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Original Article

Levocarnitine and torasemide combination improved ventricular remodeling in patients with acute exacerbation of chronic heart failure

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Abstract: Objective: The goal of this study was to investigate the effect of the combination of torasemide and levocarnitine for the treatment of acute exacerbation of chronic heart failure. Methods: A total of 128 patients with acute exacerbation of chronic heart failure were randomly divided into two groups. The control group (n = 63) was treated with levocarnitine and the observation group (n = 65) was treated with torasemide and levocarnitine and the clinical efficacy, ventricular remodeling, and quality of life were compared with the control group. Results: The total effective rate (92.3%) in the observation group was significantly higher than that in the control group (P = 0.004). After treatment, the ventricular remodeling indicators NT-proBNP, plasma renin (PRA), angiotensin II (Ang II), aldosterone (ALD), endothelin (ET) in the observation group were significantly lower than in the control group (P<0.0011). After treatment, the Living With Heart Failure questionnaire (MLWHF), and left ventricular end-diastolic volume (LVEDV) and Left ventricular end- systolic volume (LVESV) of the observation group were significantly lower than those of the control group. SF-36 left ventricular ejection fraction scores were significantly higher than those in the control group. After treatment, metalloproteinase 2 (MMP-2), 9 (MMP-9), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in the observation group were significantly lower than in the control group. Metalloproteinase inhibitor 1 (TIMP-1) and 2 (TIMP-2) were significantly higher than in the control group (all P<0.001). Significantly fewer patients experienced adverse reactions in the observation than in the control group (P<0.05). Conclusion: In the treatment of patients with acute exacerbation of chronic heart failure, the combination of torasemide and levocarnitine had a stronger therapeutic effect on the improvement of ventricular remodeling symptoms, and enhanced the quality of life of patients.

Keywords: Torasemide, acute exacerbation of chronic heart failure, ventricular remodeling, quality of life

Introduction

Chronic heart failure is a common clinical disorder [1], often related to myocardial infarction and cardiomyopathy. Chronic heart failure is a complication of hemodialysis of patients with chronic renal failure [2]. Owing to patient arrhythmia and severe myocardial injury, patients are often in a state of acute exacerbation [3]. Excessively high left ventricular end-diastolic pressure and overloaded hemodynamics may lead to decompensation of heart function, impaired ventricular filling, and impaired ejection function [4, 5].

Clinical statistics show that the incidence of chronic heart failure in cardiovascular disease is extremely high, up to 40%, and most patients have acute exacerbation of chronic heart failure. Therefore, clinical treatment has received particular attention. Patients with heart failure suffer repeated attacks and the success rate of cure is low. Therefore, the purpose of the clinical treatment is mainly to improve the quality of life of patients and to reduce the mortality rate [6, 7].

At present, drugs for the treatment of chronic heart failure are mostly diuretics, renin-angiotensin-aldosterone system inhibitors, and inotropic agents, which improve patients' clinical symptoms, increase the quality of life, and prolong lifespan. However, long-term use of these drugs could lead to adverse reactions,

such as nausea, vomiting, or rashes [8, 9]. The drug levocarnitine facilitates metabolism. It can increase cardiomyocyte oxidation and promote cardiomyocyte metabolism, which may subsequently reduce the accumulation of drug metabolites in the myocardium and prevent damage to cardiac muscle cells [10]. Torasemide, a new type of long-acting diuretic with a strong diuretic effect, can significantly reduce the common symptoms of electrolyte imbalance resulting from the use of diuretics, and is used widely in clinical applications [11]. There are currently few established clinical applications for the combination of two drugs in patients with chronic heart failure. Therefore, this study used a combination of drugs to investigate the clinical efficacy of torasemide plus levocarnitine in patients with acute acerbation of chronic heart failure.

A total of 128 patients with chronic heart failure in our hospital were selected and treated with levocarnitine or the combination of torasemide combined with levocarnitine. The clinical effect of the combined treatment in patients with acute exacerbation of chronic heart failure on the improvement of patients' ventricular remodeling and quality of life was investigated.

