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Original Article

Effect of various doses of rosuvastatin in the treatment of elderly patients with unstable angina pectoris

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Abstract: Objectives: This prospective study aimed to explore the effects of various doses of rosuvastatin on the hemodynamic changes, highly sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels in elderly patients with unstable angina pectoris. Methods: One-hundred and six elderly patients with unstable angina pectoris were enrolled and divided into group A (n=55) and group B (n=51). Under the same treatment for angina pectoris, patients in groups A and B were administered with 5 mg and 10 mg of rosuvastatin orally once every night, respectively. The two groups were compared in terms of hemorheology, coagulation indices and immune reaction (serum hs-CRP and IL-6 levels), changes of clinical indices, electrocardiograph (ECG), therapeutic effect, and incidence of adverse reactions. Serum hs-CRP and IL-6 levels were detected by ELISA method, and their correlation was analyzed by Pearson method. Results: Whole blood viscosity at high cut (BVH), whole blood viscosity at low cut (BVL), plasma viscosity (PV), and erythrocyte sedimentation rate (ESR), immunoglobulin index, and the hs-CRP and IL-6 levels decreased in both groups after treatment and were lower in group B than in group A (P<0.05). Prothrombin time (PT) and activated partial thromboplastin time (APTT) increased, while fibrinogen (FIB) decreased in both groups after treatment (P<0.05). Group B was superior to group A in the onset times of myocardial ischemia and angina pectoris, the total duration of myocardial ischemia, and the total effective rate indicated by ECG (P<0.05). No statistical difference was observed in the incidence of adverse reactions between the two groups after treatment (P>0.05). Conclusions: The optimal efficacy of rosuvastatin at 10 mg/day was higher than that of rosuvastatin at 5 mg/day.

Keywords: Various doses, rosuvastatin, elderly patients, unstable angina pectoris, hs-CRP, IL-6

Introduction

In recent years, due to population aging, emotional changes, as well as activity and satiety, the number of elderly patients with unstable angina pectoris has increased, further strengthening the status of the disease as an important factor threatening the health of the elderly population [1]. Unstable angina pectoris is a common clinical type of coronary heart disease between acute angina pectoris and stable angina pectoris [2]. Patients with unstable angina pectoris may suffer from severe angiemphraxis owing to ruptures and spasms from coronary artery plaques and acute formation of numerous thrombi, causing myocardial ischemia responses, and eventually the onset of unstable angina pectoris [3, 4]. Unstable angina pectoris can be stabilized through treatment, but it can also be accompanied by acute myocardial infarction and even sudden death. Therefore, it is necessary to select the most effective therapeutic tool for this condition [5, 6]. Rupture of coronary artery plaques is the main cause of unstable angina pectoris, which can cause inflammatory reactions and hyperlipidemia. Clinical treatment of unstable angina pectoris starts from the elimination of atherosis and plaque rupture to achieve remission and even full relief [7, 8].

Hemorheology includes whole blood specific viscosity [whole blood viscosity at high cut (BVH), whole blood viscosity at low cut (BVL)], erythrocyte aggregation (EA), plasma specific viscosity (PV), erythrocyte and platelet electrophoresis time (S), whole blood reduction specific viscosity (low-cut, high-cut), erythrocyte sedimentation rate (ESR), hematocrit (HCT), erythrocyte deformability (TK), fibrinogen (FIB)

and erythrocyte stiffness (IK). Among them, BVH, BVL, PV, EA and TK are the main indicators. BVH is mainly attributed to TK. BVH is high, TK and erythrocyte elasticity are weakened, and blood vessel walls are abnormal. BVL is mainly determined by EA, BVH, and BVL. The level of plasma viscosity is closely related to plasma proteins, especially FIB. EA can objectively reflect the degree of erythrocyte accumulation.

