ORIGINAL ARTICLE

Comparison of the effect of 40 and 80 mg/day doses of atorvastatin on changes in lipid profiles among acute coronary syndrome patients: A randomized clinical trial study

Mohammad Sahebkar[1], Nafiseh Khalilzadeh[2], Javad Movahedzadeh[3], Mahboubeh Neamatshahi[4], Mostafa Rad[5], Omid Gholami[6]

[1]Department of Nursing, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada, [2]Student Research Committee, Sabzevar University of Medical Sciences, Sabzevar, Iran, [3]Department of Cardiology, School of Medicine, Heshmatiyeh Hospital, Sabzevar University of Medical Sciences, Sabzevar, Iran, [4]Department of Social Medicine, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran, [5]Department of Nursing, School of Nursing, Iranian Research Center on Healthy Aging, Sabzevar University of Medical Sciences, Sabzevar, Iran, [6]Cellular and Molecular Research Center, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran

Background: Statins play a vital role in the management of high-risk patients with atherosclerotic cardiovascular disease. The aim of this study was to evaluate the effect of two doses of 40 and 80 mg of atorvastatin on lipid profiles and inflammatory markers among patients with acute coronary syndrome (ACS). **Materials and Methods:** This single-blind, randomized clinical trial was conducted on 60 patients with ACS referred to Heshmatiyeh Hospital, Sabzevar, Iran. Eligible subjects were randomly assigned to either 80 mg/day (atorvastatin, 80 mg/day) or 40 mg/day intervention (atorvastatin, 40 mg/day) groups. Serum lipid profiles (low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglyceride [TG], and total cholesterol), an inflammatory marker (creatine phosphokinase [CPK]), and liver function biomarkers (alanine aminotransferase, aspartate aminotransferase) were assessed before starting treatment and 3 months later. **Results:** According to the paired *t*-test, there was a significant difference before and after intervention in each group regarding mean LDL and HDL values ($P < 0.05$). The result of the ANCOVA test revealed that the LDL and CPK was substantially lower in the 80 mg/day group as compared to the 40 mg/day group after 3-month intervention (62.45 ± 16.78 mg for 80 mg/day vs. 73.63 ± 20.00 for 40 mg/day $P = 0.040$ and 84.85 ± 6.53 IU/L for 80 mg/day vs. 120.70 ± 6.41 IU/L for 40 mg/day $P = 0.001$, respectively). Although the mean of HDL, TG, and cholesterol in the 80 mg/day group was lower than that of the 40 mg/day group after implementing the intervention, these differences were not statistically significant ($P > 0.05$). **Conclusion:** Findings suggest that increasing the dose of atorvastatin decreases the mean serum levels of LDL and CPK but has no effect on the mean serum HDL levels and liver function biomarkers.

Key words: Acute coronary syndrome, atorvastatin, creatine kinase, lipoproteins

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INTRODUCTION

Acute coronary syndrome (ACS) comprises myocardial infarction (MI) with elevated ST segment, MI without ST-segment elevation, and unstable angina. Hyperlipidemia is a major modifiable cause of coronary artery disease and has been shown to reduce the risk of cardiovascular disease by lowering plasma cholesterol.[1] However, this is not the only factor and other factors could induce the myocardial injuries.[2,3] Asian populations have a distinct pattern of dyslipidemia, which includes high levels of triglycerides (TGs), cholesterol, low-density lipoprotein (LDL), and low

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Address for correspondence: Dr. Omid Gholami, Cellular and Molecular Research Center, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran.
E-mail: omidghphd@gmail.com
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levels of high-density lipoprotein (HDL).[4] Evidence has been shown that statins are effective in preventing ACS.[5]

Statins are the first line of treatment for high LDL. Studies have shown that treatment with high doses of atorvastatin plays an important role in preventing acute coronary events by reducing inflammatory responses, anti-vascular thrombotic effects, and increasing the stability of coronary atherosclerotic plaques.[6,7] Statins work through the mevalonate pathway by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the catalyst for the conversion of HMG-CoA to mevalonate. It lowers LDL and TGs. It also increases HDL by reducing very-LDL.[8]

Statins play a vital role in the management of high-risk patients with atherosclerotic cardiovascular disease (ASCVD). Treatment with high-dose statin (80 mg daily), which lowers LDL cholesterol by more than 50%, is a key factor in reducing the incidence of ACS.[9] However, high doses of statins can sometimes result in increased dose-dependent side effects, including high levels of liver enzymes, diabetes, muscle aches, and muscle disorders (myopathy).[10-12] According to the guidelines of the American College of Cardiology (ACC)/American Heart Association in 2013, high doses of atorvastatin (40–80 mg) are effective in lowering cholesterol and ASCVD.[13] According to the ACC guidelines, high-intensity statins (atorvastatin 40 or 80 mg/day) should be prescribed for secondary prevention in patients with clinical ACS.[14] However, it is not clear that which dose of atorvastatin is more beneficial among these patients.

