

# Pre-Operative Prophylactic Levosimendan for on Pump Coronary Artery Bypass Grafting in Patients with Low Ejection Fraction

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**Abstract:** Background: On pump CABG is associated with more complete revascularization as compared to OPCAB but due to the use of CPB Machine it is associated with severe Inflammatory Response eventually leading to adverse effects, especially in patients with low ejection fraction & appropriate selection of Inotropes plays a very important role in perioperative management of these patients. Aim & Objective: To study the effects of Levosimendan when it is used prophylactically in perioperative period in patients with low ejection fraction undergoing On Pump CABG. Material & Method: After Institutional ethics Committee approval and obtaining written informed consent, 60 patients undergoing elective On Pump CABG were randomly divided into two groups (n=30 each). Group A patients were started on Injection Levosimendan Infusion @ 0.1 µg/kg/min in operation theatre & hemodynamic parameters such as Heart Rate, Invasive Blood Pressure, Pulmonary Capillary Wedge Pressure (PCWP), Cardiac Index (CI), Pulse Oximetry, Nasopharyngeal Temperature Capnography, Urine Output & Arterial Blood Gas including Serum Lactate were monitored at T<sub>0</sub> (baseline), T<sub>1</sub> (15 mins after OM & PDA anastomoses), T<sub>2</sub> (at end of surgery), T<sub>3</sub> (6 hrs after surgery), T<sub>4</sub> (12 hrs after surgery), & T<sub>5</sub> (24 hrs after surgery). Results: In group A CI was significantly higher & PCWP was significantly lower compared to group B. In group B there was significantly reduction in MAP at T<sub>1</sub> & there was also a significantly number of patients who developed Acute Kidney Injury compared to group A. Group A patients had lower number of POAF, lesser need for IABP, compared to group B. Conclusion: Inpatients with low ejection fraction who are undergoing On Pump CABG, Prophylactic preoperative Levosimendan is associated with decreased hemodynamic perturbations & are associated with favorable clinical outcome.

**Keywords:** OM: Obtuse Marginal, PDA: posterior Descending Artery, LCOS: Low Cardiac Output Syndrome, POAF: Post Op atrial Fibrillation

## 1. Introduction

The main stay of treatment in patients suffering from coronary artery disease (CAD) for prolonging survival and improving quality of life is coronary artery Bypass Grafting (CABG). CABG is associated with lower mortality rate when compared to medical treatment after 5 yrs. (10.2% mortality for CABG Vs. 15.8% mortality for medical treatment P≤0.001) after 7 yrs (15.8% VS 21.7% P≤0.001) and after 10 yrs (26.4% VS 30.5% mortality P≤0.05)(2).

There are two modalities of performing CABG, On Pump CABG and Off Pump CABG (OPCAB). Both have their advantages and disadvantages. On Pump CABG is associated with more complete revascularization as compared to OPCAB (88.3% to 79.2% P=0.002)(3). Secondly OPCAB is associated with under grafting of distal anastomosis as compared to On Pump CABG (2.6±1 to 3.1±1 P≤0.001)(4). Because of incomplete revascularization patients requiring more than 3 grafts should be treated with On Pump CABG(5).

However on Pump CABG is associated with systemic inflammatory response syndrome (SIRS) because of the use of Cardiopulmonary bypass machine (CPB) which leads to inflammatory effects like renal dysfunction, gastrointestinal distress and cardiac abnormalities(6). All these changes are exaggerated in patients with low ejection fraction which is the main risk factor for post-operative low cardiac output syndrome (LCOS)(7).

Therefore to maintain an optimal hemodynamics pharmacological intervention is required to provide a better clinical outcome. The options which are available includes conventional inotropes such as beta Agonists and phosphodiesterase Inhibitors but they are associated with tachycardia and arrhythmia which is associated with increased myocardial demand (8).

Here Levosimendan plays an important role. Levosimendan is a calcium sensitizer, the mechanism of action is to increase the myocardial contractility without increasing O<sub>2</sub> consumption by sensitization of troponin C to calcium thereby leading to activation of ATP – selective potassium channel in smooth muscle fibers which leads to systemic, pulmonary and coronary arterial and venous vasodilation(9). It also possesses lusitropic action and has peripheral vasodilatory action and potential preconditioning effect (10). Apart from these effects levosimendan also has immune modulatory, cardio protective (11), Anti-stunning(12), Anti-ischemic (13), Anti-inflammatory and anti-oxidant effect (14) which helps to improve cardiac performance in presence of ischemia.

All these favorable pharmacological cardio protective actions of Levosimendan make it an ideal inotrope in patients with low ejection fraction. Therefore we instituted Levosimendan preoperatively in patients with low ejection fraction to achieve the desirable effects to mitigate the hemodynamic side effects so as to provide a better clinical outcome after on pump CABG. Therefore the main aim of the study was to assess the hemodynamic parameters and

clinical outcome by using Levosimendan prophylactically in the preoperative period, in patients undergoing On Pump CABG.

