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# Levosimendan - A Better Option than Dobutamine to Improve Haemodynamics in Patients

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ABSTRACT

**Background and Aims:** Patients of severe mitral stenosis with low cardiac output state are difficult to wean off from cardiopulmonary bypass without inotropic support. The inotropic agents like beta adrenergic agonists and phosphodiesterase inhibitors are effective in weaning from Cardiopulmonary bypass (CPB) but they increase the oxygen demand by increasing cyclic AMP (cAMP) and calcium level. Levosimendan a calcium sensitizer improves the cardiac performance without increasing intracellular calcium and cAMP level.

**Methods:** Sixty patients were randomized to receive Levosimendan 0.1 microgram/kg/min by an infusion pump in group A and Dobutamine 5 microgram/kg/min in group B after CPB. Haemodynamics were recorded at 30 min, 6 h, 12 h & 24 h. Requirement of inotropes was also noted in both the groups.

**Results:** The Cardiac Output (CO), Cardiac Index (CI), Stroke Volume (SV) were high in the Levosimendan group as compared to the Dobutamine group even at 24 h which was statistically significant. The mean arterial pressure was significantly lower in the Levosimendan group as compared to the Dobutamine group at 30 min, 12h and 24 h post CPB. After 24 h, CO was 5.7 l/min in the Levosimendan group and 5.1 l/min which is statistically significant (p value 0.02).The levosimendan group required more of inotropic support. Student t-test was used to compare the data.

**Conclusion:**Levosimendan improved the haemodynamics as compared to Dobutamine in patients undergoing mitral valve replacement with severe mitral stenosis.

**Introduction:**

Patients undergoing cardiac surgery especially mitral valve replacement with severe stenosis have left ventricular dysfunction and can present a difficult situation to come off from cardiopul monary bypass.[1,2]

Inotropic support is required to improve the ventricular functions post bypass but these inotropes increase the myocardial oxygen consumption, which leads to cardiac ischemia and further damages the myocardium and causes arrhythmias.[3,4,5]

Levosimendan an inodilator & calcium sensitizer increases the sensitivity of myocardial contractile protein to calcium resulting in positive inotropy. It is characterized by a triple mechanism of action[6,7] i.e. it acts via binding of calcium to Troponin C and opens the K- ATP channels on smooth muscle cells in the vasculature & in cardiac mitochondria. Binding of Levosimendan to Troponin C & opening of K-ATP channels on smooth muscle cells in the vessels cause inotropic and vasodilatory effects. Opening of K-ATP channels in cardiac mitochondria causes cardioprotection.[8,9,10]

The study was done to compare the haemodynamic effects of Levosimendan and Dobutamine in mitral valve replacement (MVR) in mitral stenosis patients measuring heart rate (HR), mean arterial pressure (MAP), central venous pressure(CVP), cardiac index (CI), cardiac output (CO), systemic vascular resistance(SVR), systemic vascular resistance index (SVRI), and stroke volume (SV) . We. also compared the lactate levels, inotropic requirement and post-operative atrial fibrillation outcome in both the groups .Our study is comparable to other studies done prior but different in the results obtained when comparing the variables like SV, heart rate, and lactate levels.

