

Short term high dose atorvastatin for the prevention of contrast-induced nephropathy in patients undergoing computed tomography angiography

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Original Article

Abstract

BACKGROUND: Statins are shown effective by some studies in preventing contrast-induced nephropathy (CIN). We evaluated the effectiveness of atorvastatin in the prevention of CIN in computed tomography angiography (CTA) candidates.

METHODS: This study was conducted on patients referring for elective CTA with normal renal function. Patients received atorvastatin (80 mg/day) or placebo from 24 h before to 48 h after administration of the contrast material. Serum creatinine was measured before and 48 h after contrast material injection. CIN was defined as an increase in serum creatinine level of ≥ 0.5 mg/dl or $\geq 25\%$ of the baseline creatinine.

RESULTS: A total of 236 patients completed the study; 115 atorvastatin, 121 placebo, mean age = 58.40 ± 9.80 year, 68.6% male. Serum creatinine increased after contrast material injection in both the atorvastatin (1.00 ± 0.16 - 1.02 ± 0.15 mg/dl, $P = 0.017$) and placebo groups (1.03 ± 0.17 - 1.08 ± 0.18 mg/dl, $P < 0.001$). Controlling for age, gender, comorbidities, drug history, and baseline serum creatinine level, patients who received atorvastatin experienced less increase in serum creatinine after contrast material injection (beta = 0.127, $P = 0.034$). However, there was no difference between the atorvastatin and placebo groups in the incidence of CIN (4.3 vs. 5.0%, $P = 0.535$).

CONCLUSION: In patients undergoing CTA, a short-term treatment with high dose atorvastatin is effective in preventing contrast-induced renal dysfunction, in terms of less increase in serum creatinine level after contrast material injection. Further trials including larger sample of patients and longer follow-ups are warranted.

Keywords: Kidney Diseases, Multidetector Computed Tomography, Contrast Media, Hydroxymethylglutaryl-CoA Reductase Inhibitors, Atorvastatin

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Introduction

Computed tomography angiography (CTA) is one of the novel, non-invasive, and accurate diagnostic methods for cardiac diseases, including coronary artery and valvular diseases.^{1,2} However, CTA has some complications, including contrast-induced nephropathy (CIN).³ CIN, defined as an impaired kidney function after administration of intravascular contrast agent within 3 days of contrast injection in the absence of another cause, is one of the most common causes of acute renal failure in hospitalized

patients.⁴ Previous studies in patients undergoing coronary catheterization and angiography show that the incidence of CIN in patients who have no risk factors for CIN is $< 2\%$, but the incidence in patients who are high risk for CIN is increased up to 90%.^{5,6} Due to lower dose of contrast material used and characteristics of the patients, the incidence of CIN in patients undergoing CTA is much less frequent (between 2.6% and 15%) than those who undergoing coronary catheterization and angiography.^{3,7-9} However, the CIN in CTA patients

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is important as well as this complication increases mortality, costs of medical care, and length of hospitalization.^{6,10,11}

Suggested treatment strategies for CIN are limited to supportive cares and dialysis. Therefore, screening for high-risk patients and taking appropriate preventive regimes have an important role in reducing the incidence of CIN. Previous studies proposed some preventive medications for CIN including hydration, sodium bicarbonate, N-acetylcysteine (NAC), calcium channel blockers, diuretics, dopamine, endothelin antagonists, atrial natriuretic peptide, ascorbic acid and hemodialysis, or filtering the blood during and after the administration of contrast material. Among these strategies, the increase in extracellular volume, using intravenous saline or sodium bicarbonate, minimizing the dose of contrast material, the use of non-ionic contrast medium with low osmolarity instead of the high osmotic and ionic agents, and discontinuation of nephrotoxic drugs, and medications including NAC, theophylline, and statins have been shown effective in preventing CIN.¹²⁻¹⁵

In addition to regulating the lipid profile, statins have anti-inflammatory and anti-oxidative effects that can be used in preventing CIN according to its pathophysiology.¹⁶ Recent studies evaluated the efficacy of statins in the prevention of CIN, but the results have been controversial. Meta-analyses on current randomized clinical trial concluded that the short-term treatment of high dose statins prevents CIN, but the quality of data is still unsatisfactory and further studies are required in this regard.^{17,18} Studies on the effects of statins in the prevention of CIN are not enough to introduce this method as a standard method for the prophylaxis of CIN. Moreover, most of the previous studies have been performed among the patients undergoing invasive coronary angiography, and very few studies have been done in patients undergoing CTA. Therefore, this study aimed to evaluate the effectiveness of the short-term treatment with high-dose atorvastatin in the prevention of CIN in CTA candidates with normal kidney function.