## 2. Material & Method

After Institutional Ethics Committee approval and obtaining written informed consent, 60 patients undergoing elective on pump CABG were randomly divided into two groups (n=30 each) namely Levosimendan (group A) & control (group B) group. Randomization was done using computer-generated random code. The study was carried out between November 2017 & July 2018. Patients between the age group of 50 to 75 yrs of age with Ejection Fraction  $\leq 30\%$  which was determined preoperatively by Transthoracic Echocardiography were included in the study. Patients who were undergoing Emergency CABG, Redo CABG & combined CABG were excluded from the study.

Group A & group B patients were shifted to the operation theatre & under local anesthesia intravenous access, Radial arterial cannulation & femoral arterial cannulation were performed. Both the groups underwent standard anesthesia Induction with Fentanyl (5  $\mu\text{g/kg}$ ), Etomidate (2 mg/kg), & Rocuronium (1 mg/kg), following which Swan-ganzcatheterization (Edward Life Science) for pulmonary artery pressure monitoring was performed. Continuous cardiac output monitoring using Flotrac Sensor (Edward life Science, LLC, Irvine, USA) was done. Base line hemodynamic parameters (T0) were noted at this time.

Group A patients were started on Injection Levosimendan infusion @ 0.1  $\mu\text{g/kg/min}$  under continuous hemodynamic monitoring. Infusion were continued even during the CPB period & was continued for 24 hrs, when the Mean Arterial Pressure (MAP) went to  $\leq 60$  mm of Hg, vasopressors were added. Group B patients received conventional Inotropes/vasopressors (Dopamine  $\pm$  Noradrenaline  $\pm$  Adrenaline) intra operatively.

In both the groups after Induction of anesthesia, Anesthesia was maintained with  $\text{O}_2$ air/sevoflourane & injection Vecuronium (0.02 mg/kg) was administered intermittently for Neuro-muscular blockade. All the patients were continuous monitored for heart rate, invasive blood pressure, pulmonary capillary wedge pressure (PCWP), Cardiac index (CI), pulse oximetry, nasopharyngeal temperature, capnography, urine output and arterial blood gases which also included serum lactate levels.

The sequence of anastomosis in both the groups was firstly left internal mammary artery (LIMA) to left anterior descending artery (LAD) anastomosis, then distal anastomosis of obtuse marginal (OM) and posterior descending artery (PDA) followed by proximal anastomosis of these grafts to the aorta. Hemodynamic parameters were measured at interval T0(baseline), T1(15 min after OM +/-

PDA anastomoses) ones the clamps were off and proximal anastomosis were on with the side biters in place, T2 (at the end of surgery), T3 (6hrs after surgery) T4( 12hrs after surgery) and T5 (24hrs after surgery).

Once the extubation criteria's were met, patients were extubated in ICU. Incidence of arrhythmia, acute kidney injury, length of ICU and hospital stay, LCOS were noted and were taken as short term clinical outcomes. Three criteria's were used to define LCOS firstly CI of  $<2.2\text{L/min/m}^2$ . Secondly a PCWP of  $>16\text{mm}$  of hg and finally a partial pressure of arterial oxygen less than 60 mm of hg. Increase in serum creatinine level by  $>50\%$  from base line was considered to be acute renal failure.

## 3. Statistical Analysis

Data analysis was done by using SPSS (statistical Package for Social science) . All continuous data were analysed by student's "t" test, Chi Square test, Fisher's exact test and Mid P exact test were applied for categorical data. P value of  $\leq 0.05$  was considered statistically significant

## 4. Results

The mean age group, weight, height, nature of disease and surgical characteristics of both the groups were comparable.

Parameters	Group A	Group B	P
Age (yrs)	66.67 $\pm$ 7.03	65.17 $\pm$ 5.72	0.36
Weight (kg)	69.37 $\pm$ 5.86	72.56 $\pm$ 7.29	0.24
Height(cms)	165.4 $\pm$ 7.49	165.4 $\pm$ 8.28	0.59
Sex( female/Male)	9/21	7/23	0.55
Ejection fraction	25.17 $\pm$ 5.49	25.5 $\pm$ 4.42	0.25
Duration of surgery (min)	234.83 $\pm$ 25.40	231.33 $\pm$ 23	0.60
Pre-existing renal Disease	1/30	0	0.15
Single Vessel disease	1/30	2/30	0.5
Double Vessel disease	8/30	6/30	0.48
Triple Vessel disease	21/30	22/30	0.73

