ORIGINAL ARTICLE

Successful use of levosimendan as a primary inotrope in pediatric cardiac surgery: An observational study in 110 patients

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ABSTRACT

Context : **Levosimendan is a new generation inotrope with calcium sensitizing properties and proven benefits in adults.**

Aims : **This study investigates the use of levosimendan as a first line inotrope in congenital heart surgery.**

Settings and Design : **Prospective, observational study in a tertiary care center.**

Materials and Methods : **One hundred and ten patients undergoing congenital cardiac surgery received levosimendan at a loading dose of 12 mcg/kg during rewarming on cardiopulmonary bypass followed by continuous infusion of 0.1 mcg/kg/min for 48 h. Hemodynamic parameters were recorded at the time of admission to Intensive Care Unit, and at 3 h, 6 h, 12 h, 24 h, and 48 h thereafter.**

Statistical Analysis : **Categorical variables were compared using Chi-square test. Non-normally distributed quantitative variables were compared between groups using Kruskal-Wallis test.**

Results : **At discharge from operating room (OR), 36 (32.7%) patients required levosimendan alone to maintain optimum cardiac output, 59 (53.6%) patients required the addition of low-dose adrenaline (<0.1 mcg/kg/min) and 15 (13.6%) patients required either increment in adrenaline to high-dose (≥0.1 mcg/kg/min) or starting another inotrope/vasoactive agent. Overall, there were five mortalities. Hypotension leading to discontinuation of levosimendan was not found in any patient. Arrhythmias were observed in three patients. Fifty-four patients were extubated in the OR.**

Conclusions : **Levosimendan-based inotropic regime offers optimized cardiac output with a well-controlled heart rate and a low incidence of arrhythmias in patients undergoing all categories of congenital heart surgeries.**

Keywords : Levosimendan, low cardiac output, pediatrics cardiac surgery

INTRODUCTION

Levosimendan has been used as an effective inotrope, widely in the adults and occasionally in pediatric cardiac patients, mostly as a rescue agent.[1-3] The goals of this study were to assess levosimendan as a primary inotrope, to observe the mortality, duration of ventilation, and the length of stay in Intensive Care Unit (ICU) and hospital after congenital cardiac surgery.

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MATERIALS AND METHODS

A prospective observational analysis was conducted in the Department of Pediatric Cardiac Sciences, where 243 congenital cardiac surgical procedures were performed between November 2011 and December 2012. Informed consent was obtained from the parents prior to the surgery. All varieties of open heart surgeries for congenital diseases requiring inotropes were included. Exclusion criteria for this study were:

1. Nonrequirement of inotropes,
2. Patients undergoing closed heart surgery,
3. Patients demonstrating low systemic vascular resistance on cardiopulmonary bypass (CPB), and
4. Patients on preoperative conventional inotropes.

One hundred and ten patients qualified for enrollment and were administered levosimendan [Table 1].

All 110 patients received a loading dose of levosimendan at 12 mcg/kg over 10 min started at the initiation of rewarming phase of bypass, followed by a continuous infusion of 0.1 mcg/kg/min up to a period of 48 h (extrapolated from adult literature as standard pediatric dosage not described).[4-6] Heart rate (HR), blood pressure (BP), central venous oxygen saturation ($ScvO_2$), and lactates were noted at the time of admission to the pediatric cardiac ICU, that is, at 0 h, 3 h, 6 h, 12 h, 24 h, and 48 h thereafter. Clinical evidence of low cardiac output syndrome (LCOS) (based on criterion described below) and needs to add inotropes were noted during this interval. Mortality, duration of ventilation and length of ICU and hospital stay were also recorded.

After induction standard, CPB was initiated, and blood cardioplegia was used to achieve a cardiac arrest. Modified ultrafiltration was performed after weaning from CPB. Adequacy of repair and ventricular function was assessed at the end of weaning from CPB by transesophageal echocardiography.

Table 1: Diagnostic breakup of the 110 surgical procedures performed during the study

Surgical diagnosis	Number
TAPVR repair	11
ASO (IVS/VSD)	13
BiV repairs (PTA/Rastelli/complex DORV re-routing/IAA/Yasui)	13
TOF complete repair	21
Valve repair procedures (aortic/mitral)	10
ALCAPA coronary transfer	2
VSD closure	33
CAVC repair	5
Norwood procedure	2

TAPVR: Total anomalous pulmonary venous return, ASO: Arterial switch operation, IVS: Intact ventricular septum, VSD: Ventricular septal defect, BiV: Biventricular, PTA: Persistent truncus arteriosus, DORV: Double outlet right ventricle, IAA: Interrupted aortic arch, TOF: Tetralogy of Fallot, ALCAPA: Anomalous left coronary artery from pulmonary artery, CAVC: Common atrioventricular canal

LCOS was defined as mean invasive arterial BP of less than the 5th centile (according to the height and age based normogram)[7] 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 centile according to the age based normogram.

