Comparsive study of levosimendan versus milrinone for paediatric cardiac surgery patients operated with cardio-pulmonary bypass

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ABSTRACT

BACKGROUND: Our aim is to check effectiveness of intravenous Levosimendan in comparison with intravenous Milrinone in congenital heart surgery with cardiopulmonary bypass. MATERIALS AND METHODS: 50 Paediatric patients between 2 months to 12 years of age divided into two groups. Group L (n=25) received inj. levosimendan 12µg/kg over 10 minutes¹ after cross clamp removal and 0.1µg/kg/min started after that. Group M (n=25) received inj. milrinone 50µg/kg of bolus dose over period of 10 minutes and 0.5 µg/kg/min infusion thereafter. Both the group received inj. dopamine 5-8 µg/kg/min from beginning. Inj. noradrenalin 0.1µg/kg/min added as rescue drug for persistent hypotension. The drugs compared for hemodynamic (including echocardiography parameters), respiratory parameters (including ABG), fluid requirements, urine output, temperature monitoring and also for routine laboratory investigations (including platelet count) postoperatively. Time taken for extubation after shifting the patient was also observed. Both the groups were compared for side effects and need of additional ionotropic support, anti-arrythmic drug or other medication-intervention requirements. RESULTS: Milrinone has more effect on vascular resistance. PVR reduced more in comparison with levosimendan with improved RV function. Milrinone has good effect on RV function. Milrinone had more hypotensive episodes and incidence of renal dysfunction than levosimendan. Levosimendan has more effect on LV contractility and better effect on PCWP. Levosimendan maintains hemodynamics better than milrinone. CONCLUSION: Levosimendan has better hemodynamic profile and lesser complication rate than milrinone. Keywords: Levosimendan, Milrinone, Paediatric cardiac surgery, cardiopulmonary bypass.

INTRODUCTION

Cardiopulmonary bypass (CPB) is associated with clinically asymptomatic (elevated CK-MB) to symptomatic myocardial injury. Oxygen and ATP deprivation and/or reperfusion injury following cross clamp removal are associated with myocardial insult. Myocardial stunning or hibernation cause post CPB low cardiac output. Post CPB ionotropic support is needed to counter hemodynamic instability resulting from cardiac insult. Most of the ionotropes used till now increase cardiac contractility by increasing intracellular calcium level, which ultimately increases myocardial oxygen consumption and demand and may worsen the situation.¹ Levosimendan, a pyridazinone-dinitrile derivative, belongs to new class of Ca²⁺ sensitizers. It binds to troponin-C in a Ca²⁺-dependent way and facilitate the Ca²⁺-induced conformational change of troponin-C necessary for activation of the contractile proteins.² Slowing of cardiac relaxation is a potential adverse effect subsequently increases cardiac contractility. Milrinone vasodilates vessels which help to alleviate increased afterload on the heart, thus improving its pumping action³. Milrinone enhances the effects of catecholamines, which also increase cAMP concentrations through beta-adrenergic stimulation⁴. So our aim of this study is to check effectiveness of intravenous levosimendan versus milrinone in paediatric patients posted for cardiac surgery.

MATERIALS AND METHODS

After approval from the institutional ethical committee, parental informed & written consent, this prospective randomized double blind study was carried out over a period of last four years. 50 patients aging between (2-12 years) scheduled for correction of congenital heart defect were included in our study.

Inclusion criteria:
1. Patients posted for on pump cardiac surgery–Septum premium ASD (Atrial septal defect), VSD (Ventricular septal defect), TOF (Tetrology of fallot’s), ASD with Pulmonic Stenosis, VSD with PS, unobstructed TAPVC (Total anomalous pulmonary venous connection) and PAPVC (Partially anomalous pulmonary venous connection), Atroentricular

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Canal defect, ALCAPA (Anomalous left coronary artery from pulmonary artery), type I & II Ebstein’s anomaly, DCRV (Double chamber right ventricle), Glenn’s surgery.

