Intensive Care Med (2012) 38:1198–1204
DOI 10.1007/s00134-012-2564-6

PEDIATRIC ORIGINAL

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Levosimendan infusion in newborns after corrective surgery for congenital heart disease: randomized controlled trial

Received: 6 September 2011
Accepted: 20 March 2012
Published online: 18 April 2012

Trial registration: ClinicalTrials.gov NCT01120106.

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Abstract *Purpose:* To evaluate the safety and efficacy of levosimendan in neonates with congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass (CPB). *Methods:* Neonates undergoing risk-adjusted classification for congenital heart surgery (RACHS) 3 and 4 procedures were randomized to receive either a 72 h continuous infusion of 0.1 μg/kg/min levosimendan or standard post-CPB inotrope infusion. *Results:* Sixty-three patients (32 cases and 31 controls) were recruited. There were no differences between groups regarding demographic and baseline clinical data. No side effects were observed. There were no significant differences in mortality (1 vs. 3 patients, $p = 0.35$), length of mechanical ventilation (5.9 ± 5 vs. 6.9 ± 8 days, $p = 0.54$), and pediatric cardiac intensive care unit (PCICU) stay (11 ± 8 vs. 14 ± 14 days, $p = 0.26$). Low cardiac output syndrome occurred in 37 % of levosimendan patients and in 61 % of controls ($p = 0.059$, OR 0.38, 95 % CI 0.14–1.0). Postoperative heart rate, with a significant difference at 6 ($p = 0.008$), 12 ($p = 0.037$), and 24 h ($p = 0.046$), and lactate levels, with a significant difference at PCICU admission ($p = 0.015$) and after 6 h ($p = 0.048$), were lower in the levosimendan group. Inotropic score was significantly lower in the levosimendan group at PCICU admission, after 6 h and after 12 h, ($p < 0.0001$). According to multivariate analysis, a lower lactate level 6 h after PCICU admission was independently associated with levosimendan administration after correction for CPB time and the need for deep hypothermic circulatory arrest. *Conclusions:* Levosimendan infused in neonates undergoing cardiac surgery was well tolerated with a potential benefit of levosimendan on postoperative hemodynamic and metabolic parameters of RACHS 3–4 neonates.

Keywords Low cardiac output syndrome · Levosimendan · Inodilator · Pediatric cardiac surgery · Congenital heart disease · Cardiopulmonary bypass

Introduction

Adequate support of myocardial function in neonates with congenital heart disease (CHD), both pre- and postoperatively, is of the utmost importance. Against the functional background of a physiologically limited contractile reserve [1–3], the presence of a CHD may further worsen ventricular performance by means of acidosis, hypoxia, neurohormonal activation [4], surgical manipulation, ischemia reperfusion injury, fluid overload, and systemic

inflammatory response occurring during cardiac surgery [5]. As a consequence, in the first 6–12 postoperative hours, more than 20 % of patients exhibit a low cardiac output syndrome (LCOS), characterized by poor systemic perfusion and high vasoactive drugs requirement [6].

In this setting, the ideal protocol for inotropic agents administration is currently undefined: many drugs can be used in various combinations but none is ideal. Hemodynamic effects of vasoactive drugs are complex, variable, and sometimes even counterproductive: high doses of catecholamines infusion are associated with tachycardia, tachyarrhythmias, and increased oxygen consumption [5–7].