To date, statins used in elderly patients with unstable angina pectoris have been shown to reduce the proportion of atherosclerotic plaques and inflammatory cells, as well as prevent the activation of matrix metalloproteinase, effectively regulate blood lipids, and improve endothelium function [9-12]. Highly sensitive C-reactive protein (hs-CRP) is a commonly used nonspecific inflammatory response indicator, which can sensitively reflect the minor changes in the expression of serum CRP in patients. It is also selected to detect any inflammatory response caused by cardiovascular and cerebrovascular diseases. A high hs-CRP level indicates poor cardiovascular and cerebrovascular prognosis. Meanwhile, excessive recreation of interleukin-6 (IL-6), a common inflammatory factor in the body, may damage the vascular walls and accelerate the progression of angina pectoris by promoting the formation of thrombi and FIBs [13]. The cholesterol-lowering medication called statins, like Lipitor (atorvastatin) or Crestor (rosuvastatin), will regularly be given. These drugs have been found to decrease the rate of heart attack, death from coronary heart disease, need for myocardial revascularization, and stroke. Cholesterol-lowering therapy with rosuvastatin calcium tablets may improve coronary flow reserve in patients with UAP and hypercholesterolaemia. Hence, the purpose of this study was to explore the efficacy of different doses of rosuvastatin in the treatment of elderly patients with unstable angina pectoris, and to investigate the changes in hs-CRP and IL-6 levels related to the treatment.

Materials and methods

General materials

In this prospective study, a total of 106 elderly patients diagnosed with unstable angina pectoris who were admitted to our hospital from May 2016 to December 2020 were enrolled and were divided into group A (n=55) and group B (n=51). Under the same treatment of angina pectoris, patients in groups A and B were given 5 mg and 10 mg of rosuvastatin orally once every night, respectively. The included patients consisted of 54 males and 52 females, with a mean age of 72.14±11.72 years old and a BMI of 23.53±1.62 kg/m^2; including 72 cases of hypertension and 53 cases of diabetes.

Inclusion and exclusion criteria

All included patients were over 60 years of age, provided complete clinical data and complied with the diagnosis criteria of unstable angina pectoris in the *Guidelines for Cardiovascular Disease Prevention in China (2017)* [14]. However, some patients were excluded due to acute myocardial infarction, hypofunction of the heart and other organs, concurrent disorders of the blood or immune system, allergies to the drugs used in this study, or poor compliance. All patients and their family members signed the informed consent to participate in the study, and the study was approved by the ethics committee of Ganzhou People's Hospital (No. NCT02568321).

Test reagents and materials

Test reagents and materials included rosuvastatin (Nanjing CTTQ Pharmaceutical Co., Ltd., GYZ Zi No. H20080670), an automatic hemorheological analyzer (Chongqing Shaihang Technology Development Co., Ltd.), a blood coagulation detector [Qisheng (Shanghai) Medical Appliances Co., Ltd.], an automated optical analyzer (Jiangsu Sinnowa Medical Technology Co., Ltd.), and an ELISA kit (Wuhan Genemei Biotechnology Co., Ltd.).

Test methods

Treatment methods: Patients in Group A were treated with rosuvastatin at a smaller dose than those in group B. Specifically, group A was given routine drugs for antiplatelet aggregation-clopidogrel bisulfate tablets (J20180029, Sanofi Winthrop Industrie, China, 0.6 g/time), recovery of myocardial blood supply-isosorbide mononitrate tablets (H20065685, Qilu Pharmaceutical Co., Ltd., China, 0.5 mg/time), and regulation of blood pressure-irbesartan tablets (H20000513, Jiangsu Hengrui Pharmaceutical Co., Ltd., China, 0.15 g/time) and sitagliptin

Table 1. Comparison of general materials between the two groups

Group	Group A (n=55)	Group B (n=51)	χ^2/t	*P* value
Gender (n)			5.383	0.994
Male	28 (50.91)	26 (50.98)		
Female	27 (49.09)	25 (49.02)		
Age (y)	72.19±11.58	72.52±11.38	0.148	0.883
BMI (kg/m^2)	23.63±1.63	23.59±1.61	0.127	0.899
History of smoking (n)			<0.001	0.982
Yes	29 (52.73)	27 (52.94)		
No	26 (47.27)	24 (47.06)		
History of drinking alcohol (n)			<0.001	0.922
Yes	34 (61.82)	32 (62.75)		
No	21 (38.18)	19 (37.25)		
Hypertension (n)			0.071	0.789
Yes	38 (69.09)	34 (66.67)		
No	17 (30.91)	17 (33.33)		
Diabetes (n)			0.340	0.560
Yes	26 (47.27)	27 (52.94)		
No	29 (52.73)	24 (47.06)		
Angina pectoris parting (n)			0.067	0.967
Primary labor-type angina pectoris	31 (56.36)	30 (58.82)		
Deteriorated labor-type angina pectoris	17 (30.91)	15 (29.41)		
Postinfarction angina pectoris	7 (12.73)	6 (11.76)		
Angina pectoris grading (n)			0.297	0.862
Class I	32 (58.18)	29 (56.86)		
Class II	21 (38.18)	19 (37.25)		
Class III	2 (3.64)	3 (5.88)		

