Does high-dose lovastatin therapy diminish the risk of iodinated contrast induced acute kidney injury? A double-blind placebo-controlled clinical trial

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Contrast-induced acute kidney injury (CI-AKI) is one of the common causes of acute kidney injury. Various studies have been conducted to reduce the risk of CI-AKI.
Objectives: In this study, we examined the effectiveness of lovastatin in preventing CI-AKI in patients who required iodinated contrast injection.
Patients and Methods: This double-blind clinical trial was conducted on 122 patients scheduled for coronary angiography, abdominal computed tomography (CT) scan, and pulmonary CT angiography. Patients were randomly divided into two groups of receiving lovastatin and placebo. Estimated glomerular filtration rate (eGFR) at baseline and 48 hours after iodinated contrast injection was calculated.
Results: The incidence of CI-AKI in all study population was 3.3% (1.6% in lovastatin group, and 5% in placebo group; $P = 0.309$). A significant difference in the mean changes of eGFR (the differences in the mean of eGFR at the 48 hours after iodinated contrast injection versus baseline) between placebo and lovastatin group was observed ($P < 0.001$). This finding showed that, after intervention a further decline in the mean of eGFR in the placebo group than the lovastatin group was happened.
Conclusion: After iodinated contrast agent administration, in the lovastatin group mean change eGFR was significantly less than the placebo group. This finding indicated that high-dose short-term lovastatin treatment may be effective on CI-AKI prevention.

Introduction

After pre-renal azotemia and drug nephrotoxicity, contrast-induced acute kidney injury (CI-AKI) has shown as responsible for 11% of the leading reason of in-hospital acute kidney injury (AKI) and the third cause of in-hospital AKI (1).

CI-AKI is described as a rise of serum creatinine more than 0.5 mg/dL or 25% increase from the baseline after 48 hours of administration of contrast (2).

CI-AKI is associated with more than 5% increase in

hospital mortality rate in patients with chronic kidney disease (CKD) and 2.5% in patients without CKD.

CI-AKI risk factors are divided into two groups of modifiable and non-modifiable. Non-modifiable risk factors include age, diabetes mellitus, advanced heart failure, CKD, cardiogenic shock and kidney transplant. In addition, modifiable risk factors include the volume of iodinated contrast agent, hypotension, anemia and dehydration, hypoalbuminemia (serum albumin <3.5 g/dL), administration of diuretics and angiotensin converting

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enzyme inhibitors, nonsteroidal anti-inflammatory drugs, intra-aortic pump balloon, and nephrotoxic antibiotics (3,4).

Several approaches including hydration therapy (5), administration of sodium bicarbonate (6), N-acetylcysteine (7), adenosine receptor antagonists (8), hemodialysis and hemofiltration in preventing CI-AKI have been assessed (9).

Since iodinated radio-contrast agents are involved in the pathophysiology of CI-AKI through inflammation, vasoconstriction and oxidative stress. Administration of statins, which are 3 hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, has been considered to prevent CI-AKI. However, the result of several studies to assess the effect of statins on CI-AKI prevention has been controversial.

A meta-analysis by Singh et al showed which statins significantly decrease the risk of CI-AKI (10).

In contrast, another meta-analysis by Zhang et al did not show the protective effect of short-term high-dose statins to reduce CI-AKI (11).

Similarly the study by Abaci et al showed administration of rosuvastatin before coronary angiography did not reduce the risk of CI-AKI (12).

Another study to evaluate the effect of short-term high-dose atorvastatin to reduce the risk of CI-AKI showed glomerular filtration rate (GFR) in patients receiving atorvastatin was higher than the placebo group after coronary angiography (13).

Objectives

This study aimed to evaluate the effect of lovastatin to prevent CI-AKI in patients receiving iodinated contrast agent.

