Original Article

Clinical Efficacy of Levosimendan vs Milrinone in Preventing Low Cardiac Output Syndrome Following Pediatric Cardiac Surgery

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ABSTRACT

Background: Prophylactic milrinone is commonly used to prevent Low Cardiac Output Syndrome (LCOS) after pediatric cardiac surgery. This study compares the use of levosimendan with milrinone when used as the primary inotrope following pediatric cardiac surgery.

Subjects and Methods: Forty infants undergoing corrective surgery for congenital heart disease were recruited during the study and randomized into two groups (group L and group M). During rewarming, a loading dose of levosimendan or milrinone was administered followed by a 24-hour infusion of the chosen inotrope. Echocardiographic variables were measured postoperatively. Statistical analysis was done with SPSS-20 computer package. Association between the variables was found by independent t test. $P < 0.05$ was considered statistically significant.

Results: Mean age and weight of the patient in Group L was 8.55 ± 5.83 months and 6.05 ± 2.09 kgs, while that in group M was 6.85 ± 3.57 months and 5.26 ± 2.11 kgs. 4 patients (20%) treated with levosimendan had LCOS in comparison with 6 (30%) patients in those treated with milrinone. Echocardiographic parameters in both groups L and M were comparable (cardiac index 3.47 ± 0.76 vs 3.72 ± 1.05 L/min/m^2, EF 66.10 ± 7.82% vs 59.34 ± 10.74%, stroke volume index 25.4 ± 6.3 vs 27.74 ± 10.35 mL/m^2). The duration of ventilation, ICU stay and hospital stay were lesser in group L (12.75 ± 9.69, 35.95 ± 12.11, 119.10 ± 46.397 vs 23.60 ± 22.03, 51.20 ± 29.92, 140.20 ± 52.65 hours).

Conclusions: The incidence of LCOS was lesser in those patients treated with levosimendan, when compared with those treated with milrinone. Cardiac index and stroke volume index were comparable between the two groups. Thus, levosimendan provides a non-inferior alternative to milrinone when used as the primary inotrope following pediatric cardiac surgery.

Keywords: Echocardiography, levosimendan, pediatric cardiac surgery

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INTRODUCTION

Low cardiac output syndrome (LCOS) is defined as a reduction in cardiac output and is a common occurrence following cardiac surgery in the pediatric population. It was first defined in the pediatric population by Parr and colleagues in 1975 using the dye dilution technique.[1] Early recognition and treatment of LCOS is paramount due to its adverse impact on perioperative morbidity and mortality.

A myriad of strategies exist for managing low cardiac output syndrome such as optimization of preload, inotropes, afterload reducing agents, and positive pressure

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Table 1: Demographic Data

Parameters	Mean (SD)		*P*
	Simenda Group	Milrinone Group	
Age (Months)	8.55 (5.83)	6.85 (3.57)	0.273
Weight (kgs)	6.05 (2.09)	5.26 (2.11)	0.240
Height (cms)	66.07 (9.95)	65.00 (11.77)	0.757
Body surface area	0.32 (.08)	0.30 (.08)	0.478

Table 2: Risk stratification

RACHS	Simenda Group		Milrinone Group	
	Frequency	Percentage	Frequency	Percentage
2	17	85	18	90
3	2	10	1	5
4	1	5	1	5
Total	20	100	20	100

Table 3: Pump related variables

Variable	Simenda Group		Milrinone Group		*P*
	Mean	SD	Mean	SD	
Lowest temperature	30.40	3.14	29.83	3.99	0.62
Pump Time (min)	89.70	49.91	85.15	46.12	0.76
Clamp Time (min)	61.30	31.61	59.80	34.26	0.88
Urine Output (ml)	14.50	21.26	6.00	11.98	0.12
Ultrafiltration (ml)	1075.00	343.16	1072.50	327.86	0.98
Pump Balance	-17.50	70.315	-35.65	68.128	0.41
Intraoperative Fluid Balance (ml)	122.00	165.406	57.10	103.322	0.14

