

Atorvastatin and prevention of contrast induced nephropathy following coronary angiography

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Background: Contrast induced nephropathy (CIN) is one of the most common complications after radiographic procedures using intravascular radiocontrast media. The aim of the current study was to assess the effect of atorvastatin on prevention of CIN in patients undergoing coronary angiography. **Materials and Methods:** In a clinical trial study, 200 patients referred for angiography were randomly divided into two groups of using 80 mg atorvastatin and placebo before the procedure. Furthermore, 100 patients who were under chronic treatment of statins were included as the third group. Serum creatinine (Scr) levels before and after the procedure were evaluated and incidence of CIN (post-procedural Scr of >0.5 mg/dl or >25% from baseline) was assessed. **Results:** Mean age of the participants was 60.06 ± 0.69 years and 276 (92%) were male. There were no significant differences between group with respect to age and gender. In pre-operation atorvastatin, placebo and long term statin groups, the incidence of CIN was 1%, 2% and 1%, and mean changes of Glomerular filtration rate (GFR) was 3.68 ± 1.32 , -0.77 ± 1.21 and 1.37 ± 0.86 ; and mean changes of creatinine (Cr) was -0.05 ± 0.02 , 0.02 ± 0.02 and -0.01 ± 0.01 respectively. respectively ($P = 0.776$, 0.026 and 0.041 respectively). In pre-operation atorvastatin group, Cr decreased, and GFR increased significantly ($P = 0.019$ and 0.007 respectively). **Conclusion:** pre-operation short term high dose atorvastatin use was associated with a significant decrease in serum Cr level and increase in GFR after angiography.

Key words: Angiography, atorvastatin, contrast induced nephropathy, prevention

How to cite this article: Bidram P, Roghani F, Sanei H, Hedayati Z, Golabchi A, Mousavi M, Hajiannejad A, Pourheidar B, Badalabadi MM, Gharaati M, Akhbari M, Salehi A. Atorvastatin and prevention of contrast induced nephropathy following coronary angiography. *J Res Med Sci* 2015;20:1-6.

INTRODUCTION

Contrast induced nephropathy (CIN) is one of the most common complications after radiographic procedures using intravascular radiocontrast media.^[1] CIN after percutaneous coronary intervention (PCI) is common (5-50% according to characteristics of patients) and is associated with increased rate of morbidity and mortality, chronic renal problems and longer duration of hospitalization.^[2-4] CIN is more likely in patients with baseline renal insufficiency, diabetes mellitus, volume of contrast used, congestive heart failure, older ages and administration of nephrotoxic drugs.^[4-6] The incidence of CIN is decreasing because of more risk prevention and better contrast media, but according to the increases in the number of patients undergoing PCI, the CIN cases are increasing.^[7] Pathophysiology of CIN is not well-known but some mechanisms including medullary ischemic damages, inflammation, production of oxygen free radicals and direct nephrotoxicity are mentioned.^[8]

Several strategies have been studied to reduce CIN including intravenous hydration, low and iso-osmolar

contrast, hemofiltration, using N-acetylcysteine (NAC), dopamine, ascorbic acid, furosemide, mannitol and etc. but none of them are reported to be completely useful.^[9-11] Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are reported to be effective on improvement of renal function and have an effect in the prevention of CIN.^[7,12] Statins have positive effects on endothelial function, reduce oxidative stress and increase nitric oxide production.^[13] Different studies have been done on the effect of statins in the prevention of CIN, but there are controversy results. A meta-analysis conducted by Zhang *et al.* was no conclusive for CIN preventive effect of statins before contrast exposure and more studies with larger sample sizes and better designed was recommended.^[7,14] On the study in Iran showed that short term high dose statin use before contrast injection is associated with an increase in Glomerular filtration rate (GFR) in comparison to control the group.^[15] As an effect of statin use before the angiography to prevent CIN is not well-known, the aim of the current study was to assess the effect of atorvastatin on prevention of CIN in patients undergoing coronary angiography.

