The effects of different doses of atorvastatin on serum lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident

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Original Article

Abstract

BACKGROUND: Despite established effects of atorvastatin on level of serum lipid profile in patients with different underlying clinical conditions, the effects of this drug on other serum biomarkers remain uncertain. We examined the effects of atorvastatin therapy on lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident without any history or clinical evidences of diabetes, heart failure, renal failure, or hepatic disease.

METHODS: In a randomized double-blinded controlled trial, 140 hospitalized patients with an ischemic cerebrovascular accident were included and randomly assigned to receive either atorvastatin 40 mg (n = 70) or atorvastatin 20 mg daily (n = 70) for 3 months. The levels of biomarkers were measured at the time of administrating drugs as well as at the time of completing the treatment.

RESULTS: A significant reduction was revealed in serum triglyceride, total cholesterol, low-density lipoprotein, non-high-density lipoprotein (HDL) cholesterol, and also aspartate aminotransferase levels as well as a significant increase in serum HDL level following administration of atorvastatin in both case and control groups who received the atorvastatin 40 mg/day and 20 mg/day, respectively (all P < 0.050). Although a significant increase in fasting blood sugar and hemoglobin A1c was observed in the case group received atorvastatin 40 mg/day (both P < 0.001), but this elevation was not occurred in another group treated with lower dose of the drug (both P > 0.050).

CONCLUSION: Daily administration of 20 mg and 40 mg doses of atorvastatin for 3 months provides improvement in serum lipid profiles; however, because of interfering effect of high-dose atorvastatin on glycemic control status, the use of the former dose may be preferred. This is very important in these patients because the positive effects of high-dose atorvastatin in stroke patients are not confirmed.

Keywords: 3-Hydroxy-3-Methylglutaryl-CoA Reductase Inhibitors, Statins, Atorvastatin, Hyperlipidemia

Introduction

Lipid-lowering treatment using different types of statins effectively reduce the risk for death or cardiovascular events in those with or without evidenced coronary artery disease (CAD).[1,2] Different doses of these medications are now considered for achieving a target low-density lipoprotein (LDL) cholesterol level of < 100 mg/dl and an option of extending to < 70 mg/dl for patients with established CAD or those with chronic diabetes mellitus.[3-5] In this regard, CAD is less likely if the serum LDL cholesterol level is

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below 60 mg/dl than when it is above 80 mg/dl.[6,7] The main mechanism of statins is to reduce LDL levels has been now well-identified that statins can inhibit 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase function as the first committed enzyme of the HMG-CoA reductase pathway, mediating production of cholesterol.[8]

Among different types of statins, atorvastatin is now considered one of the most effective statins, not only for its effects on LDL level as well as the ability to meet recommended treatment guidelines for this parameter, but also for its impact on other lipid profiles such as the level of triglyceride (TG) and also the capacity to modify lipoprotein composition in a non-atherogenic manner.[6,9] In some recent large trials comparing the effects of atorvastatin with other statins, it provided significantly higher lowering effects in comparison with pravastatin as such a 30 days use of the drugs led to reduce the level of LDL cholesterol by 51% and 22%; respectively.[10] Even, the beneficial lowering effects of atorvastatin on inflammatory biomarkers as a main factor for predisposing coronary atherosclerosis were considerably higher than other types of statins.[11,12]

The preventive effects of atorvastatin on cardiovascular events in some CAD risk subgroups including diabetic patients, or those with renal failure have been widely investigated. In this context, the use of atorvastatin in diabetic patients has resulted in reducing all-cause mortality by 52%, coronary mortality by 62%, coronary morbidity by 59%, and stroke by 68%.[13] Furthermore, in patients with both type 2 diabetes mellitus and chronic renal failure, atorvastatin significantly reduced the risk of fatal and nonfatal cardiac events and death from any cause if pretreatment LDL cholesterol is > 145 mg/dl.[14]

Despite established effects of atorvastatin on serum level of LDL cholesterol or other lipid particles, the effects of this drug on other biomarkers still remain uncertain. Hence, the researchers examined the effects of atorvastatin therapy on lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident without any history or clinical evidences of diabetes, heart failure, renal failure, or hepatic disease.