Statistical analysis was done using SPSS Statistics for Windows, Version 17.0. (Chicago: SPSS Inc, USA). Data were analyzed using descriptive statistics. Categorical variables were compared using Chi-square test. Non-normally distributed quantitative variables were compared between groups using Kruskal-Wallis test. A two-sided *P* value below 0.05 was considered as statistically significant.

RESULTS

Of 110 patients recruited in the study, 69 (62%) were males and 41 (37%) were females. The age ranged from 4 days to 19.6 years (interquartile range [IQR] 117-1021 days) with a median age of 346.5 days (11 neonates, 45 infants, and 54 patients >1-year). The median weight of the study population was 6.27 kg (IQR 4.1-10.9 kg). Thirty-four percentage patients weighed <5 kg, 38% were between 5 kg and 10 kg, whereas 28% were more than 10 kg. Distribution of the procedures, according to their complexity using risk adjustment for congenital heart surgery (RACHS) categories was RACHS Cat-II 56.36%, RACHS Cat-III 27.27%, RACHS Cat-IV 13.63%, and RACHS Cat-VI 2.72%.

Efficacy of levosimendan in prevention or control of low cardiac output syndrome

Requirements of inotropes in the operation room: All patients subjected to this inotropic regime were discharged from the operating room (OR) successfully. At discharge from OR, based on the need for adding inotropes to levosimendan for achieving adequate cardiac output, patients fell into three groups. Group A comprised of 36 patients (33%) who received levosimendan as the only inotrope for separation from CPB and to maintain optimum cardiac output till discharge from OR. Group B consisted of 59 patients (54%) who required the addition of low-dose of adrenaline (<0.1 mics/Kg/min) by the time of leaving the OR. Group C had 15 patients (13%) who required either increasing adrenaline to a "high-dose" (≥0.1 mics/Kg/min) or addition of a third agent prior to discharge from the OR for achieving adequate cardiac output. Hence, 86% of patients were noted to have clinically optimal cardiac output using levosimendan with or without low-dose adrenaline till discharge from OR.

Inotrope requirements and inotrope score (IS) in the ICU: During the course of the ICU stay, low cardiac output was noted in one patient of Group A requiring addition of 0.03 mics/Kg/min of adrenaline. Six patients of Group B required escalation or addition of inotropes for noted drop in cardiac output. Four patients needed the addition of noradrenaline and two needed addition of dopamine. In Group C, three out of 15 patients required increasing the inotrope level or adding another agent. Adrenaline was increased to 0.2 mics/Kg/min in two patients and noradrenaline was added in one. As levosimendan has not yet been assigned a score for its inotropic effect, the ISs were calculated using the doses of inotropic agents added to the fixed dose of levosimendan. In Group A, all patients at the time of discharge from the OR received the only levosimendan, thereby having an IS of zero. As one patient in this group required low-dose (0.03 mcg/kg/min) adrenaline at 6 h of ICU stay for developing LCOS, the IS for this single patient became five. The average IS of patients in Group B at the time of discharge from OR was 5.9 (range 3-10), which increased to a maximum of 7.4 (range 3-35) during the ICU stay. The change in average IS in Group C was from 17.1 (range 10-30) at discharge from OR to 18.5 (range 10-30) during the ICU stay. The number of patients requiring escalation of inotropes in the ICU among the three groups was found to be statistically significant [Table 2].

Mortality

Overall mortality in the cohort was 5 (4.5%). Two patients succumbed to LCOS-related renal failure and three due to multidrug-resistant Gram-negative bacterial sepsis leading to multi-organ dysfunction [Table 3]. All patients in Group A, survived. One of the 59 patients in Group B, who required the addition of noradrenaline, expired on the 17th postoperative day due to Gram-negative sepsis. There were four mortalities in Group C. Two were due to renal failure secondary to LCOS and two were attributed to sepsis related multi-organ dysfunction.