and metformin tablets (J20171012, Patheon Puerto Rico, Inc., US, 50 mg/time), and were orally administered with 5 mg of rosuvastatin (Allied Pharma Inc. Cat: 079161) every night for 3 consecutive months. Except for a higher dose of rosuvastatin at 10 mg, patients in group B received the same treatments as those in group A. In the process of treatment, both groups were strictly controlled in diet and healthy living habits. Meanwhile, patients with severe adverse reactions were withdrawn from the responsible drugs based on their conditions.

Detection methods: Fasting peripheral blood (3 ml) was extracted from patients in the morning before and after treatment. The blood was centrifuged at 3000 r/min for 6 min after standing for 20 min, and the separated plasma was placed at -80°C for further use. Moreover, BVL, BVH, PV, and ESR were detected with an automatic hemorheological analyzer. Coagulation indices such as prothrombin time (PT), activated partial thromboplastin time (APTT), and FIB were detected by coagulation detector. The antibodies IgG, IgA, and IgM were detected by immune turbidimetry. Finally, hs-CRP (cat: JYM1181Hu, Wuhan Genemei Biotechnology Co., Ltd.) and IL-6 (cat: JYM1942Hu, Wuhan Genemei Biotechnology Co., Ltd.) levels in serum were measured by ELISA in strict accordance with the kit instructions.

Observation indices

Primary outcome measurements: The changes of hemorheology, coagulation indices, and immune reaction indicators (hs-CRP, and IL-6 levels in serum) were observed and recorded in both groups before and after treatment. The adverse reactions were compared between two groups. The correlation between serum hs-CRP and IL-6 expression levels was analyzed.

Secondary outcome measurements: The treatment effects on angina pectoris were evaluated using a 12-lead ECG at resting state, while changes in clinical treatment indices were evaluated.

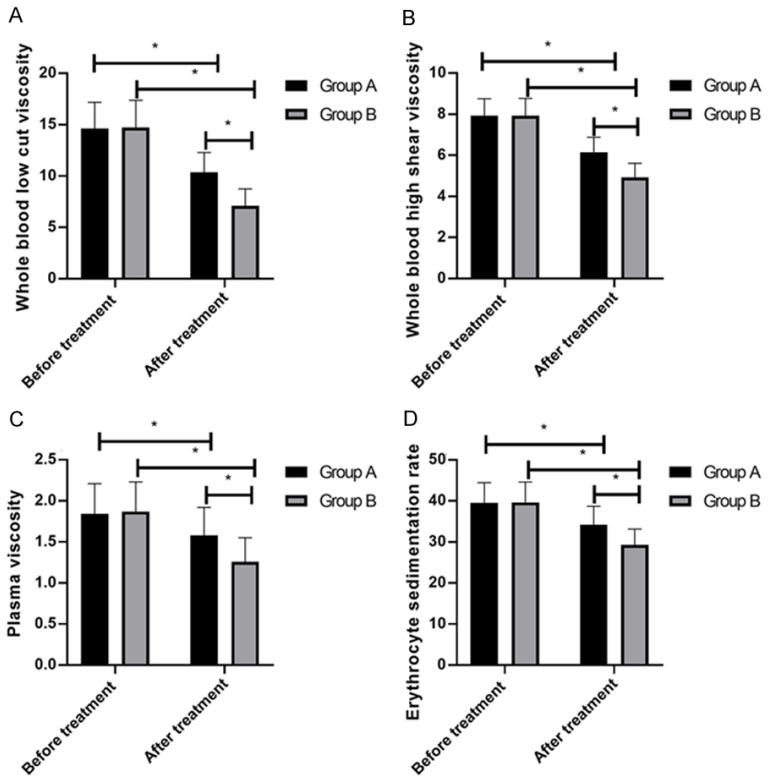

Figure 1. Comparison of changes in hemorheology before and after treatment between the two groups. After treatment, both groups achieved reductions in BVL (A), BVH (B), PV (C), and ESR (D), which were more significant in group B than in group A. Note: *represents $P<0.05$.

