Int J Clin Exp Med 2019;12(4):3961-3967
www.ijcem.com /ISSN:1940-5901/IJCEM0086316

Original Article

Effects of rosuvastatin combined with probucol on restenosis after percutaneous coronary intervention

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Received October 3, 2018; Accepted February 12, 2019; Epub April 15, 2019; Published April 30, 2019

Abstract: *Background and aim:* Percutaneous coronary intervention (PCI) is widely used for treatment of coronary heart disease, but the incidence of postoperative restenosis is still high. This study aimed to investigate the effects of rosuvastatin combined with probucol on restenosis after PCI and to explore the related mechanisms. *Methods:* One hundred and twenty patients receiving PCI were divided into an observation group (52 cases) and a control group (68 cases). After PCI, the control group was treated with rosuvastatin, and the observation group was treated with rosuvastatin combined with probucol. The treatment was continued for 6 months. Before surgery, and 24 hours, 1 month, and 6 months after surgery, the blood lipids, inflammatory response, oxidative stress, and vascular endothelial function indexes were detected, and the restenosis rate was evaluated. *Results:* Six months after surgery, compared with control group, in the observation group the restenosis rate was significantly decreased (P = 0.028), the serum total cholesterol (P = 0.038), triglyceride (P = 0.029), low-density lipoprotein cholesterol (P = 0.017), high-sensitive C-reactive protein (P = 0.021), tumor necrosis factor-α (P = 0.040), malondialdehyde (P = 0.013) and endothelin-1 (P = 0.046) levels were significantly decreased, respectively, and the serum high-density lipoprotein cholesterol (P = 0.042), superoxide dismutase (P = 0.031) and nitric oxide (P = 0.012) levels were significantly increased, respectively. There was no significant difference in incidence of adverse reactions between two groups. *Conclusion:* Compared with simple use of rosuvastatin, rosuvastatin combined with probucol can reduce restenosis after PCI. The mechanisms may be related to its stronger effect in lowering lipid, anti-inflammatory, antioxidant, and vascular endothelial function improvement.

Keywords: Rosuvastatin, probucol, restenosis, percutaneous coronary intervention

Introduction

With the continuous improvement of people's living standard, the incidence of coronary heart disease is increasing year by year. In coronary heart disease, abnormal metabolism of lipids leads to lipid deposition on the arterial wall, which causes the formation of white plaques in the artery intima, namely the atherosclerosis. These white plaques cause stenosis of the arteries, which in turn leads to blocked blood flow, insufficient blood supply to the myocardium, and angina pectoris [1]. Since the percutaneous coronary intervention (PCI) has been widely used in clinical practice, treatment of coronary heart disease has entered a new stage. However, the incidence of restenosis after simple PCI is still high [2, 3].

Rosuvastatin belongs to the statins drugs. It is a selective hydroxymethylglutaric acid monoacyl coenzyme A reductase inhibitor, and can inhibit the synthesis of endogenous cholesterol, and resist the atherosclerosis by lipid-lowering and other effects. In addition, rosuvastatin can stabilize and eliminate the plaque, thus delaying the process of atherosclerosis [4, 5]. Probucol is a new type of lipid-lowering drug, which can effectively promote the apolipoprotein E mRNA expression and reduce the plasma cholesterol. In addition, probucol has anti-inflammatory, anti-oxidant, anti-smooth muscle proliferation, and other effects [6-8]. It has been reported that, the lipid-lowering effect of combination of probucol and rosuvastatin is better than that of a single drug [9].

This study investigated the effects of rosuvastatin combined with probucol on restenosis after PCI and explored the related mechanism. The objective was to provide a basis for further

application of this strategy to prevention of restenosis after PCI.

