Effect of Levosimendan on the short-term clinical efficacy of patients with acute decompensated heart failure

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【ABSTRACT】 OBJECTIVE To observe the effect of levosimendan on the clinical efficacy of patients with acute decompensated heart failure (ADHF). METHODS Collected 124 patients with acute decompensated heart failure who were admitted to the cardiology department of our hospital from October 2019 to October 2020. According to the random number table method, they were divided into control group and levosimendan group. The control group was given traditional anti-heart failure treatment, and the levosimendan group was added with levosimendan injection on the basis of the control group. The clinical efficacy indicators, functional indicators, incidence of adverse reactions, mortality during hospitalization, rehospitalization rates and combined endpoint events within 3 months of follow-up were compared before and after treatment. RESULTS The results of clinical efficacy comparison showed that the number of significant effective number in the control

group was less than that of the levosimendan group, and there was no difference in the number of effective, ineffective and total effective groups; the improvement of dyspnea after treatment in the levosimendan group was better than that of the control group; cardiac color Doppler ultrasound LVEF in control group is higher than Levosimendan group, LVEDV and LVESV are lower than control group; The BNP control group was higher than the levosimendan group. There was no significant difference in renal function between the two groups. The urine output of the control group was less than that of the levosimendan group.There was no statistically significant difference in adverse reactions, rehospitalization rates within 3 months, and mortality between the two groups of patients, and the combined endpoint event (death or rehospitalization) was significantly lower than that of the control group. CONCLUSION Levosimendan in the treatment of patients with acute decompensated heart failure can achieve significant clinical effects, and effectively improve the patient's hemodynamic indicators and increase renal perfusion.

With the deepening of the aging of the population in China, the incidence of decompensated heart failure in the elderly population is higher, which seriously affects the normal life. Acute decompensated heart failure (ADHF), a kind of heart disease, is a clinical syndrome characterized by dyspnea with sudden onset and rapid peak based on abnormal heart function [1]. It is typical of the late stage of heart disease, usually on the basis of chronic heart failure. The disease is complex and difficult to treat. In addition, the mortality rate of patients is high [2], which endangers the health of patients and threatens their life safety, and is the key disease of current clinical attention. At present, drug therapy is mainly adopted in the clinical treatment to stabilize the hemodynamic level of patients. Clinical practice shows that it is not significantthe to adopt conventional symptomatic treatment effect , which demands a new effective treatment scheme. Levosimendan ,a new type of positive inotropic drug, can increase myocardial contractility and has significant effects in improving heart failure which will reduce mortality , improve the incidence of arrhythmia and bring hope to patients [3]. This study took 124 cases admitted to our hospital as the research object, and analyzed the therapeutic effect of levosimendan . The report are as follows.

Tob Regul Sci.™ 2021;7(6): 6572-6584
DOI: doi.org/10.18001/TRS.7.6.131

1. Materials and methods

1.1 General information

Collect patients with ADHF admitted to the Department of Cardiology of our hospital from October 2019 to October 2020. Divide them into control group (n=62) and levosimendan treatment group (n=62) according to random number table method.The diagnostic criteria of all

patients were in line with the relevant criteria for acute decompensated heart failure. Among them, there were 41 males and 21 females in the treatment group, aged 51-84 years, with an average age of (60.4±13.6) years. The primary diseases included ischemic cardiomyopathy (32 cases), dilated cardiomyopathy (22 cases), and valvular heart disease (10 cases).In the control group, there were 32 males and 30 females, aged 50-84 years, with an average age of (71.6±13.4) years. The primary diseases included ischemic cardiomyopathy (33 cases), dilated cardiomyopathy (20 cases), and valvular heart disease (9 cases). Statistical software was used to process the basic data of patients in the two groups, and the results showed no significant statistical difference (P > 0.05), showing comparability between groups.