**Methods:**

The study was conducted after due permission from the ethics committee & review board of the hospital. Written informed consent was taken from all the patients. Patients were kept nothing by mouth overnight. This study was hospital based, randomized, comparative, interventional, double blinded study. Blinding was done by an anaesthesia resident not included in the study, who prepared the study drugs and covered the syringes and tubing with a black tape. Computer generated randomization was done. Sample size was calculated to be 30 patients in each group of the two groups assuming alpha error 0.05 and power 80% with minimum detectable difference of mean arterial pressure after weaning from cardio-pulmonary bypass 4.66 with standard deviation 6.28. Mean arterial pressure (MAP) was the primary variable in our study because maintaining BP after bypass is important to bring the patient back from Cardiopulmonary bypass, hence we calculated sample size with MAP as primary outcome variable. Patients included were having mitral stenosis (valve area<1.5cm2) between the age group of 20-60 years. Patients having mitral regurgitation, other valvular pathologies, renal dysfunction (S. Creatinine> 2mg / dl), undergoing combined mitral valve surgery with CABG , re-do mitral valve surgery or re-exploration for surgical causes were excluded.Pre-anaesthetic checkup was done prior to surgery. Trans-thoracic echo before surgery was done by the cardiologist with given values of the valve area, pulmonary artery pressure and ejection fraction. Intra-operative values were obtained from the haemodynamics which were recorded from the Flo-Trac sensor (Edwards Lifesciences). In the OT 18G peripheral venous cannula was inserted in the right antecubital vein. All patients were started with Ringer lactate solution. Five lead ECG, pulse oxymetry, invasive monitoring of BP via femoral artery cannulation were done. IJV cannulation was done into right internal jugular vein. Baseline readings of MAP, HR, CVP, CO, CI, SVRI, SVR, SV& Lactates level were measured. Patients after oxygenation were induced with inj midazolam (0.15mg/kg), inj Fentanyl (3µg/kg), inj Etomidate (0.3mg/kg),inj Rocuronium (0.9mg/kg) and intubated with ETT tube of

appropriate size. Surgery was performed on cardiopulmonary bypass (CPB) with cold blood cardioplegic cardiac arrest. At separation from CPB group A received infusion of Levosimendan 0.1microgram/kg/min & group B received Dobutamine 5 microgram/kg/min via infusion pump. In both the groups HR, CVP, CO, CI, SVR, SVRI, MAP & blood lactate levels were recorded at baseline, after induction, after CPB, 30 min, 6 h, 12h & 24 h. Requirement of inotropes was also noted in both the groups as per the MAP, CI & SVRI values. We started these inotropes at the end of weaning period when MAP was not maintained between 60 to 90 mm Hg. Additional inotropes were tapered postoperatively according to the haemodynamics.

Statistical analysis- All data was entered on excel sheet. The data were normally distributed. The statistical analysis was carried out using statistical package for social sciences (SPSS Inc., Chicago, IL, version 20.0 for windows). Parametric data were analysed using unpaired t- test. Qualitative or categorical variables were compared using chi- square test. All statistical tests were performed at a significance level of $\alpha = 0.05$.

There is no conflict of interest by the authors in this study.

**Results:**

Sixty patients for elective mitral valve replacement having severe mitral valve stenosis were enrolled and randomized to one of the two study groups. Patient characteristics, demographic data, pre-operative echocardiography findings, pre op AF, pre op Pulmonary artery systolic pressure, cardio- pulmonary bypass time and aortic cross clamp time were also noted.

In our study the demographic data was comparable and did not show any statistical significance as shown in table 1. The mean value of the valve area was0.9cm2 with S,D of +-0.3 and p value of>0.8 which was insignificant statistically.

In our study Levosimendan caused a slight increase in the heart rate which was not statistically significant as compared to Dobutamine. There was a decrease in the CVP post bypass till 24 h in the Levosimendan group as compared to the Dobutamine group but was statistically insignificant. As shown in table 3the mean arterial pressure was significantly lower in the Levosimendan group compared to Dobutamine group at 30 min, 12 h and 24 h post CPB.

There was increase in the cardiac output(CO) after 30 min post CPB in the Levosimendan group 7.8± 2.3 l/min as compared to Dobutamine group 5.9 ± 1.8 l/min which was statistically significant with a p value of 0.003. The cardiac output remained elevated at 6 h and 24 h post CPB in the Levosimendan group as compared to Dobutamine and was statistically significant.

The cardiac index (CI) was increased in the Levosimendan group after 6 h post CPB & was statistically significant as compared to the Dobutamine group. Stroke Volume (SV) increased after 6 h in the Levosimendan group & was statistically significant.

Levosimendan decreased SVR to a maximal decrease of 772.0 ± 226 dyne-s-m2/cm5(versus 950 ± 332.0 for Dobutamine group). Stroke Volume increased to a maximal of 80.3 ± 29.3 ml/beat after 30 min post CPB in Levosimendan group as compared to 64.5±19.5 in the Dobutamine group.

Serum lactate levels were raised in both groups but significantly higher level was seen in the Dobutamine group compared to Levosimendan immediately after bypass and 30 minutes later. This difference was not seen at 6 h post CPB or later.

