EFFECTS OF ATORVASTATIN COMBINED WITH TRIMETAZIDINE ON THE COAGULATION INDEX, HEMORHEOLOGY, BLOOD LIPID, CYTOKINE LEVEL AND OXIDATIVE STRESS MARKERS IN PATIENTS WITH CORONARY HEART DISEASE

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ABSTRACT

Objective: *To investigate the effects of atorvastatin combined with trimetazidine on coagulation index, hemorheology, blood lipid, cytokine level and oxidative stress markers in patients with coronary heart disease.*

Methods: *90 patients with coronary heart disease admitted to our hospital from January 2017 to December 2017 were selected. According to different treatment methods, the patients were divided into control group (n=45) and observation group (n=45). All patients were treated with conventional therapy (vasodilator substance, oxygen inhalation, diuretics) after admission. The patients in the control group were given atorvastatin orally, 20 mg each time, once a day. On the basis of treatment in the control group, the observation group was given trimetazidine tablets orally, 20 mg each time, 3 times a day. Both groups were treated continuously for 3 months. The clinical efficacy and adverse reactions of the two groups were observed, and the coagulation indexes of the two groups: plasma plasminogen activating inhibitor 1 (PAI-1), tissue plasminogen activator (t-PA), von Willebrand factor (vWF), erythrocyte sedimentation rate, whole blood viscosity, plasma viscosity, low density lipoprotein cholesterol (LDL-C), glycerin trilaurate (TG), total cholesterol (TC), malondialdehyde (MDA), superoxide dismutase (SOD), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high sensitive C-reactive protein (hs-CRP) and tumor necrosis factor α (TNF-α) were compared.*

Results: *The effective rate of the observation group was 93.33%, which was significantly higher than that of the control group (P<0.05). After treatment, the levels PAI-1 and vWF of the two groups was remarkably lower than that before treatment, and t-PA level of the two groups was significantly higher than that before treatment (P<0.05). Moreover, PAI-1 and vWF levels of the patients in the observation group was markedly lower than that in the control group, and t-PA level in the observation group was obviously higher than that in the control group (P<0.05). After treatment, the whole blood viscosity, plasma viscosity and hematocrit of the two groups were significantly lower than those before treatment (P<0.05). Furthermore, the whole blood viscosity, plasma viscosity and hematocrit in the observation group were significantly lower than those in the control group (P < 0.05). After treatment, the levels of LDL-L, TG and TC in the two groups was remarkably lower than that before treatment (P<0.05) and LDL-L, TG and TC levels in the observation group was significantly lower than that in the control group (P<0.05). After treatment, the levels of NT-proBNP, hs-CRP and TNF-α in the two groups was markedly lower than that before treatment (P<0.05), and NT-proBNP, hs-CRP and TNF-α levels in the observation group was significantly lower than that in the control group (P<0.05). In addition, there were no serious adverse reactions in both groups.*

Conclusion: *Atorvastatin combined with trimetazidine is effective in the treatment of coronary heart disease with few adverse reactions. It can effectively improve the coagulation index, hemorheology, blood lipid level, decrease the level of NT-proBNP, hs-CRP, TNF-α, and play an anti-inflammatory role.*

Keywords: *Atorvastatin, trimetazidine, coronary heart disease, coagulation index, hemorheology, blood lipid, cytokines, oxidative stress.*

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Introduction

Coronary heart disease is a kind of heart disease caused by coronary atherosclerosis, which can lead to vascular stenosis or obstruction, myocardial ischemia, hypoxia or necrosis, which is easy to occur in the elderly population. The incidence of coronary heart disease is increasing year by year and tends to be younger[(1)]. Seasonal changes, emotional excitement, physical labor, satiety, smoking and drinking are all the causes of coronary heart disease. The clinical symptoms are chest tightness, dyspnea, chest pain, severe myocardial infarction or heart failure, and the clinical incidence and mortality are higher[(2)]. In the past, vasodilators, oxygen inhalation and diuretics were often used in the

treatment of coronary heart disease, but the pertinence was insufficient and the clinical effect was not ideal[3]. Therefore, it is very important to find a treatment method which can improve the clinical efficacy, improve the quality of life and reduce the mortality of patients. Atorvastatin is a drug that can reduce plasma cholesterol and lipoprotein levels and reduce low density lipoprotein production. It is often used clinically in the prevention and treatment of coronary heart disease and cerebral apoplexy[4]. Trimetazidine is a kind of myocardial protective drug which can promote myocardial metabolism, myocardial energy production and improve the balance of myocardial oxygen supply and demand. Its effect is slower than nitroglycerin, but the action lasts for a long time[5]. Both of the two drugs are effective in the treatment of hyperlipemia. Therefore, the purpose of this study was to investigate the effects of atorvastatin combined with trimetazidine on coagulation index, hemorheology, blood lipid, cytokine level and oxidative stress markers in patients with coronary heart disease.

