Effect of trimetazidine combined with bisoprolol on the cardiac function, ventricular remodeling and neuroendocrine factors in patients with chronic heart failure

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ABSTRACT

Objective: To study the effect of trimetazidine combined with bisoprolol on the cardiac function, ventricular remodeling and neuroendocrine factors in patients with chronic heart failure. Methods: A total of 52 patients with chronic heart failure who were treated in our hospital between January 2012 and November 2015 were collected and divided into the control group (n=26) who received bisoprolol therapy and the observation group (n=26) who received trimetazidine combined with bisoprolol therapy according to the double-blind randomized control method, and both groups were treated for 3 months. Before treatment and after 3 months of treatment, cardiac color Doppler diasonograph was used to determine the levels of cardiac function parameters and ventricular remodeling parameters, and RIA method was used to determine the levels if peripheral blood neuroendocrine factors. Results: Before treatment, the differences in cardiac function, ventricular remodeling and neuroendocrine factor levels were not statistically significant between two groups of patients. After 3 months of treatment, cardiac function parameters LVEDd and LVESD levels of observation group were lower than those of control group while LVEF level was higher than that of control group, and ventricular remodeling parameters LVPWT, IVSS, PWD, PWS and LVMI levels were lower than those of control group; peripheral blood neuroendocrine factors NE, ALD, Ang II, ANP and ET contents of observation group were lower than those of control group. Conclusion: Trimetazidine combined with bisoprolol can optimize the cardiac function, suppress the ventricular remodeling process and regulate the neuroendocrine factor secretion in patients with chronic heart failure, and it contributes to the patients’ overall optimization.

1. Introduction

Chronic heart failure (CHF) is the severe myocardial damage caused by myocardial infarction, cardiomyopathy, inflammation and so on, it will finally lead to the decrease of the ventricular muscle pumping/filling function, and patients can show a series of clinical manifestations such as reduced activity endurance, dyspnea and fluid retention, which seriously affect the normal working and life and even threaten life safety[1,2]. Neuroendocrine factor abnormality and the resulting left ventricular remodeling are the root causes of the CHF occurrence and development, so reversing ventricular remodeling is the ultimate goal for treatment of CHF, and how to choose reasonable therapy becomes the focus of clinical research. Bisoprolol is the common drug for coronary heart disease treatment, it is mostly applied when the curative effect of diuretics and ACE inhibitors is not significant, and it selectively antagonizes β1 adrenal receptors to play its role[3]. Trimetazidine belongs to the potent antianginal drug, and it optimizes myocardial energy metabolism, enhances the glucose oxidation, inhibits hypoxia-induced myocardial cell poisoning, etc., to protect the myocardium[4]. Now many scholars recommend trimetazidine combined with bisoprolol for the treatment of patients with CHF, but most of the studies are limited to the overall curative effect judgment. In the following study, the effect of trimetazidine combined with bisoprolol on the cardiac function, ventricular remodeling and neuroendocrine factors in patients with chronic heart failure was analyzed.
2. Information and methods

2.1 Case information

A total of 52 patients with chronic heart failure who were treated in our hospital between January 2012 and November 2015 were included, and the patients themselves or families signed consent form. According to the double-blind randomized control method, the included patients were divided into the control group (n=26) who received bisoprolol therapy and the observation group (n=26) who received trimetazidine combined with bisoprolol therapy. Control group included 14 male cases and 12 female cases, they were 48-76 years old, and the course of disease was 1-7 years and (3.18±0.59) years in average; observation group included 15 male cases and 11 female cases, they were 49-73 years old, and the course of disease was 1-6 years and (3.07±0.64) years in average. Two groups of patients were not statistically different in distribution of gender, age and course of disease (P>0.05). The hospital ethics committee approved the study after discussion.

2.2 Inclusion and exclusion criteria for chronic heart failure

Inclusion criteria: (1) conforming to the diagnostic criteria for chronic heart failure by world health organization; (2) without history of acute myocardial infarction attack within 6 months before the treatment; (3) not taking drugs with cardiac side effects in the past; (4) fully cooperating with treatment and related inspection and with complete clinical data. Exclusion criteria: (1) associated with severe liver and kidney dysfunction; (2) associated with malignant tumor diseases; (3) with trimetazidine/bisoprolol allergies; (4) dead during hospitalization.

2.3 Therapy

Both groups of patients accepted routine therapy for chronic heart failure, including oxygen uptake, diuresis, lipid regulation, angiotensin receptor blockers, and those with poor cardiac function also received oral digitalis preparations (Zhejiang Jinhua Conba Biopharm. Co., LTD., approved by H33021566).

Control group of patients, on the basis of conventional treatment, received bisoprolol therapy, specifically as follows: oral administration of bisoprolol (Hunan Juanlang Pharmaceutical Co., LTD., approved by H20113187), starting dose 2.5 mg, adjusting the dose along with the condition (maximum dose 10 mg/d), 1 time/d, for 3 months in a row.

