Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(5) (Part - II): 1756-1765
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6519.38

Comparison of Levosimendan vs. Milrinone in Pediatric Cardiac Surgery

Nirav Parikh[1], Vikram Naidu[2], Ramesh Patel[3], Abhishek Sharma[4], Himani Pandya[5]

[1]Assistant Professor, [3]Professor and Head [4]DM Resident, Department of Cardiac Anesthesia, [5]Research Associate, Department of Research, UN Mehta Institute of Cardiology and Research Centre, Ahmedabad, Gujarat 380016, India. [2]Consultant Cardiac Anesthesiologist, Department of Cardiac Anesthesia, Krishna Institute of Medical Science, Hyderabad, Telangana 500003, India.

Abstract

Background: Conventional cardiac surgery involving cardiac arrest and cardiopulmonary bypass (CPB) is well known to be associated with postoperative myocardial dysfunction and low cardiac output syndrome (LCOS). The aim of this study is to compare the effect of prophylactically administered levosimendan and milrinone on postoperative parameters and outcomes in neonates and infants after corrective open-heart surgery and comparing postoperative parameters like heart rate, mean arterial pressure, arterial and venous blood gasses at certain particular points of time. *Method:* We performed a prospective observational study at our institute. Total 100 pediatric patients undergoing complex congenital cardiac surgeries to evaluate the efficacy of milrinone and levosimendan on intraoperative and postoperative outcomes. *Result:* In the postoperative period heart rate and mean arterial pressure at three different time periods (T1, T2 and T3) did not show any statistically significant difference in both the groups. The VIS score after 48 hours was less in Group L (p = 0.0005). Serum creatinine estimated at T2 and T3 showed a statistically significant difference. (p value at T2 = <0.001, p value at T3 = 0.002). Duration of ventilation was less in Group L (p = 0.0297). *Conclusion:* In our prospective observational study of 100 infants undergoing surgery for complex congenital cardiac conditions, postoperative hemodynamic parameters and markers of tissue perfusion overtime were similar in infants with administration of either levosimendan or milrinone. Our results might be the basis of future controlled trials of levosimendan in children with a special focus on duration of mechanical ventilation and the incidence of renal complications.

Keywords: Levosimendan; Milrinone; Cardiopulmonary bypass (CPB); Low cardiac output syndrome (LCOS).

How to cite this article:

Nirav Parikh, Vikram Naidu, Ramesh Patel *et al.* Comparison of Levosimendan vs. Milrinone in Pediatric Cardiac Surgery. Indian J Anesth Analg. 2019;6(5 P-II):1756-1765.

Introduction

Conventional cardiac surgery involving cardiac arrest and cardiopulmonary bypass (CPB) is well known to be associated with postoperative myocardial dysfunction and low cardiac output syndrome (LCOS). A multitude of intraoperative factors are thought to be related to myocardial damage including: (1) type of pump priming solution (2) persistent arrhythmias, especially ventricular fibrillation (3) inadequate myocardial perfusion or protection (4) ventricular distension (5) coronary artery embolism (6) use of catecholamine (7) aortic cross- clamp time, (8) complex surgical repairs (*e.g.*, ventriculotomies) (9) reperfusion following ischemia (10) cardiopulmonary bypass time and

Corresponding Author: Vikram Naidu, Consultant Cardiac Anesthesiologist, Department of Cardiac Anesthesia, Krishna Institute of Medical Science, Hyderabad, Telangana 500003, India.

E-mail: vikramnaidu23@gmail.com

Received on 14.08.2019, **Accepted on** 04.09.2019

(11) subsequent systemic inflammatory response.[1] In addition, some patient-specific factors such as the neonatal myocardium, ventricular hypertrophy, severe cyanosis and pre-existing heart failure ("starving myocardium") affect the susceptibility of the myocardium and propensity for LCOS.[2–4]

The LCOS occurs in up to 25% of young children, even if there are no residual cardiac lesions after surgery[5] and typically occurs between 6 and 18 hours after surgery in a setting of elevated systemic and pulmonary vascular resistances, impaired myocardial function, and arrhythmias.