In the review of the literature, controversy still exists among various studies regarding the beneficial effects of atorvastatin administration on cardiovascular outcomes among ACS patients.[15] Evidence suggests that there is no study that compares high doses of atorvastatin (40 mg and 80 mg/day) in patients with ACS. In our study, we hypothesized that a dose of 40 mg atorvastatin would be as effective as 80 mg atorvastatin for achieving the goals of ACS in Iranian patients. Moreover, increasing the dose of the drug not only does not affect the lipid profiles and change the prognosis of patients but also increases the side effects of the drug. Thus, this study was aimed at the assessment of the effect of two doses of 40 and 80 mg of atorvastatin on lipid profiles and inflammatory markers among patients with ACS.

METHODS

This randomized, single-blind, parallel-group was conducted to evaluate the effect of the high versus moderate dose atorvastatin on changes in lipid profiles and inflammatory markers among patients presenting with ACS.

Subjects

The study population included all ST-elevation myocardial infarction (STEMI) patients who referred to the Intensive Coronary Care Unit ward of Heshmatiyeh Hospital at Sabzevar, Iran, between 2018 and 2019. Patients 18–75 years of age were included. Exclusion criteria were as follows; (i) Patients already on treatment with any dose of statins (ii) those with liver and kidney disease, (iii) patients with statin intolerance or contraindications to statin therapy (iv) those who taking any drug which are strong inhibitors of CYP3A4 enzymes (v) those with malignancy and diabetes, (vi) those simultaneously consuming fibrate medications, and (vii) pregnancy.

Diagnosis of ST-elevation myocardial infarction

The diagnosis of the STEMI was defined according to the criteria of the European society of cardiology and the ACC. STEMI was diagnosed by (i) presence of chest pain for at least 30 min and (ii) ST elevation >1 mm in at least two consecutive leads on the electrocardiogram or new onset left bundle branch block. All diagnoses were performed by an expert cardiologist.

Intervention

After diagnosing STEMI, eligible patients were randomly assigned into either the 80 mg/day (atorvastatin 80 mg, daily) or the 40 mg/day (atorvastatin 40 mg, daily) groups. The atorvastatin was provided by Dr. Abidi Co., Tehran, Iran. The first dose of atorvastatin was received within 24 h of first medical contact. After discharge, patients received training on the use of drugs and followed up weekly by telephone. Three months after treatment, patients were reassessed with laboratory and clinical examination. Blood samples were withdrawn before and after 3 months of intervention. Blood sampling was performed after fasting overnight in a 12-hour period. The sequential multiple analyzers with computer were used to implement complete blood chemistry profiles in one hour on a low volume of blood.

Outcome

The primary endpoints of this study were the assessment of creatine phosphokinase (CPK) and the lipid profiles (such as LDL, HDL, TG, and total cholesterol). The secondary endpoint of this study was the evaluation of liver function biomarkers namely alanine aminotransferase (ALT), aspartate aminotransferase (AST) as well as subjective expression of myalgia by patients during follow up period.

Sample size determination

According to Gavazzoni *et al.*'s study, in a 2-sided model with a type one error of 5%, a power of 80%, and 0.74

standardized effect size, the sample size was estimated at 60 individuals using G * power software version 3.0.10 (http://www.gpower.hhu.de/).[6] It should be mentioned that the sample sizes have been calculated regarding all outcomes of interest and a maximum has been determined based on those factors.

Randomization and blinding

Eligible participants were randomly assigned (1:1 ratio) to both groups using a computer-generated block randomization scheme with permutated block sizes of four (15 blocks). In this one-blind clinical trial, only subjects were unaware of the study procedure. Allocation concealment was performed using sequentially numbered, opaque sealed envelopes. Before assigning the right intervention to each subject the envelopes were shuffled and distributed among them by the investigator.