Observation group, on the basis of routine treatment, received trimetazidine combined with bisoprolol therapy, specifically as follows: trimetazidine hydrochloride tablets (Beijing Winsunny Harmony Science & Technology Co., Ltd., approved by H20065167), oral administration, 20 mg/time, 3 times/d, for 3 months in a row.

2.4 Observation indexes

2.4.1 Cardiac function and ventricular remodeling parameters

Before treatment and after 3 months of treatment, the cardiac color Doppler diasonograph (Wuhan Kai Electronics Co., Ltd., model kai-x6) was used to determine the levels of cardiac function parameters in two groups of patients, including left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction (LVEF). The levels of ventricular remodeling parameters were detected, including left ventricular posterior wall thickness (LVPWT), interventricular septum thickness at end-systole (IVSS), left ventricular end-diastolic posterior wall thickness (PWD) and left ventricular end-systolic posterior wall thickness (PWS), and the left ventricular mass index (LVMI) was calculated.

2.4.2 Neuroendocrine factor

Before treatment and after 3 months of treatment, 1.5 mL cubital venous blood was extracted from two groups of patients at the same point in time, and RIA method was used to determine neuroendocrine factor contents in it, including norepinephrine (NE), aldosterone (ALD), angiotensin II (Ang II), atrial natriuretic peptide (ANP) and endothelin (ET). RIA kits were bought from Roche biotech companies in the United States, and the article number was MD792, TYA29, NT736, OM826 and GF628 respectively.

2.5 Statistical methods

The data obtained in the study was calculated by personnel with professional statistical qualification, measurement data was in terms of (x±s), comparison within group before treatment and after treatment was by paired t test, comparison between groups after treatment was by grouping t test and P<0.05 was set as the standard of statistical significance in differences.

3. Results

3.1 Cardiac function parameters

Before treatment, the differences in cardiac function parameters LVEDd (mm), LVESD (mm) and LVEF levels were not statistically significant between two groups of patients (P>0.05); after 3 months of treatment, cardiac function parameters LVEDd and LVESD levels of both groups were lower than those before treatment while LVEF levels were higher than those before treatment, and differences within group were statistically significant (P<0.05). After 3 months of treatment, the cardiac function parameters LVEDd and LVESD levels of observation group were lower than those of control group.
while LVEF level was higher than that of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 1.

3.2 Ventricular remodeling parameters

Before treatment, the differences in ventricular remodeling parameters LVPWT, IVSS, PWD, PWS and LVMI levels were not statistically significant between two groups of patients ($P>0.05$); after 3 months of treatment, ventricular remodeling parameters LVPWT, IVSS, PWD, PWS and LVMI levels of both groups were lower than those before treatment, and differences within group were statistically significant ($P<0.05$). After 3 months of treatment, ventricular remodeling parameters LVPWT, IVSS, PWD, PWS and LVMI levels of observation group were lower than those of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 2.

3.3 Neuroendocrine factors

Before treatment, the differences in peripheral blood neuroendocrine factors NE, ALD, Ang II, ANP and ET levels were not statistically significant between two groups of patients ($P>0.05$); after 3 months of treatment, peripheral blood neuroendocrine factors NE, ALD, Ang II, ANP and ET contents of both groups were lower than those before treatment, and differences within group were statistically significant ($P<0.05$). After 3 months of treatment, peripheral blood neuroendocrine factors NE, ALD, Ang II, ANP and ET contents of observation group were lower than those of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 3.

4. Discussion

CHF is the myocardial damage caused by a variety of reasons, it subsequently forms myocardial structure and function change, patients can be characterized by dyspnea, fluid retention, etc., and it causes serious damage to the patient’s life safety and quality of life. Diuresis, vascular dilation, heart strengthening and so on are the routine measures for CHF treatment, they can partially alleviate the patient’s clinical symptoms, but the effect is limited in inhibiting the progress of the disease, and other targeted drugs are required to enhance curative effect[5]. The main composition of bisoprolol is bisoprolol fumarate, belongs to highly selective $\beta_1$-adrenal receptor antagonist and is a common drug for clinical hypertension and angina pectoris, the effectiveness of monotherapy has been confirmed, but many studies have also confirmed that it can't effectively reverse the cardiac function damage in CHF patients. Trimetazidine belongs to the potent antianginal drug, it works slowly but continues to be functional for a long time, and its mechanism of action is inhibiting free fatty acid metabolism, making the myocardium absorb more energy from glucose metabolism, improving the utilization degree of the oxygen and alleviating the symptoms of myocardial ischemia hypoxia[6,7]. Trimetazidine is widely used in clinical treatment of angina pectoris, and some scholars have put forward at present that it can be associated with bisoprolol for the treatment of CHF in
order to expand the overall curative effect and delay the process of heart failure.