1.2 Inclusion and exclusion criteria

1.2.1 Inclusion criteria

①In line with the diagnostic criteria of acute adagenesis heart failure [4], the clinical symptoms are aggravated, accompanied by acute pulmonary edema, pulmonary rale, dyspnea and other manifestations. (2) NYHA cardiac function grade was Ⅲ ~ Hor; ③ The left ventricular end-diastolic diameter was >55mm and LVEF<40% in echocardiography. (4) Medical records were complete and could be followed up; ⑤ Know the diagnosis and treatment plan, and voluntarily sign for confirmation.

1.2.2 Exclusion criteria

①Patients with other cardiac diseases (such as cardiogenic shock, acute myocardial infarction, severe heart valvular disease, hypertrophic or restrictive cardiomyopathy, etc.) or arrhythmia; ② Patients with severe diseases of other systems (such as thyroid disease, liver and renal failure, malignant tumor, severe electrolyte disturbance, severe infection, etc.); (3) Patients with consciousness or cognitive dysfunction, mental diseases; (4) Allergic constitution.

1.3 Methods

Both groups were given standard heart failure treatment, including removal of inducement, rest, oxygen intake, limiting fluid intake and infusion speed, and treatment of primary disease. Medical treatment includes positive inotropic drugs, diuretics, vasodilators and so on. Blood oxygen saturation, electrocardiogram and blood pressure were closely monitored during administration. In addition to the above treatment, levosimendan injection (Qilu Pharmaceutical) was added in the levosimendan group, which was given intravenously for 10ug/(kg•min), followed by intravenous infusion of 0.05-0.2 μg/(kg•min) for 24h.

1.4 Observation Indicators

1. Clinical efficacy indicators: ① Refer to efficacy criteria[5] significant effect: clinical symptoms were significantly relieved, NYHA cardiac function grading was improved by grade 2 or above, LVEF>45%; Efficacy: clinical symptoms were alleviated, NYHA cardiac function grade 1 improved, LVEF 40%-45%; NULL: No improvement or worsening of clinical symptoms, improvement of NYHA cardiac function grade less than 1, LVEF<40%. Total effective = significant

+ effective. Patients in both groups were assessed for dyspnea before treatment and 72 hours after treatment. ② Dyspnea score criteria: no dyspnea :1 point; Dyspnea in supine position or paroxysmal dyspnea at night, 2 points; Dyspnea in semi-decubitus position, 3 points; Sitting and breathing, 4 points. The improvement was calculated as the difference between baseline (pre-treatment) and post-treatment scores. A score of 2 or above is considered significant. 1 is effective; 0 and negative scores are invalid. Clinical indicators were graded and recorded by clinicians.

2. Functional indicators: All cases were measured before and 24-48 hours after treatment: ① Cardiac ultrasound, LVEF, LVEDV, LVESV. ② Brain natriuretic peptide (BNP) level. ③ Renal function: BUN, Cr, urine volume.

3. Safety indicators: Adverse reactions within 24 hours of drug use were observed, including hypotension, headache, arrhythmia, electrolyte disturbance, etc.

4. Prognostic indicators: Follow-up of death, readmission and combined end points within 3 months after discharge of patients in both groups. (Death: All cause death during hospitalization or follow-up. Rehospitalization: Rehospitalization of patients with heart failure from any cause for longer than 24 hours. Combined endpoint: death or readmission).

1.5 Statistical Methods

SPSS13.0 software was used for statistical analysis of the data. Orded regression analysis was used for dyspnea. Measurement data were expressed as X±S, and t test was used for comparison between groups. Enumeration data were expressed as rate (%), and $\chi 2$ test was used for comparison between groups. $P < 0.05$ was considered statistically significant.

2.Results

2.1 Comparison of general data

The results showed that there was no significant difference in the general information of patients, such as age, gender, BMI, type of primary disease, etc., and the data were comparable, as shown in Table 1.

