



Effect of Preoperative Infusion of Levosimendan on Biomarkers of Myocardial Injury and Haemodynamics After Paediatric Cardiac Surgery: A Randomised Controlled Trial

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Abstract

Objective The aim was to test the hypothesis that preoperative infusion of levosimendan would decrease patients' cardiac biomarker profiles during the immediate postoperative stage (troponin I and B-type natriuretic peptide levels) more efficiently than placebo after cardiopulmonary bypass.

Methods In a randomised, placebo-controlled, double-blinded study, 30 paediatric patients were scheduled for congenital heart disease surgery. 15 patients (50%) received prophylactic levosimendan and 15 patients (50%) received placebo from 12 h before cardiopulmonary bypass to 24 h after surgery.

Results Troponin I levels were higher in the placebo group at 0, 12, and 24 h after cardiopulmonary bypass, although the mean differences between the study groups and the 95% confidence intervals (CIs) for troponin I levels did not present statistically significant differences at any of the three time points considered (mean differences [95% CIs] – 3.32 pg/ml [– 19.34 to 12.70], – 2.42 pg/ml [– 19.78 to 13.95], and – 79.94 pg/ml [– 266.99 to 16.39] at 0, 12, and 24 h, respectively). A similar lack of statistically significant difference was observed for B-type natriuretic peptide (mean differences [95% CIs] 36.86 pg/dl [– 134.16 to 225.64], – 350.79 pg/dl [– 1459.67 to 557.45], and – 310.35 pg/dl [– 1505.76 to 509.82]). Lactic acid levels were significantly lower with levosimendan; the mean differences between the study groups and the 95% CIs for lactate levels present statistically significant differences at 0 h (– 1.52 mmol/l [– 3.19 to – 0.25]) and 12 h (– 1.20 mmol/l [– 2.53 to – 0.10]) after cardiopulmonary bypass. Oxygen delivery (DO₂) was significantly higher at 12 h and 24 h after surgery (mean difference [95% CI] 627.70 ml/min/m² [122.34–1162.67] and 832.35 ml/min/m² [58.15 to 1651.38], respectively).

Conclusions Levosimendan does not significantly improve patients' postoperative troponin I and B-type natriuretic peptide profiles during the immediate postoperative stage in comparison with placebo, although both were numerically higher with placebo. Levosimendan, however, significantly reduced lactic acid levels and improved patients' DO₂ profiles. These results highlight the importance of this new drug and its possible benefit with regard to myocardial injury; however, evaluation in larger, adequately powered trials is needed to determine the efficacy of levosimendan.

Trial registry number: EudraCT 2012-005310-19.

1 Introduction

Low cardiac output syndrome in children is mainly associated with congenital heart disease, cardiomyopathy, or sepsis. After cardiac surgery, its incidence is nearly 25% [1]. Risk factors in this context are related to the patient's preoperative condition, age, type of surgery (corrective or palliative), and duration of aortic clamping, changes in pulmonary and systemic vascular resistance, cardioplegia, and the activation or otherwise of systemic inflammatory response syndrome due to extracorporeal circulation. These factors can induce the appearance of ventricular dysfunction

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Key Points

A randomised controlled trial was conducted to test the hypothesis that preoperative infusion of levosimendan would decrease myocardial injury biomarkers (troponin I and B-type natriuretic peptide) after paediatric cardiac surgery more efficiently than placebo.

Troponin I and B-type natriuretic peptide levels were higher with placebo at 12 and 24 h after cardiopulmonary bypass, but the differences were not statistically significant. Lactic acid level was significantly lower and oxygen delivery (DO₂) was significantly higher at 12 and 24 h after surgery in Levosimendan group.

The results highlight the importance of this new drug and its possible benefit with regard to myocardial injury; however, evaluation in larger, adequately powered trials is needed to determine the efficacy of levosimendan.

secondary to myocardial ischaemia and an acute inflammatory response [2].

For these patients, the occurrence of heart failure in the immediate postoperative phase produces a considerable increase in morbidity and mortality, due to the longer period of mechanical ventilation required and the longer stay in an intensive care unit mainly. Therefore, the early treatment (and ideally, prevention) is an essential objective in the surgical intervention performed [3].

The current protocols for treating heart failure include the administration of catecholamines, milrinone, and, more recently, levosimendan [4]. Unlike the situation in adult patients, cardiac output monitoring in children is a complex matter; validated echocardiographic parameters have not yet been established and treatment is fundamentally based on clinical evaluation and the monitoring of parameters such as lactate levels, diuresis, central venous oxygen saturation, cerebral near-infrared spectroscopy (NIRS), laboratory parameters of end organ function, and haemodynamic pressures [2, 5].

The standard treatment of low cardiac output with inotropic drugs heightens contractility by increasing cyclic adenosine monophosphate (cAMP) and free intracellular calcium, which in turn increases oxygen consumption and raises the risk of arrhythmia and cell death [6]. Levosimendan belongs to a new category of inotropic drugs termed calcium sensitisers, which improve myocardial contractility by increasing the sensitivity of myofibrils to calcium during systole, thus achieving greater inotropic power without increasing the concentration of intracellular calcium, in contrast to alternative inotropic drugs. As a consequence, there is no increase in myocardial oxygen consumption, which

