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Effect of Levosimendan Compared to Conventional Inotropic Agents on Hemodynamics and Outcome in Patient with Poor LV Function Undergoing Cardiac Surgery

Mahmoud Khaled, Ahmad Naem Almogy*, Mohammed Shehata, Fahim Ragab, Khaled Zeineldin

Department of Critical Care Medicine, Cairo University, Cairo, Egypt

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***Correspondence:** Ahmad Naem Almogy. Department of Critical Care Medicine, Cairo University, Cairo, Egypt. E-Mail: ahmadpeace385@yahoo.com

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Abstract

BACKGROUND: Patients undergoing heart surgery involving cardiopulmonary bypass (CPB) experience global myocardial ischemia with subsequent reperfusion which, despite cardioplegic protection, may result in different degrees of transient ventricular dysfunction. Levosimendan is a “calcium sensitisers”, it improves myocardial contractility by sensitising troponin C to calcium without increasing myocardial oxygen consumption and without impairing relaxation and diastolic function.

AIM: To evaluate the adding effect of a calcium sensitiser (levosimendan) compared to the conventional inotropic and vasoactive agent used in the patient with poor left ventricular function undergoing cardiac surgery on different measured hemodynamic variables and the effect on the outcome.

METHODS: It is prospective observational studies were patients were divided into 2 groups of 30 patients each. The first Group received conventional inotropic and vasoactive treatment at different doses, while the other group received levosimendan additionally at a loading dose of 6-12mic/kg according to mean arterial pressure over 0.5 hr followed by 24 hrs infusion at 0.05 to 0.2 mic/kg/min. Hemodynamic data were collected at the end and 30 minutes after CPB, after that at 6, 12, 24, and 36 hours post CPB. Mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), mixed venous saturation (Svo2), and base deficit (BD) were measured.

RESULTS: Levosimendan had significantly improved postoperative hemodynamic values as in the mixed venous pressure at different times postoperative ($p < 0.05$), also the base deficit at different times postoperative ($p < 0.05$), while there was a significant reduction in systemic vascular resistance as decreased mean arterial pressure in levosimendan group compared to conventional group at 6hrs postoperative mean 77.50 ± 10.81 vs 83.73 ± 10.81 with ($p = 0.029$), and at 12 hrs postoperative mean 77.37 ± 10.10vs 84.23 ± 13.81 with ($p = 0.032$), and there was no significant difference in heart rate at different times postoperative between both groups ($p > 0.05$), while there was no significant effect on mortality between both groups ($p = 0.781$).

CONCLUSION: Levosimendan had improved hemodynamic parameters significantly with no effect on mortality compared to conventional inotropic agents in a patient with poor left ventricular function undergoing cardiac surgery.

Introduction

Patients undergoing heart surgery involving cardiopulmonary bypass (CPB) experience global myocardial ischemia with subsequent reperfusion which, despite cardioplegic protection, may result in different degrees of transient ventricular dysfunction, also known as myocardial stunning in the immediate postoperative period [1], [2]. If severe enough, this dysfunction can cause postoperative low cardiac output syndrome, a complication with an estimated prevalence of about10% and a mortality of 17% [3].

Pharmacological support, in the form of vasodilator and inotropic therapy, as well as mechanical support, such as intra-aortic balloon counterpulsation and ventricular assist devices, is often necessary to restore adequate tissue perfusion in the immediate postoperative period [2]. Perioperatively, the most frequently used inotropes are beta-adrenergic and phosphodiesterase III inhibitors [4], [5], [6].

Levosimendan is a recently introduced

indicator, it belongs to a novel group of agents called calcium sensitisers, which increase the sensitivity of contractile proteins to calcium. The use of this agent in the treatment of decompensated heart failure is based on its dual mechanism of action. It improves myocardial contractility by sensitising troponin C to calcium without increasing myocardial oxygen consumption [7] and without impairing relaxation and diastolic function [8]. Also, it causes the opening of ATP-dependent potassium channels on smooth muscle fibres, which induces systemic, pulmonary and coronary vasodilatation and may offer cardioprotective effects during myocardial ischaemia [9], [10], [11].

