

Effect of Levosimendan on the Prognosis of Cardiac Surgery in Patients with Cardiac Insufficiency

Heya Na, Xianen Fa*, Yuyang Zhou, Xiangyang Li, Rui Zhu, Lei Liu, Bing Liu

Department of Cardiovascular surgery, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, 450014, China

*Corresponding author

Xianen Fa, Department of Cardiovascular surgery, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, 450014, China.

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Abstract

Objective: To retrospectively analyze the effect of levosimendan on the survival and prognosis of cardiac surgery patients with LVEF<40%.

Methods: The clinical data of 224 patients with preoperative LVEF<40% were retrospectively analyzed. According to different treatment schemes, the patients were divided into levosimendan group (n=60) and non-levosimendan group (n=164). The control group was treated with routine treatment, and the observation group was treated with levosimendan on the basis of routine treatment. Then a multivariate logistic regression model with a propensity score analysis was used to limit biases and finally the data of 40 patients in each group were selected for analysis.

Results: Hemodynamic data showed that the cardiac index, LVEF and PAOP of patients in levosimendan group were significantly improved. The concentration of serum lactic acid in the levosimendan group was lower than that in the control group ($P<0.05$). At the same time, postoperative ICU and hospital stay were significantly reduced in levosimendan group ($P<0.05$). Logistics regression analysis showed that levosimendan was the only protective factor for Low cardiac output syndrome (LCOS) (HR=4.33; 95% confidence interval: 1.27-14.78; $P=0.019$).

Conclusion: Levosimendan can better improve hemodynamics and reduce postoperative ICU time and hospital stay. The use of it tends to decrease the incidence of LCOS significantly.

Keywords: Levosimendan, Cardiac Operative, Propensity Score Matching

Introduction

Over the last few decades, mortality associated with heart surgery has declined significantly, despite the increased complexity of the procedure. Although the average perioperative mortality rate is currently 1% to 2%, the incidence of major cardiovascular complications remains high [1]. Low cardiac output syndrome (LCOS) is the most common and serious complication associated with increased morbidity, short-and long-term mortality, and increased utilization of health-care resources. In addition, the mortality rate of LCOS patients after heart surgery can exceed 20%. The management of LCOS varies with its causes and manifestations. Recognition and treatment of precipitating factors are of prominent [2]. Levosimendan, as a calcium-sensitizing activity, is associated with positive inotropic action and increased myocardial contractility. However, compared with other inotropes, it did not increase intracellular calcium or cyclic adenosine. Thus, the absence of an associated increase in myocardial oxygen consumption also appears to be particularly beneficial for patients undergoing cardiac surgery with limited cardiac reserve [3]. This agent has been used in clinical practice since 2000, especially for the care of patients with heart failure

[4]. However, the evidence for its use in surgery is scant. Therefore, we intend to retrospectively analyze the specific efficacy of levosimendan in patients with a left ventricular ejection fraction (LVEF) less than 40% after cardiac surgery.

Material and Methods

This study was conducted with approval from the Ethics Committee of The Second Affiliated Hospital of Zhengzhou University (approval number 2018-019). As the nature of observational and retrospective study, informed consent was waived.

Selection of the Study Sample

This retrospective cohort study was conducted in the Cardiac surgery department of the Second Affiliated Hospital of Zhengzhou University from January 2017 to June 2020.

We target the recruitment of patients aged over 18, scheduled for isolated CABG, isolated valve, or combined CABG/valve surgery with cardiopulmonary bypass, who have a LVEF less than 40%, regardless of the method of assessment. All patients were consecutively evaluated. Exclusion criteria were: age <18years,

preoperative renal failure (creatinine clearance <30 ml/min), liver failure (prothrombin time <50 %, in the absence of vitamin K antagonist) Pregnancy, emergency surgery, defined as surgery within the 24h of the operative indication. During the study period, gave the attending physician full discretion to administer any other medication, including levosimendan and other vasoactive drugs, as appropriate. Levosimendan was administered without a bolus, by continuous infusion at 0.2 ug/kg/min for 24h.

Data Collection

Data were collected on: age; gender; body mass index >24 kg/m²; hypertension; diabetes mellitus; cardiopulmonary bypass time; aortic cross-clamping and serum lactic acid levels. Echocardiography was performed by the same team with three ultrasound operators at baseline, intraoperative and postoperative of each patient. The LVEF was measured using biplane Simpson's method from the two-dimensional echocardiography.