Material and methods

General information

A total of 128 patients with chronic heart failure in Traditional Chinese Medicine Hospital of the Xinjiang Uygur Autonomous Region were selected and randomly divided into two groups with a Random Number Table. There were 63 patients in the control group and 65 cases patients in the observation group. There were no significant differences in general clinical data, such as age, gender, and disease course between the two groups. All patients were aware of the clinical protocol before the trial and provided informed consent. This study was approved by the Hospital Ethics Committee.

Inclusion criteria: patients met the diagnostic criteria of the *Guidance on Chronic Heart Failure in China* of the Cardiovascular Branch of the Chinese Medical Association [12]; patients had clinical symptoms visible on a chest X-ray, such as respiratory distress and pulmonary edema; patients were NYHA Class III to IV; patient compliance was good; and patients could actively cooperate with the diagnosis and treatment of medical staff.

Exclusion criteria: patients with other cardiovascular diseases; patients with malignant tumors; patients with systemic immune system diseases; patients with allergies to treatment drugs; patients in pregnancy or lactation; and patients with mental illness.

Methods

Both groups of patients were treated with the conventional treatment. The control group was treated with an intravenous infusion of levocarnitine injection (Sigma Chemical Company, St Louis, Missouri, USA and prepared in 100 ml of physiological saline or glucose;). The applied treatment dose was 2 grams once per day for 2 days consecutively. The observation group was treated with an intravenous injection of torasemide in the control group (Taishotoyama Pharmaceutical Co. Ltd. Toshima-Ku, Tokyo, Japan; 20 mg, once per day). The course of treatment for both groups was 1 week. Samples of venous blood were collected from both groups of patients before and after treatment for the in evaluation of clinical indicators.

Observation indicators and efficacy evaluation

Clinical efficacy evaluation criteria: If the treated patient's clinical symptoms were relieved, and their cardiac function was be improved a minimum of two levels (cardiac function is grade I), the treatment was considered markedly effective. If the patient's clinical symptoms were relieved and their cardiac function was improved by at least 1 level (cardiac function is not grade I), it was deemed effective. If the patient's clinical symptoms were not improved or deteriorated, the treatment was invalid. Total efficiency = (markedly effective + effective)/ total number of cases [13].

Determination of NT-proBNP

The venous blood was centrifuged and the supernatant plasma was collected and NT-proBNP was detected by using a rapid immunoassay analyzer (Mitsubishi Kagaku Iatron, Inc.). Determination of PRA, Ang II, and ALD: The venous blood was centrifuged to collect plasma and the contents of the above indicators in plasma were detected by using enzyme-linked

Table 1. Comparison of general clinical data in two groups of patients ($\bar{x} \pm s$)

Index	Control group	Observation group	T/χ^2	P
Age (year)	58.23±6.65	60.56±6.87	-1.949	0.054
Gender (M/F)	31/32	34/31		
Left ventricular ejection fraction (%)	34.81±4.32	34.66±3.97	0.205	0.838
Left ventricular end diastolic phase (mm)	64.21±6.43	63.98±7.09	0.192	0.848
Creatinine (μmol/l)	79.23±9.86	79.23±8.87	0.000	1.000
Blood sodium (mmol/l)	139.23±14.32	139.23±17.43	0.000	1.000
Blood potassium (mmol/l)	3.89±0.43	3.79±0.56	1.131	0.260

Table 2. Comparison of clinical data in two groups of patients [n (%)]

Groups	Cases (n)	Significant	Effective	Invalid	Total efficiency
Control group	63	20	26	7	46 (73.0)
Observation group	65	30	30	5	60 (92.3)
χ^2					8.365
P					0.004

immunosorbent assay (NanJing SenBeiJia Biotechnology Co. Ltd, Najing, Jiangsu, China). Determination of ET: A radioimmunoassay was conducted in strict accordance with the kit instructions (Shanghai Xinfan Biological Technology Co. Ltd. Shanghai, China). LVEDV, LVESV, and LVEF: Color Doppler ultrasound was used for the detection of these parameters.