Furthermore, growing evidence from *in vitro* and *in vivo* studies indicates that, unlike other inotropes, levosimendan does not affect or even improves diastolic function in failing myocardium [12], [13], [14], [15].

We aimed to evaluate the adding effect of a calcium sensitiser (levosimendan) compared to the conventional inotropic and vasoactive agent used in the patient with poor left ventricular function undergoing cardiac surgery on different measured hemodynamic variables and the effect on the outcome.

Patients and Method

Our study was a prospective observational study, conducted from the period of May 2016 to May 2017, in which patients admitted to the intensive care units following cardiac surgery in different cardiac surgery centres (Cardiothoracic Department, Cairo University and other cardiothoracic centres, Cairo, Egypt).

A total of 60 patients were enrolled in our study and were subsequently divided into two groups 30 patients each, group received conventional inotropic and vasoactive treatment, while the other group received levosimendan additionally at loading dose 6-12 mic/kg according to mean arterial pressure over 0.5 hr followed by 24 hrs infusion at 0.05 to 0.2 mic/kg/min. Hemodynamic data were collected at the end and 30 minutes after CPB, after that at 6, 12, 24 and 36 hours post CPB. Mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), mixed venous saturation (Svo_2) and base deficit (BD) were measured.

Inclusion criteria

All patients with poor preoperative left ventricle function ejection fraction < 35% undergoing cardiac surgery for valvular, coronary bypass or aortic aneurysm repair.

Exclusion criteria

Patients with congenital heart disease.

Patients with allergy to levosimendan.

All patients enrolled in our study were subjected to:

- Full history and clinical examination.

- Preoperative logistic EUROSCOREII evaluation.

- Laboratory investigation including:

- Complete blood count.

- Renal and liver function tests.

- Coagulation profile.

- Pre and postoperative echocardiography.

- Chest x-ray.

- ECG.

Statistical analysis

Data were collected, revised, coded and entered to the statistical package for social science (IBM SPSS) version 20. Qualitative data were presented as number and percentages, while quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data was made by using *Chi-square test*, the comparison between two independent groups with quantitative data and parametric distribution was made by using *Independent t-test,* while the Mann Whitney test is done for two independent samples with nonparametric distribution and the comparison between more than two groups with quantitative data and parametric distribution was done by using One Way ANOVA test**.** The p-value was considered significant if < 0.05.

Results

Our study enrolled a total of 60 patients: 46 males (77%), 14 females (23%), who were admitted to ICU following cardiac surgery with preoperative echocardiography revealing impaired cardiac functions EF < 35%.

Demographic data were presented in Table 1. There was no significant statistical difference between both groups (p > 0.05) regarding age, gender, preoperative ejection fraction, while there was a significant statistical higher incidence of BMI, diabetes, hypertension in the levosimendan compared to conventional group (p = 0.001, 0.002, 0.005 respectively).

Table 1: Study group demographic data

Demographic data		Conventional group No. = 30	Levosimendan group No. = 30	P value
Age	Mean ± SD	55.20 ± 8.59	59.67 ± 9.84	0-066
	Range	34 – 72	30 – 74	
Gender	Male	20 (66.7%)	26 (86.7%)	0-067
	Female	10 (33.3%)	4 (13.3%)	
Body mass index	Mean ± SD	30.93 ± 2.56	33.50 ± 3.05	0-001
	Range	24 – 36	29 – 39	
Diabetic	No	19 (63.3%)	7 (23.3%)	0.002
	Yes	11 (36.7%)	23 (76.7%)	
		28 (93.3%)	19 (63.3%)	0-005
Hypertensive	No	2 (6.7%)	11 (36.7%)	
	Yes			
Preoperative ejection Fraction	Mean ± SD	33.20 ± 3.35	31.80 ± 4.44	0.173
	Range	20 – 36	20 – 37	

Heart Rate

There was no statistically significant difference regarding heart rate at any time postoperative between the two groups (p > 0.05) as presented in Table 2.