Levosimendan (Simdax; Orion Pharma, Espoo, Finland), a novel inodilator agent belonging to the family of calcium sensitizer agents [8], has shown preconditioning effects and positive inotropic and vasodilating properties that successfully contributed to treat congestive heart failure and post-cardiotomic heart dysfunction in adults [9–11]. So far, few data exist on levosimendan use in pediatric patients, mostly related to the treatment of heart failure [12]; nevertheless, its unique pharmacodynamics suggest a strong rationale for levosimendan use in immature hearts requiring surgery on cardiopulmonary bypass (CPB) [13]. As a calcium sensitizer, levosimendan enhances the sensitivity of contractile myofilaments to intracellular calcium concentration by binding to the C cardiac troponin [14]. The resulting inotropic effect is not mediated by adrenergic receptors and does not affect either calcium or intracellular cyclic adenosine monophosphate. Thus, besides avoiding arrhythmias from calcium overload and increased myocardial oxygen consumption, it has no negative impact on diastolic function and neutral effects on heart rhythm [15]. In addition its vasodilator effects (including coronary arterial vasodilation) have been attributed to activation of sarcolemmal K-sensitive adenosine triphosphate (KATP) channels of vascular smooth muscle cells, recently suggested as a key target in the therapy of myocardial dysfunction [11, 16, 17]. Furthermore, another key feature of levosimendan is the activation of mitochondrial KATP channels, which are important mediators of ischemic preconditioning, and may also be protective in other tissues, such as kidney and brain [18].

On the basis of the hypothesis that CHD neonates undergoing cardiac surgery may receive a benefit from improved myocardial calcium handling, the aim of this study was to evaluate the safety and efficacy of perioperative levosimendan infusion in CHD neonates undergoing cardiac surgery.

Methods

Study design and population

We conducted a prospective randomized open label study in the Pediatric Cardiac Intensive Care Unit, Ospedale Bambino Gesù, Rome, Italy from January 2008 to December 2010. We recruited newborns (age less than 30 days) undergoing risk-adjusted classification for congenital heart surgery (RACHS) [19] 3 and 4 procedures who received a 72 h continuous infusion of 0.1 μg/kg/min levosimendan and we compared them with newborns, who did not receive levosimendan. The dose was chosen on the basis of studies in adult patients [8–13] and personal experience on selected cases. We excluded newborns with major congenital associated malformations (not classified by RACHS score), sepsis, renal or liver failure before surgery, or the need for inotropic drugs before surgery. The study was approved by the local ethics committee and was registered in the Protocol Registration System (ClinicalTrials.gov NCT01120106). Informed consent was obtained from both parents.

Objectives

The primary objective of our observation was to explore if the addition of levosimendan to vasoactive support after CPB would help reduce postoperative LCOS. Patients are diagnosed with LCOS if they demonstrate clinical signs and symptoms of the syndrome such as tachycardia (heart rate over 170 beats/min), oliguria (urine output less than 0.5 mL/kg/h), cold extremities (peripheral temperature less than 27 °C) with or without at least 30 % difference in arterial-mixed venous oxygen saturation or metabolic acidosis (an increase in the base deficit of greater than 4 or an increase in the lactate of more than 2 mg/dL) on two successive blood gas measurements. Postoperative cardiac arrest or the need for extracorporeal membrane oxygenation (ECMO) was also considered LCOS [7].

Secondary objectives were to compare absolute lactate arterial plasma levels, heart rate (HR), mean arterial pressure (MAP), inotropic score (IS), diuresis, the need for peritoneal dialysis (PD), mixed venous oxygen saturation, and brain natriuretic peptide (BNP) levels in the two groups. The number of ventilation days, pediatric cardiac intensive care unit (PCICU) length of stay (LOS) and survival were also evaluated. Finally, the number of times that the drug infusion was halted because of the presence of side effects (hypotension, arrhythmias, signs of allergy) was recorded as a measure of safety.

Interventions

All patients received general anesthesia with sevorane inhalation at induction and then midazolam (0.05 mg/kg/h), fentanyl (5 μg/kg/h), and cisatracurium (0.08 mg/kg/h) infusion for maintenance. The standard institutional protocol for CPB weaning consisted of the use of milrinone (0.75 μg/kg/min and dopamine 5 μg/kg/min) started at the end of cross clamp as first choice. If MAP was below

45 mmHg and filling pressures did not indicate the need for fluid replacement, dopamine was increased to 10 μg/kg/min. If such targets were not achieved, adrenaline (0.05–0.3 μg/kg/min) was added. Clinicians were allowed to decrease the milrinone dose if MAP tended to be lower than the selected cutoff even after the addition of adrenaline.

