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Original Article

Levosimendan improves postoperative heart function recovery and prognosis in patients with heart disease

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Abstract: Background: Previous studies have shown that levosimendan can reduce mortality and complications in patients undergoing cardiac surgery. The purpose of this study was to investigate the effect of levosimendan on the recovery of cardiac function, quality of life and prognosis in patients with heart disease after operation. Methods: From October 2017 to August 2019, 93 patients admitted to our hospital for cardiac surgery were retrospectively enrolled in this study. Fifty-three patients treated with levosimendan were included in the experimental group (EG) and 40 who did not receive levosimendan were recruited into the control group (CG). After operation, the length of ICU stay and hospitalization, mean arterial pressure, central venous pressure, heart rate, the changes of cardiac parameters (left ventricular end diastolic volume (LVEDV), end-systolic volume (LVESV), left ventricular ejection index (LVEF) and cardiac index (CI) at different time points), and the changes of high sensitive troponin I (hs-cTnI), creatine kinase isoenzyme (CK-MB) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were compared between the two groups. The stroke volume index (SVI), left ventricular stroke work index (LVSWI), systemic vascular resistance index (SVRI) and other hemodynamic indexes were also compared. Results: The length of ICU stay and hospitalization time in the EG were shorter than those in the CG. After treatment, MAP (mean arterial pressure), CVP (central venous pressure), HR (heart rate), LVEDV, LVESV, HS CTN, NT proBNP and SVRI in the EG were lower than those in the CG group, while LVEF, CI, SVI and LVSWI were higher than those in the CG. The quality of life of patients in the EG was better than that of those in the CG one month after treatment. Logistics regression analysis revealed that the use of levosimendan can reduce the risk of death. Conclusion: Levosimendan can improve the cardiac function and prognosis of patients after cardiac surgery, which is worthy of clinical promotion.

Keywords: Levosimendan, cardiac surgery, cardiac function, prognosis

Introduction

Recently, with the changes in living habits and social environments, the incidence of cardiac diseases has been increasing [1]. Cardiac surgery is vital for some severe cardiac diseases [2]. For patients undergoing cardiac surgery, postoperative complications are important factors that can cause a poor prognosis, such as acute heart failure, low cardiac output syndrome and multiple organ failure, which are all serious complications [3, 4]. Therefore, it is important to reduce complications and improve the prognosis and cardiac function of patients undergoing cardiac surgery.

Levosimendan, a new calcium sensitizer, can increase myocardial contractility by increasing the binding between calcium and receptors on myocardial cells and act on ATP-sensitive potassium channels on vascular smooth muscle cell membranes and mitochondrial membranes, as well as dilate the peripheral arteries and pulmonary artery, and reduce cardiac afterload without increasing myocardial oxygen consumption [5, 6]. Previous findings have shown that levosimendan can reduce the mortality and complications of patients undergoing cardiac surgery, shorten their ICU stay after surgery, and reduce the hospital stay, which has good application prospects [7, 8]. However, Lee and Juan et al. explained that levosimendan did not improve postoperative adverse reactions and complications in patients undergoing cardiac surgery [9, 10]. This indicates that there are still some controversies about the application of levosimendan in cardiac surgery.

Therefore, to further evaluate the application value of levosimendan in recovery after cardiac surgery, we explored the role of levosimendan on the recovery of cardiac function and prognosis of patients with cardiac diseases.

Methods

Clinical data

A retrospective analysis was performed on 93 patients who underwent cardiac surgery in the Second Hospital of Hebei Medical University from March 2018 to July 2020. Among them, 53 patients treated with levosimendan were included in the experiment group (EG) and 40 who did not received levosimendan were enrolled in the control group (CG).

Inclusion criteria: Patient with an age ≥ 18 years old; patients with complete clinical data; patients who had no obvious benefit from diuretics, angiotensin converting enzyme inhibitors and digitalis, and needed short-term treatment of acute decompensated heart failure drugs to increase myocardial contractility; patients who had provided informed consent.

Exclusion criteria: Patients with malignancies; patients with other serious organ diseases; patients with blood coagulation dysfunction or hematopoiesis; patients who were allergic to levosimendan or any other excipients; patients with a history of torsade de pointes; patients with mechanical obstructive disease that dramatically affected ventricular filling and/or ejection function.