Data and methods

General information

90 patients with coronary heart disease admitted to our hospital from January 2017 to December 2017 were selected. Inclusion criteria: All the patients met the diagnostic criteria of coronary heart disease in the guidelines for the prevention of cardiovascular diseases in China. Coronary heart disease was diagnosed by clinical examination. The patients had different degrees of chest tightness, chest pain, shortness of breath, palpitation and other symptoms. The patient agreed to participate in this study and signed an informed consent form. This study was approved by the hospital committee. Exclusion criteria: Exclude those allergic to atorvastatin, trimetazidine and other related drugs. Exclude patients with severe heart failure or cardiac insufficiency. Patients with malignant tumor and autoimmune disease are excluded. Those with severe heart, liver and kidney dysfunction were excluded. Pregnant and lactating women are excluded. Exclude patients with liver cirrhosis, bronchial asthma and other serious diseases. According to the different treatment methods, the patients were divided into control group and observation group. There are 45 patients in the control group, including 25 males and 20 females, with an average age of (56.78±3.33) years old and course of disease of (7.44±1.12) years. There are 45 patients in the control group, including 23 males and 22 females, with an average age of (57.22±3.42) years old and course of disease of (7.21±7.21) years. There was no significant difference in general data between the two groups (P>0.05).

Methods

All patients were treated with conventional therapy (vasodilator substance, oxygen inhalation, diuretics) after admission. The patients in the control group were given atorvastatin (Specification: 2mg per tablet; SFDA approval number: H20381408; Made by Pfizer Pharmaceutical Co., Ltd.) orally, 20 mg each time, once a day. On the basis of treatment in the control group, the observation group was given trimetazidine (Specification: 20mg per tablet; SFDA approval number: H21455465) tablets orally, 20 mg each time, 3 times a day. Both groups were treated continuously for 3 months.

Observation indexes

Before and after treatment, the peripheral venous blood of all patients was collected and centrifuged at 3000 r/min for 10 min. The supernatant was placed in the refrigerator at -20 °C for detection.

The clinical effects of the two groups of patients were compared.

Markedly effective:

After 3 months of treatment, dizziness, chest pain and other symptoms improved significantly, and after 7 days of withdrawal, angina pectoris did not occur or the number of episodes decreased by 80%.

Effective:

The clinical symptoms of the patients were relieved, and after 7 days of withdrawal, the frequency of angina pectoris decreased by 50% to 80%.

Ineffective:

There was no significant improvement or deterioration of clinical symptoms, and the frequency of angina pectoris decreased by less than 50% after 7 days of withdrawal.

$$\text{Total effective rate} = \frac{(\text{Markedly effective} + \text{effective})}{\text{total number of cases}} \times 100\%$$

The coagulation indexes of the two groups were measured by enzyme-linked immunosorbent assay (ELISA), such as plasminogen activator inhibitor 1 (PAI-1), tissue-type plasminogen activator (t-PA) and von Willebrand factor (vWF).

Erythrocyte sedimentation rate, whole blood viscosity and plasma viscosity were measured by automatic hemorheometer. The levels of low density lipoprotein cholesterol (LDL-C), triglyceride

(TG) and total cholesterol (TC) were measured by automatic biochemical instrument.

The changes of serum oxidative stress indexes malondialdehyde (MDA) and superoxide dismutase (SOD) were measured by enzyme-linked immunosorbent assay (ELISA).

Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of N-terminal B-type natriuretic peptide (NT-proBNP), high-sensitive C-reactive protein (hs-CRP) and tumor necrosis factor α (TNF-α) in the two groups of patients.

Adverse reactions were compared between the two groups.

Statistical method

SPSS 23.0 statistical software was used to process and analyze the data. The measurement data were described in the form of $\bar{x}\pm s$ and t test were used in the comparison between groups. The counting data was expressed as a percentage n (%) and the comparison between groups was performed by χ^2 test. P<0.05 indicated the difference was statistically significant.

Results

Comparison of clinical effects between the two groups

As shown in table 1, the effective rate of the observation group was 93.33%, which was significantly higher than that of the control group (P<0.05).

Groups	n	Markedly effective	Effective	Ineffective	Total effective rate
Control group	45	20(44.44)	22(48.89)	3(6.67)	42(93.33)
Observation group	45	13(28.89)	20(44.44)	12(26.67)	33(73.33)
χ^2					6.480
P					0.011

Table. 1: Comparison of clinical effects between the two groups (n (%)).

Comparison of coagulation indexes between the two groups

After treatment, the levels PAI-1 and vWF of the two groups was remarkably lower than that before treatment, and t-PA level of the two groups was significantly higher than that before treatment (P < 0.05). Moreover, PAI-1 and vWF levels of the patients in the observation group was markedly lower than that in the control group, and t-PA level in the observation group was obviously higher than that in the control group (P < 0.05). The results were shown in table 2.