The LCOS is detected invasively or by signs of inadequate oxygen delivery to the organ systems, e.g. tachycardia, poor systemic perfusion, decreased urine output, elevated lactate, and reduced mixed venous oxygen saturation.[6] If left untreated, LCOS can lead to cardiac arrest, the need for cardiopulmonary resuscitation or extracorporeal life support[7] prolonged mechanical ventilation,[8] a prolonged intensive care stay and increased mortality.[9] Therefore, prevention, early detection, and treatment of postoperative LCOS are paramount. In the adult intensive care setting, cardia output can be measured directly by indicator dilution techniques like thermodilution,[10] by Doppler echocardiography[11] or by arterial pulse contour analysis.[12,13] A cardiac index of <2.2 L/min/m^2 is considered low.[14,15] In children, especially in neonates and infants, it is usually not feasible to employ these techniques due to device sizes, shunts, and other characteristics of cardiovascular physiology[16] as well as poor correlation with tissue oxygen delivery.[17]

With lack of a clear definition, different authors describe various parameters, which are often used as a compound measure. Such a composite parameter for LCOS may consist of several of the following findings:

- Elevated blood lactate or rapid increase in blood lactate[18]
- Decreased central venous oxygen saturation[19] Increase in arterial to central venous oxygen saturation difference
- Decreased urine output[19]
- Increased peripheral skin temperature to core body temperature difference
- Echocardiographic Doppler-derived low cardiac index
- High inotrope requirement[20]

The mainstays of treatment include catecholamine, calcium sensitizers (levosimendan), and phosphodiesterase inhibitors (milrinone).[19]

The aim of this study is to compare the effect of prophylactically administered levosimendan and milrinone on postoperative parameters and outcomes in neonates and infants after corrective open-heart surgery and comparing postoperative parameters like heart rate, mean arterial pressure, arterial and venous blood gasses at certain particular points of time.

Postoperative outcomes were compared in terms of duration of ventilation, VIS (vasoactive inotropic score), intensive care unit stay and tissue perfusion in terms of lactate levels, mixed venous oxygen levels ($SmvO_2$), difference between arterial and venous saturation ($Da\text{-}vO_2$).

Materials and Methods

Study design

We performed a prospective observational study at our institute. Total 100 pediatric patients undergoing complex congenital cardiac surgeries to evaluate the efficacy of milrinone and levosimendan on intraoperative and postoperative outcomes.

Between November 2015 and October 2016 total of 323 complex congenital cardiac surgeries were performed at our institute out of which 100 pediatric patients were included in our study.

The study was approved by our institutional ethical committee. Informed written consent was obtained from the parents or guardians of the patients.

Inclusion criteria

Pediatric patients undergoing surgeries for complex congenital cardiac anomalies.

Cardiac conditions included in our study were:

- d-TGA (D- Transposition of great arteries) with intact interventricular septum
- d-TGA with ventricular septal defect (VSD)
- Double outlet right ventricle with VSD (Taussig-Bing anomaly)
- Total anomalous pulmonary venous connection (TAPVC) (supra cardiac, intracardiac and infracardiac type)
- Atrioventricular canal defect (AVCD) (partial and complete)
- Truncus arteriosus
- AP window (Aorto pulmonary window)

- Anomalous origin of coronary artery from pulmonary artery (ALCAPA)
- Cortriatrium

Surgeries performed in the study population included:

- Arterial switch operation
- TAPVC (Total anomalous pulmonary venous connection) repair
- AVCD (atrioventricular canal defect) repair
- Cortriatrium repair
- ALCAPA (Anomalous origin of coronary artery from pulmonary artery) repair

Exclusion criteria

- Infants and children undergoing closed heart surgeries
- Preoperatively intubated patients
- Preoperative patients in renal and hepatic failure
- Patients with preoperative sepsis and septic shock
- Age more than 6 years
- History of preoperative LCOS
- History of preoperative cardiopulmonary resuscitation
- History of treatment with one of the study drugs within the 4 weeks prior to enrollment.
- Children with tetralogy of Fallot
- Patients with residual atrial or ventricular septal defect in the post-operative echocardiography with the need of reoperation during the first postoperative 48 hrs.

Assessment

Both the groups were compared for intraoperative parameters including CPB time and aortic cross-clamp time.

Postoperative parameters compared in both the groups included:

- Heart rate (at three different time intervals, T1 (1 hour postoperatively), T2 (24 hrs. postoperatively) and T3 (48 hrs. Postoperatively)
- Mean arterial pressure at three different time intervals, T1 (1 hour postoperatively), T2 (24 hrs. postoperatively) and T3 (48 hrs. postoperatively)
- Arterial and venous blood gasses at three different time intervals, T1 (1 hour postoperatively), T2 (24 hrs. postoperatively) and T3 (48 hrs. postoperatively). (pH, PcO_2, Po_2, SaO_2, $SmvO_2$ and lactate levels).
- Vasoactive inotropic score (VIS) measured at three different time intervals, T1 (1 hour postoperatively), T2 (24 hrs postoperatively) and T3 (48 hrs. postoperatively)
- Duration of mechanic ventilation
- Intensive care unit (ICU) stay
- Postoperative morbidity and mortality.

