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Full Paper

Effects of trimetazidine combined with levocarnitine on ischemic cardiomyopathy and serum levels of cardiac troponin I and homocysteine

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Abstract: We aim to evaluate the effects of trimetazidine combined with levocarnitine on ischemic cardiomyopathy and serum levels of cardiac troponin I (cTnI) and homocysteine (Hcy). A total of 208 elderly patients diagnosed with ischemic cardiomyopathy from June 2016 to June 2019 were randomly divided into two groups (n=104). The control group underwent conventional therapy for ischemic cardiomyopathy after admission, while the observation group were treated with levocarnitine injection combined with trimetazidine dihydrochloride tablets. The overall response rates of the observation and control groups were 83.65% and 68.27% respectively (P=0.009). Following treatment, the left-ventricular-end systolic diameter, the left-ventricular-end diastolic diameter and serum cTnI and Hcy levels declined significantly in both groups, and the decreases were more significant in the observation group at 2, 3 and 4 weeks after treatment (P<0.05). The incidence rates of adverse reactions in the observation and control groups were 10.58% and 7.69% respectively, without a significant difference (P=0.470). During follow-up, the risk of major adverse cardiovascular events in the control group was 2.08 times that of the observation group (P=0.008). Trimetazidine combined with levocarnitine can effectively improve the cardiac function and cTnI and Hcy levels in patients with ischemic cardiomyopathy. This combination helps improve the prognosis and does not significantly increase the incidence rate of adverse reactions.

Keywords: trimetazidine, levocarnitine, ischemic cardiomyopathy, cardiac troponin I, homocysteine

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INTRODUCTION

Coronary atherosclerotic heart disease, also known as coronary heart disease, is a common heart disease typified by high incidence and mortality rates. The incidence rate of coronary heart disease has been increasing annually as the age of global population rises [1]. Ischemic cardiomyopathy, as a special type of coronary heart disease, has the basic characteristics of coronary heart disease. Its clinical manifestations mainly include overall cardiomegaly and cardiac diastolic and systolic dysfunction accompanied by various types of arrhythmia. In the advanced stage, heart failure and other adverse cardiovascular events often occur and seriously threaten the patients' health. Therefore, it is an urgent public health problem [2]. Correct diagnosis and effective therapeutic measures are of high clinical value for the prognosis of ischemic cardiomyopathy. The disease is irreversible and treatment strategies such as antiplatelet aggregation and anti-myocardial ischemia are often applied to delay the disease's progression, although the prognosis is still poor [3]. Recently, drugs represented by trimetazidine combined with levocarnitine have shown satisfactory therapeutic effects on ischemic cardiomyopathy [4]. In this study, therefore, the effects of trimetazidine combined with levocarnitine on ischemic cardiomyopathy and the serum levels of cardiac troponin I (cTnI) and homocysteine (Hcy) were assessed, providing a reference for selecting suitable medication regimens.

MATERIALS AND METHODS

Baseline Clinical Data

Elderly patients with ischemic cardiomyopathy who were treated in our hospital from June 2016 to June 2019 were selected as the subjects. The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for ischemic cardiomyopathy of the International Society and Federation of Cardiology and the World Health Organisation [5]; (2) those in New York Heart Association (NYHA) functional class II-IV [6]; (3) those who are ≥60 years old; (4) those with left ventricular ejection fraction (LVEF) of ≤45%. The exclusion criteria were as follows: (1) patients with severe valvular heart disease; (2) those with heart failure or arrhythmia caused by other causes; (3) those with hypotension or cardiogenic shock; (4) those who took the relevant treatment drugs in this study within one month before enrollment; (5) those with severe hepatic and renal insufficiency; (6) those with primary heart disease; (7) those with malignant tumour.

A total of 208 eligible patients were enrolled and randomly divided into two groups (n=104). There were 60 males and 44 females in the observation group, with a mean age of 71.24 ± 4.24 years. There were 42 cases of NYHA class II, 38 cases of class III and 24 cases of class IV. In the control group, there were 62 males and 40 females, and 40 cases of NYHA class II, 41 cases of class III, and 23 cases of class IV. There were no statistically significant differences in the baseline clinical data between the two groups ($P>0.05$). This study was approved by the ethics committee of Nanjing First Hospital of Nanjing Medical University (approval no. KY20190404-05). All subjects were informed and signed the informed consent form.

