

# Prophylactic Preoperative Levosimendan for off-Pump Coronary Artery Bypass Grafting in Patients with Left Ventricular Dysfunction: Single-centered Randomized Prospective Study

## Abstract

**Background:** Off-pump coronary artery bypass surgery (OPCAB) is often complicated by hemodynamic instability, especially in patients with prior left ventricular (LV) dysfunction and appropriate choice of inotrope plays a vital role in perioperative management of these patients. **Aim and Objective:** To study hemodynamic effects and immediate outcome of prophylactic infusion of levosimendan in patients with the LV dysfunction undergoing OPCAB surgery and whether this strategy helps in successful conduct of OPCAB surgery. **Materials and Methods:** After Institutional Ethics Committee approval, 60 patients posted for elective OPCAB surgery were randomly divided into two groups ( $n = 30$  each). Patients with the LV ejection fraction  $<30\%$  were included. Study group was started on injection levosimendan (@  $0.1 \mu\text{g}/\text{kg}/\text{min}$ ) in the previous night before surgery and continued for 24 h including intraoperative period. Hemodynamic monitoring included heart rate, invasive blood pressure, cardiac index (CI), pulmonary capillary wedge pressure (PCWP), pulse oximetry, and arterial blood gases with serum lactates at as T0 (baseline), T1 (15 min after obtuse marginal and/or PDA anastomoses), T2 (at end of surgery), T3 (6 h after surgery in Intensive Care Unit [ICU]), T4 (12 h after surgery), and T5 (24 h after surgery in ICU). Vasopressor was added to maintain mean arterial pressure  $>60$  mmHg. Chi-square/Fisher's exact/Mid  $P$  exact test and Student's  $t$ -tests were applied for categorical and continuous data. **Results:** CI was greater and PCWP reduced significantly in Group L during intraoperative and early postoperative period. Serum lactate concentration was lower in patients pretreated with levosimendan. Incidence of postoperative atrial fibrillation (POAF) (36.6 vs. 6.6%;  $P = 0.01$ ), low cardiac output syndrome (LCOS) (30% vs. 6%;  $P = 0.02$ ), and acute kidney injury (23.3% vs. 6.7%;  $P = 0.04$ ) was less in Group L. Three patients (10%) in control group required conversion to cardiopulmonary bypass (CPB) as compared to none in the study group. There was no difference regarding ICU or hospital stay and mortality in both groups. **Conclusion:** Preoperative levosimendan helps in successful conduct of OPCAB and reduces the incidence of LCOS, POAF, conversion to CPB, and requirement of intra-aortic balloon pump.

**Keywords:** Acute kidney injury, atrial fibrillation, intra-aortic balloon pump, levosimendan, off-pump coronary artery bypass grafting

## Introduction

Off-pump coronary artery bypass (OPCAB) surgery is an alternative to conventional coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB). It avoids adverse effects such as systemic inflammatory response, impaired myocardial protection, and air or plaque embolism during CPB conduct. However, OPCAB surgery involves displacement and manipulation of heart to expose target coronary arteries, especially obtuse marginal (OM) and posterior descending coronary arteries. This manipulation may be accompanied by transient annulo-mitral distortion leading to

acute mitral regurgitation, compression of pulmonary veins and/or the right ventricle in addition to superimposed impaired cardiac contractions due to epicardial stabilizer which leads to hemodynamic instability in the form of increased filling pressures, right ventricular (RV) end-diastolic pressure and transient diastolic dysfunction.<sup>[1,2]</sup> All these changes are exaggerated intraoperatively in patients with the left ventricular (LV) dysfunction which is the main risk factor for postoperative low cardiac output syndrome (LCOS).<sup>[3,4]</sup> Transient contractile dysfunction after myocardial revascularization owing to reperfusion injury has also been described in the literature.<sup>[5]</sup> Accordingly,

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the major challenge during OPCAB surgery is to maintain optimum hemodynamics. Use of inotropes constitutes major pharmacological intervention by anesthesiologist and its appropriate selection helps in better clinical outcomes.

