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Effects of atorvastatin combined with trimetazidine on myocardial injury and inflammatory mediator in unstable angina patients during perioperative of percutaneous coronary intervention

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Abstract. – OBJECTIVE: To investigate the effects of atorvastatin combined with trimetazidine on periprocedural myocardial injury and serum inflammatory mediators in unstable angina pectoris (UAP) patients following percutaneous coronary intervention (PCI) treatment.

PATIENTS AND METHODS: 90 patients with UAP treated with conventional medications and PCI were recruited and were randomly divided into the control group and the experimental group. The control group had 42 patients were treated with atorvastatin alone, while the experimental group had 48 cases treated with atorvastatin combined with trimetazidine. All the patients were checked the preoperative 24h and postoperative 24h PCI concentrations of cardiac troponin I (cTnI), hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), serum interferon-γ (IFN-γ) and interlukin-10 (IL-10).

RESULTS: At the pre-PCI stage, every serum factors was no significant difference. 24 hours after the PCI intervention, the occurence of abnormal cTnI level in the experimental group was remarkable reduced than the control group. In the experimental group, the serum levels of TNF-α and IFN-γ significantly decreased ($p < 0.05$); while IL-10 was increased. In the control group, all the mediators were increased significantly except the hs-CRP ($p < 0.05$).

CONCLUSIONS: No unexpected symptom was found in patients with large dose atorvastatin combined with large dose trimetazidine. The administration of conventional medications together with the atorvastatin plus trimetazidine were able to reduce the prevalence of postoperative myocardial injury.

Key Words:
Unstable angina pectoris, Atorvastatin, Trimetazidine, Inflammatory mediators, Myocardial injury.

Introduction

The coronary heart disease (CHD) has become a pervasive public health problem, and seriously threaten people's expectancy and quality of life all over the world[1]. With percutaneous coronary intervention (PCI) satisfactory outcome for the CHD, now it is becoming a major approach for CHD therapy[2]. In spite of optimized preoperative medications and careful intra-operative procedures had implemented, the postoperative myocardial injury was still a big problem for PCI that would be hardly overcame[3]. No effectively measures has been reported to completely reverse the postoperative myocardial injury[4].

Recently, clinical trials showed trimetazidine given at loading dose could relieve the myocardial ischemia induced by postoperative myocardial injury[5]. A large dose oral intake of atorvastatin 2d before PCI could reduce markedly the serum level of C-reactive protein (CRP) as well as alleviate the occurence of postoperative myocardial injury. A decrease of the heart diseases risk by 88% in the first month after PCI has been reported[6].

During the periprocedural period of PCI, the levels of inflammatory factors such as TNF-α, IFN-γ and IL-10 increased largely due to myocardial injury[7]. However, the influence of atorvastatin and trimetazidine on the inflammatory factors during the periprocedural period of PCI had hardly been elucidated. In this paper, we are going to underscore the comprehensive impact of atorvastatin and trimetazidine on the myocardial injury and the levels of inflammatory mediators, during the periprocedural period of PCI.

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Patients and Methods

Patients

From May 2011 to November 2014, 90 unstable angina pectoris (UAP) patients treated by PCI were recruited in this assay and randomly divided into experimental group (48 cases) and control group (42 cases) two groups. The average age of all the patients was 59.0 years old. There are 49 males and 41 females. Some of them are hyperlipidemic and have a history of smoking and coronary heart disease. All the patients signed the informed consent. The general information of the patients are showed in Table I.

Recruited criteria[6-8]: (1) UAP confirmed according to Guidelines for the Management of Patients with Unstable Angina-ST-Elevation Myocardial Infarction published in 2007. The clinical manifestations of all UAP cases conformed to the diagnostic criteria for angina by Canadian Cardiovascular Society (CCS) and were classified as class II-IV; (2) Over one site of stenosis in blood vessels during selective coronary angiography, showing over 75% diameter stenosis; (3) Type A or type B stenosis according to American College of Cardiology (ACC)/American Heart Association (AHA); (4) All cases signed the informed consent. Exclusion criteria: (1) Elevation of cTnI level by over 0.05 □g/L; (2) Complications by tumors, severe infections, severe liver and renal insufficiency, severe underlying systemic diseases and apoplexy; (3) Intolerance to clopidogrel of aspirin, with a history of statins treatment or allergy to statins; (4) Left ventricular ejection fraction (LVEF) below 30%; (5) Critically ill, high-risk UAP cases that required emergency treatment. The control group had 42 cases, including 24 males and 18 females aged 58.7±4.6 years old on average.

The two groups didn't differ significantly in gender, age, blood pressure, blood glucose, blood lipid and smoking status ($p > 0.05$) (Table I).

