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Original Research Article

Effect of trimetazidine on ventricular remodeling, serum Cys C and ET-1 levels in patients with chronic heart failure

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Abstract

Purpose: *To evaluate the effect of trimetazidine on ventricular remodeling and serum levels of cystatin C and endothelin-1 in patients with chronic heart failure (CHF).*
Methods: *A total of 96 patients with CHF were randomly divided into two groups, given either conventional treatment (control group) or conventional treatment plus trimetazidine (study group) for 6 months. Clinical efficacy was compared between the two groups. Left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) were measured using cardiac echocardiography before and after treatment. Patients were recorded at 6 MVT before and after treatment. An automatic biochemical analyzer was used to assay serum Cys C levels before and after treatment. Serum levels of ET-1, galactose agglutinin-3 (GAL-3), brain natriuretic peptide (BNP) and heart natriuretic peptide (ANP) were determined by enzyme-linked immunosorbent assay (ELISA) before and after treatment. Incidence of adverse events in CHF patients was compared between groups.*
Results: *Study group had a significantly higher level of treatment effectiveness (91.67 %) and better improvement in left ventricular ejection fraction, left ventricular end-systolic diameter and left ventricular end-diastolic diameter than control group ($p < 0.05$). Serum levels of serum cystatin C, endothelin-1 and other biomarkers were also significantly lower ($p < 0.05$) in study group. Re-hospitalization rate was also lower in study group.*
Conclusion: *Trimetazidine exerts a therapeutic effect on CHF patients, effectively improves cardiac function and reduces the rate of re-hospitalization.*

Keywords: *Chronic heart failure, Trimetazidine, Endothelin-1, Cystatin C*

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INTRODUCTION

Chronic heart failure (CHF) is a common cardiovascular disease seen in clinical medicine. The primary cause is that patients with cardiovascular diseases (such as coronary heart disease, hypertension and myocarditis) experience myocardial damage, which leads to alterations in myocardial structure and function. Ultimately, this results in abnormal ventricular systolic and diastolic function, main clinical manifestations of which are decreased

endurance, fatigue, fluid retention and various arrhythmias which may occur at the same time [1,2]. Middle-aged and elderly individuals are at higher risk of congestive heart failure CHF) and incidence of CHF is progressively rising, as proportion of elderly population increases each year. Pathogenesis of CHF is complex and modern medicine believes that the disease is caused by abnormal myocardial systolic function caused by long-term ischemia of the heart [2]. As a result, clinical research has become focused on discovering effective drugs to treat CHF, aiming to improve patients' clinical symptoms and reduce mortality. Presently, symptomatic treatment is frequently employed in the clinical management of CHF. Trimetazidine, a piperazine derivative, can regulate carbohydrate metabolism by reducing fatty acid oxidation, inhibiting cell apoptosis, reducing cardiac oxygen consumption and delaying ventricular remodeling so as to protect cardiac function [3].

Previous studies have demonstrated that combination of trimetazidine and ramipril effectively enhances cardiac function in elderly patients with heart disease and concurrent heart failure [3]. These findings suggest that trimetazidine possesses potential to alleviate heart failure in CHF patients [3]. In order to provide more possibilities for clinical treatment of the disease, this study investigated the effect of trimetazidine on the cardiac function of CHF patients.

METHODS

Patients

Patients with CHF (96) admitted to the Department of Cardiovascular Medicine, The Second Affiliated Hospital of Hainan Medical University, Haikou, China from June 2019 to June 2021 were selected as the study subjects. They were randomly divided into control (25 males and 23 females in the control group, aged 49.36 ± 8.27 years) and study (27 males and 21 females, aged 48.45 ± 8.6 years) groups.

This study obtained approval from the Medical Ethics Committee of The Second Affiliated Hospital of Hainan Medical University (approval no. HK-19-021) and was conducted in accordance with official protocols [5].

Inclusion criteria

Firstly, patients had to fulfill the diagnostic criteria specified in the Chinese Guidelines for Diagnosis and Treatment of Heart Failure 2018 [4], which included exhibiting typical symptoms of heart failure, having a left ventricular ejection fraction (LVEF) of less than 40 % and displaying usual signs of heart failure, among other criteria. Secondly, patients were required to have an expected survival time exceeding three months. Thirdly, detailed information regarding the study's contents and methods was provided to patients and their families, who provided informed consent by agreeing to participate and signing informed consent forms.