Table 4: Echocardiographic data

Parameters	Mean (SD)		*P*
	Simenda Group	Milrinone Group	
CO (ICU)	1.14±0.46	1.09±0.37	0.683
CO (24 h)	1.05±0.288	1.11±0.37	0.625
CI (ICU)	3.47±0.76	3.72±1.05	0.400
CI (24 h)	3.33±0.65	3.67±1.16	0.263
EF (ICU)	66.10±7.82	59.34±13.50	0.060
EF (24 h)	64.04±5.68	57.69±10.74	0.025
SV (ICU)	8.36±3.56	8.36±3.61	0.999
SV (24 h)	7.84±2.36	8.84±3.80	0.327
SVI (ICU)	25.40±6.30	27.74±10.35	0.392
SVI (24 h)	24.71±5.68	30.20±12.36	0.079

Table 5: Secondary outcomes

Parameters	Mean (SD)		*P*
	Simenda Group	Milrinone	
Ventilation	12.75±9.689	23.60±22.032	0.051
ICU stay	35.95±12.111	51.20±29.922	0.041
Hospital stay	119.10±46.397	140.20±52.652	0.187

ventilation. Multiple regimens combining an inotrope or inodilator along with vasopressor are utilized in various institutes to prevent LCOS. However, most inotropes currently available cause an undesirable increase in heart rate and therefore myocardial oxygen demand. An inotropic regimen which increases myocardial performance without substantially increasing oxygen consumption is therefore desirable. Prophylactic milrinone is most commonly used to prevent LCOS following pediatric cardiac surgery. Other alternatives available include dobutamine and levosimendan.

Levosimendan is an inodilator with calcium sensitizing properties, as a result of which it has a unique catecholamine sparing property. There is probably more controlled clinical data available on levosimendan than any other inotrope in adult cardiac surgery.[2] In the pediatric population, it has been used mainly as a rescue agent, when other inotropic agents are insufficient to maintain stable hemodynamics.[3] However, studies in the pediatric population are limited. In fact, a meta-analysis of studies using levosimendan in pediatric cardiac surgery, published in the Cochrane Database of Systematic Reviews in 2017, included 5 studies and had a total number of only 212 infants and children.[4]

Therefore, it was decided to conduct a randomized prospective study at our institute, in children under 1 year of age undergoing cardiac surgery, to compare the clinical efficacy of levosimendan with milrinone and to study the incidence of LCOS with both these drugs.

SUBJECTS AND METHODS

Study design

This was a single center, randomized study comparing the efficacy of milrinone and levosimendan in preventing LCOS after congenital heart surgery in infants. This study was conducted in the Department of Cardiothoracic and Vascular Surgery at our hospital.

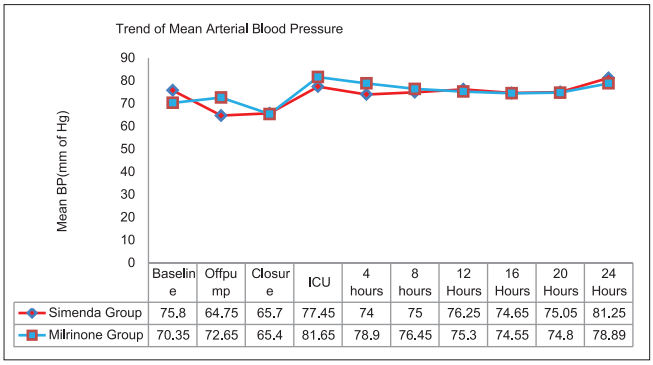
Study population

Approval from the institutional ethical committee was obtained following which written informed consent was obtained from the patients parents. 40 infants undergoing corrective open heart surgery were chosen. Patients were randomly assigned using computer- generated randomization into two groups, Group L (levosimendan) and Group M (milrinone). Some types of congenital heart diseases were not included during the study. The exclusion criteria were:

a. Single ventricle physiology
b. RACHS-I score 5, 6
c. Preoperative LCOS requiring inotropic support
d. Preoperative renal failure, cardiac arrest, thrombocytopenia.