Clinical safety

1. Hypotension — Isolated hypotension unrelated to LCOS was observed in 13 patients who responded to volume supplementation. Isolated hypotension leading to discontinuation of levosimendan was not noted in any patient.
2. Arrhythmia — Tachyarrhythmia was observed in three patients (2.7%). Of these, two patients had supraventricular tachycardia (SVT) and one had junction ectopic tachycardia. Two of them were successfully reverted and maintained by amiodarone. One SVT patient reverted spontaneously without recurrence.
3. Effect on HR — The overall cohort had a median HR was 145 bpm (IQR 129-156). The distribution

Table 2: Distribution and details of patients based on the need of inotropes (*n* = 110)

Variables	Group A (*n* = 36)	Group B (*n* = 59)	Group C (*n* = 15)	*P*
RACHS category				
1	—	—	—	
2	29	31	2	0.001[a]
3	6	17	7	
4	1	9	5	
5	—	—	—	
6	—	—	3	
Median age in days (IQR)	572 (190-2104)	323 (100-760)	67 (37-253)	0.005[b]
Median weight in kg (IQR)	10 (5.4-18.8)	6 (3.7-8.6)	3.2 (2.9-5.5)	<0.001[b]
Median CPB time (min) (IQR)	97 (86-119)	141 (100-184)	205 (122-238)	<0.001[b]
Median ACC time (min) (IQR)	48 (39-61)	63 (50-79)	68 (61-101)	<0.001[b]
Patient requiring escalation of inotropes in ICU	1	6	3	0.034[c]
Patients extubated in the OR	31	23	0	<0.001[c]
30-day mortality	0	1	4	<0.001[c]

[a]RACHS 4 and 6 were clubbed for Pearson's Chi-square test, [b]Kruskal-Wallis test, [c]Pearson's Chi-square test, IQR: Interquartile range, RACHS: Risk adjustment for congenital heart surgery, CPB: Cardiopulmonary bypass, ACC: aortic cross clamp, ICU: Intensive Care Unit, OR: Operating room

Table 3: Details of nonsurvivors

Patient number	Procedure	CPB/ACC (min)	Age (days)	Weight (kg)	Cause	Duration postoperative (days)
7	Obstructed TAPVR repair	99/51	33	2.06	Sepsis	17
33	VSD enlargement and tunneling to aorta, conduit repair+LPA plasty	346/200	1536	19.6	LCOS, renal failure	10
40	CAVC and mitral valve repair	205/101	201	4.97	LCOS, renal failure	4
42	TGA, IVS	216/68	14	2.8	Sepsis	16
78	ALCAPA and mitral valve repair	216/139	140	3.9	Sepsis, renal failure, arrhythmia	10

ACC: Aortic cross clamp, LPA: Left pulmonary artery, TGA: Transposition of great arteries, CPB: Cardiopulmonary bypass, TAPVR: Total anomalous pulmonary venous return, VSD: Ventricular septal defect, CAVC: Common atrioventricular canal, IVS: Intact ventricular septum, ALCAPA: Anomalous left coronary artery from pulmonary artery, LCOS: Low cardiac output syndrome

of median HR at various time intervals in the ICU is shown in Figure 1.

Lactate trends

The number of patients with lactate levels of <2 mmols/L in our series increased from 33 on ICU admission to 107 at 48 h of ICU stay, respectively. The average levels of lactates decreased from 3.4 to 1.4 during the 48 h study period [Figure 2]. We observed that with the levosimendan based inotropic regime, 58% ($n = 64$) of the patients had lactate values <2 mmols/L by 6 h of ICU arrival.

Central venous oxygen saturation

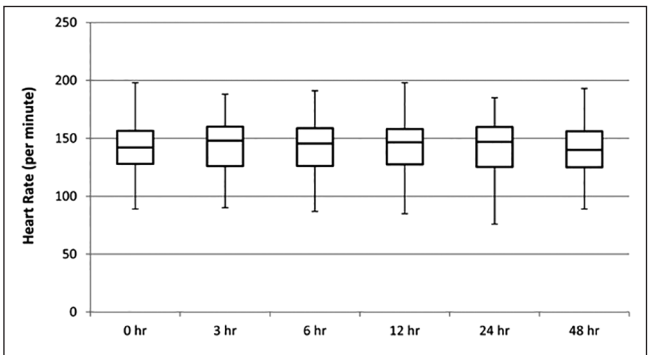
$ScvO_2$ is a surrogate for mixed venous oxygen saturation and reflects the balance between oxygen delivery and oxygen consumption. $ScvO_2$ of more than 60% is considered acceptable as a measure of adequate tissue perfusion. In this series, the average $ScvO_2$ value at admission to ICU was 62%, and consistently increased till 75% at 48 h postoperatively, which depicts a well perfused tissue status all along the study period [Figure 2].