Materials and Methods

This study was conducted on patients referring for elective CTA from July 2013 to February 2014 to Alzahra Hospital in Isfahan, Iran. Patients with the following characteristics were not included into the study; unstable angina, myocardial infarction, cardiac arrhythmias, heart failure, acute or chronic renal failure, serum creatinine level > 1.5 mg/dl,

intravascular administration of contrast material in the past month, known hypersensitivity to statins, and those who were living out of the city and were not able to refer for the follow-up evaluation. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from patients before entering the study.

The study was designed as a randomized, double-blind, comparative trial with two parallel arms, including high dose atorvastatin and placebo. Patients were consecutively entered into the study and were assigned an order number. Using the Random Allocation Software (version 1.0., Isfahan, Iran),¹⁹ two study arms of atorvastatin and placebo were randomly distributed to a set of sequential numbers. An independent investigator placed drugs in sequentially numbered, opaque and stapled, drug pockets. Allocation sequence was concealed from the investigators who enrolled patients into the study. Blinding the attending physicians and patients was achieved by administering placebo tablets identical in shape, size, and color to atorvastatin into the placebo arm. A sample of 125 patients in each group would provide us the power of 0.80 in detecting a difference of at least 10% in creatinine change between groups after operation.²⁰ The trial was registered in clinicaltrials.gov (ID: NCT02114346).

Patients in the atorvastatin group received 80 mg atorvastatin (two tablets of atorvastatin 40 mg, DarooPakhsh Co., Tehran, Iran) and patients in the placebo group received two placebo tablets from 24 h before to 48 h after administration of contrast material. Also, the non-steroidal anti-inflammatory drugs were discontinued from 24 h before to 48 h after the procedure.²¹ The CTA was done according to the clinical standards using 64-detector rows CT scanner (Light speed VCT, GE healthcare. USA). In all cases, Iopromide (ULTRAVIST® 320 mg/100 mL, Bayer healthcare Pharmaceuticals, Berlin, Germany) was used as a contrast media. All patients received a total of 100 ml of the contrast material; 15 ml for the test bolus and 85 ml for the imaging (6 ml/s injected with injector device).

Before the operation, all the patients underwent a detailed history and physical examination by a cardiologist. Age, gender, and history of hypertension, diabetes mellitus, and dyslipidemia were recorded, and weight was measured. Cardiopulmonary examination was done for the evaluation of systolic/diastolic blood pressure and heart rate. Serum creatinine was measured before, and 48 h after contrast material injection and the amount of change was considered as the study outcome. CIN was defined as an increase in serum creatinine level of

≥ 0.5 mg/dl or ≥ 25% of the baseline creatinine after 48 h of contrast material injection.²²

Data were analyzed using the SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Continuous variables were checked if normally distributed in each group. Data are presented as mean ± standard deviation or number (%). The independent sample t-test, Mann–Whitney U-test, and Chi-square test were applied for comparisons between the atorvastatin and placebo groups. Paired t-test and Wilcoxon test were applied for within group comparisons. Furthermore, a linear regression model was conducted with the amount of change in serum creatinine level from baseline to 48 h after CTA as the dependent variable and baseline characteristics and intervention type as predictors. P < 0.050 was considered to be indicating a statistical significant difference in all analyses.

Results

During the study period, 350 patients were

referred to our center for CTA from which 90 patients were not eligible to participate; 12 unstable angina, 15 serum creatinine > 1.5 mg/dl, 1 possible history of adverse reaction to atorvastatin, and 62 living out of the city and not able to refer for follow-up evaluation. 10 eligible patients were not willing to participate. A total of 250 patients were included into the trial from which 14 patients (4 in the placebo and 10 in atorvastatin groups) did not refer for the measurement of serum creatinine level 48 h after CTA and were excluded from the trial. Finally, 236 patients with a mean age of 58.40 ± 9.80 year (68.6% male) completed the study and were considered for analyses (Figure 1). Demographic data of the patients are summarized in table 1. The two groups were similar in demographic characteristics except the frequency of hypertension (79.3% vs. 64.3%, P = 0.008) and using anti-hypertensive drugs (81.0% vs. 64.3%, P = 0.003), which was higher in the placebo group.

