EFFECTS OF ATORVASTATIN COMBINED WITH TRIMETAZIDINE ON CARDIAC FUNCTION AND SERUM NT-PRO BNP AND HS-CRP IN CORONARY HEART DISEASE PATIENTS WITH CHRONIC HEART FAILURE

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ABSTRACT

Objective: To investigate the clinical efficacy of atorvastatin combined with trimetazidine in the treatment of chronic heart failure in patients with coronary heart disease and to evaluate the effects of the treatment regimen on cardiac function and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitive C-reaction protein (hs-CRP) content.

Methods: A total of 120 coronary heart disease patients with chronic heart failure from June 2016 to May 2017 were selected. The patients were randomly divided into two groups, including the atorvastatin group, in which the patients were given additional atorvastatin drug intervention (20 mg/d), and the combined treatment group, in which, the patients were treated with trimetazidine three times a day (20 mg/d). The clinical data were recorded and analyzed. By comparing the improvement in palpitation, chest distress and angina pectoris and the improvement in cardiac function in the two groups, the curative effect of chronic heart failure in patients with coronary heart disease was evaluated. Moreover, the differences of serum NT-pro BNP, hs-CRP and blood lipid levels between the two groups were analyzed.

Results: After 4 weeks of treatment, the improvement in palpitation, chest distress and angina pectoris in the combined treatment group was significantly higher than that in the atorvastatin group, and the difference was statistically significant (P<0.05). The levels of serum NT-pro BNP, hs-CRP and blood lipid levels in the combined treatment group were significantly lower than those in the atorvastatin group, and the difference was statistically significant (P<0.05).

Conclusion: Atorvastatin combined with trimetazidine significantly improved chronic heart failure and significantly reduced serum NT-pro BNP and hs-CRP levels in patients with coronary heart disease.

Keywords: atorvastatin, trimetazidine, coronary heart disease, chronic heart failure, NT-pro BNP, hs-CRP.

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Introduction

Chronic heart failure is the most common clinical symptom of coronary heart disease. Its clinical manifestation is cardiac insufficiency, which mainly refers to the clinical syndrome characterized by left ventricular systolic and/or diastolic insufficiency, decreased operating capacity and neuroendocrine activation(1). However, chronic heart failure in coronary heart disease is often associated with hyperlipidemia, which is mainly due to a significant increase in total cholesterol and triglyceride levels in the blood, often accompanied by a decrease in high-density lipoprotein cholesterol and an increase in low-density lipoprotein cholesterol. Total cholesterol, triglyceride and low-density lipoprotein cholesterol are important factors in the development of chronic heart failure in coronary heart disease patients(2). Currently, there are many kinds of routine drugs and regimens for the treatment of chronic heart failure in coronary heart disease patients, but none of them can completely prevent chronic heart failure(3).
In recent years, according to the latest research reports, statins have had a significant effect on regulating blood lipids to effectively reduce the incidence of chronic heart failure and hospitalization in patients with coronary heart disease. As an inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, atorvastatin can effectively inhibit the synthesis of cholesterol and reduce the content of total cholesterol and low-density lipoprotein cholesterol in blood(4-5).

Trimetazidine is a powerful anti-angina drug that promotes myocardial cell function and metabolism, increases the ejection fraction of the left ventricle, and enhances the systolic function of the heart by reducing vascular resistance and increasing coronary blood flow. It plays an important role in the treatment of coronary heart disease patients with chronic heart failure(6).

In addition, several studies have shown that serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitive C-reaction protein (hs-CRP) levels are strongly associated with left ventricular function, which is an important indicator of heart failure and prognosis(7). In this study, atorvastatin combined with trimetazidine was used to treat coronary heart disease patients with chronic heart failure.

Data and methods

Clinical data

A total of 120 coronary heart disease patients with chronic heart failure diagnosed in our hospital from June 2016 to May 2017 were selected, including 60 males and 60 females, aged 55-75, with an average age of 65.71 ± 10.33 years old. According to the cardiac function classification of the New York Heart Association (NYHA)(8), there were 85 patients with cardiac function less than grade III and 45 patients with cardiac function grade IV. Inclusion criteria: The selected patients met the criteria for the diagnosis and treatment of chronic heart failure.

Exclusion criteria:

- Subjects who were given statins or trimetazidine before admission;
- Subjects with tumors;
- Subjects with severe infection;
- Subjects with severe liver and kidney insufficiency;
- Subjects who were allergic to statins;
- Subjects with stroke;
- Subjects with acute heart failure.