Table 1 Comparison of general data of patients

project	治疗组（n=62）	对照组（n=62）	统计值	*P*
gender			0.259	0.6108
male	41	32		
female	21	30		
age（years）	70.4±13.6	71.6±13.4	0.495	0.6216
BMI index（kg/m²）	24.6±6.4	24.2±5.0	0.388	0.6988
hypertension	36	34	0.057	0.8113

hyperlipidemia	14	13	0.037	0.8475
Smoking history	30	22	1.231	0.2672
Systolic pressure	120.8±12.6	123.8±22	0.9317	0.3533
Diastolic blood pressure	69.7±13.5	72.5±14.5	1.1128	0.2680
Type of primary disease			0.132	0.9361
Ischemic cardiomyopathy	32	33		
Dilated cardiomyopathy	22	20		
Valvular heart disease				
Valvular heart disease	10	9		
Medication history			1.833	0.3992
ACEI/ARB	28	35		
B retardant	30	37		
Digaoxin	10	6		
Heart rate	91.5±23.5	90.6±21.3	0.2234	0.8236

2.2 Clinical indicators before treatment

The results showed that there were no significant differences between the two groups in cardiac function grading, cardiac ultrasound (LVEF, LVEDV, LVESV), BNP and renal function before treatment. Patients in the two groups were well comparable.

Table 2 Pre-treatment test indexes of patients

	Control Group	Treatment group	Statistic	P
BNP	5023.12± 3553.64	4783.04±2591.42		
NYHA			0.2900	0.5902
Ⅲ	32	29		
Ⅳ	30	33		
UCG				
LVEF	40.94±6.23	39.90±6.32	0.9228	0.3580
LVEDV	60.22±5.05	59.23±5.38	1.0564	0.2929
LVESV	45.26±6.17	47.18±6.05	1.7495	0.0827
BUN	6.11±1.35	6.62±2.60	1.3708	0.1730
CR	104.16±18.32	103.415±13.41	0.2584	0.7965
Urine output	1280.40± 337.21	1374.00±245.17	1.7753	0.0783

2.3 Comparison of clinical efficacy before and after treatment

The clinical efficacy results showed (Fig. 1) that after treatment, the number of dominant cases, 32 effective cases and 10 invalid cases in the control group was 20, while the number of dominant cases and 19 effective cases in the levosimendan treatment group were 43, with no invalid cases, and the difference between groups was significant (P <0.05).

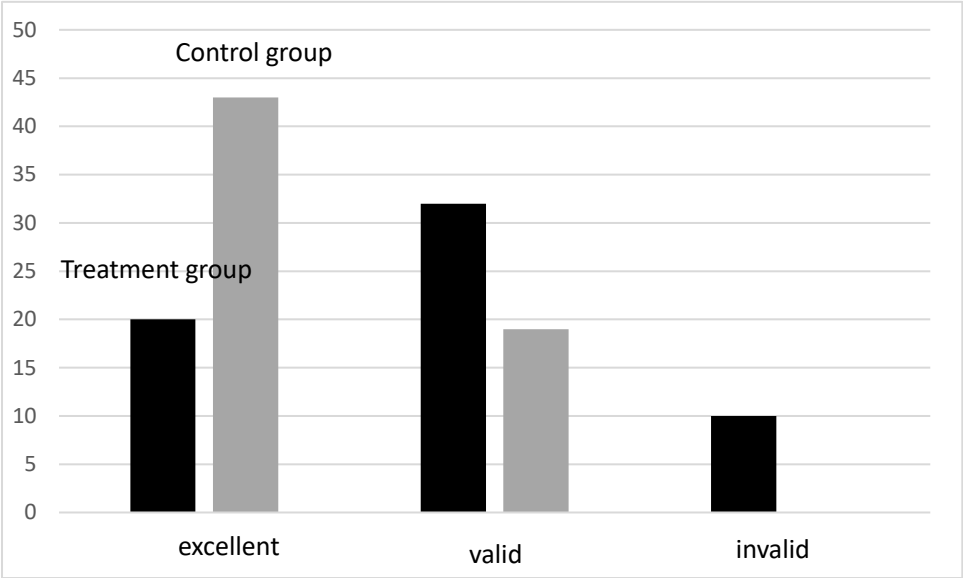

Fig. 1 Comparison of clinical efficacy between levosimendan treatment group and control group

2.4 Improvement of dyspnea before and after treatment

After treatment, the levosimendan group improved dyspnea more than the control group: the levosimendan group was 2.4 times more likely than the control group to have at least an effective improvement in dyspnea, as shown in Table 2 and Figure 2.