Morbidity in terms of renal outcomes, low cardiac output syndrome (LCOS) was defined as mean invasive arterial BP of less than the 5th percentile (according to the height and age-based nomogram) after achieving an adequate preloading condition, along with any two of the following: arterial lactates >3 mmol/L on two consecutive readings, $ScvO_2$<50% or a decreasing trend, urine output <1 ml/kg/h for two consecutive hours, HR >90th percentile according to the age-based normogram and neurological outcomes were compared in both the groups.

Inotropic score for levosimendan was not designed so the maintenance dose of levosimendan i.e., 0.1 μg/kg/min (as par to the maintenance of milrinone of 0.5 μg/kg/min) was assigned a score of 5.

Additional inotropic support was initiated at the discretion of the senior consultant in charge. To estimate and make the levels of additionally administered inotropes comparable, the inotrope score previously described by Gaies *et al*.[23] was calculated.

Randomization was done by computerized allocation of patients to both the groups. Patients were divided into Group M (n = 50) who received milrinone and Group L (n = 50) who received levosimendan during the intraoperative period and the postoperative period.

Patients were visited in the preoperative period on the previous day.

Postoperative management

Patients were shifted intubated to the ICU. The rate of weaning from mechanical ventilation and the point of time of extubation were determined by the patient's fluid balance and gas exchange, pattern of breathing, and daily radiographic findings. Sedation was not prolonged and extubation was not

delayed for study reasons. Both the study drugs and additional inotrope/vasoconstrictor agents were tapered once the patients were hemodynamically stable and showed no signs of tissue hypoperfusion as assessed by clinical signs and serial arterial and venous blood gasses. Postoperative echocardiography was performed at regular intervals and at any particular instance where the patient showed major hemodynamic changes.

Results

Between November 2015 and October 2016, total 103 patients were assessed for eligibility for the study. Two patients from the milrinone group and one patient from the levosimendan group had to be excluded from the study in view of reoperation for major residual defects. One patient in the milrinone group had moderate left valve regurgitation in the postoperative echocardiography for which he was reoperated and on milrinone group had a residual ventricular septal defect after arterial switch operation for which the infant was reoperated 48 hours later in view of hemodynamic instability. One patient in the levosimendan group had a residual ventricular septal defect detected 24 hr. After arterial switch operation for which the child was reoperated on cardiopulmonary bypass. Remaining 100 infants were randomized and 50 infants allocated to each group.

Categorical variables are presented as numbers and percentages and analyzed using the $\chi 2$ test. Continuous variables are assessed for normal distribution and presented as means and standard deviation. Continuous variables are compared using student's t test for normally distributed variables and the mann-whitney U test fornon-normally distributed variables. The level of significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS, version 20.0 (CHICAGO, IL, USA)

Demographic data

The minimum age included in the study was 3 days and maximum was 2 years. The mean age in group M was 5.07 ± 3.09 months and in Group L was 5.34 ± 4.20 months. Mean weight in Group M was 4.26 ± 1.79 kg and in Group L was 4.59 ± 2.12 kg. The mean height in Group M was 57.8 ± 10.26 cm and in group L was 58.78 ± 11.59 cm. Age (p = 0.715), weight (p = 0.401) and height (p = 0.656) were comparable in both the groups (Table 1).

Table 1: Demographic data

	Group M	Group L	p value
Age (months)	5.07 ± 3.09	5.34 ± 4.20	0.715
Weight (kg)	4.26 ± 1.79	4.59 ± 2.12	0.401
Height (cm)	57.80 ± 10.26	58.78 ± 11.59	0.656

Preoperatively 49 of 50 patients in the milrinone had moderate to severe pulmonary arterial hypertension (PAH) and 48 of 50 patients in Group L had moderate to severe pulmonary arterial hypertension as stated in the 2-D echocardiography by continuous wave Doppler method (Fig. 1).

Procedural characteristics

The duration of cardiopulmonary bypass time in Group M was 111.4 ± 46.43 minutes and in Group L was 125.9 ± 32.6 minutes. The aortic cross clamp time in Group M was 80.88 ± 37.30 minutes and in Group L was 92.12 ± 26.97 minutes. Both the cardiopulmonary bypass time and aortic cross-clamp time showed no significant difference in both the groups (Table 2).

