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Original Article

Effect of rosuvastatin dose-loading on serum sLox-1, hs-CRP, and postoperative prognosis in diabetic patients with acute coronary syndromes undergoing selected percutaneous coronary intervention (PCI)

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Abstract: Objective: To investigate the effect of rosuvastatin dose-loading on serum levels of lectin-like oxidized low-density lipoprotein receptor-1 (Lox-1) and high-sensitivity c-reactive protein (hs-CRP) and postoperative prognosis in patients with diabetes and non-ST segment elevation acute coronary syndromes (NSTEACS) undergoing selected percutaneous coronary intervention (PCI). Methods: A total of 72 patients with diabetes and NSTEACS were randomized to either the group treated with 20 mg rosuvastatin 12 hours prior to PCI with a second dose administered just before PCI (n = 33), or a control group treated with standard method according guideline (n = 39). Serum levels of sLox-1, hs-CRP, CK-MB, and cTnI were measured prior to PCI, and at 24 hours and 30 days after PCI. The 30-day incidence of major adverse cardiac events (MACE) was recorded in both groups. Results: Compared to pre-PCI, serum levels of sLox-1 and hs-CRP of the two groups were increased at 24 hours after PCI ($P < 0.05$); the levels of CK-MB and cTnI were also improved ($P < 0.01$); however, the ascended values of sLox-1, hs-CRP, CK-MB, and cTnI were significantly lower in the loading-dose rosuvastatin-treated group than in the control-treated group. Serum levels of sLox-1 and hs-CRP were higher in the loading-dose rosuvastatin-treated group than in the control-treated group at 30 days after PCI ($P < 0.05$); compared to pre-PCI, the levels of TC and LDL-C were not changed at 24 hours after PCI ($P > 0.05$) until 30 days after PCI ($P < 0.05$), but there were no difference between the two groups. The levels of ALT and Scr had no significant difference between the two groups before and after PCI; the 30-day incidence of MACE occurred in 6.06% of patients in the loading-dose rosuvastatin-treated group and in 23.08% of patients in the control-treated group ($P < 0.05$). Conclusion: The therapy of dose-loading rosuvastatin for patients with diabetes and non-ST segment elevation acute coronary syndromes undergoing selected percutaneous coronary intervention can attenuate the increase of serum levels of sLox-1, reduce myocardial injury and inflammatory reaction caused by PCI, and also reduce the occurrence of MACE 30 days after PCI.

Keywords: Lectin-like oxidized low density lipoprotein receptor-1, percutaneous coronary intervention, acute coronary syndrome, rosuvastatin

Introduction

Acute Coronary Syndrome (ACS) is a series of cardiovascular diseases with high morbidity and mortality rates, especially in patients with diabetes and non-ST segment elevation acute coronary syndromes (NSTEACS). The main pathogenesis of ACS are ruptures of atherosclerosis plaques in the coronary artery wall and creation of thrombus, which cause severe coronary artery lumen stenosis or total obstruction of coronary artery lumen, leading to myocardial ischemia and necrosis [1]. Percutaneous coronary intervention (PCI) is a commonly used effective clinical method to treat ACS patients, which can attenuate coronary artery stenosis, permitting earlier intervention with unstable plaque, and effectively reduce acute coronary artery-related events. However, PCI itself is a mechanical vascular injury process; therefore it causes local inflammation of the vessels and vascular endothelial injury.

Clinical research shows that the therapy of dose-loading rosuvastatin for patients can reduce myocardial injury and inflammatory reaction caused by PCI [2], exceed for its lipid modulation function. The protective effects of rosuvastatin may be due to its anti-inflammatory capacity and its ability to stabilize the endothelium [3], but the exact mechanisms remain unknown. According to recent findings, lectin-like oxidized low-density lipoprotein receptor-1 (Lox-1) participates in the establishment and developmental stages of atherosclerosis [4]. A previous study showed that Lox-1 was expressed in atherosclerotic plaques, and its expression had a negative correlation with the stability of the plaque itself [5]. Determination of soluble Lox-1 in serum can indicate the expression of Lox-1 *in vivo*. High-sensitivity C-reactive protein (hs-CRP) is a marker that reflects a nonspecific inflammation reaction. The serum level of hs-CRP is increased in patients with ACS [6]. An increased level of hs-CRP is not only closely related to the degree of atherosclerosis, but is also a marker that reflects vulnerability and stability of atherosclerotic plaques and atherosclerotic lesions [7]. A study confirmed that diabetes has an equivalent risk with coronary heart diseases (CHD), and affects the prognosis of PCI [8]. Currently, there are no relevant reports in China about the effect of dose-loading rosuvastatin on serum levels of Lox-1 in patients with diabetes and ACS undergoing selected PCI, which we aimed to investigate in this study. We also assessed the effect of dose-loading rosuvastatin on hs-CRP and prognosis of these patients, and the clinical value of this treatment strategy was estimated.