Statistical analysis

All the continuous and categorical parameters were expressed using means ± standard deviation, and number (percent), respectively. Normality was checked using Kolmogorov–Smirnov test. The independent *t*-test was used to compare mean age, body mass index, lipid profile, liver function biomarkers, blood count, creatinine, urea, potassium, sodium, and ejection fraction at the beginning of the study. Chi-square test was utilized to compare the categorical data between the two groups. ANCOVA test was used to compare mean lipid profile and liver function biomarkers adjusted for baseline time. Furthermore, the paired *t*-test was used to compare mean lipid profile and liver function biomarkers before and after the intervention in each group. The data were analyzed using SPSS version 21 (IBM Corp, Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

Ethical consideration

This study was approved by the ethics committee of Sabzevar University of Medical Sciences (code number: IR.MEDSAB.REC.1396.153) and was registered at the Iranian Registry of Clinical Trials (code number: IRCT20140921019240N4). At the beginning of the study, before the randomization, both written and verbal consents were obtained from participants. All the information has remained anonymous.

RESULTS

In total, of 60 participants who met the inclusion criteria, 53 participants completed the study process [Figure 1]. The mean age of the subjects in the 80 mg/day and 40 mg/day groups was 60.25 ± 7.85 and 57.60 ± 10.00 years, respectively. Furthermore, 64.50% and 53.30% were male in the 80 mg/day and 40 mg/day groups in turn. Baseline characteristics of the patients were summarized in Table 1.

The paired *t*-test indicated significant differences before and after the intervention in each group regarding mean LDL and HDL ($P < 0.05$) as shown in Table 2. In the 40 mg/day group, the difference in mean total cholesterol before and after implementation of the intervention was significant only ($P = 0.01$). Furthermore, the mean CPK was significantly lower in the 40 mg/day group ($P < 0.05$) compared to the baseline group. AST and ALT levels were lower in the 80 mg/day and 40 mg/day groups after the intervention, but this difference was not statistically significant ($P > 0.05$). It should be noted that only six patients in the 80 mg/day group and two patients in the 40 mg/day group complained of myalgia.

As shown in Table 3, the result of the ANCOVA test revealed that the mean LDL and CPK were substantially lower in the 80 mg/day group as compared to the 40 mg/day group after a 3-month intervention ($P = 0.040$ and 0.001, respectively). Although the mean of HDL, TG, and total cholesterol in the 80 mg/day group was lower than that of the 40 mg/day group after implementing the intervention, these differences were not statistically significant ($P > 0.05$). According to liver function biomarkers, there was no significant difference regarding mean AST and ALT between the two intervention groups ($P = 0.076$, 0.957, in turn).

DISCUSSION

This study was aimed at evaluating the effect of different doses of atorvastatin on changes in lipid profiles and inflammatory markers among patients with ACS. The findings of this study revealed that the mean LDL and CPK were substantially lower in the 80 mg/day group as compared with the 40 mg/day group. According to the study, atorvastatin could reduce the CPK levels significantly. However, previous studies showed contradictory results.[16,17] Studies have shown that high baseline CPK levels decrease with statin treatment. Therefore, the reduction in CPK levels in our study may be due to the high baseline levels. Moreover, there was no significant difference between the two groups regarding the mean of HDL, TG, and total cholesterol.

Previous evidence supports the benefits of statin therapy for primary and secondary prevention of cardiovascular disease. Statin initiation criteria and treatment goals are different based on the guidelines used;[18,19] however, the purpose of treatment is to use potent statins to achieve lower LDL-C. However, the response to statins varies from person to person, so physicians cannot choose the desired statin for a particular patient.[20] Therefore, physicians should correct

