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Effect of Trimetazidine Dihydrochloride Tablets adjuvant therapy on inflammatory reaction, oxidative stress, vascular endothelial function and myocardial function in patients with coronary heart disease complicated with heart failure

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ABSTRACT

Objective: To investigate the effects of Trimetazidine Dihydrochloride Tablets on inflammatory reaction, oxidative stress, vascular endothelial function and myocardial function in patients with coronary heart disease complicated with heart failure. **Methods:** A total of 98 patients with coronary heart disease and heart failure who met the criteria of the study were selected as the subjects, based on the random data table they were divided into the control group (n=49) and observation group (n=49), the patients in the control group were treated with Metoprolol Tartrate Sustained-release Tablets treatment, and the patients in the observation group were treated with Metoprolol Tartrate Sustained-release Tablets combined with Trimetazidine Dihydrochloride Tablets, the levels of inflammatory reaction, oxidative stress, vascular endothelial function and myocardial function indexes were compared between the two groups before and after treatment. **Results:** The difference of the CRP, TNF-α, MDA, SOD, NO, ET-1, LVEF, LVEDD and LVESD levels in the two groups before treatment were not statistically significant; Compared with the levels of the two groups before treatment, the two groups of CRP, TNF-α, MDA, ET-1, LVEDD and LVESD levels after treatment were significantly decreased, and the level of the observation group after treatment was significantly lower than those levels in the control group, the difference was statistically significant; The levels of SOD, NO and LVEF of the two groups after treatment were significantly higher than those in the same group before treatment, and the observation group levels [(88.09±7.51) U/ml, (72.58±14.64) mol/L, (48.34±5.09)%] were significantly higher than the control group [(79.44±7.27) U/ml, (61.89±11.06) mol/L, (44.19±4.58)%], the difference was statistically significant. **Conclusion:** Trimetazidine Dihydrochloride Tablets in the treatment of coronary heart disease with heart failure can effectively inhibit the release of inflammatory factors, improve oxidative stress state, vascular endothelial function and myocardial function, has an important clinical value.

1. Introduction

Heart failure is the most serious complication of coronary heart disease, and is the terminal stage of various cardiovascular diseases. Conventional treatment is the main treatment for coronary heart disease with heart failure, but its clinical effect is not ideal[1,2]. The occurrence of heart failure is often accompanied by the metabolic disorder of myocardial cells, which seriously affects the therapeutic effect. Therefore, in the traditional anti-heart failure treatment, supplemented by optimization of myocardial energy metabolism drug treatment, can effectively maintain cardiac function, improve prognosis[3]. Trimetazidine is a kind of anti-myocardial ischemia drug which can effectively improve the myocardial energy, and its treatment can effectively improve the therapeutic effect of coronary heart disease with heart failure[4,5]. This study analyzed the biochemical parameters and myocardial function of patients, in order to clear the clinical effect of Trimetazidine Dihydrochloride Tablets adjuvant therapy.

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2. Data and methods

2.1. Research data

Patients with coronary heart disease and heart failure treated in Department of Cardiology of our hospital from November 2015 to February 2017 were selected as the main research objects, which met the screening criteria of 98 patients. The research content and process are in line with the relevant standards of the hospital ethics committee and are approved by the ethics committee. According to the random data table method, 98 patients were divided into control group (n=49) and observation group (n=49). There were 28 male patients and 21 female patients in the control group. The age was 48 to 76 years old. 19 cases were grade NYHA, 25 cases were grade III, 5 cases were grade IV. There were 27 male patients and 22 female patients in the observation group. The age was 46 years old and -77 years old; 20 cases were grade NYHA, 23 cases were grade III, 6 cases were grade IV. By comparison, the gender, age and NYHA classification of the two groups were not statistically significant (P>0.05), so they were comparable.

