COMPARITIVE STUDY OF EFFICACY AND HAEMODYNAMIC SAFETY OF LEVOSEMENDAN WITH DOBUTAMINE IN PATIENTS WITH SEVERELY REDUCED LEFT VENTRICULAR FUNTION UNDERGOING CARDIAC SURGERY.

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Abstract

Background: Levosimendan, a novel calcium sensitizer, improves myocardial contractility without causing an increase in myocardial oxygen demand as compared to other inotropes.
Aims and Objectives: We aimed to compare the hemodynamic effects of levosimendan and dobutamine in patients with EF < 30% undergoing coronary artery bypass grafting (CABG) electively on cardiopulmonary bypass (CPB).
Materials and Methods: 60 patients were divided into 2 groups of 30 each. Group-L patients received levosimendan 6 µg/kg loading for 10 mins followed by continuous infusion of 0.2 µg/kg/min upto 24 hrs and Group-D patients received dobutamine 5 µg/kg/min while weaning off CPB without a loading dose and continued upto 24hrs. Additional inotrope and/or vasoconstrictor were started based on hemodynamic parameters. Hemodynamic data were collected at baseline, 30 minutes after CPB, thereafter at 6, 12, 24, and 36 hours post-CPB. Mean arterial pressure (MAP), central venous pressure (CVP), Pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), heart rate (HR), stroke volume (SV), CO (cardiac output) ,cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index(PVRI), and lactate levels were measured.
Results: Group-L showed increased requirement of inotropes and vasoconstrictors. The MAP, CVP, PAP were reduced more in Group-L. The CI ,CO,SV were higher in Group-L when compared to Group-D , patients showed a statistically significant increase in CI ,CO,SV even after 12 hrs of discontinuation of levosimendan. Compared with dobutamine group, SVRI and PVRI was significantly lower at 6, 12, 18, and 24 hour post CPB in levosimendan group, requiring additional inotropes. The HR was higher in Group-D. Lactate levels, intensive care unit stay, and duration of ventilation were similar in both groups.
Conclusion: Levosimendan loading dose 6 µg/kg for 10 mins followed by 0.2 µg/kg/min compared to dobutamine 5 µg/kg/min caused rapid dose-dependent improvement in hemodynamic function, showed more vasodilation and lesser inotropy in patients undergoing CABG. The requirement of another inotrope or vasopressor was frequent in levosimendan group.

Keywords: Hemodynamics variables, Levosimendan, dobutamine, CABG.

Introduction

Intravenous positive inotropic agents play an important role in the short-term management of patients with left ventricular (LV) systolic dysfunction.[18-20] β-Adrenergic agonists and phosphodiesterase

inhibitors, the most commonly used positive inotropic agents, exert a positive inotropic action primarily by increasing cAMP in cardiac myocytes, although being effective positive inotropic agents, their use may be limited by increases in heart rate and the stimulation of arrhythmias limiting dosing and can result in serious adverse effects-myocardial ischemia and sudden death[21-23] . Secondly, because of desensitization of β-adrenergic pathway, the positive inotropic effects of agents that act through this pathway may be reduced in patients with severe LV dysfunction.[24,25.]Calcium-sensitizing agents exert a positive inotropic action by increasing the sensitivity of the contractile apparatus to calcium.[26]. Levosimendan is a new calcium-sensitizing agent that binds to troponin C[27,28] . Dobutamine was chosen as the inotropic control drug since its effects on low cardiac output syndrome following surgery involving CPB are well described. [12],[13] Surgery on cardiopulmonary bypass (CPB) with aortic clamping involves global myocardial ischemia resulting in different degrees of transitory ventricular dysfunction in the immediate post-operative period. [1],[2]. β adrenergic agonists and phosphodiesterase III/IV inhibitors induce good hemodynamic improvement but may cause myocardial ischemia, arrhythmias and are associated with high mid-term mortality. [3],[4],[5]. The use of levosemendan in the treatment of heart failure with dysfunction is based on its action of improvement of myocardial contractility through the sensitization of troponin C to calcium, and systemic and coronary arterial and venous dilatation induced by activation of ATP-sensitive potassium channels of smooth muscle fibers. [3] Thus levosimendan increases cardiac output, coronary, renal blood flow also reduces the preload and afterload, has anti-arrhythmic effect, and can revert myocardial stunning. [3]

Aims and objectives

The present study was aimed to compare the hemodynamic parameters and clinical outcome and safety of levosimendan and dobutamine in a group of reduced LV function patients undergoing CABG on pump. We also compared the outcomes in terms of duration of ventilation and intensive care unit stay and tissue perfusion in terms of lactate levels.