Subjects and methods

Subjects

One hundred and twenty patients receiving PCI from March 2014 to May 2017 in our hospital were enrolled in this study. The inclusion criteria were as follows: i) the patients had stable angina pectoris, and could receive the stent implantation; ii) the stenosis was confirmed by coronary angiography, and the lumen diameter stenosis rate was greater than 75%; iii) the patients had not taken lipid-lowering drugs during the recent clinical period; iv) the patients used the stent with the same size. The exclusion criteria were as follows: i) the patients had the unsuccessful PCI; ii) the patients had the poor compliance; iii) the patients had severe arrhythmia, or heart or lung dysfunction; iv) the patients had the complicated inflammatory infection or tumor. This study was approved by the Ethics Committee of the Affiliated Hospital of Beihua University. Written informed consent was obtained from all participants.

Grouping and treatment

According to the treatment method after PCI, 120 patients were divided into observation group (52 cases) and control group (68 cases). Both groups were given health education, dietary guidance, and routine treatment such as blood pressure and blood glucose controlling, blood circulation improvement, etc. The coronary angiography and PCI were performed using standard methods. The success rate of PCI was defined by the diameter stenosis rate < 20%. After PCI, the control group was given rosuvastatin (Zhejiang Jingxin Pharmaceutical Co., Ltd., Shaoxing, China; 10 mg per times, once per day). The observation group was given rosuvastatin (10 mg per times, once per day) combined with probucol (Jufukang Pharmaceutical Group Co., Ltd., Chengde, China; 500 mg per times, twice per day). The treatment was continued for 6 months. During the treatment period, patients were asked to give up their bad habits such as smoking, drinking, etc., and receive the reasonable physical recuperation.

Observation indexes

Before surgery, and 24 hours, 1 month, and 6 months after surgery, venous blood of patients was collected. The blood lipid indexes including serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were detected using BS-600 automatic biochemical analysis instrument (Shenzhen Mairui Biomedical Electronics Co., Ltd., Shenzhen, China). Iinflammatory response indexes including high-sensitive C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) levels were detected using enzyme-linked immunosorbent assays. The oxidative stress index superoxide dismutase (SOD) was detected by the riboflavin NBT colorimetry, and the malondialdehyde (MDA) was determined by the barbiturate thiosulfate method. The vascular endothelial function index endothelin-1 (ET-1) was detected by the radioimmunoassay, and the nitric oxide (NO) was detected by nitrate reductase colorimetry. The determination procedures were according to the instruction of kits (Sigma-Aldrich Corp., MO, USA). In addition, the coronary angiography was performed. The restenosis was defined as lumen diameter stenosis > 50% at the position of stent placement or within 5 mm of stent proximity.

Statistical analysis

All statistical analysis was carried out using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data are presented as number and rate, and were compared between two groups using χ^2 test. The measurement data are presented as Mean ± SD, and were compared between two groups using t test. $P < 0.05$ was considered as statistically significant.

Results

General information of patients in two groups

In 120 patients, there were 70 males and 50 females. The age of patients was 40-72 years old, with mean age of 62.33±7.42 years. There were 36 cases of smoking history, 50 cases of drinking history, 77 cases of hypertension, and 27 cases of diabetes. There were 59, 46, and 15 cases with 1, 2 and 3 involved vessels, respectively. The general information of patients is shown in **Table 1**. There was no significant difference of age, gender, smoking, drinking, hypertension, diabetes, or number of involved vessels between the observation and control groups.

Table 1. General information of patients in two groups

Parameter	Observation group	Control group	t/χ^2	P
n	52	68		
Age (years)	61.47±10.34	63.26±11.12	0.185	0.370
Gender (male/female, n)	33/19	37/31	0.993	0.319
Smoking history [n (%)]	16 (30.77)	20 (29.41)	0.026	0.872
Drinking history [n (%)]	20 (38.46)	30 (44.12)	0.388	0.533
Hypertension [n (%)]	31 (59.62)	46 (67.65)	0.827	0.363
Diabetes [n (%)]	11 (21.15)	16 (23.53)	0.095	0.757
Number of involved vessels [n (%)]			0.081	0.960
1	26 (50.00)	33 (48.53)		
2	20 (38.46)	26 (38.24)		
3	6 (11.54)	9 (13.24)		