2.2 Screening criteria

Inclusion criteria: (1) All the subjects selected in the study were in accordance with the diagnostic criteria of coronary heart disease and heart failure[6,7]. (2) The NYHA grade of cardiac function was grade II to grade IV. (3) Detection of left ventricular ejection fraction (LVEE) <50% by ultrasonic cardiogram. (4) Informed consent was obtained from all patients and/or family members, and informed consent was signed. Exclusion criteria: (1) Heart failure caused by acute myocardial infarction and other diseases. (2) Accompanied by serious disorders of liver, kidney and other important organs, mental disorders and acute and slow infectious diseases. (3) Malignant tumor, autoimmune disease. (4) Cardiogenic shock in patients with decompensated heart failure. (5) Sustained or intermittent acceptance of beta agonist therapy. (6) There was an allergy to the drug in this study. (7) Systolic blood pressure <100 mmHg. (8) Clinical data are incomplete or unwilling to join researchers.

2.3. Therapeutic method

Two groups of patients were given routine treatment of heart failure, such as oxygen control, pressure control, lipid regulation, angiotensin converting enzyme inhibitors, digitalis and/or diuretics. On this basis, the control group was given Metoprolol Tartrate Sustained-release Tablets (Jiangxi Nanchang Jisheng pharmaceutical factory production, product batch number 160108, specification: 0.15 g × 10 s) treatment. The initial recommended dose was 6.25 mg/times, 2-3 times a day, according to the severity of the disease, increased dose (6.25-12.5 mg/times) every week, but the maximum dose should not exceed 100 mg, 2 times a day. The patients in the observation group were treated with Trimetazidine Dihydrochloride Tablets (triamcinolone on root, reyoung pharmaceutical limited company production, product batch number 160211, specifications: 20 mg × 30 s) treatment, dosage of 20 mg/times, each taking a morning and evening meal. The two groups were treated for 6 months.

2.4. Index detection

Before and after treatment, the fasting venous blood of the patients was extracted at 3-5 mL in the morning and 10 min after the specific revolution, and the serum was directly detected or placed in the refrigerator at -80 centigrade. The indexes included inflammatory factor [C reactive protein (CRP), tumor necrosis factor alpha (TNF-α)], oxidative stress [malondialdehyde (MDA),

Table 1.

Comparison of inflammatory factors between the two groups.

Group	n	Treatment time	CRP (mg/L)	TNF-α (ng/L)
Control group	49	Before treatment	9.55±1.79	45.01±8.38
		After treatment	6.67±0.84*	32.83±4.74*
Observation group	49	Before treatment	9.31±1.82	44.59±8.24
		After treatment	4.49±0.61*#	21.87±5.31*#

Note: compared with before treatment, *P<0.05; compared with after treatment, #P<0.05.

Table 2.

Comparison of oxidative stress related indexes in two groups.

Group	n	Treatment time	MDA (μmol/L)	SOD (U/mL)
Control group	49	Before treatment	8.45±1.15	62.27±8.72
		After treatment	5.94±0.96*	79.44±7.27*
Observation group	49	Before treatment	8.37±1.05	62.65±7.59
		After treatment	4.54±0.88*#	88.09±7.51*#

Note: compared with before treatment, *P<0.05;compared with after treatment, #P<0.05.

Table 3.

Comparison of vascular endothelial function between the two groups.

Group	*n*	Treatment time	NO (μmol/L)	ET-1 (ng/L)
Control group	49	Before treatment	57.51±10.19	114.62±22.08
		After treatment	61.89±11.06*	86.32±15.55*
Observation group	49	Before treatment	57.48±10.37	115.36±22.76
		After treatment	72.58±14.64*#	73.93±14.35*#

Note: *indicating a comparison with pre-treatment level, *P<0.05, #indicating a comparison with the level after treatment, #P<0.05.

Table 4.

Comparison of myocardial function between the two groups.

