Evaluating the Efficacy of Levosimendan on Ageing Chronic Heart Failure Using Blood Levels of cTnT, IGF-1 and NT-proBNP

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Abstract

Objective: To study the changes in the levels of blood troponin T (cTnT), Insulin-like Growth Factor 1 (IGF-1), and the N-Terminal of the Prohormone Brain Natriuretic Peptide (NT-proBNP) to evaluate the efficacy and safety of levosimendan on chronic heart failure.

Methods: Seventy four hospitalized ageing patients stages III-IV of cardiac function and a left ventricular ejection fraction <40% was selected. Thirty eight were administered routine treatments; the remaining 36 patients were administered routine treatments plus levosimendan. Vital signs, clinical presentations, changes in hemodynamics, and levels of IGF-1, cTnT, and NT-proBNP were monitored before and at 72 hours after treatment.

Results: The clinical effective rate was 83.3% (30/36, treatment) and 55.3% (21/38, control); the difference was statistically significant (p<0.05). The IGF-1 levels increased, the cTnT levels decreased, and the NT-ProBNP levels decreased in the treatment and control groups, respectively, at 72 hours after treatment. Systolic blood pressure decreased, mean diastolic blood pressure decreased, and heart rate decreased in the treatment and control groups, respectively, at 72 hours after treatment. The incidence rate of adverse effects was not statistically significant between the 2 groups (P > 0.05).

Conclusion: Levosimendan could be effective in treating chronic congestive heart failure; blood levels of cTnT and IGF-1 could be used to accurately evaluate its efficacy and with better specificity than with NT-proBNP.

Keywords: Levosimendan; cTnT; IGF-1; NT-proBNP; Heart failure

Introduction

Chronic heart failure could reduce cardiac output, causing poor perfusion of vital organs and, subsequently, severe complications, including shock, cardiac arrest, and death. The mortality rate of chronic heart failure is as high as 40-60%, and the 5-year survival rate is <50%. As an end-stage of heart disease, heart failure is life-threatening; however, early diagnosis and treatment could effectively control and even reverse the disease. Early diagnosis, accurate evaluation, and standardized heart-failure treatments are especially important for the management of this disease.

The main indices for the evaluation of cardiac function are echocardiography and blood biomarkers. Because blood biomarkers are easily detected and change substantially within a short period of time, they are widely used in clinical practice to evaluate the curative effects of the treatment during hospitalization. The N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) is the most commonly used biomarker in clinical practice; however, NT-proBNP could be affected by several factors, such as age, Heart Rate (HR), atrium size, ventricular size, ventricular tension, renal function, and Body Mass Index (BMI) and thus could deviate when tested for evaluating the disease.

Insulin-like Growth Factor 1 (IGF-1) is a new index for the evaluation of heart failure, but it has not been widely used in clinical practice. Current opinion is that IGF-1 is an important cardiac hormone that participates in multiple physiological and pathological processes. IGF-1 improves blood ejection, increase heart output, influence cardiac ion channels, and stimulate the growth of myocardial cells. In addition, IGF-1 dilates blood vessels; reduces vascular resistance, blood glucose, and blood lipids; and promotes cell growth, differentiation, and wound repair. The

Table 1: General characteristics of the patients in the 2 groups.

Parameters	Treatment group (n=36)	Control group (n = 38)	p-value
Male [n, (%)]	24 (66.7)	21(55.3)	0.17
Female [n, (%)]	12 (33.3)	17(44.7)	
Age (years, x ± s)	69.9 ± 11.8	68.7 ± 15.8	0.39
Weight (kg, x ± s)	69.2 ± 15.2	67.4 ± 11.3	0.23
RHD [n, (%)]	5(13.9)	4(10.5)	0.09
Hypertensive heart disease [n, %)]	3(8.3)	3(7.9)	
CHD [n, (%)]	15(41.7)	17(44.7)	
Dilated cardiomyopathy [n, (%)]	7(19.4)	10(26.3)	
Others [n, (%)]	6(16.7)	4(10.6)	
Cardiac function grade III [n, (%)]	17(47.2)	23(60.5)	0.12
Cardiac function grade IV [n, (%)]	19(52.8)	15(39.5)	0.12

p>0.05, comparing with the control group, suggesting that the differences between the 2 groups were not statistically significant.

pathophysiological effects of IGF-1 on heart failure include inhibiting myocardial apoptosis, promoting angiogenesis in the heart, and increasing myocardial growth and hypertrophy. In addition, IGF-1 could directly affect the myocardial tissues or cells in heart failure patients and increase myocardial contractility, and has been considered a reliable index for evaluating cardiac function [1-3].

