

Levosimendan is superior to dobutamine as an inodilator in the treatment of pulmonary hypertension for children undergoing cardiac surgery

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Abstract

Purpose To compare the effectiveness of levosimendan and dobutamine in reducing pulmonary artery pressure (PAP) and increasing cardiac output for children undergoing cardiac surgery.

Patients and methods The study included 50 patients with high systolic pulmonary artery pressure (PAP) undergoing surgical repair of cardiac septal defects. Patients were randomly allocated to two equal groups: group L received levosimendan and group D received dobutamine. PAP was measured preoperatively, by use of transthoracic echocardiography (baseline), intraoperatively, directly, by use of a 22-gauge catheter inserted in the pulmonary artery, and postoperatively, by use of transesophageal echocardiography (TEE). Cardiac index (CI) was recorded by use of a transesophageal 4-MHz Doppler probe.

Results Both drugs significantly reduced PAP compared with the level at the time of induction of anesthesia. Mean PAP measurement before chest closure, 1 and 20 h after ICU admission were significantly lower for patients who received levosimendan (32.7 ± 4.1 , 25.8 ± 2.8 , 19.8 ± 2 mmHg, respectively) than for those who received dobutamine (37.6 ± 2.75 , 32.8 ± 2.36 , 26.5 ± 2.2 mmHg, respectively). Both drugs significantly improved CI compared with its level at the time of induction of anesthesia. Mean CI

measurements 5 min after weaning from cardiopulmonary bypass (CPB) until 20 h after ICU admission were significantly higher for patients who received levosimendan than for those who received dobutamine (3.55 ± 0.35 , 3.8 ± 0.36 , 3.81 ± 0.34 , respectively, in group L vs. 3.4 ± 0.36 , 3.6 ± 0.33 , 3.66 ± 0.29 , respectively, in group D).

Conclusion Levosimendan is better than dobutamine for treatment of pulmonary hypertension of children undergoing cardiac surgery.

Keywords Levosimendan · Dobutamine · Congenital cardiac septal defects · Pulmonary hypertension

Introduction

Congenital cardiac defects associated with pulmonary arterial hypertension might lead to increased risk of post-operative pulmonary hypertensive crisis [1, 2].

Inotropic agents improve myocardial contractility, pulmonary capillary wedge pressure, and systemic vascular resistance. However, despite the improvement in myocardial contractility, traditional inotropic agents induce an increase in myocardial oxygen consumption and oxygen demand and may also induce cardiac arrhythmias [3, 4].

Levosimendan has a calcium-sensitizing property, and so improves myocardial contractility [5, 6]. Levosimendan also leads to vasodilatation by opening ATP-sensitive potassium channels [7]. Consequently, via these two actions levosimendan increases cardiac output without increasing oxygen demand [8]. The net effects of levosimendan infusion for 24 h are reduction of pulmonary vascular resistance and pulmonary artery pressure, and stable pulmonary capillary wedge pressure [9]. Recently, it had been proved that levosimendan has a direct inhibitory

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effect on platelet-derived growth factor-induced proliferation of pulmonary arterial smooth muscle cells [10]. Because of its strong β_1 and β_2 adrenergic stimulating effects and its reduction of α -adrenergic activity, dobutamine has been used to improve cardiac output, pulmonary arterial pressure, and pulmonary capillary wedge pressure [11, 12].

The purpose of this study was to compare the effectiveness of levosimendan and dobutamine in improving pulmonary hypertension and cardiac index for pediatric patients undergoing surgical repair of congenital heart diseases.

Patients and methods

This prospective randomized study included 50 patients with cardiac septal defects. After approval of the study protocol by the local ethics committee of Pediatric Cairo University Hospital, and obtaining parents' written fully informed consent, in the period from January 2011 until January 2012, 50 patients with either atrial or ventricular septal defects with high systolic pulmonary artery pressure (PAP) exceeding 50 % of systemic systolic pressure were assigned for surgical correction of the defect by use of cardiopulmonary bypass (CPB). Patients with hepatic or renal dysfunction, were excluded from the study.

