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Comparison of prophylactic levosimendan versus intra-aortic balloon pump for off-pump coronary artery bypass grafting in patients with low ejection fraction: A randomized-controlled trial

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ABSTRACT

Objectives: This study aims to compare the efficacy and short-term clinical outcomes of levosimendan versus intra-aortic balloon pump (IABP) in patients undergoing off-pump coronary artery bypass grafting (OPCABG).

Patients and methods: This prospective, randomized-controlled study included a total of 60 patients (44 males, 16 females; mean age 60.58+5.23 years; range, 42 to 70 years) with low left ventricular ejection fraction (<25%) undergoing OPCABG between January 2019 and September 2019. The patients were divided into two groups as levosimendan (Group L) and IABP (Group B). Hemodynamic parameters were measured at prespecified time points.

Results: Hemodynamic data recorded at baseline were comparable in both groups, while cardiac index progressively increased in both groups. Although, the increase was statistically significant on multiple measures analysis of variance in both groups, no significant difference was observed at different time points. Pulmonary capillary wedge pressure decreased in both groups; however, the decline was not statistically significant. Serum lactate concentration was consistently lower in Group B compared to Group L at all time points. The heart rate, mean arterial pressure, and Vasoactive Inotropic Score (VIS) were comparable in both groups at all time points. The mean length of intensive care unit (ICU) stay was statistically significant in Group B compared to Group L.

Conclusion: The use of prophylactic levosimendan is comparable to prophylactic IABP, when hemodynamic parameters are considered. Prophylactic levosimendan is associated with a shorter length of hospital and ICU stay. Prophylactic levosimendan can be considered an alternative to prophylactic IABP in patients with low ejection fraction in whom IABP is contraindicated.

Keywords: Coronary artery bypass grafting, intra-aortic balloon pump, levosimendan, low ejection fraction, off-pump.

Off-pump coronary artery bypass grafting (OPCABG) is often complicated by hemodynamic instability, particularly in patients with left ventricular (LV) dysfunction. One of the life-threatening complications in patient with low LV ejection fraction (LVEF, <25%), is the development of perioperative myocardial dysfunction which may lead to multiple organ dysfunction in the postoperative period, and increased duration of hospitalization and mortality.[1,2]

The main challenge during OPCABG is to maintain optimum hemodynamics. It is challenging to continue the procedures off-pump. Traditionally this has been achieved by mechanical support that is by intra-aortic balloon pump (IABP) use. Levosimendan is a novel inotropic agent, which has been used in the management of acute decompensated heart failure. It acts by binding to cardiac troponin C, enhancing myofilament responsiveness to calcium, prolonging the duration of actin-myosin overlap, thereby increasing myocardial contractility but, without increasing intracellular calcium concentration and myocardial oxygen consumption.[3,4] It also has lusitropic actions and exerts peripheral vasodilatory and potential preconditioning effects on myocardium by virtue of its action on mitochondrial adenosine triphosphate-sensitive potassium channels.[5-7] Levosimendan mediates its cardiac inotropic effect via

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the calcium sensitization of the contractile proteins. It has also been suggested that this drug protects the ischemic myocardium and that it decreases the infarct size in coronary-ligated animals.

In the present study, we aimed to compare the efficacy and short-term clinical outcomes of levosimendan versus IABP in patients with low LVEF undergoing OPCABG.

PATIENTS AND METHODS

This prospective, randomized-controlled study was conducted at Lokmanya Tilak Municipal General Hospital and Medical College, Sion, Mumbai between January 2019 and September 2019. The patients who underwent OPCABG with a low LVEF (<25%) were included. Patients undergoing emergency OPCABG or concurrent procedures in addition to OPCABG such as congenital, valve, or aortic surgery, those treated with levosimendan within the past three months or with other inotropes within the previous week were excluded from the study. Patients with significant pulmonary disease, renal dysfunction, liver dysfunction, redo-OPCABG, or arrhythmias with bundle branch block and those who did not survive for 48 h after surgery due to surgery-related causes were also excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Lokmanya Tilak Municipal General Hospital and Medical College Ethics Committee and Institutional Review Board (IEC/38/18). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The LVEF was measured using transthoracic echocardiography (TTE) both preoperatively and postoperatively.