At this time newborns were openly randomized to receive a 72 h intravenous infusion of levosimendan at the dose of 0.1 μg/kg/min added to the standard inotropic support versus the standard inotropic management. CPB was conducted in all patients with α-stat strategy, moderate hypothermia, CPB pump flow rate ranging from 150 to 200 mL/kg/min, and hematocrit values between 28 and 32 %. Deep hypothermic circulatory arrest (DHCA) after cooling to 18 °C was performed in a small subgroup of patients when aortic arch reconstruction was indicated. Conventional ultrafiltration during rewarming was performed in all patients. After PCICU admission, inotropic drug infusion was adjusted by the attending physician on the basis of a MAP target of 45 mmHg, after fluid replacement for correction of hypovolemia. The study design did not allow one to change the levosimendan infusion rate and the infusion could be stopped before the 72nd hour only if side effects (hypotension, arrhythmias, signs of allergy) were observed.

Randomization procedure

The allocation sequence was generated by a computerized random-generation program. The patients were evaluated for eligibility the day before surgery. After recruitment, on the day of operation, sealed envelopes containing the allocation group were opened by a nurse who was in charge of preparing the infusions. No blinding was necessary for the study, due to its open label design.

Data collection

Demographic data, HR, right/left atrial pressures, MAP, IS, metabolic parameters (pH, HCO_3^-, base excess, systemic and venous oxygen saturation, lactate levels, BNP levels), urine output, fluid balance, and the need for PD were recorded. Mixed venous oxygen saturation was sampled, as per protocol, from the superior vena cava. IS, representing different inotropic and vasopressor drug regimens, was calculated as previously described [20]: dopamine μg/kg/min × 1 + milrinone μg/kg/min × 10 + epinephrine μg/kg/min × 100. In the absence of other direct instrumental measures of cardiac performance, not currently available for neonates, IS was adapted to the severity of hemodynamic derangement. Data collection was performed at the start of surgery, at PCICU admission after surgery, and at 6, 12, 18, 24, 48, and 72 h postoperatively. BNP levels were only measured at 6, 18, 24, 48, and 72 h. Urine output, fluid balance, and the need for PD were recorded daily. No data were missing in either group.

Statistical analysis

Intention to treat (ITT) was applied, and all enrolled patients were considered for statistical analysis at the end of the study. The study was powered on the primary outcome considering an LCOS incidence in neonates of 50 %, a reduction of LCOS incidence by 1/3, a statistical power of 80 %, and an alpha error of 0.05. The number of patients to treat was calculated to be 30 for each group. A stopping rule was determined in case of major morbidity being detected in this phase.

Data are expressed as mean ± SD or median and interquartile range (IQR) as appropriate. Qualitative data are expressed as absolute number and percentage. Unpaired comparisons and univariate analysis were made by Student's t test, Mann–Whitney test, chi-square test, and ANOVA as appropriate, and paired comparison by Wilcoxon test or Friedman's Q test. Tests for statistical significance ($p < 0.05$) and confidence intervals were two-sided.

Two-way analysis of variance was used to compare continuous variables over time between the two groups, with the Bonferroni post hoc test for each time point. Independent risk factors for increased lactate levels after 6 h were identified by multiple regression analysis (forward conditional method, probability of stepwise entry 0.05, and removal 0.1). Covariates in the univariate analysis with a significance level of $p > 0.2$ were eliminated from the multivariate model. Statistical analysis was performed by SPSS for Windows XP version 15.00 (SPSS Inc., Chicago, IL, USA).