Materials and Methods

In a randomized double-blinded controlled trial (registered in Iran registry of clinical trials with registration number of IRCT201108177358N1), 140 hospitalized patients with ischemic cerebrovascular accident were enrolled. The patients were consecutively selected from all subjects who referred to our center within a 1 year period from July 2012 to July 2013. Patients with any history or clinical evidences of diabetes, heart failure, renal failure, or hepatic disease were not included into the study. Those who were receiving lipid-lowering therapy at the time of admission were not also considered eligible (Figure 1). The study protocol was approved by the Shahid Beheshti University of Medical Sciences review boards, and written informed consent was obtained from all patients. The baseline characteristics including demographics, medical history, and medications were collected by reviewing the hospital recorded files.
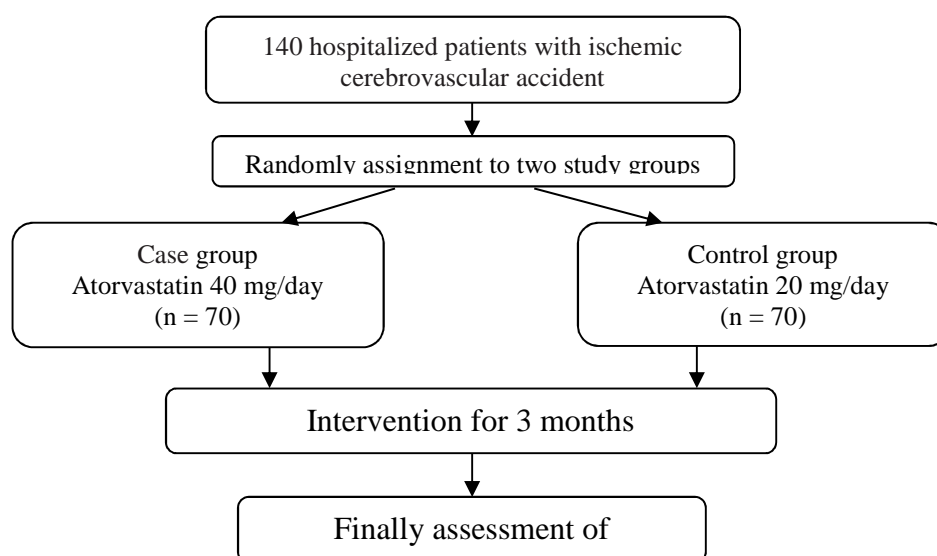

Figure 1. Consort chart for the study

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Eligible patients were randomly assigned in a 1:1 ratio to either receive 40 mg of atorvastatin (n = 70) or 20 mg of atorvastatin daily (n = 70) in a double-blind, double-dummy fashion for 3 months. At the time of administrating drugs as well as at the time of completing treatment, blood samples were obtained to measure lipids [TG, total cholesterol, LDL, HDL (high-density lipoprotein), and non-HDL cholesterol], fasting blood sugar, hemoglobin A1c, serum creatinine, and liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. The levels of blood glucose and lipid profile in the sera were determined spectrophotometrically by enzymatic method. Hemoglobin A1c was measured using an ion-exchange high-performance liquid chromatography method using the Diamat Analyzer System. Serum creatinine was also measured using an enzymatic method. Liver enzymes were measured using standard automated kinetic enzymatic assays. The endpoint of the study was to compare changes in these biomarkers following study medications.

Results were presented as mean ± standard deviation or median (1st, 3rd quartiles) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was assessed using both Kolmogorov-Smirnov tests and histograms. Continuous variables were compared using t-test or non-parametric Mann-Whitney U test whenever the data did not appear to have a normal distribution. Categorical variables were, on the other hand, compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of < 5 were observed. For assessing changes in study parameters after drug intervention compared with

before that, the paired t test or Kruskal-Wallis test was used. For the statistical analysis, the statistical software SPSS for windows (version 20.0, SPSS Inc., Chicago, IL, USA) was used. P values of 0.05 or less were considered as statistically significant.

Results

As shown in table 1, the two groups receiving different doses of atorvastatin were similar in terms of baseline characteristics including demographics, anthropometric parameters, previous history of hypertension and hyperlipidemia, current smoking, and also baseline laboratory parameters of white blood cell count, hemoglobin level, serum creatinine, and platelet count (all P > 0.050).

Table 2 presents a level of serum biomarkers after interventions compared with before that in both case and control groups. A significant reduction was revealed in serum TG, total cholesterol, LDL, non-HDL cholesterol, and also AST levels as well as a significant increase in serum HDL level following administration of 40 mg/day atorvastatin (all P < 0.001). Also, the control group who received 20 mg/day atorvastatin showed significant reduction in serum TG (P = 0.012), total cholesterol (P < 0.001), LDL (P < 0.001), non-HDL cholesterol (P < 0.001), and also AST levels (P = 0.022) as well as a significant increase in serum HDL (P = 0.005). Although a significant increase in fasting blood sugar and hemoglobin A1c was observed in the case group which received atorvastatin 40 mg/day (both P < 0.001), but this elevation was not occurred in another group received lower dose of the drug (both P > 0.050).