Materials and Methods

The study was approved by the hospital ethics committee. Patients aged 35-60 yrs with documented LV ejection fractions of ≤30% by echocardiogram or radionuclide ventriculogram scheduled for CABG on CPB were recruited in the study . Patients were screened for the study if they were currently on treatment with β blockers, ACE (angiotensin-converting enzyme) inhibitors. The patients having other valvular pathologies, hepatic , renal dysfunction (serum creatinine >2 mg/dl and/or chronic kidney disease), undergoing combined mitral valve surgery with coronary artery bypass graft surgery, redo mitral valve surgery, uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease , active myocarditis, symptomatic primary pulmonary disease, chronic obstructive pulmonary disease, requiring long-term treatment with β-agonists, serious arrhythmias, heart block rythm, re-exploration for surgical causes were excluded. Written informed consent was obtained from all the patients. Randomization was done by computerized allocation of patients to both the groups. All preoperative medications were continued until the morning of surgery except ACE inhibitors stopped the day before surgery. All patients received oral alprazolam 0.5 mg and pantoprazole 40 mg previous night and on the morning of surgery. Anaesthesia, surgery and CPB were performed in accordance with standard operating procedures and hospital's routine clinical practice. Patients were induced with midazolam 0.1 mg/kg, fentanyl 4-6 µg/kg. Vecuronium 0.1 mg/kg was used to facilitate endotracheal intubation. Routine monitoring included 5-lead ECG, pulse oximetry , capnography, invasive arterial pressure monitoring , central venous access was established using a 5 -lumen swan ganz catheter for pulmonary artery pressure monitoring . CO,CI, SV were monitored using thermodilution technique with Swan ganz catheter, SVRI,PVRI was measured after obtaining CVP,PAP,PCWP. The myocardial contractility and

preload were assessed by transesophageal echocardiography (TEE) at the time of separation from CPB. Surgery was performed on CPB with moderate hypothermia (28°C to 32°C) using cold blood cardioplegic cardiac arrest, LAD, LCX & RCA vessels were grafted as per the severity of stenotic lesions involved. LIMA (left internal mammary artery) and SVG(saphenous vein graft) conduits were harvested before institution of CPB. At separation from CPB, group-D patients received infusion of dobutamine 5 µg/kg/min and group-L received levosimendan loading 6 µg/ kg for 10 mins followed by 0.2 µg/ kg/ min continuous infusion till 24 hrs. The study drug levosimendan and dobutamine were diluted in such a way that equal infusion rates were achieved for comparable patients. Both the study drug syringes were prepared by another person blinded from the study. Syringes and extension tubing were covered with black paper to blind the anesthesiologist. Drugs were administered once patient was rewarmed to 34°C and aortic clamp released. In case of adverse events : HR >130 or an increase in HR >20 bpm above baseline for 10 minutes, symptomatic hypotension or a drop in systolic blood pressure to <75 mm Hg or life threatening arrhythmias, study was abondoned Protocol and criteria for addition of another inotrope or vasopressor (adrenaline or noradrenaline) is described below..While continuing a flow of 0.5 l/min on CPB, the CVP, the mean arterial pressure (MAP), SVRI, CI and left ventricular (LV) and right ventricular (RV) function were assessed and the vasopressor or inotropic agent was selected as described

If MAP >50 mmHg and LV , RV function adequate as assessed by TEE in mid esophageal four chamber view, the study drug was continued.

If MAP <50 mmHg, CI <1.5 dyne-sec-m ^{2} /cm ^{5} with adequate LV , RV function on TEE imaging, but SVRI <1200 units, noradrenaline 0.05 µg/kg/min was added.

If MAP <50 mmHg, CI <1. 5dyne-sec-m ^{2} /cm ^{5} with inadequate LV , RV function on TEE imaging and SVRI > 1200 units, adrenaline 0.05 µg/kg/min was added.