A total of 13 patients required inotropic support in the levosime ndan group. While 10 patients required support in the Dobutamine group. Five out of 30 patients required adrenaline in both the groups. Nor-adrenaline was required in 8 patients of Levosimendan group and 5 patients of Dobutamine group. These values were not statistically significant (p value>0.05).

In our study there was no hypotension or ventricular tachycardia. Six patients in the Levosimendan group and five patients in the Dobutamine group had atrial fibrillation. But post operatively within the study period there was no atrial fibrillation in both the groups. Pre bypass the AF was treated with beta blockers and calcium channel blockers but could not be reverted. Since the heart rate was maintained between 60-90/ min the AF did not hamper the cardiac output and cardioversion was not attempted.There were no other adverse reaction and no deaths occurred. Duration of ventilation, ICU stay were similar in both the groups and were not significant.

**Discussion:**

The main findings of this study are the haemodynamic changes i.e HR, MAP, CO, CI, & SV after a short period of Levosimendan infusion (after aortic cross clamp removal) on CPB as compared to Dobutamine and a decrease in SVR, SVRI, Lactate levels & CVP. We observed significant statistical difference in short time in the clinical outcomes in between the two groups.

Our study showed an increase in the heart rate (HR) in contrast to Gandham et al[11] but was consistent to the study of Julian et al[12]as compared to Dobutamine. Our study was also in contrast to the study done by Falloth et al[13] and Mara T Slawsky6 in which HR did not increase at the lowest infusion rate. While there was no change in the HR according to MattiKivikhoet al.[14]

Cardiac output increased in our study in the Levosimendan group which was similar in the study by Follathet al.13 Our study was similar to the results of Stefan et al[15] which also showed an increase in cardiac output.

Our study showed a decrease in the SVR (systemic vascular resistance) in the Levosimendan group than Dobutamine group and was consistent with the study of Follath et al13and Mara T.Slawsky.[6]

The increase in cardiac index (CI) is attributed to increase in stroke volume. At the end of 6 h infusion there was increase in CO, SV, CI and this was almost sustained till 24 h. This observation suggests that the haemodynamic effects of Levosimendan are maintained for 24 h and according to Matti Kivikko the effects are maintained for at least 48 h which is beneficial in cardiac surgery patients with low postoperative ejection fraction. According to HLeppikangas, Jarvelaet al[15]CI and SI were increased for four postoperative days when Levosimendan infusion was used.

In our study Levosimendan increased the CO, SV & CI which leads to the conclusion that it improves myocardial contractility by enhancing myocardial protein contraction sensitivity to calcium without increasing its intracellular concentration. Because of this action the myocardial oxygen consumption is not increased. Increase in stroke volume reflects a decrease in LV after load.

In the decompensated low output patients Levosimendan has the upper hand over the other inotropic drugs, which include prolonged drug effect after single infusion, without any arrhythmias and absence of drug induced myocardial ischemia.13Levosimendan improves cardiac performance in Left ventricular failure patients from acute coronary artery syndromes.[8,16]

However SVR also decreased indicating arterial dilatation. According to Hidea Tachibana, HenjJiecheryet al[17]Levosimendan produces arterial vasodilatation, improves LV relaxation and diastolic filling, increases contractility. It is safe & effective in altering clinical outcomes.

Kirsten Jorgensen et al[18] studied the effects of Levosimendan on LV relaxation and systolic performance and showed an improvement in LV relaxation i.e it has positive lusitropic effects in patients with LV hypertrophy.

Greater inotropic support required by the Levosimendan group showed arterial vasodilation caused by it.

Pulmonary artery pressure is important in mitral stenosis which were recorded preoperatively and post-operatively by the cardiologist because of lack of a TEE machine and it was not feasible to put PA catheter in all the patients. This was a big limitation of our study. There was a decrease in the PA pressure in the Levosimendan group but was not statistically significant.