Materials and methods

Ethics statement

This study was approved by Institutional Ethics Committee for Biomedical Research of First People's Hospital of Yangzhou.

Study subjects

We recruited 90 patients with diabetes and non-ST-segment elevation acute coronary syndrome (NSTEACS) from January 2011 to December 2012 in the Department of Cardiology of First People's Hospital of Yangzhou, who received PCI within 48 hours. Eighteen patients failed to reach the PCI indications after coronary angiography upon undergoing CABG and were therefore excluded from the rest of this study. The remaining 72 subjects were randomly divided into two groups: 1) Patients in dose-loading treatment group were treated with rosuvastatin before PCI (n = 33, male 21, female 12, average age was 59.3±11.8), or 2) control group treated with standard method according guideline (n = 39, male 26, female 12; average age was 60.9±10.7).

These patients were diagnosed NSTEACS according to the ACC/AHA guidelines in UAP/NSTEMI 2007. The coronary angiography confirmed single or multiple vascular lesions, ≥ 75% of target lesion was considered narrow. There were rows of intravascular interventional treatment of indications. The patients who had acute ST segment elevation myocardial infarction, peripheral vascular disease, chronic heart failure, thyroid disease, liver and/or kidney function failure, tumors, or had major trauma and surgery including MI, PTCA, heart failure, or coronary artery bypass grafting in the past six months, or took adrenal cortical hormone or other immune regulator recently were excluded.

Dosing methods

The control group treated with standard method according guideline, which consisted of aspirin, clopidogrel, ACEI/ARB, β-receptor blocker, station, et al. The dose-loading treatment group was pretreated with 20 mg rosuvastatin 12 hours before, and a second 20 mg rosuvastatin dose just before PCI. According to the clinical requirement, all patients were given nitrate drugs, beta-blockers, CCB, or ACEI, with dose-loading antiplatelet drugs clopidogrel ≥ 300 mg. All patients were required to take rosuvastatin 10 mg once a day 24 hours after the surgery. Study characteristics including age, gender, history of hypertension, diabetes, and smoking history were registered. Major adverse cardiovascular events (MACE) including death, myocardial infarction, angina pectoris, heart failure, target vascular reconstruction were recorded in both groups.

ELISA and biochemical marker analysis

Blood (5 ml) was collected from all subjects prior to administration of statins the next day

Table 1. Clinical data compared between two treatment groups

	Rosuvastatin dose-loading group (n = 33)	Control group (n = 39)	*P*-value
Age (year)	59.3±11.8	60.9±10.7	0.548
Sex (Male)	21	26	0.809
Smoking habit (n)	9	12	0.745
History of HBP (n)	13	15	0.936
SBP (mmHg)	136±10.87	134±9.63	0.416
DBP (mmHg)	83±8.96	85±10.08	0.3807
TC ($mmol \cdot l^{-1}$)	4.93±0.82	5.12±0.68	0.2861
TG ($mmol \cdot l^{-1}$)	1.90±0.45	1.82±0.58	0.5212
LDL-C ($mmol \cdot l^{-1}$)	3.48±0.81	3.22±0.75	0.1621
HDL-C ($mmol \cdot l^{-1}$)	1,18±0.34	1.25±0.29	0.3489
Glu ($mmol \cdot l^{-1}$)	5.78±0.31	5.90±0.40	0.1651

Note: TC: total cholesterol, TG: Triglycerides, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol.

after hospital admission, at 24 hours, and 30 days after surgery. Blood was allowed to coagulate and serum was extracted and stored at -70°C until analysis. The levels of serum hs-CRP, sLox-1, Glu, TC, TG, LDL-C, HDL-C, ALT, Scr were tested. The hs-CRP and Lox-1 were measured by ELISA by commercially available kits (ADL Inc. US), following manufacturer's instructions. Biochemical markers (Glu, TC, TG, LDL-C, HDL-C, ALT and Scr) were measured by automatic biochemical meter in the Department of Clinical Laboratory, at the First People's Hospital of Yangzhou.