In both groups, the HR,MAP, CVP, PAP,PCWP,SV,CO,CI,PVRI and SVRI were monitored at baseline, at 30 minutes after CPB, thereafter at 6, 12, 24 and 36 hours after CPB. Aortic clamp time and CPB time were recorded for all patients. Tracheal extubation was performed when patients were hemodynamically stable, warm, chest tube drainage was less than 50 ml per hour, urine output more than 0.5 ml /kg / hour, and patients breathing spontaneously with adequate blood gases as per institutional protocol. Both the study drugs and additional inotrope/vasoconstrictor were tapered once the patients were extubated and hemodynamically stable after 24hrs. Presence of any arrhythmia was recorded.

Statistics

The sample size required was determined by the criterion that an increase in the CI of >20% over baseline is obtained after 24 hours of treatment for α error of 5% and a β error of 10%. The determined sample size was 30 patients in levosimendan (L) group and 30 patients in dobutamine (D) group. Numerical results are presented as mean ± SD; mean was compared by the students *'t'* test; categorical data were compared using chi square test. Significance was set at a *P* value < 0.05.

Results

This prospective, randomized, double-blind study included 60 patients undergoing CABG on CPB over 9 months period. The demographic data was comparable between the two groups.

Both groups were comparable for ejection fraction, CPB and aortic clamp time, and surgical technique employed. The ICU stay and ventilation duration were also similar in both groups.

TABLE 1: Clinical and demographic data of patients in study Values expressed as mean ± standard deviation , number in parenthesis indicates % in total, LVEF- Left ventricular ejection fraction, CPB- cardio pulmonary bypass, ICU – intensive care unit, ACE- angiotensin converting enzyme, ASA- American Society of Anesthesiology, NYHA- New York Heart Association. p value <0.05 significant.

	LEVOSEMENDAN	DOBUTAMINE	P value
Number of patients	30	30	0.18
Age (years)	49.16 ± 6.84	47.44 ±7.22	0.16
Sex - Women (%)	11 (36.66)	12(40)	0.15
Men (%)	19 (63.33)	18(60)	0.14
Body surface area in m^2	1.8 ± 0.06	1.77 ± 0.05	0.33
Body mass index ($kg/m^{2)}$	26.5 ± 5.4	27.2 ± 4.8	0.24
Pre operative beta blockers (%)	15 (50)	14 (46.66)	0.56
Pre operative ACE inhibitors (%)	11 (36.66)	12 (40)	0.37
ASA risk classification ≥ 4 (%)	10 (33.33)	9 (30)	0.42
NYHA class 4 (%)	8 (26.66)	8 (26.66)	0.31
LVEF (%)	24 ± 5.4	24.4 ± 4.8	0.19
Duration of CPB (mins)	76 ± 8.84	72 ± 10.4	0.23
Aortic cross clamp time (mins)	46 ± 10.43	44 ± 8.86	0.21
Duration of ventilation (hrs)	6.3 ± 2.1	6.8 ± 1.8	0.18
ICU stay (hrs)	52 ± 4.2	54 ± 2.8	0.19

Table 2 shows haemodynamic variables(HR, MAP, CVP, PAP,PCWP, SVRI,PVRI, SV,CO, CI) in levosemendan & dobutamine groups at baseline, post CPB immediately ,30 mins, 6 ,12,24,36 hrs post CPB.

Haemodynamic variables		baseline	Post CPB	30 mins	6 hours	12 hours	24 hours	36 hours
HR	GROUP L	85.3±7.4	90.5±8.8*	96.4±8.9*	76.8±6.6*	78.7±7.8*	812.8±8.44*	84.6±7.7
	GROUP D	87.4±6.6	99.9±10.2*	105.4±8.2*	88.2±7.1*	86.5±8.43*	89.8±9.23*	90.4±6.2
MAP	GROUP L	54.66±8.11	57.44±6.23*	64.78±5.32*	71.12±5.84*	75.34±7.84*	70.12±6.04	69.12±5.23
	GROUP D	53.82±7.46	64.32±7.11*	69.44±6.91*	77.34±6.51*	82.12±7.91*	75.44±5.88	72.23±4.44
CVP	GROUP L	9.3±2.3	4.4±2.3*	6.74±1.88*	7.16±1.34*	7.2±1.26*	6.92±1.56	5.84±1.66
	GROUP D	10.2±1*	6.6±2.2*	8.11±1.44*	8.9±1.44*	8.4±1.77*	7.24±1.89	6.66±1.77