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Received: 25-04-2014; **Revised:** 24-05-2014; **Accepted:** 23-09-2014

PATIENTS AND METHODS

Study population

This study was a double blinded placebo controlled clinical trial conducted on a random sample of patients with chronic stable angina who were referred to Shahid-Chamran Hospital of Isfahan, Iran to be undergone coronary angiography in 2013. The inclusion criteria were; (a) having chronic stable angina who were referred for coronary angiography, (b) non-pregnant female subjects, (c) no history of the following; diabetes mellitus, renal failure, single kidney, cardiogenic shock, unstable angina, myocardial infarction, hypersensitivity to statins, previous intravascular contrast injection during 1 month before admission. Patients were excluded according to the following criteria; (a) patients with GFR <60, (b) patients with cardiogenic shock during the study and (c) patients who had a significant lesion and underwent PCI in addition to angiography. Sample size was calculated using the estimation of differences in CIN incidence rate between two groups from 15% to 2%, 95% confidence interval with 80% power.^[16] The study was approved by the Ethical Committee of the Isfahan University of Medical Sciences and is registered at ClinicalTrials.gov, number NCT02113540. An informed consent was obtained from all participants.

Intervention

According to the table of random numbers, participants were divided into two groups of placebo and statin. Both patients and investigators were blinded to study groups. Also, a group of patients who were taking atorvastatin before entering the study were selected as a third group to compare the effect of long term and pre operation taking of atorvastatin. All the participants were asked not to take non-steroidal anti-inflammatory drugs 48 h before and after the angiography. Furthermore, the subjects were asked not to use metformin by starting the angiography till 48 h after the procedures. Angiography was done using the standard technique. For all patients 30-40 cc, a nonionic, iso-osmolar (290 mOsm/kg), visipaque (iodixanole) 320 mg/dl was used in all interventions. Patients were hydrated with 1 ml/kg × h of isotonic saline solution 12 h before and after the contrast injection. All the participants were evaluated before and 48 h after the procedure. Patients in the intervention group received 80 mg oral atorvastatin (two 40 mg tablets, Darou Pakhsh Pharmaceutical Co., Tehran, Iran) 12 h before contrast injection. The placebo group was treated as the intervention group with placebo similar to the atorvastatin (produced in Faculty of Pharmacy, Isfahan University of Medical Sciences). Patients who were receiving atorvastatin before the study continued their treatment. Drug and placebo were coded before investigations and after the study they were decoded.

Assessments

Demographic characteristics of the participants including age, sex, history of other diseases such as hypertension and ischemic heart disorders and also drug history of the subjects were recorded. All participants were examined for height and weight. Body mass index (BMI) was regarded as a weight divided by height squared (kg/m²). All measurements were performed with the same tool. For the measurement of serum creatinine (Scr), blood samples were taken before and 48 h after the procedure. Also, fasting blood sugar (FBS) was measured before the study. GFR was calculated with chronic kidney disease epidemiology collaboration equation^[17] as the following; $GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] - 1.159 [if black]. Scr, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. CIN was defined as an increase in post-procedural Scr of >0.5 mg/dl or >25% from baseline in the absence of any other causes.^[18]

Data analysis

Statistical analysis was performed using SPSS for windows (Version 16.0, 2007, SPSS Inc., Chicago, IL, USA). The paired *t*-test and analysis of variance (ANOVA) followed by a *post-hoc* multiple comparisons and analysis of covariance (ANCOVA) (for continuous variable) and Chi-square test (for categorical variables) were used to compare variables. To test the normality of distributions, Kolmogoroff-Smirnoff test was used. Statistical significance was accepted at $P < 0.05$. All the values are given as mean ± standard error mean (mean ± SE) or numbers (%).