Patients were randomized using sealed envelopes and allocated into two equal groups depending on the drug used. Group L included 25 patients assigned to receive levosimendan (SimdaxTM; Abbott laboratories, USA; each vial contains 25 mg). Levosimendan infusion was started immediately after declamping of the aorta; an initial loading dose of 15 $\mu\text{g}/\text{kg}$ was given over a 10 min period followed by infusion at 0.1–0.2 $\mu\text{g}/\text{kg}/\text{min}$. Group D included 25 patients assigned to receive dobutamine (250 mg per ampoule) by infusion at 4–10 $\mu\text{g}/\text{kg}/\text{min}$, again starting immediately after aortic declamping. The rate of infusion for both drugs was titrated according to hemodynamic data. Nitroglycerine infusion, as a pulmonary vasodilator, was started at a dose of 1–2 $\mu\text{g}/\text{kg}/\text{min}$ after induction of anesthesia until weaning from CPB for both groups. It should be noted that nitroglycerine infusion was stopped just before weaning from cardiopulmonary bypass. If hypotension developed, it was treated with phenylephrine 1–2 $\mu\text{g}/\text{kg}$ bolus doses. It should be also noted that all 50 patients who were randomized completed the study and no patient was excluded because of intraoperative hemodynamic alteration.

All patients were anesthetized by a similar procedure. Patients were premedicated with atropine sulfate at a dose of 0.01 mg/kg and midazolam at 0.1 mg/kg, intramuscularly, and were monitored by pulse oximetry until sedation was adequate, then transferred to the operating room.

Oxygen 100 % with sevoflurane was administered by use of a face mask with continuous monitoring by pulse oximetry, two-channel ECG, and noninvasive arterial blood pressure (ABP) monitoring. A peripheral venous line was inserted and anesthesia was induced by fentanyl 3 $\mu\text{g}/\text{kg}$ and pancuronium bromide 0.1 mg/kg. The patients were intubated orally. An arterial catheter was inserted for monitoring of ABP and arterial blood gases. Mechanical ventilation was adjusted to achieve arterial blood pH in the range 7.36–7.44, arterial oxygen tension ≥ 100 mmHg, and arterial partial pressure of CO_2 in the range 30–40 mmHg. Thereafter, a multilumen central venous catheter was inserted in the right internal jugular vein. Anesthesia was maintained by use of isoflurane in an oxygen–air mixture with continuous fentanyl infusion at 1–3 $\mu\text{g}/\text{kg}/\text{h}$. Baseline ACT (activated clotting time) was determined and heparin was given at a dose of 4 mg/kg through the central line to achieve an ACT >480 s before cannulation. Hydrocortisone 3 mg/kg was also injected intravenously before going on CPB.

CPB was instituted with a roller pump membrane oxygenator with a non-pulsatile flow ranging between 120 and 150 ml/kg/min. During bypass, the temperature range was between 28 and 35 °C, depending on the type of surgery. In large-sized VSD, cooling to 28 °C was used; in small-sized ASD, however, the temperature was allowed to drift to 35 °C only. Hematocrit level during CPB was maintained between 25 and 30 %. This was achieved by adding whole blood to the priming of the cardiopulmonary bypass (CPB). Cardioplegia was achieved, in accordance with the hospital protocol, with a mixture of blood and crystalloid solution, in 1:1 ratio at 4 °C, with the components K^+ 30 mmol/L, NaHCO_3 24 mmol/L, Mg^{+2} 15 mmol/L, and lidocaine HCl 120 mg/L. Throughout the surgical procedure systolic (SBP), diastolic (DBP), and mean blood pressure (MBP), central venous pressure (CVP), central and skin temperature, arterial blood gases, blood glucose levels, urine output, ischemic time, and duration of CPB were recorded. Only one cardiologist performed preoperative assessment of pulmonary artery pressure, during the preoperative period by use of transthoracic echocardiography (baseline) and in the ICU by use of transesophageal echocardiography (TEE). Intraoperatively, pulmonary artery pressure was measured, by use of a 22 gauge catheter inserted directly into the pulmonary artery, after opening the pericardium (T1), 5 min after weaning from CPB (T2), before chest closure (T3), and one and 20 h after ICU admission (T4 and T5), respectively. Cardiac index (CI) was recorded after induction of anesthesia (baseline), 5 min after weaning from CPB (T2), and one and 20 h after ICU admission (T4 and T5), respectively, by use of a transesophageal 4-MHz Doppler probe (Cardio Q monitor; DeltexTM Medical model no. 9051-6901) [13].