PAP	GROUP L	27.0 ±3.9	22.1 ± 2.7*	20.1 ±2.9*	19.7 ±3.0*	20.0 ± 1.9*	21.1 ±2.1	20.7 ± 2.0
	GROUP D	26.2±3.2	25.3± 3.1*	24.1± 2.7*	23.4±2.4*	23.1 ± 2.7*	22.2±2.5	21.2±1.1
PCWP	GROUP L	18.0 ± 2.6	15.2±1.8	14.0 ± 2.0	12.8 ± 2.0	11.0 ± 2.6	12.0 ±2.0	12.8± 2.0
	GROUP D	17±2.8	16.5± 2.2	15.1±1.9	13.2± 2.1	12.2 ± 1.8	12.8±2.4	13.2±1.2
SV	GROUP L	40.5 ±4.6	56.6 ±8.6	58.8 ± 7.4	60.4 ± 7.8*	63.3± 6.6*	61.2±4.4*	58.3±2.1*
	GROUP D	41.1±3.4	49.3±7.2	54.8±5.4	54.3±3.4*	55.12±4.2*	56.13±2.3*	50.3±2.2*
SVRI	GROUP L	1674±138	1442±189	1486±144	1244±166*	1282±122*	1434±101*	1326±114*
	GROUP D	1784±144	1543±194	1623±178	1786± 158*	1689±145*	1549±122*	1589±158*
PVRI	GROUP L	286 ± 81	213 ± 58	200 ± 43*	203 ±45*	188±54*	186±32	190±24
	GROUP D	290±74	244±38	225±32*	228±34*	211±66*	198±38	201±20
CO	GROUP L	3.5 ±0.3	5.0 ±0.7	5.2 ± 0.7	5.3 ±0.6*	5.1±0.4*	4.9±0.2*	4.7± 0.4*
	GROUP D	3.2±0.4	4.9±0.8	4.8±0.6	4.8±0.5*	4.6±0.3*	4.3±0.2*	4.0±0.2*
CI	GROUP L	2.3±0.2	2.54±0.3	2.52±0.1	2.62±0.3*	2.77±0.3*	2.93±0.2*	3.12±0.1*
	GROUP D	2.2±0.1	2.66±0.2	2.63±0.2	2.58±0.1*	2.66±0.2*	2.79±0.1*	2.88±0.2*
Lactate	GROUP L	1.2±0.44	4.8±0.68	4.4±0.99	3.7±0.72	2.4±0.66	1.8±0.43	1.2±0.1
	GROUP D	1.32±0.32	4.4±0.84	4.8±0.83	3.99±0.66	2.9±0.72	2.2±0.44	1.1±0.2

Values expressed as mean ± standard deviation ,lactate -millimol/lit.CI – cardiac index (L/min/m2); CO – cardiac output (L/min), HR – heart rate (beats/min) MAP – mean arterial pressure (mm/hg), SV – stroke volume (mL/beat) ,CVP – central venous pressure (mmHg); PAP pulmonary artery pressure (mmHg); PCWP – pulmonary capillary wedge pressure (mmHg); PVRI (dyn·s/cm5/m2)– pulmonary vascular resistance index SVRI(dyn·s/cm5/m2); – systemic vascular resistance index, group L –levosemedan, group D- dobutamine. * P value < 0.05-significant,

The HR was higher in D group till 24 hrs post CPB, as compared to L group, which was statistically significant and remained higher till tapering of inotropes. The MAP, CVP and PAP were reduced more in the levosimendan group compared to dobutamine group, which was

statistically significant at weaning from CPB, 30 minutes, 6 hours, and 12 hours post CPB. This decrease in MAP was maintained even after levosemendan discontinuation. Treatment with dobutamine showed no significant changes in this respect. Levosimendan group patients showed a sustained increase in CO,CI and SV at 6,12, 24 and 36 hours postoperatively compared to dobutamine group, which was statistically significant. PCWP and lactate levels were comparable in both groups, although PCWP was lower in levosemndan group. SVRI and PVRI showed statistically significant sustained decrease in levosemndan group than dobutamine group at 6,12, 24 and 36 hrs post CPB.

16 patients needed adrenaline infusion, and 12 patients needed noradrenaline infusion in L group as compared to only 2 patients needing adrenaline and 8 patients needing noradrenaline infusion in D group as shown in Table-3. This difference in the requirement of inotropic agent and vasoconstrictor infusion was statistically significant. No malignant ventricular arrhythmias were recorded in any patient. Over 36 hours of double-blind drug infusion, adverse events were reported in 12% of levosimendan patients and 20% of dobutamine patients. 3 patients in group L and 4 patients in D group had nonsustained ventricular tachycardia, 2 patients from group D had increase in heart rate > 20 bpm, but was not sustained > 4 mins.

