Original Article

This article is accompanied by an invited commentary by Dr. Mukul Chandra Kapoor

Effect of levosimendan on hemodynamic changes in patients undergoing off-pump coronary artery bypass grafting: A randomized controlled study

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ABSTRACT

Aims and Objective: We tested the hypothesis that use of levosimendan would be associated with better perioperative hemodynamics and cardiac function during off-pump coronary artery bypass grafting (OPCAB) in patients with good left ventricular function. **Materials and Methods:** Thirty patients scheduled for OPCAB were randomized in a double-blind manner to receive either levosimendan 0.1 μg/kg/min or placebo after induction of general anesthesia. The hemodynamic variables were measured after induction of anesthesia, at 6 minute after application of tissue stabilizer for the anastomoses of left anterior descending artery, diagonal artery, left circumflex artery, and right coronary artery and at 6, 12, 18, and 24 hours after completion of surgery. **Results:** Compared with placebo group, cardiac index (CI) was significantly higher and systemic vascular resistance index (SVRI) was significantly lower at 6, 12, 18, and 24 hour after surgery in levosimendan group. Norepinephrine was infused in 60% of the patients in the levosimendan group compared to 6.7% in the control group ($P < 0.05$). Lactate and mixed venous oxygen saturation were not significantly different between groups. **Conclusions:** Levosimendan significantly increased CI and decreased SVRI after OPCAB but it did not show any outcome benefit in terms of duration of ventilation and intensive care unit stay.

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Key words: Cardiac index, Intensive care unit stay, Levosimendan, Systemic vascular resistance index

INTRODUCTION

The off-pump coronary artery bypass grafting (OPCAB) is increasingly practiced in an effort to prevent deleterious effects of cardiopulmonary bypass (CPB) including systemic inflammatory response, global myocardial ischemia and the risks of aortic manipulation. Unlike on-pump coronary artery bypass grafting (CABG), hemodynamic compromise during OPCAB is a major concern particularly during cardiac positioning. Lifting and tilting the heart to expose the posterior or lateral wall of the heart displace the atria below the corresponding ventricles, which often result in significant increase in atrial pressures, and a marked decrease in cardiac output (CO).[1,2] A vertical positioning of the heart induces distortions of the mitral and tricuspid annuli that may result in incompetence of the corresponding valves.[3] In addition, application of a stabilizer device restricts the regional myocardial wall motion.[4] These changes contribute to a decrease in preload and stroke volume, resulting in a reduced cardiac index (CI), mixed venous oxygen saturation (SvO_2), and mean arterial pressure (MAP), especially during exposure of the posterior wall.

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Preloading, head-down position, and catecholamines are used to compensate decrease in MAP and to increase CO. Catecholamines improve myocardial contractility and CI by increasing intracellular concentrations of free calcium and cyclic adenosine monophosphate. However, the myocardial contractility with these agents increases at the expense of increased myocardial oxygen consumption, risk of ischemia, and arrhythmias.[5] Levosimendan is a calcium sensitizer which increases myocardial contractility by binding to troponin C of myocytes without increasing intracellular calcium concentration; therefore, levosimendan improves ventricular function without significant increase in myocardial oxygen uptake.[6] Additionally, levosimendan has vasodilatory and anti-ischemic properties (pleiotropic effects) attributable to its effects on adenosine triphosphate-dependent potassium channels (K_{ATP} channel). Levosimendan has been shown to have favorable effects on coronary blood flow as it overrides normal auto-regulatory vasodilatory mechanisms of coronary circulation and thus dilate coronary vessels more than myocardial metabolism would indicate.[6] Levosimendan thus has a potential benefit for patients with myocardial oxygen imbalance requiring inotropic support. The present study was conducted to evaluate the effect of levosimendan on perioperative hemodynamic stability and myocardial performance during OPCAB in patients with good left ventricular function (Left Ventricular Ejection Fraction [LVEF] > 45%).

