Short-term efficacy and safety of levosimendan in patients with chronic systolic heart failure

Xiao-Ran Cui, Xiao-Hong Yang, Rui-Bin Li, Dong Wang, Min Jia, Long Bai, Ji-Dong Zhang

Abstract

The objective was to investigate and evaluate the short-term efficacy and safety of levosimendan in patients with chronic systolic heart failure. Forty-nine patients with chronic systolic heart failure during acute decompensation were randomly divided into a levosimendan group (26 cases) and a control group (23 cases). The control group received only routine treatment, while the levosimendan group received a levosimendan bolus with a load of 12 μg/kg, in addition to the same routine treatment as the control group. After 48 hours of treatment, N-terminal pro B-type natriuretic peptide (NT-proBNP) levels in the levosimendan group were significantly lower than those in the control group. In addition, the left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) cardiac function scores of the levosimendan group were significantly higher and more improved than those of the control group seven days after treatment, but there was no significant difference in the left ventricular end-diastolic diameter between the two groups. Furthermore, 48 hours after treatment, there were no significant differences in potassium, haemoglobin, haematocrit and creatinine levels between the levosimendan and control groups. During the whole hospitalisation, there was one case of sudden death in the control group and one case of palpitations in the levosimendan group, and no hypotension or severe hypokalaemia occurred in either group. Levosimendan significantly improved NT-proBNP and LVEF in patients with chronic systolic heart failure, and improved NYHA cardiac function classification without significant cardiovascular events. Levosimendan is therefore effective and safe in the short-term treatment of chronic systolic heart failure.

Keywords: levosimendan, chronic systolic heart failure, cardiac function evaluation

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The Sixth Department of Cardiovascular Medicine, Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Xiao-Ran Cui, MM
Xiao-Hong Yang, MD
Rui-Bin Li, MM
Dong Wang, MM
Min Jia, MD
Long Bai, MM
Ji-Dong Zhang, MD, zhangjidong78@163.com

Heart failure (HF) is a serious and terminal stage of various heart diseases. Chronic heart failure (CHF) is the gradual occurrence of HF symptoms and signs resulting from the original chronic heart disease. Worsening of the symptoms of chronic stable HF represents decompensated HF,[1] which has a poor prognosis, will seriously affect the quality of life of the patients, and will bring a heavy burden to their families. It has become one of the major public health problems in China.[2]

For these chronic HF patients, drug therapy is still the main treatment. Positive inotropic agents are an efficacious drug for the treatment of HF patients with low-cardiac output syndrome.[3,4] However, when these agents are used at high doses, the risk of side effects increases, including increased myocardial oxygen consumption, incidence of arrhythmia and even mortality in patients with heart failure.[5]

Cardiac troponin C (cTnC) is a molecular switch controlled by calcium ions (Ca^{2+}), which can change myocardial muscle strength during cardiac contraction and diastole. Therefore, the degree of myocardial contraction in diastole is regulated by the binding properties of Ca^{2+} and cTnC. As a new type of Ca^{2+} sensitiser, levosimendan has a dual action mechanism. Compared with positive inotropic agents, levosimendan can enhance the sensitivity of the myocardium to Ca^{2+} and increase the contractility of myocardial cells without affecting intracellular Ca^{2+} concentrations or increasing the risk of myocardial oxygen consumption and with no malignant arrhythmia. In addition, levosimendan can also mediate ATP-sensitive potassium channels on smooth muscle cells to exert vasodilation, reduce cardiac load and improve coronary artery blood supply.[6,7]

A large number of evidence-based medical studies show that levosimendan has advantages compared to traditional cardiac tonic drugs.[8-11] The guidelines for diagnosis and treatment of heart failure[1] suggest that levosimendan is not inferior to dobutamine in alleviating clinical symptoms and improving the prognosis of HF. It is used in systolic HF without severe haemodynamic symptoms (class IIa recommendation, grade B evidence). However, there are relatively few clinical studies and safety evaluations for levosimendan. The aim of this study was to evaluate the short-term efficacy and safety of levosimendan in patients with acute decompensated chronic systolic HF.