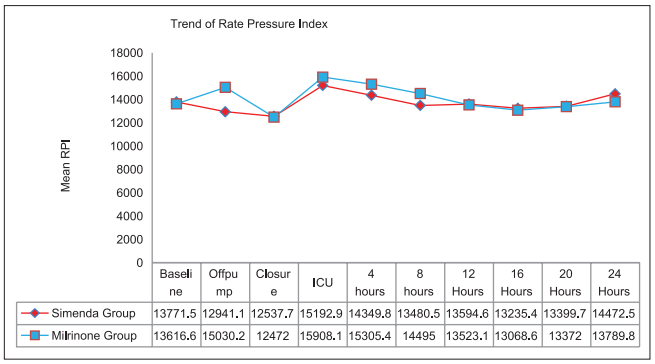
Study method

After standard induction and surgical exposure, CPB was initiated. Del Nido cardioplegia was used in all patients to achieve cardiac standstill. Continuous ultrafiltration was used in all patients to ensure zero-fluid balance at the end of CPB. The initial therapeutic intervention comprised of administration of



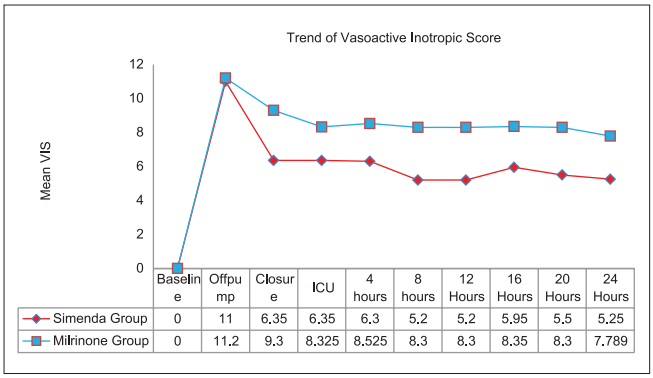
	Baseline	Offpump	Closure	ICU	4 hours	8 hours	12 Hours	16 Hours	20 Hours	24 Hours
Simenda Group	75.8	64.75	65.7	77.45	74	75	76.25	74.65	75.05	81.25
Milrinone Group	70.35	72.65	65.4	81.65	78.9	76.45	75.3	74.55	74.8	78.89

Figure 1: Trend of mean arterial pressure



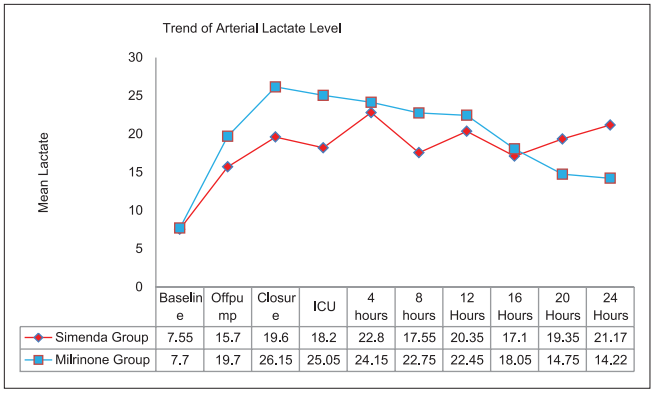
	Baseline	Offpump	Closure	ICU	4 hours	8 hours	12 Hours	16 Hours	20 Hours	24 Hours
Simenda Group	13771.5	12941.1	12537.7	15192.9	14349.8	13480.5	13594.6	13235.4	13399.7	14472.5
Milrinone Group	13616.6	15030.2	12472	15908.1	15305.4	14495	13523.1	13068.6	13372	13789.8

Figure 2: Trend of Rate Pressure Index



	Baseline	Offpump	Closure	ICU	4 hours	8 hours	12 Hours	16 Hours	20 Hours	24 Hours
Simenda Group	0	11	6.35	6.35	6.3	5.2	5.2	5.95	5.5	5.25
Milrinone Group	0	11.2	9.3	8.325	8.525	8.3	8.3	8.35	8.3	7.789

Figure 3: Trend of Vasoactive Inotropic Score



	Baseline	Offpump	Closure	ICU	4 hours	8 hours	12 Hours	16 Hours	20 Hours	24 Hours
Simenda Group	7.55	15.7	19.6	18.2	22.8	17.55	20.35	17.1	19.35	21.17
Milrinone Group	7.7	19.7	26.15	25.05	24.15	22.75	22.45	18.05	14.75	14.22

Figure 4: Trend of arterial lactate level

loading dose of either inotrope over 10 minutes at the time of rewarming during cardiopulmonary bypass. This was followed by a 24-hour infusion of the chosen inotrope. Children in group M, received milrinone, prepared and marketed as MILRON by United Biotech (P) limited. Children in group L received levosimendan, prepared by Gufic Biosciences Limited and marketed as SIMENDA by Lupin Ltd.