All patients underwent continuous monitoring of heart rate and measurement of hemodynamic parameters including pulmonary artery occlusion pressure (PAOP) and cardiac index. Time 0 was defined as the initial hemodynamic measurement, time 1 was recorded on arrival back in the cardiovascular ICU following surgery. Times 2 to 3 were 12h and 24h after arrival in the cardiovascular ICU following surgery, respectively. Patients underwent 90 days of postsurgical follow-up, with survival status during this period being recorded.

Clinical Definitions and Study Endpoints

LCOS incidence was the primary outcome of this trial. LCOS was defined as the presence of low cardiac index (<2.2 L/min/m²)², elevated PAOP (>16 mmHg) and a SO₂ <60%. Secondary outcomes for this trial included (a) durations of ICU and hospital stay, (b) serum lactic acid levels at 0, 12, and 48h post-surgery, (c) invasive hemodynamic parameters at 0, 12, and 48h post-surgery.

Statistical Analysis

Results were expressed as frequencies and percentages for categorical variables, as means and standard deviations for continuous variables. Prior to propensity score matching, continuous variables were compared using Student's t test or the Mann

Whitney test, as appropriate. Qualitative variables were compared using Pearson's Chi-square or Fisher's exact test, as appropriate. Mortality at 90 days after cardiac surgery was estimated by using the Kaplan Meier method and compared using the log-rank tests. A two-sided p<0.05 was the significance threshold. The propensity score was defined as the probability of exposure to levosimendan. In order to limit over adjustment due to the use of this score, we selected only the covariates most likely to introduce a confounding bias [5,6]. The propensity score was estimated using a logistic regression adjusted for age, sex, body mass index >24 kg/m², presence of high blood pressure and diabetes. Matching was then performed between one patient exposed to levosimendan and up to one unexposed patient, with a propensity score caliper of 0.05 [7].

After propensity score matching, Baseline demographic, clinical and echocardiographic data were estimated again to compare baseline characteristics and to therefore assess the accuracy of the matching procedure. Associations between baseline factors and LCOS incidence were assessed using univariate analysis and multivariate logistic regression modeling. Hazard ratios (HR) and their 95% confidence intervals were calculated. A two-tailed p value <0.05 was considered significant. All the statistical analyses were performed at the Second Affiliated Hospital of Zhengzhou University (Henan Province, China) with the use of SPSS software, version 25.0.

Results

Study Population

Over the study period, 271 patients in high-risk with an ejection fraction less than 40% were included in the study. Among these, 47 patients were excluded from the study (12 were <18 years, 6 had preoperative renal failure, 3 had liver failure, 6 were pregnant, 20 received emergency surgery). A total of 224 patients with severely reduced left ventricular ejection fraction (LVEF <40%) were eligible for the study. In 2017-2018, in 2018-2019, in 2019-2020 and in 2020-2021, seven out of 35 patients (20%), 20 out of 63 (31.7%), 32 out 75 (42.7%) and 11 out 51 (21.6%) were respectively treated with levosimendan. Forty propensity-matched patients were evaluated in the levosimendan group and 40 in the non-levosimendan group in Figure 1.

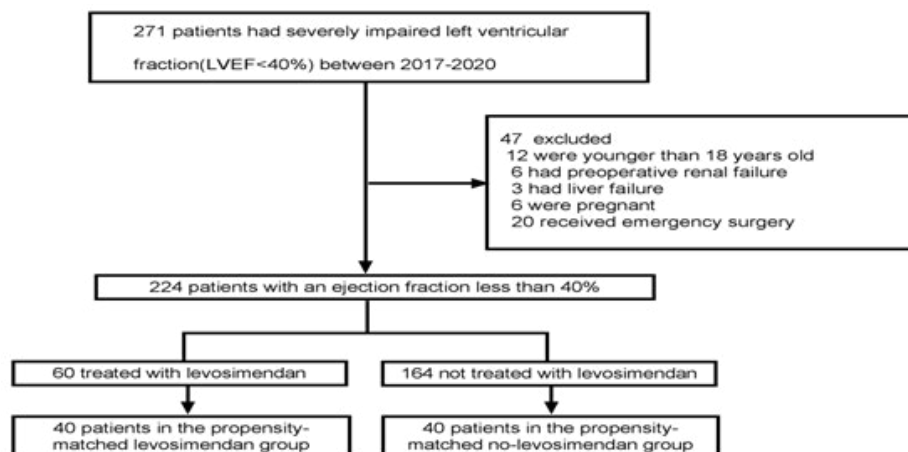


Figure 1: Selection of the Study Sample

Characteristics and Outcome of the 224 Pre-Matched Patients

Table 1 presents the basic characteristics of the included 224 patients (prior to matching). The average age was 55.29 ± 8 years and the proportion of male was 47.3%. The proportion of body mass index greater than 24 kg/m^2 accounted for 48.7% Table 1. During the study period, 60 patients were treated with levosim-