Duration of ventilation

Fifty-four (49%) patients were extubated successfully in the OR. None of them required re-intubation. Thirty-one patients in Group A, 23 in Group B, and none in Group C were extubated in the OR. Of the remaining, 56 patients who reached ICU with invasive orotracheal ventilation, five patients did not survive. Among the 51 survivors, the median time to extubation was 48 h (IQR 24-74.5). The median ventilated times were 37 (IQR 25-48), 47 (IQR 24-74.25), and 66 (IQR 40.5-80.7) hours in Groups A, B, and C, respectively [Table 2].

Intensive Care Unit and hospital length of stay

The overall group had an ICU stay of 5.1 ± 4.1 days with most patients discharged from the ICU by day 4. The patients in Group A inotropic regime were discharged from the ICU after a mean stay of 2.6 ± 1.8 days; those receiving Group B inotropes were in the ICU for 5.4 ± 3 days; and those with Group C inotropes stayed for 10.5 ± 8.1 days. The average length of hospital stay of all the patients was 8.9 (±5.6) days (Group A: 7.3 ± 5, Group B: 9.1 ± 3.7, and Group C: 14.9 ± 10.5 days).



	Median HR per min(IQR)	No of patients with sinus tachycardia (per age normogram)
0 Hours	142 (128-156)	14
3 Hours	148 (126-160)	22
6Hours	145 (126-158)	21
12 Hours	146 (127-158)	19
24 Hours	147 (125-159)	11
48 Hours	140 (125-156)	12

HR: heart rate; IQR: interquartile range.

Figure 1: Behavior of heart rate

DISCUSSION

LCOS is a common phenomenon occurring after congenital cardiac surgery. Wernovsky *et al.* reported that 25% of neonates who underwent arterial switch operation for transposition of great arteries had a significant fall in cardiac index <2 L/min/m^2, which occurs between 6 h and 18 h after surgical repair.[8,9]

Multiple regimes combining an inotrope (adrenaline, dopamine, and dobutamine), an inodilator (milrinone), or a vasoactive drug (noradrenaline) are utilized in various institutes. Tachycardia and arrhythmias are owing to increased myocardial oxygen consumption,[10,11] increased systemic or pulmonary vascular resistance, and hypotension pertaining to excessive vasodilation remain a cause for concern. An inotropic regime is desirable which would increase myocardial performance without substantially increasing oxygen consumption and with neutral chronotropic and dromotropic effects on the heart.

Levosimendan acts independently of β-adrenergic receptors and cyclic adenosine monophosphate mechanism. This mechanism of action provides levosimendan the pharmacological properties that render it with hemodynamic advantages over conventional inotropes. Levosimendan produces its effects by two mechanisms. It is a distinct calcium sensitizer, as it stabilizes the interaction between calcium and troponin C by binding to troponin in a calcium-dependent manner, improving inotropy

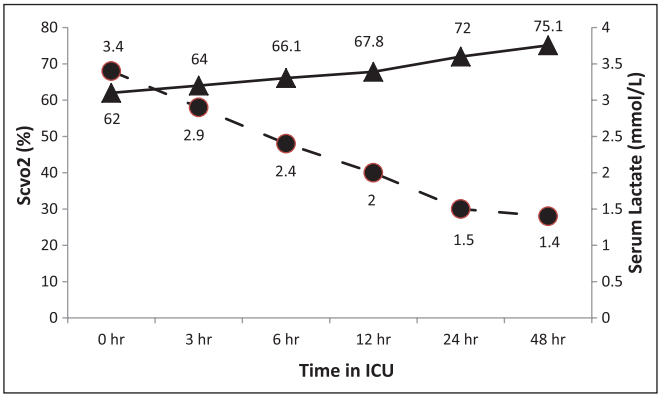


Figure 2: Average lactates and central venous oxygen saturation at various time intervals in the Intensive Care Unit

without adversely affecting lusitropy.[4,5] Diastolic relaxation remains unhampered as there is no intracellular accumulation of calcium.[6] Second, it is a potassium channel opener on vascular smooth muscle, which causes hyperpolarization leading to coronary and peripheral vasodilation. Thus, this novel drug increases the myocardial contractility without interfering with cardiac electrophysiology.[12]

Levosimendan has emerged as a promising agent in cardiac preconditioning and treatment of acute heart failure in adults.[13,14] Angadi *et al*. compiled the relevant literature of levosimendan in pediatric cardiac patients and concluded that all studies favored its use in LCOS when other drugs were insufficient; furthermore, it is best used as a rescue drug.[15] Other groups have similar conclusions.[16,17]