Determination of MMP-2, MMP-9, TIMP-1, TIMP-2, TNF-α, and IL-6: Venous blood was centrifuged at the supernatant plasma was collected and used for the determination of the serum content of the indicated proteins. An enzyme-linked immunoassay was performed in accordance with the manufacturer's instructions.

Quality of Life Assessment: Health Survey Profile and Minnesota Living with Heart Failure Questionnaire (MLWHF) were used for assessment. SF-36 scores of the patient's physiological function, vitality, general health, emotional function, mental health, social function, and physical pain were rated based on physical and psychological aspects in eight dimensions and 36 items, respectively. MLWHF questionnaires were used to assess the effect on the degree of heart failure in patients within 1 month. In total, there were 21 questions and a total of 0-5 points. A higher score indicated a greater on the impact of heart failure on patients [14].

Adverse reactions of note recorded during the treatment were nausea, electrolyte imbalance, hypokalemia, and skin rash; other symptoms were recorded during treatment.

Statistical methods

Statistical analyses of the data were computed by SPSS 20.0 software. The measurements are expressed as the mean ± standard deviation ($\bar{x} \pm s$). The t-test was used for comparison between groups. The enumeration data are expressed as a percentage (%) and χ^2 was used as the test statistic. Values of $P<0.05$ were considered to be statistically significant.

Results

Comparison of general clinical data

There were no significant differences between the two groups in terms of age, gender, left ventricular ejection fraction, left ventricular diastolic end-diastolic diameter, serum creatinine, serum sodium, serum potassium, and other general data ($P>0.05$) (**Table 1**).

Comparison of clinical efficacy

The total effective rate of the control group and the observation group was 73.0% and 92.3%, respectively. The total effective rate of the observation group was significantly higher than that of the control group ($P = 0.004$) (**Table 2**).

Comparison of NT-proBNP, PRA, angII, ALD, and ET levels before and after treatment

There were no significant differences in NT-proBNP, PRA, AngII, ALD, and ET before treatment between the two groups ($P>0.05$). After treatment, these parameters were significantly lower in the observation group than in the control group with significant differences ($P< 0.0011$) (**Table 3**).

Table 3. Comparison of NT-proBNP, PRA, Ang II, ALD and ET levels in two groups of patients ($\bar{x} \pm s$)

Index	Time	Control group	Observation group	T	P
NT-proBNP (pg/ml)	Before treatment	669.32±66.75	673.62±77.54	-0.336	0.738
	After treatment	523.44±50.76	419.76±44.75	12.268	<0.001
PRA (ng/ml)	Before treatment	2.25±0.32	2.24±0.27	0.191	0.849
	After treatment	1.89±0.19	1.60±0.23	7.764	0.000
Ang II (pg/ml)	Before treatment	185.44±20.97	183.34±19.87	0.708	0.480
	After treatment	161.27±18.54	131.76±17.53	6.294	<0.001
ALD (pg/ml)	Before treatment	237.09±28.64	236.23±27.43	0.779	0.492
	After treatment	194.83±21.54	170.23±19.97	6.784	<0.001
ET (pg/ml)	Before treatment	86.54±9.87	80.98±8.87	0.829	0.528
	After treatment	87.12±8.89	42.23±8.54	31.816	<0.001

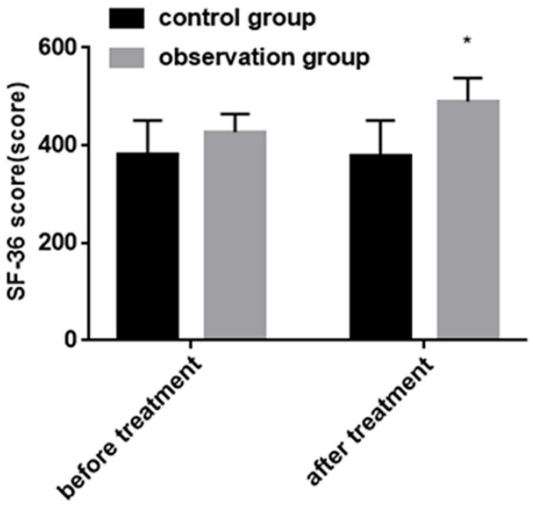

Figure 1. Comparison of SF-36 scores in the two groups of patients. *P<0.01 compared with control group after treatment.

