Original Article
Rosuvastatin attenuated contrast-induced nephropathy in diabetes patients with renal dysfunction

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Abstract: Background: The protective effect of statins against CIN is still controversial. We investigated the efficacy of pretreatment of rosuvastatin in decreasing the risk of CIN in a high-risk population of patients undergoing coronary angiography. Methods: We conducted a prospective, randomized, controlled study, involving 120 patients with diabetes and mild to moderate renal dysfunction undergoing coronary angioplasty. Patients were randomly assigned to receive rosuvastatin (n = 60, 10 mg/day) or no statins (n = 60) for at least 2 days before and 3 days after contrast media administration. Serum cystatin (SCysC), serum neutrophil gelatinase-associated lipocalin (NGAL) and urinary N-acetyl-β-D-glucosaminidase/urinary creatinine (NAG/UCr) were also observed before and after procedure. Results: Baseline demographic characteristics and nephropathy risk factors were similar between groups. The NGAL levels after procedure were higher than baseline (P < 0.05). Both the peak NGAL values occurred at 2 hours. In rosuvastatin group the peak NGAL values were lower compared with that in control group [(47.60 ± 18.72) μg/L vs (62.19 ± 44.68) μg/L, P = 0.014]. No differences of the peak values of SCr were found between the two groups. But the peak levels of SCysC in rosuvastatin group were significantly lower compared with that in control group [(0.96 ± 0.30) mg/L vs (1.08 ± 0.34) mg/L, P = 0.043]. There were significant statistical differences of NAG/Cr levels in the two groups. No clinical events occurred within the following 30 days in the two groups. Conclusions: Rosuvastatin could reduce the effect of degrading glomerular filtration function and renal tubular damage in patients with DM and mild to moderate renal dysfunction.

Keywords: Rosuvastatin, antilipemic agents, contrast media, kidney failure, acute

Introduction

The number of cardiac angiography and percutaneous coronary interventions (PCI) has increased steadily in recent years. This has resulted in the increasing incidence of contrast-induced nephropathy (CIN). This complication accounts for a significant number of cases of hospital-acquired acute kidney injury [1]. Chronic kidney disease (CKD) is the most important risk factor for the development of CIN. Other major risk factors for CIN include diabetes mellitus (DM), older age, intra-arterial contrast media (CM) administration, use of large CM doses, the concurrent use of nephrotoxic drugs, hemodynamic instability, and other comorbidities [2].

Given the adverse effect on prognosis and addition to health care costs of CIN, there has

been considerable interest in the development of preventative strategies to reduce the risk of CM induced renal deterioration in at-risk populations. Among these measures, pharmacologic prophylactic strategies based on antioxidant properties, such as statins, have been noted in recent years [3-5]. Statins are administrated by the vast majority of cardiovascular patients. They appear to have pleiotropic effects, including lower the level of low-density lipoprotein cholesterol (LDL-C), antioxidant properties and other reno-protective effects [6-8]. But there are currently no consistently shown to be effective in the studies of preventing CIN. And these findings remain tentative because of study limitations that only include serum creatinine (SCr) to evaluate the change of renal function. SCr level is known to be an imperfect indictor of glomerular filtration rate (GFR) because other fac-

tors, such as diet, tubular secretion of creatinine, muscular mass, age, and sex, also influence creatine concentration [9]. Moreover, in acute renal failure, SCr level is a poor indictor of renal function [10]. Recently studies found that other serum and urinary markers, such as serum cystatin (SCysC), serum neutrophil gelatinase-associated lipocalin (NGAL) and urinary N-acetyl-β-D -glucosaminidase/urinary creatinine (NAG/UCr), may be better suited than creatinine to evaluation of acute kidney damage after a ministration of CM [11-14].

To evaluate whether peri-operative statins treatment would reduce the risk of CIN, we designed a prospective, randomized, controlled study to test the hypothesis of whether perioperative administration of rosuvastatin would attenuate contrast induced renal function damage in patients with both type 2 diabetes mellitus (T2DM) and CKD undergoing PCI, and evaluate the influence of such potential benefit on short-term outcome. We also probed the changes in SCysC, NGAL and NAG /UCr before and after PCI in an effort to observe real renal damage.

