Original Article

Effects of Levosimendan on Hemodynamic Parameters in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting: A Randomized, Double-Blind, Placebo- Controlled Trial

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Abstract

Background: Levosimendan, a calcium-sensitizing agent, possesses positive inotropic and peripheral vasodilatory effects mediated through ATP-sensitive potassium channels. In off-pump coronary artery bypass grafting (OPCABG), hemodynamic instability during cardiac manipulation remains a challenge. The effects of levosimendan on afterload and perfusion pressure in this surgical situation are not definitively established. **Material and Methods:** This is a prospective, randomized and masked study in which 30 patients undergoing elective OPCABG were randomized to either group L(n=15) or group P(n=15). Group L patients received Levosimendan (0.07 µg/kg/min), whereas group P patients received placebo. Predefined amounts of time (before and after surgery) were taken in which the aim was to record hemodynamic variables (Mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI), stroke volume index (SVI), stroke volume variation (SVV), systemic vascular resistance (SVRI) and central venous oxygen saturation ($ScvO_2$). **Results:** There was better MAP among patients who used levosimendan (as compared to placebo) during the fourth hour after surgery up to 24 hours ($p<0.05$). At the same time, the levels of SVR and SVRI were significantly lower in the levosimendan arm than at the third-hour mark and beyond ($p < 0.05$). The CVP level was temporarily elevated in the levosimendan arm during the first 3 hours. Intergroup differences in CO, CI, SVI and ScvO2 at any time point were not significant statistically(p value >0.05). **Conclusion:** OPCABG, supported by levosimendan administration, results in sustained decreases in systemic vascular resistance, preservation of elevated mean arterial pressure and cardiac output and unimpaired global tissue perfusion.

Keywords: Levosimendan, off-pump coronary artery bypass graft, hemodynamics, systemic vascular resistance, mean arterial pressure, randomized controlled trial.

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Introduction

Off- pump coronary artery bypass grafting (OPCABG)has gained prominences a surgical plan to prevent the systemic inflammatory response and coagulopathy of cardiopulmonary bypass. Nevertheless, the process requires temporary cardiac displacement and stabilisation, which may provoke major hemodynamic perturbations. These changes tend to be characterized by decrease in preload, stroke volume, cardiac index and mean arterial pressure, especially after grafting of the posterior and lateral coronary territories. The traditional pharmacological supports like catecholamines, inotropes and vasopressors, though effective, increase the myocardial oxygen consumption and can increase ischemia in patients with severe stenosis of the coronary artery.[1-3]

Levosimendan belongs to a different pharmacological group, calcium sensitizers. Its mechanism of action is through calcium-dependent binding to cardiac troponin C, thereby augmenting myofilament calcium sensitivity and contractility without elevating intracellular calcium transients or myocardial oxygen demand. Besides, levosimendan causes vasodilation by opening adenosine triphosphate-sensitive potassium (KATP) channels in vascular smooth muscle. This dual inotropic and vasodilatory profile implies a possible therapeutic effect on the management of OPCABG-induced hemodynamic instability. Nevertheless, the overall impression of afterload and perfusion pressure within the OPCABG framework, where preload is often impaired, needs clarification. The current study was planned to assess, through systematic evaluation, the effects of a continuous low dose levosimendan infusion on a full range of hemodynamic variables in patients undergoing elective OPCABG.[4-8]

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Materials and Methods

Study Design and Ethical Approval: The study was a randomised, placebo-controlled, prospective, and double-blinded clinical trial. All the ethics protocols were approved by the Institutional Ethics Committee on Human Research at [Medical College Hospital, Kolkata]. All participants provided written informed consent before participation. The trial was conducted over 12 months from September 2016 to August 2017.

Participant Selection: Eligible patients were those under 70 years of age, scheduled for elective, primary OPCABG, with an American Society of Anaesthesiologists (ASA) physical status of II to IV and a New York Heart Association (NYHA) functional class of II to IV. Exclusion criteria encompassed: (1) concomitant moderate-to-severe aortic or mitral valve disease; (2) preoperative-renal dysfunction (serum creatinine >2 mg/dL) (3) hepatic impairment (serum albumin <3.0 g/dL); (4) significant pulmonary disease as defined by spirometric criteria; (5) planned or unplanned conversion to on-pump surgery; and (6) redo cardiac surgical procedures.