This research was approved by the Ethics Committee (Ethical batch number: 2021-P038) and conformed to the Declaration of Helsinki.

Operation plans for patients

Patients in both groups were sent back to ICU for post-operative care. Patients in the CG were injected with dopamine or dobutamine 3 μg/kg/min intravenously. The drug dose was adjusted according to hemodynamics, and the maximum dose was 8 μg/kg/min. If there were severe low cardiac output syndromes [cardiac index <2.0 L/min/m^2 is defined as low cardiac output, often accompanied by hypotension (mean arterial pressure <60 mmHg), tachycardia (heart rate >90 beats/min), metabolic acidosis (pH<7.4, lactic acid >3.0 mmol/L, Alkali residual <-2 mmol/L), mixed venous oxygen saturation <65%, pale skin, damp, cold and humid extremities, pulmonary congestion, hypoxemia], adrenaline treatment pumped to the cardiotonic could be added. If frequent ventricular extrasystole or supraventricular tachycardia occurred, it can be treated symptomatically. Patients in the levosimendan group were injected with levosimendan on the basis of routine treatment with dopamine or dobutamine; the loading dose was 6 μg/kg, intravenous injection of more than 10 min, and intravenous infusion of 0.05-0.2 μg/kg/min for 24 h according to the condition of patients.

Data

We extracted the clinical data of patients through the case system of our hospital, including the length of ICU stay and hospitalization time, mean arterial pressure, central venous pressure and heart rate 24 h before and after treatment, left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), left ventricular ejection fraction (LVEF) and cardiac index (CI); one day before operation, 1 day, 3 days and 7 days after operation, high-sensitive cardiac troponin-I (hs-cTnI), creatine kinase isoenzyme MB (CK-MB) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were detected. Hemodynamic parameters such as stroke volume index (SVI), left ventricular stroke work index (LVSWI) and systemic vascular resistance index (SVRI) were recorded immediately, 12, 24 and 48 h after operation. The quality of life of the patients was assessed with SF-36 scale before and 1 month after treatment.

Outcome measures

Main outcome measures: (1) The length of ICU stay and hospitalization time of the patients was recorded and compared. (2) The mean arterial pressure, central venous pressure and heart rate of both groups before and after treatment were recorded and compared for 24 h. (3) Logistics regression was used to analyze the risk factors for death. Secondary outcome measures: (1) All postoperative complications, including low cardiac output syndrome, acute renal injury, acute heart failure and arrhythmia, were recorded and compared. (2) SF-36 scale [11] was used to evaluate and compare the quality of life in both groups after one month of

Table 1. Baseline data

Factors	EG n=53	CG n=40	χ^2	P
Gender			0.024	0.877
Man	30 (56.60)	22 (55.00)		
Woman	23 (43.40)	18 (45.00)		
Age (Y)			0.108	0.742
≤ 65	26 (49.06)	21 (52.50)		
> 65	27 (50.94)	19 (47.50)		
BMI (kg/m^2)			0.072	0.789
≤ 23	24 (51.19)	17 (52.56)		
> 23	29 (48.81)	23 (47.44)		
History of Smoking			0.040	0.843
Yes	40 (53.57)	31 (55.13)		
No	13 (46.43)	9 (44.87)		
Basic diseases				
Hypertension	30 (70.24)	24 (70.51)	0.108	0.743
Diabetes	27 (50.94)	19 (47.50)	0.108	0.742
NYHA cardiac function classification	3.23±0.54	3.21±0.49	0.184	0.851
Operation mode			0.179	0.914
Aortic valve replacement	20 (37.74)	15 (37.50)		
Mitral valve replacement	19 (35.85)	13 (32.50)		
Coronary artery bypass grafting	14 (26.42)	12 (30.00)		

treatment, including physiological function, physical pain, social function and emotional function. The higher the score, the higher the quality of life. (3) The changes of LVESV, LVEF and cardiac index (CI) were recorded and compared. (4) Peripheral venous blood was collected on the 1st day before operation and on the 1st, 3rd and 7th day after operation to detect the changes of hs-cTnI, CK-MB and NT-proBNP. (5) The hemodynamic parameters such as SVI, LVSWI and SVRI were recorded immediately and 12, 24 and 48 h after operation.