Methods

The study protocol was approved by the ethics committee of the Second Hospital of Hebei Medical University. Informed consent was obtained from all the study subjects before enrollment.

Forty-nine patients with chronic systolic heart failure hospitalised in the Department of Cardiology, Second Hospital of Hebei Medical University from February 2017 to February 2018 were selected. The patients were randomly divided into a levosimendan group (26 cases) and a control group (23 cases).

Inclusion criteria were (1) male or female patients aged 18 to 75 years who were hospitalised for acute episodes of chronic systolic HF; (2) New York Heart Association (NYHA) classification grade III or above at admission;[12] (3) echocardiogram showing left ventricular ejection fraction (LVEF) ≤ 40% and left ventricular end-diastolic diameter (LVEDD) ≥ 55 mm.

Exclusion criteria were (1) patients with a previous history of malignant arrhythmia, such as ventricular tachycardia, ventricular flutter and ventricular fibrillation; (2) patients with severe liver or kidney dysfunction [estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2]; (3) patients with mechanical obstructive diseases that significantly affect ventricular filling and/or ejection function; (4) heart failure caused by acute myocardial infarction (within 24 hours), severe primary valvular stenosis and pericardial disease; (5) secondary HF caused by systemic diseases, such as severe anaemia (haemoglobin < 60 g/l), hyperthyroidism and heart disease; (6) severe hypotension (systolic blood pressure < 90 mmHg); (7) allergy to levosimendan or its accessories; (8) patients or their families refusing to use levosimendan.

The experimental drug was levosimendan 5 ml; 12.5 mg, Yuewen, Qilu Pharmaceutical Co, Ltd. The instruments for testing were AC-T 5diff automatic five-classification haematology analyser, Beckmann Kurt Company, USA, 800 automatic biochemical analyser, Roche, USA, AQT90 FLEX immunoanalyser, Reddle, Denmark, and IE33 echocardiography, Philips.

The control group received only routine treatment (including diuretics, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists), while the levosimendan group received a levosimendan bolus with a load of 12 μg/kg, in addition to the same routine treatment as the control group. Levosimendan was administered by maintenance intravenous infusion at a rate of 0.1 μg/kg/min for 24 hours after 10 minutes of intravenous bolus. For patients with systolic blood pressure (SBP) < 100 mmHg, the maintenance dose can be used directly without the load dose. During the treatment period, clinicians should closely observe the patient's condition and monitor for adverse drug reactions or major cardiovascular events.

The values of N-terminal B-type natriuretic peptide (NT-proBNP), blood potassium (K^+), haemoglobin (HGB), haematocrit (HCT) and creatinine (Cr) were measured before and 48 hours after treatment. At admission and seven days after administration, LVEF and LVEDD were determined by echocardiography, and NYHA cardiac function was graded. The results of LVEF and LVEDD were reviewed by two ultrasound doctors.

Table 1. Basic clinical data between the two groups

Clinical parameters	*Levosimendan group* (n = *26*)	*Control group* (n = *23*)
Gender (male/female)	22/4	19/4
Age (years)	50.15 ± 13.42	54.43 ± 13.22
Weight (kg)	75.70 ± 14.16	71.80 ± 7.20
Smoking history, *n* (%)	9 (34.6)	8 (34.8)
Drinking history, *n* (%)	8 (30.8)	6 (26.1)
Hypertension, *n* (%)	9 (34.6)	11 (47.8)
Diabetes, *n* (%)	5 (19.2)	7 (30.4)
Hyperlipidaemia, *n* (%)	7 (26.9)	6 (26.1)
Coronary heart disease, *n* (%)	4 (15.4)	9 (39.1)
Dilated heart disease, *n* (%)	20 (76.9)	10 (43.5)
Other, *n* (%)	2 (7.7)	4 (17.4)

The incidence of adverse cardiac events such as headache, hypotension, ventricular tachycardia and sudden death was recorded during the treatment. The patients were followed up for one month after discharge, and the re-hospitalisation rates of the two groups were determined.