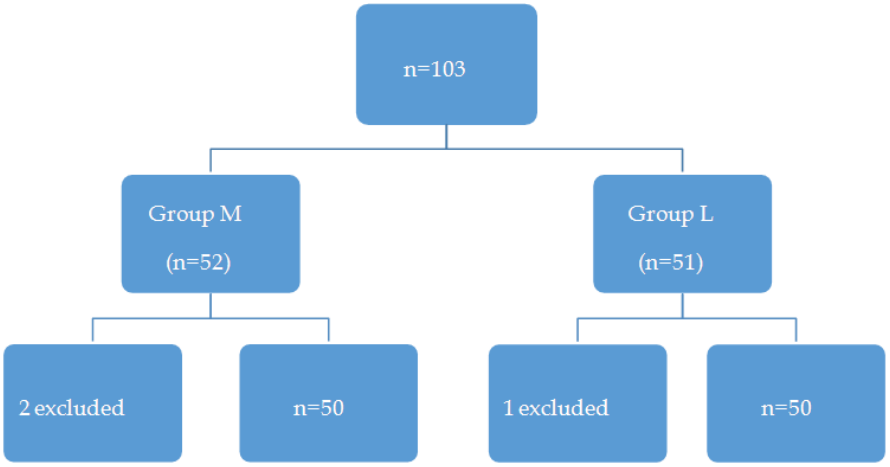

Fig. 1: Comparision of pulmonary hypertension in both the groups

Table 2: Intraoperative Parameters

	Group M	Group L	*p* value
CPB Time (minutes)	111.4 ± 46.43	125.9 ± 32.6	0.1549
AOX Time (minutes)	80.88 ± 37.30	92.12 ± 26.97	0.087

(CPB: Cardio Pulmonary Bypass), (AOX: Aortic Cross Clamp)

Hemodynamic parameters

Both the groups had similar baseline post-induction heart rate and mean arterial pressure. In the postoperative period, as shown in table 3, heart rate and mean arterial pressure at three different time periods (T1, T2 and T3) did not show any statistically significant difference in both the groups.

Table 3: Hemodynamic Parameters

	Group M	Group L	p value
Heart Rate (HR)			
Post Induction HR	137.68 ± 17.21	137.48 ± 16.69	0.953
1 hr PICU HR (T1)	145.76 ± 21.80	145.86 ± 22.65	0.982
24 hr PICU HR (T2)	145.06 ± 19.42	148.54 ± 20.87	0.390
48 hr PICU HR (T3)	142.3 ± 19.24	137.68 ± 21.64	0.262
Mean Arterial Pressure (MAP)			
Post Induction MAP	56.58 ± 9.23	60.46 ± 12.86	0.0862
1 hr PICU MAP (T1)	58.9 ± 12.07	63.82 ± 15.56	0.080
24 hr PICU MAP (T2)	61.5 ± 13.35	60.64 ± 11.86	0.734
48 hr PICU MAP (T3)	59.38 ± 11.67	58.64 ± 8.59	0.718

PICU: Pediatric ICU

Blood gasses

The arterial and venous blood gasses showed a significant difference in the pH in both the groups at T1, T2 and T3. There is no significant difference between arterial and mixed venous oxygen saturation in both the groups at all the time period. (T1, T2 and T3) There was no significant difference between arteriosus and venous serum lactate levels at all time points (Table 4).

Table 4: Comparison of Blood Gasses in Both the Groups

	Group M	Group L	*p* value
DAV			
1 hr PICU DAV (T1)	30.65 ± 11.35	28.74 ± 12.87	0.434
24 hr PICU DAV (T2)	26.27 ± 11.83	22.66 ± 9.01	1.674
48 hr PICU DAV (T3)	20.27 ± 11.14	21.08 ± 6.64	1.576
Arterial Blood Gas			
pH			
ABG 1 hr PICU pH (T1)	7.39 ± 0.06	7.45 ± 0.08	0.009
ABG 24 hr PICU pH (T2)	7.41 ± 0.07	7.40 ± 0.06	0.009
ABG 48 hr PICU pH (T3)	7.40 ± 0.06	7.38 ± 0.06	0.008
PCO_2			
ABG 1 hr PICU PCO_2 (T1)	38.99 ± 7.54	37.07 ± 6.78	1.066
ABG 24 hr PICU PCO_2 (T2)	38.95 ± 6.04	38.51 ± 5.88	0.854
ABG 48 hr PICU PCO_2 (T3)	37.26 ± 7.92	40.88 ± 7.37	1.120
PO_2			
ABG 1 hr PICU PO_2 (T1)	105.57 ± 62.23	131.06± 97.12	8.801
ABG 24 hr PICU PO_2 (T2)	178.62 ± 73.80	206.32± 75.49	10.43
ABG 48 hr PICU PO_2(T3)	167.39 ± 71.53	226.40± 96.03	10.116
SaO_2			
ABG 1 hr PICU SaO_2 (T1)	93.11 ± 11.86	97.03 ± 2.93	1.830
ABG 24 hr PICU SaO_2 (T2)	98.82 ± 1.46	99.14 ± 1.06	0.226
ABG 48 hr PICU SaO_2 (T3)	99.02 ± 1.24	99.17 ± 0.87	0.188
Lactate			
ABG 1 hr PICU Lactate (T1)	4.32 ± 2.87	3.70 ± 2.74	0.405
ABG 24 hr PICU Lactate (T2)	2.12 ± 0.94	2.07 ± 0.98	0.133
ABG 48 hr PICU Lactate (T3)	1.80 ± 1.01	1.83 ± 1.06	0.143
Venous Blood Gas			
pH			
VBG 1 hr PICU pH (T1)	7.34 ± 0.06	7.39 ± 0.07	0.008
VBG 24 hr PICU pH (T2)	7.36 ± 0.071	7.35 ± 0.05	0.010
VBG 48 hr PICU pH (T3)	7.35 ± 0.05	7.34 ± 0.05	0.008
PCO_2			
VBG 1 hr PICU PCO_2 (T1)	49.98 ± 9.09	45.09 ± 7.78	1.285
VBG 24 hr PICU PCO_2 (T2)	47.09 ± 7.35	45.16 ± 6.16	1.040
VBG 48hrs PICU PCO_2 (T3)	47.12 ± 7.22	48.47 ± 5.84	1.021
PO_2			
VBG 1hr PICU PO_2 (T1)	33.60 ± 7.58	35.54 ± 9.19	1.073
VBG 24hrs PICU PO_2 (T2)	42.63 ± 10.19	44.22 ± 8.64	1.441
VBG 48hrs PICU PO_2 (T3)	50.83 ± 24.94	45.26 ± 7.06	3.527
$SMVO_2$			
VBG 1 hr PICU $SMVO_2$ (T1)	62.19 ± 15.82	66.21 ± 12.51	2.441
VBG 24 hr PICU $SMVO_2$ (T2)	72.88 ± 12.50	76.48 ± 9.19	1.929
VBG 48 hr PICU $SMVO_2$ (T3)	79.52 ± 10.51	78.10 ± 6.54	1.585
Lactate			
VBG 1 hr PICU Lactate (T1)	4.37 ± 2.96	4.16 ± 2.48	0.419
VBG 24 hr PICU Lactate (T2)	2.23 ± 1.14	2.20 ± 1.07	0.162
VBG 48 hr PICU Lactate (T3)	1.77 ± 1.07	1.73 ± 0.62	0.152