RESULTS

In this study, 580 patients were enrolled. 252 patients were excluded as they had a positive history of diabetes mellitus, renal failure, myocardial infarction, unstable angina and single kidney. Of all the participants, 20 patients were excluded because of GFR <60. Eight patients were undergone PCI and were excluded. Finally, three groups of 100 individuals were involved in the current study [Figure 1, Consort flow diagram]. Mean age of the participants was 60.06 ± 0.69 years and 276 (92%) were male. There were no significant differences between three groups for mean age and distribution of sex ($P = 0.921$ and 0.554 respectively) [Table 1]. Also, Table 1 is reporting the comparison of mean height, weight, BMI and FBS between three groups of the study. No significant differences were observed for height and FBS comparisons ($P = 0.840$ and 0.055 respectively). However, differences were statistically significant for weight and BMI ($P = 0.002$ and 0.001 respectively). *Post-hoc* analysis showed that long term statin group had significantly higher BMI ($P = 0.007$

and 0.005 for comparing with pre-operation statin and placebo groups respectively) and weight ($P = 0.010$ and 0.009 for comparing with pre-operation statin and placebo groups respectively) in comparison to the other two groups.

The incidence of CIN in all participants was 1.3% (4 individuals). The incidence of CIN was 1%, 2% and 1% in pre-operation atorvastatin, placebo and long term statin groups respectively ($P = 0.776$). According to Table 2, there were no significant differences between three groups in mean Scr level and GFR before ($P = 0.387$ and 0.650

respectively) and after ($P = 0.674$ and 0.637 respectively) the procedure. Scr level change was significantly different between three groups according to ANOVA test (0.041). The difference was shown between group with high dose short term atorvastatin and placebo group ($P = 0.033$). The differences of Cr changes were not statistically significant between high dose pre operation atorvastatin group and long term statin groups ($P = 0.295$) and also between placebo and long term statin groups ($P = 0.554$). GFR change was significantly different between groups according to ANOVA test ($P = 0.026$). *post-hoc* analysis showed that the only difference of GFR changes between pre-operation high dose atorvastatin and placebo groups was statistically significant ($P = 0.019$). The differences of GFR changes were not statistically significant between high dose pre-operation atorvastatin group and long term statin group ($P = 0.416$) and also between placebo and long term statin group ($P = 0.507$). Comparison of each group before and after the procedure showed that in pre-operation atorvastatin group, Cr decreased and GFR increased significantly ($P = 0.019$ and 0.007 respectively) but in two other groups there were no significant differences before and after the procedure for serum Cr level and GFR ($P > 0.05$). Test of normality showed that Cr and GFR changes were not normally distributed ($P < 0.05$) but according to a large sample size (more than 30), ANCOVA test was used. Results showed that Scr and GFR changes between the groups had statistically significant

Table 1: Comparison of demographic and baseline characteristics of the three groups of the study

Demographic variables	Groups			P
	Preoperation atorvastatin	Placebo	Long-term statins	
Sex (male) (%)	89 (89)	92 (92)	94 (94)	0.436
Age (years)	59.98±1.08	60.40±1.34	59.83±1.16	0.942
Height (cm)	169.98±0.66	170.00±0.63	169.52±0.37	0.840
Weight (kg)	77.18±1.14	77.33±1.00	81.67±0.93	0.002*
Body mass index (kg/m ²)	26.77±0.42	26.83±0.38	28.52±0.33	0.001*
Fasting blood sugar (mg/dl)	107.33±2.47	118.41±4.55	114.37±2.00	0.073

Data are given as mean±SE or number (%); *Significant difference was between long-term statins and placebo groups and also between long-term statins and pre-operation atorvastatin groups (using *post-hoc* analysis); SE = Standard error