Table 2. Comparison of restenosis rate between two groups [n (%)]

Group	24 h after surgery	1 month after surgery	6 months after surgery
Observation (n = 52)	0 (0)	0 (0.00)	6 (11.54)
Control (n = 68)	0 (0)	5 (7.35)	19 (27.94)
χ^2	-	3.990	4.807
P	-	0.046	0.028

Comparison of restenosis rate between two groups

One month after surgery, there were 0 cases (0.00%) of restenosis in observation group and 5 cases (7.35%) of restenosis in the control group. Six months after surgery, there were 6 cases (11.54%) of restenosis in the observation group and 19 cases (27.94%) of restenosis in the control group. The restenosis rates in the observation group at these two time points were significantly lower than those in the control group, respectively (1 month after surgery: P = 0.046; 6 months after surgery: P = 0.028) (**Table 2**).

Comparison of serum lipid levels between two groups

Before surgery and 24 hours after surgery, there was no significant difference of serum TC, TG, LDL-C, or HDL-C level between two groups. At later time points, the serum TC, TG, and LDL-C levels in each group decreased, respectively, and the serum HDL-C level in each group increased. There were significant difference of serum TC, TG, LDL-C, or HDL-C level between two groups 6 months after surgery (TC: P = 0.038; TG: P = 0.029; LDL-C: P = 0.017; HDL-C: P = 0.042), respectively (**Figure 1**).

Comparison of serum hs-CRP and TNF-α levels between two groups

As shown in **Figure 2**, before surgery, there was no significant difference of serum hs-CRP or TNF-α level between two groups. Twenty-four hours after surgery, the serum hs-CRP and TNF-α levels in each group increased, respectively. At later time points, each index in each group decreased, respectively. There were significant difference of serum hs-CRP and TNF-α level between two groups 24 hours after surgery (hs-CRP: P = 0.016; TNF-α: P = 0.008), 1 month after surgery (hs-CRP: P = 0.023; TNF-α: P = 0.035), and 6 months after surgery (hs-CRP: P = 0.021; TNF-α: P = 0.040), respectively.

Comparison of serum SOD and MDA levels between two groups

Figure 3 shows that before surgery there was no significant difference of serum SOD or MDA level between two groups. Twenty-four hours after surgery, compared with before surgery, in control group the serum SOD level decreased, and the serum MDA level increased, but those in observation group did not significantly change. At later time points, in the two groups the serum SOD level increased, and the serum MDA level increased. There was a significant difference of serum SOD and MDA level between the two groups 24 h after surgery (SOD: P = 0.042; MDA: P = 0.038), 1 month after surgery (SOD: P = 0.028; MDA: P = 0.004) and 6 months after surgery (SOD: P = 0.031; MDA: P = 0.013), respectively.

Comparison of serum ET-1 and NO levels between two groups

Before surgery, there was no significant difference of serum ET-1 or NO level between two

