



Effect of rosuvastatin intensification therapy on blood lipid metabolism, adipocytokines and plaque stability after PCI in ACS patients

Xiu-Quan Sun[✉], Yan-Fang Li, Ying-Jie Meng, Gui-Fang Shi

Cardiology Department No. 2, Jizhong Energy Fengfeng Group Hospital in Fengfeng District Hebei Province, Handan City, Hebei Province, 056200

ARTICLE INFO

Article history:

Received 27 Sep 2017

Received in revised form 30 Sep 2017

Accepted 3 Oct 2017

Available online 14 Oct 2017

Keywords:

ACS

Rosuvastatin

Blood lipid metabolism

Adipocytokines

Plaque stability

ABSTRACT

Objective: To explore the effect of rosuvastatin intensification therapy on blood lipid metabolism, adipocytokines and plaque stability after PCI in ACS patients. **Methods:** ACS patients who received PCI in the hospital between July 2015 and January 2017 were reviewed and divided into the routine dose group ($n=60$) who received rosuvastatin routine dose therapy after PCI and the intensification therapy group ($n=46$) who received rosuvastatin intensification therapy after PCI. The differences in blood lipid metabolism, adipocytokines and plaque stability were compared between the two groups before and after treatment. **Results:** Before PCI, the differences in blood lipid metabolism, adipocytokines and plaque stability were not statistically significant between the two groups. 1 month after PCI, lipid metabolism indexes HDL-C and ApoA1 levels in peripheral blood of intensification therapy group were higher than those of routine dose group while LDL-C and ApoB levels were lower than those of routine dose group; adipocytokines APN and Leptin levels in serum were higher than those of routine dose group while Resistin level was lower than that of routine dose group; plaque stability-related indexes ICAM-1, MMP-1 and TIMP-1 levels were lower than those of routine dose group. **Conclusion:** Rosuvastatin intensification therapy after PCI could effectively regulate the lipid metabolism and increase the plaque stability in ACS patients.

1. Introduction

Acute coronary syndrome (ACS) is the clinical syndrome caused by unstable atherosclerotic plaque, the pathological basis is the completely/incompletely occlusive angiopoiesis, and the clinical mortality is high without timely active treatment[1,2]. Percutaneous coronary intervention (PCI) is the most important method for the treatment of ACS patients in time window, which can effectively reduce the mortality rate. Blood lipid metabolism abnormality and atheromatous plaque formation are the foundation of the ACS, and the probability of long-term in-stent thrombosis is high if there are still lipid metabolism abnormality and plaque instability after PCI[3,4]. Rosuvastatin is currently considered as the most biologically powerful drug in statins, but it is not long before it is used in ACS patients after PCI, and the specific dose selection remains controversial. In the research, different doses of rosuvastatin

was used in patients with ACS who received PCI in our hospital between July 2015 and January 2017 in order to seek the optimal lipid-regulating dose for such patients and provide reference for further clinical practice.

2. Information and methods

2.1 Case information

A total of 106 patients with ACS received treatment in the hospital and were included after the family members signed informed consent. The patients were retrospectively analyzed and divided into the routine dose group ($n=60$) who received rosuvastatin routine dose therapy after PCI and the intensification therapy group ($n=46$) who received rosuvastatin intensification therapy after PCI. Routine dose group included 33 men and 27 women that were 40-72 years old; intensification therapy group included 25 men and 21 women that were 41-75 years old. The differences in basic data were not different between the two groups, the follow-up clinical indexes were comparable, and the hospital ethics committee approved the study.

[✉]Corresponding author: Xiu-Quan Sun, Cardiology Department No. 2, Jizhong Energy Fengfeng Group Hospital in Fengfeng District Hebei Province, Handan City, Hebei Province, 056200.

Fund Project: Handan Science and Technology Research and Development Plan Project No: 1623208102ZC.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) meeting the diagnostic criteria for ACS; (2) without history of ACS attack within the past year; (3) without long-term ruisuvastatin-taking history; (4) cooperating with and completing the whole treatment and without dropping out. Exclusion criteria: (1) rosuvastatin allergy; (2) combined with severe heart, liver and kidney insufficiency; (3) combined with diabetes mellitus and endocrine system diseases.

