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Prospective Study on the Postoperative Use of Levosimendan After Conventional Heart Valve Replacement

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF **Wei Sheng***
ABCDEF **Hui Qiao***
BCE **Zhaozhuo Niu**
BCE **Tianyi Wang**
CDE **Haoyou Li**
CDE **Wenfeng Zhang**
CDE **Jiantao Wu**
ADEF **Xiao Lv**

Department of Cardiovascular Surgery, Qingdao Municipal Hospital, Medical College of Qingdao University, Qingdao, Shandong, PR China

* Wei Sheng and Hui Qiao contributed equally to this work and should be considered co-first authors

Corresponding Author: Xiao Lv, e-mail: sw8011@126.com
Financial support: Departmental sources

Background: The aim of this study was to explore the effect of levosimendan in patients after heart valve replacement and its influence on postoperative recovery.

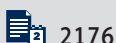
Material/Methods: This prospective study included 185 patients with valvular diseases undergoing conventional valve replacement. Patients were divided into 2 groups using a random number table before surgery. Patients in the levosimendan group were administered levosimendan intravenous infusion immediately after entering the Intensive Care Unit (ICU). The left ventricular ejection fraction (LVEF), cardiac output, and heart failure-related index, such as B-type natriuretic peptide (BNP) level, were recorded at 1, 3, and 7 days after surgery. The dosage and administration time of dopamine and epinephrine, mechanical ventilation time, ICU length of stay, and postoperative adverse events were recorded.

Results: Cardiac output and LVEF of patients in the levosimendan group were significantly higher than those in the control group at different time points ($P < 0.05$), and BNP level was lower than that of the control group ($P < 0.0001$). Dosage and administration time of dopamine and epinephrine in the levosimendan group were lower than those of the control group ($P < 0.0001$, $P < 0.0001$, respectively). ICU length of stay and total incidence of postoperative adverse events were lower than those of the control group ($P < 0.0001$, $P = 0.002$, respectively).

Conclusions: Levosimendan administration immediately after heart valve replacement effectively improved the heart function of patients, reduced administration of vasoactive drugs, shortened length of ICU stay, reduced incidence of postoperative adverse events, and promoted recovery of patients after surgery.

Keywords: **Cardiac Output • Heart Valve Diseases • Simendan**

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Background

Despite great advances in cardioprotective strategies, surgical techniques and skills, cardiopulmonary bypass techniques, and postoperative management, myocardial injury is still a common complication following cardiopulmonary bypass surgery, inducing myocardial dysfunction and circulatory impairment [1], arrhythmia, myocardial energy metabolism disturbance, microcirculation disorder, and low cardiac output syndrome (LCOS) [2,3], thus severely threatening the postoperative recovery of patients. The therapeutic management of LCOS includes hemodynamic support with inotropic agents, vasopressors, and circulatory assist devices. Catecholamine vasoactive drugs are the most commonly used drugs after cardiac surgery, which can effectively enhance myocardial contractility of patients; however, at the same time, they lead to increased myocardial oxygen consumption, which results in an increase in associated complications. Levosimendan, as a new calcium sensitizer, can significantly improve cardiac function by increasing myocardial contractility and dilating blood vessels, and this effect of improving cardiac contractility does not lead to increased myocardial oxygen consumption and arrhythmia. It has recently been suggested that levosimendan can effectively improve cardiac function and long-term prognosis in patients with severe heart diseases during the perioperative period [4,5]. In this study, we prospectively observed the effect of the immediate administration of levosimendan on postoperative cardiac function and postoperative echocardiographic and hemodynamic indexes in patients undergoing conventional valve replacement.

Material and Methods

Patients undergoing conventional heart valve replacement in our cardiac surgery department from January 2017 to May 2019 were prospectively enrolled in this study. All patients were diagnosed with valvular heart disease by echocardiography before surgery. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of our hospital (No.10), and written informed consent was obtained from all study participants. The inclusion criteria were as follows: (1) echocardiography showed mitral valve and/or aortic valve lesions, including valve thickening, calcification with moderate or severe stenosis, and/or moderate or severe insufficiency (with or without tricuspid valve lesions); (2) patients aged between 40 and 75 years old; (3) New York Heart Association classification II to IV; and (4) all patients signed informed consent before surgery. The exclusion criteria were as follows: (1) severe liver and kidney dysfunction; (2) tachyarrhythmia (ventricular rate >150 beats per min); (3) coronary heart disease or patients who underwent coronary artery bypass grafting