However, conventional inotropes such as beta-agonists and phosphodiesterase inhibitors are associated with tachycardia and arrhythmia which leads to increased myocardial oxygen demand.<sup>[6]</sup>

In this context, levosimendan, a novel inotrope, is superior to conventional ones. It binds to cardiac troponin C, enhances myofilament responsiveness to calcium, prolongs the duration of actin-myosin overlap, thereby increasing myocardial contractility; but, without increasing intracellular calcium concentration and myocardial oxygen consumption.<sup>[7,8]</sup> It also possesses lusitropic<sup>[9]</sup> actions and exerts peripheral vasodilatory and potential preconditioning effect<sup>[10,11]</sup> on myocardium by virtue of its action on mitochondrial ATP-sensitive potassium channels. In addition, it provides beneficial immunomodulatory, cardioprotective,<sup>[12]</sup> anti-stunning,<sup>[13]</sup> anti-ischemic,<sup>[14]</sup> anti-inflammatory, and antioxidant effects<sup>[15]</sup> to improve cardiac performance in the presence of ischemia. Its active protein-bound metabolites OR-1855, OR-1896 exert clinical effects up to 1 week.<sup>[16]</sup>

All these characteristics make it a near-ideal inotrope in patients with the LV dysfunction. Hence, we hypothesized that preoperative commencement of levosimendan would produce all these desirable effects which will mitigate hemodynamic perturbations and help in smooth and successful conduct of OPCAB surgery. Therefore, this study aimed at evaluating effects and outcome of prophylactic preoperative levosimendan infusion on hemodynamic parameters and short-term clinical outcomes in patients with LV dysfunction undergoing OPCAB surgery.

## Materials and Methods

After Institutional Ethics Committee approval and obtaining written informed consent, 60 patients undergoing elective OPCAB were randomly divided into two groups ( $n = 30$  each), namely, levosimendan (Group L) and control (Group C) group. Randomization was done using computer-generated random code. The study was carried out between January and September 2015. Patients between 35 and 75 years of age with severe LV dysfunction (LV ejection fraction  $<30\%$  determined by preoperative transthoracic echocardiography) were included. Patients undergoing emergency/redo/combined CABG, those requiring preoperative pharmacological or mechanical support, renal, and hepatic dysfunction were excluded.

Group L patients were transferred to the cardiac Intensive Care Unit (ICU) 12 h (night) before surgery, and Swan-Ganz catheterization (Edward Life Science) for pulmonary artery pressure monitoring and radial arterial cannulation was performed under local anesthesia.

Continuous cardiac output monitoring using FloTrac sensor (Edward life science, LLC Irvine, USA) was done. Baseline hemodynamic parameters (T0) were noted at this time. These patients were started on injection levosimendan infusion @0.1  $\mu\text{g}/\text{kg}/\text{min}$  (Inj.Levosimed 12.5mg/vial; Samartha Laboratory) under continuous hemodynamic monitoring. Infusion was continued for 24 h including intraoperative period. Vasopressor was added intraoperatively to maintain mean arterial pressure (MAP) to  $>60$  mmHg.

Group C patients were directly shifted to operation theater and baseline hemodynamic parameters were noted (T0) before induction. These patients received conventional inotropes/vasopressor (dobutamine  $\pm$  adrenaline  $\pm$  noradrenaline) intraoperatively.

Both groups underwent standard anesthesia induction with fentanyl (10  $\mu\text{g}/\text{kg}$ ), midazolam (0.1 mg/kg) + propofol (0.5 mg/kg), and pancuronium bromide (0.1 mg/kg) and maintained on  $\text{O}_2/\text{air}/\text{isoflurane}$ . Vecuronium (0.02 mg/kg) was administered intermittently for neuromuscular blockade. All patients were continuously monitored for heart rate, invasive blood pressure, cardiac index (CI), PCWP, pulse oximetry, urine output, capnography, nasopharyngeal temperature, and arterial blood gases with serum lactate levels. Noradrenaline infusion was added to maintain MAP  $>60$  mmHg throughout surgery, if required. Left internal mammary artery (LIMA) to left anterior descending anastomosis was done first in all patients. Then, either proximal anastomoses to aorta followed by distal anastomoses to OM and posterior descending artery (PDA) or LIMA-Right IMA 'Y' sequential anastomoses to distal target coronary arteries were done. Hemodynamic parameters were measured at intervals T0 (baseline), T1 (15 min after OM and/or PDA anastomoses), T2 (at end of surgery), T3 (6 h after surgery in ICU), T4 (12 h after surgery), and T5 (24 h after surgery in ICU).