Inotropic score

At least one catecholamine was administered on the decision of the senior consultant in 49 of the 50 patients in the milrinone group and 48 of the 50 patients in the levosimendan group for treatment of arterial hypotension refractory to fluid replacement or treatment of reduced myocardial contractility in the operation theater after weaning from cardiopulmonary bypass. The use of additional catecholamines, reflected in the vasoactive inotrope score did not differ between the groups in the initial 1 hour of PICU arrival and after 24 hours of PICU arrival (Table 5). An additional milrinone infusion was started after 48 hours in 8 patients in

Group L and in 15 patients in Group M, milrinone infusion was continued because of biologic and/or clinical signs of LCOS persisted. The VIS score after 48 hours showed a significant difference ($p = 0.0005$) between both the groups because of the prolonged action of levosimendan and its metabolite so the drug was weaned within 48 hours in Group L whereas milrinone was continued in Group M even after 48 hours in few patients due to the relatively shorter duration of action of milrinone compared to levosimendan.

Table 5: Comparison of Inotropic Score in Both the Groups

	Group M	Group L	*p* value
1 hr PICU Ionotropic Score (T1)	12.94 ± 4.27	12.24 ± 4.22	0.077
24 hr PICU Ionotropic Score (T2)	9.22 ± 5.16	9.08 ± 6.11	0.901
48 hr PICU Ionotropic Score (T3)	7.16 ± 6.24	4.68 ± 7.59	0.0005

Serum creatinine

Preoperative renal parameters (serum creatinine) showed a significant difference in both the groups. The serum creatinine estimated at T2 and T3 Showed a statistically significant difference. (p value at T2=<0.001, p value at T3=0.002) (Table 6).

Table 6: Comparison of Serum Creatinine in Both the Groups

	Group M	Group L	*p* value
Pre induction Sr. Creatinine	0.462 ± 0.109	0.387 ± 0.098	0.0009
24 hr PICU Sr. Creatinine	0.502 ± 0.097	0.435 ± 0.099	<0.001
48 hr PICU Sr. Creatinine	0.536 ± 0.250	0.408 ± 0.138	0.002

This finding extrapolates to the significant reduction of the incidence postoperative acute kidney injury (6 vs. 16) in Group L.

Postoperative outcomes

The duration of ventilation in Group M was 68.1 ± 56.02 hours and in Group L was 46.26 ± 41.23 hours. Duration of ventilation showed a significant difference ($p = 0.0297$) between both the groups with a reduction of ventilation duration in the levosimendan group. There was no statistically significant difference in the duration of ICU stay in both the groups (Table 7).

