 DOI: 10.19600/j.cnki.issn2152 - 3924.2023.04.018

Clinical Study of Intermittent Levosimendan in the Treatment of Acute Heart Failure

Yanmei ZHAO△, Chunmei ZENG△, Zhihai LIN, Zhengdong WANG*

The First People's Hospital of Yulin, Yulin 537000, China

Abstract [**Objectives**] To investigate the clinical efficacy of intermittent levosimendan in the treatment of acute heart failure. [**Methods**] 100 patients diagnosed with acute heart failure and hospitalized in the internal medicine-cardiovascular department in The First People's Hospital of Yulin from January 2019 to February 2020 were randomly divided into two groups, 50 cases in each group. Both groups were treated with conventional anti-heart failure drugs. The control group was given levosimendan once, and the observation group was given levosimendan three times, with an interval of one month. The creatinine (Cr) level, serum NT proBNP, left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVEDD) were observed at 48 h before and after treatment and one month and two months after treatment in both groups. [**Results**] Compared with before treatment, the levels of NT-proBNP decreased in the two groups at 48 h after treatment, and the difference was statistically significant ($P<0.05$). The Cr level of the control group did not change significantly before and after treatment, and the Cr level of the observation group decreased at one and two months after treatment compared with before treatment, with statistically significant differences ($P<0.05$). Compared with before treatment, NT-proBNP and LVEDD decreased and LVEF increased at one and two months after treatment, and the differences were statistically significant ($P<0.05$). There were no obvious adverse reactions in the two groups of patients during the treatment. [**Conclusions**] Repetitive use of levosimendan in the treatment of acute heart failure could significantly improve the renal function, cardiac contractility and cardiac function of patients, and with the passage of time, the treatment effect was improved, which is worthy of clinical promotion.

Key words Intermittent use, Levosimendan, Acute heart failure

1 Introduction

At present, the main clinical treatment methods for acute heart failure are general treatment and drug treatment. Common drugs mainly include vasodilators, positive inotropic drugs and diuretics. Traditional positive inotropic drugs such as milrinone, dobutamine and cedilanide can improve symptoms, but simultaneously increase myocardial oxygen consumption, affect cardiac diastolic function, and induce arrhythmia, so they cannot improve the prognosis of patients. Levosimendan, a new positive inotropic drug, is a calcium sensitizer, which increases the sensitivity of troponin to calcium ions, does not increase the concentration of intracellular calcium ions and myocardial oxygen consumption, and plays an important role in enhancing myocardial contractility, expanding blood vessels, and protecting the myocardium. At present, some studies have confirmed that the use of levosimendan can significantly improve the symptoms of patients with acute heart failure and reduce related biomarkers, but few observation studies have been conducted on the curative effect of intermittent use of levosimendan in patients with acute heart failure. Therefore, this study aimed to explore the clinical efficacy of intermittent use of levosimendan in the treatment of acute heart failure.

Received: May 7, 2023 Accepted: July 11, 2023

Supported by Scientific Research and Technology Development Program of Yulin City (20204031).

△These authors contributed equally to this work.

* Corresponding author. E-mail: ylsyzym1968@163.com

2 Information and methods

2.1 General information The subjects of this study were 100 patients with acute new-onset heart failure or acute exacerbation of chronic heart failure hospitalized in The First People's Hospital of Yulin from January 2019 to February 2020. They were randomly divided into a control group and an observation group, with 50 patients in each group. In the control group, there were 19 females and 31 males, aged 46 - 85 years, with an average age of (68.5 ± 10.1) years; and the observation group included 21 females and 29 males, aged 46 - 86 years, with an average age of (69.2 ± 10.2) years. Inclusion criteria: (i) The patient had been diagnosed with acute heart failure through a series of clinical examinations, based on the *Guidelines for Diagnosis and Treatment of Heart Failure in China in* 2018[1]; (ii) the patient had no mental or disorders of consciousness and voluntarily participated in the study; and (iii) the patient was approved by the ethics committee of the hospital. Exclusion criteria: (i) Patients who were unwilling to participate in the study; (ii) those who had severe heart, liver, and kidney dysfunction; and (iii) those who had infectious diseases. The general data of the two groups of patients showed no statistical difference ($P>0.05$), indicating comparability.