Treatment Methods

After admission, the control group received conventional treatments for ischemic cardiomyopathy, which included lipid regulatory treatment, cardiotonic, anti-platelet, anti-myocardial ischemic, vasodilatory and diuretic treatments. In addition to the conventional treatments, the observation group were treated with levocarnitine injection (Dongweili®, Northeast

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Pharmaceutical Group Co., China) and trimetazidine dihydrochloride tablets (Xingfu®, Hubei Sihuan Pharmaceuticals Co., China). Specifically, 2 g of levocarnitine injection was added into 200 mL of 0.9% sodium chloride and intravenously infused into each patient once daily. Meanwhile, trimetazidine dihydrochloride tablets were administered 3 times a day [1 tablet (20 mg)/time]. Both groups were continuously treated for 28 days. After the research was completed, all patients underwent conventional treatments.

Observation of Indices

The changes in the levels of serum cTnI and Hcy and the echocardiographic indices before and after treatment were compared between the two groups. The clinical efficacy and adverse reactions during treatment were recorded.

Evaluation Criteria for Clinical Therapeutic Effects

The NYHA cardiac function class and clinical symptoms of both groups were recorded before and after treatment as follows.

- Markedly effective. The cardiac function was improved (NYHA cardiac function was above class II or in class I). Dyspnea, fatigue and chest tightness were obviously relieved and the heart rate reached the normal level.
- Effective. The cardiac function was improved (NYHA cardiac function was above class I but below class II). Dyspnea, fatigue, chest tightness and other symptoms partly disappeared and the heart rate tended to be normal.
- Ineffective. No obvious alleviation of clinical symptoms and no change or even deterioration in cardiac function.

Overall response rate = [(markedly effective cases + effective cases)/total cases] × 100% [5].

Detection of Cardiac Function Indices

Before treatment and in the first week after treatment, the cardiac function indices of the left-ventricular-end systolic diameter (LVESD), the left-ventricular-end diastolic diameter (LVEDD) and LVEF were measured using XAR10 colour ultrasound machine (Jiangsu Jiahua Electronics Co., China).

Measurement of cTnI and Hcy Levels

One day before treatment and on the 1st days after 2, 3 and 4 weeks of treatment, 5 mL of venous blood were drawn in the early morning after fasting for 12 hr and centrifuged at 4°C. Then the serum was obtained, placed in an Eppendorf tube and stored at -20°C for later detection. The level of cTnI was determined by enzyme-linked immunosorbent assay using the kit purchased from Tianjin Xiangsheng Tongda Biotechnology Co. (batch no. 4521256712), and the level of Hcy was measured by enzymatic cycling assay using the kit purchased from Nanjing Jiancheng Bioengineering Institute (batch no. 802865065), strictly following the instructions of the kits.

Follow-up

All subjects were followed up for 3 years through outpatient visit, re-examination, re-hospitalisation and telephone call. The end-point event of the follow-up was defined as major adverse cardiovascular events (MACE) after treatment, which included cardiac death, recurrent

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myocardial infarction, congestive heart failure, atherosclerotic heart disease, hypoxic encephalopathy, fatal and non-fatal ischemic stroke, and emergency and selective revascularisation.

Statistical Analysis

SPSS16.0 software was utilised for statistical analysis. The count data were expressed as percentages and the chi-square test or Fisher's exact test was conducted for intergroup comparisons. The measurement data were expressed as mean ± standard deviation, and the independent t-test and paired t-test were performed for intergroup and intragroup comparisons respectively. Repeated measures analysis of variance was carried out at various time points. In detail, the differences between the two groups and the time differences of measured values at each time point were analysed first. If there were differences between the two groups, the differences at each time point were further compared. The independent sample t-test was utilised to compare the differences at each time point between groups, and the SNK-q test was employed to compare the time differences between groups. The survival curves were plotted using Kaplan-Meier analysis, and the event-free survival rates were compared using the log-rank test. $P<0.05$ suggested that the difference was statistically significant.