Statistical methods

SPSS 20.0 (ND Times) was used for statistical analysis. The measurement data were expressed by means ± standard deviation and compared by t test. The comparison before and after treatment was conducted with paired t test, the comparison among multiple groups was done by one-way ANOVA followed with LSD/T test. Multiple time points were compared by Repeated Measures followed with Bonferroni test. Logistics regression was used to analyze the independent risk factors for death. The counting data were tested by Chi-square test. A *P* value of <0.05 was statistically significant.

Results

Therapeutic methods

According to their individual conditions, the patients in the EG were given levosimendan (Qilu Pharmaceutical Co., Ltd., SFDA Approval No. H20100043) with micro-pump immediately after returning to the ICU after operation. The initial dose was 24 μg/kg with intravenous pump for 10 min, and then the maintenance dose was 0.1 μg/(kg·min) for 48 h. In the CG, patients were not treated with levosimendan.

General information

There was no significant difference in gender, age and operation type between the two groups (*P*>0.05) (**Table 1**).

Length of ICU stay and hospital stay

The length of ICU stay and hospital stay of the EG were 5.14±0.78 d and 24.02±2.74 d, while those in the CG were 6.90±1.27 d and 28.88±3.53 d respectively, indicating that those in the EG were evidently shorter than those in the CG (*P*<0.05) (**Table 2**).

Table 2. ICU treatment time and hospital stay

Index	EG (n=53)	CG (n=40)	t	p
Length of ICU stay (d)	5.15±1.11	6.90±1.27	7.073	<0.001
Hospital stay (d)	24.02±2.74	28.88±3.53	7.477	<0.001

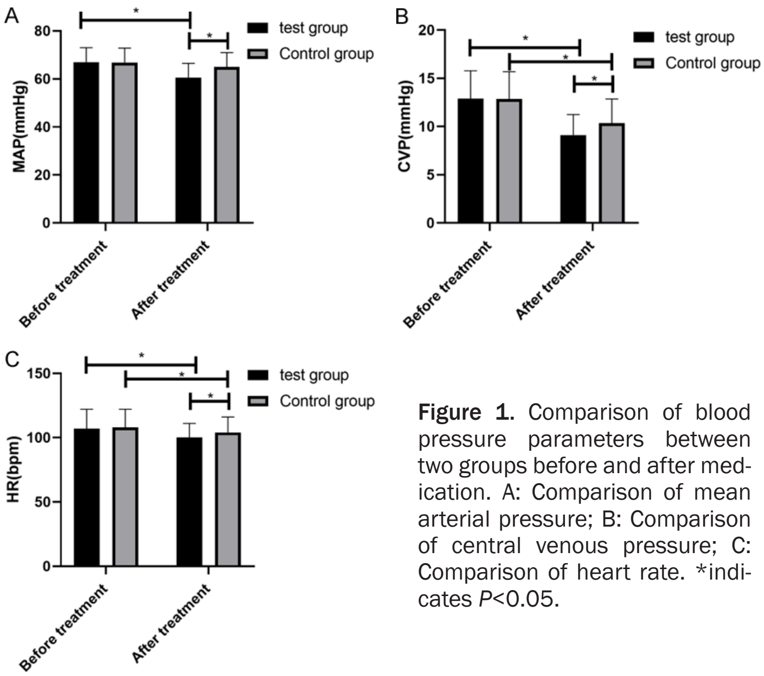

Figure 1. Comparison of blood pressure parameters between two groups before and after medication. A: Comparison of mean arterial pressure; B: Comparison of central venous pressure; C: Comparison of heart rate. *indicates $P<0.05$.