Table 1. Baseline characteristics of the study population

Characteristics	Case group (At. 40 mg) (n = 70)	Control group (At. 20 mg) (n = 70)	P
Male gender	32 (48.3)	31 (44.3)	0.635
Cigarette smoking	17 (25.8)	18 (25.7)	0.989
Marital state	66 (94.3)	65 (92.9)	0.735
Hyperlipidemia	7 (10.6)	6 (8.6)	0.688
Hypertension	24 (36.4)	22 (31.4)	0.532
Family history of CAD	4 (6.1)	5 (7.1)	0.812
Serum creatinine (mg/dl)	0.90 (0.88-1.12)	0.98 (0.90-1.1)	0.770
WBC count × 1000 (/mm^3)	7.8 (6.5-8.1)	7.7 (6.8-7.9)	0.664
Body mass index (kg/m^2)	26.65 ± 3.55	27.67 ± 3.29	0.081
Height (cm)	167.56 ± 7.82	165.21 ± 8.85	0.098
Weight (kg)	76.24 ± 15.97	77.97 ± 12.24	0.473
Serum hemoglobin (mg/dl)	13.85 ± 1.87	14.42 ± 2.25	0.105
Platelet count (/mm^3)	257.60 ± 75.56	249.26 ± 82.25	0.533
Age (year)	57.70 ± 10.08	58.84 ± 9.90	0.501

At: Atorvastatin; CAD: Coronary artery disease, WBC: White blood cell, Data are presented as number (%), mean ± MD, or median (1st, 3rd quartiles)

Table 2. Serum biomarkers following use of atorvastatin between case and control groups before and after interventions

Serum biomarkers	Case group (At. 40 mg) (n = 70)			P	Control group (At. 20 mg) (n = 70)			P	P (between-group)
	Before	After	Difference		Before	After	Difference		
FBS	85.67 ± 13.59	99.86 ± 16.22	92.77 ± 15.52	< 0.001	84.63 ± 26.26	85.21 ± 14.19	84.92 ± 20.18	0.656	< 0.001
HbA1C	5.54 ± 0.55	5.89 ± 0.56	5.72 ± 0.52	< 0.001	5.49 ± 0.66	5.52 ± 0.59	5.51 ± 0.61	0.442	< 0.001
TG	186.17 ± 85.92	156.42 ± 66.98	171.30 ± 77.42	< 0.001	187.46 ± 82.25	158.77 ± 80.25	173.12 ± 81.18	0.012	0.222
CHOL	196.38 ± 37.58	159.88 ± 32.52	178.13 ± 34.42	< 0.001	197.75 ± 34.45	161.21 ± 30.56	179.48 ± 32.14	< 0.001	0.565
LDL	120.89 ± 34.02	90.07 ± 26.50	105.48 ± 30.20	< 0.001	119.25 ± 30.25	94.45 ± 28.08	108.50 ± 29.55	< 0.001	0.112
HDL	35.68 ± 8.80	39.73 ± 9.15	37.71 ± 37.07	< 0.001	34.59 ± 7.79	38.41 ± 10.12	36.50 ± 8.89	0.005	0.065
Non-HDL	160.70 ± 38.77	120.18 ± 31.71	140.44 ± 32.35	< 0.001	158.74 ± 38.89	136.30 ± 34.28	147.52 ± 36.66	< 0.001	0.129
AST	35.67 ± 7.23	27.03 ± 7.92	31.35 ± 7.76	< 0.001	34.46 ± 25.59	27.28 ± 7.75	30.87 ± 29.19	0.022	0.556
ALT	28.14 ± 14.68	25.86 ± 9.33	27.00 ± 10.12	0.224	28.85 ± 12.12	27.54 ± 15.48	28.20 ± 13.03	0.778	0.886

At: Atorvastatin; FBS: Fasting blood sugar; HbA1C: Hemoglobin A1C; TG: Triglyceride; CHOL: Cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Data are presented as mean ± SD

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Discussion

Recent evidences have supported vigorous lipid and glucose interventions in primary and secondary prevention of acute cerebrovascular disease so these evidences support intensive lipid intervention with high-dose statins to produce clinical event reduction in these patients,[15] However, the optimal doses of statins required for clinical relevance of cerebrovascular disease remain obscure. In fact, it is now questioned if doses of statins even higher than standard lipid-lowering doses will result in additional benefit.