simultaneously; and (4) infective endocarditis. One hundred and eighty-five patients were enrolled finally in our study, including 122 men and 63 women. The patients were divided into 2 groups using a random number table after admission. All patients underwent the same preoperative treatment strategy, anesthesia methods, and anesthesia drugs during surgery. All patients underwent conventional valve replacement under cardiopulmonary bypass, including 89 cases of mitral valve replacement, 53 cases of aortic valve replacement, and 43 cases of double valve replacement, which was concomitant with tricuspid valvuloplasty in 52 patients. There were 93 patients in the levosimendan group. The patients underwent levosimendan infusion immediately after returning to the Intensive Care Unit (ICU). The specific usage was as follows: levosimendan injection 12.5 mg was added to 45 mL of 5% glucose solution. The levosimendan infusion was started with a bolus dose of 10 µg/kg over 10 min, and was then followed by a rate of 0.1 to 0.2 µg/kg/min for 24 h. There were 92 patients in the control group, in which 50 mL of 5% glucose solution was given as a placebo. Usage and other treatments were the same as those of the levosimendan group. The perioperative characteristics of patients were recorded and analyzed. The general characteristics of the 2 groups are shown in **Table 1**. Cardiac output, B-type natriuretic peptide (BNP) level, and left ventricular ejection fraction (LVEF) were recorded at 1, 3, and 7 days after surgery. Dosage and administration time of vasoactive drugs, mechanical ventilation time, and the ICU length of stay were recorded. The incidence of postoperative adverse events, including LCOS, renal insufficiency, perioperative myocardial infarction, new atrial fibrillation, malignant arrhythmia, and re-exploration, was recorded.

Statistical Analysis

Statistical analysis was carried out using SPSS version 19.0. Measurement data with a normal distribution were presented as mean±standard deviation, and data with non-normal distribution were presented as median and interquartile range. Enumeration data were presented as percentages. The *t* test was used to compare measurement data, and the chi-squared test was used for analysis of enumeration data. A *P* value of less than 0.05 was considered statistically significant.

Results

Comparison of Preoperative and Intraoperative Clinical Characteristics Between the 2 Groups

A total of 200 patients were initially enrolled, of which 9 patients did not meet the inclusion criteria, 5 patients refused to participate in the trial, and 1 patient withdrew for other reasons. Finally, 185 patients were enrolled. There were no

Table 1. Comparison of preoperative and intraoperative clinical characteristics between the 2 groups.

Characteristics	Levosimendan (n=93)	Control (n=92)	χ^2 or t	P value
Age (year, mean±SD)	66.5±7.4	65.9±7.2	0.559	0.577
Sex (%)			0.523	0.470
Male	59 (63.4)	63 (68.5)		
Female	34 (36.6)	29 (31.5)		
Body mass index (Kg/m ²)	22.8±3.1	23.5±3.2	1.511	0.133
Hypertension (%)	19 (20.4)	17 (18.5)	0.112	0.737
Diabetes mellitus (%)	8 (8.6)	7 (7.6)	0.061	0.805
Chronic obstructive pulmonary disease (%)	3 (3.2)	2 (2.2)	0.195	0.659
Smoking history (%)	51 (54.8)	53 (57.6)	0.144	0.704
NYHA classification (%)			0.253	0.615
Class II~III	72 (77.4)	74 (80.4)		
Class IV	21 (22.6)	18 (19.6)		
Preoperative BNP (pg/mL, mean±SD)	285.6±23.9	279.8±22.3	1.706	0.090
Preoperative serum creatinine (μmol/L, SD) (umol/L, mean±SD)	85.2±11.3	86.5±11.9	0.762	0.447
Preoperative LVEF (% , mean±SD)	52.1±2.4	51.6±2.1	1.507	0.133
Operation (%)			0.504	>0.05
MVR	47 (50.5)	42 (45.7)		
AVR	26 (28.0)	27 (29.3)		
DVR	20 (21.5)	23 (25.0)		
CPB time	115.2±10.5	117.4±11.5	1.359	0.176
Cross-clamping time	78.5±6.8	80.2±7.1	1.663	0.098

NYHA – New York Heart Association; BNP – B-type natriuretic peptide; LVEF – left ventricular ejection fraction; MVR – mitral valve replacement; AVR – aortic valve replacement; DVR – double valve replacement; CPB – cardiopulmonary bypass.

statistically significant differences in age, sex, body mass index, smoking history, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, serum creatinine, preoperative NYHA classification, preoperative BNP level, LVEF, types of surgical procedure, cardiopulmonary bypass time, and aortic cross-clamping time between the 2 groups (Table 1).

Comparison of Cardiac Function After Surgery Between the 2 Groups

The cardiac output and LVEF of the levosimendan group at 1, 3, and 7 days after surgery were significantly higher than those of the control group ($P<0.05$). The levels of BNP in the levosimendan group were significantly lower than that of the control group at 1, 3, and 7 days after surgery ($P<0.05$) (Table 2).