Randomization and Blinding: A computer-generated random number sequence was used to allocate 30 patients with written informed consent into two equal groups: the Levosimendan group (Group L) and the Placebo group (Group P). The allocation sequence was concealed from the investigators and clinical staff. A trainee anaesthesiologist not involved in data collection or patient management prepared the study infusions. In the Group L case, levosimendan was diluted (12.5 mg in 50ml Normal saline) and infused at a continuous infusion rate of 0.07 µg/kg/min. In Group P, the same amount of normal saline was used, impregnated with multivitamins; the injection was prepared to mimic levosimendan's colour. The infusion was started via syringe pump 5 minutes after general anaesthesia and continued according to study protocol.

Anaesthetic and Surgical Management: A standardised anaesthetic protocol was used. Premedication was done with oral lorazepam 1 mg two hours before surgery. The induction of anaesthesia was done using intravenous fentanyl (3-5 µg/kg) and etomidate (0.3-0.5 mg/kg). Vecuronium was used to attain neuromuscular blockade. Maintenance of anaesthesia entailed oxygen, nitrous oxide, isoflurane, and additional amounts of fentanyl and midazolam. Experienced cardiac surgeons carried out all the surgical operations through the median sternotomy technique. The heparin prevented haemostasis at the desired activated clotting time of 200-300 seconds, which was reversed with protamine sulphate at the end of the procedure.

Hemodynamic Monitoring and Data Collection: Invasive arterial pressure monitoring was established via radial or femoral artery catheterisation. Central venous access was obtained using a triple-lumen catheter. Hemodynamic parameters were recorded at the following periods: baseline (following induction, referred to as 0 hour) and then at 1, 2, 3, 4, and 5 hours intraoperative. Measurements were performed at 11, 17 and 24 hours after induction.

- SCADA Primary Monitoring Devices: There was a Philips Intellivue MP30 multi-parameter monitor that monitored heart rate (HR), invasive arterial pressure and central venous pressure (CVP).
- Advanced Hemodynamic Monitoring: An EV1000 clinical platform (Edwards Lifesciences, Irvine, CA, USA) with Flo Trac/Vigileotechnology was used as an ongoing measure of cardiac output (CO), stroke volume (SV)and related parameters such as cardiac index (CI), stroke volume index (SVI), stroke volume variation (SVV), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI) and central venous oxygen saturation (ScvO 2).

Statistical Analysis: The statistical analysis was performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive data are displayed as means with standard deviations (SD) for continuous variables and frequencies for categorical variables. The test used to determine the normality of the distribution was the Shapiro-Wilk test. The independent-samples Student t-test was used to compare continuous hemodynamic variables across time points. A p-value of below 0.05 was taken to be significant at a two-tailed value.

Results

Baseline Demographic and Clinical Characteristics

Thirty patients completed the study protocol, with 15 patients in each group. [Tables 1,2] in the supplementary data present the comparative analysis of the preoperative variables. In between the groups there was no statistically significant differences in relation to age, male/female distribution, body weight, height, body mass index (BMI), NYHA physical status classification or AS physical status classification ($p < 0.05$ in all cases). This establishes the success of randomization and the comparability of the baseline between the two study groups.

Hemodynamic Outcomes

The temporal profiles of significant hemodynamic parameters are shown below.

Mean Arterial Pressure (MAP): [Table 1] shows that both groups diverged during the later intraoperative and postoperative phases, with a much greater MAP increase in the Levosimendan group. This difference persisted throughout the 24-hour observational period, reaching statistical significance at 4 hours (81±6 vs. 75±9 mmHg, p=0.038) and 5 hours (81±9 vs.71 ± 12 mmHg, p=0.032), 17 hours (82 ± 9 vs. 72 ± 9 mmHg, p=0.008) and 24 hours (81 ± 6 vs. 71 ± 8 mmHg, p=0.001).

Table 1: Comparative Mean Arterial Pressure (MAP)

Time Point	Levosimendan Group (mmHg)	Placebo Group (mmHg)	p-value
0 hour	86 ± 9	85 ± 13	0.677
1hour	84 ± 9	81 ± 9	0.455
2 hours	83 ± 10	77 ± 10	0.161
3 hours	82 ± 9	87 ± 16	0.245
4 hours	81 ± 6	75 ± 9	0.038
5 hours	81 ± 9	71 ± 12	0.032

11 hours	84 ± 9	77 ± 10	0.059
17 hours	82 ± 9	72 ± 9	0.008
24 hours	81 ± 6	71 ± 8	0.001

Systemic Vascular Resistance (SVR) and Index (SVRI): The strongest response of levosimendan was noted on the afterload parameters. SVRI showed a meaningful and long-term decrement in the Levosimendan group three hours after the infusion was initiated. Table 2 indicates that SVRI values were significantly and consistently lower in the intervention group than in the placebo group during the third intraoperative hour and up to the 24-hour postoperative examination ($p<0.05$ at all times after 3 hours). There was a statistically significant decrease in SVR, which was parallel.