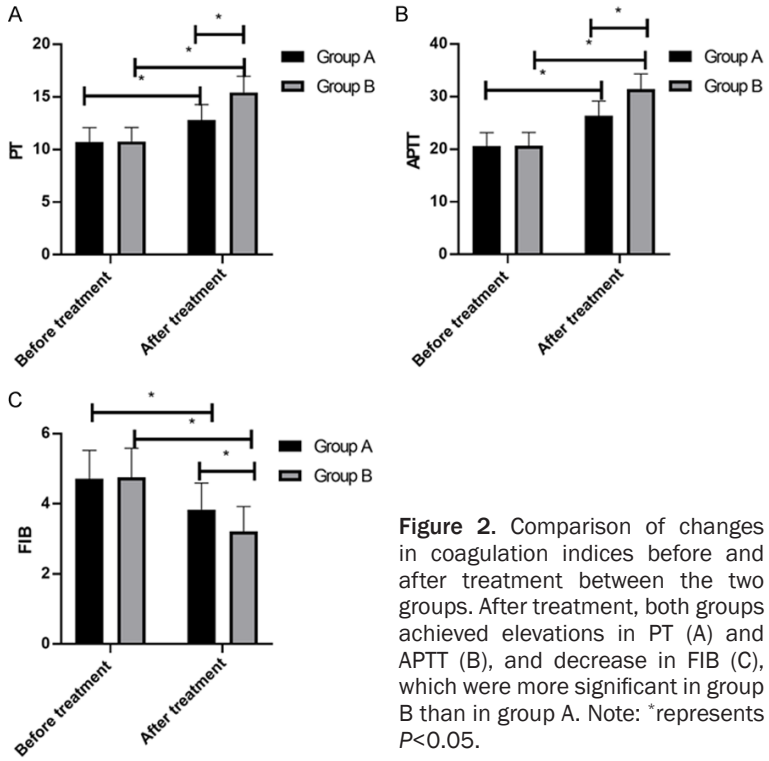

Figure 2. Comparison of changes in coagulation indices before and after treatment between the two groups. After treatment, both groups achieved elevations in PT (A) and APTT (B), and decrease in FIB (C), which were more significant in group B than in group A. Note: *represents $P<0.05$.

Statistical analysis

Statistical analysis was performed using the SPSS 19.0 (Beijing NDTimes Technology Co., Ltd.). Enumeration data were compared by χ^2 test; measurement data were expressed as mean ± standard deviation (mean ± SD) and were compared by *t* test for intergroup comparison, and results before and after treatment were compared in each group by paired *t* test. Correlative analysis was performed by Pearson analysis, and figures were drawn with Graphpad Prism 8. For all statistical comparisons, significance was defined as $P<0.05$.

Results

Comparison of general data between the two groups

The two groups had no statistical difference in gender, age, and histories of smoking as well as drinking alcohol ($P>0.05$, **Table 1**).

Comparison of changes in hemorheology, coagulation indices, and immune reaction before and after treatment between the two groups

No significant difference was observed in hemorheology before treatment ($P>0.05$). BVH, BVL, PV, and ESR decreased in both groups after treatment and the decrease was more significant in group B than in group A ($P<0.05$, **Figure 1**).

No significant difference was found in coagulation indices before treatment ($P>0.05$). After treatment, PT and APTT increased, while FIB decreased in both groups, and the changes were more significant in group B than in group A ($P<0.05$, **Figure 2**).