Table 7: Comparison of Postoperative Parameters in Both the Groups

	Group M	Group L	*p* value
MVT (hrs)	68.1 ± 56.02	46.26 ± 41.23	0.0297
ICU Stay (days)	8.06 ± 5.74	7.5 ± 3.33	0.5521

MVT: Mechanical ventilation time. ICU: Intensive care unit

ICU Morbidity and Mortality

There was no loss of atrioventricular synchrony or any sustained and serious atrial or ventricular tachyarrhythmia in the 100 patients who finished the study. Eight Patients in the Group L and six patients in the Group M had their chest left open at the end of the surgery. Both drugs were well tolerated in the immediate postoperative period and no serious adverse event occurred throughout the ICU stay. None of the patients needed mechanical circulatory support. Eight patients in Group M had postoperative surgical drainage and were re-explored in the first 12 hours where as two patients were re-explored in the levosimendan group.

Six patients in the milrinone group and ten patients in Group L had low cardiac output syndrome (LCOS) as measured by echocardiography. Sixteen patients in Group M and six patients in Group L had immediate postoperative acute kidney injury which was managed by peritoneal dialysis. Nine versus four patients in Group M and Group L respectively were re-intubated as they could not maintain adequate saturations on conventional oxygen therapy. Four patients in Group M expired in the intensive care unit. Out of the four, two patients developed severe sepsis and septic shock and were hemodynamically unstable even on high inotropic support and later expired. Two patients developed pneumonic patch after extubation and were re-intubated later succumbed to sepsis and expired. Four patients in the levosimendan group expire due to which two developed acute kidney injury and expired and two of them succumbed due to sepsis.

Discussion

Levosimendan improves myocardial contractility without increasing myocardial oxygen consumption, impairing diastolic relaxation, or causing an increase in intracellular calcium concentration.[22,23]

Levosimendan has been extensively evaluated in the adult population[24,25] but has received little attention in the pediatric field in the past and has been gaining greater attention in the last few years.

Due to its mechanism of action through calcium sensitization and its additional inotropic and vasodilator properties, levosimendan might be considered superior to milrinone in prevention and treatment of LCOS after open-heart surgery in children and infants.

We conducted a prospective observational study in 100 infants, who underwent surgeries for complex cardiac conditions on cardiopulmonary bypass and prophylactically received either a loading dose of milrinone (Group M) or levosimendan (Group L) followed by a maintenance dose, immediately after aortic cross clamp removal to evaluate the effect of these inotropic agents on hemodynamics (heart rate, mean arterial pressure), markers of tissue perfusion like lactate, mixed venous saturation, difference between arterial and venous saturations and the effects on postoperative outcomes, duration of ventilation, ICU stay, morbidity (renal, cardiovascular and neurological) and mortality.

In a piglet model, Stocker *et al*.[26] showed that prophylactically administered levosimendan as well as milrinone protected against reduction in CO and prevented from increase in left ventricular afterload early after cardiopulmonary bypass. In this animal model, levosimendan but not milrinone, improved myocardial contractility and led to an increase of CO above baseline. In our study we found no difference in the heart rate and mean arterial pressure in both the groups. The markers of tissue perfusion did not show any statistical difference between both the groups.

In a recently published randomized controlled trial in children after congenital heart surgery, Momeni *et al*.[27] compared the prophylactic use of milrinone against the prophylactic of levosimendan in a small and heterogeneous group of study subjects of various ages with all-age spectrum of diagnoses and different types of cardiac surgery. The primary endpoint, serum lactate concentrations[4] hrs after surgery, did not differ between the groups as was seen in our study. The only statistically significant difference found in the artrial was mean heart rate in the levosimendan group after 24 and 48 hrs. Our findings are consistent with their observations and the difference in the heart rate did not reach significance in our study.

Considering that the quantitative measurement of cardiac index in the pediatric population is limited, most pediatric intensivists use clinical and biochemical signs to support the diagnosis of LCOS. Among biochemical markers routinely used to support the diagnosis of LCOS, the serum lactate level is considered as one of the most important biochemical markers of early adverse outcome after complex congenital cardiac surgery.[28–30]

Duke *et al*.[28] showed that 4 hours after pediatric intensive care unit admission, lactate remained a clinically significant predictor of a major adverse event when greater than 4.5 mmol/L. Our study population did not show any significant difference in arterial and venous lactate levels at all time points in both the groups.

Milrinone and Levosimendan have different pharmacokinetics

Milrinone acts immediately when intravenously administered. The onset of action of levosimendan takes 3 to 4 hrs and exceeds the duration of administration because it acts through metabolites.

This prolonged duration of action of levosimendan led to a significant difference in the postoperative inotropic score at 48 hours (p value = 0.0005). Lecher *et al*.[31] in their study proposed no difference in the inotropic score in both the groups, but the study used the IS score proposed by Wernovsky *et al*.[32]

Two major drawbacks of the IS score proposed by Wernovsky *et al*.[33] were that it neither included milrinone or levosimendan and that it did not include vasopressin in the score which was used in few cases in our study.