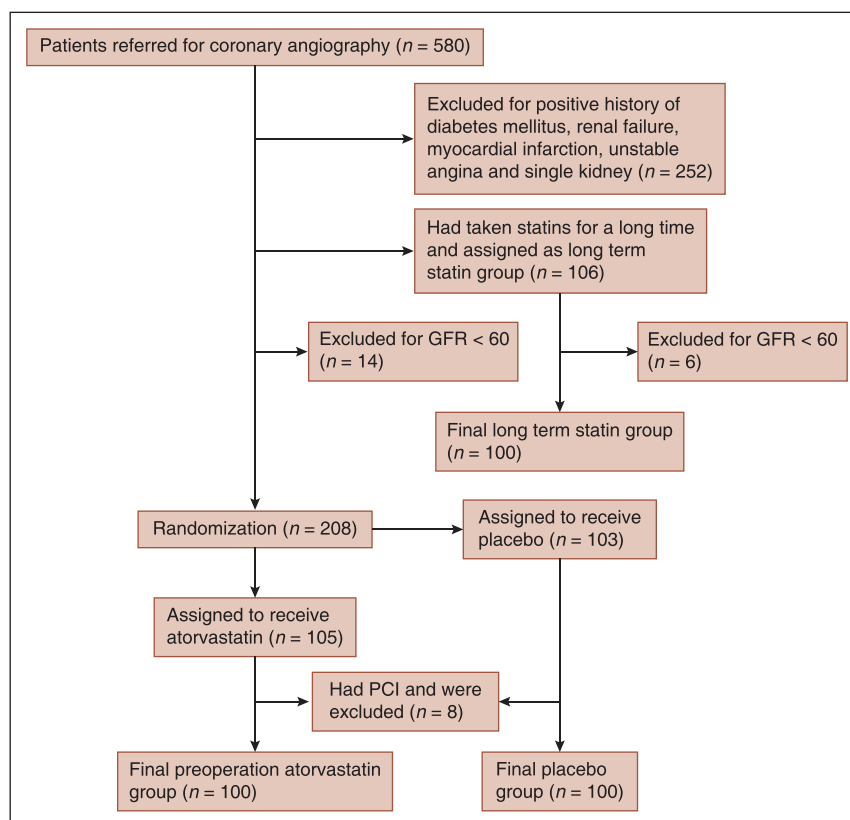


Figure 1: Consort flow diagram

Table 2: Comparison of serum creatinine level and GFR before and after angiography between three groups of the study

Variables	Groups			P*	P [†]
	Pre-operation atorvastatin	Placebo	Long term statins		
Serum creatinine level (mg/dl)					
Before	1.18±0.02	1.14±0.02	1.17±0.01	0.387	
After	1.13±0.02	1.15±0.02	1.16±0.02	0.674	
P**	0.019	0.423	0.409		
Serum creatinine changes	-0.05±0.02	0.02±0.02	-0.01±0.01	0.041 [†]	0.046
GFR (mg/dl)					
Before	68.02±1.80	70.22±1.73	68.76±1.53	0.650	
After	71.70±1.81	69.45±1.87	70.13±1.48	0.637	
P**	0.007	0.523	0.118		
GFR changes	3.68±1.32	-0.77±1.21	1.37±0.86	0.026 [†]	0.01

Data are given as mean ± SE; ANOVA = Analysis of variance; SE = Standard error; FBS = Fasting blood sugar; BMI = Body mass index; GFR = glomerular filtration rate. *Analysis is done by ANOVA; **Analysis is done by paired t-test; [†]Significant difference was only between placebo and pre-operation atorvastatin groups (using *post-hoc* analysis); [‡]After adjustment for BMI and FBS

differences ($P = 0.046$ and 0.01 respectively) when adjusted for the covariates of BMI and FBS.

DISCUSSION

Different studies have been done on the effect of statins in the prevention of CIN, but there are controversy results and the data are not conclusive to prove the preventive effect of statins. So the aim of the current study was to assess the effect of atorvastatin on prevention of CIN in patients undergoing coronary angiography.

Our result couldn't show any association between pre operation atorvastatin and also long term use of statins and prevention of CIN. The incidence of CIN in the current study was 1% in both pre operation and long term statins groups and 2% in the placebo group. In addition, our results showed that taking 80 mg atorvastatin (high dose) 12 h before the angiography was associated with a significant decrease in Scr level and also a significant increase in GFR after the procedure. But long term statin use and also placebo consumption did not show the mentioned effect. Different studies have reported different incidence of CIN. A study conducted by Jo *et al.* on patients with baseline renal insufficiency revealed that the incidence of CIN was 2.5% in patients treated by short term high dose of simvastatin and 3.4% in placebo group and the difference was not statistically significant. They have reported no relation between statin use and prevention of CIN after angiography.^[19] They have mentioned that they have enrolled patients with normal or mildly impaired renal function and it can be the reason of the lower incidence of CIN. Also they have mentioned that short term use of statins may not be enough to develop the anti-oxidant effect of the drug. Also, more following was suggested in that study. Another study has reported that 3.3% in the atorvastatin group (short term high dose use) and 10% in the control group developed CIN, and the difference was not significant. But similar to our results