Table 2: Systemic Vascular Resistance Index (SVRI)Over Time

Time Point	Levosimendan Group (dyne·s/cm⁵/m²)	Placebo Group (dyne·s/cm⁵/m²)	p-value
0 hour	1816.1 ± 136.48	2053.3 ± 232.91	0.200
1 hour	1806.5 ± 126.57	2046.1 ± 103.59	0.100
2 hours	1773.7 ± 115.26	1927.2 ± 89.93	0.600
3 hours	1723.8 ± 100.17	2077.4 ± 204.92	0.030
4 hours	1666.0 ± 150.15	1993.9 ± 189.37	0.030
5 hours	1743.2 ± 185.96	2041.0 ± 171.46	0.020
11hours	1815.0 ± 119.39	1995.0 ± 189.27	0.043
17 hours	1773.7 ± 115.27	2047.7 ± 179.82	0.030
24 hours	1723.8 ± 100.17	1926.8 ± 89.61	0.040

Central Venous Pressure (CVP): CVP had a distinct temporal trend. CVP values in the Levosimendan group were, during the first three hours of surgery, considerably higher (1 hour: 14 + 3 against 10 + 3 mmHg, p=0.001; 2 hours: 13 + 3 vs. 9 + 3 mmHg, p=0.013; 3 hours: 14 + 3 vs. 11 + 3 mmHg, p=0.020). From the fourth hour onward and during the postoperative period (8 hours), a significant difference in CVP was not observed between groups (p<).

Parameters of Cardiac Performance and Tissue Perfusion: Contrary to apparent differences in afterload and MAP, measures of cardiac pump performance and global oxygenation distribution showed similarities across groups. There were no statistically significant differences at any measurement interval of Cardiac Output (CO), Cardiac Index (CI), or Stroke Volume Index (SVI) (p.05). Likewise, a surrogate, central venous oxygen saturation (ScvO2), was not significantly different, except for a single lower value in the levosimendan group at the 5-hour intraoperative time point (76 2.8/79.2 2.5, p=0.003).

Graphical Depictions of Hemodynamic Trends:

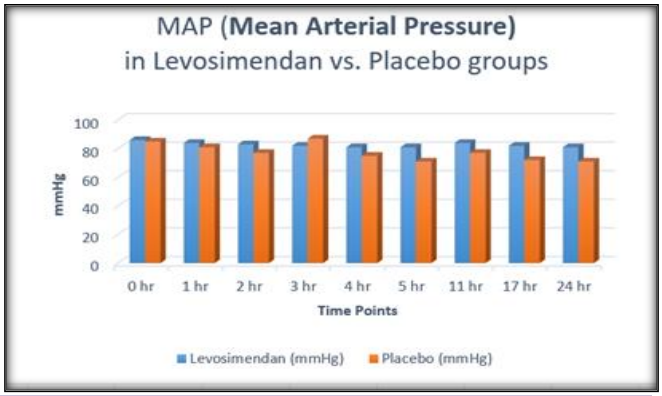

Fig1 MAP (Mean Arterial Pressure) in Levosimendan vs. Placebo groups

Stroke Volume Variation (SVV): SVV is a dynamic measure of responsiveness of fluid, which was significantly less in the Levosimendan group at the first postoperative hour up to the 24-hour measure ($p<0.05$ at all-time points except at baseline), indicating the state of improved preload and decreased volume dependency.

[Figure 1] shows the time tendency of MAP, indicating that the difference in the groups did not decrease, as it was during the third hour.

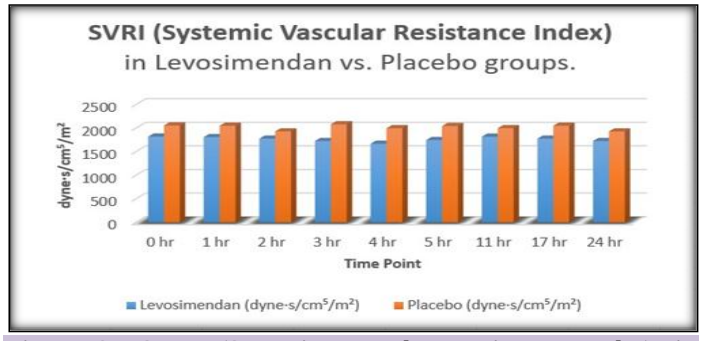

Figure 2: SVRI (Systemic Vascular Resistance Index) in Levosimendan vs. Placebo groups.

[Figure 2] shows that there was a gradual decrease in the SVRI in the Levosimendan group relative to the relatively stable values in the Placebo group.