Myocardium impairment can occur in chronic heart failure, which allows several proteins, including Cardiac Troponin (cTn), to be released from myocardial cells and, subsequently, appear in peripheral circulation. An increase in cTnI in the myocardium was first discovered in 1987 in a patient with Myocardial Infarction (MI), although during the past decade, studies have shown that an increase in cTn was found in patients with severe chronic heart failure (New York Heart Association [NYHA] grade III or IV) and that the level of cTn was significantly associated with the severity of hemodynamic abnormalities and could be used to predict the risk of mortality after discharge or rehospitalization [5-8]. According to these close associations, we speculated that cTnT could also be used as an important biochemical biomarker to evaluate the prognosis of patients with heart failure and treatment efficacy.

Levosimendan, a calcium sensitizer, is a new positive inotropic drug that has been applied in clinical practice in recent years and has been commercially available in Sweden since 2000. Previous studies showed that levosimendan induced several changes in the heart and blood vessels and, subsequently, increased blood flow in the coronary arteries, pulmonary circulation, and peripheral circulation [9]. Previous clinical studies about levosimendan focused mainly on the improvement of the symptoms in patients or changes in the levels of NT-proBNP. In the present study, the changes in serum (plasma) levels of IGF-1, cTnT, and NT-ProBNP after treatment were compared between the treatment and control groups to explore the values of these as new biomarkers for evaluating the efficacies of treating heart failure with levosimendan, and thus provide new methods by which to evaluate the clinical efficacies of heart-failure drugs.

Subjects and Methods

Subjects

Inclusion criteria of the patients in this study were as follows: 1) Symptoms or signs of cardiac dysfunction; 2) Ages between 60 and 91 years; 3) Met the criteria for the diagnosis of NYHA grades III-IV (American Heart Association, AHA); 4) Echocardiography in Qilu

Table 2: Insulin-like growth factor 1 (IGF-1) levels before and at 72 hours after treatment in the 2 groups.

Group	n	Before the treatment	After the treatment
Treatment group	36	108.2 ± 85.5	129.8 ± 54.1[ab]
Control group	38	115.3 ± 63.2	122.1 ± 71.3

[a]p<0.05, comparing with the levels before treatment; [b]p<0.05, comparing with the control group.

hospital of Shandong University confirmed that the Left Ventricular Ejection Fraction (LVEF) was ≤ 40%; and 5) Signed informed-consent forms. The exclusion criteria were as follows: 1) Acute left-sided heart failure caused by acute MI or other factors; 2) Severe simple valvular stenosis (aortic valve or mitral valve), hypertrophic cardiomyopathy, or restrictive cardiomyopathy; 3) Severe liver/renal failure and severe ventricular arrhythmia; 4) Allergy to the tested drugs or contraindications to the tested drugs; 5) Uncontrolled thyroid diseases; 6) Supine systolic pressure <90 mmHg or >180 mmHg; 7) Impaired liver/renal function; 8) Cardiogenic shock, hypovolemia, or could not use vasodilator; and 9) Participated in other clinical studies within the past 3 months.

Seventy four hospitalized ageing patients who met the criteria of diagnosis and classification of heart failure (American College of Cardiology ACC/AHA, 2011) and who were initially diagnosed or rediagnosed in the Department of Cardiology, Qilu Hospital of Shandong University, Shandong, China, between January 2013 and December 2013 were included in the present study. There were 45 males and 29 females; the underlying diseases of these patients comprised coronary heart disease (CHD, n=32), dilated cardiomyopathy (n=17), Rheumatic Heart Disease (RHD, n=9), hypertensive heart disease (n=6), and other heart diseases (n=10). Chronic heart failure was diagnosed according to the guidelines for the diagnosis and management of heart failure in adults issued by ACC/AHA in 2005.The study protocol was approved by The Ethics Committee of Qilu Hospital of Shandong University.

Patient grouping

Routine heart-failure treatments were administered to all patients. Aspirin, statins, vasodilators, diuretics, digitalis, β-receptor blockers, aldosterone receptor antagonists, angiotensin receptor blocker, and angiotensin converse enzyme inhibitors were used according to each patient's conditions. Thirty six patients were randomly selected from these eligible patients as the treatment group; the remaining 38 were the control group. The treatment group was administered levosimendan (12.5 mg/5 ml, Yuewen, Shandong Qilu

Pharmaceutical Company, Jinan, China) in addition to routine heart-failure treatment, with the initial loading dose of 12 μg/kg and a pump injection time >10 minutes. If the patient tolerated the treatment and had no obvious adverse effects, pump injection with a dose of 0.1 μg·min^{-1}·kg^{-1} was administered for 24 continuous hours. The control group was administered only routine heart-failure treatment.