2.3 Therapy

Both groups of patients received PCI, and control group received routine dose of rosuvastatin after surgery, specifically as follows: rosuvastatin (Zhejiang Hisun Pharmaceutical Co., Ltd., approved by H20143339), taken orally, 5 mg/d, 1 time/d, lasting for 1 month. Observation group received rosuvastatin intensification therapy after PCI, which was specifically as follows: resuvastatin, taken orally, 10 mg/d, 1 time/d, lasting for 1 month.

2.4 Blood sample obtaining

Before PCI and 1 month after PCI, 4.0 mL of fasting cubital venous blood was extracted from two groups of patients and anti-coagulated, 2.0 mL of blood was directly cryopreserved; the other 2.0 mL was centrifuged at 3 500 r/min and 4 °C for 10 min, and the supernatant fluid was collected and also cryopreserved.

2.5 Observation indexes

Flow cytometer was used to detect the levels of lipid metabolism indexes in peripheral blood, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB). Radioimmunoassay was used to detect the levels of

adipocytokines in serum, including adiponectin (APN), Resistin and Leptin. Enzyme-linked immunosorbent assay method was used to detect the serum contents of plaque stability-related factors, including intercellular adhesion molecule-1 (ICAM-1), matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1).

2.6 Statistical processing

Lipid metabolism indexes, adipocytokines and plaque stability-related factors belonged to measurement data and were in terms of mean ± standard deviation, and comparison within group and between groups was both by *t* test. Data processing software was SPSS 26.0 and *P*<0.05 was the standard of statistical significance in differences in data comparison in the study.

3. Results

3.1 Lipid metabolism indexes

Comparison of lipid metabolism indexes HDL-C (mmol/L), LDL-C (mmol/L), ApoA1 (mg/L) and ApoB (mg/L) levels in peripheral blood between two groups of patients was as follows: before PCI, the differences in peripheral blood HDL-C, LDL-C, ApoA1 and ApoB levels were not significant between the two groups (*P*>0.05); 1 month after PCI, HDL-C and ApoA1 levels in peripheral blood of both groups were higher than those before PCI while LDL-C and ApoB levels were lower than those before PCI, and the changes in peripheral blood levels of these indexes in intensification therapy group were greater than those in routine dose therapy (*P*<0.05), shown in Table 1.

Table 1.

Lipid metabolism index levels in peripheral blood.

Groups	n	HDL-C		LDL-C		ApoA1		ApoB	
		Before PCI	1 month after PCI	Before PCI	1 month after PCI	Before PCI	1 month after PCI	Before PCI	1 month after PCI
Routine dose group	60	0.93±0.11	1.17±0.12	2.47±0.35	1.98±0.21	942.16±100.45	1 103.57±134.98	642.82±71.92	517.64±58.39
Intensification therapy group	46	0.92±0.12	1.35±0.18	2.45±0.33	1.51±0.17	939.75±101.39	1 215.83±140.76	639.77±68.53	394.17±45.24
<i>T</i>		0.193	5.271	0.217	4.927	0.298	13.284	0.253	11.672
<i>P</i>		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Table 2.

Adipocytokine levels in serum.

Groups	n	APN		Resistin		Leptin	
		Before PCI	1 month after PCI	Before PCI	1 month after PCI	Before PCI	1 month after PCI
Routine dose group	60	8.49±0.91	9.57±1.19	9.83±1.75	7.14±0.86	4.37±0.48	5.11±0.58
Intensification therapy group	46	8.37±0.94	11.05±1.64	9.79±1.64	5.28±0.64	4.41±0.45	6.09±0.75
<i>T</i>		0.271	9.273	0.364	7.837	0.184	7.231
<i>P</i>		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Table 3.

Plaque stability-related factor levels in serum (pg/mL).