MATERIALS AND METHODS

Following approval of local ethical committee and obtaining written informed consent, 30 patients undergoing isolated elective OPCAB were enrolled. Patients were randomly allocated to levosimendan (Group L) (Simenda injection, manufactured by Lupin Ltd., India) and placebo (Group P) groups. This study was conducted at Sri Ramachandra Medical College and Research Institute between June 2011 and December 2011. Exclusion criteria included LVEF < 45%, renal dysfunction (pre-operative creatinine level > 2 mg/dL), abnormal liver function (serum albumin < 30 g/L), significant pulmonary disease, acute myocardial infarction, left bundle branch block, moderate to severe valvular heart diseases, redo CABG, unplanned CPB, need of intra-aortic balloon pump and re-exploration for surgical bleeding.

All preoperative medications were continued until the morning of surgery, except angiotensin-converting enzyme inhibitors, which were stopped the day before surgery. During surgery, the patients were monitored with electrocardiogram, invasive blood pressure, pulmonary artery catheter (PAC), pulse oximetry, nasopharyngeal temperature, arterial blood gas, urine output, and capnography. The study drug [levosimendan 0.1 μg/kg/min] or normal saline was administered as an intravenous infusion after induction of anesthesia in double-blinded fashion. During surgery the pulmonary capillary wedge pressure (PCWP) was kept between 10 and 14 mmHg in all patients by administration of intravenous fluids. If the CI decreased below 2.1 L/min/m^2, epinephrine was infused in an escalating manner from 0.05 to 0.2 μg/kg/min. Hypotension, defined as a MAP < 60 mmHg, was treated with norepinephrine 0.05-0.1 μg/kg/min, increased incrementally by 0.05 μg/kg/min until MAP increased to > 60 mmHg. Nitroglycerine infusion 0.15 μg/kg/min was started after insertion of PAC for all patients. After completion of the surgery, all patients were shifted to intensive care unit (ICU) for elective ventilation. Propofol was started in ICU at a rate of 1 mg/kg/h until the patients reached extubation criteria. Weaning from mechanical ventilation and tracheal extubation followed a standard protocol using the following criteria: temperature > 36°C, stable hemodynamics (defined as the ability to increase body oxygen consumption (e.g., spontaneous breathing) without the need for increased inotropic support), chest tube drainage < 100 mL/h, and urine output ≥ 0.5 mL/kg/h. Weaning from inotropic support was at the discretion of the responsible anesthesiologist in the ICU and was based on the assessment of hemodynamic data, urine output, and the patient's physical status. Anesthesia and surgical technique was standardized. The same surgical team performed surgery in all investigated patients. The MAP, heart-rate (HR), CI, PCWP, systemic vascular resistance index (SVRI) were obtained after induction of anesthesia (baseline), at 6 min after application of the tissue stabilizer for the anastomoses of left anterior descending artery (LAD), diagonal artery (DX), left circumflex artery (LCX), and right coronary artery (RCA) and at 6, 12, 18, and 24 hour after completion of surgery. Lactate and SvO_2 were measured at baseline, before grafting (BG), after grafting (AG), and at 6, 12, 18, and 24 hour after completion of surgery. Norepinephrine and epinephrine requirements, duration of ventilation (DOV), and duration of ICU stay (DIS) were also measured. The CI and SVRI were monitored using FloTrac sensor and

Vigileo monitor (SN: VL007565, Edwards Life sciences LLC Irvine, CA 92614 USA).

Based on power analysis a minimum of 13 patients per group were required to detect a 15% differences in CI between groups after intubation ($\alpha = 0.05$, $\beta = 0.2$). To compensate for any unexpected dropouts, we enrolled 15 patients in each group. All continuous data were analyzed by student's *t* test (independent samples '*t*' test); Chi-square test, Mann-Whitney U-test, and Fisher's exact test were applied wherever applicable. The Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. *P* value < 0.05 was considered statistically significant.