Methods

Study population

From April 2009 through December 2009, a total of 120 consecutive patients undergoing angioplasty for unstable angina at our center were enrolled. Criteria for inclusion were: 1. T2DM; 2. Mild to moderate CKD, which was defined as estimated glomerular filtration rate (eGFR) 30 to 89 ml/min per 1.73 m²; 3. Total CM administrated dose of volume ≥ 100 ml. The following exclusion criteria were used: pregnancy, lactation, Ketoacidosis, Lactic acidosis, prior CM administration within 7 days of study entry, emergent coronary angiography, history of hypersensitivity reaction to CM and statins, New York Heart Association class IV congestive heart failure, unstable renal function, and use of aminophylline or prostaglandin E1 within 7 days of the procedure. Importantly, all patients who were recent statin users (with 14 days before the procedure) were excluded. This study was approved by the institutional review board at our institution. All patients provided written, informed consent for participation in this trial.

Study protocol

After study candidates were identified based on preliminary laboratory test results, informed consent was obtained and eligible patients were randomized. Patients divided into rosuvastatin group receive 10 mg everyday for at least 48 hours before and 72 hours after CM administration. Patients randomized to control group received no statins during the trial.

PCI was conducted routinely, via femoral or radial approach. According to the necessary, renal arteriography or left ventriculography was done. The iso-osmolar, nonionic CM iodixanol (Visipaque, 320 mg iodine/mL, GE Healthcare) was used exclusively, based on the PCI guideline of American College of Cardiology/American Heart Association [15].

All patients received intravenous hydration with isotonic saline (0.9% sodium chloride 1-1.5 ml/kg/hour for 3-12 hours before and 6-24 hours after the procedure). The use of other cardiovascular and hypoglycemic agents was left to the physicians' discretion. After the study all patients were discharged with long-term statin therapy.

According to the study design, blood samples were taken on the day of admission (d-1), the day of angiography (d0), and 24 (d1), 48 (d2) and 72 (d3) hours after the procedure to measure the SCr. The peak post procedural value was used to calculate the change in SCr. The eGFR was calculated via the abbreviated Modification of Diet in Renal Disease (MDRD) study equation [16] in Chinese: eGFR (ml/min/1.73 m²) = 175 × SCr (mg/dl)$^{-1.234}$ × age$^{-0.179}$ (if female × 0.79). The plasma level of SCysC was measured using immunoturbidimetry method at the day of PCI and 24, 48, 72 hours after PCI. The plasma NGAL levels were measured via the enzyme-linked immunosorbent assay method at the day of PCI and 2, 24, 48 hours after PCI. Urinary NAG levels were measured using MNP-GlcNAc method before and 24 hours after PCI. At the same time UCr levels were measured. SCr and UCr levels were determined with the picric acid method. All the renal damage parameters were measured in a blind fashion by laboratory personnel.

Study end points

The first goal was to examine the peak serum NGAL level within 48 hours after administration