Drug dosages

Patients in group L received a loading dose of 10 μg/kg levosimendan followed by a 24-hour infusion at 0.1 μg/kg/min. On the other hand, patients in group M received a loading dose of 50 μg/kg milrinone followed by a 24-hour infusion at 0.5 μg/kg/min. The dose has been extrapolated from adult literature as standard pediatric dosage has not been described. Adrenaline was used to aid separation from cardio-pulmonary bypass in both the groups and was continued in the ICU, if required.

Parameters measured

Hemodynamic parameters like heart rate, blood pressure, saturation, central venous pressure, and urine output were measured at the time of induction, coming off CPB, chest closure, transfer to the ICU and subsequently every 4 hours through 24 hours. Clinical evidence of LCOS and inotropic requirements were recorded during this period.

LCOS was defined as two or more of the following:[4]

a. Arterial lactates >27 mg/dL (or 3 mmoL/L) on two consecutive readings
b. Increase in blood lactate of at least 18 mg/dL (or 2 mmoL/L) from baseline
c. Central venous oxygen saturation <50% in the absence of intracardiac shunts
d. Decrease in central venous oxygen saturation by at least 20% from baseline
e. Urine output <1 mL/kg/hour for two consecutive hours
f. Cardiac index less than 2.2 L/min/m^2.

Inotropic requirements were measured with the Vasoactive Inotropic Score (VIS) for group M and Levosimendan- Vasoactive Inotropic Score (LVIS)[5] for group L. Arterial blood gases along with central venous oxygen saturation were serially monitored. Echocardiographic measurement of cardiac output, cardiac index, ejection fraction, stroke volume, and stroke volume index was done on arrival in the ICU and 24 hours later. Ejection fraction was measured using Simpsons monoplane method, while the Doppler- VTI method was used to derive the cardiac output. Morbidity, duration of ventilation, ICU stay and duration of hospital stay were also recorded.

Primary outcomes measured were the incidence of LCOS, while the secondary outcomes were hemodynamic parameters, inotropic requirements, duration of mechanical ventilation, ICU stay, and hospital stay.

Statistical analysis

Data entry was made in the Microsoft Excel software in codes and analysis was done with SPSS-20 computer package. Categorical variables are expressed as percentages whereas continuous variables are expressed as mean ± standard deviation. The trend of vitals and biochemical parameters of the study participants were followed and their mean ± standard deviation assessed.

RESULTS

Demographic data

Forty patients received one of the two inotropes during the study and were randomized into two groups. There was no statistically significant difference between the two groups as regards the demographic data. The demographic data in both the groups has been represented in the Table 1.

The RACHS-I scoring in both the groups were comparable. Most of the patients (85% in group L, 90% in group M) enrolled were in the RACHS 2 category of patients [Table 2].

Pump-related variables

Pump-related variables in both the groups were also identical [Table 3]. Patients in both the groups had similar pump times and clamp times. None of the patients required low flows during CPB. We followed a zero-balance continuous ultrafiltration technique to ensure nil balance at the end of cardiopulmonary bypass. However, post- CPB, patients treated with levosimendan had a slightly higher fluid requirement compared with those treated with milrinone. This was indicated by the difference in intraoperative fluid balance between both the groups.

(122 + 165.406 mL in group L vs 57.10 + 103.322 mL in group M).

Primary outcomes

We found that 4 patients (20%) had LCOS in the levosimendan group, in comparison to 6 patients (30%) in those treated with milrinone during the first 24 hours post surgery. However, none of the 40 patients had LCOS by echocardiographic criteria on arrival in the ICU and 24 hours thereafter.

Secondary outcomes

Hemodynamic parameters

The mean arterial pressure in both the groups was comparable at all points of time after arrival into the ICU for the first 24 hours [Figure 1]. None of the patients in the two groups had severe hypotension requiring vasopressor therapy during the study. The heart rate of patients in both the groups was comparable during this time frame. None of the patients in either group had any tachyarrhythmia during the first 24 hours post-surgery. The rate-pressure index (RPI) was used to assess the myocardial oxygen demand. It was found that the RPI was comparable between both groups and was lower during the first 24 hours in those patients treated with levosimendan [Figure 2].