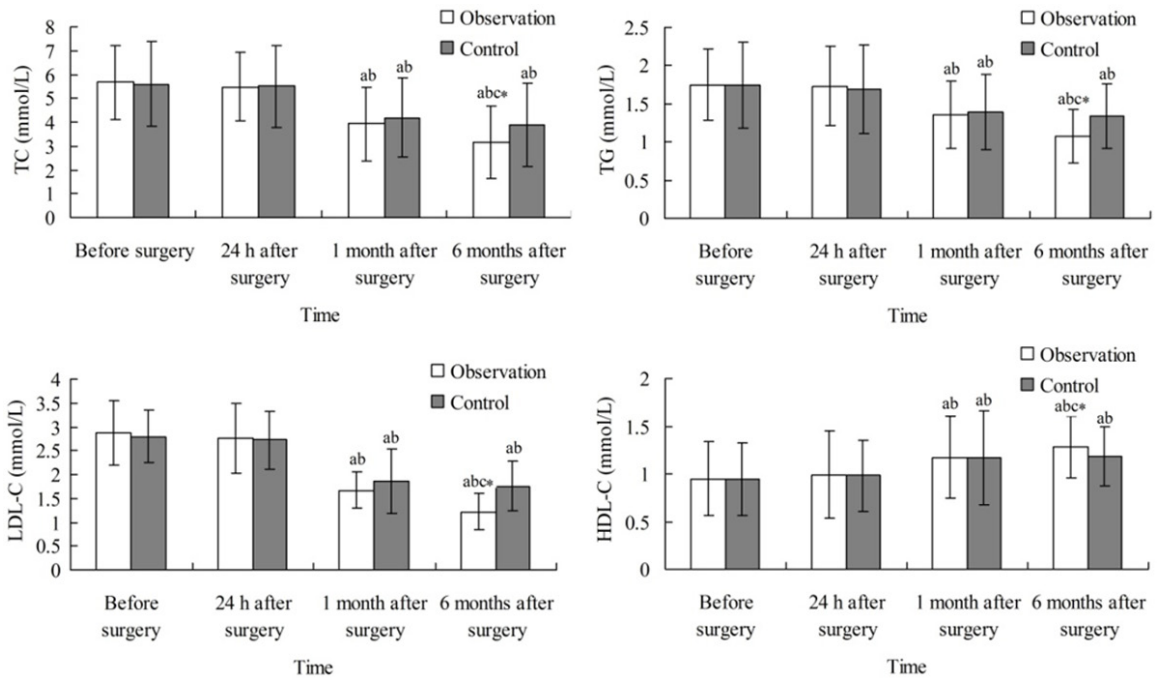

Figure 1. Comparison of serum lipid levels between the two groups. [a]P < 0.05 compared with before treatment; [b]P < 0.05 compared with 24 hours after surgery; [c]P < 0.05 compared with 1 month after surgery; *P < 0.05 compared with the control group. TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

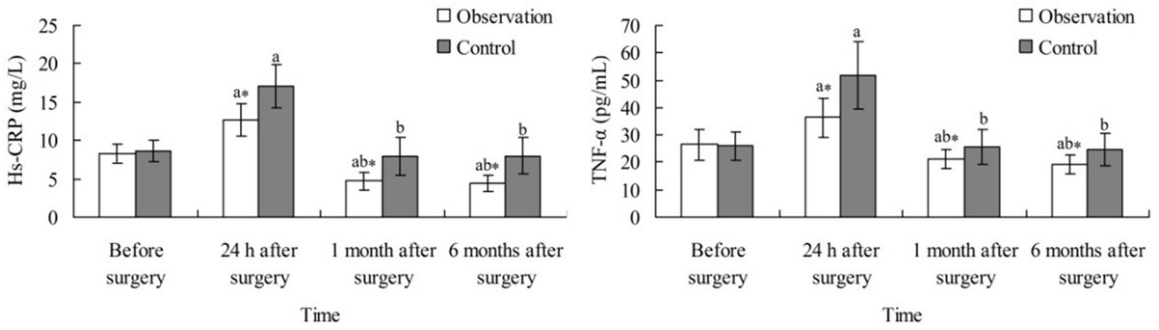

Figure 2. Comparison of serum hs-CRP and TNF-α levels between the two groups. [a]P < 0.05 compared with before treatment; [b]P < 0.05 compared with 24 hours after surgery; *P < 0.05 compared with the control group. Hs-CRP, high-sensitive C-reactive protein; TNF-α, tumor necrosis factor-α.