Table 2 Improvement of dyspnea in levosimendan treatment group and control group (cases)

Group	Cases	Excellent	Valid	Invalid
Treatment group	62	25（40.3%）	32（51.6%）	5（8.1%）
Control group	62	13（21.0%）	37（59.7%）	12（19.3%）
Parameter estimation		OR=2.3654,95%CI：1.3128-4.6874		
P		0.005		

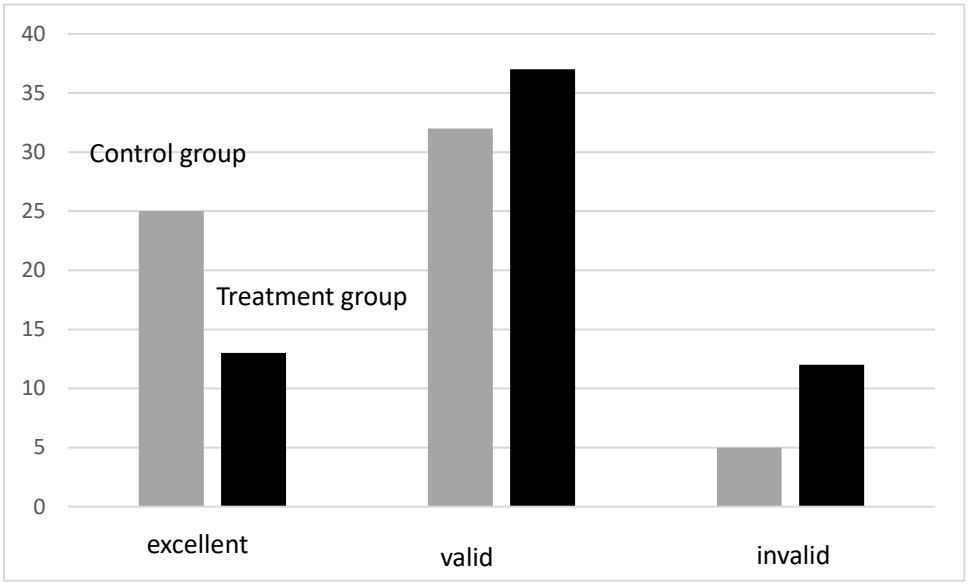

Fig. 2 Respiratory improvement in levosimendan treatment group and control group

2.5 Functional indicators we detection before and after treatment

The detection results of heart color Doppler ultrasound (LVEF, LVEDV, LVESV) indexes showed (Figure 3) that there was no statistical difference in the heart color Doppler ultrasound of each group before treatment, and the heart color Doppler ultrasound of the two groups showed an increase in LVEF after treatment compared with before treatment, and the levosimendan treatment group was significantly higher than the control group. Both LVEDV and LVESV decreased compared with before treatment, and the levosimendan treatment group was lower than the control group, with statistical significance ($P<0.05$). Plasma test results of B-type natriuretic peptide (BNP) showed (Fig. 4) that compared with before treatment, the BNP in both groups was significantly decreased after treatment ($P<0.05$), but the decrease was more significant in the levosimendan group. The test results of renal function indexes showed (Fig. 5) that there was no statistically significant difference in BUN and Cr between the two groups before and after treatment, nor was there any difference between the two groups. However, the urine volume of the two groups increased after treatment compared with before treatment, and the levosimendan treatment group was more than the control group, with statistical significance ($P<0.05$).