Statistical analysis

All statistical analyses were performed by SPSS13.0 statistics software. Measurement data which met normal distribution were expressed by mean ± standard deviation (mean ± SD), Student *t* test was used for comparing the average of the two groups, count data by chi-square test, and if $P < 0.05$ then the difference was considered statistically significant.

Results

Basic clinical data

There were no difference between the two groups in regard to age, gender, history of high blood pressure, smoking history, blood pressure, blood glucose, and blood lipids levels ($P > 0.05$; **Table 1**).

Serum levels of sLox-1, hs-CRP, blood lipid analysis, liver function, renal function after PCI

Compared with before PCI, serum levels of sLox-1 and hs-CRP of the two groups were increased at 24 hours after PCI ($P < 0.05$), and the levels of CK-MB and cTnI were also improved ($P < 0.01$). However, the increased values of sLox-1, hs-CRP, CK-MB, and cTnI were significantly lower in the rosuvastatin dose-loading group than in the control-treated group. Serum levels of sLox-1 and hs-CRP were higher in the rosuvastatin dose-loading group than in the control group at 30 days after PCI ($P < 0.05$). Compared with before PCI, the levels of TC and LDL-C did not change at 24 hours after PCI ($P > 0.05$) until 30 days after PCI ($P < 0.05$), but there was no difference between the two groups. Additionally, the levels of ALT and Scr were not elevated in the two groups before and after PCI (**Table 2**).

Characteristics of coronary artery lesions after PCI

We assessed coronary arterial lesions following PCI treatment and found that there was no difference between the rosuvastatin dose-loading group and the control-treated group ($P > 0.05$; **Table 3**).

Incidence of MACE following PCI treatment

We found that while 30-day incidence of MACE (including death, myocardial infarction, angina pectoris, heart failure, target vascular reconstruction) occurred in patients from both treatment groups after discharge, the occurrence was lower in the rosuvastatin dose-loading group than in the control group ($P < 0.05$; **Table 4**).

Discussion

Percutaneous Coronary Intervention (PCI) can attenuate coronary artery stenosis, permitting earlier intervention of unstable plaques and effectively reduce acute coronary artery-related events. However, PCI itself is a mechanical vascular injury process. The success of coro-

Table 2. Serum levels of sLox-1, hs-CRP, ALT, and Scr, blood lipid analysis in two treatment groups

	Rosuvastatin dose-loading group (n = 33)			Control group (n = 39)		
	Before PCI	24 hours after PCI	30 days after PCI	Before PCI	24 hours after PCI	30 days after PCI
sLox-1 ($ng \cdot l^{-1}$)	236.30±48.34	270.32±52.98[a]	150.78±38.45[b,c]	241.65±49.54	298.93±61.70[a]	198.61±36.88[b]
hs-CRP ($mg \cdot l^{-1}$)	11.27±2.30	14.70±3.35[a]	3.34±1.26[b,c]	10.96±2.78	20.45±4.67[a]	5.86±1.48[b]
CK-MB ($ng \cdot ml^{-1}$)	11.16±2.09	23.12±6.24[b,c]	10.35±2.33	10.95±1.98	30.66±8.79[b]	11.52±2.68
cTnI ($ng \cdot ml^{-1}$)	0.06±0.02	0.11±0.02[b,c]	0.05±0.02	0.07±0.02	0.46±0.13[b]	0.06±0.03
TC ($mmol \cdot l^{-1}$)	6.52±1.72	6.33±1.96	4.60±1.41[a]	6.65±2.09	6.43±1.75	4.71±1.39[a]
LDL-C ($mmol \cdot l^{-1}$)	3.58±0.81	3.50±0.71	2.46±0.61[a]	3.62±0.76	3.49±0.70	2.67±0.65[a]
ALT ($u \cdot l^{-1}$)	27.45±9.68	28.65±10.25	28.96±10.15	26.95±8.36	27.03±9.64	28.19±11.08
Scr ($umol \cdot l^{-1}$)	75.62±12.36	78.66±11.52	80.25±12.59	78.39±12.33	79.48±10.36	78.89±11.85

Note: Compared with rosuvastatin dose-loading group before the PCI, [a]$P < 0.05$, [b]$P < 0.01$; Compared with the control group at the same time, [c]$P < 0.05$.