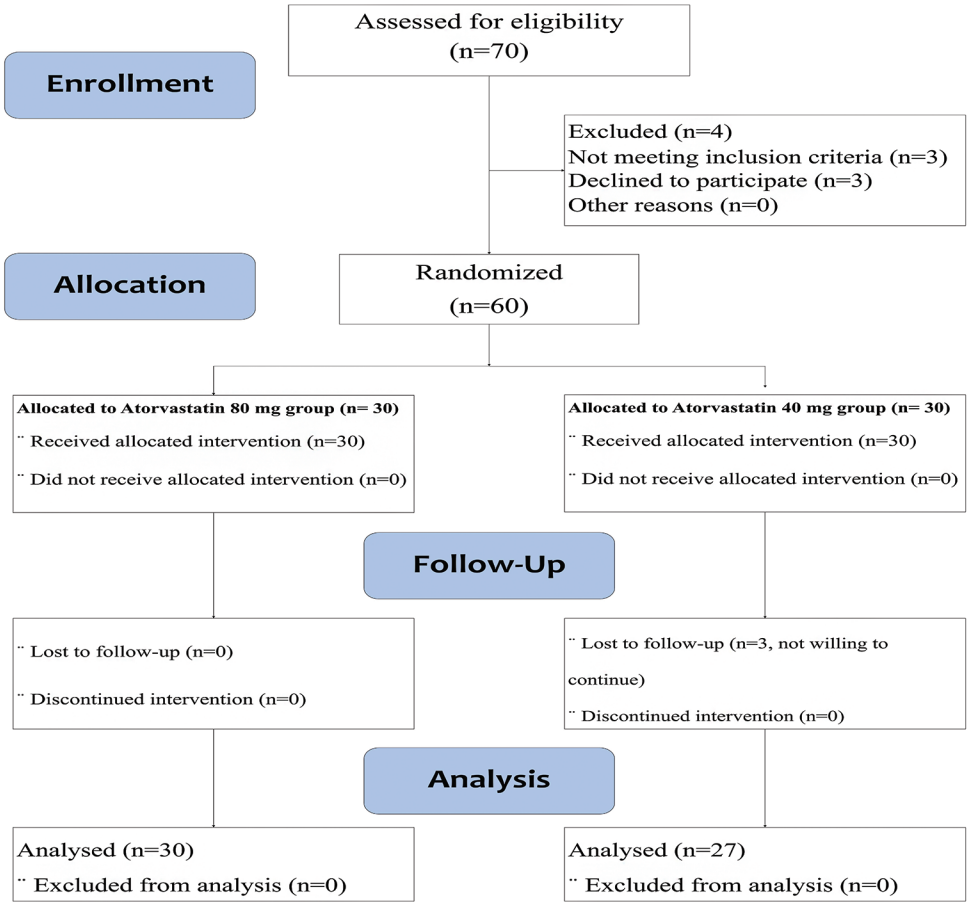

Figure 1: Trial profile

statin therapy in practice beyond the general guidelines. However, in some cases, several parameters, including insufficient knowledge regarding guidance and side effects concerns can result in lower doses of statins prescription by physicians.[21,22]

Gavazzoni *et al*.'s study revealed that atorvastatin could improve lipid profile at day 30 in ACS patients.[6] According to this study and our findings, 80 mg/day of atorvastatin could improve the lipid markers better than 40 mg/day. However, these effects are not significant for the reduction in HDL, TG, total cholesterol, AST, and ALT. Moreover, Agrawal *et al*. stated that 40 mg and 80 mg atorvastatin doses are essential in ASCVD reduction. They mentioned that to reduce dyslipidemia, the effect of 40 mg atorvastatin and 80 mg atorvastatin is the same. However, these high doses of statins are related to increased complications, including elevated liver enzymes, new-onset diabetes, and dose-related myalgia/myopathy.[23] Thus, we concluded that 80 mg/day atorvastatin may have better outcomes than 40 mg/day atorvastatin among ACS patients. Our findings may turn the path in choosing the right dose of atorvastatin for ACS patients by physicians.

In this study, SGOT and SGPT levels were not different between the two groups. The result of this study is not in line with the Agrawal *et al*.'s study as they stated the significant difference between the two groups regarding SGOT and SGPT levels after 3- and 6-month intervention. This difference may stem from the different settings, populations, and follow-up periods. Another reason for these differences may be due to high baseline LDL cholesterol in Agrawal *et al*.'s study. Baseline mean LDL-Cholesterol was 136.72 ± 22.57 mg/dl and 136.43 ± 18.81 which decreased to 70.25 ± 25.63 mg/dl and 67.07 ± 20.69 mg/dl in 40 mg versus 80 mg group, respectively, at the end of 3 months. In our study, the baseline mean LDL-cholesterol was 90.00 ± 18.30 mg/dl and 80.30 ± 22.50 mg/dl in 40 mg versus 80 mg group, respectively.

Moreover, we found a significant difference in mean CPK between groups which is inconsistent with the results of Agrawal *et al*.'s study as they stated the greater CPK levels in the 80 mg atorvastatin group compared to the 40 mg atorvastatin group. However, in terms of complaints of myalgia, the result of our study and Agrawal *et al*.'s study is the same. Further studies are needed for assessing the

Table 1: Baseline characteristics of the participant in the study, mean±standard deviation and *n* (%)