endan (26.8%). There was no difference in mean cardiopulmonary bypass time and aortic cross clamp time compared with the control group. All the patients in the levosimendan group and the no-levosimendan group had severely reduced left ventricular ejection fraction with LVEF $<40\%$, but the difference between the groups was statistically significant ($P=0.02$).

Table 1: Baseline Patient Characteristics in Pre-Matched Groups

Variables	Total	Levosimendan		P value
	(n=225)	No(n=164)	Yes(n=60)	
Male	106(47.3)	76(46.3)	30(50)	0.627
Age (years)	55.29 ± 8.360	52.60 ± 7.877	62.63 ± 4.214	0.000
BMI $>24 \text{ kg/m}^2$	109(48.7)	75(45.7)	34(56.7)	0.147
Isolated CABG	70(31.3)	52(31.7)	18(30)	0.951
Isolated valve surgery	86(38.4)	62(37.8)	24(40)	
Combined CABG and valve	68(30.4)	50(30.5)	18(30)	
Diabetes mellitus	93(41.5)	64(39.0)	29(48.3)	0.211
Hypertension	103(46.0)	75(45.7)	28(46.7)	0.901
CPB (min)	128.37 ± 21.086	129.38 ± 21.318	125.60 ± 20.352	0.235
Aortic cross clamp time (min)	96.83 ± 16.219	97.62 ± 16.129	94.68 ± 16.406	0.231
LVEF (%)	35.49 ± 3.131	35.20 ± 3.216	36.30 ± 2.751	0.012

Results are expressed as mean \pm SD or number (%), CABG: Coronary Artery Bypass Grafting, BMI: Body Mass Index, LVEF: Left Ventricular Ejection Fraction, CPB: Cardio Pulmonary Bypass

Characteristics and Outcome of the 80 Matched Patients

After propensity score matching, the difference in the characteristics of patients between the levosimendan group and the non-levosimendan group were not statistically significant Table 2. Baseline hemodynamic parameters and serum lactate concentration were comparable in both groups Figure 2. Hemodynamic

data demonstrate a rapid improvement in cardiac index, LVEF and PAOP in patients receiving levosimendan. Serum lactate concentration was consistently lower in levosimendan group at majority of time intervals. These effects persisted at all time intervals during and after surgery. Significant reduction in ICU and hospital stay occurred in levosimendan group at the postoperative period as compared to no levosimendan group ($P < 0.05$).