2.2 Methods Both groups of patients were given conventional anti-heart failure drugs such as vasodilators, diuretics, angiotensin converting enzyme inhibitors. The control group was given levosimendan once (approval number: GYZZ H20100043, produced by Qilu Pharmaceutical Co., Ltd., specification: 12.5 mg/piece) for treatment. Administration mode: The drug was not given with the loading dose, but the maintenance dose directly, and 0.2

μg/(kg · min) was continuously pumped intravenously for 24 h. For the observation group, after levosimendan was given once, it was then used twice at an interval of one month. The medication mode was the same as that of the control group. During the medication, ECG monitoring was required to closely monitor patients' vital signs: SB ≥85 mm Hg, mean arterial pressure (MAP) ≥ 65 mm Hg, and heart rate ≤110 times/min. And the dosage of treatment medication was adjusted according to patients' specific situation.

2.3 Observed indexes The creatinine level (Cr), serum N-terminal B-type natriuretic peptide precursor (NT proBNP), left ventricular ejection fraction (LVEF), and left ventricular end diastolic diameter (LVEDD) of the two groups were observed at 48 h before and after treatment and at one month and two months after treatment. Meanwhile, adverse reactions such as symptomatic hypotension and severe arrhythmia were not observed in both groups.

2.4 Statistical methods SPSS 22.0 statistical software was used for analysis, with measurement data represented by $\bar{x} \pm s$. Inter-group comparison was carried out by t test, with $P<0.05$ indicating a difference with statistical significance.

3 Results

3.1 Comparison of biochemical indicators between two groups at 48 h after treatment Compared with before treatment, the NT proBNP levels in the two groups decreased significantly at 48 h after treatment ($P<0.05$) (Table 1).

Table 1 Comparison of biochemical indicators between two groups at 48 h after treatment

Group	Time	Cr//μmol/L	NT-proBNP//pg/mL
Control group	Before treatment	75.51 ± 5.02	1 840.28 ± 429.74
	After treatment	75.46 ± 5.00	1 608.73 ± 441.64
t/p		1.93/0.059	13.9/0.000
Observation group	Before treatment	75.47 ± 7.91	1 767.17 ± 373.32
	After treatment	75.33 ± 7.97	1 475.87 ± 396.53
t/p		1.96/0.056	6.7/0.000
t/p before treatment		0.03/0.98	0.908/0.366

Note: NT-proBNP: Serum N-terminal B-type natriuretic peptide precursor.

3.2 Comparison of biochemical and cardiac function indicators between two groups at one and two months after treatment There was no significant change in Cr level in the control group before and after treatment, while in the observation group, Cr level decreased at one and two months after treatment compared with before treatment, with statistically significant differences ($P<0.05$). Compared with before treatment, NT proBNP and left ventricular end diastolic diameter (LVEDD) decreased and left ventricular ejection fraction (LVEF) increased in both groups one month and two months after treatment, with statistically significant differences ($P<0.05$) (Table 2).

Table 2 Comparison of biochemical and cardiac function indicators between two groups at one and two months after treatment

Group	Time	Cr//μmol/L		NT-proBNP//pg/mL		LVEF//%		LVEDD//mm	
		One month	Two months	One month	Two months	One month	Two months	One month	Two months
Control group	Before treatment	75.51 ± 5.02	75.51 ± 5.02	1 840.28 ± 429.74	1 840.28 ± 429.74	36.72 ± 14.59	36.72 ± 14.59	57.48 ± 11.00	57.48 ± 11.00
	After treatment	75.54 ± 4.96	75.55 ± 4.96	1176.16 ± 420.76	837.20 ± 382.29	39.54 ± 12.75	40.22 ± 12.36	55.12 ± 9.77	54.88 ± 9.19
t/p		1.12/0.27	1.13/0.19	16.42/0.000	19.17/0.000	3.24/0.002	3.2/0.002	5.77/0.001	4.3/0.001
Observation group	Before treatment	75.47 ± 7.91	75.47 ± 7.91	1 767.17 ± 373.32	1 767.17 ± 373.32	41.36 ± 13.91	41.36 ± 13.91	55.96 ± 9.62	55.96 ± 9.62
	After treatment	74.88 ± 7.43	74.07 ± 7.14	980.71 ± 462.91	705.45 ± 438.19	45.38 ± 15.13	47.02 ± 14.39	53.64 ± 9.41	52.64 ± 8.62
t/p		2.14/0.038	3.73/0.001	13.73/0.000	16.73/0.000	5.55/0.000	6.34/0.001	5.53/0.001	5.56/0.000
t/p before treatment		0.03/0.98	0.03/0.98	0.908/0.366	0.908/0.366	1.63/0.107	1.63/0.107	0.7/0464	0.7/0464