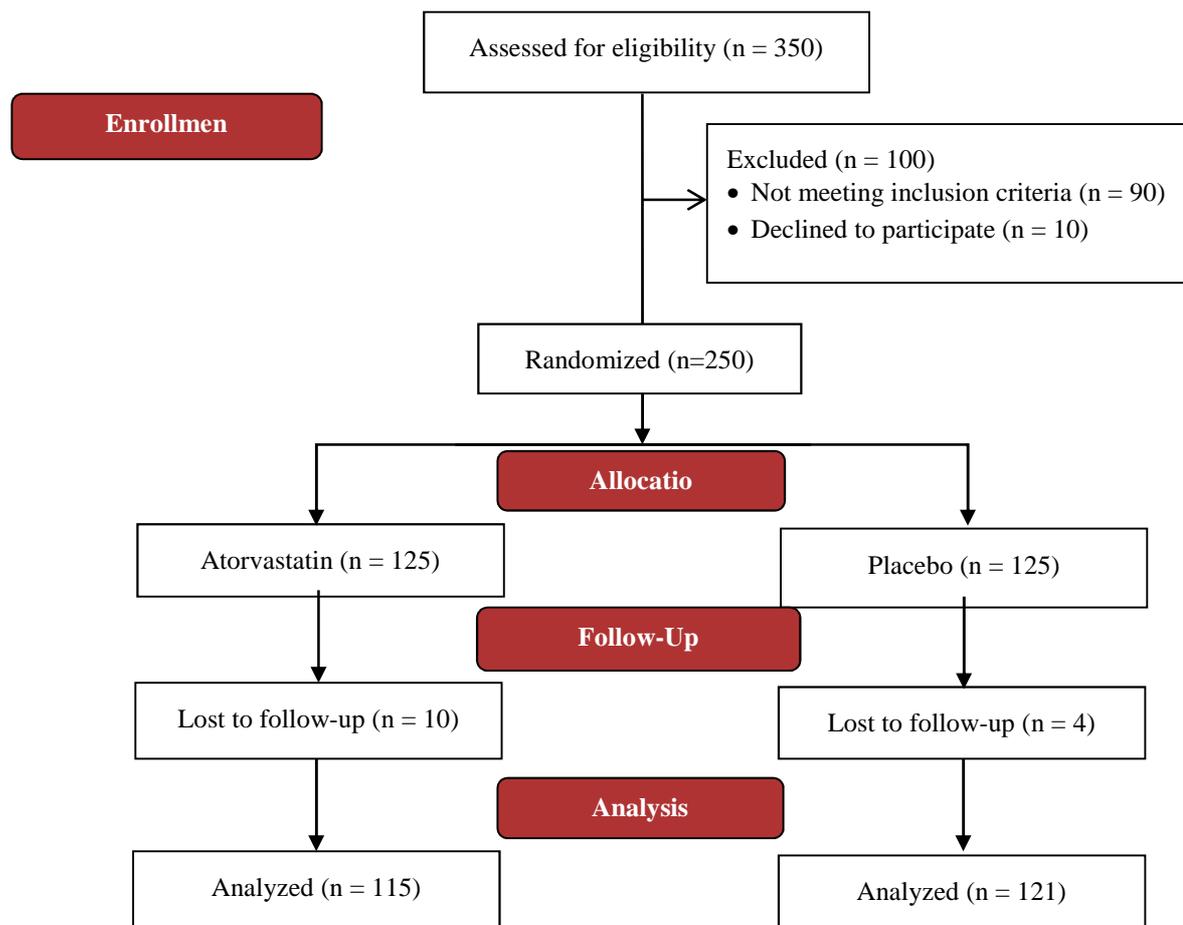


Figure 1. Patients’ flow diagram

Table 1. Demographic data of the patients

Demographic data	Atorvastatin (n = 115)	Placebo (n = 121)	P
Male/female (%)	77 (67.0)/38 (33.0)	85 (70.2)/36 (29.8)	0.343 [†]
Comorbidities			
Hypertension	74 (64.3)	96 (79.3)	0.008 [‡]
Dyslipidemia	60 (52.2)	74 (61.2)	0.104 [‡]
Diabetes	36 (31.3)	48 (39.7)	0.114 [‡]
Drug history			
Statins	63 (54.8)	62 (51.2)	0.339 [‡]
Antihypertensive	74 (64.3)	98 (81.0)	0.003 [‡]
Hypoglycemic	35 (30.4)	45 (37.2)	0.169 [‡]
Cardiac examination			
Systolic blood pressure, mmHg	124.10 ± 11.70	122.50 ± 10.90	0.176 [‡]
Diastolic blood pressure, mmHg	79.70 ± 7.00	78.10 ± 6.10	0.071 [‡]
Heart rate, beat/min	73.20 ± 9.50	71.50 ± 11.30	0.096 [‡]
Age	58.10 ± 10.40	58.70 ± 9.30	0.636 [*]

Data are presented as mean ± SD or number (%); * Independent sample t-test; † Chi-square test; ‡ Mann-Whitney U-test; SD: Standard deviation

Table 2. Comparison of study outcomes between the atorvastatin and placebo groups

	Atorvastatin (n = 115)	Placebo (n = 121)	P
Baseline creatinine (mg/dl)	1.00 ± 0.16	1.03 ± 0.17	0.231 [*]
48 h creatinine (mg/dl)	1.02 ± 0.15	1.08 ± 0.18	0.039 [*]
Delta creatinine (mg/dl)	0.02 ± 0.10	0.04 ± 0.09	0.076 [*]
Creatinine change (%)	2.80 ± 10.9	4.70 ± 9.30	0.124 [*]
P [†]	0.017	< 0.001	
Contrast-induced nephropathy	5 (4.3)	6 (5.0)	0.535 [‡]

Data are presented as mean ± SD or number (%); * Mann-Whitney U-test; † Wilcoxon test; ‡ Chi-square test; SD: Standard deviation

The two groups were similar in baseline serum creatinine (Table 2). A significant change was observed in serum creatinine 48 h after contrast material injection in both the atorvastatin (1.00 ± 0.16 - 1.02 ± 0.15 mg/dl, $P = 0.017$) and placebo groups (1.03 ± 0.17 - 1.08 ± 0.18 mg/dl, $P < 