Evaluation of the treatment efficacies

1) Vital signs, symptoms of heart failure, and the other signs, including weakness, pulmonary rales, liver enlargement, lower limb edema, and distention of the jugular vein were recorded in the patients in each group. Treatment efficacy was evaluated at 72 hours after treatment as follows: excellent: symptoms completely or nearly disappeared and cardiac function improved by ≥ 2 grades; effective: symptoms alleviated and cardiac function improved by 1 grade; and ineffective: symptoms were nearly identical to those before treatment or the improvements were below the effective criteria and cardiac function was not improved or even aggravated. Cardiac function was classified according to the NYHA functional classification criteria.

2) The IGF-1 levels in the treatment and control groups were measured before and at 72 hours after treatment. In brief, 3.0 mL of fasting morning blood were taken from the cubital vein, centrifuged at 4.0°C and 3000 rpm for 15 minutes and the serum collected and stored at -80°C. An automatic Enzyme-Linked Immunosorbent Assay (ELISA) system was used for the analysis of IGF-1; the ELISA kits were purchased from Shanghai Yanhui Biological Technology Co., Ltd (Shanghai, China).

3) The serum cTnT levels in the treatment and control groups were measured before and at 72 hours after treatment. In brief, serum was collected using the methods described for measuring IGF-1 levels. A double-antibody sandwich ELISA was then performed to measure cTnT using the ELISA kits from Shanghai Yanhui Biological Technology Co., Ltd.

4) The plasma NT-ProBNP levels in the treatment and control groups were measured before and at 72 hours after treatment. In brief, 3.0 mL of fasting morning blood were taken from the cubital vein and centrifuged at 4°C and 3,000 rpm for 15 minutes. Plasma was collected, anti-coagulated with heparin, and stored at -20°C. Triage Meter Plus (Biosite, San Diego, CA, USA) and an automatic ELISA system were used for the analyses. 5) Changes in the patient hemodynamic indices were compared between the 2 groups. 6) ECG, vital signs, experimental examinations and incidence rate of adverse effects, were collected. Routine tests included collecting blood and urine samples to analyze electrolytes, liver function, renal function, blood lipids and blood glucose.

Measuring hemodynamic indices

Blood pressure and heart rate of the patients in each group were measured at the same time each at morning, at noon and at the same time each night before and at 72 hours after treatment. All measurements were taken at same time and with the patients in the same position, and the mean values were calculated.

Statistical analyses

SPSS 17.0 was used for the statistical analyses. Quantitative data were described as means and standard divisions and qualitative data were described as frequencies and rates. A paired t-test was used for the comparisons between the levels before and after treatment within each group, a chi-squared test was used for the comparisons of the

Table 3: Cardiac troponin T (cTnT) levels (pg/mL) before and at 72 hours after treatment in the 2 groups.

Group	n	Before the treatments	After the treatments
Treatment group	36	96.1 ± 48.9	70.4 ± 45.1[ab]
Control group	38	77.2 ± 58.9	65.9 ± 44.3[a]

[a]p<0.05, comparing with the level before the treatments; [b]p<0.05, comparing with the control group.

Table 4: N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) levels (pg/mL) before and at 72 hours after treatment in the 2 groups.

Group	n	Before the treatment	After the treatment
Treatment group	36	8692.0 ± 3855.7	5733.9 ± 1429.8[ab]
Control group	38	7087.7 ± 3386.3	5151.6 ± 2143.9

[a]p<0.05, comparing with the level before the treatments; [b]p<0.05, comparing with the control group.

rates and a Spearman rank correlation analysis was used to investigate the associations among the clinical parameters. All statistical analyses were 2-sided and p<0.05 was considered statistically significant.

Results

General characteristics of the patients

Seventy-four patients comprising 36 in the treatment group and 38 in the control group were included in the statistical analyses. The sex, age, weight, cardiac function (NYHA) and underlying heart diseases were not significantly different between the 2 groups (Table 1). During the study, 2 patients died in both the treatment and control groups. In the treatment group, 1 patient died from ventricular fibrillation and 1 from respiratory failure; in the control group, both patients died from fatal arrhythmia caused by sudden cardiac death, large area MI and poor motility of the ventricular wall.