In the given period, we operated 82 patients with low LVEF (<25%), of which 68 patients were eligible for the study, of which only 64 patients consented. Of these, only 60 patients (44 males, 16 females; mean age 60.58+5.23 years; range, 42 to 70 years) survived for 48 h and were included in the study. These 60 patients were divided into two equal groups including 30 in each as follows: levosimendan (Group L) and IABP (Group B). The patients were randomly assigned to the respective groups. Randomization was carried out through the random allocation via computer-generated random numbers.

Management protocol

All patients were admitted to the cardiac intensive care unit (ICU) 24 h prior to surgery. A Swan-Ganz catheter was inserted for pulmonary artery pressure monitoring and radial arterial cannulation was performed for systemic arterial monitoring. The levosimendan or IABP therapy was started 24 h prior to surgery in the respective groups.

In Group L, patients received a preoperative dose of levosimendan (Inj. Semenda-12.5 mg/mL, Lupin lab.) 200 µg/kg dose dissolved in 50 mL of normal saline (NS) and started at a rate of 2 mL/h for 24 h.

In Group B, the IABP was inserted through the femoral artery by the percutaneous technique using an 8F IABP catheter (Arrow International, Reading, PA, USA) connected to the Arrow® pump. The position of the balloon was confirmed by radiography. Heparin infusion was started at a rate of 5 to 10 U/kg/h to maintain the activated coagulation time within 140 to 160 sec.

All patients underwent continuous monitoring of heart rate (HR), ambulatory blood pressure (ABP), cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP). Central venous pressure (CVP), urine output, Vasoactive Inotropic Score (VIS), and lactate levels were also monitored. Hemodynamic parameters recorded at various time points before or after the drug were administered or IABP was inserted. All the parameters were measured at regular time points, i.e., at baseline (T0), 30 min (T1) after beginning levosimendan or IABP, 6 h (T2), 12 h (T3) after starting levosimendan or IABP respectively, prior to induction (T4), 15 min after induction (T5), immediately after completion of revascularization (T6), 6 h after surgery (T7), 12 h after completion of surgery (T8), 24 h after surgery (T9), and 48 h after surgery (T10).

Anesthetic management and surgical procedures were the same in both groups. Induction and maintenance of general anesthesia with endotracheal intubation was standardized in both groups. All procedures were performed using the off-pump technique. The OPCABG was performed using the left internal mammary artery (LIMA) and reversed saphenous vein grafts (rSVGs) as conduits. Left anterior descending (LAD) artery was revascularized by LIMA, while other coronary arterial targets were revascularized by rSVGs via an aortocoronary anastomosis.

Definitions

High inotropic support was defined as the requirement of dobutamine >5 μg/kg/min and/or adrenaline >0.1 μg/kg/min and/or noradrenaline >0.1 μg/kg/min. The VIS was calculated as a weighted sum of all administered inotropes and vasoconstrictors, reflecting pharmacological support of the cardiovascular system.[8] It was calculated using the formula described by Koponen et al.,[9] during the first 48 h after postoperative ICU admission, which were retrieved from the ICU critical care information system.

Low cardiac output syndrome (LCOS) was defined as the presence of low CI (<2.2 L/min/m^2) with elevated PCWP (>16 mmHg) and a partial pressure of arterial oxygen (PaO_2) of <60 mmHg. Acute renal failure was defined when serum (S) creatinine increases by >50% from baseline with or without oliguria (urine output <0.5 mL/kg/h) or requiring dialysis.[8]

Cerebrovascular accidents were defined, if there was development of a new focal neurological deficit or coma persisting for >48 h, after metabolic causes were ruled out.[3] A neurological alteration persisting <48 h was considered as a transient ischemic attack. Postoperative mortality was defined as death occurring during hospitalization or within 30 days after surgery.

Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Student's t-test and analysis of variance (Wilcoxon signed-rank test) were used to determine the differences between the groups. The multiple measures analysis of variance (ANOVA) was used for within the group analysis. A p value of <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 concentrations were also comparable in both groups. Hemodynamic data were recorded and compared at various time points. Preoperative ICU stay was uneventful in both groups. Seven patients in Group L developed mild hypotension, which resolved with fluid resuscitation. Two patients (n=1 in each group) required vasopressors support and one patient in Group B required removal of IABP due to limb ischemia and re-insertion of IABP in the opposite femoral artery.