Atrial fibrillation occurs in 40-75% of patients who are symptomatic for MS, and precipitation of symptoms , increases the risk of systemic embolisation and decreases the cardiac output.19 In severe MS because of the stenotic mitral valve the left atrium gets stretched and enlarged which may lead to this irregular rhythm. Because of AF there is an increase in the ventricular rate which in turn causes a decrease in diastolic filling time and increase in left atrial pressure.The ventricular rate can be slowed acutely by the administration of intravenous beta-blockers/ calcium channel blockers, digoxin , amiodarone or via electric cardioversion. In our study a total of eleven patients had pre-operatively AF in both the groups and the number remained the same post surgery. Intra-operatively we used beta-blocker/ calcium channel blockers which caused a decrease in the ventricular rate so the hemodynamics were maintained, Cardioversion was tried in some patients but it really did not change the pattern.

Additonal inotropes were required more in the Levosimendan group than the Dobutamine group.The inotropes were started when the patients were coming off bypass after reducing the flows gradually and the adequate MAP were not maintained.The inotropes were given for 1-2 days in the post operative period depending on the maintenance of the vital parameters and clinical conditions of the patients.

Lactate levels were lower in the Levosimendan group as compared to the Dobutamine group thus indicating better tissue perfusion in the Levosimendan group due to the vasodilatation seen with it even though the inotrope requirement was more in this group. Studies have shown that Levosimendan administration after rewarming from DHCA as compared to Epinephrine led to a significantly better preservation of myocardial ATP control as well as energy change & to a reduction in plasma lactate concentration.[20]

In our study the LVEF>50% in both the groups .. The length of ICU and hospital stay were the same in both the groups. The patients were shifted from the ICU on 4th day and from the hospital on the 8th day. Tasauli et al used Levosimendan infusion at an early start intropreratively which was associated with a short ICU stay (21). Since 1998, there have been lot of studies of Levosimendan being used in cardiac surgery patients.[22] In most of these studies , Levosimendan was started after cardiac surgery due to low cardiac output syndrome [23] or during CPB weaning in the case of severe LV dysfunction. Only a few studies focused on the use of Levosimendan before CPB.[24] De Hert et al[25] compared Levosimendan with milrinone in the patients with LVEF of less than 30% using levosimendan without loading dose and started immediately after aortic cross clamp release in fixed combination with Dobutamine. The main hemodynamic findings of De Herts study was better preservation of SV after surgery in Levosimendan treated patients.[8]

Vigileo/Flo Trac system (Edwards lifesciences) determines cardiac output, without calibration by analysis of the arterial pulse wave.To assess the accuracy it was compared with the pulmonary artery catheter bolus thermodilution method and came to the conclusion that the described deviation from the standard must be regarded according to the need of the user. Considering the 30% limits of agreement the vigileo system (version 1.01) seems sufficiently accurate; applying the 20% criteria it is not.

**Conclusion:**

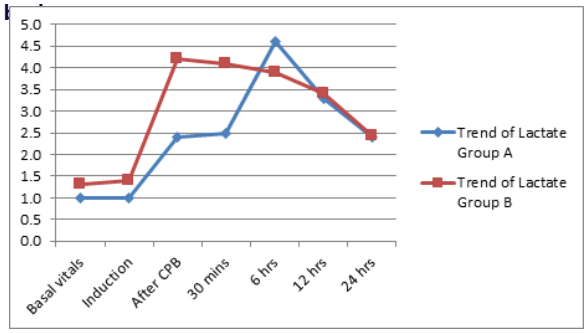
The present study demonstrates that Levosimendan in low doses causes an improvement in the hemodynamic function in patients undergoing mitral valve replacement after CPB. So it may be of value in the short term treatment of patients with LV dysfunction after mitral valve replacement. As compared to Dobutamine, Levosimendan maintained the haemodynamic parameters better in mitral valve replacement patients by better preserving the stroke volume, cardiac index and the lactate levels.