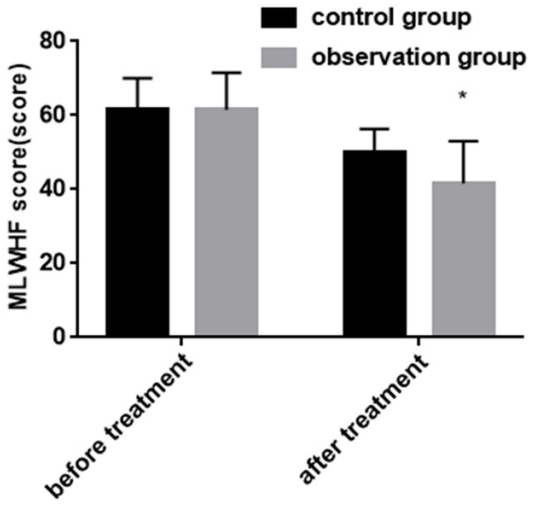

Figure 2. Comparison of MLWHF scores in the two groups of patients. *P<0.01 compared with control group after treatment.

Comparison of SF-36 and MLWHF scores

There were no differences in SF-36 and MLWHF scores before treatment between the two groups; after tre atment, the scores of SF-36 in the observation group were significantly higher than those in the control group (P<0.001) and the scores of MLWHF in the observation group were significantly lower than those in the control group (P<0.01) (**Figures 1** and **2**).

Comparison of cardiac function indicators

Before treatment, there were no significant differences in cardiac function parameters, such as LVEDV, LVESV, and LVEF, between the two groups. After treatment, LVEDV and LVESV were significantly higher in the control group than those in the observation group (P<0.001). LVEF was significantly higher in the observation group than that in the control group (**Table 4**).

Comparison of HR and blood pressure before and after treatment

Before treatment, there were no significant differences in HR and blood pressure indicators (SBP and DBP) between the two groups. After treatment, these parameters were significantly lower in the observation group than in the control group (P<0.001) (**Table 5**).

Comparison of inflammatory factors before and after treatment

Before treatment, there were no significant differences in inflammatory factors, such as MMP-2, MMP-9, TIMP-1, TIMP-2, TNF-α, and IL-6, between the two groups. After treatment, MMP-2, MMP-9, TNF-α, and IL-6 were significantly lower in the observation than in the control

Table 4. Comparison of cardiac function in two groups of patients ($\bar{x} \pm s$)

Index	Time	Control group	Observation group	T	P
LVEDV (ml)	Before treatment	152.33±17.64	154.98±11.86	0.432	0.498
	After treatment	145.65±15.86	126.43±13.54	7.665	<0.001
LVESV (ml)	Before treatment	74.54±8.09	73.83±7.99	0.292	0.621
	After treatment	62.32±6.54	50.92±5.87	12.308	<0.001
LVEF (%)	Before treatment	42.31±4.56	41.90±4.97	0.923	0.459
	After treatment	51.87±6.54	59.53±6.87	-7.542	<0.001

Table 5. Comparison of heart rate and blood pressure before and after treatment in two groups of patients ($\bar{x} \pm s$)

Index	Time	Control group	Observation group	T	P
HR (t/min)	Before treatment	92.37±10.98	91.95±9.54	0.623	0.739
	After treatment	89.93±9.99	72.54±6.87	11.950	<0.001
SBP (mmHg)	Before treatment	138.54±17.43	136.86±17.54	0.592	0.621
	After treatment	119.09±12.45	101.21±11.21	9.693	<0.001
DBP (mmHg)	Before treatment	83.45±9.09	84.56±9.98	0.502	0.498
	After treatment	85.54±8.99	60.63±7.09	20.042	<0.001