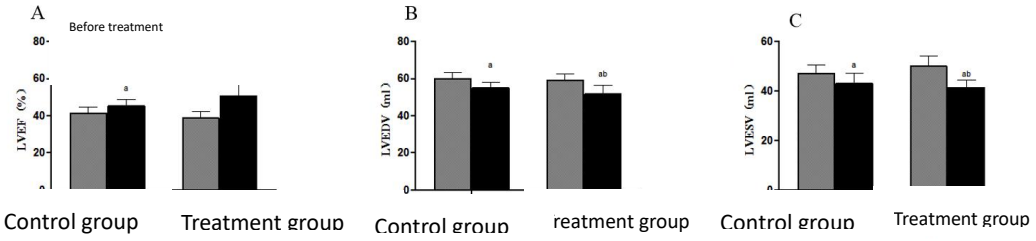

Figure 3 Cardiac color Doppler ultrasonography before and after treatment

A: $P<0.05$ comparison with before treatment, B: $P<0.05$ comparison with the control group

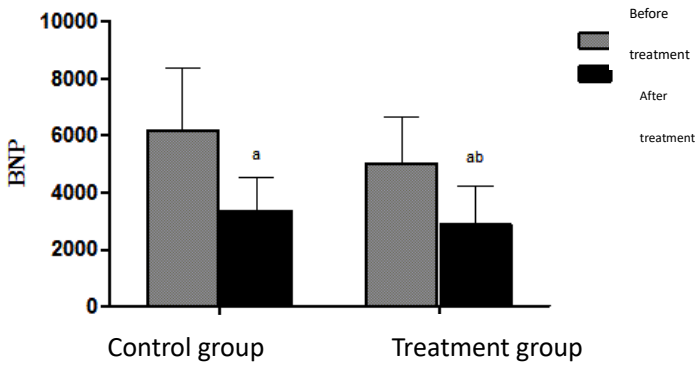

Fig. 4 Detection of BNP indexes before and after treatment

A: P<0.05 comparison with before treatment, B: P<0.05 comparison with the control group

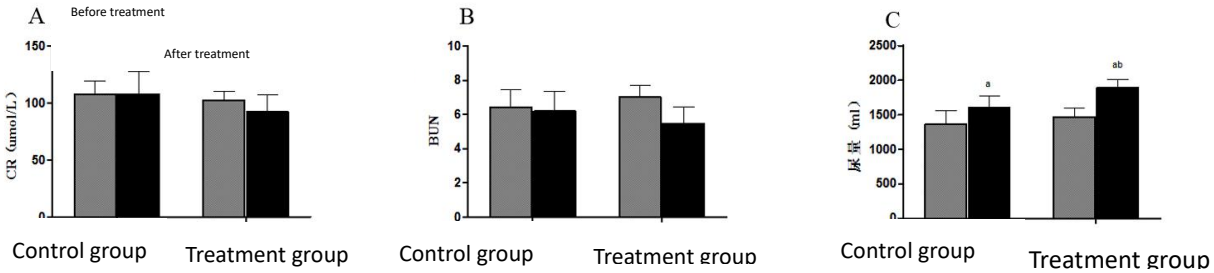

Fig. 5 Detection of renal function indexes before and after treatment

A: P<0.05 comparison with before treatment, B: P<0.05 comparison with the control group

2.5 Safety evaluation results

Safety evaluation results showed that there was no statistically significant difference in the incidence of adverse reactions within 24 hours of treatment between the two groups. See table 3.

Table 3 Adverse reactions within 24h

	Control group	Treatment group	Statistic	P
Hypotension N（%）	3（5%）	3（5%）	0.000	1.000
Headache N（%）	0	2（3%）	0.000	1.000
Hypokalemia N（%）	0	3（5%）	0.000	1.000
Arrhythmia N（%）	1（2%）	0	0.000	1.000

2.5 Outcome statistics

There was no statistically significant difference in mortality between the levosimendan

treatment group and the control group during the observation period (but the levosimendan treatment group was 14.3% less than the control group), as shown in Table 4. The mortality and readmission rates in the levosimendan treatment group were 24% and 26% lower than those in the control group at 3 months follow-up, respectively, but were not statistically significant, while the combined endpoint event (death or readmission) was significantly lower than that in the control group.