Statistical analysis

SPSS17.0 was used for statistical data analysis. All measurement data are expressed as mean ± SD. Before and after treatment, a paired-samples *t*-test was used for comparison within groups and an independent samples *t*-test was used for comparison between groups. The basic clinical data between the two groups were examined with a χ^2 test. A *p*-value < 0.05 was taken as a statistically significant difference.

Results

There was no significant difference in clinical data between the levosimendan and control groups (Table 1). There was also no significant difference in indicators of detection between the levosimendan and control groups (Table 2).

Before treatment, NT-proBNP values of the levosimendan and control groups were 4715.60 ± 6881.17 and 4380.39 ± 4350.10 pg/ml, respectively. There was no significant difference between the two groups. At 48 hours after treatment, NT-proBNP values of the levosimendan and control groups were 1801.08 ± 1947.43 and 3221.57 ± 2833.16 pg/ml, respectively. NT-proBNP was significantly downregulated in both groups. At 48 hours, NT-proBNP was significantly lower in the levosimendan-treated group compared to the control group (Fig. 1, Table 3).

Before treatment, the LVEF of the levosimendan and control groups was 30.24 ± 7.19 and 33.35 ± 4.66%, respectively. There was no significant difference between the two groups. After seven days of treatment, the LVEF was 38.90 ± 8.97% in the levosimendan group and 34.57 ± 5.51% in the control group, which was significantly higher than that before treatment. In addition, the LVEF in the levosimendan group was statistically higher than that in the control group after treatment (Fig. 2, Table 4).

Similar results were shown in LVEDD. Before treatment, there was no significant difference in LVEDD between the two groups. However, compared with before the treatment, LVEDD

Table 2. Indicators of detection between the two groups before the treatment

Variables	*Levosimendan group*	*Control group*
Heart rate (beats/min)	86.15 ± 13.13	82.65 ± 16.57
Systolic blood pressure (mmHg)	121.88 ± 14.51	126.74 ± 24.55
Diastolic blood pressure (mmHg)	80.42 ± 11.91	83.74 ± 14.94
NT-proBNP (pg/ml)	4715.60 ± 6881.17	4380.39 ± 4350.10
Potassium (mmol/l)	4.02 ± 0.48	4.02 ± 0.53
Haemoglobin (g/l)	146.65 ± 10.93	140.35 ± 14.02
Haematocrit (%)	45.06 ± 4.32	42.68 ± 4.07
Creatinine (μmol/l)	81.64 ± 24.56	85.66 ± 22.02
NYHA III, *n* (%)	14 (53.8)	12 (52.2)
NYHA IV, *n* (%)	12 (46.2)	11 (47.8)
LVEF (%)	30.24 ± 7.19	33.35 ± 4.66
LVEDD (mm)	70.31 ± 7.86	66.22 ± 6.61

NYHA, New York Heart Association classification; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

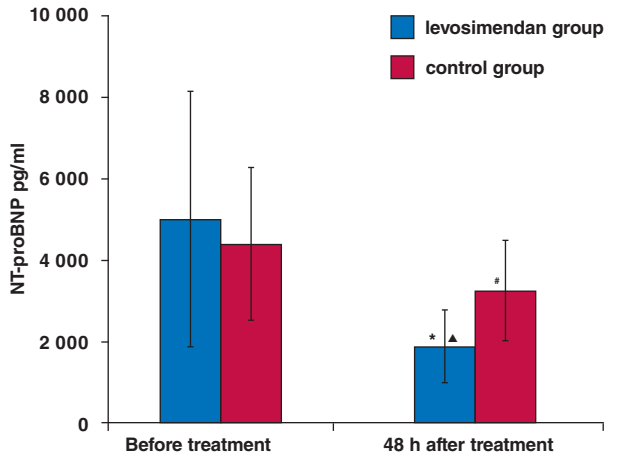

Fig. 1. Comparison of NT-proBNP between the two groups before and 48 hours after treatment. $^{*}p < 0.05$ vs levosimendan group before treatment, $^{\#}p < 0.05$ vs control group before treatment, $^{\blacktriangle}p < 0.05$ vs control group 48 hours after treatment.