Evaluation of the efficacies

1) Efficacy: The overall effective rate was 83.3% (30/36) and 55.3% (21/38) in the treatment and control groups, respectively; the difference was statistically significant (P=0.027).

2) IGF-1: The IGF-1 levels were 108.2 ng/mL ± 85.5 ng/mL in the treatment group and 115.3 ng/mL ± 63.2 ng/mL in the control group before treatment; however, the levels increased to 129.8 ng/mL ± 54.1 ng/mL in the treatment group and 122.1 ng/mL ± 71.3 ng/mL in the control group after treatment, respectively. Compared with those before treatment, the IGF-1 levels increased by 44.6 ng/mL ± 29.6 ng/mL and 6.8 ± 5.6 ng/mL (95% Confidence Interval [CI]: 7.0-68.7) in the treatment and control groups, respectively; the difference was statistically significant (t=2.486, P=0.018) (Table 2).

3) cTnT: The cTnT levels were 96.1 pg/mL ± 48.95 pg/mL in the treatment group and 77.2 pg/mL ± 58.9 pg/mL in the control group before treatment; however, the levels decreased to 70.4 pg/mL ± 45.1 pg/mL in the treatment group and 65.9 pg/mL ± 44.3 pg/mL in the control group after treatment. Compared with those before treatment, the cTnT levels decreased by 40.3 pg/mL ± 20.8 and 11.3 pg/mL ± 6.9 pg/mL (95% CI: 5.98-52.05) in the treatment and control groups, respectively; the difference was statistically significant (t=2.53, P= 0.015) (Table 3).

4) NT-proBNP: The NT-proBNP levels were 8692.0 pg/mL ± 3855.7 pg/mL in the treatment group and 7087.7 pg/mL ± 3386.3 pg/mL in the control group before treatment; however, the levels decreased to 5733.9 pg/mL ± 1429.8 pg/mL and 5151.6 pg/mL ± 2143.9 pg/mL after treatment, respectively. Compared with those before treatment, the NT-proBNP levels decreased by 2958.1 pg/

Table 5: Changes in hemodynamic indices in the 2 groups before and after the treatments.

Group	Systolic pressure (mmHg)		Diastolic pressure (mmHg)		Heart rate (beats/min)	
	Before the treatments	After the treatments	Before the treatments	After the treatments	Before the treatments	After the treatments
Treatment group	117.4 ± 17.9	111.3 ± 20.8	75.1 ± 10.8	64.3 ± 11.3[a]	76.3 ± 17.2	73.4 ± 15.7[a]
Control group	118.5 ± 15.5	102.3 ± 15.1[ab]	80.6 ± 17.0	59.9 ± 11.2[ab]	81.9 ± 12.1	75.2 ± 11.3

[a]$p < 0.05$, comparing with the level before the treatments; [b]$p < 0.05$, comparing with the control group.

mL ± 1001.1 pg/mL and 1936.1 pg/mL ± 1400.9 pg/mL (95% CI: -1084.03~3127.88) in the treatment and control groups, respectively; the difference was statistically significant (t = 0.97, p > 0.05) (Table 4).

5) Associations among IGF-1, cTnT and NT-proBNP levels: NT-proBNP release was positively associated with the level of cTnT (r=0.546, P=0.01) but negatively associated with the level of IGF-1 (r=-0.25, p<0.01). In addition, cTnT levels were negatively associated with IGF-1 levels (r=-0.30, p<0.05).

6) Hemodynamic indices: The decreases in the systolic and diastolic pressures of the patients in the treatment group were more pronounced than in the control group. The systolic pressure was 118.5 mmHg ± 15.5 mmHg and 102.3 mmHg ± 15.1 mmHg in the treatment group before and after treatment, respectively, and 117.4 mmHg ± 17.9 mmHg and 111.3 mmHg ± 20.8 mmHg in the control group before and after treatment, respectively; the difference was statistically significant (p< 0.05). The diastolic pressure was 80.6 mmHg ± 17.0 mmHg and 59.9 ± mmHg 11.2 mmHg in the treatment group before and after treatments, respectively, and 75.1 mmHg ± 10.8 mmHg and 64.3 mmHg ± 11.3 mmHg in the control group before and after treatment, respectively; the difference was statistically significant (p<0.05). The changes in HR were not significantly different between the treatment and control groups. The HR was 81.9 beats/min ± 12.1beats/min and 75.2 beats/min ± 11.3 beats/min in the treatment group and 76.3 beats/min ± 17.21 beats/min and 73.4 beats/min ± 15.71 beats/min in the control group before and after treatment, respectively. The difference was not statistically significant between the 2 groups (p>0.05) (Table 5).