For postoperative care, all patients were transferred to the ICU intubated and ventilated. Immediately, after arriving in the ICU, together with stabilization of ventilation and hemodynamics an arterial blood sample was taken to check for adequate oxygenation, ventilation, acid–base balance, electrolytes, and hematocrit. In the ICU all the patients received the same management with continuous infusion of intravenous fentanyl at 1–2 $\mu\text{g}/\text{kg}/\text{h}$ for 2 h from the time of admission to the ICU. Postoperative infusion of both studied drugs was continued for 24 h from the time of admission to the ICU. Before performing the last pulmonary artery pressure and cardiac index measurements (T5), patients were premedicated with midazolam (0.05–0.1 mg/kg intravenous) to facilitate examination.

Statistical analysis

Data are presented as mean \pm SD, ranges, numbers, and ratios. Results were analyzed by use of the Wilcoxon ranked Z-test and the chi-squared test. Statistical analysis was conducted by use of the statistical package SPSS for Windows (version 15, 2006). A P value <0.05 was considered statistically significant.

Results

Concerning demographic data, there were no significant differences between the groups (Table 1). All patients had elevated PAP exceeding 50 % of SBP, with no significant difference between enrolled patients as regards hemodynamic data. Mean reported ischemic and CBP times were not significantly different ($P > 0.05$) between the groups (Table 2).

Both levosimendan and dobutamine significantly reduced PAP compared with its level at the time of induction of anesthesia. Mean PAP measurement before chest closure and 1 and 20 h after ICU admission were significantly lower for patients who received levosimendan

than for those who received dobutamine. Moreover, the percentage decrease of PAP from 5 min after weaning from CPB until 20 h after ICU admission was significantly lower in the levosimendan group than in the dobutamine group ($P < 0.05$) (Fig. 1).

Concerning cardiac index (CI), both levosimendan and dobutamine significantly induced improvement of CI compared with its level at time of induction of anesthesia. Mean CI measurement 5 min after weaning from CPB, and 1 and 20 h after ICU admission were significantly higher for patients who received levosimendan than for those who received dobutamine. Moreover, the percentage of CI increase until 20 h after ICU admission was significantly higher in the levosimendan group than in the dobutamine group ($P < 0.05$) (Fig. 2). There was no statistical difference between the study groups in the duration of intubation or in the length of ICU stay (Table 2). There was no mortality.

Discussion

Both levosimendan and dobutamine induced improvement of hemodynamic measurements, manifested by increased CI and reduced PAP. For both drugs time-course improvement was observed with no significant difference between the groups 5 min after weaning from CPB, despite being significantly better than baseline values. Thereafter, both drugs induced significant improvement compared with previous measurements, with a significant difference in favor of levosimendan. For a better assessment, the percentage change of both CI and PAP compared with baseline values was estimated; this revealed a significant difference between levosimendan and dobutamine.

Levosimendan seemed to have a better outcome than dobutamine. This was clear from the improvement of both cardiac contractility and pulmonary vascular resistance. The improvement of myocardial contractility was obvious from increase in CI; pulmonary vascular resistance, however, was improved by reduction of PAP. Some studies reported that levosimendan infusion was associated with a reduction in cardiac troponin release and postoperative atrial fibrillation. These studies also concluded that levosimendan has good cardioprotective effects which could result in reduced postoperative mortality after adult cardiac surgery [14–16].

Momeni et al. [17] reported that levosimendan was superior to milrinone as an inotropic support after corrective congenital cardiac surgery. Braun et al. [18] showed that levosimendan was also effective during weaning from biventricular mechanical support with full recovery of myocardial function for children with acute myocarditis. Lobacheva et al. [19] reported that left ventricular preload

Table 1 Patients' preoperative data

	Group D	Group L	P value
Age (months)	17.5 \pm 7.8 (7–34)	19.8 \pm 9.9 (9–38)	0.075
Gender			
Males	13 (52 %)	16 (64 %)	0.127
Females	12 (48 %)	9 (36 %)	
Body weight (kg)	10.8 \pm 2 (7.5–15)	11.9 \pm 1.9 (8.5–15)	0.219
Body height (cm)	77.3 \pm 7.8 (64–93)	79 \pm 9.1 (68–94)	0.156