Table 4 Comparison of prognosis after treatment

	Control group	Treatment group	Statistic	*P*
Hospitalization				
Death	14	12	0.154	0.6947
Follow-up for 3 months				
Death	25	19	0.818	0.3658
Rehospitalization	23	17	0.900	0.3428
Joint endpoint event	47	29	4.263	0.0389

3. Discuss

Heart Failure (HF) is a group of syndromes caused by a variety of cardiac structural or functional disorders that result in impaired ventricular filling and/or ability to eject blood. Although the treatment of heart failure has improved, acute decompensated heart failure (ADHF) is still a fatal pathological disease [6-7]. ADHE is clinically characterized by dyspnea as the main symptom, manifested as acute pulmonary edema or cardiogenic shock. The patient needs timely treatment once they attack the disease because of the urgency and seriousness of the disease. If the treatment is not timely, the patient is likely to die and the prognosis is poor.With the advent of an aging society, the incidence and mortality of heart failure have increased significantly. There are several positive inotropic drugs that have been widely used with limitations such as increased mortality and the risk of arrhythmia [8].As a new Korean sensitization agent, levosimendan can increase myocardial contractility without increasing myocardial oxygen consumption and the incidence of arrhythmia. Since it was first marketed in Sweden in October 2000, it has been marketed in more than 50 countries such as European Union, Brazil and Argentina, with definite efficacy and good safety.Levosimendan has two main functions: first, it enhances myocardial contraction by selectively binding Ca2+ saturated cardiac troponin C (CTNC) and increasing calcium sensitivity without increasing oxygen demand; second, levosimendan also activates the opening of ATP-sensitive K+ channels in the vascular system, causing vasodilation [9]. In other words, the difference between levosimendan and its inotropic agents is that its positive inotropic effects do not require excessive myocardial oxygen consumption [10].

More and more animal experiments and clinical studies have confirmed that the dual effects of levosimendan's positive muscle strength and vasodilation can have a beneficial effect on the hemodynamics of the heart. The combined application of levosimendan and traditional positive inotropic drugs such as dobutamine has a synergistic effect in improving the hemodynamics of patients which is significantly better than that of dobutamine alone with no obvious adverse reactions [11] . In this study, 124 patients with ADHF were randomly divided into two groups. The control group received cardiac strengthening, diuresis, and vasodilator therapy according to the guidelines for heart failure. Levosimendan was added to the experimental group on the basis of the control group. Table 1 shows that there is no statistical difference between the two groups in terms of age, gender, BMI, type of primary disease and other general information.Table 2 showed that there were no statistical differences between the two groups in cardiac function grading, cardiac color Doppler ultrasound (LVEF, LVEDV, LVESV), BNP and renal function before treatment. Patients in the two groups were well comparable. [12] Mavrogeni M, Mavrogeni M, Mavrogeni M, et al. LVEF increases in patients with heart failure (HF). [13] Katsaragakis M, Kandasamy M, Kandasamy M, et al.In this study, after treatment, LVEF of patients in the two groups was improved by heart color ultrasound, and that in the levosimendan group was significantly higher than that in the control group. Both LVEDV and LVESV decreased compared with before treatment, while the levosimendan group was lower than the control group, and the difference was statistically significant. In this study, LVEF was selected as the main clinical efficacy index to evaluate the therapeutic effect of levosimendan. The comparison of clinical efficacy showed that the difference between the groups was statistically significant. The number of effective patients in the levosimendan group was 43 than that in the control group (20), suggesting that levosimendan can significantly improve the cardiac function of ADH patients, which may be due to the fact that levosimendan can improve heart failure through positive inotinia, vasodilation and inhibition of cardiomyocyte remodeling and other ways.