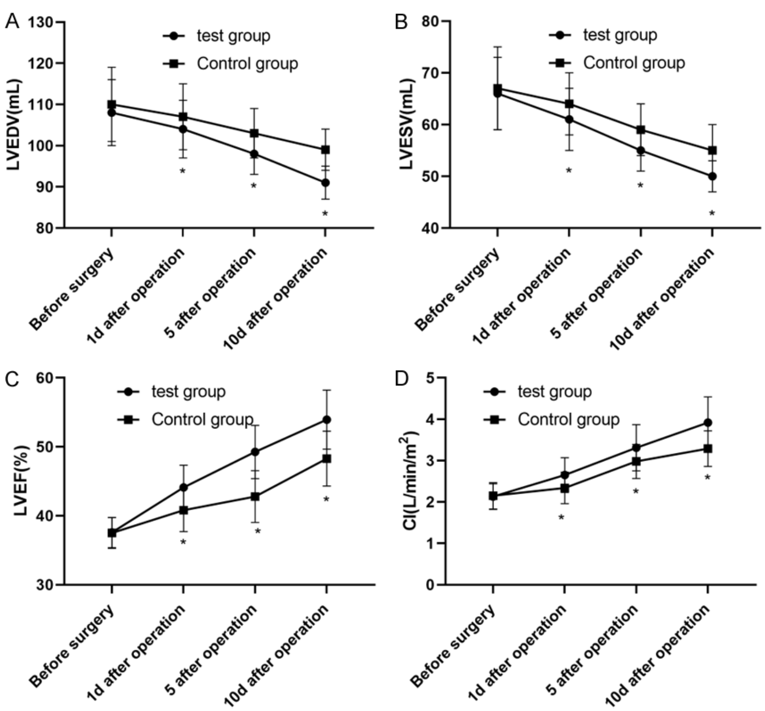

Figure 2. Cardiac function indexes before and after operation in both groups. A: Comparison of LVEDV; B: Comparison of LVESV; C: Comparison of LVEF; D: Comparison of CI. *indicates $P<0.05$.

Comparison of blood pressure parameters

There was no remarkable difference in mean arterial pressure, central venous pressure and heart rate between the two groups before treatment ($P>0.05$). After treatment, the mean arterial pressure, central venous pressure and heart rate in the EG were evidently improved ($P<0.05$), while those in the CG were not obviously changed ($P>0.05$) (**Figure 1**).

Cardiac function indexes

In the two groups, LVEDV and LVESV decreased from 1 to 10 d after operation ($P<0.01$), and those in the EG were evidently lower than those in the CG at the same time point ($P<0.05$). CI and LVEF of patients increased in both groups ($P<0.01$), and the values in the EG were evidently higher than in the CG ($P<0.01$) (**Figure 2**).

Detection of serum related indexes

There was no obvious difference in hs-cTnI, CK-MB and NT-proBNP between the two groups one day before operation ($P>0.05$). There was no significant difference in CK-MB level at 1 and 7 days after treatment (P>0.05). Compared with the CG, the levels of HS cTnI and NT proBNP in the EG decreased significantly on days 1, 3 and 7 after treatment (all P<0.05) (**Table 3**).

Comparison of hemodynamic indexes

Compared with the CG group, the SVRI of the EG decreased significantly at 48 and 72 hours after treatment, while

Table 3. Detection of serum related indexes

	EG (n=53)	CG (n=40)	t	P
hs-cTnI (pg/ml)				
One day before operation	15.93±1.06	15.92±1.03	0.046	0.964
One day after operation	1553.6±24.49	1837.89±27.09	52.95	<0.001
Three days after operation	164.12±7.59	240.28±9.24	43.61	<0.001
Seven days after operation	13.98±1.3	24.09±1.78	31.67	<0.001
CK-MB (U/L)				
One day before operation	20.14±2.17	20.58±2.54	0.899	0.371
One day after operation	96.17±4.9	97.74±5.57	1.442	0.153
Three days after operation	34.35±2.37	36.3±2.53	3.816	<0.001
Seven days after operation	12.25±1.19	12.51±1.43	0.956	0.342
NT-proBNP (pg/ml)				
One day before operation	527.65±36.44	526.24±40.14	0.177	0.860
One day after operation	1512.79±148.04	1834.2±163.69	9.904	<0.001
Three days after operation	884.82±55.29	1232.47±77.89	25.18	<0.001
Seven days after operation	260.23±21.46	362.00±36.36	16.87	<0.001

Table 4. Comparison of hemodynamic indexes

	EG (n=53)	CG (n=40)	t	P
SVRI (dyn·s·cm-5)				
Immediately after surgery	1915±297	2031±426	1.547	0.125
24 h after operation	1908±298	2020±333	1.706	0.092
48 h after operation	1644±319	1780±297	2.096	0.039
72 h after operation	1564±230	1725±298	2.942	0.004
SVI (ml/m^2)				
Immediately after surgery	29.44±2.37	29.29±2.49	0.296	0.768
24 h after operation	35.1±3.27	31.92±3.54	4.481	<0.001
48 h after operation	39.47±3.3	34.02±3.91	7.280	<0.001
72 h after operation	41.87±3.82	37.41±3.89	5.531	<0.001
LVSWI (g/m/m^2)				
Immediately after surgery	35.12±3.14	35.45±2.46	0.549	0.584
24 h after operation	40.08±3.16	38.12±3.22	2.937	0.004
48 h after operation	43.21±3.74	39.29±2.54	5.706	<0.001
72 h after operation	45.07±3.49	40.44±3.9	6.021	<0.001

the SVI and LVSWI increased after treatment (all $P<0.05$) (**Table 4**).