Table 3. Comparison of NT-proBNP between the two groups before and 48 hours after treatment

	Levosimendan group		*Control group*	
Variable	*Before treatment*	*48 h after treatment*	*Before treatment*	*48 h after treatment*
NT-proBNP (pg/ml)	4715.60 ± 6881.17	1801.08 ± 1947.43	4380.39 ± 4350.10	3221.57 ± 2833.16
p-value	0.007[a]		0.025[a]	
p-value	0.044[b]			

[a]$p < 0.05$ compared with before the treatment; [b]$p < 0.05$ compared with the control group 48 hours after treatment.

in both groups decreased significantly seven days after treatment. There was no significant difference in LVEDD between the two groups after treatment (Fig. 3, Table 4).

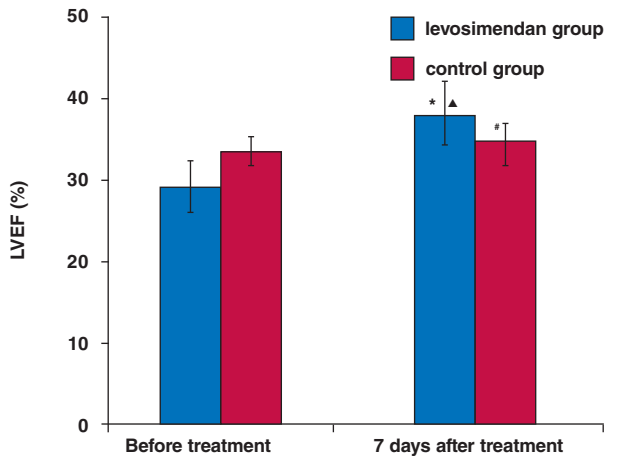

Fig. 2. Comparison of LVEF between the two groups before and seven days after treatment. $^{*}p < 0.05$ vs levosimendan group before treatment, $^{\#}p < 0.05$ vs control group before treatment, $^{\blacktriangle}p < 0.05$ vs control group 48 hours after treatment.

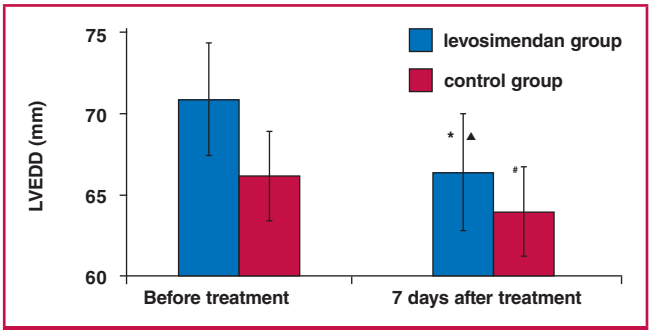

Fig. 3. Comparison of LVEDD between the two groups before and seven days after treatment. $^{*}p < 0.05$ vs levosimendan group before treatment, $^{\#}p < 0.05$ vs control group before treatment, $^{\blacktriangle}p < 0.05$ vs control group 48 hours after treatment.

Table 4. Comparison of LVEF and LVEDD between two groups before and seven days after treatment

	Levosimendan group		*Control group*	
Variable	*Before treatment*	*7 days after treatment*	*Before treatment*	*7 days after treatment*
LVEF (%)	30.24 ± 7.19	38.90 ± 8.97	33.35 ± 4.66	34.57 ± 5.51
p-value	0.000[a]		0.029[a]	
p-value	0.046[b]			
LVEDD (%)	70.31 ± 7.86	65.85 ± 7.91	66.22 ± 6.61	64.04 ± 6.54
p-value	0.000[a]		0.001[a]	
p-value	0.393[b]			

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter. [a]$p < 0.05$ compared with before treatment; [b]$p < 0.05$, compared with the control group seven days after treatment.