In our study vasoactive inotropic score (VIS score) proposed by Gaies *et al*.[33] was used and the usual maintenance dose of levosimendan (0.1 μg/kg/min) was given a score of 5 so as to match the inotropic score of the maintenance dose of milrinone (0.5 μg /kg/min) which in the VIS score had a score of 5. The use of additional catecholamines did not differ between the groups.

To avoid a heterogeneous study population, we intentionally excluded patients with single ventricle lesions and with preoperative myocardial failure.

Our study patients were possibly not sick enough to form a valid study population. One could speculate that in a study population with pre-existing congestive heart failure or more complex cardiac lesions, levosimendan might have been more advantageous due to its inotropic properties and pharmacologic profile.

A further remarkable finding of this study is that levosimendan was very well tolerated and did not cause arterial hypotension, increased heart rate, and increased fluid requirement, or an excessive need of inotropes or vasoconstrictors when administered through a continuous infusion.

Both the groups showed a statistically significant difference in the duration of mechanical ventilation. Serum creatinine measured 24 hrs and 48 hrs Postoperatively showed a significant difference between both the groups likely due to the peripheral vasodilatory effect of levosimendan. The

postoperative renal outcomes showed a significant difference between both the groups with a significant reduction in the incidence of postoperative acute kidney injury in the levosimendan group.

Limitations

Overall, this study and its findings were limited by its small number of included study subjects.

One limitation of our study was the fact that there are currently no pulmonary artery catheters of appropriate size available for infants. Therefore, we could not perform invasive measurement of CO.

We could not include patients with preoperative ventricular dysfunction where the expected effect of levosimendan seems to have better outcome as stated in several adult studies and one pediatric retrospective study.

However, the study demonstrates that levosimendan can be used in children and that its use is associated with an overall trend toward hemodynamic benefit in a critically ill pediatric patient population.

To evaluate the effect on duration of ventilation which is a major contributing factor for the ICU stay larger study population are required.

Further studies are required on the Reno protective effect of levosimendan observed in this study to confirm its effect. This effect of levosimendan can advocate for its utilization in patients with acute kidney injury due to LCOS and or various etiologies in the immediate postoperative period.

Several subsets like premature infants, low-birth weight children, cyanotic heart disease, infants with preoperative ventricular dysfunction and infants with preoperative altered renal parameters have to be evaluated to confirm the superiority of this drug over various available inotropic and indicator agents.

Conclusion

In our prospective observational study of 100 infants undergoing surgery for complex congenital cardiac conditions, postoperative hemodynamic parameters and markers of tissue perfusion overtime were similar in infants with administration of either levosimendan or milrinone.

We observed decrease in the VIS score in the levosimendan group after 48 hrs. Due to the prolonged action of levosimendan and its metabolites compared to milrinone.

Duration of mechanical ventilation was significantly reduced in infants administered levosimendan in the immediate perioperative period.

The renal parameters showed a significant difference in both the groups with a significant reduction in the incidence of postoperative acute kidney injury.

This prospective observational study has primarily serve experience using the new drug levosimendan in neonates and infants and to initiate further multi center trials in pediatric patients.

Our results might be the basis of future controlled trials of levosimendan in children with a special focus on duration of mechanical ventilation and the incidence of renal complications.

References

1. Wessel DL. Managing low cardiac output syndrome after congenital heart surgery. Crit Care Med. 2001;29(10 Suppl):S220–30.
2. Kumar G, Iyer PU. Management of perioperative low cardiac output state without extracorporeal life support: What is feasible? Ann Pediatr Cardiol. 2010;3(2):147–58.
3. Takeuchi K, Buenaventura P, Cao-Danh H, *et al*. Improved protection of hypertrophied left ventricle by histidine-containing cardioplegia. Circulation. 1995; 92(9 Suppl): II395–9.
4. Del Nido PJ, Mickle DAG, Wilson GJ, *et al.* Inadequate myocardial protection with cold cardioplegic arrest during repair of tetralogy of Fallot. J ThoracCardiovascSurg. 1988;95:223–9.
5. Bailey JM, Hoffman TM, Wessel DL, Nelson DP, Atz AM, Chang AC, *et al.* A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. Journal of Pharmacokinetics and Pharmacodynamics. 2004; 31(1):43–59.
6. Stocker CF. Recent developments in the perioperative management of the pediatric cardiac patient. Current Opinion in Anesthesiology. 2006;19(4):375–81.
7. Delmo Walter EM, Alexi-Meskishvili V, Huebler M, *et al.* Extracorporeal membrane oxygenation for intraoperative cardiac support in children with congenital heart disease. Interactive Cardiovascular and Thoracic Surgery. 2010;10(5):753–8.
8. Shi S, Zhao Z, Liu X, *et al*. Perioperative risk factors for prolonged mechanical ventilation following cardiac surgery in neonates and young

infants. Chest. 2008;134(4):768–74.