Table -3 Concomitant use of vasoactive drugs during levosimendan and dobutamine infusion study

Inotrope or vasopressor requirement	**Levosemendan group**	**Dobutamine group**
Noradrenaline	**16 (53.3%)**	**8 (26.67%)**
Adrenaline	**12 (40%)**	**2 (6.66%)**

Discussion

Post-operative myocardial stunning defined as transitory myocardial dysfunction induced by ischemia through aortic clamping followed by reperfusion involves depletion of high energy phosphates, intracellular calcium overload, generation of free radicals, and impairment of the coronary microcirculation.[2] Myocardial stunning, anaesthetic agents, vasodilatation and hyperthermia caused by the inflammatory response associated with CPB, all contribute to haemodyanamic instability in the early post-operative period [6] .The recovery from this phenomenon starts after one hour of termination of CPB, and continues till 24 hours post-CPB[1]. Patients with this condition usually respond to positive inotropic agents [1]. .Few studies on the use of levosimendan in the immediate post-cardiac surgery patients have been undertaken [7],[8],[9],[10]. In the present study levosimendan was started at smaller loading dose of 6µg/kg/min for 10 mins followed by 0.2 µg/kg/mins to avoid profound hypotension. [11] In our study, levosimendan showed sustained increase in CO, CI, SV even after 36 hrs post-CPB, helping to improve the myocardial dysfunction associated with CPB. Levosimendan increased SV,CO,CI while causing only a small increase in heart rate Julian *et al.*, [14] in their study found significant hypotension with levosimendan infusion 0.2 µg/kg/min with a bolus dose of 12 µg/kg. In our study,although we did not find significant hypotension because of smaller loading dose. In contrast to the study of Julian *et al.* [14] our study showed less increase in HR in levosimendan group compared to dobutamine group.. The prolonged effects of levosimendan are owed to the pharmacokinetic properties of its metabolites, especially the molecule known as OR-1896. This has a pharmacodynamic profile identical to that of levosimendan, with a half life of

approximately 80 hours and activity period of 2 weeks. [11],[15],[16],[17] In healthy humans, levosimendan increased SV and CI without increasing heart rate.[29] When administered as a bolus to patients shortly after coronary bypass surgery, levosimendan increased coronary blood flow without increasing myocardial oxygen consumption.[31] Levosimendan increases the sensitivity of myocardial filaments to calcium.[27,31,32] Consistent with this thesis is the observation that levosimendan does not impair myocardial relaxation.[17–20] Levosimendan causes vasodilation, attributed to the activation of potassium-dependent ATP channels[21] and decreasing the sensitivity to calcium.[22] .MAP, CVP.PAP ,SVRI,PVRI were significantly lower in levosemendan group than dobutamine thus required additional inotropes more.12 patients in levosimendan group needed adrenaline for maintaining adequate MAP and CI indicating that 0.2 μg/kg/min levosimendan did not produce enough inotropy. This might be attributed to decrease in dosage of levosimendan.16 patients in the levosimendan group were started on nor-adrenaline infusion to increase SVRI indicating that levosimendan infusion at 0.2 μg/kg/min with a small 6 μg/kg for 10 mins bolus dose produces significant vasodilation. 2 patients needed adrenaline infusion and 8 patients needed noradrenaline infusion in dobutamine group indicating relatively less vasodilation with dobutamine. Lactate levels, intensive care unit stay, and duration of ventilation were similar in both groups.

Conclusion

Levosimendan loading dose of 6 μg/kg followed by 0.2 μg/kg/min produces more vasodilation as compared to dobutamine 5 μg/kg/min in the post bypass period in patients undergoing CABG surgery on pump. Levosimendan showed a statistically significant increase in CI even after 12 hours of stopping the infusion when compared to dobutamine. The requirement of another inotrope or vasopressor was more frequent in levosimendan group than in dobutamine group. There was no significant difference in the lactate levels and duration of ventilation and ICU stay in both the groups. In summary, the present study demonstrates that levosimendan is safe and efficacious drug causing rapid dose-dependent improvement in hemodynamic function in patients with reduced LV function.

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