The primary main point of the study was to demonstrate the beneficial effect of administrating atorvastatin with the two dosages of 40 mg/day and 20 mg/day for 3 months on different serum lipid profiles. Although it was previously believed that the most prominent effects attributable to statin therapy are its only potent LDL-C lowering properties, but, nowadays, it has been well established that statins, especially atorvastatin can significantly reduce non-HDL-C, and TG. In some recent studies, atorvastatin could reduce TG levels in the range of 10-20%.[16] Even, it has been acknowledged that the higher the baseline TG level, the greater the TG-lowering effect that the baseline TG levels exceeding 250 mg/dl was associated with reductions in the range of 22-45%, whereas more modest reductions have been observed with lower baseline levels.[17] Although these lipid-lowering effects have been shown following administration of different types of statins, but atorvastatin produces greater plasma LDL and TG reductions than other statins that may be due to its long-lasting action, presumably a reflection of longer residence time of atorvastatin and its active metabolites in the liver. The TG reduction with atorvastatin seems to stem from limiting very low-density lipoprotein (VLDL) secretion from the liver and increase in clearance of TG-rich lipoprotein via induced LDL receptors from plasma.[18]

In this particular study, the effects of atorvastatin on lipid profile was similar considering different dosages of the drug and thus administrated lower dose of the drug might be more preferable due to its probable side-effects. Moreover, because of its effects on elevating blood sugar and hemoglobin A1c by the higher considered dose, the use of atorvastatin with 20 mg/day is more emphasized to prevent adverse effects. Similar studies had revealed that the dosage range of atorvastatin is10 to 80 mg once daily provides significant reductions from baseline in TG and LDL levels as well as an increase in HDL cholesterol levels with a well toleration.[19] Even, it has been shown that high-dose atorvastatin therapy does not have a significant additional effect on the reduction of TG compared with a standard dose of 10 mg in both diabetics and non-diabetics patients.[16-20]

Observed elevating effects of high-dose atorvastatin on fasting blood sugar and on hemoglobin A1C can be considered as a major side-effect which could be prevented by using a lower dose of 20 mg/day. Previous studies have presented different controversial findings in triggering/inhibiting effects of atorvastatin on blood sugar and insulin resistance. In previous animal study atorvastatin the inhibited increase in plasma glucose level and in clinical studies, patients with type II diabetes mellitus exhibited significant decrease in HbA1c level after treatment with atorvastatin.[21] In another clinical study, atorvastatin significantly inhibited increase in the 30-min glucose level, decreased plasma insulin levels before 30 and 60 min after glucose loading, and decreased the insulin resistance index, compared with corresponding values in control groups, indicating that atorvastatin seemed to improve glucose metabolism by reduction in insulin resistance.[22] The U.S. Food and Drug Administration announced that the prescribing information for cholesterol reducing drugs in the statin class will include warnings about risk of increased blood sugar levels, HbA1c, and diagnoses of diabetes. Furthermore, some large clinical trials have confirmed our results in elevation of blood sugar following administration of statins. In an Intervention Trial evaluating Rosuvastatin (JUPITER study),[23] the risk of diabetes was 27% higher in patients who received rosuvastatin than placebo treated patients. In that study, 3% of patients that received rosuvastatin compared to 2.4% of patients who received placebo developed diabetes. In pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE-IT TIMI 22) study, high-dose atorvastatin was associated with increased blood glucose.[24] Therefore, analysis of other published studies along with this study shows that statins increase HbA1c and/or fasting blood glucose, and the risk of being diagnosed with diabetes regarding of the dose of statin used. In fact, the side effect can be appeared only if higher doses of atorvastatin are being administered; thus, it is more advisable to administer 20 mg of atorvastatin daily. This is very important in these patients because the positive effects of high-dose

atorvastatin in stroke patients are not confirmed.

The present study led to reductions in serum level of AST. Some other studies could also show this effect. In a study by Karpisek et al., after the 3 months therapy, a significant reduction in AST value was observed with no difference in ALT value.[25] Also, Jurukovska-Nospal et al. showed that the elevation in ALT and AST levels greater than twice the upper limit of normal were rarely seen after 12 months of atorvastatin therapy.[26] Farsang et al. also showed that the incidence of AST/ALT < 3 times of the upper limit of the normal range in all patients was only 0.8 % without any rhabdomyolysis.[27] Nonetheless, the hepatic complication of atorvastatin with the two 20 mg/day and 40 mg/day for 3 months is very rare and thus it is ignorable.

The advantages of this study can be discussed from two points. First and foremost, the subjects admitted to study were without previous underlying comorbidities such as renal failure, hepatic dysfunction, diabetes mellitus, or congestive heart failure. Second, the effects of different dosages of atorvastatin were purely examined in patients with cerebrovascular accident. However, small sample size of the study along with a partially short following-up is two potential limitations that should be considered in future studies.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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