Table 1. Baseline clinical characteristics

	Rosuvastatin group (n = 60)	Control group (n = 60)	P value
Mean age (yrs)	61.6 ± 8.1	61.5 ± 7.6	0.908
Male	41 (68.3%)	44 (73.3%)	0.547
Body mass index (Kg/m^2)	25.9 ± 6.1	25.2 ± 2.5	0.445
Risk factors			
Current smoking	28 (46.7%)	30 (50.0%)	0.715
Family history of coronary heart disease	5 (8.3%)	4 (6.7%)	1.00
Hypertension	48 (80.0%)	48 (80.0%)	1.00
Hyperlipidemia	6 (10.0%)	3 (5.0%)	0.491
Cerebral vascular disease	15 (25.0%)	14 (23.3%)	0.831
Chronic kidney disease	1 (1.7%)	0 (0)	1.00
Previous myocardial infarction	15 (25.0%)	16 (26.7%)	0.835
New York Heart Association heart Function classification	1.3 ± 0.6	1.5 ± 0.7	0.170
Hemoglobin (g/L)	131.0 ± 14.3	133.4 ± 15.0	0.370
Admission serum creatinine (μmol/L)	99.8 ± 18.4	99.9 ± 23.8	0.969
Admission eGFR (ml/min/1.73 m^2)	59.5 ± 12.5	61.2 ± 15.0	0.422
Clinical medications			
β-blockers	58 (96.7%)	53 (88.3%)	0.163
Angiotensin-converting enzyme inhibitor	47 (78.3%)	46 (76.7%)	0.827
Angiotensin receptor blocker	12 (20.0%)	11 (18.3%)	0.817
Calcium channel blocker	31 (51.7%)	23 (38.3%)	0.142
Diuretics	14 (23.3%)	14 (23.3%)	1.00
Insulin	24 (40.0%)	17 (28.3%)	0.178
Dopamine	2 (3.3%)	0 (0)	0.496
Sodium bicarbonate	3 (5.0%)	4 (6.7%)	1.00

Data are expressed as mean ± SD or n (%).

of contrast agent. Additional goal was to examine the peak SCr and SCysC levels, the development of CIN within 72 hours after the procedure, and the urinary NAG/UCr levels at 24 hours post procedure. CIN was typically defined as a relative increase in baseline SCr of ≥ 25% and/or an absolute increase of ≥ 0.5 mg/dL (44.2 μmmol/L) within 72 hours after contrast administration [17]. Length of hospital stay and a composite clinical outcome of hospitalization for aggravated renal function, acute renal failure (ARF), dialysis or hemofiltration, aggravated at least 1 class of heart function, acute left ventricular failure, and death for all causes during hospitalization and 30 days after procedure were also analyzed. ARF was defined as a rapid decrease in renal glomerular filtration with a > 2 mg/dL (176.8 μmmol/L) creatinine increase from baseline [18].

Statistical analysis

The sample size was calculated assuming a maximum NGAL levels (2 hours after the proce-

dure) of 67 μg/L and 45 μg/L in the statin and control groups, respectively, resulting from preceding study in our laboratory. Assuming an SD of 20 μg/L for each group and a 2-sided significance level of 5% and 90% power, a sample size of 60 patients per group was planned.

Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentage. Student's t test was used for comparing continuous variables. Chi-square or Fisher's exact test was used for categorical data. All statistical tests were 2-tailed, and a *p* value of < 0.05 was considered statistically significant. Analyses were carried out using SPSS 16.0 for windows (SPSS Inc., Chicago, Illinois).

Results

Baseline clinical and procedural characteristics

The mean age, gender, risk factors and the pre-procedural hemoglobin levels were similar

Table 2. Procedural characteristics

	Rosuvastatin group (n = 60)	Control group (n = 60)	P value
Interval from admission to procedure (days)	4.0 ± 1.9	4.0 ± 2.4	0.966
Diseased Coronary artery			0.927
Single-vessel lesion	13 (21.7%)	14 (23.3%)	
Two-vessel lesions*	22 (36.7%)	20 (33.3%)	
Three-vessel lesions	25 (41.7%)	26 (43.3%)	
PCI	56 (93.3%)	51 (85.0%)	0.142
Peripheral artery angiography	9 (15.0%)	10 (16.7%)	0.803
Peripheral artery intervention	1 (1.7%)	1 (1.7%)	1.00
Left ventriculography	3 (5.0%)	8 (13.3%)	0.114
Total contrast volume (ml)	204.3 ± 74.7	212.3 ± 84.6	0.603

Data are expressed as mean ± SD or n (%).

between the two groups. The medications, used before and after the procedure, were not significantly different statistically. The SCr and eGFR at admission were also similar between the two groups (**Table 1**).

The average time from admission to procedure was 4.0 ± 1.9 days in the rosuvastatin group and 4.0 ± 2.4 days in the control group ($P = 0.966$). The target vessel numbers and the rate of PCI were similar between the two groups. The rate of peripheral artery angioplasty and left ventriculography were also similar. The total contrast volume used during the procedure was not significantly different statistically between the two groups (**Table 2**).