As per the institutional protocol, patients were extubated as per intensivists discretion when deemed feasible. Short-term clinical outcomes such as incidence of arrhythmia, acute kidney injury, LCOS, length of ICU, and hospital stay were noted. LCOS was defined as CI ( $2.2 \text{ L}/\text{min}/\text{m}^2$ ) with elevated PCWP ( $>16$  mmHg) and partial pressure of arterial oxygen  $<60$  mmHg. Acute renal failure was considered as  $>50\%$  increase in serum creatinine from baseline or requiring dialysis.

## Statistical analysis

Sample size was calculated based on power analysis to detect 20% difference in CI (assuming  $\alpha = 0.05$  and  $\beta = 0.2$ ). Accordingly, minimum 46 patients were required. However, 60 patients were included to compensate for dropouts and improve accuracy. IBM Statistical Package for Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA) was used for the statistical

analysis. All continuous data were analyzed by Student's *t*-test; Chi-square test, Fisher's exact test, and Mid *P* exact test were applied for categorical data wherever applicable. The results are reported as the mean  $\pm$  standard deviation.  $P < 0.05$  was considered statistically significant.

## Results

Demographic data, nature of the disease and surgical characteristics of all patients, were comparable in both groups [Table 1]. Baseline hemodynamic parameters and serum lactate concentration were comparable in both groups. Although CI progressively increased in both groups, it was significantly higher in Group L at all-time intervals during and after surgery. PCWP was significantly lower with levosimendan, especially during surgery and early postoperative period. Significant reduction in MAP occurred in control group at T1 interval as compared to levosimendan. Serum lactate concentration was consistently lower in levosimendan group at majority of time intervals [Table 2]. Majority of patients in control group developed acute kidney injury evident by rise in serum creatinine concentration which was managed with fluids and diuretics; although two patients required hemodialysis, none of the patients in levosimendan group needed it. Incidence of postoperative atrial fibrillation (POAF) was higher in control group. Three patients in control group required conversion to CPB and intra-aortic balloon pump (IABP) for completion of surgery due to hemodynamic instability as compared to none in the levosimendan group in which only one patient needed IABP support. ICU and hospital stay were similar in both groups. Two patients died in control group due to cardiogenic shock and sepsis as compared to none in the study group [Table 3].

## Discussion

This study highlights favorable hemodynamic profile of levosimendan in terms of reduced PCWP and improved CI

after its administration. We consistently observed higher CI in patients treated with levosimendan during intraoperative and postoperative periods. These effects are translated in terms of reduced serum lactate concentrations indicating improved microcirculation at peripheral tissue level. Although there is a sparse literature on the regarding use of levosimendan during cardiac surgery in patients with low EF, our results are in agreement with the available recent studies.<sup>[17,18]</sup>

Literature also shows that levosimendan improves stroke volume index, contractility indices such as LV stroke work index (LVSWI)/RVSWI, significantly reduces systemic vascular resistance index (SVRI) due to its inodilator properties, and has been successfully used in heart failure patients with poor LV function.<sup>[19]</sup>

Loading dose of levosimendan is invariably associated with hypotension due to decreased SVRI, especially when started during intraoperative period as anesthetics induced peripheral vasodilation potentiates this effect. Some studies<sup>[20,21]</sup> even suggested that loading dose of levosimendan needs to be omitted in decompensated heart failure patients. Hence, we hypothesized that preoperative commencement without loading dose would gradually achieve therapeutic concentration without causing sudden hypotension. Our patients did not develop significant hypotension, any hemodynamic instability, and other side effects such as nausea and headache<sup>[22,23]</sup> in the preoperative period and the regimen was tolerated well.