Patients and Methods

Study population

This is a double-blind placebo-controlled clinical trial planned on a random group of patients who required elective coronary angiography and iodinated contrast-enhanced computed tomography in Tohid hospital of Sanandaj, Iran in 2016. Patients who were required iodinated contrast injection in elective diagnostic procedures including computed tomography (CT) scan and coronary angiography were enrolled to the study. Exclusion criteria were acute kidney injury caused by conditions other than iodinated contrast administration, presence of acute coronary syndrome, acute myocardial infarction, sensitivity to statins and patient's dissatisfaction. Patients were randomly assigned into lovastatin and placebo groups using block randomization. Sixty-one patients who met the inclusion criteria were enrolled in each group (122 in total).

Administration of non-steroidal anti-inflammatory drugs, metformin, and diuretics stopped from 48 hours before to 48 hours after the procedure. Iso-osmolar iodinated contrast agent iodixanol was administered for all patients. Additionally, intravenous hydration with 1 mL/kg/h isotonic saline from 12 hours before the procedure and 1200 mg N-acetyl cysteine twice daily from the day before through 24 hours after procedures were administered in all patients.

In the experimental group, 60 mg of lovastatin (three 20 mg tablets, Hakim pharmaceutical Company, Tehran, Iran) on the day before the procedure, the day of the procedure, and the day after the procedure were administered. The control group received placebo similar to lovastatin tablets (produced in the school of pharmacy, Hamadan University of Medical Sciences). Likewise, statins were continued in patients who were taking it before the study. Serum creatinine assessed at baseline (by the Jaffe method using standard kit manufactured by Pishtaz Teb Company, Tehran, Iran) and at 48 hours after iodinated contrast administration. Accordingly eGFR was calculated using the MDRD formula (14).

All patients' demographic information was recorded at the beginning of the study. In addition eGFR and serum creatinine were measured before and 48 hours after iodinated contrast injection. CI-AKI was defined as 0.5 mg/dL increase in serum creatinine or 25% increase in the baseline level in the absence of other causes (2).

Ethical issues

The research followed the tenets of the Declaration of Helsinki; informed consent was obtained; the research was approved by the ethical committee of Kurdistan University of Medical Sciences (Grant # 1394.143), and was registered at the Iranian registry of clinical trial database (identifier: IRCT2017041033359N1; http://en.search.irct.ir/).

Statistical analysis

Statistical analysis has been carried out by SPSS version 21. Results were analyzed using descriptive statistic formulas as percentage or mean. Given that the study is a clinical trial with inferential statistics, we used standard error of the mean to inference statistics information. Chi-square test, independent and dependent t test and analysis of covariance (ANCOVA) were applied too. P values <0.05 was considered statistically significant. The differences in the mean of eGFR at the baseline and 48 hours after the iodinated contrast injection in each group were expressed as mean changes.

Results

A total of 122 patients who were scheduled to coronary angiography and computed tomography were enrolled to the study. Around 48.4% of patients were male. They were randomly divided into two groups receiving lovastatin and placebo. The mean age of lovastatin and placebo groups were 56.9 ± 13.9 years and 54.5 ± 15.5 years respectively (P = 0.37). The baseline mean serum creatinine in lovastatin and placebo groups were 1.01 ± 0.02 mg/dL and 1.09

± 0.04 mg/dL respectively ($P = 0.394$). Accordingly, in lovastatin and placebo groups, the baseline eGFR was 72.7 ± 1.8 mL/min/1.73 m^2 and 69.9 ± 2.6 mL/min/1.73 m^2 respectively ($P = 0.121$).

In this study, changes of eGFR in 48 hours after administration of iodinated contrast versus baseline in lovastatin group (2.52 ± 1.12 mL/min/1.73 m^2; $P = 0.029$) and placebo group (4.24 ± 1.38 mL/min/1.73 m^2, $P = 0.03$) were significant (Table 1).

