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Comparison of Levosimendan Versus Dobutamine In Patients With Moderate Left Ventricular Dysfunction Undergoing OffPump Coronary Artery Bypass Grafting.

Sanjay Soloman Raj M.D,FNB,[1] Ragha Deepti Kilambi M.D[2], Leena Shekinah M.D[3]

[1]*Assistant Professsor, Department of Anaesthesia , NRI medical college & Hospital, Chinakakani, Andhra Pradesh.*
[2]*Assistant Professsor, Department of Anaesthesia ,NRI medical college & Hospital, Chinakakani Andhra Pradesh .*
[3]*Senior resident, Department of Anaesthesia ,NRI medical college & Hospital, Chinakakani , Andhra Pradesh.*
***Correspondence Info:**1. Dr. Ragha Deepti Kilambi M.D.*
Assistant Professor, Department of Anaesthesia NRI medical college & Hospital , Chinakakani Andhra Pradesh.

Abstract:
Off-pump coronary artery bypass grafting (OP-CABG) surgery without the use of cardiopulmonary bypass (CPB) has come into practice for the surgical treatment of Coronary artery disease to reduce the post-operative systemic inflammatory response and post-operative morbidity. However, manipulation of the beating heart during OP-CABG surgery brings significant fluctuations in the patients haemodynamics leading to occult hypo-perfusion (low cardiac output syndrome) and global tissue hypoxia (GTH) ,a decrease in oxygen utilization leading to anaerobic metabolism . Various inotropic agents are chosen to support the vulnerable myocardium for haemodynamic stability and contractility especially in the early post operative period after cardiac surgery. However these drugs are limited by significant increases in myocardial oxygen consumption, pro arrhythmias and neuro hormonal activation. Lactic acidosis along with tachycardia following cardiopulmonary bypass surgery are indicative of inadequate organ perfusion .The resulting hypoxia is usually associated with clinical evidence of insufficient oxygen delivery which is associated with poor prognosis. Levosimendan is a calcium sensitizer which exerts its inotropic effect by increasing sensitivity of Ca^{+2} at the contraction site. Unlike the other traditionally used inotropes it does not increase intracellular concentrations of free calcium, but binds to cardiac troponin C in a calcium dependent manner and stabilises without increasing the total myocardial energy demand and oxygen consumption.

***Key word**: Off-Coronary Artery Bypass Grafting(OP-CABG), Lactic acidosis, Left ventricular dysfunction, Levosimendan, Dobutamine*

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I. Introduction:

Coronary artery bypass graft surgery (CABG) was first performed in India in 1975 about 13 years after its advent in 1962. The first successful Off Pump CABG (without the use of CPB) was performed in 1961. Despite the multiple ongoing debates regarding the superiority or inferiority of off-pump coronary artery bypass grafting, it is shown to decrease the inflammatory response caused due to CPB. In the early postoperative period after cardiac surgery, the heart is in a vulnerable state ,recovering from ischemia and hemodynamic instability due to it's frequent displacement and manipulation during CABG. This is more significant in patients with compromised LV function. During this period of transient myocardial dysfunction, inotropic agents are usually chosen for hemodynamic support. Traditionally used inotropic agents such as Epinephrine, Dobutamine, and Dopamine are limited by significant increases in myocardial oxygen consumption, pro arrhythmias, or neurohormonal activation. These agents should be used judiciously particularly, after CABG since these drugs can aggravate the consequences of ischemia and it has been demonstrated that ischemia and evolving myocardial infarction account for a large proportion of patients with postoperative heart failure . Levosimendan is a calcium sensitizer which exerts its inotropic effect by increasing sensitivity of Ca^{2+} in the contraction site. It does not increase intracellular concentrations of free calcium but binds to cardiac troponin C in a calcium dependent manner and stabilises it. The cardiac performance and contractility are significantly improved with no increase in the total myocardial energy demand and oxygen consumption. The potential for arrhythmia is also

reduced as total intracellular calcium levels are not raised. Lactic acidosis following cardiopulmonary bypass surgery and tachycardia is indicative of low cardiac output syndrome, and the resulting hypoxia is usually associated with clinical evidence of insufficient oxygen delivery, which is associated with poor prognosis. So we planned a randomized prospective study at our institute with an aim to compare the haemodynamic effects and immediate postoperative outcomes with levosimendan and dobutamine in patients with moderate to severe LV dysfunction undergoing off-pump coronary artery bypass grafting (OPCAB) using Blood lactate and as an index of adequacy of oxygen delivery to the tissues which in turn indicates the postoperative outcome of the patients.