Primary end point---peak NGAL within 48 hours

For both groups, the level of serum NGAL increased significantly after the procedure, the peak value occurred at 2 hours and then began to decrease. Compared with the peak level, the NGAL level at 48 hours after the procedure had both decreased significantly ($P < 0.001$), but failed to recover to the baseline level ($P < 0.001$).

The serum NGAL levels before the procedure were not significantly different between the two groups. However, through peri-operative rosuvastatins treatment, the level of NGAL at 2 hours in the rosuvastatin group was significantly lower than the level in the control group ($P = 0.014$; **Figure 1**).

Secondary end point

The SCr levels before the procedure were similar between the two groups. Compa-red with the base-line, the SCr levels at 24 hours after administration of contrast agent did not increased significantly ($P > 0.05$) and the peak levels occurred at 48 hours post procedure. Then the SCr levels began to decrease, but failed to recover to the baseline level ($P < 0.05$). The SCr levels were not significantly different statistically after the procedure between the two groups (**Figure 2**).

The level of SCysC increased after the procedure in both groups, with the peak value occurring at 48 hours and decreased thereafter. The SCysC level in the rosuvastatin group at 72 hours after the procedure had decreased to baseline level ($P > 0.05$), but the level in the control group failed to recover to the baseline level ($P < 0.05$).

The SCysC levels before the procedure were not significantly different between the two groups. However, the level of NGAL at 48 hours in the rosuvastatin group was significantly lower than the level in the control group ($P = 0.043$; **Figure 3**).

After the procedure, each group had the same low incidence of CIN. Only two cases of CIN occurred in every group.

The urinary NAG/UCr levels before the procedure were similar between the two groups. The level of NAG/UCr at 24 hours post procedure in the control group increased significantly. However the NAG/UCr level in the rosuvastatin group failed to increase, and was lower than the level in the control group ($P = 0.001$; **Table 3**).

Inhospital, 30-day clinical outcomes and length of hospital stay

No post procedural adverse events occurred. There was no difference between the two groups in the length of hospital stay (rosuvastatin 7.0 ± 1.9 days vs control 7.0 ± 2.5 days, $P = 0.934$).
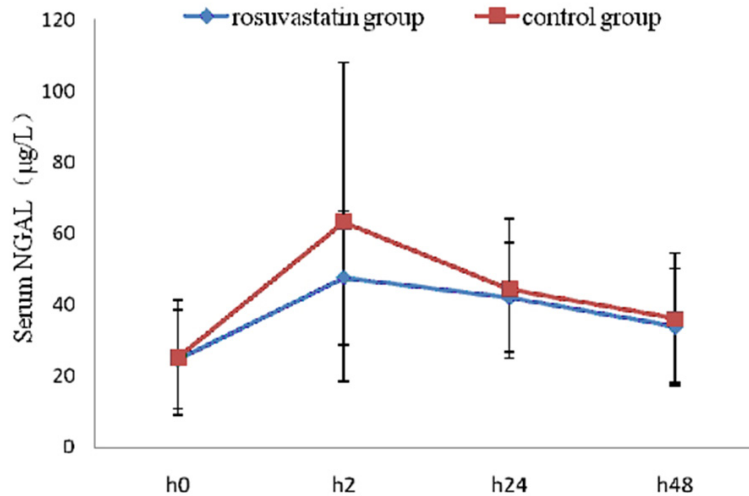
Figure 1. Changes in serum NGAL level at different points.
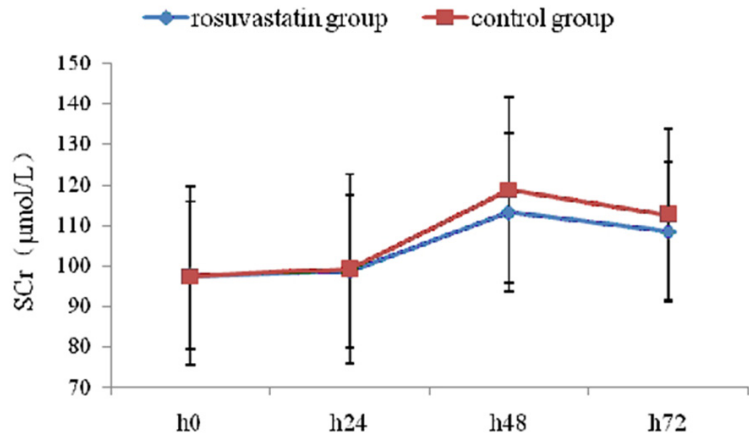