Comparison of Other Perioperative Parameters Between the 2 Groups

The dosage and administration time of dopamine in the levosimendan group were significantly lower than those in the control group ($P<0.05$). The hemodynamics were stable in the levosimendan group after surgery, and without epinephrine infusion. In the control group, some patients needed intravenous infusion of epinephrine, and the dosage of epinephrine (non-normal distribution data) was 31.8 (0, 48.5) g/kg. The ICU length of stay in the levosimendan group was shorter than that of the control group ($P<0.05$). There was no significant difference in mechanical ventilation time between the 2 groups, as shown in Table 3. The incidences of LCOS, renal insufficiency, new atrial fibrillation, and total adverse events in the levosimendan group were significantly lower than those in the control group ($P<0.05$).

Table 2. Comparison of cardiac function at different time points between the 2 groups.

Parameters	Time (after surgery)	Levosimendan (n=93)	Control (n=92)	χ^2 or <i>t</i> value	<i>P</i> value
CO (L/min, mean±SD)	1 day	4.5±0.9	4.2±0.8	2.395	0.018
	3 days	4.7±1.1	4.3±0.9	2.705	0.008
	7 days	5.2±1.0	4.4±1.1	5.177	0.000
LVEF (%, mean±SD)	1 day	51.3±2.2	48.3±2.1	9.486	0.000
	3 days	53.5±2.4	48.9±2.1	13.868	0.000
	7 days	55.7±2.5	50.5±2.2	15.012	0.000
BNP (pg/mL, mean±SD)	1 day	520.7±47.2	986.5±55.1	61.772	0.000
	3 days	420.5±39.6	747.3±50.2	49.188	0.000
	7 days	312.5±34.6	455.4±45.2	24.161	0.000

CO – cardiac output; LVEF – left ventricular ejection fraction; BNP – B-type natriuretic peptide.

Table 3. Comparison of other perioperative parameters between the 2 groups.

Parameter	Levosimendan (n=93)	Control (n=92)	χ^2 or <i>t</i> value	<i>P</i> value
Average dosage of dopamine after surgery (mg/Kg, mean±SD)	11.5±1.8	20.4±2.1	30.960	0.000
Administration time of dopamine after surgery (h, mean±SD)	70.4±11.2	110.5±12.1	23.396	0.000
Duration of mechanical ventilation (h, mean±SD)	13.5±3.6	14.2±4.2	1.218	0.225
ICU length of stay (h, mean±SD)	24.6±4.3	32.5±4.6	12.068	0.000
Perioperative adverse events	9	25	9.438	0.002
Low cardiac output	0	5	5.195	0.023
Renal insufficiency	1	7	4.772	0.029
Perioperative myocardial infarction	0	0	5.283	0.022
New atrial fibrillation	6	16	0.350	0.554
Malignant arrhythmia	0	0		
Re-exploration	1	2		

ICU – Intensive Care Unit.

Discussion

Ischemia-reperfusion injury, additional heparin-induced thrombocytopenia of cardiopulmonary bypass, direct surgical injuries such as myocardial incision, and perioperative myocardial infarction in patients undergoing cardiac surgery inevitably induce different degrees of myocardial injury, and even heart failure [6,7]. Positive inotropic drugs are the most important drugs to improve cardiac function in patients after cardiac surgery. However, most positive inotropic drugs often give rise to adverse effects, such as increasing myocardial contractility and myocardial oxygen consumption, leading to local myocardial ischemia and

subsequent myocardial damage and the incidence of arrhythmia increases [8,9]. As a new type of positive inotropic drug, levosimendan induces calcium to bond with cardiac troponin C and increases the sensitivity of myofilament to calcium ions to increase myocardial contraction. Its binding is calcium-dependent but it does not increase the concentration of calcium ions in the cytoplasm, so it does not increase myocardial oxygen consumption [10,11]. The mechanism of action of levosimendan also includes the activation of adenosine triphosphate-sensitive potassium channels, which results in improved myocardial contractility, vasodilation, and cardioprotection. Results of recent clinical trials have shown that the administration of the

calcium sensitizer levosimendan after cardiac surgery can improve cardiac and renal functions of patients [12-14]. However, these benefits were greatest for the cardiac surgery patients with severe valvular disease or patients with severe coronary heart disease with diminished LVEF. A number of meta-analyses have shown that levosimendan can significantly improve general and pulmonary hemodynamics in patients with perioperative heart failure [15-17]. Zangrillo et al [18] demonstrated that levosimendan can improve kidney function in patients with mitral valve surgery and chronic kidney disease who develop perioperative myocardial dysfunction. Khaled et al [19] showed that levosimendan significantly improved hemodynamic parameters and had no effect on mortality in patients with left ventricular dysfunction undergoing cardiac surgery, compared with conventional inotropic agents. Weber et al [20] reported a meta-analysis of the beneficial effects of prophylactic levosimendan administration in patients with severe impairment of left ventricular function undergoing heart surgery. However, there have been few studies of the benefits of levosimendan in patients without perioperative heart failure. In the present prospective study, we explored the effect of levosimendan on patients undergoing conventional heart valve replacement. In our study, levosimendan was administered immediately when patients returned to the ICU after heart valve replacement. We confirmed that the heart function indexes at 1, 3, and 7 days after surgery in the levosimendan group were better than those of the control group. We showed that levosimendan significantly improved heart function in patients undergoing conventional cardiac valve replacement. Our results also demonstrated that the duration of ICU stay was significantly shortened in the levosimendan group, indicating that the administration of levosimendan enhanced the recovery of patients undergoing conventional cardiac valve replacement.