After the intervention, with regard to baseline eGFR, a significant difference in the mean changes of eGFR (the differences in the mean of eGFR at the 48 hours after iodinated contrast injection versus baseline) between placebo and lovastatin group was observed ($P < 0.001$). One patient (1.6%) in the lovastatin group and three patients (5%) in the placebo group suffered CI-AKI. The incidence of CI-AKI was calculated as 3.3%. While CI-AKI cases in the placebo group were higher than lovastatin group, however, it was not statistically significant ($P = 0.309$) (Table 2).

Discussion

Although, pathophysiology of CI-AKI is not exactly clear, nevertheless, different mechanisms have been proposed on the pathogenesis of CI-AKI. One of the considered mechanisms is vasoconstriction of afferent arterioles that reduces renal blood flow followed by medulla hypoxia and oxidative stress. In most cases, CI-AKI is temporary; however, it is often associated with increased risk of mortality. Therefore, prevention of CI-AKI, especially in at-risk patients, seems more critical. Statins had anti-inflammatory (15) and antioxidant effects and also improved endothelial function (16) that might have an advantageous effect in preventing CI-AKI.

After receiving iodinated contrast, patients in the lovastatin group experienced fewer changes of serum creatinine and GFR that was in contrast to placebo group. This means that after iodinated contrast injection fewer reduction of eGFR in the lovastatin group than the placebo group was existed. Consistent with prior studies, the results of our study indicated the beneficial effect of lovastatin to prevent CI-AKI.

However, Toso et al showed that in CKD patients who underwent coronary angiography or angioplasty, a short-term high-dose atorvastatin had not significant effect on onset of CI-AKI ($P = 0.86$) (17).

In a prospective, randomized trial conducted by Leoncini et al, patients with acute coronary syndrome subjected to coronary invasive strategy, received 40 mg/d of rosuvastatin, 15-44 hours before the procedure and 20 mg/d after the procedure. They found that incidence of contrast-induced nephropathy was significantly lower compared to the control group ($P = 0.003$) (18).

Conclusion

Regarding fewer mean changes in eGFR in the lovastatin group than placebo group, and more occurrence of contrast induced acute kidney injury in the placebo group, the results of the present study highlights that short-term high-dose administration of lovastatin may have protective effect on CI-AKI. However, further research on the effectiveness of lovastatin in reducing CI-AKI is required.

Limitations of the study

This study was conducted in a single center. Due to the limited sample size in this study, all patients receiving contrast in the coronary angiography, CT of chest, and pulmonary angiography procedures were enrolled.

Authors' contribution

MSF; considered initial idea to design the study, moreover, prepared and writing the final manuscript. SV and KF; contributed to gather data. MSF, SV and SA and DR contributed to data analysis and explanation of data.

Conflicts of interest

There were no points of conflicts.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Table 1. Comparison of serum creatinine and glomerular filtration rate before and after iodinated contrast injection in the groups taking drug and placebo

Variables	Groups	
	Lovastatin	Placebo
MDRD eGFR (mL/min/1.73 m^2)		
Baseline eGFR	72.71 ± 1.88 SE	69.95 ± 2.62 SE
After 48 hours eGFR	70.18 ± 1.6 SE	65.70 ± 2.16 SE
eGFR changes	2.52 ± 1.12 SE	4.24 ± 1.38 SE
P value	0.029	0.003
Serum creatinine (mg/dL)		
Baseline serum creatinine	1.01 ± 0.02 SE	1.09 ± 0.04 SE
After 48 hours serum creatinine	1.05 ± 0.02 SE	1.12 ± 0.03 SE
Serum creatinine changes (standard error of the mean)	-0.035 ± 0.20 SE	-0.039 ± 0.02 SE
P value	0.024	0.096

Table 2. Incidence of CI-AKI

Groups	CI-AKI incidence, No. (%
Lovastatin group, n = 61	1 (1.6)
Placebo group, n= 61	3 (5)
Total, N = 122	4 (3.3)
P value	0.309

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