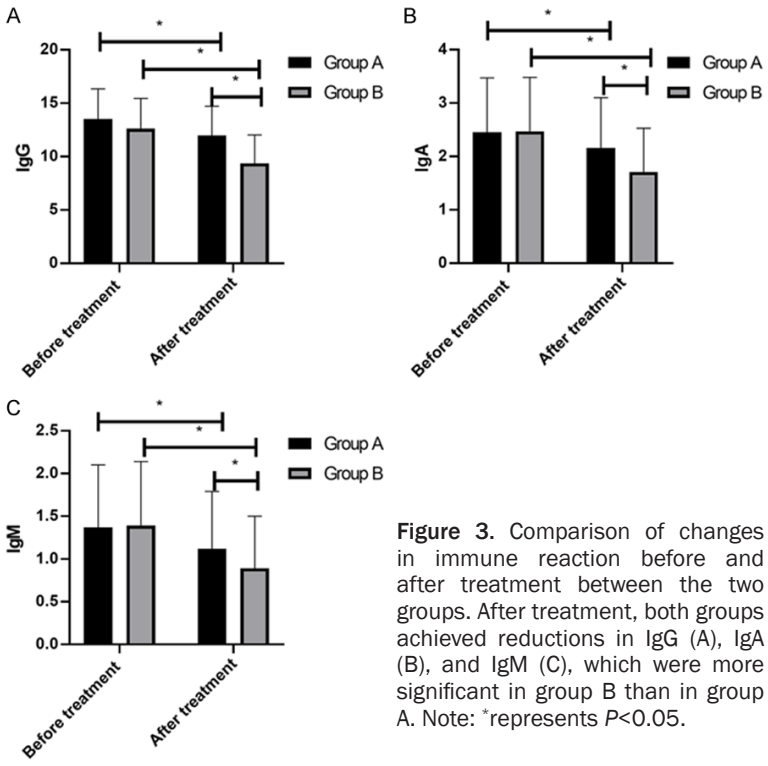

Figure 3. Comparison of changes in immune reaction before and after treatment between the two groups. After treatment, both groups achieved reductions in IgG (A), IgA (B), and IgM (C), which were more significant in group B than in group A. Note: *represents $P<0.05$.

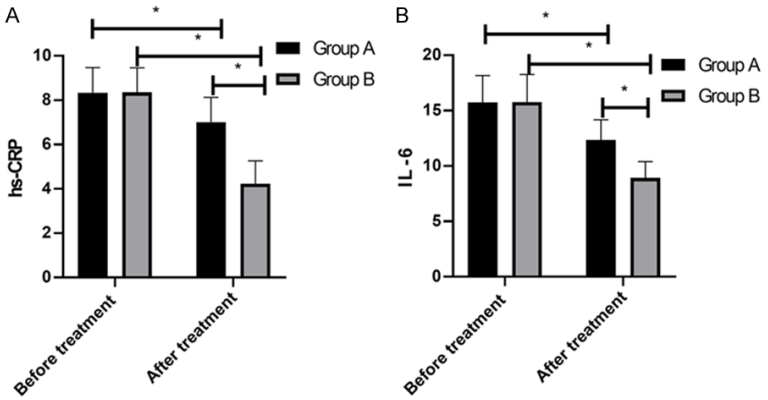

Figure 4. Comparison of serum hs-CRP and IL-6 levels before and after treatment between the two groups. After treatment, both groups achieved reductions in hs-CRP (A) and IL-6 (B), which were more significant in group B than in group A. Note: *represents $P<0.05$.

No significant difference was found in immune reaction before treatment ($P>0.05$). After treatment, immunoglobulin index decreased in both groups which was more significant in group B than in group A ($P<0.05$, **Figure 3**).

Comparison of serum hs-CRP and IL-6 levels before and after treatment between the two groups

No significant difference was found in serum hs-CRP and IL-6 levels before treatment ($P>0.05$). After treatment, the hs-CRP and IL-6 levels decreased in both groups, and the decrease was more significant in group B than in group A ($P<0.05$, **Figure 4**).

Analysis of the correlation between the hs-CRP and IL-6 levels in elderly patients with unstable angina pectoris

Pearson analysis showed that there was a positive correlation between the hs-CRP and IL-6 levels in elderly patients with unstable angina pectoris ($r=0.649$, $P<0.001$, **Figure 5**).

Comparison of changes in clinical indices and treatment efficacy indicated by ECG between the two groups

Group B was superior to group A in the onset times of myocardial ischemia and angina pectoris as well as the total duration of myocardial ischemia ($P<0.05$, **Table 2**). After treatment, group B yielded a better total effective rate indicated by ECG than group A ($P<0.05$, **Table 3**).

Comparison of the therapeutic effect and the incidence of adverse reactions after treatment between the two groups

After treatment, group B was superior to group A in the total effective rate of the therapeutic effect on angina pectoris ($P<0.05$, **Table 4**). There was no statistical difference in the incidence of adverse reactions between the two groups after treatment ($P>0.05$, **Table 5**).