is the main disadvantage of other inotropic drugs. Levosimendan, unlike milrinone, does not progressively increase intracellular calcium levels and therefore does not aggravate the risk of arrhythmia [7] or produce other effects associated with increased intracellular calcium, such as cell death, systolic and/or diastolic dysfunction, or increased consumption of oxygen by myocytes [8, 9]. In addition, levosimendan exerts a cardioprotective effect on the cardiac muscle by opening the mitochondrial potassium channels of the cardiomyocyte. These features mean that levosimendan has a cardioprotective effect and, from a theoretical standpoint, makes an ideal drug for the management of low cardiac output [9–11]. Levosimendan does not provoke any increase in myocardial oxygen consumption, due to its combined vasodilatory effect, which reduces the afterload. This effect is responsible for its myocardial anti-ischaemic action, thus improving the stunned myocardium function, preventing myocardial apoptosis and stimulating a pre-ischaemic myocardial conditioner [12–17]. The haemodynamic effects of levosimendan are greatest in the first 72 h after administration and persist for at least 7 days after the infusion is concluded [18]. Mindful of these cardioprotective effects, the present study was designed to evaluate the efficacy of levosimendan in the pre-ischaemic myocardial conditioning of paediatric patients considered at high risk of suffering low cardiac output in the immediate postoperative period.

This study, therefore, tests the hypothesis that levosimendan infusion, when started in the preoperative stage of congenital heart disease surgery, could prevent postoperative myocardial dysfunction in children. The primary study aim was to study the effect of levosimendan versus placebo treatment, administered during the preoperative stage of congenital heart disease surgery, on troponin I and B-type natriuretic peptide (BNP), biomarkers of myocardial injury, during the immediate postoperative period.

2 Methods

The study was approved by the Andalusian Regional Ethics Committee (code: EudraCT 2012-005310-19; date of approval, 12 December 2012). Signed informed consent was obtained from the parents/guardians of all the participants. This randomised, phase III, double-blind, placebo-controlled clinical trial was conducted in a single hospital (Virgen de las Nieves University Hospital, Granada, Spain). The participants, aged between 28 days and 13 years, were randomised in a 1:1 procedure into two groups. The intervention was masked from the investigator, the nursing staff, and the patients. Two intervention branches were analysed: levosimendan versus placebo. The duration of the treatment phase was 36 h.

2.1 Inclusion and Exclusion Criteria

All patients were transferred from the operation room to the paediatric intensive care unit (PICU) in Virgen de las Nieves University Hospital in Granada, Spain. Patients were aged between 28 days and 13 years, and were scheduled for cardiopulmonary bypass. The patients needed to have at least two of the following risk factors for developing low cardiac output after surgery:

- Aged less than 6 months or weighing less than 7 kg at the time of surgery
- Heart failure before the surgery (defined as clinical stage III–IV according to the modified Ross Classification of cardiac insufficiency in children [19])
- Due to the complexity of the surgery, an estimated bypass time exceeding 100 min
- Preoperative pulmonary hypertension (defined by a mean pulmonary artery pressure greater than 25 mmHg at rest, with systolic pressure greater than 35 mmHg by echocardiography [20]) or a high risk of postoperative pulmonary hypertension (heart disease with pulmonary shunting).

Exclusion criteria were patients aged less than 28 days or more than 13 years, patients not meeting at least two of the above factors, refusal by the parents/guardians to participate in the study or refusal to provide informed consent, allergy or hypersensitivity to levosimendan or other components of Simdax[®], or patients to whom the study medication cannot be prescribed because it is contraindicated according to the technical data sheet, such as mechanical obstructions that affect ventricular filling or emptying or both, severe renal insufficiency (creatinine clearance [CrCl] < 30 ml/min), severe hepatic insufficiency, refractory arterial hypotension, and malignant arrhythmia (torsades de pointes). Excluded patients included those with a history of autoimmune disease and patients who were receiving inotropic infusions before surgery.

2.2 Settings

This clinical trial took place at the Virgen de las Nieves University Hospital in Granada, Spain. Patients were enrolled at the PICU, where levosimendan or placebo infusion was initiated 12 h before surgery. The infusion was continued in the operation room during the cardiopulmonary bypass and later when the patients came back to the PICU, where the infusion was maintained 24 h more.

2.3 Intervention

Patients were selected consecutively among those who met the inclusion criteria. On receipt of the corresponding signed informed consent forms, the patients were assigned to a specific treatment group (levosimendan or placebo) by a simple randomisation process, in which a succession of random numbers were generated using specialised software for this purpose (M.A.S. 2.1[®], GlaxoSmithKline). This randomisation was performed by the hospital pharmacy service 24 h before the cardiopulmonary bypass.

In accordance with the study protocol, the levosimendan or placebo infusion was initiated 12 h before the cardiopulmonary bypass procedure, continued during the surgery, and subsequently maintained for 24 h in the PICU.

The endpoints were assessed on arrival from the operating room and at 12 h and 24 h after postoperative admission. This last matched in time with the end of the levosimendan or placebo infusion.

The appropriate dosage of levosimendan, according to the drug package insert, is 0.05–0.2 µg/kg/min, with a prior loading dose of 6–12 µg/kg. Previous comparable studies of paediatric patients have used dosages of 0.1–0.2 µg/kg/min, in most cases, also with a loading dose. However, in the present trial, it was decided not to administer the loading dose, but rather to start perfusion at the maximum dosage recommended in the drug package insert. This dosage has been shown to be safe, and in the absence of a loading dose, the risk of hypotension or excessive vasodilatation is reduced [21]. After randomisation, the patients were given a continuous infusion of levosimendan or placebo from 12 h before the surgery until 24 h afterwards (i.e. 36 h of treatment), as described below:

- *Experimental group:* Levosimendan was supplied intravenously at a dosage of 0.2 µg/kg/min diluted in 5% glycated serum from 12 h before the surgery until 24 h after surgery (with no loading dose) (Levo, Anatomical Therapeutic Chemical [ATC] Classification group code C01CX: other cardiac stimulants; trade name: Simdax[®]; presentation: 2.5 mg/ml; concentrate for infusion solution; pack with 5-ml vial; route of administration: intravenous).
- *Placebo group:* These patients received a continuous intravenous infusion of glucose serum at 5% (GS5%), prepared in opaque syringes identical in appearance and with the same volume as those used for the intravenous administration of levosimendan.