Immediate postoperative outcomes also improved in levosimendan group with notably reduced incidence of POAF which can be attributed to antioxidant and anti-inflammatory properties of levosimendan.<sup>[18,24-26]</sup>

Our findings also suggest renoprotective effects of levosimendan depicted by lower serum creatinine in the postoperative period. None of the patients treated with levosimendan required hemodialysis. This also strengthens the conclusion in other studies<sup>[22,27]</sup> in cardiac surgical patients. Levosimendan increases renal blood flow due to decreased renal vascular resistance and simultaneously increases glomerular filtration rate (GFR) unlike dopamine which did not increase GFR.<sup>[27-29]</sup>

There was a reduced incidence of LCOS, conversion rate to CPB, and requirement of IABP support in the study group. These findings can be correlated with favorable surgical conditions produced by levosimendan because of improved myocardial contractility and reduced pulmonary pressures making heart supple and easy to operate upon. However, the authors are also of the opinion that surgical expertise plays an important role in these aspects. A study<sup>[30]</sup> which compared levosimendan and IABP in high-risk cardiac patients concluded that the infusion of levosimendan after anesthesia induction in cardiac

**Table 1: Demographic and general clinical characteristics**

Parameter	Group C	Group L	P
Age (years)	60.17 $\pm$ 5.72	61.67 $\pm$ 7.03	0.36
Weight (kg)	67.56 $\pm$ 7.29	64.37 $\pm$ 5.86	0.24
Height (cm)	160.4 $\pm$ 8.28	161.4 $\pm$ 7.49	0.59
Sex (female/male)	7/23	9/21	0.55
Ejection fraction (%)	25.5 $\pm$ 4.42	25.17 $\pm$ 5.49	0.25
Baseline serum creatinine (mg/dl)	1.2 $\pm$ 0.18	1.26 $\pm$ 0.16	0.52
Duration of surgery (min)	221.33 $\pm$ 23	224.83 $\pm$ 25.40	0.60
Diabetes (%)	19/30 (63)	21/30 (70)	0.58
Hypertension (%)	22/30 (73)	24/30 (80)	0.54
Preexisting renal disease	0	1/30	0.15
Single vessel disease	1/30	0/30	0.5
Double vessel disease	4/30	6/30	0.48
Triple vessel disease	25/30	24/30	0.73

Values expressed as mean $\pm$ SD. SD: Standard deviation

**Table 2: Hemodynamic parameters including serum lactates at various time intervals**

Time	Group	HR	MAP	PCWP	CI	Lactates
Time 0	Group C	70.8±7.06	84.13±6.06	15.5±2.47	2.06±0.16	1.71±0.36
	Group L	71.86±8.31	86±7.22	16±1.96	2.09±0.23	1.76±0.57
	<i>P</i>	0.59	0.28	0.38	0.55	0.68
Time 1	Group C	86.3±9.47	67.03±6.51	15.9±2.51	2.26±0.27	4.09±1.41
	Group L	78.73±5.7	78.13±7.01	12.7±2	2.92±0.4	3.18±0.54
	<i>P</i>	0.0004*	<0.0001*	<0.0001*	<0.0001*	0.001*
Time 2	Group C	86.33±7.09	73.5±7.39	13.67±2.28	2.82±0.51	3.42±1.14
	Group L	80.33±6.58	81.66±4.91	11.6±1.57	3.20±0.47	2.47±0.41
	<i>P</i>	0.001*	0.64	<0.0001*	0.003*	<0.0001*
Time 3	Group C	79.33±9.59	80.57±7.87	12.67±2.20	2.99±0.49	2.78±0.77
	Group L	80.23±7.55	80.06±5.47	11.46±1.75	3.64±0.44	2.43±0.38
	<i>P</i>	0.68	0.77	0.03*	<0.0001*	0.03*
Time 4	Group C	78±9.20	75.43±6.47	12.1±1.45	3.29±0.51	2.26±0.52
	Group L	78.66±5.33	79.5±5.5	11.06±1.11	3.84±0.31	2.28±0.36
	<i>P</i>	0.73	0.01*	0.002*	<0.0001*	0.86
Time 5	Group C	81.5±8.14	77.2±5.81	12.13±1.63	3.55±0.51	1.91±0.29
	Group L	78.4±6.02	82.8±4.99	11.4±1.3	3.91±0.29	1.67±0.25
	<i>P</i>	0.09	0.0001*	0.06	0.001*	0.001*