Comparison of complications

The cases of low cardiac output syndrome, acute kidney injury, acute heart failure and arrhythmia in the EG were 1, 1, 1 and 2, respectively, with a complication rate of 9.43%. The number of cases in the CG were 3, 4, 3 and 5, respectively, with a complication rate of 37.50% (**Table 5**).

Quality of life

The scores of physiological function, social function, emotional function and physical function in the EG were evidently higher than those in the CG, indicating that the quality of life in the EG was statistically higher than those in the CG group ($P<0.05$) (**Table 6**).

Analysis of risk factors of death

In this study, the mortality of patients within one year was counted. Four patients died in the

Table 5. Comparison of incidence of complications

Complication	EG (n=53)	CG (n=40)	X^2	P
Low cardiac output syndrome	1 (1.89)	3 (7.50)	-	-
Acute kidney injury	1 (1.89)	4 (10.00)	-	-
Acute heart failure	1 (1.89)	3 (7.50)	-	-
Arrhythmia	2 (3.77)	5 (12.50)	-	-
Total incidence rate	5 (9.43)	15 (37.50)	10.64	0.001

Table 6. Comparison of quality of life (SF-36) between both groups of patients

project	EG (n=53)	CG (n=40)	t	P
Physiological function	16.17±1.55	10.09±0.97	21.78	<0.001
Social function	15.96±1.41	10.35±1.16	20.47	<0.001
Emotional function	15.75±1.28	11.29±1.33	16.36	<0.001
Somatic function	15.57±1.16	10.79±1.11	20.04	<0.001

EG and 10 died in the CG. The patients were grouped according to their one-year survival. Univariate analysis revealed that age, hypertension and medication were the risk factors of death (P<0.05). While multivariate analysis demonstrated that age and mode of medication were independent risk factors for death (P<0.05) (**Table 7**).

Discussion

The overall cardiac function of patients with severe cardiac disease is poor, and operation in this population has high risk, which easily induces adverse complications such as low cardiac output syndrome. The occurrence of postoperative complications after cardiac surgery is also one of the main causes of postoperative death [12, 13].

At the moment, positive inotropic drugs, such as adrenaline and digitalis, are mostly applied in clinical treatment. Although the functional routes of various drugs are different, the final effect is to increase the intracellular calcium concentration, thus enhancing the myocardial contractility of patients [14]. However, clinical studies [15, 16] suggest that the increase of calcium ion concentration in patients' cells will hinder the oxidative phosphorylation process in mitochondria, thus leading to irreversible damage to cells. Long-term use of adrenalin inhibitors will have a certain impact on myocardial relaxation and induce arrhythmia, thus greatly increasing the probability of death of patients.

In our research, the application effect of levosimendan in patients undergoing cardiac surgery was analyzed. First, we compared the length of ICU stay and hospitalization time of patients. This revealed that both in the EG were evidently less than those of the CG, indicating that the application of levosimendan in patients undergoing cardiac surgery could effectively promote their recovery.

As a new type of positive inotropic drug, levocetirizine not only has positive inotropic effect, but also dilates blood vessels. The mechanism is that it binds with cardiac troponin C in a calcium concentration-dependent manner to produce positive inotropic effects, which enhances myocardial contractility and has no obvious effect on diastolic function [17, 18]. Levosimendan has been mainly used in cardiac surgery over recent years. Some studies [19] have revealed that for patients with a LVEF of less than 30% who underwent coronary artery bypass grafting, that levosimendan can evidently improve cardiac function and reduce the incidence of low cardiac output syndrome. Previous study [20] has pointed out that perioperative use of levosimendan can shorten the hospitalization time, improve the short-term prognosis, and promote the recovery of patients, which are basically consistent with our findings. Then, we further compared the blood pressure parameters and cardiac function related indexes between the two groups after operation. The results showed that the postoperative blood pressure parameters and cardiac function indexes of the two groups were significantly improved compared with those before treatment, and the indices in the levosimendan group were more significantly improved, suggesting that levosimendan has a better effect on cardiac function in patients undergoing cardiac surgery. Previous study [21] has also demonstrated that levosimendan can effectively improve cardiac function and increase cardiac output of patients undergoing cardiac surgery, which is consistent with our observation. NT-proBNP is a sensitive and specific quantitative marker reflecting ventricular dysfunction, and hs-cTnI and CK-MB are also indicators with high sensitivity to