Table 6. Comparison of inflammatory factors before and after treatment in the two groups of patients (pg/ml, ($\bar{x} \pm s$))

Index	Time	Control group	Observation group	T	P
MMP-2	Before treatment	369.54±45.54	362.65±39.75	0.764	0.865
	After treatment	259.54±30.97	185.23±19.54	16.726	<0.001
MMP-9	Before treatment	269.34±29.75	268.87±29.09	0.684	0.524
	After treatment	182.12±20.87	130.34±11.54	18.301	<0.001
TIMP-1	Before treatment	188.87±21.23	250.09±29.75	0.732	0.493
	After treatment	189.56±19.97	299.75±30.97	-24.695	<0.001
TIMP-2	Before treatment	156.09±17.54	162.75±19.65	0.486	0.386
	After treatment	230.07±27.43	309.23±32.65	-15.073	<0.001
TNF-α	Before treatment	192.76±19.87	199.45±21.09	0.497	0.397
	After treatment	153.23±17.43	100.12±11.86	21.006	<0.001
IL-6	Before treatment	207.23±22.54	210.34±23.09	0.573	0.486
	After treatment	144.98±17.53	112.97±17.53	10.647	<0.001

group. Conversely, TIMP-1 and TIMP-2 were significantly higher in the control group (P<0.001) (**Table 6**).

Comparison of adverse reactions

In the observation group, five patients reported adverse reactions. The incidence was 7.7%. In the control group, nine patients reported adverse reactions and the incidence was 14.3%. The number of patients experiencing adverse reactions in the observation group was significantly lower than that in the control group (P<0.05) (**Figure 3**).

Discussion

Clinical treatment of heart failure is to enhance myocardial contractility and reduce the heart load, thereby improving the hemodynamics of patients with heart failure [15]. The clinical medication for the disease mainly comprises diuretics or inotropic agents. These can alleviate the condition and improve the quality of life [16]. In this study, the effects of torasemide combined levocarnitine was investigated on ventricular remodeling and quality of life in patients with acute exacerbation of chronic heart failure. After treatment, improved ven-

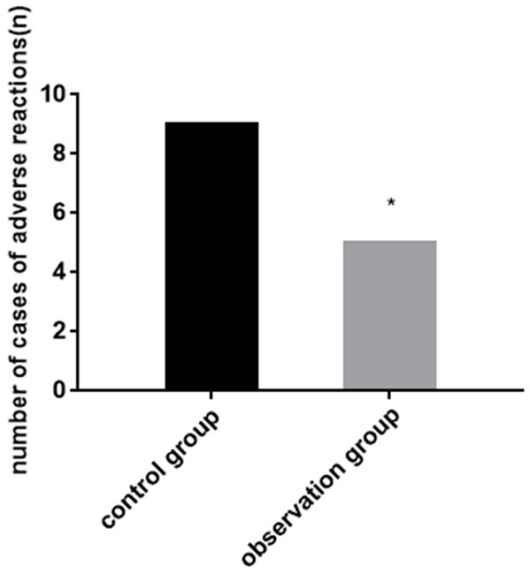

Figure 3. Comparison of adverse reactions in the two groups of patients. *P<0.05 compared with control group.

tricular remodeling was observed along with increased heart and lung function, reduced levels of inflammatory factors, and enhanced patient quality of life. These results suggest a more effective clinical treatment and have provided a scientific basis for further clinical research.

Levocarnitine is involved in the lipid metabolism process. Significant reductions in the level of levocarnitine in the body are found in cases of heart failure. After *in vitro* levocarnitine administration, acyl-CoA is produced in myocardial cells from the mitochondria of patients with heart failure, which inhibits destruction of metabolic enzymes, protects the cell membrane, and ensures normal function of myocardial cells [17], which is confirmed by our study as both LVEDV and LVESV levels improved.