Groups	n	ICAM-1		MMP-1		TIMP-1	
		Before PCI	1 month after PCI	Before PCI	1 month after PCI	Before PCI	1 month after PCI
Routine dose group	60	143.28±15.96	127.53±14.29	4.83±0.57	3.79±0.45	163.28±18.93	140.17±15.32
Intensification therapy group	46	144.17±15.83	113.76±12.74	4.81±0.53	2.64±0.31	162.77±18.52	121.64±13.85
T		0.219	9.271	0.174	7.283	0.188	13.281
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

3.2 Adipocytokines

Comparison of adipocytokines APN (mg/L), Resistin (μg/L) and Leptin (μg/L) levels in serum between two groups of patients was as follows: before PCI, the differences in APN, Resistin and Leptin levels in serum were not significant between the two groups ($P>0.05$); 1 month after PCI, APN and Leptin levels in serum of both groups were higher than those before PCI while Resistin levels were lower than those before PCI, and the changes in serum levels of these indexes in intensification therapy group were greater than those in routine dose therapy ($P<0.05$), shown in Table 2.

3.3 Plaque stability-related factors

Comparison of plaque stability-related factors ICAM-1, MMP-1 and TIMP-1 levels in serum between two groups of patients was as follows: before PCI, the differences in ICAM-1, MMP-1 and TIMP-1 levels in serum were not significant between the two groups ($P>0.05$); 1 month after PCI, ICAM-1, MMP-1 and TIMP-1 levels in serum of both groups were lower than those before PCI, and the changes in serum levels of these indexes in intensification therapy group were greater than those in routine dose therapy ($P<0.05$), shown in Table 3.

4. Discussion

Persistent lipid metabolism abnormality can lead to arterial plaque formation, and the plaque stability decline and rupture will directly lead to the occurrence of ACS. PCI is the most effective clinical therapy for patients with ACS within time window, but current study has shown that in-stent thrombosis may occur in some patients after PCI and even lead to death, which is closely related to the abnormal lipid metabolism regulation after operation. ACS patients need to take statin lipid-regulating drugs for a long time after PCI, rosuvastatin, as selective HMG-CoA reductase inhibitor, can increase the number of liver cell surface receptors and promote the absorption and catabolism of LDL[5-7], and is the common drug for patients with ACS after PCI, but the optimal dose is controversial. In this study, the routine dosage and intensive dosage were used respectively for the treatment of patients with ACS after PCI in order to seek the optimal dosage for optimizing the patient's condition.

The contents of lipid metabolism indexes can directly reflect the lipid metabolism status in patients with ACS after treatment

and evaluate the lipid-regulating effect. HDL-C and LDL-C are typical lipid molecules, HDL-C has the "fattening" effect, and it can transfer the fatty acid to the fat and decompose it to reduce the hyperlipidemia state[8]; the high expression of LDL-C is one of the direct causes of cardiovascular events, and its content is consistent with the level of hyperlipidemia[9]. Both ApoA1 and ApoB are typical apolipoprotein, ApoA1 is the main composition of high density lipoprotein and can transport the cholesterol in circulating blood and ease hyperlipidemia illness, and ApoB is one of the apolipoprotein of low density lipoprotein and very low density lipoprotein, and participates in the formation of hyperlipidemia[10,11]. It was found in the study that HDL-C and ApoA1 levels in peripheral blood of both groups increased while LDL-C and ApoB levels decreased 1 month after PCI, and the changes in the levels of these indexes were greater in intensification therapy group, illustrating that 10 mg/d rosuvastatin intensification therapy can more effectively reduce the hyperlipidemia in ACS patients after PCI.