Table 1
Baseline demographic and clinical characteristics of patients

	Levosimendan (Group L) (n=30)		IABP (Group B) (n=30)		
Variable	n	Mean±SD	n	Mean±SD	p
Age (year)	30	60.2±5.7	30	161.2±8.5	0.55
Sex					0.55
Male	23		21		
Female	7		9		
Height (m)		162.4±7.3			
Weight (kg)		65.6±6.3		66.6±6.9	0.56
Hypertension (%)	19/30		20/30		0.78
Diabetes mellitus	21/30		22/30		0.77
Left ventricular ejection fraction		20.5±4.4		20.4±4.52	0.93
Number of grafts		2.6+0.8		2.5+0.8	0.64
Baseline serum creatinine (mg/dL)		1.1±0.2		1.2±0.1	0.15
Hemoglobin (%)		13.5+0.8		13.4+0.8	0.62

IABP: Intra-aortic balloon pump; SD: Standard deviation.

Hemodynamic data recorded at baseline were comparable in both groups (Tables 2, 3). A progressive increase in the CI was observed in both groups. The increase was observed to be statistically significant on within the group in both groups. However, the differences in the CI at different time points between

Table 2
Hemodynamic variables at time points

	HR	MAP	VIS
Time	Mean±SD	Mean±SD	Mean±SD
Time 0			
Group L	70.8±7.1	90.2±4.3	1.9±0.4
Group B	71.9±8.3	88.4±6.6	1.7±0.6
P	0.59	0.21	0.17
Time 1			
Group L	78.2±7.1	84.1±6.1	1.8±0.5
Group B	77.9±8.3	86.1±7.2	1.6±0.3
P	0.86	0.24	0.06
Time 2			
Group L	68.8±5.3	86.1±5.3	1.6±0.5
Group B	70.7±6.3	88.3±6.4	1.6±0.9
P	0.22	0.15	1
Time 3			
Group L	74.8±6.1	85.4±6.9	1.8±0.8
Group B	74.7±7.3	88.5±7.2	1.7±0.8
P	0.91	0.1	0.63
Time 4			
Group L	80.2±4.3	88.5±4.1	2.1±0.9
Group B	78.9±6.6	87.4±6.4	2.3±1.1
P	0.32	0.43	0.44
Time 5			
Group L	88.2±7.1	82.2±8.0	5.7±2.1
Group B	90.8±4.3	80.4±7.2	6.4±1.8
P	0.09	0.36	0.17
Time 6			
Group L	84.2±7.1	88.8±5.9	6.3±2.3
Group B	83.9±8.4	88.6±6.6	6.9±2.7
P	0.87	0.9	0.35
Time 7			
Group L	75.2±9.2	88.4±5.9	6.4±2.1
Group B	76.9±8.5	86.5±6.4	7.1±2.6
P	0.46	0.21	0.25
Time 8			
Group L	76.2±8.1	88.4±5.9	5.4±1.8
Group B	75.6±8.3	86.3±6.4	6.1±2.3
P	0.77	0.19	0.19
Time 9			
Group L	68.8±4.3	84.1±6.1	3.7±1.3
Group B	69.2±6.2	86.1±7.2	4.2±1.5
P	0.81	0.24	0.17
Time 10			
Group L	66.5±5.1	88.7±5.9	1.9±0.8
Group B	65.5±6.3	87.5±6.8	1.7±1.1
P	0.5	0.47	0.42

HR: Heart rate; MAP: Mean arterial pressure; VIS: Vasoactive Inotropic Score; SD: Standard deviation.