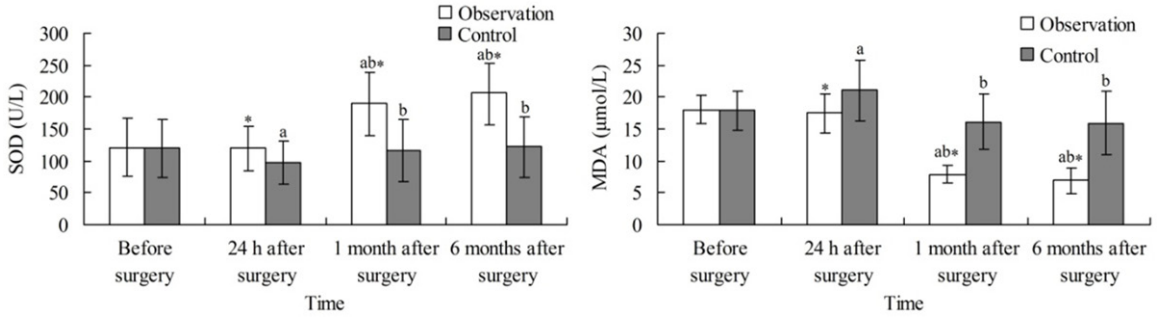

Figure 3. Comparison of serum SOD and MDA levels between the two groups. [a]P < 0.05 compared with before treatment; [b]P < 0.05 compared with 24 hours after surgery; *P < 0.05 compared with the control group. SOD, superoxide dismutase; MDA, malondialdehyde.

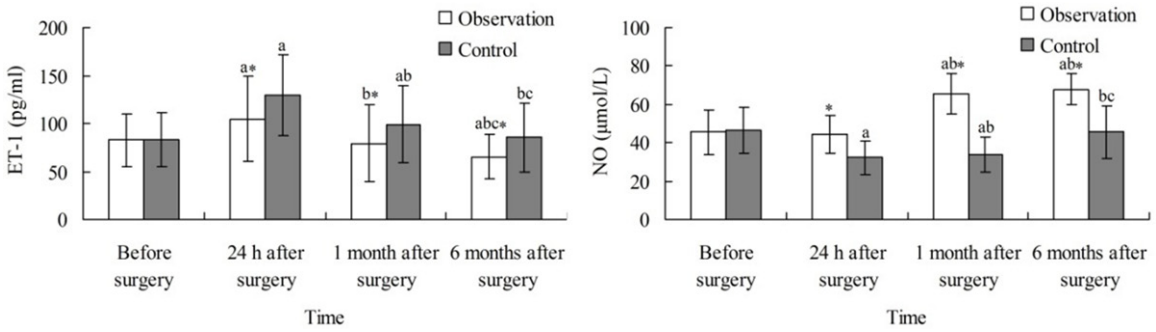

Figure 4. Comparison of serum ET-1 and NO levels between the two groups. [a]P < 0.05 compared with before treatment; [b]P < 0.05 compared with 24 hours after surgery; [c]P < 0.05 compared with 1 month after surgery; [*]P < 0.05 compared with the control group. ET-1, endothelin-1; NO, nitric oxide.

Table 3. Comparison of adverse reactions between two groups

Parameter	Observation group	Control group	χ^2	P
n	52	68	0.590	0.442
Abnormal liver function [n (%)]	3 (5.77)	2 (2.94)	0.590	0.442
Abnormal kidney function [n (%)]	2 (3.85)	1 (1.47)	0.682	0.409
Dizziness and headache [n (%)]	4 (7.69)	4 (5.88)	0.155	0.694
Rash [n (%)]	3 (5.77)	2 (2.94)	0.590	0.442
Myalgia [n (%)]	2 (3.85)	2 (2.94)	0.075	0.784
Nausea and vomiting [n (%)]	6 (11.54)	7 (10.29)	0.047	0.828
Gastrointestinal reaction [n (%)]	9 (17.31)	8 (11.76)	0.745	0.388

groups. Twenty-four hours after surgery, in two groups the serum ET-1 level increased and the serum NO level decreased. At later time points, in two groups the serum ET-1 level gradually decreased, and the serum NO levels gradually increased. There was a significant difference of serum hs-CRP and TNF-α level between two groups 24 hours after surgery (ET-1: P = 0.036; NO: P = 0.038), 1 month after surgery (ET-1: P = 0.041; NO: P = 0.002), and 6 months after surgery (ET-1: P = 0.046; NO: P = 0.012), respectively (**Figure 4**).