2. Paediatric cardiac surgery in which probable maximum aortic cross clamp time 60 to 90 minutes.

Exclusion criteria:
1. Pre-operative renal impairment.
2. Pre-operative hepatic impairment.
3. History of anaphylactic reaction to levosimendan or milrinone.
4. Cardiac defects needing prolonged cross clamp time for repair.
5. Thrombocytopenia.
6. History of arrhythmia or torda de pointes.
7. Cardiac defects which shows inflow or outflow residual obstruction by TEE while coming off bypass.
8. Patients who require prolonged ventilation after shifting also excluded from the study.
9. Patients with preoperative prolonged QTc and postoperative myocardial ischemia by ECG.

After detail pre-anæsthetic evaluation, routine and specific investigations, parents were informed regarding the type of study. Preoperative adequate fasting hours (8 hours) were confirmed and baseline vital parameters (pulse rate, blood pressure, respiratory rate, temperature), ECG, SpO2 were recorded. All the patients were given premedication inj. glycopyrrolate 10µg/kg, inj. midazolam 0.05 mg/kg iv. and inj. ranitidine 1 mg/kg iv. Inj. ketamine 2 mg/kg iv. used for non-cooperative paediatric patients. All the patients were induced in usual manner by using inj. fentanyl 10 µg/kg iv., inj. midazolam 0.1 mg/kg iv., inj. vecuronium 0.2 mg/kg iv. followed by maintenance with inj. fentanyl 2 to 5 µg/ /kg/hour, inj. midazolam 5 µg /kg/min, inj. vecuronium 0.2 mg/kg/hour and O₂-air-Isoflurane. Arterial pressure monitoring & cvp line inserted, TEE probe inserted in to oesophagus after induction. Now 50 patients were randomly allocated into two groups. Group L (n=25) received inj. levosimendan 12 µg/kg iv. Over 10 minutes after cross clamp removal followed by 0.1 µg/kg/min. Group M (n=25) received inj. milrinone 50 µg/kg of bolus dose over period of 10 minutes and then 0.5 µg/kg/min infusion. Both the groups received inj. dopamine 5-8 µg/kg/min after cross clamp removal. During the study, patients of both groups received same cardioplegia solution and we adopted same strategy for myocardial protection during cross clamp for both the groups. We tried to maintain haemoglobin around 10 gm% post surgery. PA pressure monitoring was done by PA line inserted through atrial septum by surgeon which is inserted via femoral venous route at time of induction and was kept in RA. TEE (Transoesophageal Echocardiography) used in all patients. Both the group will be studied for following parameters. Patients will be monitored intra-operatively for ECG, heart rate, mean arterial pressure, PAP. TEE data like stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), pulmonary capillary wedge pressure (PCWP), compared for both the group. Respiratory parameters (Respiratory rate and PaO₂), urine output, laboratory investigations such as S.creatinine level, platelet counts, troponin i level (0,12,24 hours) and serum lactate level (0,24 hours), fluid requirements intra and post operative were also monitored in both the groups. After the surgery, patients were monitored for the above said parameters in the post operative period at interval of 0,6,12,18 and 24 hours after shifting to SICU. Both study drugs along with dopamine were stopped average 24-48 hours after shifting to SICU from operation theatre.

Statistical analysis: All data were analyzed statically using T-test and a value of P<0.05 was considered significant. All the data was presented as mean ± S.D. and percentage. Data was analyzed using computer software called as Graph pad-prism V.6.0.

RESULTS
A total of 50 patients were recruited for the study. There were no significant differences between the two groups in demographic data and duration of surgery (Table 1).

Table 1: Demographic profile

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group L n=25</th>
<th>Group M n=25</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4.1 ± 1.3</td>
<td>4.0 ± 1.5</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>17 ± 1.9</td>
<td>16.5± 1.7</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>16/9</td>
<td>17/8</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>258.6 ± 27.2</td>
<td>250.4 ± 23.4</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

NS – Non Significant     S- Significant

In both the groups ECG was compared, group L showed no significant changes in ECG pattern which we can attribute to the drug, while group M showed average PR interval of 0.11 sec which is minimally shortened. In M group three patients developed sustained VT which had to be reverted pharmacologically or by cardio version. Ventricular extra systoles were seen in 2 patients of group M.
Figure 1: Change in heart rate and mean arterial pressure

Figure 2: Change in PCWP and PAP

Figure 3: Change in cardiac output

- Stroke volume in group L increases from baseline of average 26 ml to 34 ml after maximum effect achieved while in group M it increases from 28 ml to 30 ml when peak effect is achieved.
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Figure 4: Change in SVR and PVR