Therapeutic method

The selected patients were randomly divided into two groups: the atorvastatin group and the combined treatment group, with 60 patients in each group. The cardiac function was measured by color Doppler ultrasound in each group, the signs and symptoms of the patients were recorded, and the biochemical parameters, including blood lipid, blood glucose and liver and kidney function, were measured. Patients were treated with a routine heart failure regimen, including diuretics, angiotensin inhibitor, aldosterone receptor inhibitor and β receptor inhibitor. On the basis of the basic treatment, patients in the atorvastatin group were given additional atorvastatin drug intervention treatment (Lipitor, Pfizer Pharmaceutical Co., Ltd., 20 mg/d). The combined treatment group was treated with trimetazidine (Vasorel, France Servier Pharmaceutical Co., Ltd., 20 mg/d, three times a day) on the basis of the atorvastatin regimen. The duration of treatment in both groups was 4 weeks(9).

Curative effect determination method

According to the grading criteria of cardiac function, it was divided into three levels: significant effects, that is, within the normal range of activity, and palpitation, chest distress and angina pectoris showed obvious improvement; effective, that is, within the normal range of activity, and palpitations, chest distress and angina pectoris improved; invalid, namely, that the physical activity was significantly restricted and palpitations, chest distress and angina pectoris did not improve or worsened.

Cardiac function test method

The heart function was detected by a color Doppler ultrasound diagnostic instrument in each group. The probe frequency of supersonic instrument was 2.5 MHz. The left ventricular internal dimension-diastole (LVIDd), left ventricular internal dimension in systole (LVIDs) and fractional shortening (FS) were measured in the long axis section of the patient’s left ventricle of the heart. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were measured by the modified Simpson method.
Collection and detection method of serum samples

Blood was collected from all the patients in each group on admission and 4 weeks after treatment. The requirements for blood collection were as follows: in the morning, the patients had an empty stomach for 12 hours or more and rested for 10-15 min; then, 2 mL of peripheral venous blood was collected. The samples were anticoagulated with heparin sodium. Within 30 min, the collected blood was centrifuged at 2000 rpm/min for 10 min and the upper serum was preserved at -80 °C. The content of Nt-pro BNP in serum was determined by the electrochemiluminescence method (Roche 170 immune analyzer), and the content of Hs-CRP in serum was determined by latex-enhanced immuno-projection turbidimetry (Roche P800 automatic biochemical analyzer).

Determination of blood lipid level

The blood lipid parameters were measured at admission and after treatment in both groups. Total cholesterol (TC) was determined by the endpoint method, triglyceride (TG) was measured by the oxidase method, and high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined by direct determination methods.

Six-minute walking test

The patients in each group were tested with a 6 min walking test after 4 weeks of treatment. The patient walked back and forth as fast as possible in a 50 m corridor, and the maximum walking distance was recorded within 6 min. Prior to the trial, the patient was informed of the method, purpose and requirements of the trial. At the end of the corridor, the medical staff recorded the walking distance of the patients, and when they observed the patient's angina pectoris, dyspnea, dizziness, obvious fatigue, sweating, syncope and other symptoms, the test was stopped immediately. The medical staff encouraged patients while they were walking and informed patients of the walking time at intervals of 2 min, and the maximum test time was 6 min. The 12-lead electrocardiogram was measured before and after the trial, and the results were compared and analyzed.

Statistical method

SPSS 19.0 statistical software was used to process and analyze the data. The count data were expressed as a percentage. Comparisons between groups were performed by the \( \chi^2 \) test, measurement data were described in the form of \( \bar{x} \pm s \), and the t test was used in the comparison between groups.

Results

Comparison of the general clinical data of patients

There were no significant differences in general clinical data, including age, sex, heart function, blood lipid level, history of cardiovascular disease and other data between the two groups (\( P > 0.05 \)). The two groups of patients in this test were comparable as shown in table 1 for specific information (table 1).