Results

We recruited 63 patients (32 cases and 31 controls) of the 74 newborns eligible for the study. Eleven newborns did not enter the study: in seven cases because the parents denied the consent and four were excluded for the use of inotropic drugs before surgery. There were no differences between groups regarding age, weight, sex, RACHS, and baseline clinical data (Table 1). The levosimendan (L) and control (C) groups also had similar diagnoses: aortic arch hypoplasia (3 L; 2 C), abnormal left coronary artery from pulmonary artery (1 L; 0 C), interruption of aortic arch (2 L; 1 C), transposition of the great arteries with ventricular septal defect (5 L; 4 C), transposition of the great arteries with intact septum (17 L; 20 C), transposition of the great arteries with aortic coarctation (2 L; 1 C), truncus arteriosus (2 L; 3 C) ($p = 0.78$).

Table 1 Baseline data

	Group L	Controls	*p*
Total (*n*)	32	31	–
Sex (m/f)	20/12	17/14	0.53
Age (days)	18.7 (14)	15.5 (9.2)	0.42
Weight (kg)	3.2 (0.47)	3.2 (0.46)	0.96
BSA (m^2)	0.2 (0.01)	0.2 (0.01)	0.90
RACHS (3/4)	18/14	21/10	0.35
CPB (min)	256 (69)	279 (77)	0.19
Cross clamp (min)	141 (40)	155 (47)	0.16
DHCA (yes/no)	8/34	3/38	0.11
Surgical procedure (h)	7.6 (1.7)	8.0 (1.8)	0.35
T_{min} during CPB (°)	25 (4.4)	26 (3.2)	0.45

Univariate analysis of age, weight, sex, RACHS, and baseline clinical data. Continuous variables are expressed as mean (standard deviation)

Group L levosimendan, *BSA* body surface area, *RACHS* risk-adjusted classification for congenital heart surgery, *CPB* cardiopulmonary bypass, *DHCA* deep hypothermic circulatory arrest, T_{min} minimum temperature during CPB

Regarding the primary objective of the study LCOS incidence was 37 % (12/32) in the levosimendan group and 61 % (19/31) in controls ($p = 0.059$, OR 0.38, 95 % CI 0.14–1.0).

No side effects related to levosimendan infusion were reported and therefore the drug was never halted. There were no significant differences in length of mechanical ventilation (6.9 ± 8 vs. 5.9 ± 5 days, $p = 0.54$) and PCICU LOS (14 ± 14 vs. 11 ± 8 days, $p = 0.26$). Three patients died in the control group (1 postsurgical severe left ventricular dysfunction, 1 multiple organ dysfunction syndrome, and 1 necrotizing enterocolitis) and one in the levosimendan group (multiple organ dysfunction syndrome) ($p = 0.35$).

In addition, no significant differences were found in diuresis, MAP, left/right atrial pressure, mixed venous saturation, and BNP levels (Table 2). However, postoperative HR tended to be lower in levosimendan patients, with a significant difference at 0 h (159 ± 15 vs. 169 ± 14 bpm, $p = 0.008$), 6 h (158 ± 14 vs. 166 ± 15 bpm, $p = 0.037$), and 12 h (158 ± 13 vs. 165 ± 14 bpm, $p = 0.046$) (Table 2). IS was significantly lower in the levosimendan group in the first postoperative hours (PCICU admission, $p < 0.0001$; 6 h, $p < 0.0001$; and 12 h, $p < 0.0001$) (Fig. 1). Lactate levels tended to be lower in the levosimendan group, with a significant difference at PCICU admission (5.1 ± 2 vs. 6.9 ± 3 mg/dL, $p = 0.015$) and at 6 h (3.9 ± 2 vs. 5.4 ± 3 bpm, $p = 0.05$) (Fig. 2). According to multivariate analysis, a lower lactate level at 6 h was independently associated with levosimendan administration after correction for CPB time and DHCA ($R = 0.59$, $p < 0.001$, Table 3).

When renal function was examined, urine trended from 6 to 9 mL/kg/h in both groups (Table 2) and the need for PD was similar in the two groups (4/4; $p = 0.85$).