Exclusion criteria

Patients with either acute heart infarction, or crucial visceral malignancy, or known allergies to the drugs used in the study and/or incomplete clinical data were excluded.

Treatments

Patients in control group were referred to the "New Quadruple Therapy Clinical Decision Pathway Expert Consensus" [5] for treatment of chronic heart failure. Sacubitril/valsartan (Novartis Pharma Schweiz AG, National Drug Administration H20170362, Specification: 50 mg/tablet) was given at a dose of 25 mg/day orally twice per day, blood pressure was monitored and the dose was increased 1-fold every 2 weeks until it reached 400 mg/day. Initial dose of Dapagliflozin (AstraZeneca Pharmaceutical Co., Ltd., London, UK State Pharmacopoeia J20170040; Specification: 10 mg × 10 tablets) was 5 mg/day adjusted to 10 mg/day if hemoglobin level did not improve. Spironolactone (Suzhou Hongsen Pharmaceutical Co. Ltd, Suzhou, China, State Pharmacopoeia H32020050; Specification: 20 mg) was administered at an initial dose of 10 mg/day while initial dose of metoprolol succinate (Zhejiang Pulokongyu Pharmaceutical Co., Ltd., Dongyang, China, State Pharmacopoeia H20213769; specification: 47.5 mg × 10 tablets; orally) was 47.5 mg once a day. The dose was adjusted at intervals of 7 to 14 days according to the patient's condition and maintained after reaching the maximum tolerated dose. All patients continued to use the drug for 3 months.

Study indices

Baseline data collection: A questionnaire for baseline data was designed according to the content and purpose of study and relevant data were collected through electronic medical record system of hospital cases, which included gender, age, heart rate, underlying diseases and cardiac function (NYHA grading).

Clinical efficacy was evaluated after 6 months of treatment [6]

Clinical symptoms and signs disappeared basically when ECG returned to normal and cardiac function grade returned to grade I from a higher grade. Clinical symptoms and signs obviously improved when the electrocardiogram basically returned to normal and cardiac function grade decreased. There was no significant change in clinical symptoms and signs when any change in ECG and cardiac function level was considered invalid. Total effective rate is the sum of obvious efficiency and effective rate.

Cardiac function

Before and after treatment, cardiac echocardiography (Wuhan Cambeno Medical Equipment Co., LTD.) was used to measure LVEF, left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD). Before and after treatment, an indoor walking test was conducted for 6 min and walking distance for 6 min (6 MVT) was recorded.

Serum indicators

A measurement of 5 mL fasting venous blood was collected from each of CHF patients in two groups before and after treatment. The serum cystatin C (Cys C) level was assayed by immunoturbidimetry using a PUZS-300 Automatic Biochemical Analyzer (Shanghai Dibs Biotechnology Co., LTD., Shanghai, China). Serum levels of endothelin-1 (ET-1), galactose agglutinin-3 (GAL-3), brain natriuretic peptide (BNP) and cardiac natriuretic peptide (ANP) were determined by enzyme-linked immunosorbent assay (ELISA) before and after treatment. ELISA kit and supporting reagents were purchased from Shenzhen Yahualong Biotechnology Co., LTD.

Adverse events

Patients were counted from admission and followed up for 1 year and the outcome of all patients was recorded. The end event was cardiac death.

Statistical analysis

Statistical analysis was performed using IBM's Statistical Package for the Social Sciences (SPSS) version 23.0 software (IBM, Armonk, NY, USA). Measurement data, including LVEDD, LVESD, LVEF, 6MVT, Cys C, ET-1, GAL-3, BNP, and ANP, were expressed as mean ± standard deviation (SD). Inter-group comparisons were conducted using two-sample independent *t*-test, while paired *t*-tests were used for intra-group comparisons. Counting data, such as clinical efficacy and adverse events, were presented as (cases (%)) and analyzed using Chi-square test for inter-group comparisons. Statistical significance was determined when $p < 0.05$ for two-sided tests, indicating a significant difference in data.

RESULTS

Clinical data

There were no significant differences in gender, age, heart rate, NYHA grade and underlying diseases between the Study and control groups (Table 1, $p > 0.05$).