Catecholamine vasoactive drugs can enhance myocardial contraction by increasing myocardial oxygen consumption and can simultaneously increase heart rate and increase the incidence of arrhythmia [21,22]. Therefore, they will inevitably lead to an increase in morbidity and mortality [23]. Zatloukalová et al [24] showed that 100 mg/kg of isoprenaline by subcutaneous injection in a catecholamine model of acute myocardial infarction increased mortality, myocardial calcium overload, histological impairment, and peripheral hemodynamic disturbances 24 h after administration and could lead to late myocardial impairment and ventricular fibrillation due to myocardial calcium overload. In the present study, we showed that levosimendan administration significantly decreased the dosage and duration of catecholamine dopamine infusion, compared with the control group, and no epinephrine was administered in the levosimendan group. The results also demonstrated that the incidence of postoperative atrial fibrillation was significantly lower in the levosimendan group, and no malignant arrhythmias occurred in those patients, which showed that levosimendan

administration reduced the incidence of arrhythmias and did not increase the incidence of malignant arrhythmias, while improving the cardiac function of patients after routine heart valve replacement. Reduction in the administration of other positive inotropic drugs, such as dopamine and epinephrine, also reduced the occurrence of related adverse events. This finding is similar to that of Abacilar et al [25] who found that the occurrence of atrial fibrillation was significantly lower in the levosimendan group (12% vs 36%), and the duration of atrial fibrillation in the levosimendan group was significantly shorter compared with that of the control group in patients with poor left ventricle function after coronary artery bypass graft surgery. In our study, the results also demonstrated that the incidence of renal insufficiency was significantly lower in the levosimendan group, which was consistent with the results of many studies that showed levosimendan can improve kidney function in cardiac surgery. Guerrero Orriach et al [26] demonstrated that the incidence of kidney failure was lower with the postoperative administration of levosimendan than with the administration of beta-agonists in patients undergoing cardiac surgery with LCOS. However, some studies have drawn different conclusions. For instance, van Diepen et al [27] demonstrated that levosimendan was associated with lower 90-day mortality and LCOS in patients undergoing isolated coronary artery bypass graft surgery but not in patients undergoing isolated valve or combined coronary artery bypass graft surgery/valve procedures. Furthermore, Mehta et al [28] demonstrated that prophylactic levosimendan did not affect the rate of the short-term composite endpoint of death, renal replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device, and was lower than the rate with placebo among patients with a reduced LVEF who were undergoing cardiac surgery with cardiopulmonary bypass. Landoni et al [29] demonstrated that, compared with placebo, low-dose levosimendan in addition to standard care did not result in lower 30-day mortality in patients who required perioperative hemodynamic support after cardiac surgery. Different trials had heterogeneous results, which may be related to the administration dose and timing of levosimendan, different causes of cardiac dysfunction, and different choice of endpoint; therefore, to confirm the efficacy of levosimendan in cardiac surgery, more detailed and adequately powered clinical trials are needed.

There are some limitations in our study that should be emphasized. First, the patient population enrolled in this study was in a single institution and relatively small; therefore, the conclusions might not be applicable to other centers. Second, additional hemodynamic parameters, such as central venous pressure, mean arterial pressure, systemic vascular resistance, and pulmonary arterial wedge pressure, were not analyzed in this study. Finally, our study presented only short-term outcomes, and median and long-term follow-up might be needed to further assess the effect of levosimendan.

Conclusions

In conclusion, levosimendan administration immediately after surgery effectively improved heart function and protected renal function of patients after heart valve replacement. It reduced the postoperative administration of catecholamines, such as dopamine and epinephrine, reduced the occurrence of postoperative adverse events, shortened the duration of ICU stay, and enhanced the recovery of patients after cardiac valve

replacement. The curative effect of levosimendan was better than that of traditional positive inotropic drug treatment with dopamine and epinephrine infusion. Levosimendan was safe and effective to administer for 24 h of continuous infusion after surgery for patients undergoing cardiac valve replacement.

Conflicts of Interest

None declared.

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