Group	*n*	Treatment time	LVEF (%)	LVEDD (mm)	LVESD (mm)
Control group	49	Before treatment	40.09±5.07	58.98±6.91	60.77±8.10
		After treatment	44.19±4.58*	53.47±5.49*	48.07±5.76*
Observation group	49	Before treatment	40.21±4.84	28.94±6.65	60.16±7.24
		After treatment	48.34±5.09*#	49.05±5.23*#	42.43±5.04*#

Note: *indicating a comparison with pre-treatment level, *P<0.05, #indicating a comparison with the level after treatment, #P<0.05.

superoxide dismutase (SOD) and vascular endothelial function of nitric oxide (NO) and endothelin-1 (ET-1)]. CRP, TNF-alpha and SOD levels were detected by ELISA method, and NO was nitrate reductase method (CRP, TNF-α, SOD and NO kits were provided by Shanghai enzyme Biotechnology Co., Ltd.). The level of MDA was determined by thiobarbituric acid method (the kit was purchased from Nanjing Institute of Bioengineering). ET-1 was detected by radioimmunoassay (The detection kit provided by Shanghai Harling Biotechnology Co. Ltd.). At the same time, LVEF, left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) were compared between the two groups before and after treatment. Color Doppler echocardiography was used in the instrument.

2.5. Statistical processing and analysis

The statistical analysis software of this study is SPSS 17.0. The levels of inflammatory factors, oxidative stress, vascular endothelial function and cardiac function in the study were verified by normality test and homogeneity test of variance, which was expressed by Mean ± SD. t test was used to compare the indexes between two groups (before and after treatment, or between groups), and the difference was statistically significant by P<0.05.

3. Result

3.1 Comparison of inflammatory factors

As shown in Table 1, there was no significant difference in the levels of CRP and TNF-α between the two groups before treatment (P>0.05). After treatment, the levels of CRP and TNF-α in the two groups were significantly lower than those in the group before treatment (P<0.05). Moreover, the levels of CRP and TNF-α in the observation group [(4.49±0.61) mg/L, (21.87±5.31) ng/L] were significantly lower than those in the control group [(6.67±0.84) mg/L, (32.83±4.74) ng/L], respectively, and the difference was statistically significant (P<0.05).

3.2 Comparison of oxidative stress

MDA and SOD levels of oxidative stress before and after treatment in the two groups were shown in Table 2. Before treatment, the MDA and SOD levels of the two groups were close to each other, and the difference was not statistically significant (P>0.05). Compared with MDA before treatment, the levels of the two groups decreased significantly after treatment (P<0.05), and the level of the observation group (4.54±0.88) mol/L was significantly lower than that of the control group (5.94±0.96) mol/L. The difference was statistically significant (P<0.05). After treatment, the SOD levels of the two groups were significantly higher than those before treatment (P<0.05). And the level of the observation group (88.09±7.51) U/mL was significantly higher than that of the control group (79.44±7.27) U/mL, the difference was statistically significant (P<0.05).

3.3 Comparison of vascular endothelial function

As shown in Table 3, there was no significant difference in NO and ET-1 values between the two groups before treatment (P>0.05). The levels of NO were significantly increased after treatment (P<0.05). The observation group level (72.58±14.64) mol/L was significantly higher than the control group (61.89±11.06) mol/L, the difference was statistically significant (P<0.05). After treatment, the levels of ET-1 in the control group and the observation group were (73.93±14.35) ng/L and (86.32±15.55) ng/L, respectively, which were significantly lower than those before the treatment of ET-1. And the level of ET-1 in the observation group was significantly lower than that in the control group, the difference was statistically significant (P<0.05).

3.4 Comparison of myocardial function

As shown in Table 4, there was no significant difference in the LVEF, LVEDD and LVESD values between the two groups before treatment (P>0.05). Compared with the levels of LVEF, LVEDD and LVESD before treatment, the level of LVEF increased significantly in the control group and the observation group after treatment, the levels of LVEDD and LVESD were significantly decreased, the difference was statistically significant (P<0.05). And after treatment, the LVEF level of the observation group (48.34±5.09)% was significantly higher than the control group (44.19±4.58)%, LVEDD and LVESD level [(49.05±5.23) mm, (42.43±5.04) mm] was significantly lower than the control group [(53.47±5.49) mm, (48.07±5.76) mm]. The difference was statistically significant (P<0.05).