Adipocytokines are the important elements that regulate the body's lipid metabolism, APN can decrease the degree of atherosclerosis, and studies have confirmed that APN levels in patients with coronary heart disease drop with the increased number of diseased blood vessels[12,13]. Resistin is the polypeptide hormone secreted by adipokines, it is the inflammatory marker of atherosclerosis, its serum content is positively correlated with fasting glucose levels, and study has confirmed that the Resistin levels in ACS patients are higher than those in normal people[14]. Leptin is a protein hormone synthesized by adipokines, it can increase energy consumption and inhibit fat synthesis, and Leptin content decreases in obese patients[15,16]. It was found in the study that APN and Leptin levels in serum of both groups increased while Resistin levels decreased 1 month after PCI, and the changes in serum levels of these indexes were greater in intensification therapy group, confirming that high dose of rosuvastatin therapy may be more effective to optimize the secretion of adipocytokines and adjust lipid metabolism, and this is one of the direct causes of improved lipid index contents in the study.

The plaque stability decrease and even rupture is the direct cause of the occurrence of ACS. The ultimate aim of actively regulating blood lipid after PCI is also to increase the plaque stability and avoid the occurrence of secondary plaque rupture events. ICAM-1, MMP-1 and TIMP-1 are the factors directly related to plaque stability, inflammatory response activates endothelial cells and increases ICAM-1 expression, and the ICAM-1 interacts with a variety of inflammatory factors to influence plaque stability

and promote the occurrence of ACS[17,18]. MMP-1 and TIMP-1 are opposite in function, and it is found that MMP-1 expression increases in vulnerable plaques, which is directly related to its roles in degrading the collagen in the extracellular matrix, increasing the brittleness of the fiber cap and so on[19,20]. The increase of MMP-1 content can reactively stimulate the synthesis and secretion of its inhibitor TIMP-1, so change trend of MMP-1 and TIMP-1 are consistent. It was found in the study that the ICAM-1, MMP-1 and TIMP-1 levels in serum of both groups decreased 1 month after PCI, and the changes in serum levels of these indexes were greater in intensification therapy group, confirming that high dose of rosuvastatin therapy may be more effective to stabilize the atheromatous plaque.

Thus, compared with the routine dose of 5 mg/d rosuvastatin therapy, the 10 mg/d of rosuvastatin intensification therapy can more effectively regulate the body's lipid metabolism state and stabilize the plaques in patients with ACS after PCI, it helps to reduce the occurrence of re-embolic events, and it is worthy of popularization and application in clinical practice in the future.