7) Cardiac function: The cardiac function of 7 patients in the treatment group improved from grade IV to III at 5-7 d after treatment, while the cardiac function improved from grade IV to III in only 3 patients in the control group (p< 0.05). In addition, the cardiac function of 16 patients in the treatment group improved from grade III to II, while the cardiac function improved from grade III to II in only 7 patients in the control group (p< 0.05). The improvement in cardiac function was greater in the treatment group than in the control group.

Safety analysis

The incidence rate of adverse effects was 8.3% (3/36) and 5.2% (2/38) in the treatment group and control group, respectively; the difference was not significant (p>0.05). The adverse effects in the treatment group comprised ventricular fibrillation (n=1), hypotension (n=2), and dizziness and blurred vision (n=1); and the adverse effect in the control group was tachycardia (n=1). The hypotension, blurred vision, and tachycardia were effectively alleviated after symptomatic treatments or drug withdrawal.

Discussion

Heart failure is one of the most important epidemiological diseases in the world. The incidence rate of heart failure is 1% to 2% in adults and 6% to 10% in subjects over 65 years of age in developed countries [10]. Previous studies showed that the 2-year mortality rate is 37% and 33% in males and females, respectively, after the diagnosis of heart failure, and the mortality rate could increase to 60 % to 70% in heart failure patients with cardiogenic shock [11,12]. Early diagnosis and treatment of heart failure is very important. As an important clinical symptom, no universally accepted biochemical index that is easily detected and valuable for the treatment of heart failure is available except for BNP and NT-proBNP; therefore, identification of more representative biochemical biomarkers that are closely associated with heart failure could provide new methods by which to diagnose and treat heart failure [13].

NT-proBNP is a commonly used index in clinical practice to evaluate the severity of heart failure or efficacy of treatment, and the accuracy is higher than that of BNP. NT-proBNP is a metabolite of proBNP. In response to the stretch of the myocardial cells or ventricular tension, BNP is synthesized as a prohormone (proBNP) and is secreted into the bloodstream with cleavage into an N-terminal fragment, namely NT-proBNP (76 amino acids) and a bioactive C-terminal fragment, namely proBNP (32 amino acids) [14]. The half-life of NT-proBNP (1hour to 2 hours) in the human body is longer than that of BNP (20 min). In addition, the blood concentration of NT-proBNP is also ~15-to 20-fold higher than that of BNP [16]. Previous studies showed that several factors, including age, sex, obesity and renal function, could affect the blood levels of NT-proBNP. In the present study, the correlation indices of the parameters were compared and it was found that the correlation index of NT-proBNP was highest before and after treatment (r=0.949). In addition, the findings showed that assessing the NT-proBNP levels could sensitively evaluate the improvement of cardiac function; however, when the results were compared between the treatment and control groups, a significant difference was found in cTnT and IGF-1 but not in NT-proBNP, either before or after treatment. We speculated that these results could be associated with the fact that the NT-proBNP level is associated with age, BMI and renal functions, as discussed above.

cTnT is found in myocardial cells as free or combined protein. cTnT cannot enter into the bloodstream when the membrane of the myocardial cell is integrated; however, when injuries or necrosis of the myocardial cells occur, the free cTnT in the cytoplasm can be released into the blood, causing increased blood cTnT levels, which can last from several days to 3 weeks [7]. When heart failure occurs, several factors, including hypoxia, ischemia, energy depletion, mechanical damages, and reactive oxygen species, can induce injury or necrosis of the myocardial cells. Recent studies found that the cTnT level in Congestive Heart Failure (CHF) patients increased significantly, which was parallel to the severity of the disease and was of great value in predicting the prognosis in the CHF patients [8,12]. In the present study, we found that the cTnT levels in each group decreased significantly after treatment, but was more pronounced in the treatment group (measured at 72 hours after treatment). These findings showed that serum cTnT concentration could not only help

diagnose heart failure, but also aid in the evaluation of the efficacy of heart-failure treatments and in the prediction of a prognosis for the patients. In summary, the application of levosimendan could significantly improve the treatment efficacies and further reduce the serum level of cTnT in patients with heart failure.