RESULTS

Clinical Treatment Outcomes

In the observation group the treatment was significantly effective in 60 cases, effective in 27 cases and ineffective in 17 cases, with a total response rate of 83.65%. In the control group the treatment was significantly effective in 40 cases, effective in 31 cases and ineffective in 33 cases, with a total response rate of 68.27%. The total response rate of the observation group was significantly higher than that of the control group ($\chi^2=6.740$, $P=0.009$) (Table 1).

Table 1. Clinical treatment outcomes [n (%)]

Group	Treatment outcome			Total response rate
	Significantly effective	Effective	Ineffective	
Observation (n=104)	60 (57.69)	27 (25.96)	17 (16.35)	87 (83.65)
Control (n=104)	40 (38.46)	31 (29.81)	33 (31.73)	71 (68.27)
χ^2				6.740
P				0.009

Cardiac Function Indices Before and After Treatment

One day before treatment, no significant differences were observed in the cardiac function indices LVEDD, LVESD and LVEF between the two groups ($P>0.05$). After treatment, LVESD and LVEDD evidently decreased in both groups, being more pronounced in the observation group at 2, 3 and 4 weeks after treatment. There were significant differences at different time points between the two groups ($P<0.05$).

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After treatment, the LVEF values of both groups increased significantly, especially in the observation group at 2, 3 and 4 weeks after treatment. There were also significant differences at different time points between the two groups (P<0.05) (Table 2).

Table 2. Cardiac function indices before and after treatment

Index		1 d before treatment	2 w after treatment	3 w after treatment	4 w after treatment
LVEDD ($\bar{x}$ ± s, mm)	Observation group (n=104)	68.09±7.11	62.94±6.25*,#	57.84±6.25*,#	53.21±5.32*,#
	Control group (n=104)	67.78±8.27	65.69±6.88#	63.03±6.19#	59.84±6.01#
	Intergroup	F=57.192, P<0.01			
	Time	F=118.470, P<0.01			
	Intergroup × time	F=11.287, P<0.01			
LVESD ($\bar{x}$ ± s, mm)	Observation group (n=104)	58.94±6.17	55.14±5.43*,#	50.76±5.03*,#	46.89±4.27*,#
	Control group (n=104)	58.83±6.37	57.52±5.49#	54.95±4.97#	52.78±5.22#
	Intergroup	F=66.914, P<0.01			
	Time	F=112.199, P<0.01			
	Intergroup × time	F=11.872, P<0.01			
LVEF ($\bar{x}$ ± s, %)	Observation group (n=104)	37.11±4.56	39.34±2.24*,#	43.44±3.11*,#	47.59±4.33*,#
	Control group (n=104)	37.27±3.89	38.01±1.89#	40.57±2.43#	43.01±3.98#
	Intergroup	F=91.037, P<0.01			
	Time	F=221.934, P<0.01			
	Intergroup × time	F=17.657, P<0.01			

* Intergroup comparison, P<0.05; # Comparison with 1 day before treatment of the same group, P<0.05.

Blood Biochemical Indices Before and After Treatment

One day before treatment, there were no significant differences in the serum levels of cTnI and Hcy between the two groups (P>0.05). At 2, 3 and 4 weeks after treatment, the serum levels of cTnI and Hcy decreased significantly in both groups (P<0.05), particularly in the observation group (P<0.05) (Table 3).

Table 3. Blood biochemical indices before and after treatment

Index		1 d before treatment	2 w after treatment	3 w after treatment	4 w after treatment
cTn I ($\bar{x}$ ± s, ng/L)	Observation group (n=104)	68.55±6.36	62.89±6.88*,#	57.68±6.29*,#	51.37±5.67*,#
	Control group (n=104)	67.98±7.02	64.99±7.18#	62.09±6.72#	59.77±6.15#
	Intergroup	F=60.051, P<0.01			
	Time	F=145.348, P<0.01			
	Intergroup × time	F=17.716, P<0.01			
Hcy ($\bar{x}$ ± s, pg/ml)	Observation group (n=104)	28.46±3.85	22.95±2.98*,#	17.86±2.33*,#	11.53±2.14*,#
	Control group (n=104)	28.32±3.66	24.89±3.05#	20.52±2.77#	16.22±1.97#
	Intergroup	F=117.581, P<0.01			
	Time	F=981.999, P<0.01			
	Intergroup × time	F=25.001, P<0.01			

* Intergroup comparison, P<0.05; # Comparison with 1 day before treatment of the same group, P<0.05.