Treatments

All the patients in the two groups were treated with conventional medications, for example low-molecular-weight heparin, angiotensin converting enzyme inhibitors (ACEI), Plavix, aspirin or β-receptor blocker. Besides conventional medications, 80 mg atorvastatin three times daily was given for the control group 2d before PCI. As for the experimental group, 80 mg atorvastatin three times daily 2d before PCI combined with 60 mg trimetazidine 1h before PCI, after PCI, the dose of trimetazidine was reduced to 20 mg three times per day.

Specimen Collection and Detection

Stenting was indicated for the treatment of coronary heart disease on coronary angiography. 24h preoperative and postoperative, 2 mL of peripheral venous blood was collected, respectively. The natural solidification of the blood samples took 20 min. The blood samples were subjected to centrifugation for 10 min at 2000 rpm/min. The sera supernatant was preserved at -80°C fridge. The TNF-α, IFN-γ and IL-10 were detected by ELISA (Beijing BLKW Biotechnology, Beijing, China). The hs-CRP was detected by rate nephelometric (Hunan Yonghe-Yangguang Science and Technology Co., Ltd, Changsha, China), and cTnI by chemiluminescence immunoassay (Bioscience Diagnostic Technology, Tianjin, China). Normal cTnI was defined as 0-0.3 g/L; otherwise cTnI level was abnormal. All the procedure followed the manufacture's protocol.

Table I. Comparison of general information of cases in two groups (mean value).

Item	Experimental group (48 cases)	Control group (42 cases)	p
Gender (male/female)	25/23	24/18	0.631
Age (years)	59.3	58.7	0.566
Hypertension (years)	31	27	0.977
Diabetes mellitus (years)	12	10	0.896
Hyperlipidemia (years)	14	11	0.753
Smoking (years)	20	18	0.909
Systolic pressure (mmHg)	141.7	140.8	0.725
Diastolic pressure (mmHg)	89.6	88.3	0.506
History of coronary heart disease	11	9	0.865

Table II. PCI-related parameters of UAP cases.

Item	Experimental group (48 cases)	Control group (42 cases)		
Number of damaged blood vessels (%)			χ^2	*p*
Left anterior descending branch	35	28	0.417	0.519
Left main coronary artery	8	6	0.097	0.756
Circumflex branch	22	18	0.080	0.777
Right coronary artery	17	19	0.900	0.343
Number of damaged blood vessels			*t*	*p*
One	25	21	0.044	0.978
Two	14	13		
Three and above	9	8		
Number of stents	1.9 ± 0.4	1.8 ± 0.6	0.941	0.349
Length (mm)	25.9 ± 1.2	25.8 ±1.3	0.379	0.705
Diameter (mm)	3.4 ± 0.9	3.3 ± 0.8	0.554	0.581
Pressure released by the placing of stent (mmHg)	13.1 ± 1.6	13.7 ± 2.4	-1.411	0.162

Statistical Analysis

Statistical analysis was used the SPSS18.00 software (IBM Company, NY, USA). Measurement data were expressed as mean ± standard deviation (). Grouped *t*-test was used for inter-group comparison. Count data was presented as frequency or percentage (n, %). For intra-group comparison, □^{2}-test was performed. $p < 0.05$ indicated statistically significant difference.

Results

PCI-related Parameters of UAP Cases

PCI-related parameters of UAP cases in the two groups were compared. The main parameters of PCI included: position and number of damaged blood vessels, length and diameter of stents and pressure released by the placing of stents. As for this characters, there were no significant difference between groups ($p > 0.05$) (Table II).

Incidence of High Normal cTnI Level

The occurence of abnormal cTnI level was detected 24h postoperative of PCI. The cTnI level was prominent lower in the experimental group than in the control group ($p < 0.05$) (Table III).

Comparison of hs-CRP, TNF-α, IFN-γ and IL-10

The serum levels of hs-CRP, TNF-α, IFN-γ and IL-10 were measured in the two groups at 24h pre-PCI and post-PCI. At the pre-PCI stage, there was no difference of each inflammatory factor between the two groups ($p > 0.05$). 24 h post-PCI, the serum levels of TNF-α and IFN-γ decreased in the experimental group compared with that of pre-PCI, but the hs-CRP did not decrease ($p < 0.05$). For the control group, after PCI the levels of all factors increased considerably except hs-CRP and TNF-α ($p < 0.05$). The two groups did not show significant difference in the serum level of IL-10 at pre-PCI ($p > 0.05$). After the PCT, the IL-10 in the two groups were increased ($p < 0.05$), the extent of increasing in the experimental group was much greater than in the control group ($p < 0.05$) (Table IV).