Values expressed as mean±SD. \**P*<0.05 (student's unpaired *t*-test). SD: Standard deviation, MAP: Mean arterial pressure, PCWP: Pulmonary capillary wedge pressure, CI: Cardiac index, HR: Heart rate

**Table 3: Perioperative adverse events and other data**

Parameter	Group C	Group L	<i>P</i>
Postoperative atrial fibrillation (%)	11/30 (36.67)	2/30 (6.67)	0.01*
Conversion to CPB (%)	3/30 (10)	0	0.23
IABP requirement (%)	3/30 (10)	1/30 (3.33)	0.61
Serum creatinine at day 2 (mg/dl)	1.65±0.27	1.56±0.24	0.22
AKI (%)	7/30 (23.33)	2/30 (6.67)	0.04*
LCOS (%)	9/30 (30)	2/30 (6.67)	0.02*
Noradrenaline requirement (%)	14/30 (47)	23/30 (77)	0.01*
ICU stay (days)	3.67±0.76	3.4±0.62	0.14
Hospital stay (days)	7.57±1.01	7.3±1.06	0.31
Mortality	2/30 (6.67)	0/30	0.24

Values expressed as mean±SD. \**P*<0.05. SD: Standard deviation, CPB: Cardiopulmonary bypass, IABP: Intra-aortic balloon pump, AKI: Acute kidney injury, LCOS: Low cardiac output syndrome, ICU: Intensive Care Unit

surgical patients contributes to lower cardiac Troponin I concentration and improved hemodynamics compared with a preoperative IABP. Severi *et al.*<sup>[31]</sup> also found short ICU stay in patients pretreated with levosimendan as compared to patients receiving prophylactic IABP. Kandasamy *et al.*<sup>[18]</sup> also observed reduced requirement of mechanical circulatory support in their patients. We did not find any difference in terms of ICU and hospital stay unlike other studies<sup>[32-34]</sup> which have documented shorter stay, and we also believe that surgical expertise, minimal handling of heart, and short anastomoses time might have contributed in this regard. We did not find any mortality benefit with the study drug.

Apart from being a nonblinded, this study is also limited by failure to monitor hemodynamics for entire

duration of action of levosimendan and its metabolites which are known to exert clinical effects up to 7–9 days due to their long half-life of 70–80 h.<sup>[35,36]</sup> This would have further highlighted sustained beneficial effects in these sick patients. Myocardial protection offered by levosimendan (through opening of K-ATP channels in cardiac mitochondria)<sup>[37]</sup> in terms of cardiac biomarkers such as troponin measurement assays was not demonstrated either. Echocardiographic documentation of systolic function and degree of diastolic dysfunction along with cardiac contractility indices such as LVSWI/RVSWI would have validated results comprehensively. The authors did not perform cost-effective analysis of this regimen which needs either ICU stay or monitoring suit preoperatively.

## Conclusion

Prophylactic preoperative levosimendan infusion in patients with poor LV function undergoing OPCAB surgery results in significant increase in CI, improves diastolic dysfunction in the form of reduced PCWP, and reduces incidence of postoperative arrhythmia, acute kidney injury, emergency conversion to CPB, and trend toward decreased requirement of mechanical circulatory support, thereby helping in a smooth and successful conduct of surgery.

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## Conflicts of interest

There are no conflicts of interest.

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