Table 2 Perioperative parameters

	Surg start		PCICU		6 h[a]		12 h[a]		18 h[a]		24 h[a]		48 h[a]		72 h[a]	
	L	C	L	C	L	C	L	C	L	C	L	C	L	C	L	C
HR (bpm)	133 (16)	131 (10)	160 (15)	165 (16)	158 (16)*	169 (14)	157 (14)*	166 (16)	160 (12)*	166 (15)	158 (13)*	165 (14)	155 (15)	162 (14)	149 (12)	152 (13)
MAP (mmHg)	47 (9)	48 (14)	57 (10)	59 (11)	55 (7)	59 (8)	57 (8)	58 (9)	55 (7)	54 (6)	55 (6)	56 (6)	55 (8)	57 (8)	60 (10)	58 (6)
RAP (mmHg)	8 (4)	9 (4)	9(3)	7 (2)	7 (2)	7 (2)	8 (3)	7 (2)	9 (1)	7 (2)	8 (3)	7 (1)	9 (3)	7 (2)	7 (3)	8 (2)
LAP (mmHg)	–	–	7.8 (3)	7.7 (2)	6.9 (2)	7.5 (2)	7.4 (2)	7.0 (2)	7.5 (2)	6.6 (2)	7.1 (2)	6.8 (2)	7.3 (2)	6.8 (2)	7.6 (3)	7.1 (2)
ScvO2 (%)	49 (20)	62 (21)	51 (19)	55 (15)	57 (18)	57 (16)	64 (14)	67 (13)	63 (13)	65 (13)	67 (9)	70 (9)	65 (10)	67 (9)	66 (11)	61 (9)
BNP (pg/ml)	693 (652)	1,004 (1,021)	–	–	–	–	1,021 (881)	1,211 (802)	–	–	617 (551)	535 (405)	492 (443)	427 (374)	567 (448)	502 (320)
Diuresis (mL/kg/h)	–	–	–	–	9.1 (5)	9.5 (5)	7.3 (3)	7.8 (3)	5.7 (2)	6.6 (3)	5.6 (3)	6.7 (3)	6.5 (2)	7.2 (2)	7.0 (6)	6.9 (3)

Univariate analysis of most important perioperative parameters. All data are expressed as mean (standard deviation)

L levosimendan group ($n = 32$), *C* control group ($n = 31$), *surg start* data collection time 0 (before beginning of surgical procedure), *PCICU* data collection at PCICU admission, *HR* heart rate, *MAP* mean arterial pressure, *RAP/LAP* left/right atrial pressure, *ScvO2* mixed venous saturation, *BNP* brain natriuretic peptide

* $p < 0.05$

[a] Data collection times expressed in hours (h) after PCICU admission

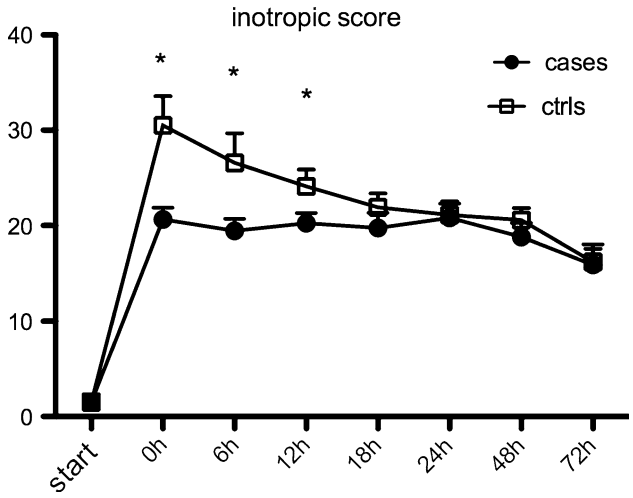

Fig. 1 Inotropic score variations over time in the two groups. *Cases* levosimendan patients, *ctrls* controls, *$p < 0.05$, *0 h* PCICU admission