![Graph showing Change in SVR and PVR](image)

Figure 5: PaO2 and respiratory rate

![Graph showing PaO2 and respiratory rate](image)

PaO2: in mmHg. Respiratory rate/minute

Table 2: Side effects and complications

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group L (n=25)</th>
<th>Group M (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache/Irritability</td>
<td>4 (16%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (8%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>2 (8%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Altered RFTs</td>
<td>1 (4%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Elevation of S. Aminotransferase</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
</tbody>
</table>

We have also observed significant thrombocytopenia (platelet <0.3 lacs) in 12% patients in group M. All these patients were managed with PRC. Platelet count came back within normal range after stopping of Milrinone. It is a drug profile of Milrinone which is causing more arrhythmia than leovsimendan. Raised serum aminotransferase to 58-60 IU/ml was noted in one patient in group L. It was on downward trend from 4th day of discharge from cardiac recovery.

Table 3: Perioperative and postoperative outcome measures

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group L</th>
<th>Group M</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheal Extubation time (hour)</td>
<td>5.4 ± 0.9</td>
<td>7.6 ± 1.2</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Requirement of Nor epinephrine</td>
<td>1 (4%)</td>
<td>10 (40%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Urine Output (ml/kg/hr)</td>
<td>1.17 ± 0.12</td>
<td>0.82 ± 0.08</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Serum Creatinine level raised</td>
<td>1 (4%)</td>
<td>4 (16%)</td>
<td>-</td>
</tr>
<tr>
<td>Troponin I level</td>
<td>0.72 ± 0.02</td>
<td>0.86 ± 0.05</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Serum Lactate level</td>
<td>2.48 ± 0.14</td>
<td>2.64 ± 0.13</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Length of stay ICU (hours)</td>
<td>76.3 ± 5.9</td>
<td>102.9 ± 7.7</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>-</td>
</tr>
<tr>
<td>ECMO Support (sent to higher centre for eco)</td>
<td>0</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
</tbody>
</table>

One death registered in group L because of residual defect while three cases in group M. Those three were because of residual defect, acute kidney injury requiring dialysis, ARDS requiring ECMO support.