Table (2): Comparison of postoperative measured heart rate between both groups

Heart rate		Conventional group No. = 30	Levosimendan group No. = 30	P-value
Immediate postoperative	Mean ± SD	102.13 ± 14.00	101.57 ± 20.08	0.900
	Range	77 – 132	65 – 160	
0.5hr postoperative	Mean ± SD	101.90 ± 13.17	101.90 ± 19.71	1.000
	Range	71 – 124	76 – 170	
6hrs postoperative	Mean ± SD	101.73 ± 12.67	99.17 ± 18.94	0.540
	Range	71 – 125	62 – 146	
12hrs postoperative	Mean ± SD	102.13 ± 15.14	101.50 ± 18.99	0.887
	Range	70 – 139	73 – 163	
24hrs postoperative	Mean ± SD	102.90 ± 15.83	106.33 ± 20.72	0.474
	Range	75 – 142	63 – 150	
36hrs postoperative	Mean ± SD	97.33 ± 18.96	107.37 ± 23.67	0.075
	Range	60 – 140	54 – 170	

Mean arterial blood pressure

Regarding mean arterial pressure, there was a statistically significant difference between both groups at 6hrs postoperative wherein the conventional group mean arterial pressure was higher 83.73 ± 10.81mmHg compared to the levosimendan group mean arterial pressure was 77.50 ± 10.81 mmHg (p = 0.029).

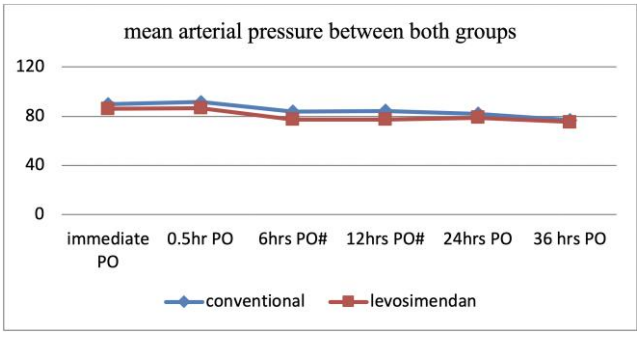

Figure 1: Mean arterial pressure between both groups (PO) postoperative; (#) significant P-value

Also, there was a statistically significant difference between both groups at 12 hrs postoperatively wherein the conventional group mean arterial pressure was higher 84.23 ± 13.81 mmHg compared to the levosimendan group mean arterial pressure was 77.37 ± 10.10 mmHg (p = 0.032). While there was no statistically significant difference at immediate, 0.5 hr, 24hrsand at 36hrs postoperatively (p > 0.05) as shown in Figure 1.

Central venous pressure (CVP)

Regarding central venous pressure, there was statistically significant lower CVP at 6hrs postoperative in the conventional group with median 6.00 (3.00 – 9.00) cm H2O compared to the levosimendan group median was10.00 (5.00 – 12.00) cmH2O (p = 0.004). Also, there was statistically significant lower CVP at 12hrs postoperative in the conventional group with median 7.50 (4.00 – 9.00) cmH2O compared to the levosimendan group median 10.00 (9.00 – 13.00) cmH2O (p = 0.006).

There was no statistically significant difference at immediate, 0.5 hr, 24 hrs and 36 hrs postoperatively (P > 0.05) as shown in Figure 2.