II. Aims And Objectives:

To compare hemodynamic effects in the immediate post-operative period and the outcomes with Levosimendan and Dobutamine in patients with moderate left ventricular dysfunction undergoing Off-pump coronary artery bypass grafting. Post-opreative hemodynamic stability was measured with the following parameters, heart rate, blood pressure and serum lactate.

III. Material And Methods:

This prospective observational study, after acquring approval from the ethics committee was conducted on 60 patients with moderate Left Ventricular dysfunction posted for Off Pump Coronary Artery Bypass Grafting at NRI Medical College and hospital. Patients were randomly divided into two groups of 30 each –

•Group L received Levosimendan at 0.1 µg/kg/min, and Group D received Dobutamine at 5 µg/kg/min .

Inclusion criteria:

-Age between 30 and 65 years of either sex

- Patients with moderate Left Ventricular dysfunction scheduled for OP-CABG(EF 35%-45%)

Exclusion criteria:

-Patients with EF <35%,& EF >45%.-Patients on pre-operative ventilation and on ionotropic support and with co-existing valvular heart disease.

-Emergency/re-do CABG,patients with severe COPD/renal failure and patients not consenting for study.

Procedure:- All the patients included in the study had a standardized anaesthesia technique as per our cardiac anaesthesia unit protocol, a balanced anaesthesia technique with midazolam (0.05-0.1mg/kg),ethomidate (0.1-0.3mg/kg), or propofol(1mg/kg) with fentanyl(5-10mcg/kg) and non depolarising muscle relaxants (rocuronium or vecuronium) and sevolurane were used for induction of anaesthesia. Anaesthesia was maintained with air, oxygen and sevoflurane with incremental doses of fentanyl and muscle relaxant. Central venous pressure monitoring along with radial and Femoral Arterial cannulation were performed for invasive artery pressure monitoring and for Arterial Blood Gas sampling respectively .The heart rate and mean arterial pressure (MAP) was monitored continuously and the MAP was maintained between 50-60mm of Hg during the surgery. Noradrenaline, nitroglycerine and dobutamine were added to attain the desired hemodynamics. Milrinone was added if there was impaired left or right ventricular function or pulmonary artery hypertension. The study drug levosimendan and dobutamine was diluted in such a way that equal infusion rates was achieved for comparable patients and was started 10 min after induction and was continued for 24 hrs into post-operative period. Postoperatively all the patients were shifted to the cardiothoracic icu where they were electively ventilated and continous monitoring of hemodynamic parameters and arterial blood gas analysis were done at regular intervals. Serum Lactate levels were taken preop and at 1,6,12,24 hrs after shifting to ICU. The blood samples were drawn from an intra arterial catheter and the lactate values were obtained from standard arterial blood gas analyser. The hemodynamic effects and immediate postoperative outcomes with Levosimendan and Dobutamine was compared and serum lactate levels were used as indicator of adequate tissue perfusion. Heart rates and Mean Arterial Pressures in both the groups were noted at baseline ie before anaesthetic induction and in the immediate postoperative ICU at 1st ,6th,12th and 24th hours and the results were analysed.

IV. Results:

Table 1: EJECTION FRACTION

EF%	DOBUTAMINE	LEVOSIMENDAN
31-35	5	6
36-40	10	10
41-45	15	14
TOTAL	30	30

The EF% of both groups were comparable with referenve to range distribution. Group D had a mean of 42.1 with SD of 1.88 and Group L had a mean of 41.93 withSD of 2.14,P value is 0.70.