DISCUSSION

Myocardial dysfunction following CPB commonly occurs in patients with good preoperative ventricular function. Following separation from CPB, ventricular function improves initially, then begins to worsen and reaches a nadir between 4 and 6 hours after surgery with full recovery occurring around 24 hours postoperatively. However, in patients with preoperative ventricular dysfunction, the depression of ventricular function is more severe and recovery is longer. The most common factors correlating with the need for inotropic or vasoactive support at the time of CPB separation are low EF, cardiomegaly, prolong CPB and aortic cross clamp (ACC). Ventricular function reduces in as much as 96% of patients following CPB. Low cardiac output syndrome (LCOS) has been defined as the inability to wean off CPB despite maximal support with a low cardiac index (<2.0-2.5 l/min/m²) and evidence of end-organ dysfunction (e.g., urine output < 0.5 ml/kg/h). The prevalence of LCOS ranges from 0.2% to 6% and leading to increased postoperative morbidity and mortality, increasing hospital length of stay, resource utilization, and overall costs. In earlier studies, levosimendan was started from the beginning of the cardiac surgery as prophylactic agent but we have started levosimendan after removal of the cross clamps because yet interaction of levosimendan with CPB has not been studied fully. Milrinone is already accepted as ionotropic agent as single agent or with other ionotropes in weaning from CPB. Efficacy of milrinone in treating LCOS is already established. CPB is associated with constricted renal circulation. Efficacy of dopamine in improving renal plasma flow is well established. Choudhury M. et al showed increase in renal flow by 17% by...
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dopamine following CPB. We have used dose of dopamine 5-8 µg/kg/min and avoided dose more than it because guller et al.\textsuperscript{15} showed increased arrhythmia with dopamine above 10 µg/kg/min. We have included 60-90 minutes of cross clamp time surgery in our study because prolonged cross clamp time causes low cardiac output, prolonged ventilation time, renal complications, prolonged hospital stay, blood transfusion and increased mortality\textsuperscript{25}, so it becomes difficult to assess whether any pathology is due to drug under study or it is the effect of prolonged cross clamp time. Renal and liver disease patients excluded from our study because milrinone is metabolized 12% in liver and 80% in kidney\textsuperscript{17}. Levosimendan causes torsi de pointes so we have excluded it as well\textsuperscript{18}. P. Malliotakis et al.\textsuperscript{19} has mentioned no change in heart rate and slight reduction in mean arterial pressure (MAP) with levosimendan while in our study we have noticed slight increase in heart rate and MAP which can be combined effect of levosimendan and dopamine or may be sole effect of dopamine. In our study, levosimendan causes less increase in heart rate than milrinone and less reduction of SVR than milrinone. This ultimately leads to better hemodynamics. In group L increase in stroke volume is significant in comparison with group M. So increase in cardiac output is much significant in group L than group M. Improved stroke volume with better hemodynamics causes more fall in pulmonary capillary wedge pressure (PCWP) in group L than group M\textsuperscript{20}. In our study, group L showed 20% reduction in PVR while group M showed around 45% reduction in PVR. Givertz MM et al\textsuperscript{21}. Showed similar results in his study with maximal effect achieved 5-10 minutes after bolus injection of milrinone causing around 35% reduction in PVR. More reduction in PVR causes better emptying of right ventricle (RV) and reduces RV oxygen requirement. Victor G et al\textsuperscript{22}. demonstrated that RV dysfunction occurs frequently in patients with LCOS and is associated with a high in-hospital mortality rate. So, milrinone is quite effective in reducing mortality by reducing pulmonary artery pressure in patients of RV dysfunction. Transthoracic catheter is placed by surgeons directly into the pulmonary artery at the time of re-warming on CPB. Its advantage is tip location is assured by direct vision and disadvantage is there is low risk of cardiac tamponade when these catheters are removed percutaneously.\textsuperscript{23} Group M had 40% cases of hypotension requiring norepinephrine infusion out of these 28% had mean arterial blood pressure below 55 mmHg which were considered as severe hypotension which is significant as well. Group L had one patient of hypotension requiring norepinephrine. We have observed lower troponin I and serum lactate level in group L which is suggestive of its myocardial preconditioning effect which remained consistent with previous studies as well. Previous studies also demonstrate that pre-treatment with levosimendan in patients undergoing surgical myocardial revascularization resulted in less myocardial injury, a reduction in tracheal extubation time, less requirement for inotropic support, and a shorter length of ICU stay. De Hert et al\textsuperscript{24} compared levosimendan with milrinone in the patients with LVEF of less than 30% used without loading dose and started immediately after aortic cross-clamp release in fixed combination with dobutamine. In our study, we have used dopamine instead of dobutamine in a fixed dose thus we have observed lesser requirement of norepinephrine compared to previous studies. Kidney injury incidence rate is 3-8% after CPB, due to combined effects of hypothermia and reduced MAP causing release of angiotensin, renmin, catecholamine, this circulatory hormones cause renal vasoconstriction and reduce renal blood flow. In our study, we have observed low urine output in group M that leads to increase in serum creatinine level. Out of 16% patient, 8% had raised serum creatinine that had norepinephrine infusion started, as nor epinephrine itself causes raised serum creatinine level. Prophylactic levosimendan use lowers length of hospital stay and 30-day mortality in previous studies as well. In our study also, length of ICU stay was significantly lower in group L (p<0.05) thus it reduces cost and provides better patient outcome as well. Metabolites of levosimendan OR-1855 and OR-1896 are formed slowly, and their maximum concentrations are seen on average 2 days after stopping a 24-hour infusion. In our study, we have not studied effect of metabolites of levosimendan which has mild effect of parent drug and it was not feasible to continue the study as we start removing the intra-arterial and central venous line once patient is stable\textsuperscript{25}.

CONCLUSION
Levosimendan has better hemodynamic profile and lesser complication rate than milrinone. Loading dose of levosimendan followed by infusion gives excellent results with satisfactory hemodynamics than milrinone.

Acknowledgement
We are thankful to our patients and we express our gratitude towards our surgical team. We are thankful to the entire cardiac unit for their support.

REFERENCES