Discussion

As an important treatment to coronary heart disease, PCI has greatly reduced CHD mortality. With the advancing of technology, the PCI had markedly improved, only a few patients required

Table III. Incidence of abnormal cTnI level.

Group	Incidence of abnormal cTnI level (%)	*p*
Experimental group	18.4 ± 3.4	0.000
Control group	28.3 ± 2.7	

Table IV. The comparison of the Pre-PCI and Post-PCI hs-CRP, TNF-α and IL-10 in the two groups.

Inflammatory factor		Experimental group	Control group	*t*	*p*
hs-CRP (mg/L)	pre-PCI	2.6 ± 1.8	2.6 ± 1.9	0.000	1.000
	post-PCI	2.4 ± 1.6	3.1 ± 1.7	-2.011	0.047
	t	0.575	-1.271		
	p	0.566	0.207		
TNF-α (pg/mL)	pre-PCI	7.8 ± 1.6	7.8 ± 1.5	0.000	1.000
	post-PCI	7.2 ± 1.3	8.4 ± 2.1	-3.303	0.001
	t	2.016	-1.507		
	p	0.047	0.136		
IFN-γ (pg/mL)	pre-PCI	225.7 ± 21.3	226.8 ± 23.4	-0.233	0.816
	post-PCI	214.3 ± 19.4	238.2 ± 24.6	-5.147	0.000
	t	2.741	-2.176		
	p	0.007	0.032		
IL-10 (pg/mL)	pre-PCI	7.7 ± 1.3	7.6 ± 1.2	0.377	0.706
	post-PCI	17.3 ± 2.5	13.8 ± 3.6	5.409	0.000
	t	-23.604	-10.589		
	p	0.000	0.000		

emergency coronary artery bypass grafting after the PCI[9,10]. However, the prevalence of postoperative myocardial injury remains high rate, which greatly affects CHD prognosis, increases mortality and induces other cardiovascular diseases. For example, the prevalence of elevation of CK-MB level following PCI was 5%-20%[11] and the occurence of abnormal cTnI level is generally 30%-40% and sometimes reaches 74%[12]. cTnI is superior to CK-MB in terms of diagnostic sensitivity in myocardial injury[13]. PCI is a stimulus to peripheral blood lymphocytes and influence the oxidative stress. This will further lead to the increasing of inflammatory factors such as TNF-α, IFN-γ and IL-6 and, hence, the occurrence of myocardial inflammation and myocardial injury[14,15].

Atorvastatin is a representative of statins and known for its effect in abating lipids and low-density lipoprotein. Atorvastatin is widely applied to treating atherosclerosis, improving endothelial functions, preventing lipid oxidation, changing plaque composition and ameliorating the prognosis of patients with atherosclerosis[16]. The use of atorvastatin before PCI can reduce the level of CRP, thereby controlling the risk of postoperative myocardial injury and improving the short-term prognosis. A large dose of atorvastatin mitigated myocardial ischemia-reperfusion injury and improved myocardial functions[16]. Here, we confirmed that a large dose of atorvastatin reduced the inflammatory factor levels in UAP cases preoperative of the PCI. Thus, reducing the occurence of PCI myocardial injury, no side symptom was founded about the large dose of the atorvastatin.

Trimetazidine can partly block fatty acid β-oxidation, and the glucose will be consumed as substrate with priority to supply myocardial energy[17,18]. This process is beneficial for cardiac function improvement, alleviating myocardial ischemia, acidosis and intracellular calcium overload as well as damage caused by oxygen free radicals. The cTnI level within 24h after PTCA in patients who took 60 mg trimetazidine daily for 2 weeks before operation was lower compared with the control[19,20]. Patients who orally took 80 mg trimetazidine daily before PCI had a significant decrease of serum level of cTnI after PCI compared with the control[5].

In the present study, the occurence of high abnormal level of cTnI in the two groups within 24h after PCI was 18.4 ± 3.4% and 28.3 ± 2.7%, respectively. This indicated that atorvastatin combined with trimetazidine effectively reduced the prevalence of myocardial injury in patients with UAP. During the periprocedural period, the levels of hs-CRP, TNF-α and IFN-γ all decreased considerably, while the level of IL-10 increased. These results indicated that atorvastatin combined with trimetazidine inhibited the expression of inflammatory factors during the periprocedural period, reduced myocardial inflammatory response and decreased the occurence of myocardial injury.

Conclusions

A large dose of atorvastatin combined with trimetazidine before PCI could effectively reduce the levels of inflammatory factors such as hs-CRP, TNF-α and IFN-γ and increased the level of IL-10. This means that the risk of myocardial injury following PCI is reduced and the cure rate is improved with a great alleviation of patients' pain.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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