RESULTS

The data from all 30 patients were included in statistical analysis. All patients had successful OPCAB without converting to emergency on-pump CABG. The two groups were comparable with respect to demographic data and preoperative clinical characteristics and medication [Tables 1 and 2]. Table 3 shows hemodynamic variables (MAP, HR, CI, and PCWP) measured at various time-intervals in both groups. No significant differences in baseline hemodynamic values were seen among groups [Table 3]. The CI measured at 6, 12, 18, and 24 hour after surgery was significantly higher in group L [Table 3]. The SVRI measured at same time points was significantly lower in group L [Table 3]. There were no significant differences in perioperative lactate levels and SvO_2 between the two groups [Table 4]. Table 5 summarizes the intraoperative data, use of epinephrine and norepinephrine, and clinical outcomes. No significant differences were observed in operation time and numbers of vessels grafted. The need of norepinephrine was significantly higher in group L. The DOV and DIS were similar in both groups [Table 5]. No mortality or major complications, such as myocardial infarction, major neurological deficit or end-organ failure were observed in either group. No patient developed significant arrhythmias, which required medical intervention during the study period. No patient required use of an intra-aortic balloon pump.

Table 1: Patient characteristics

Variable	Group L (*n*=15)	Group P (*n*=15)	*P* value
Sex			
Male	12	8	0.121
Female	3	7	0.121
Single vessel disease	0	0	
Two vessel disease	5	6	0.705
Three vessel disease	10	9	0.705
Unstable angina	3	3	0.624
Previous MI	4	3	0.666
Hypertension	11	12	0.142
Diabetes mellitus	10	12	0.409
Beta blockers	13	13	1
ACE inhibitors	6	7	0.713

All values are represented in numbers, *n*: number of patients, MI: Myocardial infarction, ACE: Angiotensin converting enzyme

Table 2: Pre-operative variables

Variable	Group L	Group P	*P* value
Age in years	56 ± 8.1	52.5 ± 8.9	0.277
Height in cm	163 ± 4.5	167 ± 8.1	0.061
Weight in kg	68.5 ± 9.6	68.5 ± 7.3	0.980
Ejection fraction in %	58 ± 4	61 ± 2.5	0.654

Values are represented as mean ± standard deviation

DISCUSSION

Our results show that levosimendan infusion significantly increases post-operative CI compared with placebo in patients with good pre-operative left ventricular function undergoing OPCAB. Despite the beneficial effect of levosimendan on post-operative cardiac function, no statistically significant differences were detected between the groups in DOV or duration of ICU stay.

Despite the use of contemporary cardioprotective strategies variable degrees of myocardial stunning occur after cardiac surgery. Myocardial stunning plays a pivotal role in post-operative myocardial dysfunction. Myocardial stunning represents a prolonged post-ischemic contractile dysfunction of myocardium salvaged by reperfusion.[7] Studies have demonstrated contractile dysfunction over the first few hours after myocardial revascularization that generally resolves spontaneously over 24-48 h.[8] During the period of transient myocardial dysfunction, there is a need to improve the myocardial functions, inotropic agents are usually chosen for hemodynamic support. Unlike traditional inotropes, levosimendan improves myocardial contractility primarily by enhancing myocardial contractile protein sensitivity to calcium without increasing its intracellular concentration. This action does not result in an increase in myocardial oxygen consumption.[9,10] Levosimendan acts by direct binding with troponin C, thereby increasing the affinity of troponin C for Ca^{2+}. A lack of Ca^{2+} sensitization