Groups	Time	PAI-1 (U/ml)	vWF (%)	t-PA (U/ml)
Control group	Before treatment	1.01±0.36	189.63±9.82	0.26±0.02
	After treatment	0.92±0.21[a]	179.91±7.91[a]	0.34±0.04[a]
Observation group	Before treatment	1.23±0.23	188.56±9.56	0.23±0.03
	After treatment	0.79±0.21[ab]	161.31±7.91[ab]	0.37±0.05[ab]

Table. 2: Comparison of coagulation indexes between the two groups ($\bar{x}\pm s$).

Note: Compared with before treatment, [a]P<0.05; and compared with control group after treatment, [b]P<0.05.

Comparison of hemorheology between the two groups

After treatment, the whole blood viscosity, plasma viscosity and hematocrit of the two groups were significantly lower than those before treatment (P<0.05). Furthermore, the whole blood viscosity, plasma viscosity and hematocrit in the observation group were significantly lower than those in the control group (P<0.05). The results were shown in table 3.

Groups	Time	Whole blood viscosity(mPa/s)		Plasma viscosity (mPa/s)	Hematocrit (%)
		High shear situation	Low shear situation		
Control group	Before treatment	6.90±0.78	11.98±1.32	1.91±0.33	56.98±3.78
	After treatment	5.93±0.65[a]	10.26±1.26[a]	1.72±0.37[a]	47.76±3.71[a]
Observation group	Before treatment	7.25±0.72	11.71±1.31	2.08±0.36	57.11±3.41
	After treatment	5.22±0.62[ab]	8.14±1.23[ab]	1.13±0.32[ab]	40.45±3.39[ab]

Table. 3: Comparison of hemorheology between the two groups ($\bar{x}\pm s$).

Note: Compared with before treatment, aP<0.05; and compared with control group after treatment, bP<0.05.

Comparison of blood lipid levels between the two groups

After treatment, the levels of LDL-L, TG and TC in the two groups was remarkably lower than that before treatment (P<0.05) and LDL-L, TG and TC levels in the observation group was significantly lower than that in the control group (P<0.05). The results were shown in table 4.

Groups	Time	LDL-C (mmol/L)	TG (mmol/L)	TC (mmol/L)
Control group	Before treatment	2.81±0.56	2.45±0.52	4.98±0.54
	After treatment	2.34±0.51[a]	1.93±0.49[a]	3.49±0.46[a]
Observation group	Before treatment	2.87±0.61	2.53±0.53	4.84±0.43
	After treatment	1.64±0.44[ab]	1.52±0.43[ab]	2.65±0.43[ab]

Table. 4: Comparison of blood lipid levels between the two groups ($\bar{x}\pm s$).

Note: Compared with before treatment, [a]P<0.05; and compared with control group after treatment, [b]P<0.05.

Comparison of cytokine levels between the two groups

After treatment, the levels of NT-proBNP, hs-CRP and TNF-α in the two groups was markedly lower than that before treatment (P<0.05), and NT-proBNP, hs-CRP and TNF-α levels in the observation group was significantly lower than that in the control group (P<0.05). The results were shown in table 5.

Groups	Time	NT-proBNP (pg/mL)	hs-CRP (mg/mL)	TNF-α (ng/mL)
Control group	Before treatment	3825.68±341.34	57.54±6.26	261.59±77.76
	After treatment	3353.13±312.69[a]	20.13±2.21[a]	96.84±21.16[a]
Observation group	Before treatment	3866.04±358.34	56.93±6.85	261.64±76.61
	After treatment	1903.15±190.78[ab]	8.45±1.48[ab]	178.43±38.55[ab]

Table. 5: Comparison of cytokine levels between the two groups ($\bar{x}\pm s$).

Note: Compared with before treatment, [a]P<0.05; and compared with control group after treatment, [b]P<0.05.

Comparison of oxidative stress indexes between the two groups

After treatment, the level of MDA in both groups was significantly lower than that before treatment, and the level of SOD was significantly higher than that before treatment (P<0.05). Moreover, the level of MDA in the observation group was markedly lower than that in the control group, and the level of SOD in the observation group was obviously higher than that in the control group (P<0.05). The results were shown in table 6.

Groups	MDA (μmol/mL)		*T*	*P*	SOD (U/mL)		*t*	*P*
	Before treatment	After treatment			Before treatment	After treatment		
Control group	12.25± 3.75	9.93± 2.67	3.381	0.001	60.24± 16.16	81.72± 19.46	5.697	*P*<0.001
Observation group	12.49± 4.83	4.76± 1.71	10.120	*P*<0.001	61.32± 12.74	112.27± 24.52	12.369	*P*<0.001
t	0.263	10.938			0.352	6.547		
P	0.793	*P*<0.001			0.725	*P*<0.001		

Table. 6: Comparison of oxidative stress indexes between the two groups ($\bar{x}\pm s$).