Comparison of adverse reactions between two groups

As shown in **Table 3**, the main adverse reactions in the two groups were the nausea and vomiting and gastrointestinal reaction. There was no significant difference in incidence of each adverse reaction between two groups.

Discussion

The present study applied rosuvastatin combined with probucol to prevention of restenosis after PCI and observed the efficacy and safety. The results show that, one month and 6 months after surgery, in the observation group the serum lipid levels were significantly lower than the control group, and the restenosis rates was significantly lower than the control group. This indicates that, compared with single use of rosuvastatin, the rosuvastatin combined with probucol can further decrease the blood lipids in patients with PCI and reduce the restenosis.

Studies [10, 11] have shown that, the inflammatory response plays an important role in the cardiovascular diseases, and it is considered to be one of the main causes of restenosis after PCI. Hs-CRP is one of the inflammatory markers the most popularly emerging in recent years, and is an important precursor to cardiovascular diseases. Hs-CRP can bind to the oxidized low-density lipoprotein and deposit in the vascular wall. It up-regulates the expression of adhesion factors, resulting in the vascular endothelial dysfunction [12] TNF-α is a cytokine with a variety of biological effects [13]. It can inhibit the fibrinolysis, leading to the thrombosis and angiostenosis [14]. Results of this study showed that, 24 hours after surgery, the serum hs-CRP and TNF-α levels in each group were significantly higher than those before surgery. At later time points, the serum hs-CRP and TNF-α levels in each group were decreased. This indicates that, PCI can cause the inflammatory response, and the treatments can alleviate the

inflammatory response. At each time point after surgery, the serum hs-CRP and TNF-α levels in the observation group were significantly lower than the control group. This indicates that, rosuvastatin combined with probucol can improve the anti-inflammatory effect compared with single use of rosuvastatin.

In pathological state, this balance of oxidant and antioxidant functions is easy to break, leading to the increased lipid peroxides and decreased antioxidant enzymes. SOD is a metal enzyme that catalyze the disproportionation of superoxide anion radicals (O^{2-}). It can scavenge the superoxide anions in body and protect the cells from injury [15]. MDA is a kind of lipid peroxides induced by oxygen free radicals. Its content reflects the degree of cell damage [16]. Results of this study showed that, 24 hours after surgery, compared with before surgery, in the control group the serum SOD level was significantly decreased, and the serum MDA level was significantly increased, but those in the observation group did not significantly change. There was significant difference of serum SOD and MDA levels at each time point after surgery between two groups, respectively. This indicates that, PCI can lead to the vascular oxidative stress. Compared with single use of rosuvastatin, the combined use of rosuvastatin and probucol can further alleviate vascular oxidative stress, thus reducing restenosis after PCI.

NO and ET-l are important vasodilator and vasoconstrictor secreted by the vascular endothelial cells. They co-maintain the balance of vascular and blood environment [17]. In PCI, the structural integrity of vascular endothelial cells is unavoidably damaged, leading to the consequent functional impairment such as intimal tearing and exfoliation, plaque rupture, decrease of NO synthesis, and increase of ET-l release. Thus, serum ET-l level is increased, and NO level is decreased [18, 19]. In this study, at each time point after surgery, there was a significant difference of serum ET-1 and NO level between two groups. This indicates that, compared with single use of rosuvastatin, the combined use of rosuvastatin and probucol can further block the ET-1 action and restore NO secretion and release, thus reducing the restenosis after PCI.

In conclusion, compared with single use of rosuvastatin, the combined use of rosuvastatin and probucol can reduce restenosis after PCI. The mechanisms may be related to its stronger effect in lowering lipids, anti-inflammatory, antioxidant, and vascular endothelial cell functions. In addition, the combined method dose not obviously increase the incidence of adverse reaction. It is an effective and safe strategy for prevention of restenosis after PCI, and is worthy of translation into clinical application.

Acknowledgements

This work was supported by Project of Jilin Provincial Department of Education (No. JJKH-20170061KJ).

Disclosure of conflict of interest

None.

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