Table 3: Hemodynamic variables

Variable	Group	Basal	LAD	DX	LCX	RCA	6 h	12 h	18 h	24 h
HR	L	65 (13.9)	76 (16.8)	79 (5.9)	88 (14)	83 (12.7)	91 (19.9)	96 (15.9)	95 (14.3)	98 (12.4)
	P	66 (12.8)	80 (12.7)	79 (7.29)	81 (6.4)	81 (6.4)	99 (15.4)	101 (15.3)	101 (16.8)	104 (12.0)
P value		0.729	0.553	0.479	0.113	0.729	0.257	0.421	0.288	0.168
MAP	L	78 (8.7)	77 (4.6)	71 (7.5)	71 (4.8)	71 (7.8)	77 (5.0)	75 (6.8)	79 (9.3)	82 (9.0)
	P	73 (8.05)	76 (8.5)	76 (9.6)	72 (5.0)	78 (8.3)	81 (9.8)	80 (10.0)	80 (8.2)	81 (8.0)
P value		0.124	0.528		0.960	0.608	0.164	0.220	0.936	0.237
CI	L	2.7 (0.41)	3.0 (0.69)	3.1 (0.35)	2.7 (0.72)	2.9 (0.37)	3.6 (0.99)*	3.7 (0.75)*	3.8 (0.67)*	3.8 (0.75)*
	P	2.4 (0.55)	2.8 (0.58)	3.4 (0.38)	2.7 (0.72)	2.6 (0.34)	2.8 (0.08)*	2.9 (0.71)*	2.8 (0.70)*	3.1 (0.92)*
P value		0.175	0.264	0.130	0.834	0.487	0.027	0.013	0.001	0.041
SVRI	L	0.2352 (418)	1802 (448)	1625 (314)	1478 (292)	1666 (288)	1693*(473)	1654*(427)	1497*(346)	1603*(398)
	P	2337 (495)	1997 (540)	1545 (135)	1666 (288)	1942 (525)	1970*(354)	2003*(354)	1927*(448)	2054*(453)
P value		0.927	0.291	0.559	0.269	0.348	0.034	0.022	0.007	0.006
PCWP	L	11 (2.5)	10 (0.9)	11 (2.3)	11 (1.4)	11 (1.4)	9 (1.8)	10 (2.5)	10 (2.0)	10 (2.1)
	P	12 (1.2)	12 (2.4)	10 (2.2)	12 (4.5)	12 (2.0)	9 (2.0)	9 (1.9)	10 (2.1)	10 (1.6)
P value		0.214	0.074	0.521	0.561	0.434	0.467	0.210	0.880	0.247

HR: Heart rate, MAP: Mean arterial pressure, CI: Cardiac index, SVRI: Systemic vascular resistance index, PCWP: Pulmonary capillary wedge pressure, LAD: Left anterior descending artery, DX: Diagonal artery, LCX: Left circumflex artery, RCA: Right coronary artery,*: Statistically significant, (): Standard deviation

Table 4: Mixed venous saturation and lactate levels at various time intervals

Variable	Group	Baseline	BG	AG	6 h	12 h	18 h	24 h
SvO_2	L	74.5 (4.5)	75.1 (1.3)	75.8 (2.3)	76.0 (25)	75.2 (4.7)	76.5 (4.6)	75.8 (5.0)
	P	76.8 (4.2)	74.2 (2.3)	75.6 (2.2)	74.8 (1.5)	74.1 (4.5)	73.4 (3.8)	73.1 (3.3)
P value		0.168	0.611	0.831	0.136	0.552	0.170	0.094
Lactate	L	1.4 (0.52)	2.0 (0.61)	1.8 (0.49)	1.9 (0.39)	2.2 (0.57)	1.9 (0.46)	1.9 (0.56)
	P	1.4 (0.48)	2.0 (0.71)	2.1 (0.44)	2.4 (0.96)	2.5 (0.96)	2.3 (1.1)	2.1 (0.77)
P value		0.971	0.957	0.112	0.133	0.281	0.265	0.425

AG: After grafting, BG: Before grafting, SvO_2: Mixed venous oxygen

Table 5: Intraoperative data, inotrope requirement and outcomes

Variable	Group L	Group P	*P* value
% LAD grafts	100	100	1.0
% DX grafts	86	60	0.09
% LCX grafts	60	73	0.43
% RCA grafts	66.7	66.7	1.0
Noradrenaline (% of patient)	60%	6.7%	0.002
Adrenaline (% of patient)	0	0	_
Duration of surgery (min)	246 ± 47.4	261.8 ± 58.2	0.85
Duration of ICU stay (days)	3.3 ± 0.7	3.5 ± 0.6	0.20
Duration of ventilation (hours)	7.0 ± 1.9	7.1 ± 1.5	0.16