Table 3. Characteristics of coronary artery lesions following PCI treatment

Characteristics of coronary artery lesions	Rosuvastatin dose-loading group (n = 33) (%)	Control group (n = 39) (%)	*P*-value
Lesions vascular for treatment			
Left anterior descending	16 (48.5)	19 (48.7)	0.984
Left circumflex artery	11 (33.3)	16 (41.0)	0.501
Right coronary artery	8 (24.2)	13 (33.3)	0.396
Left main coronary artery	0	0	
Lesion vessel number			
Single-vessel disease	8 (24.2)	10 (25.6)	0.891
Double-vessel disease	14 (42.4)	16 (41.0)	0.905
More than three and triple-vessel disease	12 (36.4)	14 (35.9)	0.967
The average of stent number	1.5±0.6	1.7±0.9	0.1307
Stent diameter (mm)	3.1±0.4	3.0±0.36	0.2682
Length of stent (mm)	18.6±5.7	17.9±5.3	0.2913
Relief pressure (atm)	10.86±4.6	12.0±4.9	0.3153

nary artery stent implantation process does not mean a real success of the treatment. The mechanical injury to the coronary vascular caused by stent implantation often induces the release of vasoactive substances, which can cause vasoconstriction and inflammatory reactions, resulting in dysfunction of vascular endothelium, myocardial ischemia and necrosis. These events injure myocardial cells in a short time, and cause complications such as perioperative myocardial injury and infarction. According to a report from Cantor [9], the elevation of cTnI after surgery correlates with adverse cardiac events, such as death, myocardial infarction, and serious recurrent myocardial ischemia which require urgent vascular remodeling. A meta-analysis study [10] also found that there was a positive correlation between exceeding levels of CK-MB when compared to the normal upper limit and mortality rate: patients with 1-3 times, 3-5 times, and > 5 times CK-MB level higher than normal standard will likely have 1.7%, 2.8% and 7.4% mortality rates elevation respectively. Therefore, PCI-related complications have gradually attracted the attention of clinical doctors, and the research studies into the pathogenesis, possible treatments to alleviate PCI-related myocardial injury, and prognosis improvement have become the focus of clinical research in recent years. ARMYDA [2] research has triggered a new round of "statins revolution", which has provided a new direction to ACS patients for rational use of PCI perioperative medicine. ARMYDA-ACS [11] clinical trial selected cases of patients with non-ST segment elevation acute coronary syndromes (NSTEACS) who did not take any statins before PCI and then observed the effect of dose-loading atorvastatin (80 mg 12 hours before surgery and 40 mg 2 hours before surgery) on the postoperative prognosis at 30 days. Their results showed

Table 4. The 30-day incidence of MACE following PCI treatment

Adverse events	Rosuvastatin dose-loading group (n = 33)	Control group (n = 39)
Death	0	0
Stable angina	2	5
MI	0	1
Cardiac failure	1	2
TVR	0	1
Total	2[a]	9

Note: Compared with the control group, [a]$P < 0.05$.

that taking dose-loading atorvastatin before PCI could reduce the major postoperative cardiac events for 88% of patients and increase the survival rate of free-cardiac events significantly.