Discussion

Unstable angina pectoris can be induced by living environment, emotional stimuli, and basic diseases affecting blood sugar or pressure [15], which is clinically manifested as pectoralgia, burning sensation, and increased heart rate. These symptoms may cause great dis-

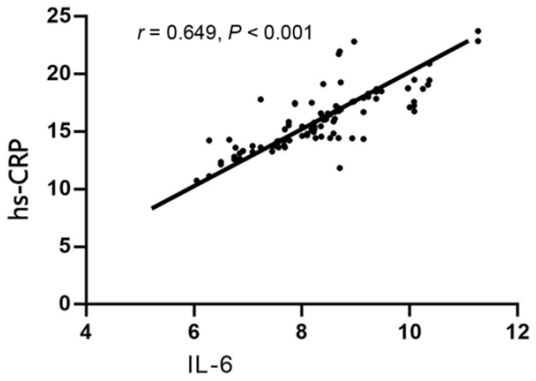

Figure 5. Analysis on the correlation between the hs-CRP and IL-6 levels in elderly patients with unstable angina pectoris. Pearson analysis demonstrated a positive correlation between the hs-CRP and IL-6 levels in elderly patients with unstable angina pectoris (r=0.649, P<0.001).

comfort in patients and affect their quality of life and well-being [16]. Elderly patients with unstable angina pectoris are most likely to have a worsened condition, and be accompanied by high-risk complications, such as sudden death and myocardial infarction, thereby threatening the safety of patients [17]. Statins work by inhibiting the apoptosis of myocardial cells through antioxidation. For instance, rosuvastatin selectively inhibits hydroxyglutaric reductase in liver cells as hydrophilic calcium hydroxylate with common medicinal dihydroxyheptenic acid groups. In the liver, rosuvastatin is highly selective and has an extended half-life as well as a low lipophilic and metabolic rate, thereby achieving a variety of functions, such as effective ventricular remodeling, atherosclerosis repair, lipid regulation, and vascular endothelial functions [18, 19]. The efficacy of rosuvastatin against angina pectoris is confirmed in clinical reports, but few reports focus on its dosage in this regard. In this study, the effects of different doses of rosuvastatin on the inflammatory reaction indices of hs-CRP and IL-6 in elderly patients with unstable angina pectoris were investigated in detail.

The hemorheological results in this study revealed that after treatment, BVH, BVL, PV, and ESR were reduced significantly in both groups as compared before treatment, and group B was considerably lower than group A. In some studies [20], abnormal lipid levels lead to increased blood viscosity and affected hemorheology, resulting in impaired myocardial cell function and insufficient blood supply. Rosuvastatin is the latest lipid-lowering statin whose application is well demonstrated in numerous studies involving patients whose lipid levels remained uncontrolled after diet regulation, weight loss, and exercise [21]. In addition, rosuvastatin has been proven effective in reducing cholesterol and C-LDL levels. Therefore, rosuvastatin can improve hemorheology in elderly patients with unstable angina pectoris by lowering lipid levels, with a better effect at a dose of 10 mg/day. Meanwhile, the analysis of coagulation functions showed that both groups with administration of 5 mg and 10 mg rosuvastatin achieved an increase in PT and APTT and a decrease in FIB after treatment, and such results were more significant in group B than in group A. According to a previous study [22], the hypercoagulative state of serum resulted in an elevated content of plasma plasminogen activators and prostacyclin, followed by a high possibility of thrombus formation and an increased incidence of angina pectoris due to thrombi. These facts support that rosuvastatin at a dose of 10 mg/day is more effective in regulating coagulation function than at 5 mg/day, effectively controlling the abnormal hemorheology and thrombi caused by the coagulation system dysfunction. In terms of immunologic functions, immunoglobulin indices decreased in both groups after treatment; such reduction was more significant in group B than in group A. The inflammatory reaction of angina pectoris is associated with most immunoglobulins as indices of immunologic function, considering that immunoglobulins can affect the release reaction of histamine, followed by the VSMC functions and platelet aggregation, leading to angiospasm and damage to the blood supply of patients with angiocardiopathy; as a result, such patients experience a poor immunologic function compared with those with strong immunologic function [23]. Accordingly, immunologic function determines hemorheology and coagulation function to a certain extent. During the course of onset, patients' immunity is one of the decisive factors of prognosis, and compared with a dose of 5 mg, 10 mg of rosuvastatin can achieve better immune protection and regulation in elderly patients with unstable angina pectoris, thereby contributing to the overall effective rate of recovery in the process of treatment. Further studies of the inflamma-

Table 2. Comparison of changes of clinical indices after treatment between the two groups