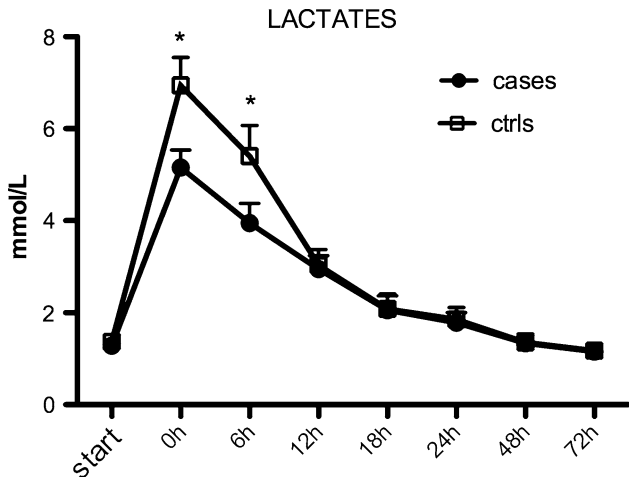

Fig. 2 Lactate level variations over time in the two groups. *Cases* levosimendan patients, *ctrls* controls, *$p < 0.05$, *0 h* PCICU admission

Table 3 Multiple regression analysis

Model	Beta coefficient (standardized)	*p*
Constant		0.426
Circulatory arrest (0 = no; 1 = yes)	0.458	0.000
Levosimendan (0 = yes; 1 = no)	0.289	0.015
Time of cross clamp (min)	0.231	0.047

Independent variables that predict plasma lactate levels at 6 h after CPB by multiple regression analysis ($R = 0.59$; $p < 0.0001$)

In order to explore the impact of levosimendan infusion on different organs function occurring after the enrollment in the two groups, the pediatric multiple organ dysfunction score (P-MODS) [21] was calculated and reported in Table 4. Average scores were low (both groups fell in the P-MODS category 1) and not significantly different in the two groups: 1.64 (0.9) in the levosimendan group versus 1.9 (0.7) in the control group ($p = 0.54$).

Table 4 Characteristics and number of organ failures that occurred after the enrollment in the two groups according to the P-MODS

	Group L	Controls	*p*
Lactates score	2.8 (0.8)	3.2 (0.7)	0.13
PaO2/FIO2 score	1.5 (0.5)	1.8 (0.7)	0.80
Bilirubin score	0.8 (1.2)	0.9 (0.9)	0.78
Fibrinogen score	1.9 (0.9)	2.1 (0.5)	0.56
BUN score	1.2 (1.5)	1.5 (0.9)	0.55
P-MODS	1.64 (0.9)	1.9 (0.7)	0.54

The P-MODS [21] evaluates heart function (by lactate levels), respiratory function (by PaO2/FIO2), liver function (by plasma bilirubin), hematopoietic function (by fibrinogen level), and renal function (by plasma BUN levels): each organ may achieve a level of severity from 0 to 4. According to P-MODS, the addition of individual components of the score yields a range of values from 0 (no organ dysfunction) to 20 (maximal organ dysfunction), divided into five categories of organs dysfunction. Organ scores were calculated as the mean (standard deviation) of the worst value for each patient during the 72 h of data collection

Group L levosimendan patients, *PaO2/FIO2* arterial oxygen to inspired fraction oxygen ratio, *BUN* blood urea nitrogen