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Incidence of Adverse Reactions After Treatment

In the observation group there were 3 cases of hypotension, 2 cases of nausea, 1 case of dry mouth and 5 cases of gastrointestinal discomfort, with the incidence rate of adverse reaction of 10.58%. In the control group there were 1 case of hypotension, 2 cases of nausea, 2 cases of dry mouth and 3 cases of gastrointestinal discomfort, with the incidence rate of 7.69%. There were no significant differences in the incidence rate of adverse reaction between the two groups (P=0.470) (Table 4).

Table 4. Incidence of adverse reactions after treatment [n (%)]

Group	Adverse reaction				Incidence rate
	Hypotension	Nausea	Dry mouth	Gastrointestinal discomfort	
Observation (n=96)	3 (2.89)	2 (1.92)	1 (0.96)	5 (4.81)	11 (10.58)
Control (n=96)	1 (0.96)	2 (1.92)	2 (1.92)	3 (2.89)	8 (7.69)
P					0.470

Event-free Survival Analysis Results

During follow-up, there were 17 cases of MACE in the observation group, viz. 4 cases of cardiac death, 6 cases of myocardial infarction, 5 cases of congestive heart failure and 2 cases of emergency and selective revascularisation. There were 31 cases of MACE in the control group, i.e. 6 cases of cardiac death, 8 cases of myocardial infarction, 9 cases of congestive heart failure, 4 cases of ischemic stroke and 4 cases of emergency and selective revascularisation. The risk of MACE in the control group was 2.08 times that of the observation group (95% confidence interval = 1.18-3.66, P=0.008). The results of Kaplan-Meier survival analysis demonstrate that the difference is statistically significant (P<0.05) (Figure 1).

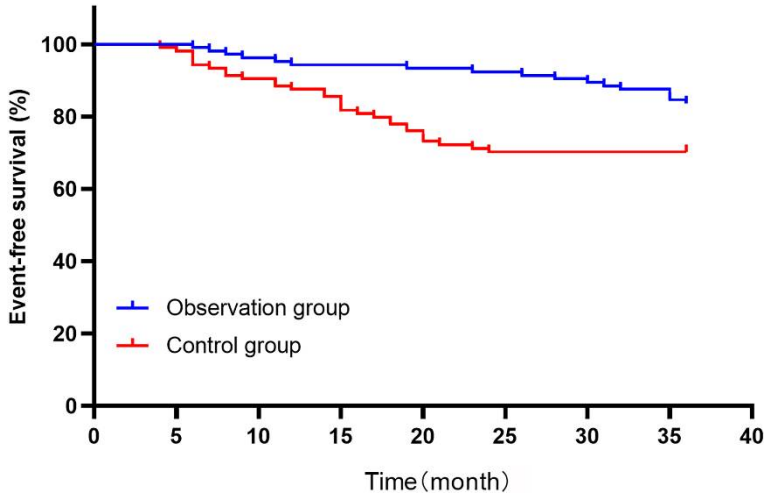

Figure 1. Kaplan-Meier survival curves

DISCUSSION

Ischemic cardiomyopathy is not only an irreversible heart disease, but also the most common cause of heart failure among the elderly [7]. It is triggered by myocardial fibrosis. To compensate for cardiac function, non-necrotic cardiomyocytes enlarge progressively and the myocardium thickens [8]. Myocardial cell necrosis and myocardial hypertrophy are the main pathological changes of ischemic cardiomyopathy, which result in clinical symptoms such as heart

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failure and arrhythmia [9]. If no effective measures are taken in time, the disease deteriorates easily, seriously threatening the life of patients. At present, treatment regimens based on diuretics, vasodilators, cardiac glycosides, lipid regulation and antiplatelet drugs have been widely applied. However, the myocardial contractility in the diseased area is markedly attenuated due to insufficient myocardial blood supply, and the cardiac function of elderly patients gradually declines with aging, leading to poor treatment outcomes and prognosis [10].