Torasemide is a new type of diuretic and play a role in the retention of sodium and the removal of potassium, which can promote urination and reduce the cardiac load [11]. This is also consistent with our findings. In the observation group, the level LVEDV and LVESV were significantly lower than in the control group, which indicates better cardiac functions. The improvement of heart rate and blood pressure in the observation group was also significantly better than that in the control group, which indicated that the combination therapy improved heart function and enhanced treatment. Pharmacological studies also found that potassium removal by torasemide mainly occurs in the liver, so there is less damage to renal function, and a lower incidence of hypokalemia following long-term use [18]. Related studies have established the diuretic effect of torasemide, which has a long duration in the body and a higher bioavailability than conventional diuretics. Therefore, the drug has been used widely in clinical practice and has become a major representative diuretic.

It has been reported that the treatment of torasemide in mice with chronic heart failure can improve the symptoms of ventricular remodeling and have a good therapeutic effect on myocarditis [21]. Pharmacological studies have shown that ET has a strong vasoconstrictor effect, so the level of ET in patients with heart failure is significantly increased. ET synthesis and secretion are promoted through various mechanisms. Therefore, this indicator is also considered to be the main factor in the determination of heart failure function. The main indicator in the determination of the efficacy of heart failure treatment is NT-proBNP, which is released from the ventricle. When the myocardial wall is damaged, the content of released NT-proBNP is increased; thus, the more serious the heart failure, the higher the content in the body, making it a specific, sensitive indicator of heart failure [19].

When heart failure occurs, MMPs (MMP-2 and MMP-9) are activated, resulting in damage to the myocardial cells through the destruction of the collagen network structure. During this process, the MMP/TIMP balance system is destroyed, TIMP is significantly reduced, and left ventricle remodeling occurs in response to continuous wall pressure. In addition, MMPs are related to the inflammatory cytokines TNF-α and IL-6. Prolonged overexpression of TNF-α and IL-6 in patients with heart failure inhibits myocardial contractile function. Through the regulation of MMP expression, this type of inflammatory factor causes ventricular remodeling, myocardial damage, and aggravated heart failure [20]. In this study, it was found that the improvement of the ventricular remodeling indicator in the observation group was better than that in the control group, which indicated that the combination therapy protected cardiomyocytes and reduced damage to the myocar-

dial wall. A significant reduction of inflammatory cytokines TNF-α and IL-6 was also observed, which inhibited MMP activation and prevented myocardial damage. Combination therapy can therefore improve the symptoms arising from the overactivation of multiple systems in the body and restore the balance of various factors and hormones in the body, to return multiple indicators to normal levels, reduce the incidence of heart failure, and decrease ventricular remodeling.

Quality of life indicators were assessed by using the SF-36 and MLWHF scales. The SF-36 scale determines the patient's physical and mental health, whereas the MLWHF scale determines the severity of the patients' heart failure symptoms; thus, the combination of both scales produces a more accurate assessment of the patient's quality of life. The improvement of the quality of life scale MLWHF in the observation group was also significantly better than that in the control group, which demonstrated that the combination therapy could significantly relieve the patients' clinical symptoms and improve their health. The results of this study are similar to previous studies. It has been reported that levocarnitine significantly improved cardiac function in patients with chronic heart failure and the six-minute walking distance test was also significantly better than that of a placebo group, which demonstrated a clear improvement in the quality of life of patients. The use of torasemide in patients with chronic heart failure improved the symptoms of myocardial remodeling. The improved quality of life was significantly greater than that in the control group furosemide [10, 22].

There are some limitations to this study. The clinical effects of L-carnitine alone and the combination of the two drugs were discussed separately. The therapeutic effect of torsemide alone was not analyzed. Therefore, the next step of this topic can be further studied in this aspect. In addition, the therapeutic effect of combination therapy in patients with chronic heart failure and other disorders can be studied to provide more medical treatment for the disease.

In summary, the combination of torasemide and levocarnitine in patients with chronic heart failure significantly improved the symptoms of ventricular remodeling, enhanced the quality of life and had a high clinical value. Therefore, it is worth investigating the drug combination and developing it for clinical practice.

Disclosure of conflict of interest

None.

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