Table 3
Data at various time points

	PCWP	CI	Lactates
Time	Mean±SD	Mean±SD	Mean±SD
Time 0			
Group L	20.5±2.5	2.1±0.2	1.7±0.4
Group B	19.2±3.0	2.1±0.2	1.8±0.6
P	0.08	0.55	0.68
Time 1			
Group L	15.9±2.5	2.2±0.2	1.7±0.3
Group B	12.7±2.4	2.2±0.2	1.7±0.4
P	<0.0001*	0.57	0.9
Time 2			
Group L	16.34±3.27	2.1±0.3	1.6±0.2
Group B	15.63±1.26	2.2±0.4	1.7±0.6
P	0.27	0.38	0.72
Time 3			
Group L	15.6±3.7	2.3±0.2	1.8±0.1
Group B	15.0±2.8	2.2±0.3	1.6±0.5
P	0.41	0.09	0.08
Time 4			
Group L	15.2±4.3	2.1±0.2	2.0±0.2
Group B	16.7±3.9	2.1±0.2	1.8±0.8
P	0.15	0.24	0.13
Time 5			
Group L	14.3±3.3	2.2±0.2	1.8±0.4
Group B	14.7±2.3	2.2±0.1	1.7±0.5
P	0.67	0.48	0.27
Time 6			
Group L	15.3±3.3	2.2±0.1	1.7±0.3
Group B	14.6±2.3	2.2±0.3	1.6±0.6
P	0.33	0.85	0.56
Time 7			
Group L	16.3±3.2	2.2±0.2	1.6±0.3
Group B	15.7±1.6	2.2±0.2	1.5±0.7
P	0.35	0.84	0.22
Time 8			
Group L	15.6±3.7	2.2±0.1	1.7±0.2
Group B	14.2±1.6	2.2±0.2	1.7±0.5
P	0.18	0.09	0.54
Time 9			
Group L	16.3±3.3	2.2±0.3	1.6±0.4
Group B	15.7±1.6	2.2±0.2	1.5±0.9
P	0.32	0.47	0.35
Time 10			
Group L	16.3±3.2	2.3±0.1	1.6±0.3
Group B	15.6±1.3	2.2±0.2	1.5±0.7
P	0.29	0.12	0.19

PCWP: Pulmonary Capillary Wedge Pressure; CI: Cardiac Index; SD: Standard deviation.

Table 4
Postoperative findings and outcomes

Variable	Levosimendan (Group L)			IABP (Group B)			p
	n	%	Mean±SD	n	%	Mean±SD	
Ventilation time (h)			8.5+4.1			9.7+7.2	0.17
Blood loss in first 24 hrs (mL/kg)			5.7+3.4			5.3+2.7	0.58
Need for inotropic support	7/20	35		6/20	30		0.75
Postoperative atrial fibrillation (%)	4/30	13.33		12/30	40		0.01
LCOS (%)	2/30			2/30			1
Norepinephrine requirement (%)	14/30			15/30			0.79
ICU stay (days)			4.4+0.2			6.5+0.1	<0.001
Hospital stay (days)			10.1+1.0			13.3+0.1	<0.001

IABP: Intra-aortic balloon pump; LCOS: Low cardiac output syndrome; ICU: Intensive care unit; SD: Standard deviation.

the two groups were not statistically significant. The PCWP decreased in both groups; however, the decline was not statistically significant, either. Serum lactate concentration was consistently lower in Group B compared to Group L at all time points. However, this difference was not statistically significant. The HR, MAP, and VIS were comparable in both groups at all time points.

The mean ICU stay in Group B was 6.5+0.1 days compared to Group L (4.4+0.2 days), indicating a statistically significant difference (p<0.001). The patients in Group B had delayed hospital discharge at 13.4 days, compared to Group L (10.2 days), indicating a statistically significant difference (p<0.001).

Two patients in Group B required femoral artery embolectomy due to development of acute thrombosis. None of the patients in Group L and Group B developed acute kidney injury. The incidence of postoperative atrial fibrillation was lower in Group L, compared to Group B, indicating a statistically significant difference (p=0.01). Noradrenaline requirement (%) and incidence of LCOS were similar in both groups. Totally, two patients (one in each group) died due to sepsis and multiple organ dysfunction. The length of ICU and hospital stay were higher in Group B, compared to Group L, indicating a statistically significant difference (p=0.001).

DISCUSSION

Off-pump coronary artery bypass grafting involves displacement and manipulation of heart to expose target coronary arteries, particularly obtuse marginal and posterior descending coronary arteries. This manipulation may be accompanied by transient annular 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 the epicardial stabilizer. This results in hemodynamic instability in the form of increased filling pressures, right ventricular end-diastolic pressure and transient diastolic dysfunction.[10,11] All these changes are exaggerated intraoperatively in patients with LV dysfunction, which is the main risk factor for intra- and postoperative LCOS.[12,13]

The main challenge during OPCABG is to maintain optimum hemodynamics. This can be achieved by mechanical or pharmacological means. Use of inotropes constitutes major pharmacological intervention and its appropriate selection helps in better clinical outcomes. However, conventional inotropes such as beta-agonists and phosphodiesterase inhibitors are associated tachycardia and arrhythmia, leading to an increased myocardial oxygen demand.[14]

Levosimendan is a novel inotropic agent. It also provides beneficial immunomodulatory, cardioprotective, anti-stunning, anti-ischemic, anti-inflammatory, and antioxidant effects to improve cardiac performance in the presence of ischemia.[15-18] All these characteristics make it a near-ideal inotrope in patients with LV dysfunction.