References

- [1] Usta C, Bedel A. Update on pharmacological treatment of acute coronary syndrome without persistent ST segment elevation myocardial infarction in the elderly. *J Geriatr Cardiol* 2017; **14**(7): 457-464.
- [2] Mischie AN, Andrei CL, Sinescu C, Bajraktari G, Ivan E, Chatziathanasiou GN, et al. Antithrombotic treatment tailoring and risk score evaluation in elderly patients diagnosed with acute coronary syndrome. *J Geriatr Cardiol* 2017; **14**(7): 442-456.
- [3] Cantor WJ, Mehta SR, Yuan F, Davik V, Worthley M, Niemela K, et al. Radial versus femoral access for elderly patients with acute coronary syndrome undergoing coronary angiography and intervention: insights from the RIVAL trial. *Am Heart J* 2015; **170**(5): 880-886.
- [4] Aykan AC, Gokdeniz T, Bektas H, Boyaci F, Gul I, Hatem E, et al. Assessment of silent neuronal injury following coronary angiography and intervention in patients with acute coronary syndrome. *Clin Appl Thromb Hemost* 2016; **22**(1): 52-59.
- [5] Ye Z, Lu H, Su Q, Guo W, Dai W, Li H, et al. Effect of high-dose rosuvastatin loading before percutaneous coronary intervention in Chinese patients with acute coronary syndrome: A systematic review and meta-analysis. *PLoS One* 2017; **12**(2): e0171682.
- [6] Shah CP, Shah BP, Dani SI, Channa BB, Lakshmanan SS, Krishnamani NC, et al. Efficacy and safety of the intensive dose of rosuvastatin 40 mg/day in patients with acute coronary syndrome and at high risk of cardiovascular disease-ROSUVEES-2. *Indian Heart J* 2016; **68**(6): 766-771.
- [7] Jung LY, Lee SR, Jung JM, Kim YS, Lee SH, Rhee KS, et al. Rosuvastatin reduces blood viscosity in patients with acute coronary syndrome. *Korean Circ J* 2016; **46**(2): 147-153.
- [8] Koncos P, Fulop P, Juhasz I, Biro K, Mark L, Simonyi G, et al. Changes in triglyceride, HDL-C, and non-HDL-C levels in patients with acute coronary syndrome. *Wien Klin Wochenschr* 2016; **128**(23-24): 858-863.
- [9] Aditya GP, Bari MA. Lipid profile in post-acute coronary syndrome setting: lipidic risk assessment in young people beyond LDL-C. *Mymensingh Med J* 2015; **24**(4): 697-703.
- [10] Aditya GP, Bari MS, Bari MA, Mutalib MA, Paul GK. Association of metabolic syndrome with hyper apolipoprotein b status in young people with acute coronary syndrome. *Mymensingh Med J* 2017; **26**(1): 68-74.
- [11] Aditya GP, Bari MS, Bari MA, Mutalib MA, Islam MZ, Paul GK, et al. Risk of acute coronary syndrome is better predicted by apolipoprotein b in young people than dyslipidemic parameter of conventional lipid profile. *Mymensingh Med J* 2016; **25**(4): 663-668.
- [12] Bergmark BA, Cannon CP, White WB, Jarolim P, Liu Y, Bonaca MP, et al. Baseline adiponectin concentration and clinical outcomes among patients with diabetes and recent acute coronary syndrome in the EXAMINE trial. *Diabetes Obes Metab* 2017; **19**(7): 962-969.
- [13] Singh P, Sridhar MG, Rajappa M, Balachander J, Kadhiraivan T. Adiponectin-resistin index and its strong association with acute coronary syndrome in South Indian men. *Inflamm Res* 2014; **63**(11): 961-968.
- [14] Khara AV, Qamar A, Murphy SA, Cannon CP, Sabatine MS, Rader DJ. On-statin resistin, leptin, and risk of recurrent coronary events after hospitalization for an acute coronary syndrome (from the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 study). *Am J Cardiol* 2015; **116**(5): 694-698.
- [15] Michalski B, Szymczyk E, Peczek L, Nawrot B, Kupczynska K, Krzemi ska-Pakuła M, et al. The role of selected adipokines and ghrelin in the prognosis after myocardial infarction in a 12-month follow-up in the presence of metabolic syndrome. *Arch Med Sci* 2017; **13**(4): 785-794.
- [16] Puurunen VP, Kiviniemi A, Lepojarvi S, Piira OP, Hedberg P, Junttila J, et al. Leptin predicts short-term major adverse cardiac events in patients with coronary artery disease. *Ann Med* 2017; **49**(5): 448-454.
- [17] Celano CM, Beale EE, Beach SR, Belcher AM, Suarez L, Motiwala SR, et al. Associations between psychological constructs and cardiac biomarkers after acute coronary syndrome. *Psychosom Med* 2017; **79**(3): 318-326.
- [18] Jia P, Wu N, Zhang X, Jia D. Association of matrix metalloproteinase-1 -519A/G polymorphism with acute coronary syndrome: a meta-analysis. *Int J Clin Exp Med* 2015; **8**(4): 5675-5682.
- [19] Parkkonen O, Nieminen MT, Vesterinen P, Tervahartiala T, Perola M, Salomaa V, et al. Low MMP-8/TIMP-1 reflects left ventricle impairment in takotsubo cardiomyopathy and high TIMP-1 may help to differentiate it from acute coronary syndrome. *PLoS One* 2017; **12**(3): e0173371.
- [20] Allal-Elasmi M, Zayani Y, Zidi W, Zaroui A, Feki M, Mourali S, et al. The measurement of circulating matrix metalloproteinase-8 and its tissue inhibitor and their association with inflammatory mediators in patients with acute coronary syndrome. *Clin Lab* 2014; **60**(6): 951-956.