Echocardiographic data

Echocardiography demonstrated a consistently good cardiac function in both the groups [Table 4]. The cardiac index in both the groups were similar at arrival in ICU (3.47 ± 0.765 in group L vs 3.72 ± 1.05 in group M) and 24 hours after surgery (3.33 ± 0.65 in group L vs 3.67 ± 1.16). None of the patients in both the groups had LCOS by echocardiographic criteria at the time of measurement. The ejection fraction in patients treated with levosimendan was similar to those treated with milrinone at the time of arrival into the ICU (66.10 ± 7.82% vs 59.34 ± 13.50) and 24 hours thereafter (64.05 ± 5.68 vs 57.69 ± 10.74). The stroke volume index in both the groups was comparable as well (25.40 + 6.30 vs 27.7 + 10.35).

Inotropic requirements

Only 3 patients in group L required adrenaline to maintain adequate cardiac output on arrival into the ICU. This was in contrast to 11 patients requiring adrenaline in group M. Thus, almost 85% of the patients in group L were discharged from the operation theatre on a single inotrope. One patient in both the groups required high inotropic support (more than 0.1 μg/kg/min adrenaline) at the time of arrival into the ICU. Overall inotropic requirements were much lesser in those patients treated with levosimendan compared to milrinone following surgery [Figure 3].

Lactates and mixed venous oxygen saturation

Lactate levels on arterial blood gases were consistently lower in those patients treated with levosimendan in the immediate post surgical period, until 16 hours. Thereafter, there was a slight increase in lactate levels in group L, which coincided with the timing of diuretic administration [Figure 4]. The mixed venous oxygen saturation was comparable in both groups.

Fluid requirements

The intraoperative fluid requirements was higher in group L, compared with group M. Only 2 patients (10%) in group L had a negative fluid balance at the end of surgery, in

comparison to 5 patients (25%) in group M. However, at the end of 24 hours, most patients in both the groups (13 in group L vs 11 in group M) had a negative fluid balance. The fluid overload index at 24 hours was comparable in both groups (-0.66 ± 3.53% in group L vs -0.99 ± 2.85% in group M).

Other secondary outcomes

Patients in group L had a shorter (statistically insignificant) duration of ventilation (12.75 ± 9.68 hours in group L vs 23.60 ± 22.03 hours in group M), as well as hospital stay (119.10 ± 46.397 hours in group L vs 140.20 ± 52.65 hours in group M). The duration of ICU stay was also lesser in those patients treated with levosimendan (35.95 ± 12.11 hours) as compared to those treated with milrinone (51.20 ± 29.92 hours). This difference in ICU stay was statistically significant [Table 5].

DISCUSSION

Levosimendan is an exciting inodilator with a unique non-catecholamine-based mechanism of action. It improves cardiac function, hemodynamic performance and survival in critically ill adult patients, but limited data exists on levosimendan use in the pediatric population.[6] In these patients therefore, its use is off-label, where it is mainly used as a rescue agent.[7,8]

Several smaller trials in the past have suggested a beneficial effect with levosimendan in the perioperative scenario. A meta-analysis published in the Cochrane Database of Systematic Reviews in 2017 evaluated studies in the pediatric population and concluded that the current level of evidence is insufficient to judge whether levosimendan prevents LCOS in pediatric patients.[4] In the wake of several neutral or inconclusive trials of late in the adult population, (CHEETAH, LEVO-CTS, LICORN) this study was designed with the purpose of addressing one quintessential question: How effective is levosimendan, when compared with standard inotropic regimens in preventing LCOS in children? We also aimed to study its hemodynamic repercussions and whether it had any outcome on the duration of ICU and hospital stay.

Unlike most other inotropes available today, levosimendan acts independently of the β-adrenergic receptors and cyclic adenosine monophosphate mechanism. It produces its effects by two mechanisms. First, being a calcium sensitizer, it stabilizes the interaction between calcium and troponin C, thereby improving inotropy without adversely affecting lusitropy.[9] Diastolic relaxation remains unhampered as there is no intracellular accumulation of calcium.[10] Second, it is a potassium-channel opener on vascular smooth muscle, which causes hyperpolarization leading to coronary and peripheral vasodilatation.[11] This renders it with several hemodynamic advantages over other conventional inotropes available today. Thus, amongst the wide spectrum of inotropic agents available today, levosimendan offers a unique alternative to prevent LCOS following cardiac surgery in the pediatric population.