Baseline hemodynamic parameters were comparable in both the groups. In group A patients CI was significantly higher at all-time intervals during and after surgery whereas PCWP was significantly lower in group A patients during surgery and in early post-operative period. In group B patients there was significant reduction in MAP at T1 interval as compared to group A. In group A patients lactate concentration were lower during most of the intra and post-operative period (Table 2). In group B most of the patients developed acute kidney injury who were managed with IV fluids and diuretics and few required hemodialysis whereas in group A no patients developed acute kidney injury. Post operative atrial fibrillation and need for IABP was high in group B patients when compared to group A patients . However there was no difference between the groups when it came to stay in ICU and hospital (Table3)

**Table 2:** Demographic characteristic and general clinical characteristic

Time	Group	HR	MAP	PCWP	CI	Lactate
Time 0	group A	75.8±7.06	89.13±6.06	15±2.47	2.11±0.16	1.75±0.36
	group B	76.86±8.31	91±7.22	15.5±1.96	2.14±0.23	1.81±0.57
	P	0.56	0.28	0.38	0.55	0.68
Time 1	group A	91.3±9.47	72.03±6.51	15.4±2.51	2.31±0.27	4.14±1.41
	group B	83.73±5.7	83.13±7.01	13.2±2	2.97±0.4	3.23±0.54
	P	0.0004*	≤0.0001*	≤0.0001*	≤0.0001*	0.001*
Time 2	group A	91.33±7.09	78.5±7.39	13.72±2.28	2.87±0.51	3.47±1.14
	group B	85.33±6.58	86.66±4.91	12.01±1.57	3.25±0.47	2.52±0.41
	P	0.001*	0.64	≤0.0001*	0.003*	<0.0001*
Time 3	group A	84.33±9.59	85.57±7.87	12.72±2.20	3.04±0.49	2.83±0.77
	group B	85.23±7.55	85.06±5.47	11.51±1.75	3.69±0.44	2.48±0.38
	P	0.68	0.77	0.03*	<0.0001*	0.03*
Time 4	group A	83±9.20	79.43±6.47	12.6±1.45	3.34±0.51	2.31±0.52
	group B	83.66±5.33	84.5±5.5	11.11±1.11	3.89±0.31	2.33±0.36
	P	0.73	0.01*	0.002*	≤0.0001*	0.86
Time 5	Group A	86.5±8.14	82.2±5.81	12.18±1.63	3.59±0.51	1.96±0.29
	group B	83.4±6.02	87.8±4.99	11.9±1.3	3.96±0.29	1.72±0.25
	P	0.09	0.0001*	0.06	0.001*	0.001*

P<0.05 (students unpaired & test) HR: Heart Rate, MAP : Mean Arterial Pressure; PCWP : pulmonary Capillary Wedge Pressure, CI : Cardiac Index

**Table 3:** Peri-Operative Adverse Effects

Parameters	Group A	Group B	P
IABP requirement	1/30 (3.33)	3/30 (10)	0.61
LCOS	2/30 (6.67)	9/30 (30)	0.02*
Post-operative AF (%)	2/30 (6.67)	11/30 (36.67)	0.01*
Serum Creatinine at day 1 (mg/dl)	1.51±0.24	1.60±0.27	0.22
AKI (%)	2/30 (6.67)	7/30 (23.33)	0.04*
Nor adrenaline requirement (%)	23/30 (77)	14/30 (47)	0.01*
ICU Stay	3.00±0.62	3.27±0.76	0.14
Hospital Stay	7.00±1.06	7.27±1.01	0.31

P ≤ 0.05 : IABP : Intra-aortic Ballon Pump, LCOS : Low Cardiac Output Syndrome; AKI : Acute Kidney Injury; ICU : Intensive Care Unit

## 5. Discussion

On pump CABG is associated with more complete revascularization as compared to OPCAB, however On-pump CABG is associated with systemic Inflammatory Response Syndrome due to the use of CPB Machine, which leads to adverse clinical outcome. Our study has shown a favorable hemodynamic response when Levosimendan was used in terms of decreased incidence of LCOS which was reflected by decreased PCWP & Increased CI, this further reflected reduced serum Lactate levels which indicated good micro-circulation at peripheral tissue level.

In the immediate post-operative period, the incidence of post-operative Atrial Fibrillation, Acute Kidney Injury, need for hemodialysis, requirement of IABP was much lesser in the Levosimendan group when compared to the control group & these effects of Levosimendan are attributed to its beneficial effects like Cardio protective Immunomodulation [11] anti stunning [12], anti-Ischemic [13], anti-Inflammatory & anti-oxidant effects [14], which helps to improve cardiac performance.

Several studies have found shorter ICU & hospital stay In patients who were given Levosimendan injection as compared to patients who received Prophylactic IABP(15). However in our study there was no difference in terms of ICU & hospital stay.

## 6. Conclusion

We found that when Levosimendan is used prophylactically preoperatively in patients undergoing On pump CABG it significantly Improve the CI, decreases the PCWP thereby decreasing the incidence of LCOS. It also decreases the incidence of post-operative atrial fibrillation & Acute Kidney Injury, all these leading to favorable clinical outcome

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