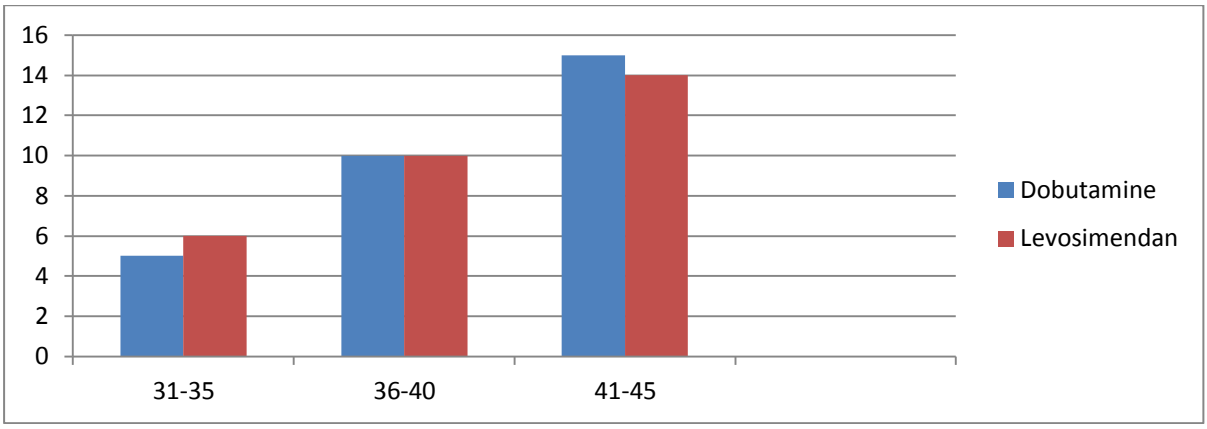


Table: 2 NUMBER OF GRAFTS

NUMBER OF GRAFTS	Dobutamine	Levosimendan
Two	6	5
THREE	24	25
TOTAL	30	30

The number of graft anastamosis in both the patient groups was comparable with P value being 0.74.Group D had a mean of 2.80 with SD of 0.40 and Group L had a mean of 2.83 with SD of 0.37.

TABLE 3: HEART RATE AT VARIOUS TIME INTERVALS

HEART RATE	DOBUTAMINE	LEVOSIMENDAN	P-VALUE	STANDARD DEVIATION	SIGNIFICANCE
BASELINE	75.93	75.26	0.209	2.03	NOT SIGNIFICANT
PO-1ST HOUR	92.76	79	<0.001	2.05	SIGNIFICANT
PO-6ST HOUR	93.63	79.53	<0.001	2.26	SIGNIFICANT
PO-12THHOUR	94.4	79.66	<0.001	1.89	SIGNIFICANT
PO-24THHOUR	95.43	80.76	<0.001	2.15	SIGNIFICANT

In our study heart rates from base line and different time intervals in the postoperative ICU period were noted. No significant difference in both the groups of baseline values were noted, however in the postoperative settings the heart rates in group D were higher compared to group L, the P value of heart rate in postoperative periods was <0.001indicating the difference was highly significant.

Table 4: SERUM LACTATE AT VARIOUS TIME INTERVALS

	DOBUTAMINE	LEVOSIMENDAN	P VALUE	STANDARD DEVIATION	SIGNIFICANCE
BASE LINE	1.07	1.05	0.205	0.05	Not Significant
PO -1 st HOUR	3.49	2.55	<0.001	0.43	Significant
PO-6 th HOUR	2.99	1.93	<0.001	0.35	Significant
PO-12th HOUR	2.33	1.9	0.001	0.31	Significant
PO-24 th HOUR	1.51	1.08	<0.001	0.12	Significant

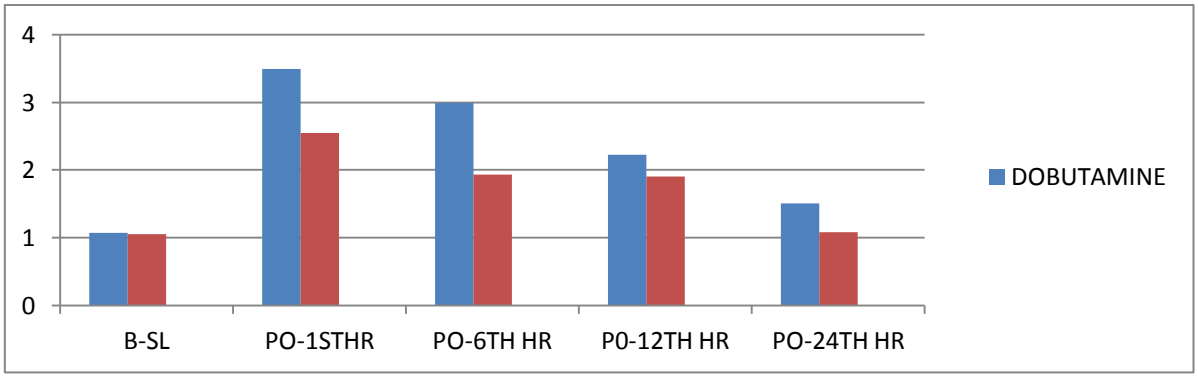


Table 5: MEAN ARTERIAL PRESSURES AT VARIOUS TIME INTERVALS

MEAN ARTERIAL PRESSURE	DOBUTAMINE	LEVOSIMENDAN	P VALUE	STANDARD DEVIATION	SIGNIFICANCE
BASE LINE	85.13	84.86	0.749	3.21	Insignificant
PO -1 st HOUR	75.2	63.33	<0.001	2.55	Significant
PO-6 th HOUR	76.1	65.63	<0.001	2.13	Significant
PO-12th HOUR	76.23	66.1	<0.001	2.18	Significant
PO-24 th HOUR	77.83	69.13	<0.001	2.65	Significant

The group L had lower MAP in the postoperative time intervals requiring additional ionotropres.