<table>
<thead>
<tr>
<th>Groups</th>
<th>male</th>
<th>Average age (years)</th>
<th>Cardiac function grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin group</td>
<td>29(60)</td>
<td>64.87 ± 9.18</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>31(60)</td>
<td>66.34 ± 9.43</td>
<td>25 (60)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Body mass index</th>
<th>Course of disease (years)</th>
<th>Systolic pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin group</td>
<td>23.44 ± 3.12</td>
<td>8.67 ± 2.34</td>
<td>118.34 ± 20.02</td>
</tr>
<tr>
<td>Combined treatment</td>
<td>23.34 ± 4.11</td>
<td>8.12 ± 2.14</td>
<td>120.01 ± 20.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total cholesterol (mmol/L)</th>
<th>Triglyceride (mmol/L)</th>
<th>Fasting Bloodglucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin group</td>
<td>6.32 ± 1.33</td>
<td>2.40 ± 0.99</td>
<td>5.63 ± 1.33</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>6.31 ± 1.31</td>
<td>2.40 ± 0.97</td>
<td>5.64 ± 1.45</td>
</tr>
</tbody>
</table>

Table 1: General clinical data of patients.

Comparison of the curative effect between the two groups

To evaluate the curative effect of the two groups, the total effective rate of the combined treatment group was significantly higher compared with that of the atorvastatin group, and the difference was statistically significant (\( P<0.05 \)). The specific information is shown in table 2.
Comparison of cardiac function indexes between the two groups

At admission, there were no significant differences in cardiac function indexes, including LVIDd, LVIDs, FS and LVEF, between the two groups (P > 0.05). The cardiac function indexes of the two groups were significantly improved after different treatments compared with the cardiac function indexes at admission (P < 0.05). Compared with the treatment results of the atorvastatin group, the improvement of cardiac function in the combined treatment group was better than that in atorvastatin group (P < 0.05). The specific information is shown in table 3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>LVIDd (mm)</th>
<th>LVIDs (mm)</th>
<th>FS (%)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>On treatment</td>
<td>On admission</td>
<td>After treatment</td>
<td>On admission</td>
</tr>
<tr>
<td>Atorvastatin group</td>
<td>64.12±6.23</td>
<td>56.22±3.78*</td>
<td>54.12±6.12</td>
<td>46.67±4.49*</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>64.56±6.99</td>
<td>51.21±3.54*#</td>
<td>52.67±6.87</td>
<td>40.22±4.55*#</td>
</tr>
</tbody>
</table>

Table 3: Improvement of cardiac function in both groups before and after treatment (n = 30, x̅±s).
* compared with admission, P < 0.05; # compared with the atorvastatin group after treatment, P < 0.05.

Comparison of serum Nt-proBNP and hs-CRP between the two groups

The levels of Nt-proBNP and Hs-CRP in serum of the two groups were measured at admission, and there was no significant difference between the two groups (P > 0.05). The blood lipid indexes of TC, TG and LDL-C in the two groups after different treatment regimens were significantly lower than those at admission (P < 0.05). Compared with that in the atorvastatin group, the decrease in Nt-proBNP and Hs-CRP in the combined treatment group was significant relative to the atorvastatin group (P < 0.05). The specific information is shown in table 4.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nt-proBNP (pg/mL)</th>
<th>Hs-CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>On treatment</td>
<td>On admission</td>
</tr>
<tr>
<td>Atorvastatin group</td>
<td>1255.34±247.25</td>
<td>954.23±166.23*</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>1233.93±287.37</td>
<td>587.22±154.12*</td>
</tr>
</tbody>
</table>

Table 4: Levels of Nt-proBNP and Hs-CRP in both groups before and after treatment (n = 30, x̅±s).
* compared with admission, P < 0.05; # compared with the atorvastatin group after treatment, P < 0.05.

Comparison of 6-min walking distance between two groups

After admission, the walking distance of patients in the two groups was measured at 6 min, and there was no significant difference in the walking distance between the two groups (P > 0.05). The walking distance in the two groups after different treatment regimens was significantly increased relative to that at admission (P < 0.05). Compared with the atorvastatin group, the walking distance at 6 min in the combined treatment group was higher than that in the atorvastatin group, and the difference was statistically significant (P < 0.05). The specific information is shown in table 6.

Discussion

Chronic heart failure (CHF) in coronary heart disease (CHD) patients is the change in myocardial structure and function caused by myocardial injury.
The ventricular pumping capacity decreases, and its pathogenesis includes decreased cardiac function in ventricular cardiomyocytes. Recent studies have shown that myocardial ischemia leads to the dysmetabolism of cardiac myocytes, myocardial fibrosis and ventricular remodeling, which are important factors in chronic heart failure(10). Previous studies have indicated that trimetazidine blocks part of the process of β-oxidation of free fatty acids, so the substrate of cardiac myocyte metabolism is transformed from fatty acids to glucose. This can make more efficient use of oxygen to produce more adenosine triphosphate, which improves myocardial function and myocardial ischemia. In addition, trimetazidine can effectively enhance cardiac function indexes such as FS and LVEF in the process of chronic heart failure. This study shows that the combination of atorvastatin and trimetazidine can elevate the LVIDd, LVIDs, FS and LVEF of patients more effectively, thus improving the myocardial function and alleviate the development of chronic heart failure in patients with coronary heart disease(11).