9. Baysal A, Samazel A, Y ld r m A, Koçak T, Sunar H, Zeybek R. The effects of thyroid hormones and interleukin-8 levels on prognosis after congenital heart surgery. Turk Kardiyoloji Dernegi Arsivi. 2010;38(8):537–43.
10. Lemson J, De Boode WP, Hopman JC, *et al.* Validation of transpulmonary thermodilution cardiac output measurement in a pediatric animal model. Pediatric Critical Care Medicine. 2008; 9(3):313–9.
11. Huntsman LL, Stewart DK, Barnes SR, *et al.* Noninvasive Doppler determination of cardiac output in man. Clinical validation. Circulation. 1983;67(3):593–602.
12. Kim J, Dreyer J, Chang A. Arterial pulse wave analysis: an accurate means of determining cardiac output in children. Pediatric Critical Care Medicine. 2006;7:532–5.
13. Tibby SM, Murdoch IA. Measurement of cardiac output and tissue perfusion. Current Opinion in Pediatrics. 2002;14:303–9.
14. Hochman JS, Sleeper LA, Webb JG, *et al.* Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. New England Journal of Medicine. 1999;341(9):625–34.
15. Rao V, Ivanov J, Weisel RD, *et al.* Predictors of low cardiac output syndrome after coronary artery bypass. Journal of Thoracicand Cardiovascular Surgery. 1996;112(1):38–51.
16. Teng S, Kaufman J, Pan Z, *et al.* Continuous arterial pressure waveform monitoring in pediatric cardiac transplant, cardiomyopathy and pulmonary hypertension patients. Intensive Care Medicine. 2011;37(8):1297–301.
17. Bohn D. Objective assessment of cardiac output in infants after cardiac surgery. Seminarsin Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual. 2011;14(1):19–23.
18. Charpie JR, Dekeon MK, Goldberg CS, *et al.* Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. Journal of Thoracic and Cardiovascular Surgery. 2000;120(1):73–80.
19. Stocker CF. Recent developments in the perioperative management of the pediatric cardiac patient. Current Opinion in Anesthesiology. 2006;19(4):375–81.
20. Shore S, Nelson DP, Pearl JM, *et al.* Usefulness of corticosteroid therapy in decreasing epinephrine requirements in critically ill infants with congenital heart disease. American Journal of Cardiology. 2001; 88(5):591–4.
21. Gaies MG, Gurney JG, Yen AH, *et al.* Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010;11(2):234–38.
22. Haikala H, Nissinen E, Etemadzadeh E, *et al.* Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol. 1995;25:794– 801.
23. Lehmann A, Boldt J, Kirchner J. The role of Ca^{2+}-sensitizers for the treatment of heart failure. Curr Opin Crit Care. 2003;9:337–44.
24. Moiseyev VS, Poder P, Andrejevs N, *et al.* Safety and efficacy of an ovel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J. 2002;23:1422–32.
25. Follath F, Cleland JG, Just H, *et al.* Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002;360:196–202.
26. Stocker CF, Shekerdemian LS, Nørgaard MA, *et al.* Mechanisms of a reduced cardiac output and the effects of Milrinone and Levosimendan in a model of infant cardiopulmonary bypass. Crit Care Med. 2007;35:252–9.
27. Momeni M, Rubay J, Matta A, *et al.* Levosimendan in congenital cardiac surgery: a randomized, doubleblind clinical trial. J Cardiothorac Vasc Anesth. 2011;25:419–24.
28. Duke T, Butt W, South M, *et al.* Early markers of major adverse events in children after cardiac operations. J Thorac Cardiovasc Surg. 1997; 114:1042–52.
29. Cheung PY, Chui N, Joffe AR, *et al.*: Postoperative lactate concentrations predict the outcome of infants aged 6 weeks or less after intracardiac surgery: A cohort follow-up to 18 months. J Thorac Cardiovasc Surg. 2005;130:837–43.
30. Charpie JR, Dekeon MK, Goldberg CS, *et al.* Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. J Thorac Cardiovasc Surg. 2000;120:73–80.
31. Lechner E, Anna H, Gabriele L, *et al.* Levosimendan versus milrinone in neonates and infants after corrective open heart surgery: a pilot study. Paediatr Crit Care Med. 2012;13:542–8.
32. Wernovsky G, Wypij D, Jonas RA, *et al.* Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest.

Circulation. 1995;92:2226–35.

33. Gaies MG, Gurney JG, Yen AH, *et al.* Hirsch JC. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010; 11(2):234–38.