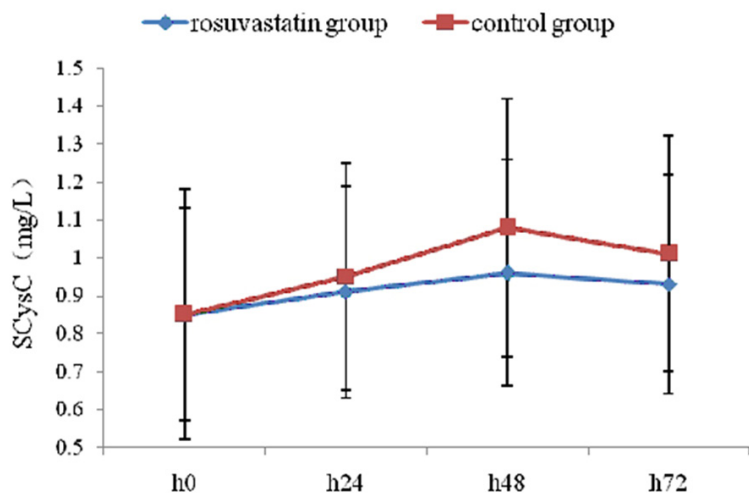**Figure 2.** Changes in SCr level at different points.

Figure 3. Changes in SCysC level at different points.

Changes in serum total cholesterol, LDL cholesterol

There was a significant decrease in mean total cholesterol and LDL cholesterol in the patients who received rosuvastatin treatment. In contrast, for patients who received no statins, there was no change in the mean level of either total cholesterol or LDL cholesterol (**Table 4**).

Discussion

The exact mechanism of renal toxicity of contrast is not well known. Most studies confirmed that contrast superimposed acute vasoconstriction caused by the release of adenosine, endothelin, and other renal vasoconstrictors triggered. The reduction in renal blood flow to the outer medulla leads to medullary hypoxia and ischemic injury. The ischemic injury sets off a cascade of events largely driven by oxidative injury causing apoptosis of renal tubular cells. Contrast, which is in the renal tubules and collecting ducts, also results in direct cellular injury and apoptosis to renal tubular cells. If a sufficient mass of nephron units are affected, then a recognizable rise in SCr will occur [2].

While most cases of CIN reflect mild transient impairment of renal function, CIN is associated with increased risk of death and other adverse cardiovascular events. Thus, it is important to prevent CIN. The antioxidant statins has been investigated as a potential agent for CIN prevention. Statins appear to have other reno-preventive effects, including anti-inflammatory, improvement of vascular endotheli-

Table 3. Change in urinary NAG/UCr at 24 hours after the procedure

NAG/UCr (U/mmol·Cr)	Rosuvastatin group (n = 60)	Control group (n = 60)	P value
Baseline	1.51 ± 1.17	1.60 ± 1.08[#]	0.662
24 hours	1.75 ± 1.27	2.60 ± 1.48[#]	0.001

[#]P < 0.0001.

Table 4. Changes in total cholesterol and LDL at 72 hours after the procedure

		Rosuvastatin group (n = 60)	Control group (n = 60)	P value
Total cholesterol	Baseline	4.58 ± 1.30*	4.72 ± 1.20	0.580
(mmol/L)	72 hours	3.93 ± 1.04*	5.10 ± 1.13	< 0.0001
LDL (mmol/L)	Baseline	2.39 ± 0.60*	2.47 ± 0.57	0.547
	72 hours	2.10 ± 0.50*	2.55 ± 0.55	< 0.0001

*P < 0.05.