The intervention was masked to the investigator who assigned the treatment groups, to the patients' parents/guardians, and to the nurse who administered the intervention (observer). The Hospital Pharmacy Service was responsible

for supplying the intervention material and the placebo as individualised daily doses through dose drug dispensing system. Identical syringes and opaque infusion systems were used in order to prevent visualisation of the drug's colour (levosimendan is a yellow-orange solution). The systems for administration of the drug were received pre-purged (with 1.5 ml of GS5%) to facilitate direct administration.

The intervention materials were labelled in accordance with the regulations set out in Annex 13 on the labelling of drugs used in clinical research, issued by the Spanish Agency of Medicines and Medical Devices. Following the cardiopulmonary bypass, patients in both groups received the additional inotropic treatment needed according to their individual haemodynamic situation, following the recommendations for the management of the postoperative myocardial dysfunction after cardiopulmonary bypass [4].

Regarding the potential adverse effects of levosimendan, it was decided that patients would be excluded from the study if any of the following situations arose: a serious adverse event, serious adverse reaction, a severe intercurrent disease, or the withdrawal of consent by the patient's parents/guardians.

2.4 Endpoints of the Study

The primary endpoint of the study was at 24 h after surgery, when levels of troponin I and BNP were determined.

To date, no echocardiographic parameters have been validated for cardiac output monitoring in children, so the present assessment is based on the evaluation of multiple physiological parameters and analytical parameters such as lactate levels and central venous oxygen saturation [2]. However, troponin I is a sensitive and specific biomarker of myocardial injury after cardiopulmonary bypass and an independent predictor of postoperative myocardial dysfunction after congenital heart disease surgery in children [22].

Parameters such as the safety of levosimendan infusion in children, possible adverse effects during the intravenous infusion, the duration of mechanical ventilation, the length of stay in the PICU, and the 30-day mortality rate were addressed in the secondary study aims.

When patients were assigned to the corresponding study groups, the following demographic variables were collected: sex, age, weight, body surface area, surgically treatable congenital heart disease, Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, prior pharmacological treatment with angiotensin-converting enzyme inhibitors, digoxin, or beta-blockers, and preoperative levels of BNP. After surgery, aortic clamping time, length of cardiopulmonary bypass (minutes), and modified ultrafiltration volume (millilitres) were recorded.

From the preoperative stage to 24 h after surgery, all patients were continuously monitored, and physiological

variables such as heart rate, respiratory rate, central and peripheral temperature (rectum and foot, respectively), arterial pressure, and pulse oximetry were recorded before starting the study infusion.

Acid–base status, lactate levels, haemoglobin concentration, and BNP (pg/dl) were studied at the patient's admission to the PICU. Intermediately after the surgical procedure and later at 12 and 24 h after the surgery, all these parameters were determined in addition to troponin I levels.

In addition, the following variables were measured when the patient was admitted to the PICU after the surgical procedure and at 12 and 24 h after the surgery: heart rate, mean arterial pressure (MAP; mmHg), central venous pressure (CVP; mmHg), thermal gradient (°C), capillary refill time (seconds), diuresis (ml/kg/h), creatinine (mg/dl), CrCl (ml/min/1.73 m²), arrhythmia, vasoactive-inotropic index (VIS) score, central venous oxygen saturation (%), and oxygen delivery (DO₂) (ml/min/m²).

Prior to discharge from the PICU, data on length of stay (days), days of invasive mechanical ventilation required, appearance of complications and/or adverse effects, and the rate of survival at 30 days were collected.

2.5 Statistical Analysis

The sample size required for the study was calculated by reference to data obtained in previous research in this field. Regarding other study parameters, decreased BNP levels have been observed after levosimendan infusion in patients with acute heart failure, although without quantifying the difference versus placebo treatment. In contrast, other haemodynamic variables have been reported to improve. Thus, Magliola et al. [23] described a 50% improvement in the inotropic score and in the arteriovenous oxygen difference (AVDO₂) in patients with postoperative myocardial dysfunction after cardiopulmonary bypass when they were administered levosimendan versus patients who did not receive this treatment. Therefore, to detect differences in the test of the null hypothesis (H₀) that $p_1 = p_2$ by a bilateral χ^2 test for two independent samples, with a power of 0.8 and an error $\alpha = 0.05$, we calculated that 15 patients should be included in each group.

The study data were analysed using SPSS Statistics for Windows (version 19; IBM Corp., Armonk, New York, USA), according to intention to treat. The continuous variables are expressed as means and 95% confidence intervals (CIs) and the qualitative ones in terms of absolute and relative frequencies. The normality of the data distribution was determined by the Shapiro-Wilk test. Possible differences between the groups were identified by means of a bivariate analysis, applying Student's *t* test for independent samples. For non-normal distributed variables, bootstrap simulation was performed to calculate the 95% CIs and the differences

in means. The qualitative variables were analysed using Pearson's chi-square or Fisher's exact test, and the continuous variables by calculating the mean differences between the two groups and the corresponding 95% CIs. For the qualitative data, odds ratios (ORs) and 95% CIs were calculated. Two-tailed *P* values less than 0.05 were considered statistically significant.

3 Results

During the study period (January 2013 to November 2016), 30 patients were scheduled for paediatric cardiac surgery at the Virgen de las Nieves University Hospital. 15 (50%) received levosimendan and 15 (50%) received the placebo. The trial concluded in accordance with the date foreseen in the protocol presented to the Andalusian Progress and Health Foundation.