Comparison of adverse reactions between the two groups

There were no serious adverse reactions in both groups.

Discussion

Clinically, patients with coronary heart disease are usually treated with vasodilators and diuretics on the basis of improving their lifestyle and diet. However, most patients have poor prognosis and are prone to recurrent attacks. Both trimetazidine and atorvastatin belong to statins. Atorvastatin is commonly used in clinical treatment of coronary heart disease and widely used in hypercholesterol and coronary heart disease. Atorvastatin can reduce blood lipid and anti-inflammation by inhibiting the synthesis of LDL-C, reducing the content of plasma fibrin, and then regulating the level of blood lipid[6]. Atorvastatin can inhibit the formation of atherosclerotic plaques, prevent atherosclerosis and protect blood vessels[7]. Trimetazidine can inhibit free fatty acid metabolism and free radical formation, inhibit platelet aggregation, and then reduce blood viscosity[8]. The results in this study showed that the effective rate of the observation group was 93.33%, which was significantly higher than that of the control group (P<0.05). Moreover, there were no serious adverse reactions in both groups. The PAI-1 and vWF levels of the observation group was significantly lower than that of the control group, and the t-PA of the observation group was significantly higher than that of the control group (P<0.05). It is suggested that atorvastatin combined with trimetazidine has significant clinical effect and few adverse reactions. Coagulation index can be used as an important index to evaluate the prognosis of patients with coronary heart disease.

Clinical studies have shown that patients with coronary heart disease are usually accompanied by abnormal blood lipidemia, hyperfibrinogenemia and abnormal blood rheology[9]. The patient's blood is in a state of high viscosity or hypercoagulation, easy to form thrombus, which in turn leads to coronary artery stenosis or obstruction. Therefore, the patient's condition, especially the LDL-C level, can be improved clinically by improving the level of blood lipid and hemorheology[10]. Statins have gradually developed from lowering cholesterol to one of the important drugs for the prevention and treatment of cardiovascular and cerebrovascular diseases, which has a good effect on improving hemorheology[11]. Clinical studies have shown that trimetazidine can improve cardiomyocyte metabolism, relieve chest pain, palpitation and other clinical symptoms[12]. The results in this study showed that the whole blood viscosity, plasma viscosity

and hematocrit in the observation group were significantly lower than those in the control group (P<0.05). The level of LDL-L, TG and TC in the observation group was significantly lower than that in the control group (P<0.05). These results indicated that atorvastatin combined with trimetazidine could effectively enhance the efficacy, improve the level of blood lipid and hemorheology, and stabilize the condition. Clinical studies have shown that the occurrence and development of coronary heart disease is closely related to oxidative stress.

SOD is an antioxidant enzyme that can reflect the ability of antioxidant free radicals and scavenging oxygen free radicals, and evaluate the degree of lipid peroxide. By measuring the level of SOD in patients, it can indirectly reflect the damage degree of oxygen free radicals to the body[13]. When a large amount of oxygen free radicals produced by myocardial ischemia are combined with the side chains of the unsaturated fatty acid in the membrane, the level of SOD is reduced, which leads to a change of the membrane structure of the cardiac muscle cells, thereby causing the myocardial injury of the coronary heart disease patients. MDA is an important product of membrane lipid peroxide metabolism, which can indirectly reflect the rate of lipid peroxide and the degree of oxidative injury. The more serious tissue damage is, the higher the content of MDA is (14). In this study, the results showed that the level of MDA in the observation group was significantly lower than that in the control group, and the level of SOD in the observation group was remarkably higher than that in the control group (P<0.05). It is suggested that atorvastatin combined with trimetazidine could significantly improve the oxidative stress response of patients, play a common antioxidant role. NT-proBNP can reflect the condition of heart failure and evaluate the degree of cardiac function damage[15]. Hs-CRP is an important factor affecting the occurrence and development of coronary heart disease and an important index of nonspecific inflammatory response. TNF-α is an important inflammatory factor that can promote cell proliferation and differentiation and participate in the pathological injury of some autoimmune diseases. The results in this study showed that the level of NT-proBNP, hs-CRP and TNF-α in the observation group was significantly lower than that in the control group, indicating that atorvastatin combined with trimetazide obviously reduced NTproBNP, hsCRP and TNF-α levels and had anti-inflammatory effects.

In conclusion, atorvastatin combined with trimetazidine is effective in the treatment of coronary heart disease with few adverse reactions, which can effectively improve the coagulation index, hemorheology, blood lipid level and decrease the level of NT-proBNP, hs-CRP and TNF-α, and play an anti-inflammatory role.

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