Cardiac damage is the main sonographic finding in patients with CHF; it is also the gold standard for disease diagnosis, and it is mainly characterized by myocardial ejection capacity reduction, blood retention in atrium and ventricle as well as heart dilation\(^8,9\). Cardiac damage degree is highly consistent with the CHF severity, so early detection of cardiac function indexes can quantifiably reflect the therapeutic effect of drugs\(^10\). In the study, color Doppler ultrasound was used to evaluate cardiac function change of two groups of patients before and after the treatment, and it was found that that compared with before treatment, cardiac function parameters LVEDd and LVESD levels of both groups of patients reduced while LVEF levels increased; further compared with control group, the observation group were with lower LVPWT, IVSS, PWD, PWS and LVMI levels after treatment, indicating that both kinds of treatments can reduce PWS and LVMI levels of both groups of patients were lower after treatment. LVPWT, IVSS, PWD, PWS and LVMI levels after the treatment, and it was found that that compared with before treatment, cardiac function parameters LVEDd and LVESD levels of both groups of patients reduced while LVEF levels increased; further compared with control group, the observation group were with lower LVPWT, IVSS, PWD, PWS and LVMI levels after treatment, indicating that both kinds of treatments can reduce PWS and LVMI levels of both groups of patients were lower after treatment, and it was found that compared with before treatment, cardiac function parameters LVEDd and LVESD levels of both groups of patients reduced while LVEF levels increased; further compared with control group, the observation group were with lower LVPWT, IVSS, PWD, PWS and LVMI levels after the treatment, and it was found that compared with before treatment, cardiac function parameters LVEDd and LVESD levels of both groups of patients reduced while LVEF levels increased; further compared with control group, the observation group were with lower LVPWT, IVSS, PWD, PWS and LVMI levels after treatment, explaining that trimetazidine combined with bisoprolol can more effectively inhibit ventricular remodeling process and reverse ventricular remodeling. The above effect of trimetazidine may be related to its metabolic myocardial protective effect, and the drug reduces the Ca\(^2\+\) and Na\(^+\) overload in the cells to reduce ketone body formation in myocardial cells and restrain the cytotoxic effect caused by hypoxia\(^15\). At the same time, Trimetazidine can maintain the normal function of myocardial mitochondria and reduce the free radical generation in the myocardium to eventually resist a series of adverse reactions produced by myocardial ischemia.

Excessive sympathetic nerve excitement is closely related to the occurrence and development of CHF, and the degree of excitement is positively correlated with incidence of sudden death inpatients with CHF\(^16\). It is found in previous study that the 24 h sympathetic nerve in patients with CHF is in the continued excited state, and the direct result is that NE, ADL, Ang II and other factors lose the circadian rhythm change, are kept at high levels and lead to accelerated heart rate and increased heart work. At the same time, there is the RAS activity enhancement and continuous myocardial cell hypertrophy in CHF patients, ANP can inhibit myocardial cell and vascular smooth muscle thickening, ANP content reactivly increases with CHF aggravation, and therefore, the content of ANP is positively correlated with CHF severity\(^17\). Vascular endothelium is the biggest endocrine organ of human body, the ET that is secreted overphysiologival dose can induce coronary sustained contraction and increase myocardial ischemia, and therefore, there are ubiquitous high levels of ET in patients with CHF\(^8,19\). In the study, the contents of these neuroendocrine factors in peripheral blood were detected, the differences in curative effects of different therapies were judged from hematology levels, and it was found that compared with before treatment, the peripheral blood NE, ALD, Ang II, ANP and ET levels of both groups of patients reduced after treatment, showing that both therapies can optimize the neuroendocrine system in CHF patients; Further compared with the control group, the observation group were with lower peripheral blood NE, ALD, Ang II , ANP and ET contents after treatment, indicating that trimetazidine combined with bisoprolol can more effectively inhibit ventricular remodeling process and reverse ventricular remodeling. The above effect of trimetazidine may be related to its metabolic myocardial protective effect, and the drug reduces the Ca\(^2\+\) and Na\(^+\) overload in the cells to reduce ketone body formation in myocardial cells and restrain the cytotoxic effect caused by hypoxia\(^15\). At the same time, Trimetazidine can maintain the normal function of myocardial mitochondria and reduce the free radical generation in the myocardium to eventually resist a series of adverse reactions produced by myocardial ischemia.

Trimetazidine combined with bisoprolol can effectively improve the cardiac function of patients with CHF, and the main reason is that after combined mediation, the ventricular remodeling process is reversed and the neuroendocrine system is adjusted. This study mainly focuses on ultrasound and hematology index detection, case sample size is small, molecular study is not involved, and the conclusion remains to be further improved in subsequent research.
References