they have reported that the baseline Cr and GFR levels were similar before the study and after the procedure a significant Cr decrease and GFR increase in the atorvastatin group were shown.^[20] In that study, patients with diabetes mellitus were not excluded. Toso *et al.* in their study concluded that short term administration of high dose atorvastatin before and after the contrast injection is not effective on reduction of CIN.^[21] In that study, all patients received NAC, and it was a mentioned limitation of the study by the authors. Furthermore, larger sample size and longer period of follow-up are recommended in that study. Some factors including renal dysfunction, diabetes, congestive heart failure, older age and using nephrotoxic drugs are associated with a higher incidence of CIN.^[22] We excluded patients with renal dysfunction and diabetes mellitus, and this can be the reason of the lower incidence of CIN in our study compared with previous studies. Also in our study patients with PCI were excluded. In PCI, more contrast media than angiography is used, and higher incidence of CIN is expected. Some other studies have reported the same results like our study and have reported that pre-operation statin use is not associated with prevention of CIN.^[23,24] In contrast to our results, study conducted by Khanal *et al.* on 29409 patient undergoing PCI showed that pre-operation statin use is associated with lower incidence of CIN (4.37 vs. 5.93) in comparison to no statin use group.^[25] Also, another study showed that pre PCI statin use was associated with a lower incidence of CIN and better Cr clearance.^[26] Attallah *et al.* reported that prophylactic use of statins is associated with better Scr levels and lower incidence of CIN.^[27] A previous study in Iran conducted by Sanadgol *et al.* was conclusive that short term high dose simvastatin before contrast exposure is associated with less CIN. But in that study incidence of CIN is not reported, and only GFR changes are evaluated. That study only revealed the increase of GFR after statin therapy in comparison to control the group.^[15] According to our results, the effect of long term use of statins was similar to placebo and had lower effects

on Scr level and GFR in comparison to pre-operation high dose atorvastatin use. A study conducted by Xinwei *et al.* showed that higher doses (80 mg vs. 20 mg) of simvastatin was more effective on decrease of Scr level and increase of Cr clearance after the PCI.^[16]

A meta-analysis conducted by Zhang *et al.* was no conclusive for CIN preventive effect of statins before contrast exposure and more studies with larger sample sizes and better designed was recommended.^[7] But another study conducted by Pappy *et al.* showed different conclusion and they have reported that statin use is associated with a significant reduction of CIN in patient undergoing coronary angiography.^[22] According to these results and results of the current study, more well-designed studies with larger sample sizes are recommended.

Limitations

The small sample size could be a limitation of this study. Although the sampling was random but finally, most of the participants were male which may another limitation of this study. Also, we excluded the patients with renal dysfunction, diabetes and congestive heart failure. Including these patients and evaluating them separately will provide more information. Longer duration of follow-up of the patients may provide more results and better conclusions.

CONCLUSION

In conclusion, our results didn't reveal any association between pre-angiography high dose atorvastatin and also long term statin use and prevention of CIN. But our results showed that pre operation short term high dose atorvastatin use is associated with a significant decrease in Scr level and increase in GFR after the procedure.

AUTHOR'S CONTRIBUTION

PB contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work as a first author. FR contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work as a supervisor. HS contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work as a supervisor. ZPH contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work as a nephrologist consultant. AG contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM contributed in the conception of

the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AH contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. BP contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MMB contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MG contributed in the conception and design of the work, drafting and revising the draft and accumulating data. MA contributed in the design of the work, revising the draft approval of the final version of the manuscript, and agreed for all aspects of the work. AS contributed in analysing data and designing tables and consort flow diagram as a statistics consultant.

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Source of Support: Nil, **Conflict of Interest:** None declared.