4. Discussion

Myocardial ischemia, myocardial ischemia and myocardial infarction caused by coronary heart disease are the most important factors for heart failure. Epidemiological studies have pointed out that with the aging of the population in China, the incidence of coronary heart disease and hypertension and other cardiovascular diseases are increasing year by year, and the incidence of coronary heart disease with heart failure is increasing[8,9]. In recent years, a large number of studies at home and abroad have shown that chronic inflammatory reaction, oxidative stress injury and endothelial dysfunction caused by these are involved in the occurrence and development of heart failure[10-12]. In addition, the occurrence of heart failure also weakens the vasodilation effect of coronary artery and peripheral blood vessels, leading to myocardial dysfunction[13]. In recent years, a large number of studies have pointed out that myocardial cell metabolism disorder plays an important role in the occurrence and development of coronary heart disease with heart failure[14]. Trimetazidine has been shown to be a unique regulator of myocardial cell metabolism. It mainly through selective inhibition of fatty acid beta oxidation process, increase aerobic metabolism process, improve oxygen consumption, regulate myocardial cell energy metabolism. In addition, trimetazidine can also reduce the release of oxygen free radicals and endothelin, alleviate the myocardial dysfunction caused by myocardial cell injury or apoptosis, so as to achieve the purpose of improving myocardial function[15,16].

It has been proved that inflammatory factors play an important role in the pathogenesis of coronary heart disease with heart failure, and the degree of inflammatory stress is closely related to the myocardial function and the severity of the disease[17]. As a routine inflammatory cytokine, CRP and TNF-alpha levels increased significantly in patients with coronary heart disease and heart failure[18]. The results of this study showed that the level of inflammatory factors was further reduced after trimetazidine treatment, and the level of improvement was significantly better than that of metoprolol alone, and the results were consistent with the previous reports[19]. It is further confirmed that the combination of two drugs can effectively inhibit the release of inflammatory factors and relieve the degree of inflammatory stress. The reason may be that metoprolol can increase the sensitivity of myocardial cells to catecholamine, and then reduce the damage degree of catecholamine to myocardium. On this basis, combined with trimetazidine, the internal environment of myocardial cells has been improved, thereby further reducing the degree of myocardial cell damage. The specific reason remains to be further explored.

Oxidative stress injury is considered to be one of the important mechanisms leading to heart failure in coronary heart disease. After the occurrence of coronary heart disease with heart failure, excessive active oxygen in the body directly on the unsaturated fatty acids, and thus lead to lipid peroxidation, causes oxidative damage (expressed as MDA level increased, SOD level decreased). Oxidative stress and chronic inflammation are important factors in the damage of vascular endothelial structure and function, and are also one of the main causes of the aggravation of the disease[20]. MDA and SOD are important indicators for assessing oxidative stress status and disease outcomes in patients. NO and ET-1 are vascular relaxing and contracting vascular substances synthesized by vascular endothelial cells, respectively, which play an important role in normal maintenance of vascular smooth muscle cells[21,22]. The study indicated that the vascular endothelial function was impaired in patients with coronary heart disease after heart failure, and the main clinical manifestations were decreased NO levels and elevated ET-1 levels[23]. In this study, the two regimens can effectively improve the levels of MDA, SOD, NO and ET-1. However, the improvement of the combination of trimetazidine group is more significant, which reveals that trimetazidine can effectively improve the oxidative stress status and repair the vascular endothelial function. The reason may be related to the effects of trimetazidine on the inhibition of oxygen free radicals and ET release, and the improvement of myocardial environment. In addition, the myocardial function of the patients was analyzed. The results showed that the improvement of LVEF, LVEDD and LVESD levels was better in the combined trimetazidine treatment group. The results further confirmed that trimetazidine adjuvant therapy can effectively improve myocardial function in patients. The mechanism may be related to the improvement of myocardial intracellular environment and the enhancement of myocardial energy metabolism by Trimetazidine[24].

To sum up, sibutramine trimetazidine in adjuvant treatment of coronary heart disease and heart failure can effectively inhibit the release of proinflammatory cytokines, reduce the inflammatory stress, reduce oxidative stress, restore vascular endothelial function, protect myocardial cells. Which reveals that the pharmacological effects of trimetazidine in the treatment of coronary heart disease with heart failure may be related to the improvement of the above indicators.

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