NYHA cardiac function was graded at admission. There was no significant difference between the levosimendan and control groups. After seven days of treatment, NYHA cardiac functional class was re-evaluated. In the levosimendan group, it was becoming effective in 10 patients (38.5%), in 14 (53.8%) it was effective and in two (7.7%) it was ineffective, while in the control group, in four patients (17.4%) it was becoming effective, in 10 (43.5%) it was effective and in nine (39.1%) it was ineffective. After comparison, the improvement in cardiac function in the levosimendan group was more significant than that in the control group (Table 5).

There were no significant differences in K^{+}, HGB, HCT and Cr between the levosimendan and control groups before and 48 hours after treatment (Table 6).

During the whole hospitalisation, there was one case of sudden death in the control group and one case of palpitations in the levosimendan group, and no incidents of hypotension or severe hypokalaemia in either group. There was no significant difference between the two groups.

Follow up for one month after discharge showed that the re-hospitalisation rate of both groups was zero.

Table 5. Comparison of NYHA grade between the two groups after treatment

Groups	*NYHA class improved by at least two grades*	*NYHA class improved by only one grade*	*Failure to improve NYHA class*
Levosimendan group	10	14	2
Control group	4	10	9
p-value		0.023	

Table 6. Comparison of laboratory results between the two groups before and 48 hours after treatment

	Levosimendan group		*Control group*	
Variables	*Before treatment*	*48 h after treatment*	*Before treatment*	*48 h after treatment*
Potassium (mmol/l)	4.02 ± 0.48	3.96 ± 0.43	4.02 ± 0.53	3.96 ± 0.47
Haemoglobin (g/l)	146.65 ± 10.93	146.96 ± 13.26	140.35 ± 14.02	138.78 ± 16.75
Haematocrit (%)	45.06 ± 4.32	44.89 ± 4.77	42.68 ± 4.07	42.35 ± 5.53
Creatinine (μmol/l)	81.64 ± 24.56	75.14 ± 18.16	85.66 ± 22.02	85.23 ± 17.64

Discussion

HF is a serious manifestation of various heart diseases and represents the final stage. With the aging of the population in China, the incidence of chronic diseases such as coronary heart disease and hypertension is on the rise. Improvements in medical treatment prolong the survival period of patients with heart disease and eventually it develops into HF, which means a steady increase in the prevalence of HF.[13] Acute decompensated HF (ADHF) is an advanced stage of HF and it has a very serious impact on the quality of life of patients.

Myocardial contractility was shown in one study to increase because of increased sympathetic excitability and an activated renin–angiotensin–aldosterone system in patients with ADHF.[14] Positive myodynamic agents used clinically can enhance myocardial contractility, but their adverse reactions are serious, and long-term use may even lead to an increase in mortality rate.[15]

Levosimendan is an intracellular calcium sensitiser. The main mechanisms of levosimendan in the treatment of ADHF are as follows: (1) increasing the sensitivity of myocardial contractile proteins to Ca^{2+} and acting as a selective Ca^{2+} sensitiser during systole, thereby enhancing myocardial contractility and cardiac output, but without affecting intracellular Ca^{2+} concentration; (2) activating ATP-sensitive K^+ channels on cell membranes to exert vasodilation and reduce cardiac load; (3) producing an anti-inflammatory and anti-oxidative stress response to reduce neuroendocrine activation and endothelin-1 (ET-1) levels; (4) selective inhibition of phosphodiesterase III at high doses is rare.

The half-life of the prototype drug is about one to 1.5 hours, and the active metabolites OR-1896 and OR-1855 are formed after acetylation in the liver. They have similar effects to levosimendan, but the half-life is about 75 to 80 hours. Therefore, the haemodynamic effects of the prototype drug can be maintained several days after discontinuation of administration.[6,16-18] In addition, patients with ADHF have a poor response to drugs, lack of response to treatment and deterioration of multi-organ function, and require repeated hospitalisation.[19] In our study, ADHF patients with significant impairment of LVEF were selected as the subjects to observe the short-term efficacy and safety of levosimendan.