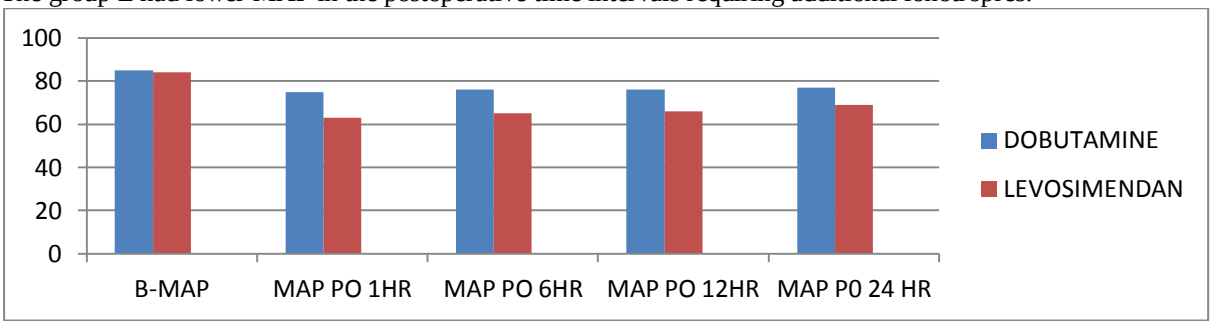
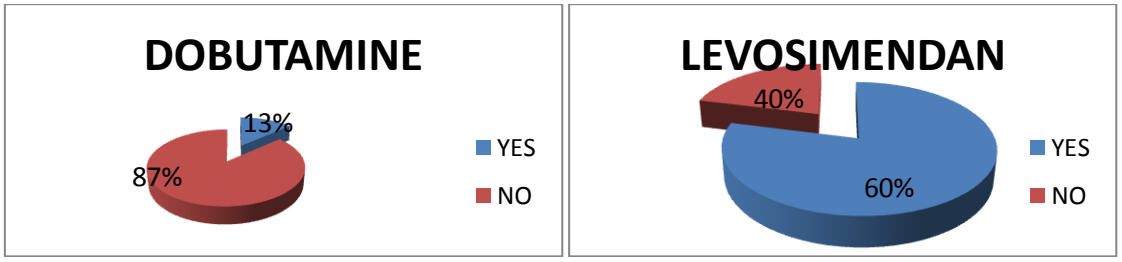


Table 6:ADDITIONAL INOTROPES

INOTROPES	DOBUTAMINE	LEVOSIMENDAN
YES	4	12
NO	26	18



V. Discussion:

Coronary artery bypass grafting (CABG) could be performed as on pump CABG or as off pump CABG. Each method has its own set of merits and demerits. Several studies have shown beneficial effects of avoiding cardiopulmonary bypass. These are reduction in duration of mechanical ventilator support, length of intensive care unit stay and total in hospital stay. The degree of myocardial injury as assessed by biochemical markers is much less after OPCAB when compared to CABG. In a retrospective study involving 17,000 patients undergoing OPCAB and ONCABG, Mack MJ et al[9] concluded that following OPCAB the degree of myocardial injury is much less. Al-Ruzzeh S et al[10] . Shennib H et al[11] and Ascione et al[12] have demonstrated that the degree of myocardial injury is lesser after OPCAB in patients with impaired LV function.Various inotropes are used to maintain intraoperative hemodynamics each having their own set of merits and demerits.

Dobutamine is most often the first-line inotrope administered. Its principal action is on β1-adrenergic receptors, with lesser stimulation of β2- and α adrenergic receptors. This drug predominantly enhances ventricular contraction and slightly decreases vascular tone[15](decreases pulmonary and systemic vascular resistance) resulting in, increase in stroke volume, cardiac output; without significantly increasing heart rate. This favorable effect is associated with increased DO2 and coronary blood flow due to an improved coronary perfusion pressure and direct vasodilation of the coronary arteries. However Inspite of its varied beneficial effects and studies postulating its merits, due to its β1 adrenergic effect causing tachycardia and hence increase in myocardial work load and oxygen demand in an already failing myocardium , this can have detrimential effects .