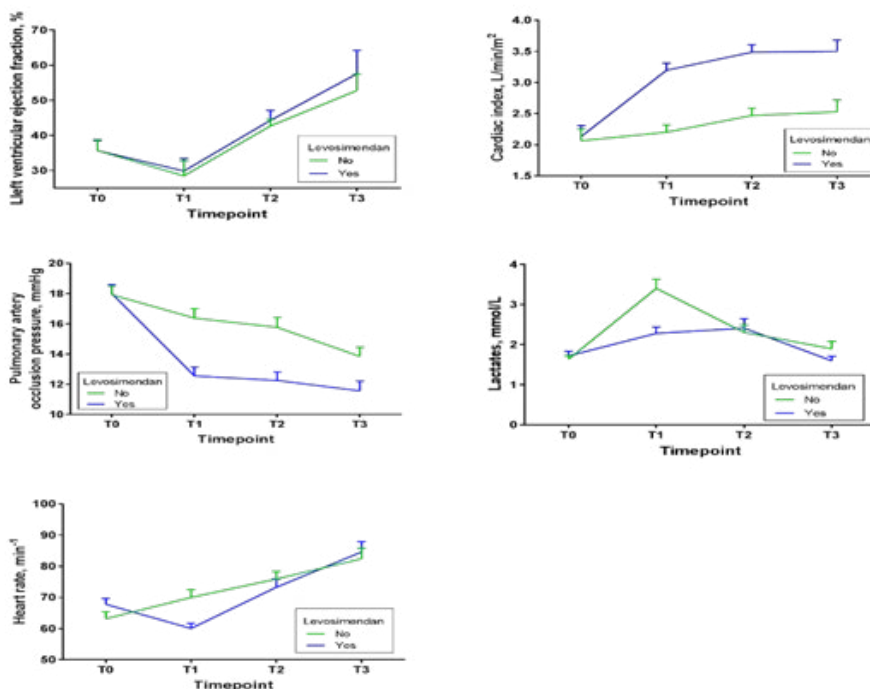


Figure 2

Table 2: Patient Characteristics in Propensity-Matched Groups

Variables	Total	Levosimendan	
	(n=80)	No (n=40)	Yes (n=40)
Male	41 (51.25)	20 (50)	21 (20.5)
Age (years)	43 (53.75)	21 (52.5)	22 (55)
BMI > 24kg/m ²	60.53 ± 3.978	60.30 ± 4.345	60.75 ± 3.614
Isolated CABG	22 (27.5)	18 (28.6)	4 (23.5)
Isolated valve surgery	34 (42.5)	26 (41.3)	8 (47.1)
Combined CABG and valve	24 (30)	19 (30.2)	5 (29.4)
Diabetes mellitus	34 (42.5)	16 (40)	18 (45)
Hypertension	30 (37.5)	13 (32.5)	17 (42.5)
CPB (min)	125.66 ± 19.573	124.35 ± 18.530	126.98 ± 20.715
Aortic cross clamp time (min)	99.91 ± 14.995	102.30 ± 14.235	97.53 ± 15.528
Duration of mechanical ventilation (hour)	41.00 (36.00-47.75)	45.5 (38-52.25)	38 (34-45)
ICU stay (day)	4.5750 (4.11-5.61)	5.6 (4.77-6.53)	4.13 (3.74-4.53)
Hospital stay (day)	9.4450 (8.44-11.86)	11.82 (10.55-13.25)	8.49 (7.69-9.08)
LCOS	17 (21.25)	13 (32.5)	4 (10)

Results are expressed as mean ± SD or number (%), CABG: Coronary Artery Bypass Grafting, BMI: Body Mass Index, LVEF: Left Ventricular Ejection Fraction, CPB: Cardio Pulmonary Bypass, LCOS: Low Cardiac Output Syndrome, ICU: Intensive Care Unit

Out of 80 patients, 63 patients (78.75%) were not presented in the postoperative phase with low cardiac output syndrome (LCOS). After propensity score matching, exposure to levosi-

mandan was the only remaining factor associated with a significant reduction in the occurrence of LCOS rates (hazard ratio = 4.33; 95% confidence interval: 1.27-14.78; P = 0.019) Table 3.

Table 3: Baseline Factors Predictive of LCOS Incidence

Variables	LCOS		P value
	No (n=63)	Yes (n=17)	
Male	34 (54)	7 (41.2)	0.349
BMI > 24kg/m ²	35 (55.6)	8 (47.1)	0.533
Age (years)	60.41 ± 4.01	60.94 ± 3.94	0.63
Isolated CABG	18 (28.6)	4 (23.5)	0.891
Isolated valve surgery	26 (41.3)	8 (47.1)	
Combined CABG and valve	19 (30.2)	5 (29.4)	
Diabetes mellitus	28 (44.4)	6 (35.3)	0.489
Hypertension	24 (38.1)	6 (35.3)	0.832
CPB (min)	124.83 ± 19.46	128.76 ± 20.28	0.465
Levosimendan	36 (57.14)	4 (23.5)	0.014
LVEF	35.42 ± 3.02	36.65 ± 2.74	0.137
HR	65.73 ± 3.05	64.59 ± 3.20	0.179
CI	2.10 ± 0.18	2.09 ± 0.19	0.843

Results are expressed as mean ± SD or number (%), CABG: Coronary Artery Bypass Grafting, BMI: Body Mass Index, LVEF: Left Ventricular Ejection Fraction, CPB: Cardio Pulmonary Bypass, LCOS: Low Cardiac Output Syndrome, ICU: Intensive Care Unit, HR: Heart Rates, CI: Cardiac Index

Discussion

This retrospective study suggests that patients with a severely reduced left ventricular ejection fraction due to impaired contractility may probably benefit from levosimendan.