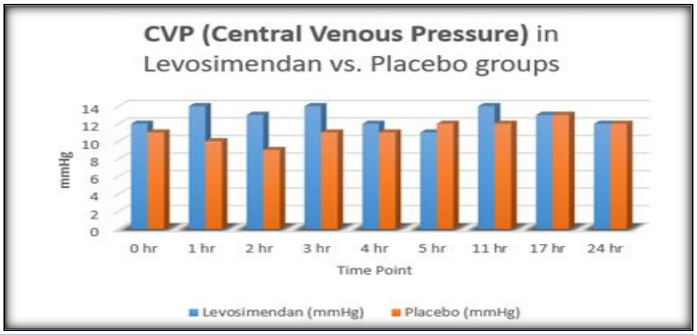

Figure 3: CVP (Central Venous Pressure) in Levosimendan vs. Placebo groups

[Figure 3] presents the early alteration in the highest values of CVP in the intervention group and thereafter converges.

Discussion

The overall conclusions of this randomized controlled trial are that, levosimendan (0.07 0 0 -1) as a continuous low-dose infusion, initiated after induction of anaesthesia in patients who underwent OPCABG, causes a significant and prolonged decrease in systemic vascular resistance. At the same time, there is no harm to cardiac output, cardiac index, or global tissue oxygenation as measured by ScvO2. The stimulated decrease in SVR and SVRI is in line with the known pharmacodynamic profile of levosimendan as a vasodilator. The mechanism of this effect is largely because it causes ATP-sensitive potassium channels in vascular smooth muscle to open, hence the resulting membrane hyperpolarization, decreased calcium influx and consequent vasodilation; the onset of this effect, some three hours after commencing a steady-state plasma concentration in the case of a continuous infusion, was a purposeful strategy to avoid precipitous hypotension. Preservation of increased MAP despite decreased afterload is an interesting and clinically relevant outcome. This implies that the increased cardiac index and the preserved stroke volume were compensating for the reduced perioperative peripheral resistance and were offset by the increased cardiac inotropic effect mediated by calcium-sensitized cardiomyocyte troponin C. The momentary increase in CVP at the first three hours in the levosimendan group is curious. Although CVP is a weak independent predictor of volume status, this initial increase may reflect an early change in venous capacitance or even a slight change in ventricular compliance before the inotropic and vasodilatory balance of this specific drug has been fully achieved. Alternatively, it can be a compensatory response to maintain preload during vasodilation. This was only a short-lived effect with no sustained hemodynamic outcome, as the subsequent normalization of CVP values between groups would show. The fact that the scvo2 between the groups did not significantly differ, except in one case, only shows that the overall balance between systemic oxygen delivery and consumption was not negatively influenced by levosimendan. Such a pattern of uniformly low SVV in the intraoperative intervention group continues to indicate that these patients were engaged in a more favourable section of the Frank-Starling curve, with reduced preload dependency and may provide the benefit of greater hemodynamic stability during moments of fluid shift or blood loss. Our research adds to the current body of literature by outlining the precise hemodynamic profile of low dose levosimendan in OPCABG. Whereas past research findings have shown mixed results regarding the intervention's effect on outcomes (such as vasopressor need), which one of the companion papers should discuss, the current investigation provides high-quality evidence of its activity as an afterload-reducing agent that maintains perfusion pressure. The profile could prove beneficial, especially in OPCABG patients with an increased systemic vascular resistance caused by a high sympathetic tone or preexisting hypertension. There are a few shortcomings that should be mentioned. The first limitation of the study was its 24-hour duration, which prevented testing the prolonged effect, which could be mediated by the active metabolite OR-1896. Second, the study was not powered to test the differences in clinical endpoint, e.g., myocardial infarction or renal failure. Third, pulmonary artery catheterization was not performed, so direct measurements of pulmonary and left ventricular filling pressures were not obtained. Finally, the patient population had, on average, preserved ventricular function; the hemodynamic effects might differ in a cohort with significant systolic dysfunction.

Conclusion

In patients undergoing off-pump coronary artery bypass grafting, a continuous infusion of levosimendan at 0.07 µg/kg/min produces a significant and sustained reduction in systemic vascular resistance. Crucially, this afterload reduction is accompanied by the maintenance of a higher mean arterial pressure, without compromise of cardiac output or evidence of impaired tissue oxygenation. These hemodynamic effects support the role of levosimendan as a valuable pharmacological agent for modulating afterload and supporting perfusion pressure in the perioperative management of OPCABG. Further research is warranted to define its impact on organ-specific outcomes and its cost-effectiveness in this surgical setting.

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Conflicts of interest

There are no conflicts of interest.

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