The Chinese guidelines for the diagnosis and treatment of heart failure[1] recommended NT-proBNP monitoring for the diagnosis and treatment of acute and chronic HF. It is an important indicator for evaluating the severity of HF.[1] NT-proBNP has no biological activity and its half-life is 60 to 120 minutes. By detecting NT-proBNP in patients with HF, clinicians can roughly infer the severity of cardiac insufficiency, which is of great significance for the diagnosis and treatment of HF.[20,21]

Zhang *et al*. compared the efficacy of domestic levosimendan and dobutamine in the treatment of ADHF, and concluded that levosimendan could better reduce NT-proBNP level and improve the heart function of patients with acute HF.[22] Other studies have also shown that levosimendan combined with anti-heart failure drugs was more effective than anti-heart failure drugs alone in the treatment of refractory HF. While levosimendan improved the symptoms of HF, NT-proBNP levels also decreased significantly.[23] Similar results were shown in our study. Compared with the control group treated with only conventional HF drugs, NT-proBNP level decreased more significantly in the experimental group treated with levosimendan.

LVEF refers to the percentage of stroke output to end-diastolic volume, which is related to contractile state. It is a commonly used index to reflect cardiac function and is widely used in clinical diagnosis, treatment and research. NYHA cardiac function classification is usually used to determine the severity of HF symptoms, which is clearly related to survival rate.[1]

Several studies have shown that levosimendan significantly increased cardiac output, improved HF symptoms and reduced mortality rates.[24-26] Wang *et al*. found that levosimendan improved dyspnoea and systemic symptoms more significantly than dobutamine in patients with severe decompensated HF.[27] In our study, the level of LVEF in both groups increased after treatment, especially in the levosimendan group. After treatment, LVEDD in each group was significantly lower than that before administration, but there was no significant statistical difference between the groups.

The selected HF subjects were patients with significant impairment of LVEF, so most were admitted repeatedly, the course of disease was long, and the improvement in cardiac remodelling was slow. However, the observation time of this study was short, and the effect of levosimendan on cardiac structure is not apparent, which could partly explain the results of comparison of LVEDD between the two groups after treatment. In addition, the experimental group was given levosimendan once only, so the long-term efficacy of intermittent repeated administration of levosimendan needs further study.

Comparing the NYHA grading of the levosimendan and control groups, the difference was statistically significant. These results show that levosimendan could improve cardiac function. No re-hospitalisation occurred in either group within one month of discharge, indicating that the effect of levosimendan was clear and it has certain long-term application prospects.

Levosimendan was found to be well tolerated.[28] Its main side effects included headache (8.7%), hypotension (6.5%) and hypokalaemia (5%), whereas other treatments include tachycardia and hypokalaemia as side effects.[29,30] In this study, there were no significant differences in the values of K^+, HGB, HCT and Cr between the levosimendan and control groups before and 48 hours after treatment. During hospitalisation, one patient in the levosimendan group developed palpitations and was diagnosed with sinus tachycardia. There was no incidence of hypotension or severe hypokalaemia in either group. These results suggest that levosimendan is safe for short-term treatment.

Limitations of this experiment are: (1) the sample size of this study was relatively small, and the number of cases selected was limited. A larger study is needed to include more cases. (2) The follow-up time was short and no further follow up was carried out. The prognostic effects of levosimendan therefore need to be further studied. (3) There was no monitoring of pulmonary capillary wedge pressure, cardiac output, central venous pressure and other invasive haemodynamic indicators,

so there is a need to further explore the effect of levosimendan on the haemodynamics. (4) There was no stratified analysis of clinical endpoints for related factors.

Conclusion

Levosimendan significantly improved NT-proBNP level and LVEF in our patients with chronic systolic HF, and improved NYHA cardiac functional class without significant cardiovascular events. Therefore levosimendan could be an effective and safe drug for patients with chronic systolic HF.

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