0.001$). Serum creatinine at 48 h after contrast material injection was significantly higher in the placebo group as compared with the atorvastatin group ($P = 0.039$). However, the difference between the two groups in the amount of change in serum creatinine after contrast material injection was not statistically significant ($P = 0.076$). A total of 11 (4.7%) patients experienced CIN, all of them had > 25% increase in serum creatinine. There was no difference between the atorvastatin and placebo groups in this regard ($P = 0.535$).

Considering some differences between the study groups in baseline characteristics, a linear regression model was conducted controlling for age, gender, comorbidities, drug history, and baseline serum creatinine level. Results showed an association between intervention type (atorvastatin) with the

amount of change in serum creatinine level from baseline to 48 h after contrast material injection [R^2 (adjusted) = 0.271 (0.239), $\beta = 0.127$, $P = 0.034$] (Figure 2). Chronic statin pretreatment has no association in this regard ($\beta = -0.043$, $P = 0.633$).

Discussion

Various interventions are evaluated for the prevention of CIN. Among the most studied medications, theophylline, NAC, and statins are shown to be effective in this regard,^{23,24} with controversy on the efficacy of NAC²⁵ and statins.^{26,27} We evaluated the effectiveness of short-term treatment with high-dose atorvastatin (4 days, 80 mg) in the prevention of CIN in CTA candidates with normal kidney function. Our study results showed that atorvastatin is effective in preventing CIN in terms of less increase in serum creatinine level after contrast material injection. However, it was not effective in reducing the incidence of CIN, a clinically important outcome.