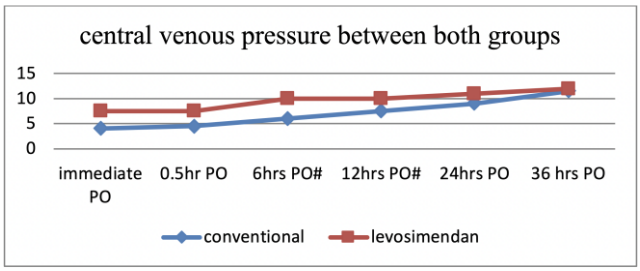

Figure 2: Central venous pressure between both groups (PO); postoperative (#) significant P-value

Base deficit

There was a highly statistically significant higher base deficit in the conventional group compared to the levosimendan group at immediate, 0.5 hr, 6 hrs, 24 hrs and 36 hrs postoperatively (p = 0.001, 0.001, 0.009, 0.021 and 0.001) respectively. While there was no statistically significant difference in the base deficit between both groups at 12 hrs postoperatively (p = 0.104) as shown in Figure 3.

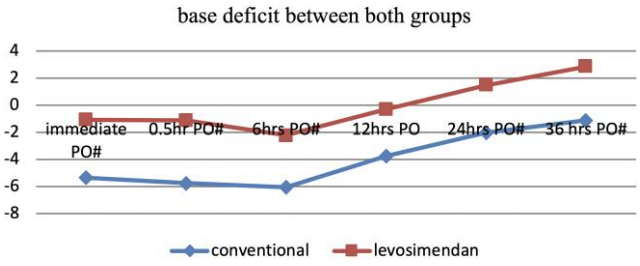

Figure 3: Base deficit between both groups (PO) postoperative; (#) significant P-value

Mixed venous oxygen saturation

There was a highly statistically significant higher mixed venous oxygen saturation in the

levosimendan group compared to the conventional group at immediate, 0.5 hr, 6 hrs, 12 hrs, 24 hrs and 36hrs postoperatively (p = 0.013, 0.015, 0.032, 0.024, 0.005 and 0.011) respectively as shown in **F**igure 4.

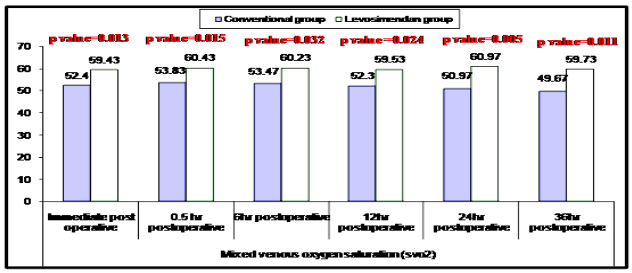

Figure 4: Mixed venous pressure between both groups

Outcome

Postoperative ejection fraction was significantly higher in the levosimendan group than the conventional group (p = 0.002), length of hospital stay was significantly lower in the levosimendan group than in conventional group (p = 0.028). Also, there was a statistically significant higher logistic EUROSCOREII in the levosimendan group than in the conventional group (p = 0.046) as presented in Table 3.

Table 3: Outcomes in the conventional and levosimendan group

Outcomes		Conventional group No. = 30	Levosimendan group No. = 30	P value
Postoperative ejection fraction	Mean ± SD Range	33.73 ± 2.96 25 – 39	36.90 ± 4.53 25 – 44	0.002
Mechanical ventilation duration in hours	Mean ± SD Range	51.43 ± 66.29 6 – 288	43.27 ± 36.48 6 – 120	0.557
Length of ICU stay in days	Mean ± SD Range	4.03 ±2.71 2 – 12	3.27 ± 1.68 2 – 8	0.193
Length of hospital stay in days	Mean ± SD Range	15.43 ± 9.70 5 – 46	10.87 ± 5.41 5 – 29	0.028
Logistic EUROSCOREII	Median (IQR) Range	1.88 (1.20 – 3.57) 0.76 – 21.06	3.19 (1.76 – 6.70) 0.68 – 21.72	0.046

There was no statistically significant difference between both groups regarding mortality with lower mortality in the levosimendan group 9 patients (30%) did not survive compared to conventional group were10 patients (33.3%) did not survive (p = 0.781) as presented in Table 4.