Parameters	Groups		*P**
	80 mg/day group (atorvastatin 80 mg) (*n*=30)	40 mg/day group (atorvastatin 40 mg) (*n*=30)	
Gender, male	20 (64.50)	16 (53.30)	0.375
Age, years	60.25±7.85	57.60±10.00	0.262
BMI	26.70±4.40	27.00±3.50	0.776
Lipid profile			
LDL, mg	78.85±22.20	86.90±20.75	0.297
HDL, mg	48.10±9.65	51.00±13.15	0.547
TG, mg	122.35±58.70	165.40±114.60	0.128
Total cholesterol, mg	153.00±39.40	168.40±36.35	0.332
Liver function biomarkers			
AST, mg	29.60±19.20	29.20±23.70	0.337
ALT, mg	50.12±72.80	49.00±44.30	0.475
Blood count			
WBC, $\times 10^9$/L	7.50±2.60	6.75±1.20	0.639
Hb, g/dl	16.80±1.80	13.75±1.40	0.390
Platelets, $\times$ 10^9/L	235.50±49.80	225.50±45.55	0.390
FBS, mg	118.10±38.50	129.80±67.40	0.445
Creatinine, mg	1.11±0.20	1.12±0.22	0.901
Urea, mg	31.40±8.65	31.10±9.40	0.915
Potassium, mg	4.35±0.31	4.3±0.33	0.597
Sodium, mg	141.10±2.60	140.30±1.45	0.332
EF, %	43.90±8.25	42.00±9.35	0.596
CPK, IU/L	332.90±72.70	523.70±82.20	0.336

*Independent *t*-test and Chi-square test as appropriate. BMI=Body mass index; WBC=White blood cells; Hb=Hemoglobin; FBS=Fasting blood pressure; EF=Ejection fraction; CPK=Creatine phosphokinase; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; TG=Triglyceride; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

Table 2: Comparison of lipid profile and liver function before and after intervention in each group

Parameters	80 mg/day group (Atorvastatin 80 mg), mean±SD		*P**	40 mg/day Group (atorvastatin 40 mg), mean±SD		*P**
	Before	After		Before	After	
CPK[a], IU/L	169.65±146.80	119.65±41.45	0.068	259.23±235.00	86.00±24.00*	0.013
Lipid profile						
LDL, mg	80.30±22.50	64.45±16.80*	0.045	90.00±18.30	73.60±20.00*	0.041
HDL, mg	47.40±9.90	41.50±8.20*	0.046	51.61±12.90	45.00±10.80*	0.042
TG, mg	128.60±60.10	122.30±56.10	0.086	177.70±118.40	161.65±92.00	0.095
Total cholesterol, mg	163.70±45.70	139.80±28.00	0.078	185.10±35.00	157.75±24.20*	0.013
Liver function biomarkers						
AST, mg	30.40±20.20	23.70±9.40	0.12	29.10±25.35	20.00±5.60	0.19
ALT, mg	32.00±21.50	22.50±10.22	0.057	29.75±20.40	24.00±12.40	0.059

*Paired *t*-test, *P*<0.05. CPK=Creatine phosphokinase; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; TG=Triglyceride; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; SD=Standard deviation

Table 3: Comparison of both groups regarding lipid profile and liver function after intervention

Parameters	After intervention		*P**
	80 mg/day group (atorvastatin 80 mg), mean±SD	40 mg/day group (atorvastatin 40 mg), mean±SD	
CPK, IU/L	84.85±6.53	120.70±6.41	0.001
Lipid profile			
LDL, mg	62.45±16.78	73.63±20.00	0.040
HDL, mg	41.48±8.20	45.10±10.80	0.532
TG, mg	122.30±56.11	161.65±92.08	0.556
Total cholesterol, mg	139.80±24.04	157.70±24.20	0.191
Liver function biomarkers			
AST, mg	23.80±9.36	20.00±5.60	0.116
ALT, mg	22.48±10.22	24.00±12.40	0.578

*ANCOVA test adjusted for baseline time. CPK=Creatine phosphokinase; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; TG=Triglyceride; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; SD=Standard deviation

effect of inflammatory markers on lipid profiles among these patients with different follow-up periods.

i. The main limitations of this study are as follow (i) lack of follow-up period of more than 3 months which may influence the results; (ii) selecting patients from a single center using a limited group of patients with ACS, which may affect the generalizability of the study results; (iii) lack of sufficient patients do not allow conducting more complex statistical analysis, including multivariate analysis; and (iv) lack of evaluating the effect of inflammatory markers on lipid profile.

The results of this study suggest that increasing the dose of atorvastatin decreases the mean serum levels of LDL and CPK; however, it has no effect on the mean serum HDL levels and liver function biomarkers.

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Conflicts of interest

There are no conflicts of interest.

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