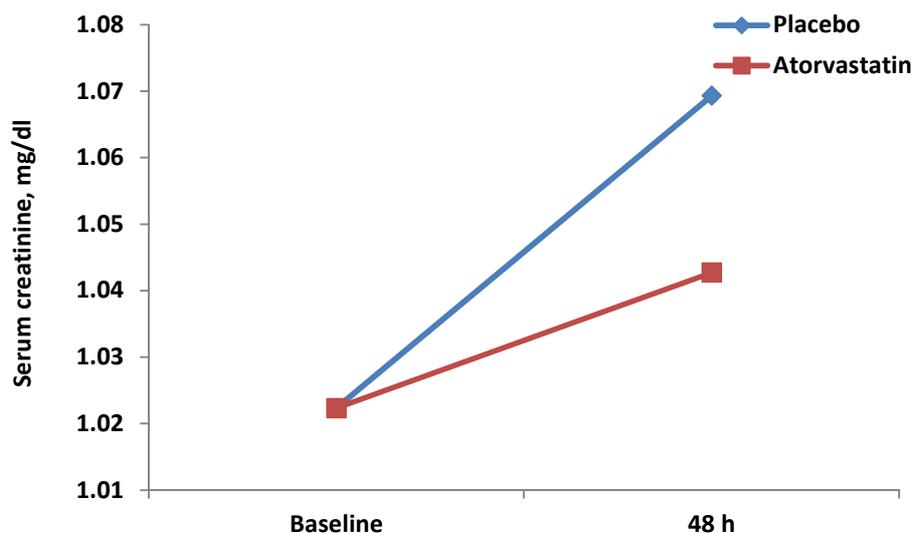


Figure 2. Change in serum creatinine level from baseline to 48 h after contrast material injection in the atorvastatin versus placebo group adjusting for demographic data and baseline characteristics

Beta = 0.127; P = 0.034

The pathophysiology of CIN is not completely clear. It seems that the contrast-induced renal dysfunction is due to a change in renal blood flow accompanied with a reduction in flow of the central part of the kidney and direct tubular epithelial toxicity. Although the mediators behind these changes are not completely identified, alteration in the metabolism of angiotensin, adenosine, endothelin, nitric oxide, and prostaglandins are proposed in this regard.^{4,28,29} Statins may counteract to various pathological mechanisms underlying the CIN. These agents can decrease the activity of the angiotensin receptor,³⁰ decrease synthesis of endothelin and increase the bioavailability of nitric oxide,³¹ leading to an increase in renal blood flow and prevention of CIN. Also, statins reduce inflammation,³² inhibit oxidative stress reactions,³³ and protect kidney from the injuries of complements.³⁴

Results of the previous studies have been controversial on the preventive effects of statins against CIN. In a meta-analysis by Zhang et al. on 4 randomized controlled trials including 751 patients, administration of statins was not effective in reducing the incidence of CIN, but it was effective in reducing the serum creatinine level by -0.06 mg/dl (95% CI -0.12 - 0.00 mg/dl).¹⁸ A recent meta-analysis by Takagi and Umemoto on 7 randomized controlled trials including 1251 patients undergoing angiography showed that a short-term treatment with atorvastatin before angiography can reduce the

change in serum creatinine by 0.07 mg/dl and the incidence of CIN by 44%.¹⁷ Another meta-analysis by Zhang et al. was not conclusive due to the limitations of the included studies, albeit a preventive effect against CIN for chronic statin pretreatment is reported.²⁶ Although we found a protective effect for high dose atorvastatin in change of serum creatinine after contrast material injection, we found no effect for chronic low dose statin pretreatment in this regard. It must be noted that most of the previous studies were conducted on patients undergoing coronary angiography, which according to using a higher dose of contrast material in these patients, have a higher risk of CIN. Furthermore, several of previous trials have been conducted on patients with abnormal renal function. In contrast, we included patients with normal renal function undergoing CTA for whom a lower dose of contrast material is used. Also, various statins have been used in previous studies. It has been shown that atorvastatin is more effective than simvastatin in reducing the oxidative stress.^{35,36} The difference among the previous study results can be due to these factors, and further studies, and head-to-head comparative trials are still required before a precise conclusion in this regard.

Our study has some limitations. First, the trial was a single-center study, which may reduce its generalizability. Second, our study sample size was small, and we were not able to show statistical significant effects of the medications in terms of

CIN incidence, which is a clinically important outcome. Finally, we monitored our patients for 48 h. Longer follow-ups can provide more information on the efficacy of preventive measures.

Conclusion

The results of this study showed that, in patients undergoing CTA, a short-term treatment with high dose atorvastatin is effective in preventing contrast-induced renal dysfunction, in terms of less increase in serum creatinine level after contrast material injection. We found no effect for chronic low dose statin pretreatment in this regard. Further trials, including larger sample of patients and longer follow-ups are warranted.

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Conflict of Interests

Authors have no conflict of interests.

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