Table 4: Mortality in the two study groups

Mortality	Conventional group No. = 30	Levosimendan group No. = 30	P-value
Survival	20 (66.7%)	21 (70.0%)	0.781
Non survival	10 (33.3%)	9 (30.0%)	

Discussion

In our study using of levosimendan achieved statistically significant improvement in left ventricular function (EF%) postoperatively determined by echocardiography compared to conventional group (36.90 ± 4.53 VS 33.73 ± 2.96), (p = 0.002).

Supporting our results Husedzinovic et al., [16] in a double-blind, randomised trial evaluating the effect of levosimendan as a new strategy during off-pump coronary artery bypass grafting enrolling 24 patients received either placebo or levosimendan at a dose of 12 mic/kg as an infusion for 15 min before CABG. At 10 min and 60 min post-infusion, the cardiac index and the LVEF were significantly higher with levosimendan than with placebo (P = 0.018 each). The stroke volume index was significantly higher for levosimendan at 10 min (P = 0.018), but not at 60 min (P = 0.063).

In concordance to our study, Barisin S et al., [17] in his study levosimendan in off-pump coronary artery bypass: a Four-time masked, controlled study enrolling 31 patients: 10 patients received a high dose,10 patients received a low dose, and 11 patients received a placebo.

Two dose schedules: low dose(12 mic/kg), high dose (24 mic/kg) over 10min; treatment was given 20min before start of surgery result in significant increases in cardiac output and LVEF occurred after high-dose (P = 0.001; P = 0.006) and low-dose levosimendan (P = 0.001; P = 0.002). Both levosimendan doses produced significant increased stroke volume and decreased systemic vascular resistance.

In our study, the heart rate showed no significant statistical difference at all times postoperative between both groups (p > 0.05).

This went side by side with Stefan G. DeHert et al., [18] who conducted a study enrolling 30 patients evaluating the effects of levosimendan in cardiac surgery patients with poor left ventricular function had found that there was no statistically difference in the heart rate at all times postoperatively between both groups (p > 0.05).

Also, Polychronis Malliotakis et al., [19] who conducted a study enrolling12 patients evaluating the hemodynamic effects of levosimendan for low cardiac output after cardiac surgery had determined that there were no significant changes in heart rate postoperatively (p > 0.05).

In contrast, Ravikumar Gandham et al., [20] who conducted a study enrolling 60 patients evaluating a comparison of hemodynamic effects of levosimendan and dobutamine in patients undergoing mitral valve repair/replacement for severe mitral stenosis had found that there was a significant difference in heart rate being higher in the conventional group at mostly all times postoperatively (p < 0.05) this variance may be due to that he was mainly comparing dobutamine with levosimendan.

In our recent study, the mean arterial pressure was statistically significant at 6 and 12 hrs

postoperatively (p = 0.029 and 0.032 respectively) being higher in the conventional group than the levosimendan group.

This was concordance to Julian Alvarez et al., [21] who conducted a study enrolling 50 patient evaluating the hemodynamic effects of levosimendan compared with dobutamine in patients with low cardiac output after cardiac surgery had found that there was a significant mean arterial pressure difference between both groups at 6, 12, 24 and 48 hrs postoperatively (p < 0.05) being higher in the conventional group.

Polychronis Malliotakis et al., [19] showed significance mean arterial pressure difference between both groups at 6 and 24 hrs postoperatively (p < 0.05) being higher in the conventional group.

Ravikumar Gandham et al., [20] had found that significance means arterial pressure difference between both groups at immediate, 6 and 12 hrs postoperatively (p < 0.05) being higher in the conventional group.

Those agreements may be conducted to systemic and pulmonary vasodilator effect of levosimendan, leading to a reduction in blood pressure.

In our study, evaluating central venous pressure at 6 and 12 hrs postoperatively were statistically significant (p = 0.004 and 0.006 respectively) between both groups were lower in the conventional group.