The demographic and baseline clinical characteristics of all patients are shown in Table 1. We are aware that we have included a heterogeneous population of patients due to the low prevalence of paediatric patients requiring cardiac surgery nowadays. There were no statistically significant differences between the groups in terms of clinical characteristics prior to the intervention, pharmacological treatment, pre-surgical BNP values, or RACHS-1 score. Table 2 is attached in order to describe each of the performed procedures in each study group.

Two patients presented severely low cardiac output that caused the blinding to be suspended. Both patients were originally assigned to the placebo group, and when the blinding was suspended, they initiated levosimendan. One of these patients had three episodes of cardiorespiratory arrest, which were survived, and the other one required extracorporeal membrane oxygenation therapy. This second patient subsequently died of a cerebral haemorrhage.

Among all the patients in the treatment group, haemodynamic tolerance to the administration of levosimendan was excellent, and it was not associated in any case with adverse effects that required suspension of the treatment. In fact, no patients in levosimendan group required suspension of blinding, extracorporeal membrane oxygenation therapy or heart transplantation. No patients of any group required a heart transplant.

Table 3 shows the results obtained for each study group (levosimendan vs. placebo), collected on admission to the PICU and at 12 and 24 h after the cardiopulmonary bypass procedure. Troponin I was higher in the placebo group at 0, 12, and 24 h after cardiopulmonary bypass, although the differences were not statistically significant. BNP levels were higher 12 and 24 h after cardiopulmonary bypass, although the differences were not statistically significant either.

Table 1 Demographic and baseline clinical characteristics of the two groups of patients

	Levosimendan (<i>n</i> = 15)	Placebo (<i>n</i> = 15)	<i>P</i>
Male/female, <i>n</i> (%)	9 (60)/6 (40)	10 (66.7)/5 (33.3)	0.705
Weight, kg	6 [5.1–13.5]	7 [5.2–13]	0.678
Height, cm	66 [63–100]	65 [61–92]	0.835
Age, years	0.6 [0.5–4]	0.9 [0.6–8]	0.517
Body surface area, m ²	0.3 [0.3–0.6]	0.3 [0.3–0.5]	0.824
Pharmacological preoperative treatment, <i>n</i> (%)			
ACE inhibitors, <i>n</i> (%)	7 (46.7)	3 (20)	0.121
Beta-blockers, <i>n</i> (%)	0 (0)	2 (13.3)	0.483
Digoxin, <i>n</i> (%)	0 (0)	1 (6.7)	1
Preoperative PHT, <i>n</i> (%)	9 (60)	5 (33.3)	0.143
Preoperative BNP, pg/dl	104.5 [42.85–155.5]	32.5 [22.6–81]	0.063
Corrective surgery, <i>n</i> (%)	15 (100)	14 (93.3)	1
Bypass duration (min)	113 [95–130]	113 [106–154]	0.519
Clamp duration (min)	77 [55–91]	85 [72–120]	0.329
MUF, ml	416.67 ± 186.76	325.00 ± 224.07	0.248
RACHS-1	2 [2, 3]	2 [2–2]	0.671

Normal numerical variables are expressed as mean and standard deviation, and the nonparametric variables as median [P25–P75]. Qualitative variables are expressed in frequency and percentage

ACE angiotensin-converting enzyme inhibitors, BNP B-type natriuretic peptide, MUF modified ultrafiltration volume, PHT pulmonary hypertension, RACHS-1 Risk Adjustment for Congenital Heart Surgery

Lactate levels were higher with the placebo at 0 and 12 h after cardiopulmonary bypass, and significant differences were observed also with the DO₂ values, which were higher in the experimental group at 12 and 24 h after surgery. Figures 1, 2, 3, and 4 are attached in order to summarise part of the information shown in Table 3.

Our analysis of the other study parameters such as the VIS and of physiological variables such as CVP did not reveal statistically significant differences between the groups, although both parameters were higher with placebo at each of the three time points. Regarding the other physiological variables analysed, there were no significant differences between the groups.

There were no statistically significant differences between the groups regarding the incidence of arrhythmia in the postoperative period (13.3% in the levosimendan group

Table 2 Procedures performed in each group

	SMI	CIV	AV canal	AV canal + T. Fallot	CIA + CIV	T. Fallot	CIV + DO-RV	SPI	AoS	PVR
Levosimendan (<i>n</i> = 15)	1	5	4	0	0	2	0	1	1	1
Placebo (<i>n</i> = 15)	3	2	2	1	2	3	2	0	0	0

AoS subaortic stenosis resection, *AV canal* surgical correction of atrioventricular canal defects, *CIA* surgical correction of atrial septal defects, *CIV* surgical correction of ventricular septal defects, *DO-RV* surgical correction of double-outlet right ventricle, *PVR* total pulmonary vein repair, *SMI* surgical correction of mitral insufficiency, *SPI* surgical correction of pulmonary insufficiency, *T. Fallot* surgical correction of tetralogy of Fallot

and 13.3% in the control group; mean difference [95% CI] 1 [0.12–8.21]; Table 4). This table also shows that for the duration of invasive mechanical ventilation and the length of stay in the PICU, there were no statistically significant differences between the groups. Regarding the outcome variables, 30-day survival was 100% in the levosimendan group, but 13.3% of the patients in the control group died during this period.