Clinical efficacy of CHF patients

Overall effective rate in observation study group was 91.67 %, which was significantly higher than 79.17 % observed in control group (Table 2, $p < 0.05$).

Cardiac function

Before treatment, there were no significant differences in LVEDD, LVESD, LVEF and 6MVT

Table 1: Comparison of clinical data of CHF patients between Study group and Control group (n=48)

Item	Study group	Before treatment	t /χ^2	*P*-value
Gender (male/female)	27/21	25/23	0.168	0.682
Age (years)	48.45±8.63	49.36±8.27	0.527	0.599
Heart rate (times/min)	80.53±8.11	81.13±8.22	0.359	0.719
NYHA classification			0.263	0.877
Class II	21 (43.75)	19 (39.58)		
Class III	24 (50.00)	25 (52.08)		
Class IV	03 (6.25)	04 (8.33)		
Underlying disease				
Coronary heart disease	16 (33.33)	17 (35.42)	0.046	0.830
Hypertension	22 (45.83)	24 (50.00)	0.167	0.683
Diabetes mellitus	12 (25.00)	13 (27.08)	0.054	0.816
Atrial fibrillation	11 (22.92)	12 (25.00)	0.057	0.811

Table 2: Comparison of clinical efficacy in CHF patients between Study group and Control group (n=48)

Group	Significantly effective	Effective	Invalidity	Total effective rate
Study	18 (37.50)	27 (56.25)	04 (6.25)	45 (91.67)
Control	11 (22.92)	26 (54.17)	10 (20.83)	38 (79.17)
χ^2				4.360
P-value				0.037

Table 3: Comparison of cardiac function between the Study group and the control group before and after treatment (n=48)

Group	Time	LVEDD (mm)	LVESD (mm)	LVEF (m)	6MVT (m)
Study	Pre-treatment	58.61±5.93	50.65±5.17	31.89±3.24	108.67±10.96
	Post-treatment	50.72±5.14 [a]	43.78±4.45[a]	40.61±4.11[a]	193.28±20.06[a]
Control	Pre-treatment	59.14±6.03	50.09±5.10	32.04±3.30	108.15±10.74
	Post-treatment	53.49±5.41	46.82±4.77	36.84±3.75	173.49±17.58

Note: [a]$p < 0.05$ Compared with control group at the same time point

Table 4: Comparison of serological indexes of CHF patients between the Study group and the control group before and after treatment (n=48)

Group	Time	Cys C (mg/L)	Et-1 (g/L)	Gal-3 (μg/L)	BNP (G /L)	P (g/L)
Study group	Pre-treatment	2.52±0.27	80.53±8.07	8.96±0.93	375.64±38.43	215.86± 22.61
	Post-treatment	1.57±0.16[a]	66.35±6.78[a]	4.48±0.53[a]	312.67±32.55[a]	189.18±19.94[a]
Control group	Pre-treatment	2.63±0.31	80.74±8.16	8.91±0.90	371.68±38.27	211.23±22.55
	Post-treatment	1.77±0.18	70.62±7.14	6.83±6.95	338.91±34.72	198.09±20.82

Note: Compared with control group at the same time point, [a]$p < 0.05$

between the 2 groups ($p > 0.05$). However, after treatment, LVEDD and LVESD levels in the 2 groups decreased while LVEF and 6MVT levels increased, and LVEDD and LVESD levels in the study group was significantly lower than in the control group, while LVEF and 6MVT levels were significantly higher than in the control group ($p < 0.05$; Table 3).

Serological indices

There were no significant differences in serum levels of Cys C, ET-1, GAL-3, BNP and ANP between the groups before treatment ($p > 0.05$). After treatment, serum Cys C, ET-1, GAL-3, BNP and ANP levels in the groups decreased significantly ($p < 0.05$). However, serum Cys C, ET-1, Gal-3, BNP and ANP levels in study group were significantly lower than in control group ($p < 0.05$). See Table 4.

Adverse events between two groups of CHF patients during treatment

Re-hospitalization rate of patients in study group was lower than that in control group ($p < 0.05$). There was no significant difference in mortality between groups ($p > 0.05$). See Table 5.