The IABP counter pulsation is currently the most used mechanical assistance device for patients with cardiogenic shock due to acute myocardial

infarction. Its beneficial physiological effects have been established. The IABP increases diastolic blood pressure.[19,20] and, thus, it improves diastolic coronary perfusion. Furthermore, it increases cardiac output and stroke volume by reducing afterload. The ability to act on diastolic pressure has a great importance in clinical practice, since the elevated diastolic pressure results in a redistribution of coronary blood flow toward ischemic areas of the myocardium.[21]

A multi-center study showed that prophylactic use of IABP improved outcomes in high-risk cardiac patients.[22] The main disadvantages of IABP, particularly in patients with systemic atherosclerosis, is the development of complications associated with instillation of the balloon including includes limb ischemia, damage to the vessels, and bleeding.[23,24]

This study highlights the favorable hemodynamic profile of levosimendan and IABP in terms of reduced PCWP and improved CI after its administration. We consistently observed higher CI in patients treated with IABP during intra- and postoperative period, compared to levosimendan; however, the increase was not statistically significant. The rise in CI leads to reduced serum lactate concentrations, indicating improved microcirculation at peripheral tissue level. Although data are scarce regarding the use of levosimendan during cardiac surgery in patients with low EF, our results are consistent with the recent studies.[24] In a meta-analysis, Landoni et al.[21] emphasized that the use of levosimendan contributed to a significant reduction of mortality in cardiac patients with favorable outcomes. In the study conducted by Alvarez et al.,[25] they concluded that a loading dose of levosimendan needed to be omitted in decompensated heart failure patients to prevent hypotensive episodes. Hence, we preferred an approach of gradually achieving the therapeutic concentration without causing any hypotensive episodes in our institution.

In the current study, none of the patients developed significant hypotension, any hemodynamic instability, and other side effects such as nausea and headache in the preoperative period and the regime was tolerated well. Immediate postoperative outcomes also improved in the levosimendan group with a notably reduced incidence of postoperative atrial fibrillation which can be attributed to antioxidant and anti inflammatory properties of levosimendan.[23] Although several studies have emphasized the increased incidence of ventricular arrythmias after administration of levosimendan, we found no similar result in our study.

In their study, Baysal et al.[26] suggested that levosimendan increased renal blood flow by decreasing renal vascular resistance and increasing glomerular filtration rate. In another study using propensity score analysis, Lorusso et al.[27] concluded that patients with IABP support in the preoperative period had a lower risk of acute kidney injury. Our findings are also consistent with the aforementioned studies, as none of our patients developed acute kidney injury requiring dialysis.

Furthermore, we observed a decreased incidence of LCOS in both groups. These findings can be attributed to favorable surgical conditions produced by levosimendan and IABP owing to improved myocardial contractility and reduced pulmonary pressures which make the heart supple and easy to operate upon. In another study, Lomivorotov et al.[28] compared levosimendan and IABP in high-risk cardiac surgery patients and concluded that the infusion of levosimendan after anesthesia induction in cardiac surgical patients contributed to lower cardiac troponin I concentrations and improved hemodynamics compared to preoperative IABP. Similarly, Severi et al.[29] also observed a shorter ICU stay in patients pretreated with levosimendan compared to patients receiving prophylactic IABP. In our study, we found a significant difference in the length of ICU and hospital stay between the two groups. The patients in Group B stayed in the ICU for a longer duration (mean 6.5±0.1 days) compared to the patients in Group L (mean 4.6±0.2 days) group. Although two patients in Group B needed an additional procedure in the form of an embolectomy, it did not influence the total ICU stay in the study population.

The single-center design is the main limitation of the present study. In addition, we were unable to consider serum-specific cardiac markers (troponin levels) which would in detail highlight the cardiac status of the patients in both groups. Also, the immediate postoperative mortalities (within 48 h) were unable to be analyzed.

In conclusion, the use of prophylactic levosimendan is comparable to prophylactic IABP, when hemodynamic parameters are taken into consideration. Prophylactic levosimendan is associated with lower hospital and ICU stay. Prophylactic levosimendan can be considered as an alternative to prophylactic IABP in patients with low ejection fraction in whom IABP is contraindicated.

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