In the course of the occurrence of chronic heart failure in patients with coronary heart disease, various endogenous neuroendocrine and cytokines are involved. Brain natriuretic peptide (BNP) was mainly synthesized and secreted by cardiomyocytes, and active BNP and the inactive metabolite Nt-proBNP are produced by cleavage. Elevated levels of Nt-proBNP in the circulating blood indicate poor prognosis in patients(12).

Hypersensitive C-reactive protein (hs-CRP) is a nonspecific marker of systemic inflammatory response synthesized by the liver. It plays a protective role in the immune process of the organism, but in the process of chronic heart failure in patients with coronary heart disease, the concentration of hs-CRP in peripheral blood was significantly increased, which is a risk factor for the disease. This study demonstrated that atorvastatin combined with trimetazidine could effectively reduce the levels of Nt-proBNP and hs-CRP in serum of patients. These results suggest that the combination of trimetazidine and atorvastatin can effectively improve the prognosis of chronic heart failure and reduce the risk of cardiovascular disease in patients with coronary heart disease(13).

Coronary heart disease as a common clinical cardiovascular disease is one of the common causes of death of patients. The pathological mechanism of coronary heart disease is vascular atherosclerosis. Reducing the incidence of coronary heart disease can fundamentally solve the occurrence of chronic heart failure. The increase of blood lipid levels is also an important factor for angina pectoris in patients with coronary heart disease(14). Hyperlipidemia is mainly due to a significant increase of the levels of TC and TG in the blood, often accompanied by a decrease of HDL-C and an increase of LDL-C. Among them, TC, LDL-C and TG are important factors for the development of coronary heart disease. Atorvastatincalcium can effectively inhibit the synthesis of endogenous cholesterol, regulate blood lipid levels, and reduce TC and LDL-C levels in the blood of patients. The mechanism of atorvastatinis the specific inhibition of HMG - CoA activity, reducing the incidence of coronary heart disease and fundamentally solving the occurrence of chronic heart failure in patients with coronary heart disease(15).

In sum, coronary heart failure is caused by the occurrence of coronary heart disease, which leads to myocardial injury. Atorvastatin combined with trimetazidine can effectively restore cardiac

<table>
<thead>
<tr>
<th>Groups</th>
<th>TC (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
<th>LDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On admission</td>
<td>After treatment</td>
<td>On admission</td>
<td>After treatment</td>
</tr>
<tr>
<td>Atorvastatin group</td>
<td>6.32 ± 1.33</td>
<td>4.45 ± 0.67*</td>
<td>1.67 ± 0.55*</td>
<td>1.47 ± 0.66</td>
</tr>
<tr>
<td>Combined treatment</td>
<td>6.31 ± 1.31</td>
<td>3.67 ± 0.25*</td>
<td>3.75 ± 0.89</td>
<td>2.23 ± 0.66*</td>
</tr>
</tbody>
</table>

Table 5: Levels of blood lipid indexes in both groups before and after treatment (n = 30, x̅±s).

* compared with admission, P < 0.05; # compared with the atorvastatin group after treatment, P < 0.05.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nt-proBNP(pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On admission</td>
</tr>
<tr>
<td>Atorvastatin group</td>
<td>186.54 ± 37.27</td>
</tr>
<tr>
<td>Combined treatment</td>
<td>184.99 ± 37.16</td>
</tr>
</tbody>
</table>

Table 6: Changes of walking distance at 6 min in two groups (n = 30, x̅±s)

* compared with admission, P < 0.05; # compared with the atorvastatin group after treatment, P < 0.05.
function and reduce the levels of Nt-proBNP and hs-CRP in the blood, thus reducing the incidence of chronic heart failure. The 6 min walking test was used to judge the state of cardiac function and exercise tolerance to improve the patient’s exercise tolerance and reduce the incidence of clinical adverse events.

References

1) Mishra S, Mohan JC, Nair T, Chopra VK, Harikrishnan S. Management protocols for chronic heart failure in India. Indian Heart J 2018; 70: 105-127.


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