4 Discussion

Levosimendan may be advantageous in patients requiring inotropic support who are also at risk of myocardial ischaemia. Activation of adenosine triphosphate-regulated potassium channels during infusion of levosimendan may produce cardioprotective effects while simultaneously enhancing ventricular contractile function. Experimental evidence indicates that K_{ATP} -channel activation is the end-effector of a cardioprotective signal transduction pathway activated during ischaemic preconditioning. Levosimendan stimulates glyburide-sensitive K_{ATP} -channel currents in ventricular and arterial myocytes, and this occurs independently of myofilament Ca^{2+} -sensitising properties of this drug, hyperpolarises arterial smooth muscle cells in vitro, decreases intracellular calcium concentration, and relaxes coronary arteries independently of intracellular calcium concentration. Levosimendan increased coronary blood flow and increased subepicardial and midmyocardial collateral perfusion at a dose that produces a concomitant positive inotropic effect [11].

In order to assess the haemodynamic effects of the preoperative infusion of levosimendan in paediatric patients scheduled for cardiopulmonary bypass surgery, we examined two cardiac biomarker profiles: troponin I and BNP levels. These parameters were determined at three time points during the first 24 h after surgery. From the results obtained, we cannot conclude that levosimendan versus placebo reduces postoperative troponin I or BNP levels. Although both biomarkers were higher at 12 and 24 h after surgery with the placebo, the differences were not statistically significant.

Previous studies have shown that BNP and N-terminal prohormone of brain natriuretic peptide (NT-proBNP),

rather than being independent predictors of mortality in patients with heart failure, are in fact predictors of postoperative myocardial dysfunction [24]. In this respect, Parissis et al. reported a significant decrease in plasma BNP levels after the administration of levosimendan in patients with abnormal left ventricular diastolic function [25], and a recent meta-analysis concluded that levosimendan infusion in adult patients with acute heart failure appeared to reduce BNP, compared with placebo or furosemide [26].

According to prior research, the preoperative infusion of levosimendan reduces troponin I levels in the immediate postoperative period, although these results were not confirmed in our study. A prospective randomised study by Tritapepe et al. concluded that patients who received levosimendan before cardiopulmonary bypass surgery presented lower troponin I levels and had a significantly higher index of cardiac output than the control group [27]. These findings were corroborated by Momeni et al., who performed the first randomised, double-blind, prospective study of paediatric patients undergoing cardiac surgery, to compare the intraoperative administration of levosimendan versus milrinone. These authors obtained similar results, reporting lower postoperative plasma troponin I levels in the patients who received intraoperative levosimendan [28].

Levosimendan treatment also failed to have any significant impact on mortality and length of stay in the PICU, days of mechanical ventilation, or survival rates. Nevertheless, the survival rate was 100% with levosimendan, and none of these cases required suspension of the blinding, while with placebo, two patients presented a severe postoperative myocardial dysfunction, and it was necessary to suspend the blinding before 24 h after the cardiopulmonary bypass.

The patients in the levosimendan group did not present reduced MAP values, higher heart rate, or greater development of arrhythmia at any time during follow-up. In fact, no adverse effects due to levosimendan infusion were observed.

Only limited information has been published about the proportions of paediatric patients experiencing side effects from the administration of levosimendan. In this respect, values ranging from 0% to 54% have been reported [24–26]. The prevalence of hypotension, one of the most dangerous side effects, has been estimated at 11–30% according

Table 3 Results obtained for each study group collected on admission to the paediatric intensive care unit (PICU) and at 12 and 24 h after the cardiopulmonary bypass procedure