3.3 Comparison of biochemical and cardiac function indicators in different periods of intermittent use of levosimendan in the observation group In the observation group, at different time periods of 48 h, one month, and two months, the above indicators gradually improved over time, and the differences were statistically significant ($P<0.05$) (Table 3).

Table 3 Comparison of biochemical and cardiac function indicators in different periods of intermittent use of levosimendan in the observation group

Time	Cr//μmol/L	NT-proBNP//pg/mL	LVEF//%	LVEDD//mm
Before treatment	75.47 ± 7.91	1 767.17 ± 373.32	41.36 ± 13.91	55.96 ± 9.62
1 month	74.88 ± 7.43[ab]	980.71 ± 462.91[ab]	45.38 ± 15.13[ab]	53.64 ± 9.41[ab]
2 months	74.07 ± 7.14[c]	705.45 ± 438.19[c]	47.02 ± 14.39[c]	52.64 ± 8.62[c]

Note: [a] represents that the difference between the values at one month and before treatment is significant ($P<0.05$); [b] stands for a significant difference between the values at one month and two months ($P<0.05$); and [c] indicates that the difference between the values at two months and before treatment is significant ($P<0.05$).

3.4 Adverse reactions During the treatment period, there were no significant adverse reactions observed in both groups of patients.

4 Discussion

The pathogenesis of heart failure is relatively complex, mainly related to neuroendocrine hormones, ventricular remodeling, hemodynamic abnormalities, and myocardial damage. Acute left heart failure is a series of clinical complications caused by abnormal cardiac structure or function due to various reasons, which leads to decreased myocardial contractility, decreased cardiac output, and peripheral tissue hypoperfusion. At present, the treatment schemes

are mainly diuretics, vasodilators, and positive inotropic drugs. Traditional positive inotropic drugs, such as digitalis, β-agonists and phosphodiesterase inhibitors, mainly improve the contractility by increasing the concentration of calcium ions in myocardial cells. They improves heart failure while increasing myocardial oxygen consumption[2]. As a new type of calcium sensitizer, levosimendan has a different mechanism of action from traditional positive inotropic drugs. It can enhance myocardial contractility, and exert effects such as anti-myocardial stunning, anti-apoptosis, antioxidant, anti-inflammatory, *etc.*[3]. It can also expand surrounding blood vessels and coronary arteries, increase the sensitivity of myocardial contractile proteins to Ca^{2+}, and improve cardiac function, without increasing myocardial oxygen consumption.

The results of this study showed that the Cr levels one month and two months after intermittent use of levosimendan were lower than that before treatment, indicating that intermittent use of levosimendan could improve the renal function of patients with heart failure. The reason might be that the decrease of renal perfusion pressure is an important factor to promote the deterioration of renal function, while levosimendan can activate the opening of ATP sensitive potassium channels in the vascular smooth muscle of renal afferent arteriole, shorten cell action potential duration, and inhibit the inflow of Ca^{2+}, which leads to expansion of blood vessels, which further causes increased blood perfusion of the heart and kidney, indirectly increased blood flow of the kidney by increasing the cardiac output, and promoted excretion of Scr and NT proBNP, resulting in improved renal function[4-6]. It is consistent with the research results of other scholars both domestically and internationally[7-9].

Furthermore, in the study, the patients with acute heart failure who were treated with levosimendan intermittently were followed up at 48 h, one month and two months, and it was also found that NT proBNP, LVEF and LVEDD were all improved compared with those before treatment, and the above indicators were gradually improved over time, indicating that levosimendan could significantly increase cardiac output and stroke volume of patients with heart failure, and reduce peripheral vascular resistance[10], thereby improving patients' haemodynamics, cardiac function status and prognosis, improving quality of life, and further reducing long-term mortality[11-13]. In this study, we observed that there were no significant adverse reactions in the two groups of patients during the treatment period. The age range of patients studied was from 46 to 85 years old, which was a wide range. Patients of different ages showed good safety, which is consistent with the research results of Jiang *et al.*[14].