Morita et al. [15] found that NT-proBNP could increase in patients with acute MI even though no decrease of left ventricular function was found; therefore, for the patients with severe myocardial injuries, as evidenced by an increase in the cTnT level, an increase in the level of NT-proBNP could also be found. Previous studies showed that the level of circulatory cTnT was also positively associated with the level of NT-proBNP in non-heart-failure patients. In the present study, we also found that the release of NT-proBNP was positively associated with the level of cTnT, which was similar to the pattern in non-heart-failure patients (r=0.546, P=0.01); therefore, we speculated that the release of cTnT in the non-heart-failure patients could be associated with subtle signals, including the potential increase in ventricular wall tension, but these changes could not cause the symptoms and signs of heart failure. Combined use of cTnT (for the evaluation of myocardium necrosis) and NT-proBNP (for the evaluation of heart failure) could be valuable in predicting a prognosis of the patients. In the present study, these 2 indices were used in combination to provide further evidence for the evaluation of treatment efficacy and prediction of a patient prognosis.

Previous studies demonstrated that the decrease in free or total plasma IGF-1 levels is associated with an increase in the risk of cardiovascular diseases, especially angina, MI, heart failure and ischemic stroke. In a large prospective study performed by JUUL et al. [16] the investigators found that the risk of developing ischemic heart disease is approximately 2-fold higher in patients with lower plasma IGF-1 levels than in those with normal IGF-1 levels 15 years later, suggesting that IGF-1 could be an independent risk factor of cardiovascular diseases. Other studies also demonstrated that IGF-1 could provide important protective effects on the cardiovascular system in patients with chronic heart failure as follows: 1) Animal experiments [17] showed that exogenous IGF-1 directly affected the myocardial tissues of myocardial cells to promote the growth, development, and regeneration of myocardial cells and thus improve cardiac function and myocardial contractility; 2) IGF-1 could directly promote the expression of vascular endothelial growth factor and angiogenesis, [18] and thus promote the formation of new blood vessels; and 3) IGF-1 could reduce the apoptosis of myocardial cells induced by ischemia-reperfusion of myocardium in mouse models [18]. In recent years, the important roles of IGF-1, IGF-1 receptor, and relevant combining proteins in the development and progression of certain cardiovascular diseases have increasingly gained the attention of researchers. The findings of the present study showed that the IGF-1 level increased with the improvement of heart failure, and treating with levosimendan could further increase the IGF-1 level and improve cardiac function.

As a new calcium sensitizer, the curative effects of levosimendan on heart failure could be as follows [20-22]: 1) Levosimendan could combine with the N-terminal of the Troponin C (Tnc) and thus increase the stability of Tnc-Ca^{2+} compound, which in turn, improves myocardial contractility; 2) Levosimendan could dilate the blood vessels by opening the adenosine triphosphate-sensitive potassium channels and thus could dilate both veins and arteries to reduce cardiac preload and after load; 3) Levosimendan could promote the synthesis of nitric oxide by regulating the amount of nitrous oxide and thus regulate the blood flow in the coronary arteries; 4) Levosimendan could reduce the levels of malondialdehyde, tumor necrosis factor, IL-6, BNP, and Fas/Fas ligand and thus play roles in anti-inflammation, anti-oxidation, and anti-apoptosis of myocardial cells; and 5) OR-1896, a metabolite of levosimendan, has effects similar to levosimendan; however, the half-life of OR-1896 (about 80 hours) is much longer than that of levosimendan (about 1 hour) and thus or-1896 could help maintain positive hemodynamic effects.

The findings of the present study showed that the clinical effective rate was significantly higher in the treatment group than in the control group (83.3% vs. 55.3%), increase in the blood IGF-1 level was significantly greater in the treatment group than in the control group (44.6 ng/mL ± 29.6 ng/mL vs. 6.8 ng/mL ± 5.6 ng/mL), and the decrease in the blood cTnT level was significantly greater in the treatment group than in the control group (40.3 pg/mL ± 20.8 pg/mL vs. 11.3 pg/mL ± 6.9 pg/mL). The NT-proBNP level decreased in both the treatment and control groups after treatment; however, the difference between the 2 groups was not statistically significant. These findings demonstrated that levosimendan could be effectively used in treating chronic congestive heart failure.

In summary, the findings of the present study showed that levosimendan could improve the symptoms of and signs in patients with chronic congestive heart failure, significantly increase the blood IGF-1 level, and decrease the blood cTnT level. Quantitatively evaluating the efficacy of levosimendan using only NT-proBNP has several limitations; however, the combined assessment of blood cTnT and IGF-1 levels could accurately evaluate the efficacies of the drugs for chronic heart failure.

Acknowledgments

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