Table 5: Comparison of adverse events between groups during treatment (n=48)

Group	Re-admission rate	Mortality rate
Study	19 (39.58)	0 (0.00)
Control	10 (20.83)	1 (2.08)
χ^2	4.002	1.011
P-value	0.045	0.315

DISCUSSION

In this study, total effective rate of trimetazidine in treating CHF patients was significantly higher than that of conventional treatment, suggesting that trimetazidine has better efficacy. This study also found that after treatment, LVEDD and LVESD levels in study group were significantly lower than in control group and LVEF and 6MVT levels were significantly higher than in control group, suggesting that trimetazidine treatment effectively improved cardiac function of patients. Trimetazidine hydrochloride has potential to nourish myocardium, improve myocardial metabolism, reduce myocardial injury and protect the heart. It achieves these effects by inhibiting fatty acid oxidation and promoting increased glucose metabolism [7,8]. When used in combination with conventional treatment drugs, trimetazidine exhibits a synergistic effect. It

dilates blood vessels, reduces cardiac workload, inhibits cardiac enlargement and delays progression of heart failure. In this study, the serum Cys C, ET-1, GAL-3, BNP and ANP levels in CHF patients in groups significantly decreased after treatment. Serum Cys C, ET-1, GAL-3, BNP and ANP in patients treated with trimetazidine were significantly lower than those treated with conventional drugs. The onset and progression of CHF leads to abnormal expression of risk factors such as Cys C, ET-1, and GAL-3, which promote development of disease. Previous studies have shown that the higher the cardiac function grade of CHF patients, the higher the serum CysC concentration [9,10]. When correcting heart failure, CysC level also decreases with enhancement of heart function. ET-1 (Endothelin-1) is a biologically active substance known for its diverse effects. It promotes cardiac myocyte hypertrophy and fibroblast proliferation, thereby contributing to cardiac hypertrophy and exacerbation of pathological progression of heart failure. Additionally, ET-1 plays crucial role in angiogenesis, vascular remodeling and regulation of vasoconstriction [11].

Animal studies have demonstrated that treatment can decrease serum ET-1 levels in CHF rats, leading to improved left ventricular diastolic and systolic functions [12]. GAL-3, a lectin family member, is involved in various physiological and pathological processes such as tissue fibrosis, cell adhesion and apoptosis [13]. Studies have shown that serum GAL-3 levels gradually increased with aggravation of NYHA cardiac function in CHF patients [14]. The changes in GAL-3 levels were closely associated with cardiac function of CHF patients, implying that trimetazidine treatment in CHF patients may have potential to inhibit myocardial fibrosis formation, delay ventricular remodeling and regulate ejection function by reducing GAL-3 levels. B-type natriuretic peptide (BNP), a naturally occurring peptide hormone with biological activity, is predominantly expressed in ventricular cardiomyocytes and serves as an important indicator for diagnosing CHF, as it reflects cardiac systolic and diastolic functions [15]. Atrial natriuretic peptide (ANP), primarily secreted by atrial myocytes, exhibits close correlation with left atrial pressure and pulmonary artery systolic pressure. Expression levels of the groups can be used to judge severity of cardiac insufficiency [16].

Previous studies have shown that trimetazidine hydrochloride effectively improves cardiac function and reduces serum BNP levels in elderly CHD patients, which is consistent with results of this study [17]. The results of this study show that trimetazidine treatment significantly reduced serum Cys C, ET-1, GAL-3, BNP and ANP levels in CHF patients, suggesting that trimetazidine may delay ventricular remodeling and improve cardiac function by regulating these indicators. Safety of drug therapy determines whether it can be put into clinical use. Re-hospitalization rate of central study group was lower than that of control group. There was no significant difference in mortality between groups, indicating that trimetazidine treatment decreases the rate of re-hospitalization for heart failure exacerbation in CHF patients to certain extent. Furthermore, potential of trimetazidine to reduce mortality in CHF patients needs to be further investigated using large-scale clinical studies.

Limitations of the study

This study has some limitations: clinical sample size is small and it is a single-center study. Therefore, data may be biased. It is necessary to expand sample size for further studies and analysis.

CONCLUSION

Use of trimetazidine in treating CHF patients demonstrates significant improvements in efficacy, particularly in promoting cardiac diastolic function. Furthermore, trimetazidine exhibits favorable safety profiles in this context.

DECLARATIONS

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Ethical approval

This study was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Hainan Medical University, China (approval no. HK-19-021).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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