Group	Group A (n=55)	Group B (n=51)	*t*	*P* value
Onset times of myocardial ischemia (n)	6.85±1.03	3.24±0.82	19.860	<0.001
Onset times of angina pectoris (n)	4.64±0.84	2.15±0.68	16.690	<0.001
Total duration of myocardial ischemia (s)	31.52±3.35	18.58±2.84	21.370	<0.001

Table 3. Comparison of the treatment efficacy indicated by ECG after treatment between the two groups

Group	Group A (n=55)	Group B (n=51)	χ^2	*P* value
Markedly effective	37 (67.27)	38 (74.51)	-	-
Effective	11 (20.00)	12 (23.53)	-	-
Ineffective	7 (12.73)	1 (1.96)	-	-
Total effective rate	48 (87.27)	50 (98.04)	4.396	0.036

Table 4. Comparison of the therapeutic effect after treatment between the two groups

Group	Group A (n=55)	Group B (n=51)	χ^2	*P* value
Markedly effective	35 (63.64)	39 (76.47)	-	-
Effective	7 (12.73)	10 (19.61)	-	-
Ineffective	13 (23.64)	2 (3.92)	-	-
Total effective rate	42 (76.36)	49 (96.08)	8.466	0.004

Table 5. Comparison of the incidence of adverse reactions after treatment between the two groups

Group	Group A (n=55)	Group B (n=51)	χ^2	*P* value
Myolysis	1 (1.82)	0	-	-
Acute renal failure	1 (1.82)	1 (1.96)	-	-
Nausea and vomiting	2 (3.64)	1 (1.96)	-	-
Total incidence of adverse reactions	4 (7.27)	2 (3.92)	0.557	0.456

tory reaction indices of the two groups showed that after treatment, the hs-CRP and IL-6 levels decreased in both groups, and such decrease was more significant in group B than in group A. Meanwhile, according to the Pearson correlation analysis, a positive correlation was observed between the two factors in elderly patients with unstable angina pectoris (r= 0.649, P<0.001), indicating that inflammatory reactions may deteriorate in elderly patients with unstable angina pectoris, followed by an tendency of increased hs-CRP and IL-6 expression levels with the deterioration of the patients' conditions. Rosuvastatin administration is an effective way to control the inflammatory reaction in patients, especially at a dose of 10 mg. A previous study showed that [24] in elderly patients, the progression of unstable angina pectoris is similar to the chronic inflammatory reaction of cardiac muscle cells in which some cell factors were mutually induced and assisted each other in local plaques and continuously infiltrated, resulting in rupture; eventually, the disease progressed to a life-threatening situation. Furthermore, rosuvastatin can improve vascular endothelial function by promoting nitric oxide synthesis, and its nonspecific anti-inflammatory ability can inhibit the adhesion and activity of inflammatory cells [25]. In addition to the study results and literature findings mentioned above, the ability of rosuvastatin to improve hemorheology and coagulation function, its effects on thrombus formation, and its indirect contribution to enhancing anti-inflammatory ability have been demonstrated, especially at a dose of 10 mg. The study was further extended to include the efficacy and incidence of adverse reactions. In this instance, group B was better than group A in clinical indices, ECG results, and treatment efficacy against angina pectoris, but there was no statistical difference in adverse reactions after treatment. These findings are consistent with the previous conclusion that 10 mg of rosuvastatin had higher overall efficacy and anti-inflammatory ability without sacrificing the incidence of adverse reactions in medication compared to the 5 mg dose.

In conclusion, compared with low-dose rosuvastatin, high-dose rosuvastatin can improve patients' serum inflammatory factor level, coagulation function, and hemorheology more

effectively, with a higher optimal efficacy and lower onset frequency and duration of angina pectoris. Hence, based on the strict control of elderly patients for safe medication, it is clinically recommended to use high-dose rosuvastatin in the treatment of elderly patients with unstable angina pectoris in the initial stage to prevent acute myocardial infarction and improve the clinical treatment of cardiovascular disease. The mechanism of the rosuvastatin function may be associated with lesion regression in concert with LDL levels [26]. LDL-C enhances inflammation, which may be associated with multiple inflammation parameters like hs-CRP and IL-6 [27]. However, the study has some limitations. For instance, only hs-CRP and IL-6 were selected for study of the inflammatory reactions. Although these two inflammatory indices can represent most of the inflammatory reactions, they are not specific. Thus, additional inflammatory indices should be investigated to further prove the effectiveness of rosuvastatin and provide scientific data for clinical treatment.

Disclosure of conflict of interest

None.

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