In concordance to our results other studies like Julian Alvarez et al., [21] had found that significant difference in central venous pressure at 6, 12, 24 and 48 hrs postoperatively between both groups with (p < 0.05).

Polychronis Malliotakis et al. determined that there was a significant difference in central venous pressure at 6, 12 and 24 hrs postoperatively from baseline levosimendan infusion (p < 0.05).

Ravikumar Gandham et al., [20] found that there was a significant difference in central venous pressure at immediate, 6 and 12 hrs postoperatively from baseline levosimendan infusion with (p < 0.05).

They all found that there was a significant reduction in central venous pressure in levosimendan group as a result of a reduction in systemic and pulmonary vascular resistance this variation from our study may be due to there was no fixed postoperative IV fluid protocol among our patients.

In the current work, we used base deficit and mixed venous saturation being an indicator for adequate cardiac output and tissue perfusion they were strongly significant at almost all times postoperatively more base deficit in the conventional group than levosimendan group and higher mixed venous saturation in the levosimendan group than conventional group (p < 0.05).

In concordance with other studies Julian Alvarez et al., [21] showed that significant difference in mixed venous oxygen saturation at 6, 12, 24 and 48 hrs postoperatively between both groups with (p < 0.05).

Polychronis Malliotakis et al., [19] determined that there was a significant difference in mixed venous oxygen saturation at 6, 12 and 24 hrs postoperatively from baseline levosimendan infusion (p < 0.05).

Also, E. Al shawaf et al., [22] who conducted a study enrolling 30 cardiac surgery patients comparing levosimendan Vs milrinone in type2 diabetic patient with low LVEF undergoing elective coronary artery surgery found that there were significantly higher cardiac index and mixed venous oxygen saturation with levosimendan (p < 0.05), significantly lower pulmonary capillary wedge pressure, systemic vascular resistance and oxygen extraction ratios.

In our study, there was no statistically significant difference in mortality between the conventional and levosimendan groups (10 patients Vs 9 patients) with (p = 0.781).

Our results went hand by hand with Stefan G. DeHert et al., [18], who showed a non-significant effect on mortality (p = 0.224).

Also, Rajendrah Mehta et al., [23] in the mega trial levo.cts enrolled 880 patients evaluating the effect of levosimendan in patients with left ventricular systolic dysfunction undergoing cardiac surgery on cardiopulmonary bypass had found that levosimendan did not affect the primary outcome (mortality) (p = 0.45). Other studies like Julian Alvarez et al., [21], Polychronis Malliotakis et al., [19], and Ravikumar Gandham et al., [20] they were focusing mainly on the hemodynamic effect of levosimendan.

Limitation: The present study has the following limitations:

1. The small number of patients was a certainly serious drawback.

2. Presence of several confounding factors (e.g. mode and parameters of mechanical ventilation, amount of fluids or blood products infused during the observation period).

3. Lack of invasive cardiac function monitoring (cardiac index, stroke volume index, systemic and pulmonary vascular resistance) that might have affected our results cannot be ruled out.

4. The infusion of the drug beyond 36hours, particularly in the subgroup with low cardiac output syndrome, will not be addressed in the study. As we seek to evaluate the efficacy of levosimendan on the short and intermediate-term outcomes in patients undergoing high-risk cardiac surgery on CPB and will be unable to provide insights into the long-term efficacy of the drug.

In conclusion:

- Significant improvement in postoperative ejection fraction in the group receiving levosimendan ($p = 0.002$) and significant decrease in-hospital stay ($p = 0.028$).

- Significant improvement in hemodynamic parameters base deficit ($p < 0.05$) at almost all times postoperative, mixed venous Saturation ($p < 0.05$) at almost all times postoperative with no effect on heart rate ($p > 0.05$), with a mild reduction in mean arterial pressure due to inodilator effect of levosimendan.

- Levosimendan had no significant effect on mortality compared to the conventional group ($p = 0.781$).

- We recommend an increasing number of the study population, use fixed IV fluid protocol and more invasive cardiac function monitoring.

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