Comparing milrinone and levosimendan, Lechner *et al*. in a double-blinded randomized trial started a continuous infusion of milrinone or levosimendan just before weaning from CPB and observed that cardiac output and cardiac index remained stable in milrinone group, whereas cardiac output and cardiac index increased overtime in levosimendan group.[18] A similar study was done by Momeni *et al*. in 41 infants and noted that levosimendan was as efficacious as milrinone and lower HR and lower rate pressure index were noted in levosimendan group.[19] A study on 18 piglets, comparing the effects of milrinone and levosimendan on LCOS after CPB has proposed that both the drugs prevent rise in afterload early after CPB but levosimendan unlike milrinone has better impact in improving myocardial contractility.[20,21] Lobacheva *et al*. used levosimendan in 75 children undergoing cardiac surgical interventions and found an increase in left ventricular ejection fraction from 21% to 27% with increase in mean BP and reduction in left atrial pressure, and thus, justified the use of levosimendan as an alternative to phosphodiesterase-III inhibitors in LCOS.[22]

Levosimendan had been used conventionally as rescue therapy when conventional inotropes failed to improve hemodynamics for smooth weaning from CPB.[16] In our study by administering levosimendan at the time of weaning from CPB, we smoothly separated 86% of our patients using either levosimendan alone or with a combination of levosimendan and a small dose of adrenaline. In smaller age and weight babies undergoing prolonged intraoperative myocardial ischemia need for the addition of a third agent were noted. Using this strategy, we noticed overall mortality of 4.5%. Tasouli *et al*. also advocated in favor of its "early" use and demonstrated its beneficial effects in the hemodynamic profile of 45 adults undergoing open heart surgery.[23]

A very well controlled HR was noted with use of levosimendan [Figure 1], which is a surrogate marker denoting optimum cardiac output state. By virtue of its β-1 adrenergic sparing action, it does not have a potential to increase HR. Thus, it improves cardiac index without increasing myocardial oxygen consumption. Our findings are consistent with those of Momeni *et al*.[19] who used levosimendan or milrinone in infants undergoing open heart surgery and found that HR and rate pressure index were lower in levosimendan group.

Another significant observation related to the chronotropic-dromotropic advantage of levosemendan over other currently used inotropes/inodilators is the low incidence of arrhythmia. Arrhythmia was observed in 2.7% of patients in our study group. The mechanism leading to arrhythmias by conventional inotropes is based on their strong potential to increase cytosolic calcium; on the other hand, levosimendan, being a calcium sensitizer, sensitizes cardiac troponin C to calcium during systole and does not increase intracellular calcium levels.[10,11] A study conducted in heart failure patients, to analyze the potential of levosimendan and to produce arrhythmias has proven that levosimendan has electro-physiologically neutral profile and is not pro-arrhythmogenic.[12]

Hypotension necessitating discontinuation of levosimedan infusion was not seen in the study group. Lobacheva *et al*. also observed mild hypotension within the 1st h of infusion, which settled with fluid boluses and epinephrine.[22]

CONCLUSION

In the present study, we observed that it can be used in all age groups and all complexity of congenital cardiac procedures with minimal side-effects. Overall, levosimendan based inotropic regime showed effective control of LCOS, demonstrated by a low LCOS-related mortality of <5%. It was noted that levosimendan alone controlled LCOS in most children beyond 1.5 years with a body weight above 10Kg undergoing simpler surgeries (RACHS-II) requiring shorter myocardial ischemia and CPB times. A supplemental low-dose adrenaline was required in older infants with a mean age of 10.7 months undergoing complex surgeries with longer ischemic and pump times. As expected, smaller infants and neonates with almost similar intraoperative ischemia times as the previous group, but longer CPB times required high-doses of adrenaline and/or addition of other agents. A well-controlled HR found in the whole study group can be attributed to the β-1 sparing action of levosimendan and need for lower doses of inotropes minimizing their undesirable chronotropic side-effect.

Limitations and strengths

An important shortcoming of this study is that there were no controls in the study as it was a pilot study in our country undertaken to prove the efficacy and safety of levosimendan as a primary inotrope in congenital heart surgery. Second, the inotropic score was calculated from the conventional formula that does not take levosimendan into consideration and has not been assigned any inotropic score. Third, we did not have any quantitative assessment of cardiac output, and the diagnosis of LCOS was made by the in-house attending pediatric intensivist using well-defined clinical guidelines. Finally, this is only a single center's experience, and further randomized, multicenter, comparative studies are needed.

The strengths of the study include the use of levosimendan in all RACHS groups. To our knowledge, this is the largest, prospective trial using levosimendan as a primary inotrope after pediatric cardiac surgery.

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Conflicts of interest

There are no conflicts of interest.

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