In our study, we found that the incidence of low cardiac output syndrome was lower in patients treated with levosimendan compared with those treated with milrinone. This was in conjunction with multiple studies conducted in the pediatric population in the past.[12,13]

LCOS is a common occurrence following pediatric cardiac surgery with an incidence as high as 25%.[14] No stringent diagnostic criteria exist at present for the diagnosis of LCOS in the pediatric population. The existing criteria rely on hemodynamic measurements, rather than an objective measurement of cardiac output. This is in contrast to the adult population, where a definition based on objective measurement of cardiac index exists.[15] Levosimendan offers a better hemodynamic profile compared to standard inotropic therapy owing to its catecholamine independent mechanism of action.[12] This reliance on hemodynamic parameters for diagnosis of LCOS in children, in conjunction with the better hemodynamic profile offered by levosimendan may account for the low incidence of LCOS in these patients.

The mean arterial pressures in both the groups were comparable, as was the rate pressure index. The rate pressure index can be used as a surrogate marker of myocardial oxygen demand and was found to be lower in those patients treated with levosimendan. Our findings were consistent with those of Momeni *et al*.[12]

Fluid requirement in patients treated with levosimendan was higher in the immediate postoperative period. This maybe explained in part due to the fact that we used a loading dose of levosimendan given over 10 minutes at the time of rewarming during cardiopulmonary bypass. Most studies in the past have avoided using the loading dose of levosimendan or milrinone due to fear of hypotension. Therefore, although almost all patients had a zero fluid balance at coming off CPB, those treated with levosimendan required additional fluids to maintain optimal hemodynamics. This difference was in stark contrast to the patients treated with milrinone, whose reliance on fluid therapy was minimal.

Serum lactate level is considered to be one of the most important biochemical markers of early adverse outcome after congenital cardiac surgery. It is one of the biochemical markers used to support the diagnosis of LCOS. In our study, levosimendan was found to cause a greater reduction in lactate levels between 4-12 hours post surgery, compared with milrinone. Thus, the beneficial effects of levosimendan administration were more pronounced in the typical time frame when LCOS is known to occur. A parallel conclusion was drawn by Ricci *et al*., in his study published in 2012.[16] In our study, the lactate levels in patients treated with levosimendan were consistently lower during the first 16 hours of stay in the ICU. Thereafter, there was a slight increase in lactate levels in these patients, which coincided with the time of diuretic administration (1 mg/kg of furosemide). This may suggest a reliance on optimal preload for levosimendan to maintain adequate cardiac output.[17]

The ejection fraction of patients treated with levosimendan was slightly higher than those treated with milrinone at the time of arrival in ICU. A study published in 2018, found that the inotropic and lusitropic properties of levosimendan and milrinone were comparable at clinically relevant and equipotent infusion rates.[18] This difference in ejection fraction was despite the fact that most of these patients (almost 85%) were on a single inotrope on arrival in the ICU. Thus, levosimendan clearly allowed an early weaning of catecholamines in our patients, ensuring that these patients were on minimal inotropes on arrival in the ICU. This benefit was sustained during the entire length of stay in the ICU. Similar conclusions were drawn in multiple studies published earlier.[8,19] Levosimendan, therefore, reduced the reliance on catecholamine pathways to maintain an optimal cardiac output.[20]

In our study, patients who were supported post cardiac surgery with levosimendan had a shorter duration of ventilation and stay in the ICU. This led to an earlier discharge of these patients from the hospital. None of the patients in both the groups had any sustained arrhythmias or required mechanical circulatory support. There were no in-hospital mortalities in both the groups.

Limitations

Our study had several limitations. Most glaring was the lack of a definitive definition of LCOS and the dependence on clinical parameters for the diagnosis of the same. Also, we excluded patients in the RACHS 5 and 6 category, along with single ventricle physiology. Thus, sicker patients were excluded. The study also does not delve into the different dose ranges of levosimendan to study its effect. The study population, though more or less homogenous, is restricted. Thus, larger, multicenter studies may be warranted.

CONCLUSIONS

We found that the incidence of LCOS was lesser in patients treated with levosimendan, when compared with those treated with milrinone. Also, the hemodynamic profile offered by levosimendan was better, as suggested by the rate-pressure index (RPI). These effects were exerted at a time when the heart most required it and when the incidence of LCOS was highest. However, the cardiac output enhancement by levosimendan was more sensitive to changes in the fluid status of the patient. Also, children treated with levosimendan had a shorter duration of ICU stay and hospital stay. Thus, levosimendan offers a unique, timely, attractive, and equipotent alternative to standard inotropes in use today to prevent LCOS following cardiac surgery in the pediatric population.