As a new type of drug which improves energy metabolism, trimetazidine can selectively inhibit β-oxidation, promote glucose metabolism and enhance cardiac contractility [11]. In addition, trimetazidine can also reduce Ca^{+} overload and prevent cell acidosis during myocardial ischemia, thus protecting cardiomyocytes. Clinically, it is commonly used to treat angina pectoris [12]. Levocarnitine (L-carnitine) is a necessary small molecular amino acid derivative in the process of cell energy metabolism. Levocarnitine plays an important role in fatty acid oxidation, which can facilitate the transport of long-chain fatty acids to the mitochondrial matrix for metabolism and increase the ATP level in cardiomyocytes, thus improving the energy supply [13]. Moreover, ischemia causes massive accumulation of fatty acyl coenzyme A in cardiomyocytes, and free carnitine in the mitochondria decreases due to great consumption, resulting in structural changes of cell membrane and cell apoptosis [14]. In contrast, levocarnitine can restore cell metabolism by supplementing free carnitine, thus relieving myocardial injury. In the study of Golwala et al. [15], 64 elderly patients with ischemic cardiomyopathy were treated with trimetazidine combined with levocarnitine. Their cardiac function was significantly improved after 2 weeks of treatment. In the present study, the total response rate of the observation group was 83.65%, which was significantly higher than that of the control group (68.27%). Moreover, LVESD and LVEDD of the observation group were significantly smaller than those of the control group at 2, 3 and 4 weeks after surgery, while LVEF of the observation group was higher than that of the control group, suggesting that trimetazidine combined with levocarnitine was effective and the cardiac function was remarkably improved. Probably, trimetazidine combined with levocarnitine can better promote the energy metabolism of cardiomyocytes, reduce the ventricular remodelling caused by cardiomyocyte apoptosis and necrosis, and prevent myocardial tissue injury.

Hyperhomocysteinemia is an independent risk factor for cardiovascular and cerebrovascular diseases [16]. Hcy can significantly reduce the concentration of intracellular glutathione peroxidase, leading to vascular endothelial cell injury and dysfunction and triggering coagulation-fibrinolysis imbalance *in vivo*, which induces vascular smooth muscle proliferation and promotes the formation of atherosclerotic plaques, thus resulting in heart failure. Romashko et al. [17] found that the serum level of Hcy in 128 patients with ischemic cardiomyopathy was evidently higher than that in healthy people. In the study of Lolodziejczak et al. [18], patients with ischemic cardiomyopathy were treated with statins, which decreased the serum level of cTnI significantly. Currently, whether trimetazidine combined with levocarnitine can improve the levels of cTnI and Hcy is rarely reported. The results of this study demonstrate that after 2, 3 and 4 weeks of treatment, the levels of serum cTnI and Hcy decrease significantly in both groups ($P<0.05$), being more so in the observation group ($P<0.05$). These findings prove again that trimetazidine combined with levocarnitine exerts a positive effect on ischemic cardiomyopathy.

Adverse reactions and prognosis are important criteria for drug compliance. In this study no adverse reaction was observed in the course of treatment and the treatment was well tolerated by patients. To further evaluate the prognosis of patients with ischemic cardiomyopathy treated with trimetazidine combined with levocarnitine, they were followed up for 3 years after treatment. The

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results of Kaplan-Meier survival analysis show that the event-free survival rate of the observation group is significantly higher. Thus, trimetazidine combined with levocarnitine can better improve the prognosis and quality of life of patients without increasing the risk of adverse reactions.

CONCLUSIONS

Trimetazidine combined with levocarnitine can effectively improve the cardiac function and the levels of cTnI and Hcy in patients with ischemic cardiomyopathy. Moreover, the incidence rate of adverse reactions does not increase, which is helpful to the prognosis of patients. However, the detailed mechanism of the treatment needs to be further studied.

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