vascular endothelium in patients with HFpEF was evaluated. It was revealed that atorvastatin treatment improved FMD. However, variations in FMD were not dramatically associated with the decrease of LDL in serum. According to the literature, this is one of the first studies addressing the effect of statins on endothelial function in normolipidemic patients with HFPEF. Due to time limitations, we could not assess the effect of statin therapy on mortality and morbidity in these patients.

This research had some limitations, including the small sample size and the short duration of patient follow-up. Considering the different stages of HF, it seems necessary to design a study to investigate statin drugs in different stages of HFpEF. With the arrival of the new generation of drugs of the statin family, the effects of other drugs of this

family can also be examined in HFpEF patients. Although their mechanism of action is the same, their effect may be different and can be investigated in future studies.

Conclusion

The present study showed that short-term daily use of atorvastatin in patients with no ischemic HFpEF could considerably increase the FMD as a reliable indicator of endothelial function. Furthermore, the increase in FMD and the improvement of vascular endothelial function were independent of the effect of atorvastatin on serum lipids.

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Authors' Contribution

Conceptualization: Saeed Yazdankhah, Shahla Madjidi.
Data curation: Ali Kardooni.
Formal analysis: Saied Hesam.
Funding acquisition: Saeed Yazdankhah.
Investigation: Seyed Mohammad Hassan Adel.
Methodology: Ali Kardooni.
Project administration: Saeed Yazdankhah, Shahla Madjidi.
Resources: Shahla Madjidi.
Software: Saied Hesam.
Supervision: Seyed Mohammad Hassan Adel.
Validation: Saeed Yazdankhah.
Visualization: Ali Kardooni.
Writing–original draft: Seyed Mohammad Hassan Adel.

Competing Interests

None declared.

Ethical Approval

The present study was conducted after acquiring the ethics code from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1393.414); written informed consent was obtained from all patients.

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