ICU: Intensive care unit

under low calcium concentrations (i.e., during diastole) has been shown to prevent worsening of diastolic dysfunction in patients with heart failure. Levosimendan causes vasodilatation, which has been attributed to the activation of K_{ATP} channels and decreasing the sensitivity to calcium.[11,12] An increase in coronary blood flow and a reduction in coronary vascular resistance have been reported.[13]

Our findings are in agreement with the results observed in recent studies, strengthening the conclusion that the observed increase in CI produced by levosimendan probably result from the combined actions of reduced left ventricular afterload and modest increase in myocardial contractility. Levosimendan itself has a short elimination half-life of about 1 h in humans. The short half-life of levosimendan enables fast onset of drug action; however, its effects are long-lasting due to its active metabolite OR-1896, which has an elimination half-life of 70-80 h. The long half-life of its active metabolite results in its efficacy maintained for up to 9 days after a 24 hour infusion.[14,15] Levosimendan have advantages over traditional inotropic therapy, including prolonged drug effect after a 24 hour infusion, absence of complicating cardiac arrhythmias, and lack of episodes of drug-induced myocardial ischemia.[16,17] Data suggest that this effect might also be related to anti-inflammatory and anti-apoptotic properties.[18] Levosimendan also exhibits phosphodiesterase III-inhibiting properties.[17] This effect, however, is predominantly observed at higher concentrations and is less pronounced at concentrations in the clinically recommended therapeutic range. Levosimendan has also been shown to activate K_{ATP} channels in arterial and ventricular myocytes.[11] K_{ATP}-channel activation is an important

mediator of ischemic pre-conditioning, and stimulation of K_{ATP} channels decreases myocardial infarct size and enhances recovery of stunned myocardium.[19-21]

In the present study, levosimendan was administered without an initial bolus dose. Administration of a bolus dose often results in profound hypotension due to fall in SVRI, which may not be fully compensated by an increase in CI. It has therefore been suggested that the initial loading dose be reduced or even omitted.[22] In spite of avoiding bolus dose, 9 of 15 patients in Levosimendan group developed hypotension during surgery. As per study protocol, all nine patients received norepinephrine to maintain a MAP > 60 mmHg. Norepinephrine infusion was required in only one patient in control group. As we have used low dose of levosimendan, there was no evidence of tachycardia in our patients as observed in other studies. There was no difference between lactate level and SvO_2 between the two groups. The authors believe that patients overcame transient post-operative myocardial dysfunction because of good pre-operative left ventricular function and did not show any difference in lactate levels and SvO_2 between the two groups. Although levosimendan increased myocardial performance after surgery, we did not find any significant difference in clinical outcome in terms of DOV and DIS. Levosimendan is generally well-tolerated. Most of its adverse effects are dose-related and due to its vasodilator effect. The most frequent adverse effects associated with levosimendan include headache (5%), hypotension (5%), dizziness (1-10%), and nausea (1-10%).[16,23-25]

Our study has several limitations, the CI and SVRI were measured only for the first 24 h of the post-operative period, in spite of levosimendan duration of action lasting for 1 week. Moreover, the assessment of myocardial contractility by echocardiogram was not performed and we did not measure cardiac markers for myocardial damage, which would have shown cardio-protective actions of levosimendan. These measurements would have improved the validity of the study in assessing the effect of levosimendan on myocardial performance. We did not include patients with low LVFE; hence, the results of this study may not be extended to patients with low LVEF.

In conclusion, the results of our study indicate that in OPCAB patients with good pre-operative left ventricular fraction, prophylactic use of levosimendan infusion improves cardiac function. Further studies are required to determine whether outcome benefit can be achieved in high-risk patients in these settings.

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