To sum up, the intermittent use of levosimendan in the treatment of acute heart failure had obvious effect. It could effectively improve patients' renal function and heart function and reduce the markers of heart failure, and is thus safe and worthy of clinical promotion.

References

[1] Heart Failure Group of the Cardiovascular Disease Branch of the Chinese Medical Association, Heart Failure Professional Committee of the Chinese Physicians Association, Editorial Board of the Chinese Journal of Cardiovascular Diseases. Guidelines for diagnosis and treatment of heart failure in China in 2018[J]. Chinese Journal of Cardiology, 2018, 46(10): 760-789. (in Chinese).

[2] PENG YF, SONG CP. To evaluate the advantage of betaloc extended-release tablets and betaloc tablets in patients with chronic congestive heart failure[J]. Journal of Hunan Normal University (Medical Sciences), 2020, 17(2): 106-109. (in Chinese).

[3] LIU JW, WU ZG, YAN XC. Therapeutic effect of levosimendan on aged patients with acute heart failure and its influence on cardiac function, serum levels of Gal-3 and CPP[J]. Chinese Journal of Cardiovascular Rehabilitation Medicine, 2019, 28(1): 61-65. (in Chinese).

[4] CHEN G, YANG F, WEI G, *et al.* Analysis of clinical efficacy of recombinant human brain natriuretic peptide combined with levosimendan in the treatment of acute decompensated heart failure complicated with renal insufficiency[J]. Chinese Pharmacy, 2020, 31(21): 2639-2644. (in Chinese).

[5] WANG YB, HAO GZ, JIANG YF, *et al.* Effects of levosimendan on right ventricular function in patients with acutely decompensated heart failure [J]. Chinese General Practice, 2019, 22(27): 3328-3332. (in Chinese).

[6] DELGADO JF, OLIVA F, REINECKE A. The inodilator levosimendan in repetitive doses in the treatment of advanced heart failure[J]. European Heart Journal Supplements, 2017, 19(Suppl C): C8-C14.

[7] YUAN WJ, LI WF, LUO G, *et al.* Effects and mechanisms of levosimendan in dilated cardiomyopathy[J]. Chinese Journal of Gerontology, 2019, 39(1): 180-182. (in Chinese).

[8] DU H, SHI CY, CH SP. New progress in the study of levosimendan [J]. Chinese Circulation Journal, 2014, 29(7): 555-557. (in Chinese).

[9] YAO Y, HE L, ZHAO Y. The effect of levosimendan on postoperative bleeding and blood transfusion in cardiac surgical patients: A PRISMA-compliant systematic review and meta-analysis[J]. Perfusion, 2021, 36 (7): 694-703.

[10] ASIF M. A review on role of the calcium sensitive inotropic agent, levosimendan and its metabolites[J]. Mini-Reviews in Medicinal Chemistry, 2018, 18(16): 1354-1362.

[11] JAWITZ O K, STEBBINS AS, RAMAN V, *et al.* Association between levosimendan, postoperative AKI, and mortality in cardiac surgery: Insights from the LEVO-CTS trial[J]. American Heart Journal, 2021, 231: 18-24.

[12] JIA T, WANG S, LUO C, *et al.* Levosimendan ameliorates post-resuscitation acute intestinal microcirculation dysfunction partly independent of its effects on systemic circulation: A pilot study on cardiac arrest in a rat model[J]. Shock, 2021, 56(4): 639-646.

[13] LONG Y X, CUI D Y, KUANG X, *et al.* Effect of levosimendan on renal function in background of left ventricular dysfunction: A meta-analysis of randomized trials[J]. Expert Opinion on Drug Safety, 2021, 20 (11): 1411-1420.

[14] JIANG HT, FENG JP, REN B, *et al.* Efficacy of levosimendan in elderly refractory heart failure patients[J]. Chinese Journal of Heart Failure and Cardiomyopathy, 2019, 3(1): 23-27. (in Chinese).