Discussion

Our study is the first prospective trial of levosimendan administered to post cardiac surgery neonates. The pharmacological properties of levosimendan make this drug an ideal adjunct to the typical post-CPB vasoactive "mixture". In fact, by increasing the affinity of troponin C to calcium, levosimendan's effect could be additive to the action of myocardial cyclic adenosine monophosphate elicited by milrinone and dopamine/epinephrine that increases calcium concentration in the sarcolemmal membrane. In addition, optimization of the intracellular calcium concentration and affinity exerted by levosimendan appears to be particularly useful in neonatal immature hearts with a decreased sensitivity to calcium. So far, only case series and small retrospective experiences have been described in the pediatric setting. To our knowledge, this is the first study on a homogeneous group of newborn patients, who are the most delicate population in terms of LCOS incidence after cardiac surgery. As far as the results of our pilot study are concerned, levosimendan can be used safely in CHD after CPB as opposed to a recent trial in adults with acute decompensated heart failure that showed a higher incidence of atrial fibrillation, hypokalemia, and headache in patients receiving levosimendan infusion [22]. No side effects were observed, nor increased

incidence of other organ failures between the levosimendan group and controls, as shown in Table 4.

In our cohort, the incidence of LCOS was reduced by 24 % in the levosimendan group, although the difference was not significant. Similarly, several signs of organ perfusion were not significantly different between the two populations. It must be highlighted, however, that "severe LCOS" occurred rarely in both groups with no cardiac arrest nor the need for ECMO, suggesting that a larger cohort of patients was needed to achieve a significant result. The major concern with the use of levosimendan regarded its vasodilation properties that could have resulted in excessive hypotension or increased need for vasopressors: for this reason the dose was limited to the lowest described in adults and no boluses were administered [23] while the infusion was prolonged for 72 h. Our data showed that the dual inodilator strategy (levosimendan added to milrinone) did not cause a MAP reduction or an IS increase in the study group. Instead, early lactate levels, IS, and HR were reduced in levosimendan patients. In particular, the significant lower level of lactates up to 6 h after PICU admission remained significant even after adjustment for CPB time and the need for deep hypothermic circulatory arrest, which are well-known causes of derangement in organ perfusion. Lactate levels can be considered the most sensitive indirect sign of organ perfusion and a linear correlation between absolute lactate level and tissue dysoxia has been demonstrated in previous studies [24]: the beneficial effects of levosimendan administration were particularly pronounced in the typical time frame when LCOS severity is more pronounced.

This study has several limitations and some strengths. First, this was a pilot open label uncommitted trial: however, all examined outcomes are objective and unlikely to be biased by the open label strategy [25]. Second, because of the different incidence and severity of LCOS in different institutions, it is not possible to exclude that the primary outcome was not reached owing to an inadequate sample size (type II error). We predict that a future larger multicenter prospective trial with a cohort of about 150 patients per arm is needed to detect a reduction in severe LCOS incidence. Third, no data on mortality can be drawn from our results because of the very low number of deaths in the analyzed population, as was the case in the PRIMACORP trial [7, 26]. Fourth, only corrective surgery (patients with biventricular anatomy) with a medium surgical risk score was considered for our analysis: RACHS 5 and 6 patients were excluded because of their lower enrollment rate and to avoid potential confounding factors. Fifth, IS was calculated using the traditional formula that, obviously, does not take into account levosimendan. It is possible that the addition to the formula of a drug with a similar coefficient to that of milrinone (dose $\times$ 10) could have significantly reduced the gap in IS between the two groups. However, it is likely that, considering a standard milrinone dose of 0.75 μg/kg/min, the observed IS reduction was substantially due to lower catecholamine requirements in the levosimendan group (that potentially affected the higher HR in the controls): the potentially harmful effects of high catecholamine doses in immature heart have been described [20]. Finally, in the complex issue of postoperative management of hemodynamic parameters many variables other than MAP are routinely considered to optimize inotrope doses. However, we thought that titration of inotropes to recommended MAP was the easiest to recognize and, interestingly, was not included in the LCOS definition.

Conclusions

Levosimendan infusion did not significantly affect postoperative LCOS in a small cohort of neonates undergoing corrective cardiac surgery: however, levosimendan was well tolerated and significantly improved important postoperative hemodynamic parameters. Larger prospective data on hospital LOS, patients' survival, and cost analysis should confirm our results before levosimendan use in pediatric cardiac surgery can be recommended.

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