Abbreviations used in text

LCOS: Low Cardiac Output Syndrome; RACHS: Risk Adjustment for Congenital Heart Surgery; VIS: Vasoactive Inotropic Score; RPI: Rate Pressure Index.

Abbreviations used in tables and figures

BSA: Body Surface Area; CO: Cardiac Output; CI: Cardiac Index; EF: Ejection Fraction; SV: Stroke Volume; SVI: Stroke Volume Index.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Parr GV, Blackstone EH, Kirklin JW. Cardiac performance and mortality early after intracardiac surgery in infants and young children. Circulation 1975;51:867-74.
2. Rognoni A, Lupi A, Lazzero M, Bongo AS, Rognoni G. Levosimendan: From basic science to clinical trials. Recent Pat Cardiovasc Drug Discov 2011;6:9-15.
3. Suominen PK. Single-center experience with levosimendan in children undergoing cardiac surgery and in children with decompensated heart failure. BMC Anesthesiol 2011;11:18.
4. Hummel J, Rücker G, Stiller B. Prophylactic levosimendan for the

prevention of low cardiac output syndrome and mortality in paediatric patients undergoing surgery for congenital heart disease. Cochrane Database Syst Rev 2017;3:CD011312.
5. Favia I, Vitale V, Ricci Z. The vasoactive-inotropic score and levosimendan: Time for LVIS? J Cardiothorac Vasc Anesth 2013;27:e15-6.
6. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, *et al*. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med 2012;40:634-46.
7. Silvetti S, Silvani P, Azzolini ML, Dossi R, Landoni G, Zangrillo A. A systematic review on levosimendan in paediatric patients. Curr Vasc Pharmacol 2015;13:128-33.
8. Namachivayam P, Crossland DS, Butt WW, Shekerdemian LS. Early experience with Levosimendan in children with ventricular dysfunction. Pediatr Crit Care Med 2006;7:445-8.
9. Ng TM. Levosimendan, a new calcium-sensitizing inotrope for heart failure. Pharmacotherapy 2004;24:1366-84.
10. Haikala H, Nissinen E, Etemadzadeh E, Levijoki J, Lindén IB. Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol 1995;25:794-801.
11. Milligan DJ, Fields AM. Levosimendan: Calcium sensitizer and inodilator. Anesthesiol Clin 2010;28:753-60.
12. Momeni M, Rubay J, Matta A, Rennotte MT, Veyckemans F, Poncelet AJ, *et al*. Levosimendan in congenital cardiac surgery: A randomized, double-blind clinical trial. J Cardiothorac Vasc Anesth 2011;25:419-24.
13. Namachivayam P, Crossland DS, Butt WW, Shekerdemian LS. Early experience with Levosimendan in children with ventricular dysfunction. Pediatr Crit Care Med 2006;7:445-8.
14. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, *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.
15. Pérez Vela JL, Martín Benitez JC, Carrasco Gonzalez M, de la Cal López MA, Hinojosa Pérez R, Sagredo Meneses V, *et al*. [Summary of the consensus document: "Clinical practice guide for the management of low cardiac output syndrome in the postoperative period of heart surgery"]. Med Intensiva 2012;36:277-87.
16. Ricci Z, Garisto C, Favia I, Vitale V, Di Chiara L, Cogo PE. Levosimendan infusion in newborns after corrective surgery for congenital heart disease: Randomized controlled trial. Intensive Care Med 2012;38:1198-204.
17. Charpie JR, Dekeon MK, Goldberg CS, Mosca RS, Bove EL, Kulik TJ. 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.
18. Fredholm M, Jörgensen K, Houltz E, Ricksten SE. Inotropic and lusitropic effects of levosimendan and milrinone assessed by strain echocardiography-A randomised trial. Acta Anaesthesiol Scand 2018;62:1246-54.
19. Egan JR, Clarke AJ, Williams S, Cole AD, Ayer J, Jacobe S, *et al*. Levosimendan for low cardiac output: A pediatric experience. J Intensive Care Med 2006;21:183-7.
20. Milligan DJ, Fields AM. Levosimendan: Calcium sensitizer and inodilator. Anesthesiol Clin 2010;28:753-60.