	Admission to the PICU after surgery			12 h after surgical intervention			24 h after surgical intervention		
	Levosimendan 15 (50%)	Placebo 15 (50%)	Mean diff. [95% CI]	Levosimendan 15 (50%)	Placebo 15 (50%)	Mean diff. [95% CI]	Levosimendan 15 (50%)	Placebo 15 (50%)	Mean diff. [95% CI]
Laboratory variables									
BNP (pg/dl)	175.54 [68.02 to 330.19]	138.67 [52.36 to 262.29]	36.86 [-134.16 to 225.64]	744.69 [446.16 to 1,085.17]	1095.48 [239.72 to 2234.66]	-350.79 [-1,459.67 to 556.98]	556.98 [304.00 to 935.18]	867.33 [292.43 to 1,979.69]	-310.35 [-1505.76 to 509.82]
Troponin (pg/ml)	30.38 [19.07 to 41.70]	33.70 [21.31 to 46.08]	-3.32 [-19.34 to 12.70]	19.55 [10.79 to 30.48]	21.97 [10.10 to 38.27]	-2.42 [-19.78 to 13.95]	15.86 [8.88 to 24.66]	89.80 [3.61 to 278.59]	-79.94 [-266.99 to 16.39]
Lactate (mmol/l)	1.26 [1.00 to 1.60]	2.78 [1.51 to 4.45]	-1.52 [-3.19 to -0.25]	0.97 [0.79 to 1.18]	2.18 [1.12 to 3.50]	-1.20 [-2.53 to 0.10]	1.72 [0.67 to 3.84]	1.65 [0.77 to 3.10]	0.06 [-2.12 to 2.62]
Creatinine (mg/dl)	0.50 [0.44 to 0.57]	0.53 [0.43 to 0.63]	-0.03 [-0.14 to 0.08]	0.50 [0.42 to 0.57]	0.62 [0.50 to 0.73]	-0.12 [-0.25 to 0.01]	0.58 [0.45 to 0.72]	0.64 [0.52 to 0.81]	-0.06 [-0.27 to 0.12]
Physiological variables									
MAP (mmHg)	60.62 [54.38 to 66.86]	62.67 [53.46 to 71.88]	-2.05 [-12.67 to 8.58]	58.54 [52.51 to 64.57]	62.11 [58.23 to 66.00]	-3.57 [-10.43 to 3.28]	61.11 [57.24 to 64.99]	59.81 [50.49 to 69.12]	1.31 [-8.05 to 10.66]
HR (bpm)	138.13 [124.04 to 152.23]	134.47 [114.62 to 154.31]	3.67 [-19.58 to 26.92]	125.87 [115.51 to 136.22]	133.33 [114.59 to 127.07]	-7.47 [-27.92 to 12.98]	128.67 [114.92 to 142.41]	128.21 [111.32 to 145.11]	0.45 [-20.17 to 21.08]
Thermal gradient (°C)	4.01 [2.76 to 5.26]	5.36 [3.86 to 6.86]	-1.34 [-3.19 to 0.51]	3.73 [2.28 to 5.32]	3.94 [2.08 to 6.57]	-0.22 [-2.95 to 2.15]	3.93 [2.79 to 5.33]	2.78 [1.43 to 4.22]	1.15 [-0.73 to 3.18]
Capillary filling (s)	2.79 [2.19 to 3.46]	3.27 [2.69 to 4.00]	-0.49 [-1.37 to 0.46]	2.37 [1.95 to 2.82]	2.78 [2.00 to 3.67]	-0.41 [-1.43 to 0.44]	2.08 [1.50 to 2.61]	2.55 [1.71 to 3.40]	-0.47 [-1.50 to 0.57]
Diuresis ml/kg/h	3.29 [2.50 to 4.26]	3.14 [2.65 to 3.64]	0.15 [-0.74 to 1.16]	1.64 [1.33 to 1.99]	1.27 [0.92 to 1.70]	0.37 [-0.13 to 0.83]	2.18 [1.51 to 2.90]	1.90 [1.06 to 2.77]	0.28 [-0.80 to 1.35]
CVP (mmHg)	9.80 [7.91 to 11.69]	12.67 [10.27 to 15.06]	-2.87 [-5.78 to 0.04]	8.80 [6.27 to 11.33]	11.27 [9.20 to 13.33]	-2.47 [-5.59 to 0.65]	11 [8.81 to 13.19]	12.50 [10.72 to 14.28]	-1.5 [-4.21 to 1.21]
Arrhythmia n (%)	2 (13.3%)	0 (0.00%)	-	2 (13.3%)	3 (20%)	0.615 [0.09 to 4.34]†	2 (13.3%)	2 (13.3%)	1 [0.121 to 8.210]‡
Calculated parameters									
DO ₂ (ml/min/m ²)	1325.14 [959.74 to 1690.55]	1164.59 [675.69 to 1653.49]	160.55 [-420.19 to 741.29]	1489.81 [1120.48 to 1997.98]	862.11 [562.80 to 1184.41]	627.70 [122.34 to 1,162.67]	1,686.17 [1065.83 to 2,360.36]	853.82 [428.61 to 1327.79]	832.35 [58.15 to 1651.38]
ScvO ₂ (%)	62.82 [56.48 to 68.30]	64.86 [54.67 to 74.22]	-2.04 [-13.65 to 9.77]	64.03 [59.18 to 69.84]	58.92 [46.62 to 69.54]	5.10 [-6.65 to 18.70]	66.14 [61.04 to 70.76]	61.66 [53.10 to 68.61]	4.49 [-4.09 to 13.83]
VIS	13.50 [4.50 to 30.99]	133.18 [4.50 to 406.20]	-119.68 [-394.37 to 14.86]	31.87 [-7.61 to 71.34]	79.71 [-14.12 to 173.55]	-47.85 [-145.07 to 49.38]	27.10 [-11.33 to 65.53]	78.79 [-67.58 to 225.16]	-51.69 [-191.12 to 87.74]
CrCl (ml/min. 1.73 m ²)	81.29 [67.26 to 97.63]	86.40 [67.16 to 108.34]	-5.10 [-31.64 to 18.39]	87.74 [72.32 to 105.00]	82.79 [57.64 to 106.44]	4.96 [-26.52 to 36.10]	88.43 [61.78 to 115.09]	75.22 [51.05 to 99.41]	13.20 [-21.41 to 47.83]

Numerical variables are expressed as mean and 95% confidence interval (CI). Qualitative variables are expressed in frequency and percentage. For numerical variables mean difference and CI was calculated, and odds ratio (OR) and 95% CI for categorical data

MAP mean arterial pressure, HR heart rate, CVP central venous pressure, BNP B-type natriuretic peptide, DO₂ oxygen delivery, ScvO₂ central venous oxygen saturation, VIS vasoactive-inotropic score, CrCl creatinine clearance

†OR and 95% CI

Fig. 1 B-type natriuretic peptide (BNP) levels obtained for each study group, collected on admission to the PICU and at 12 h and 24 h after the cardiopulmonary bypass procedure. *PICU* paediatric intensive care unit BNP profile during first twenty-four hours after cardiopulmonary bypass procedure for each study group