Levosimendan is a novel calcium sensitizer, which has inotropic effect by increasing sensitivity of Ca2+ at the contraction site. Levosimendan improves myocardial contractility without increasing intracellular

cyclic Adenosine Monophosphate (cAMP) or Ca2+ concentration[17] . But levosimendan does not affect heart rate and increase myocardial oxygen consumption. In addition, the inotropic effect of levosimendan is not affected by β blockers, so that levosimendan can be used accompanied by β blockers. Short-term use of levosimendan has been shown to cause rapid dose-dependent improvement in hemodynamics and symptoms in patients with decompensated heart failure[1,3]. González et al found that levosimendan improved haemodynamic parameters in critically ill patients with reduced LVEF . A hemodynamic improvement (increase in cardiac output and decrease in PCWP) was associated with a lower mortality at one- and six-months with levosimendan compared to dobutamine[2]. Hence in our study we compared the effects of levosimendan and dobutamine to asses hemodynamic stability and post operative outcomes in patients posted for OFF-PUMP CABG.

Lactate is the end product of anerobic glycolysis. Serum lactate level increases in states of cellular hypoxia or low peripheral perfusion; thus, serum lactate level is considered a surrogate of cellular perfusion[19] . Therefore in our study we compared the serum lactate levels in patients of both our study groups levosimendan and dobutamine at preoperative and at 1 st,6th,12th and 24th hour after shifting to post operative ICU to asses adequacy of organ perfusion. The pre-induction baseline value was not statistically significant having a p value of 0.205 with a standard deviation of 0.05. The serum lactate levels taken at the 1st,6th,12th and 24th hour after shifting to the post operative ICU showed a statistically highly significant difference with the levosimendan group having a lower value than the dobutamine group with p value of <0.001 during the post-operative period.

A similar study was conducted by Kandasamy et al[4] in moderate left ventricular dysfunction patients undergoing off pump coronary artery bypass grafting which showed lower levels of serum lactate in the levosimendan group when compared to the dobutamine group. In our study we also compared the heart rates of patients in both the groups taken preop and at 1st,6th,12th and at 24th hour after shifting to the postoperative ICU. The baseline heart rates of the patients taken before induction of anaesthesia in both the groups was comparable and not statistically significant with a p value of 0.20 with a standard deviation of 2.03. However in the postoperative period at 1st,6th,12th and 24th hour in the ICU patients in the levosimendan group had statistically significant lower heart rates with a p value of <0.001 than patients in the dobutamine group.

A similar finding of significantly lower hearts were found in the patients of levosimendan group compared to dobutamine group in the study conducted by kandasamy et al[4]. Mean arterial pressure was measured in our study groups at baseline, just before anaesthetic induction and at 1st, 6th,12th and 24th hour after shifting to post operative ICU. The baseline values in both levosimendan and dobutamine groups was comparable and not significant with a p value of 0.749 with a standard deviation of 3.21. However in the postoperative period at 1 st,6th,12th and 24th hour in the ICU patients in the levosimendan group had statistically significant lower mean arterial pressures with a p value of <0.001 than patients in the dobutamine group.

According to Nieminen M S et al [21S] in their research article on Levosimendan current data ,clinical use and future development most of the studies in the regulatory clinical development of levosimendan comprising of about 3500 patients was compared the infusion of levosimendan has consistently been shown to enhance left ventricular performance and to decrease left ventricular filling pressure , without increasing myocardial oxygen consumption. The haemodynamic and neurohumoral improvement is associated with a symptomatic benefit that is sustained and superior to placebos used in various studies. In contrast to dobutamine, the effects of levosimendan are not attenuated with concomitant beta-blocker use. In addition to contractility increasing effects, levosimendan has profound vasodilatory effects.

Clinical studies have indicated that levosimendan should be given cautiously to patients with low blood pressure, especially in case of hypovolaemia. In our study patients in levosimendan group had significantly lower blood pressures needing additional inotrope. In group L 40% needed additional inotropes whereas in group D only 13.3% of the patients needed additional support.

LIMITATION OF STUDY

Though there are various studies showing that serum lactate levels are a good indicator of tissue perfusion , this alone is inadequate in assessing the tissue perfusion.. Mixed Venous Oxygen Saturation and Cardiac output monitoring devices would better indicate perfusion status of tissues, placement of the PA catheter in all patients is not cost effective.

VI. Conclusion:

The results of our study show that Levosimendan is superior to dobutamine in patients with moderate left ventricular dysfunction undergoing cardiac surgery in terms of decreased serum lactate levels- there by indicating better perfusion, decreased heart rate- myocardial oxygen demand and work load is reduced.

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