Our study has found that serum levels of CK-MB and cTnI were elevated significantly after operation ($P < 0.01$); however, the increased values of CK-MB and cTnI were significantly lower in rosuvastatin dose-loading group than in control-treated group. This suggests that PCI treatment results in perioperative myocardial injury, and rosuvastatin dose-loading improves the levels of myocardial injury markers. Additionally, rosuvastatin dose-loading treatment before PCI significantly alleviated the degree of myocardial injury and decreased CK-MB and cTnI levels in patients, which likely protected the myocardium of NSTEACS patients. Inflammation plays an important role in the formation and development of atherosclerosis, and is one of the pathogenesis features that affect the stability of atherosclerotic plaques. Diabetes is regarded as an autoimmune disease, as well as an important risk factor of cardiovascular diseases [12]. Inflammation in patients with diabetes is more severe and more easily to cause plaque rupture than those without diabetes. Hs-CRP is one of the sensitive indices to reflect the nonspecific inflammation reaction. For ACS patients, the serum levels of their hs-CRP are increased. The hs-CRP level is not only closely related to the degree of atherosclerosis, but is also a marker of vulnerability and stability of atherosclerotic plaques and atherosclerotic lesions [13]. Yun *et al.* [14] and other studies confirmed that the serum level of hs-CRP in patients with ACS increased dramatically after undergoing PCI, and those with elevated degree > 3 mg/l tended to have higher perioperative myocardial infarction rates. Lox-1 is the receptor of oxidized low-density lipoprotein (ox-LDL) which was identified for the first time in the bovine aortic endothelial cells by Sawamura *et al.* in 1997. Lox-1 plays a key role in mediating ox-LDL from damaging the function of endothelial cells as well as activating and promoting the formation of atherosclerosis [15]. Lox-1 is a type II 50 kDa surface glycoprotein composed of 273 amino acids, and its molecular structure contains four regions, which includes one short N-end cytoplasm region, one transmembrane region, one neck region and one long C-end phytohemagglutinin region. Among them, the phytohemagglutinin region outside the cell is the recognition site of Lox-1 ligand. Lox-1 exists in the body in both the water-soluble and membrane-bound states. Research has confirmed that membrane-bound Lox-1 can be hydrolyzed into water-soluble Lox-1 by a certain *in vivo* protein hydrolysate, and soluble and membrane-bound Lox-1 exhibit a strong positive correlation [16]. In clinical research, the *in vivo* expression of Lox-1 is determined by the water soluble Lox-1 in serum. Recently, Lox-1 was found to also play a vital role in the formation and development of diabetic angiopathy, whose pathogenesis may have some relationship with oxidative stress and inflammation reaction [17]. Recent studies also discovered that CRP is one of the ligands for Lox-1 [18, 19]. When CRP binds Lox-1, the event activates the secretion of proinflammatory cytokines in the vascular endothelium and destabilizes atherosclerotic plaques. *Vice versa*, the activated Lox-1 may help promote dysfunction of blood vessel. In recent years, many studies have focused on the research and development of anti-atherosclerotic pharmaceutical drugs targeting Lox-1. Studies have found that statins can inhibit the expression of Lox-1 in the atherosclerotic plaque, and inhibit the up-regulated expression of endothelial cell Lox-1 induced by ox-LDL, uptake of ox-LDL, expression of adhesion molecules and up-regulated expression of eNOS [20, 21], thus, inhibiting Lox-1 has become an important focus of statins for anti-atherosclerosis. According to our research, compared with before PCI, the serum levels of sLox-1 and hs-CRP in the two groups were elevated at 24 hours after PCI, while the increased values of sLox-1 and hs-CRP were significantly lower in rosuvastatin dose-loading group than in the control group. This result suggests that PCI

therapy injures the coronary artery intimae, triggering and aggravating local inflammation of the coronary artery, and the levels of hs-CRP and sLox-1 elevate significantly in the blood in a short time after PCI. However, rosuvastatin dose-loading therapy can effectively inhibit the occurrence of inflammation and the expression of Lox-1 and hs-CRP, which will likely improve the vascular endothelial function of coronary artery and stabilize its atherosclerotic plaque. In this study, we also found that, compared with before PCI, the levels of blood lipids TC and LDL-C were not changed at 24 hours after PCI until 30 days after PCI ($P < 0.05$). These findings indicate that the inhibition function of inflammation and the expression of Lox-1 of rosuvastatin dose-loading therapy were independent from its lipid-regulating function, and elaborated the importance and necessity of this type of extra intensive treatment.

This study also finds that the 30-day incidence of MACE occurred in 6.06% of patients in rosuvastatin dose-loading group and in 23.08% the control group, the incidence probability of the rosuvastatin dose-loading group was significantly lower than the control group. This result indicated the protective effect of intensive rosuvastatin dose-loading treatment before PCI, plays an important role in stabilizing the plague, inhibiting the inflammation and the expression of Lox-1, improving endothelial function and reducing myocardial injury not only *via* lipid regulations. The safety of rosuvastatin dose-loading therapy has always been clinical doctors' key point of research. This study shows the levels of ALT and Scr were not elevated in two groups before and after PCI ($P > 0.05$), and the patients were free of symptoms after the procedure, which shows the safety of intensive rosuvastatin dose-loading treatment.

In conclusion, rosuvastatin dose-loading therapy for patients with diabetes and non-ST segment elevation acute coronary syndromes undergoing selected percutaneous coronary intervention can attenuate the increase of serum levels of hs-CRP, sLox-1, CK-MB, cTnI, and reduce myocardial injury and inflammatory reaction caused by PCI. The occurrence of MACE in 30 days after PCI was also reduced with rosuvastatin dose-loading treatment, while the levels of ALT and Scr were not elevated in two groups before and after PCI. Therefore, rosuvastatin dose-loading is a simple and practical treatment which can effectively improve the postoperative prognosis after PCI in patients with diabetes and NSTEACS. However, due to the small number of cases and short time to observe in this research, we need larger and longer-term studies to assess effect of rosuvastatin dose-loading on long-term prognosis.

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Disclosure of conflict of interest

None.

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