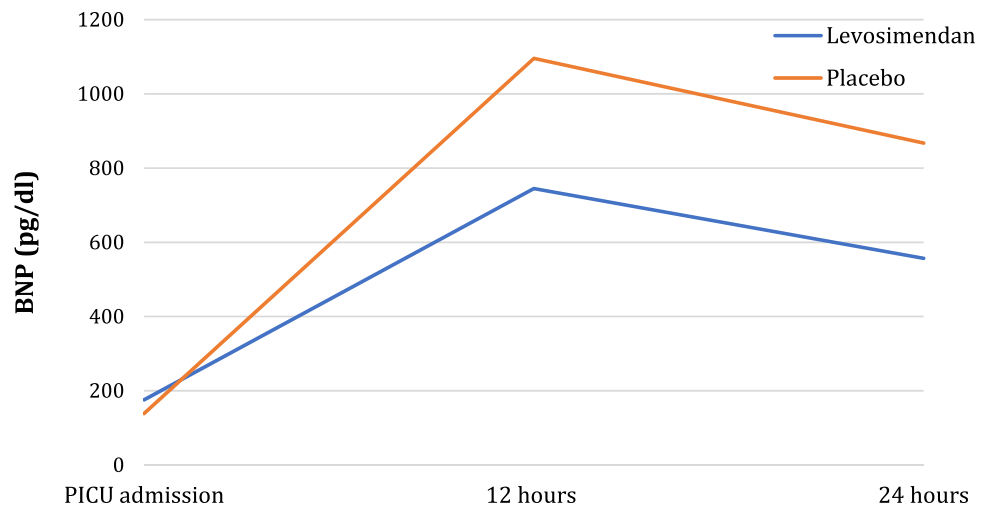


Fig. 2 Troponin I levels obtained for each study group, collected on admission to the PICU and at 12 h and 24 h after the cardiopulmonary bypass procedure. *PICU* paediatric intensive care unit Troponin I profile during first twenty-four hours after cardiopulmonary bypass procedure for each study group

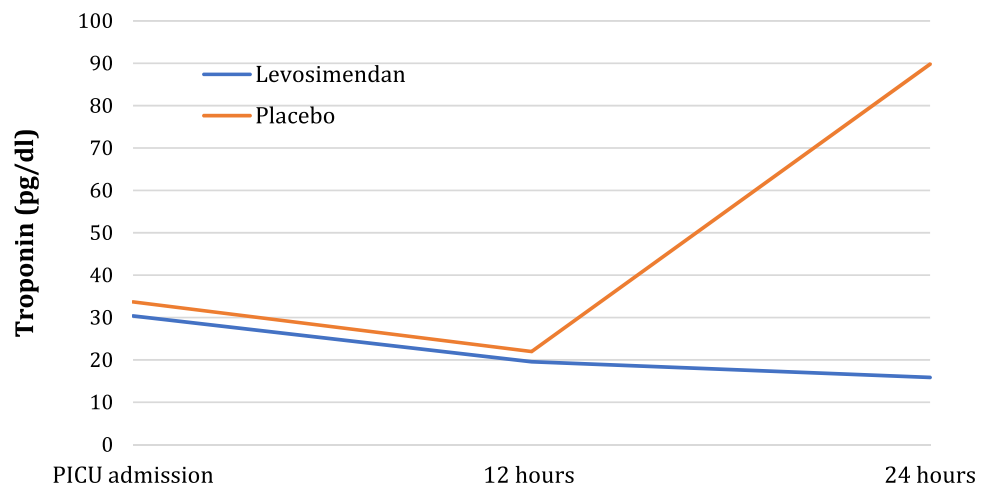
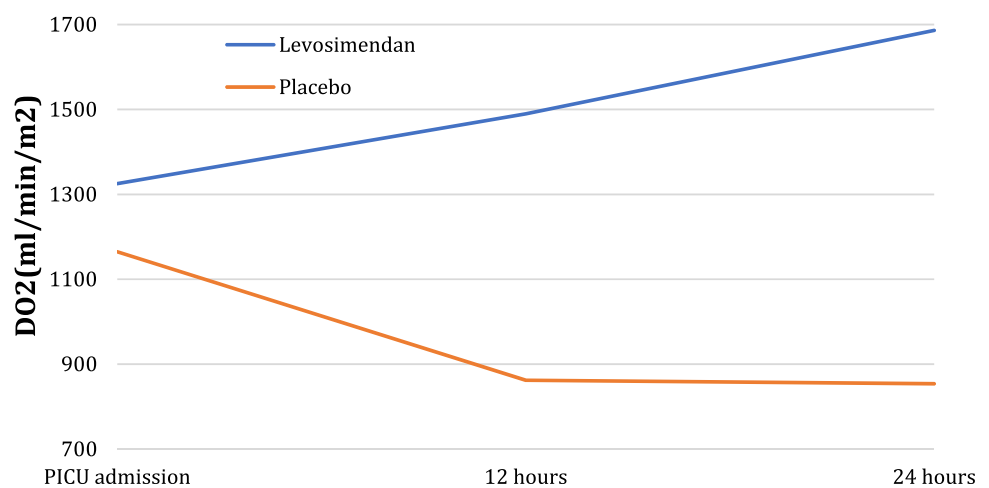


Fig. 3 Oxygen delivery (DO_2) levels obtained for each study group, collected on admission to the PICU and at 12 h and 24 h after the cardiopulmonary bypass procedure. *PICU* paediatric intensive care unit DO_2 profile during first twenty-four hours after cardiopulmonary bypass procedure for each study group



to retrospective studies [29]. Other adverse effects of levosimendan have been described as arrhythmia, dizziness, headache, insomnia, hypocalcaemia, anaemia, and

gastrointestinal disorders. No fatal adverse effects have been reported [16].