This agent acutely improves hemodynamics during postopera-

tive recovery and also reduces the length of ICU stay and the length of hospital stay. As far as we known, levosimendan's unique properties are attributed to its multiple and complementary mechanisms of action. In addition to its hemodynamic actions on coronary and pulmonary vessels, another hypothesis for the beneficial effects of levosimendan that might have positive

effects on systemic vasodilation [3]. This is relevant to the reduction on serum lactic acid. Bravo et al conducted a study in the critically ill infants with congenital heart defects suffering from LCOS and found that many poor perfusion physiological variables and biomarkers indicators showed a different profile after levosimendan infusion, such as a significant decrease in serum lactate levels. Finally, levosimendan served a beneficial function on cerebral and systemic perfusion in these restricted patients [8].

In addition, the patients with severe, low-output heart failure were also able to benefit from levosimendan [9,10]. In our view, extending the study population to non-cardiac surgery patients is relevant for physicians in the field because low cardiac output syndrome may occur in many cases. To our knowledge, two other randomized controlled trials (RCTs) have not shown beneficial effects of the use of levosimendan compared with placebo in patients with preoperative severely depressed LVEF [11,12]. Wang et al. also suggested that levosimendan had no significance on the improvement of the incidence of postoperative LCOS [13]. The beneficial effects of levosimendan are still debated in clinical practice. Nonetheless, researchers in the first study reported a beneficial effect in a subgroup of patients with a more severe reduction of LVEF [12]. Another analysis also showed that the beneficial effect of levosimendan can only be observed in patients with LVEF <50% [14].

Van et al., divided the patients into different cardiac surgery methods [15]. Desai et al studied patients undergoing off-pump coronary artery bypass surgery [16]. In terms of the incidence of LCOS, no significant results were observed in either study, which is consistent with our observation. A large meta analysis also suggested that levosimendan could benefit the patients with lower LVEF (<35%) in terms of the incidence of postoperative LCOS [17]. Levosimendan can reduce the incidence of LCOS after heart surgery, which can only be observed in patients with a more severe reduction of LVEF [17]. All of our patients had significant hemodynamic disorders with an ejection fraction less than 40%. In addition, Orriach et al. found that levosimendan can improve the renal function of postoperative LCOS patients [18]. This suggests that levosimendan can not only reduce the incidence of LCOS, but can also benefit the patients who have already experienced LCOS, expanding the scope of application of levosimendan to a certain extent.

Limitations

Our study has several limitations. The retrospective nature of the analysis is clearly a weakness. In addition, our study may be restricted due to the low number of patients and events evaluated. The main limitation of our study is that the administration of levosimendan was not randomized. However, to limit biases due to the absence of randomization, we used a multivariate logistic regression model with a propensity score analysis.

Abbreviations

LCOS: Low Cardiac Output Syndrome
LVEF: Left Ventricular Ejection Fraction
ICU: Intensive Care Unit

Conclusion

This study suggests that levosimendan can improve hemodynamics and reduce postoperative ICU time and hospital stay. And the use of levosimendan tended to decrease the incidence of LCOS significantly.

Declarations

Ethical Approval and Consent to participate

This study was conducted with approval from the Ethics Committee of The Second Affiliated Hospital of Zhengzhou University (approval number 2018-019). The need for informed consent was waived because of the observational and retrospective nature of the study.

Availability of supporting data

The data used and/or analyzed in the present study are available from the corresponding author on reasonable request.

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Authors' contributions

Heya Na and Xianen Fa had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Heya Na, Xianen Fa and Yuyang Zhou conceptualized and designed the study. Heya Na, Xiangyang Li, Rui Zhu and Bing Liu were involved in acquisition of data. Heya Na, Xiangyang Li, Rui Zhu, Lei Liu and Bing Liu analyzed and interpreted the data. Heya Na and Bing Liu drafted the manuscript. Xianen Fa, Yuyang Zhou and Lei Liu critically revised the manuscript for important intellectual content. Heya Na and Xiangyang Li carried out the statistical analysis. Xianen Fa and Yuyang Zhou were involved in funding, administrative, technical or material support. Xianen Fa, Yuyang Zhou, Xiangyang Li, Rui Zhu, Lei Liu and Bing Liu supervised the study. All authors read and approved the final manuscript.

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