**Table1.Demographic data and clinical parameters**

| | Group A-Levosimendan | | Group B-Dobutamine | | P value btw groups |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| No of patients | 30 | | 30 | | |
| Age (Yrs) | 40.0 | 11.7 | 39.0 | 12.7 | 0.5900 |
| Sex | | | | | |
| Women | 15 | | 17 | | |
| Men | 15 | | 13 | | |
| Weight (Kg) | 45.1 | 8.1 | 44.9 | 10.3 | 0.9200 |
| Height (Cm) | 166.0 | 9.2 | 160.0 | 9.7 | 0.0590 |
| Body surface area (m2) | 1.47 | 0.118 | 1.4 | 0.88 | 0.2100 |
| Valve area (cm2) | 0.9 | 0.3 | 0.9 | 0.3 | 0.8200 |
| LVEF (%) | 52.8 | 10.4 | 55.3 | 8.4 | 0.4200 |
| CPB time (mins) | 57.9 | 15.2 | 60 | 17.7 | 0.6900 |
| Cross clamp time (mins) | 40.7 | 13.3 | 42.2 | 11.6 | 0.7300 |
| Ventilation (hrs) | 8.42 | 1.8 | 7.67 | 2.0 | 0.2200 |
| ICU stay (days) | 2.83 | 1.1 | 2.9 | 0.3 | 0.7700 |
| Pre- op AF | 6 | 5 | | | |

S.D- Standard deviation, PASP- Pulmonary artery, CPB- Cardiopulmonary bypass

**Graph 1. Graph showing trend of Lactate level (mmol/l) in**




Lactate levels significantly lower in group A compared to group B just after CPB (2.4±1.2 vs 4.2±1.3, p value -0.0001) and 6hrs post bypass (2.5±0.8 vs 4.1±0.9, p value- 0.0001).

**Table 2. Table showing HR, MAP, CVP at baseline, after induction, after CPB, 30min, 6hr, 12hr, 24hr thereafter.**

| Time | HR (beats/min) | | MAP (mm Hg) | | CVP (mm Hg) | |
|---|---|---|---|---|---|---|
| | Group A | Group B | Group A | Group B | Group A | Group B |
| Basal | 86.9±21.9 | 94±17.9 | 87.3±10.5 | 84.5±16.9 | 9.1±4.4 | 8.7±3.4 |
| Induction | 90.5±18.4 | 104±29.7 | 81.6±12.4 | 80.5±15.9 | 10.6±3.5 | 8.6±3.1 |
| After CPB | 87±17.5 | 88.4±16.3 | 64.5±11.2 | 66.2±12.9 | 10.1±4.2 | 9.2±4.3 |
| 30 min | 100±18.1 | 91.3±13.3 | 71.2±12.6 | 79.8±10.2 | 5.2±2.6 | 6.5±2.2 |
| 6 hr | 95.3±13.7 | 86.8±8.6 | 74±11.9 | 79.8±10.2 | 4.9±2.7 | 6.8±2.7 |
| 12 hr | 88.8±11.2 | 86.8±7 | 71.2±12.6 | 79.8±10.2 | 5.3±2.6 | 6.5±2.2 |
| 24 hr | 87.7±9.7 | 86.9±11.7 | 73.0±8.8 | 80.2±10.8 | 6±2.7 | 6.5±2.5 |

**Table 3. Table showing CI, SVRI, SV at baseline, after induction, after CPB, 30min, 6hr, 12hr, 24hr thereafter.**

| Time | CI (l/min/m2) | | SVRI (dyne-s-$m^2/cm^5$) | | SV (ml/beat) | |
|---|---|---|---|---|---|---|
| | Group A | Group B | Group A | Group B | Group A | Group B |
| Basal | 4.1±1.7 | 3.6±1.1 | 1715±624 | 1818±535 | 70.2±23.8 | 54.1±16.9 |
| Induction | 4±1.5 | 3.5±0.9 | 1617±665 | 1775±467 | 64.6±20.9 | 49.3±14.9 |
| After CPB | 3.3±1 | 4.1±2.1 | 1413±454 | 1244±473 | 57±17.6 | 63.6±25.7 |
| 30 min | 5.3±1.5 | 4.4±2.1 | 1136±330 | 1359±451 | 80.3±29.3 | 64.5±19.5 |
| 6 hr | 4.4±1.3 | 3.4±0.7 | 1361±458 | 1756±365 | 68.7±19.7 | 54.5±10.1 |
| 12 hr | 3.2±0.7 | 3.3±0.8 | 1732±527 | 1852±374 | 53.5±13.9 | 54±14.1 |
| 24 hr | 3.9±0.8 | 3.7±0.8 | 1423±308 | 1681±387 | 65.4±10 | 59.2±12.1 |

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