Heart failure can cause pulmonary congestion, with various forms of dyspnea and pulmonary edema. Currently, levosimendan is considered to be effective in alleviating dyspnea in patients because of its vasodilation effect through the activation of enzyme dependent potassium channels, which leads to a decrease in pre - and post-load, a significant increase in cardiac output, a decrease in PCWP, improved pulmonary congestion, and relief of dyspnea symptoms. In addition to directly playing a role in hemodynamics, it can also reduce interleukin-6 (IL-6), tumor necrosis factor-α, lipid peroxide malondialdehyde (MDA), brain natriuretic titanium in patients with heart failure The level of BNP and the reduction of soluble apoptotic signaling factor Fas/Fas ligand, which have anti-inflammatory, anti-oxidant and anti-cardiomyocyte apoptosis effects, and can more comprehensively combat heart failure. The study by Mebazaa et al. [15] is a double-blind, double-simulation, parallel, multi-center clinical study conducted in patients with acute decompensated heart failure which were given intravenous diuretics or vasodilators with poor

efficacy. Simendan can significantly improve the patient's symptoms such as fatigue and dyspnea. This study found that after treatment, dyspnea in both groups was better than before treatment. The levosimendan group had a significant advantage over the control group which may be related to the rapid increase and decrease of cardiac output of levosimendan. Compared with traditional heart failure drugs, levosimendan can improve dyspnea and reduce lung noise in patients. This is basically consistent with the above research results. BNP is mainly derived from ventricular muscle of which secretion varies with the level of ventricular filling pressure.In heart failure, the tension of the ventricular wall increases, and the ventricular myoendocrine increases, which increases the blood load level, and the degree of increase is positively correlated with the severity of the heart failure. Lee et al. [16] found that BNP can better reflect changes in cardiac function. In heart failure, the pressure load or volume load of the heart increases, the myocardium is stretched or the ventricular wall pressure increases, the secretion of BNP in the ventricular muscle increases, and the concentration of plasma BNP increases. In this study, the BNP of patients was significantly lower than before treatment, and the levosimendan group was lower than the control group. The difference is statistically significant and consistent with foreign literature reports.

Studies have shown that Levosimendan can increase renal blood perfusion, improve glomerular filtration rate, resist inflammation and anti-apoptosis, thereby improving renal function [17].In this study, there was no statistical significance in the difference of BUN and Cr between the two groups before and after treatment, nor was there any difference in the comparison between the two groups, which may be due to the normal renal function of all enrolled patients. However, the urine volume in the two groups increased after treatment compared with before treatment, and the levosimendan group was more than the control group, the difference was statistically significant.Studies have shown that levosimendan can cause hypokalemia, tachycardia, hypotension, headache and other side reactions, which are secondary to the primary disease or related to vasodilation and neuroendocrine activation. However, in this study, there was no statistical difference in the incidence of adverse reactions between the two groups within 24 hours of treatment, which may be related to the small sample size of the selected cases. There remains controversial of the outcome of levosimendan in the treatment of heart failure remains controversial in current clinical trials. The Meta-analysis results of Ribeiro Ra et al. [18] also failed to prove that the levosimendan group had a significant advantage in case fatality. In contrast, the Meta-analysis of Delaney A et al. [19] suggested that although levosimendan did not improve the survival of patients with heart failure compared with placebo, levosimendan had an advantage in improving hemodynamic parameters and survival compared with dobutamine. The results showed that there was no statistically significant difference in the in-hospital mortality between the levosimendan group and the control group. The mortality and readmission rates of the levosimendan group within 3 months were 24% and 26% lower than those of the control group, respectively, but no statistically significant difference was reached, while the incidence of the

combined endpoint event (death or readmission) was significantly lower than that of the control group. This may be related to the small number of selected cases and short follow-up time, which still needs to be further tested in large-scale clinical studies.

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