al function [5] and other roles. But there are currently no consistently shown to be effective in the studies of statins preventing contrast induced acute kidney injury. Attallah et al [3], in a retrospective study that evaluated patients with CKD underwent PCI, showed that patients with pretreatment of statin before the procedure had a significantly lower peak SCr level and incidence of CIN. The similar outcomes were found in a retrospective large-sample study of Khanal et al [19]. However, the first randomized prospective study by Jo et al [5] showed that in patients with CKD undergoing coronary angiography, pretreatment (48 hours) with short-term simvastatin (40 mg 2/days) couldn't reduce the incidence of CIN. That short period might be an important reason for the lack of effectiveness. Another reason may be that the study, in which patients were followed for only 48 hours, missed the peak SCr levels. Recently reported randomized prospective study used long-term (48 hours before and 48 hours after angioplasty) atorvastatin (80 mg/day) administration to protect CIN. There were no differences in the incidence of CIN between the two groups. But the study did not design a parallel group of patients not pretreated with oral NAC. Some trials [2] showed NAC reduced SCr below baseline values because of decreased skeletal muscle production. Thus, the effect of NAC on SCr level couldn't be excluded.

Importantly, these studies chose SCr to evaluate the change of glomerular filtration function.

However, SCr do not directly reflect cell injury but rather delayed functional consequences of the injury [21].

We tested whether rosuvastatin exerts a lowering CM-induced acute renal damage effect, by simultaneously measuring SCr, SCysC, NGAL and NAG/UCr concentrations. The levels of SCr, SCysC and NGAL in blood correlated with the glomerular filtration function [2, 22-28]. There have been studies suggesting that NGAL levels predicted the onset of acute kidney injury 2-4 hours after angioplasty in children and adult, 2-4 days before acute kidney injury was identified by changes in SCr [22-26]. SCysC, which are independent of gender, age, height, weight, and muscle mass [2], is better than SCr in reflecting acute renal function change [11, 12]. The level of urinary NAG/UCr was used as an indicator of the degree of the renal tubular damage after angioplasty [14].

In our study, the serum NGAL level increased at first, reached a peak value at 2 hours, and then gradually decreased. Compared with control group, rosuvastatin group significantly lowered the peak serum NGAL level. SCysC level increased to its highest value at 48 hours and then gradually recovered at 72 hours. The lower SCysC level at 48 hours in the rosuvastatin group had returned to the baseline level completely at 72 hours. However, in the control group, it had not. In the control group, the NAG/UCr level was significantly higher than baseline level at 24 hours. However, in the rosuvastatin group, it was not. These findings confirmed that compared with SCr, serum NGAL and urinary NAG are earlier, and serum SCysC are more sensitive in diagnosing acute renal damage. Although rosuvastatin failed to reduce peak increase in SCr or lower the incidence of CIN compared to control group, by analysis of SCysC, NGAL and NAG, we found that alleviation of glomerular filtration function and reductions of renal tubular injury are postulated mechanisms by which rosuvastatin may have reno-protective effects.

Although Su Jinzi et al [29] also found that patients with 20 mg atorvastatin had lower

SCysC and urinary α_1-microglobulin after coronary angiography compared with control group, that study had some differences compared with our study. In addition to the different study population (normal kidney function vs CKD), their study used different statin type and acute renal damage markers. We studied patients with CKD using more sensitive marker NGAL.

Limitations

The study has some limitations. First, we couldn't measure the admission levels of serum NGAL, SCysC and urinary NAG/UCr corresponded with the admission SCr level. The reason was that it was difficult to take the same time blood and urine sample. Second, we didn't examine the level of NGAL at 72 hours, we couldn't know if NGAL returned to the baseline level. Third, in this study we didn't measure the factors about anti-inflammatory, antioxidant effect and preservation of endothelial function of rosuvastatin.

Conclusions

SCysC, serum NGAL and urinary NAG are more sensitive than SCr about diagnosing acute renal damage at early stage. In contrast to reported retrospective and prospective studies, this trial support a role for rosuvastatin as prophylactic agents in the prevention of acute renal damage.

Disclosure of conflict of interest

None.

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