Fig. 4 Lactate levels obtained for each study group, collected on admission to the PICU and at 12 h and 24 h after the cardiopulmonary bypass procedure. *PICU* paediatric intensive care unit Lactate levels profile during first twenty-four hours after cardiopulmonary bypass procedure for each study group

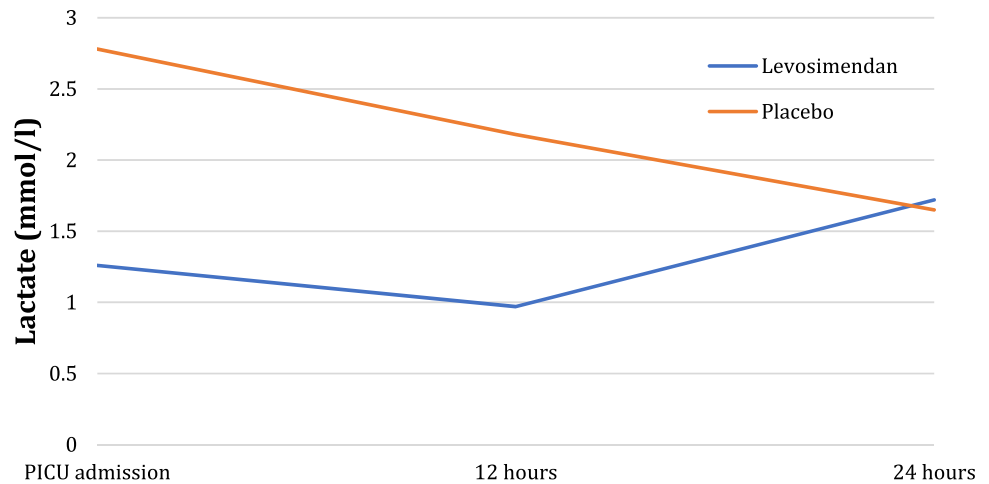


Table 4 Results for invasive mechanical ventilation, duration of stay in PICU, and 30-day survival

	Levosimendan 15 (50%)	Placebo 15 (50%)	Mean diff. [95% CI]
Invasive mechanical ventilation (days)	4.06 [0.67–9.97]	3.02 [0.92–6.30]	1.05 [–4.14 to 7.41]
PICU (days)	10.73 [4.86–18.13]	8.27 [6.06–11.00]	2.47 [–4.24 to 10.42]
Post operative arrhythmia (n)	2 (13.3%)	2 (13.3%)	1 [0.121 to 8.210] ^a
Exitus	0 (0%)	2 (13.3%)	–

Numerical variables are expressed as mean and 95% confidence interval (CI). Qualitative variables are expressed in frequency and percentage

PICU Pediatric intensive care unit

^aOR 95% CI

Current evidence for the administration of levosimendan as a myocardial conditioner for adult patients remains slight, and this treatment is not recommended [30]. For children, even less research evidence is available about prophylactic levosimendan infusion as a pre-ischaemic myocardial conditioner. Thus, a recent Cochrane meta-analysis evaluated only five clinical trials. Our study was cited in this meta-analysis, but not assessed because the outcome data had not yet been published [16]. It is important to note certain differences between our study and those included in the meta-analysis. On the one hand, none of the latter studied levosimendan versus placebo. On the other, our trial is the first to include the application of a conditioning protocol during the preoperative stage; other researchers have studied the administration of levosimendan initiated either intraoperatively or in the immediate postoperative period.

Analysis of other parameters related to the patients' haemodynamic status suggests that ours may be a valuable approach. Significant differences were recorded between the lactate levels in each group, both on admission to the operating theatre and at 12 h after the cardiopulmonary bypass surgery. In addition, DO_2 levels at 12 and 24 h after surgery were statistically significantly higher with levosimendan

than with the placebo. These results support those published by Egan et al. [31] and Ricci et al. [32], both of whom reported a significant decrease in lactate levels with levosimendan infusion. Moreover, these results are in line with those obtained in small-scale paediatric research, such as that performed by Osthau et al. [33], who reported that while haemodynamic parameters such as heart rate, CVP, and MAP were not improved by levosimendan, there was a significant increase in venous oxygen saturation and a significant decrease in lactate levels at 24 and 48 h after the start of the levosimendan infusion. This outcome is further evidence of the known inotropic effect of the drug.

The present study presents certain limitations that should be acknowledged. Although the clinical trial was randomised and double blinded, the number of patients was small. Moreover, no echocardiographic parameters were measured, because none had yet been validated for cardiac output monitoring in children, which is why the present assessment is based exclusively on the evaluation of physiological and analytical parameters. Finally, although no adverse effects of levosimendan infusion were recorded, the lack of statistical power of this study with regard to the safety of levosimendan should be taken into account. In consequence,

further research in this area, with particular reference to the paediatric population, is needed to corroborate and extend the findings reported in this paper.

5 Conclusions

Levosimendan does not significantly influence the postoperative cardiac biomarker profile during the immediate postoperative stage (troponin I and BNP levels) in comparison with placebo, though both biomarker levels were numerically higher with placebo after cardiopulmonary bypass. Levosimendan, however, significantly reduced lactic acid levels and improved patients' DO₂ profiles after surgery. These results are indicative of the favourable effects of levosimendan on the cardiac muscle; however, we agree with other authors in this field that further research based on larger-scale, randomised, controlled trials is needed to enhance our understanding of the myocardial conditioning effect of levosimendan and its role in the complex management of postoperative myocardial dysfunction in the paediatric population.

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Declarations

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Conflict of Interest The authors, AA-M, JMG-L, FP, ME-M, AF-M, CF-G, and EO-H, declare that there is no conflict of interest.

Ethics approval The study was approved by our Regional Ethics Committee (ethical committee code EudraCT 2012-005310-19); Andalusian Regional Ethics Committee, Seville, Avda, Innovación, s/n Edif, Arena 1, CP: 41020 Spain (date of approval 12.12.2012; ethics committee president Antonio Velázquez Martín).

Consent for participation Written informed consent was obtained from the parents before participation. Patients were enrolled at the Virgen de las Nieves University Hospital of Granada, Spain.

Consent for publication Not applicable.

Availability of data and materials The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author Contributions All authors contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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