Table 7. Analysis of risk factors of death

Indexes	Univariate analysis			Multivariate analysis		
	P value	OR value	95% CI	*P* value	OR value	95% CI
Gender	0.629	1.324	0.424-4.132			
Age	0.027	4.610	1.193-17.809	0.031	4.783	1.153-19.846
BMI	0.920	1.061	0.337-3.342			
Smoking history	0.640	1.356	0.379-4.842			
Hypertension	0.037	0.189	0.242-2.359	0.122	0.277	0.054-1.410
Diabetes	0.629	0.756	0.257-2.548			
NYHA cardiac function classification	0.718	0.809	0.668-2.754			
Operation mode	0.398	1.357	1.175-14.186			
Administrations	0.027	4.083	0.424-4.132	0.043	3.943	1.043-14.91

patients' myocardial function [22, 23]. Therefore, we detected the serum indexes related to myocardial function before and after treatment in both groups. This showed that there was no difference in CK-MB at 1, 3 and 7 days after operation, but hs-cTnI in the EG was evidently lower than that in the CG at 3 and 7 days after operation. This suggested that levosimendan can effectively reduce the degree of myocardial injury after cardiac surgery. Then, we also found that SVRI in the EG was evidently lower than that in the CG, while SVI and LVSWI were higher. Combined with the results of serological indicators, it suggested that levosimendan had a marked effect on improving the hemodynamic state of heart after cardiac surgery. Some study [24] has pointed out that the use of levosimendan can effectively improve the cardiac output of patients undergoing cardiac surgery, which is consistent with our observation.

For patients undergoing cardiac surgery, postoperative complication is the main factor bringing about poor prognosis [25]. Therefore, we recorded and compared the incidence of postoperative complications between the two groups. The results showed that the incidence of postoperative complications in the EG was evidently lower than that in the CG, suggesting that the use of levosimendan could reduce the incidence of postoperative complications. Previous study [26] has shown that perioperative use of levosimendan can reduce the incidence of acute kidney injury after cardiac surgery, which is consistent with our observed results. Finally, we compared the quality of life of patients one month after operation. The results showed that the quality of life score of the EG was evidently higher than that of the CG. All these suggested that the application of levosimendan in the postoperative treatment of patients undergoing cardiac surgery can effectively improve their recovery and quality of life.

At the end of the study, we conducted a one-year survival follow-up, and found that 4 patients in the EG died, while 10 in the CG died, with a total mortality rate of 15.05%, which is basically consistent with the statistics of Mori et al. [27]. Then, through logistics regression analysis, we found that young age was a protective factor for death, while non-use of levosimendan was a higher risk factor. Carolyn et al. [15] found that the use of levosimendan could reduce death rates after heart surgery and the occurrence of acute renal injury. This is consistent with the results of our study, which further shows that levosimentan can effectively improve the short-term prognosis of patients.

We experimentally revealed the role of levosimendan in patients with heart disease after surgery. However, there are still some limitations to this research. First of all, as a retrospective study, the results may be biased. Secondly, the sample size is small, so it is vague whether it will affect the overall results. Finally, the specific mechanism by which levosimendan ameliorates postoperative adverse reactions and complications in patients with heart disease remains unclear. Therefore, we hope to carry out prospective studies, collect more samples and conduct further research as follow-up to validify our research conclusions.

To sum up, the application of levosimendan in patients with cardiac disease after operation can effectively improve the cardiac function, promote the postoperative recovery, reduce the occurrence of postoperative complications and improve the prognosis of patients, which is worthy of clinical application. Nevertheless, there are still some limitations, and the specific mechanism of the application of levosimendan in patients undergoing cardiac surgery has not been analyzed, which needs to be further explored in subsequent experiments.

Disclosure of conflict of interest

None.

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