Data are presented as mean \pm SD, numbers, ranges, and percentages

Table 2 Patients’ preoperative hemodynamic and operative data

	Group D	Group L	P value
Heart rate (beat/min)	92 ± 12.1 (75–120)	90 ± 15.2 (70–115)	0.219
SBP (mmHg)	96.3 ± 8 (80–107)	95.9 ± 9.4 (82–110)	0.182
DBP (mmHg)	64.2 ± 5.7 (55–72)	65.6 ± 5.7 (56–74)	0.178
PAP data			
Measurements	50.8 ± 4 (43–57)	50.6 ± 4.8 (43–58)	0.458
% of SBP	52.8 ± 1.3 (50.5–55.1)	52.7 ± 1.2 (50.9–55.4)	0.654
Operative data			
Ischemia time (min)	40.5 ± 3 (35–45)	40.9 ± 3.2 (35–47)	0.723
CPB time (min)	60.3 ± 5.7 (50–68)	60.6 ± 5.9 (53–66)	0.657
Duration of mechanical ventilation (h)	7 ± 1.6 (5–12)	6 ± 1.9 (3–8)	0.108
Duration of ICU stay (h)	49.3 ± 3.4 (46–55)	47.3 ± 2.9 (41–49)	0.096

Data are presented as mean ± SD, numbers, ranges, and percentages

SBP systolic blood pressure, DBP diastolic blood pressure, PAP pulmonary artery pressure

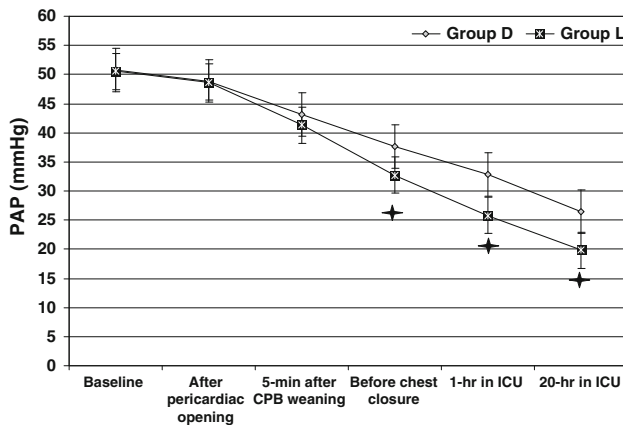


Fig. 1 Mean PAP estimated for both groups throughout the study. The cross symbol indicates a significant difference from group D

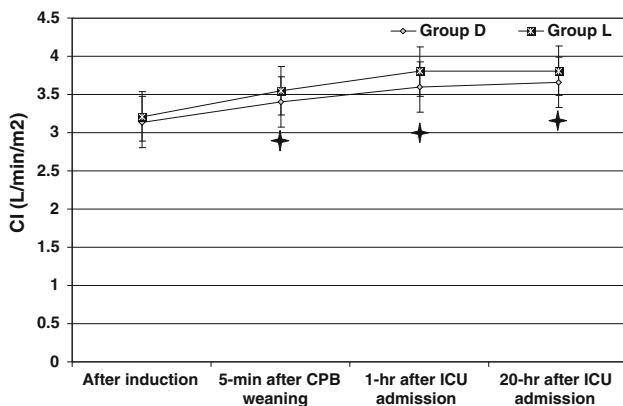


Fig. 2 Mean CI estimated for both groups. The cross symbol indicates a significant difference from group D

changes as a result of significant reduction of left atrial pressure, and left ventricular ejection fraction significantly increased from 21 to 27 %, respectively, 6 and 12 h after the start of levosimendan therapy. They also concluded that levosimendan may be used as an inodilator in pediatric

cardiac surgery as an alternative to phosphodiesterase III inhibitors after surgical correction for CHD. All these findings were in agreement with our results, that levosimendan is effective in improving the myocardial contractility.

In a study by Malliotakis et al. [20] to evaluate the hemodynamic effects of levosimendan for low cardiac output after cardiac surgery, they concluded that levosimendan was effective in improving cardiac output for such patients. This was in agreement with our study, in which we observed good improvement in cardiac index for the group of patients who received levosimendan rather than dobutamine. A study by Buerkem et al. [21] also showed the effectiveness of levosimendan for treating cardiogenic shock and improving myocardial contractility, which was also in agreement with our results. A study by Eremenko et al. [22] to evaluate the effectiveness of levosimendan in cardiac surgery patients with chronic heart failure showed that levosimendan was also effective in managing such patients. Another study by Ouanes et al. [23], to compare the initial hemodynamic effects of both levosimendan and dobutamine, showed the superiority of levosimendan. These results are all in agreement with ours.

Dobutamine had been studied by Mandal et al. [24], who compared it with nitroglycerine in secondary pulmonary hypertension. They concluded that both drugs were of similar efficacy. Torres et al. [25] studied the effect of different pharmacological agents including inotropes, nonselective vasodilators, and prostacyclin, in reversing severe pulmonary hypertension among end-stage heart failure patients and concluded that all these agents had a vasodilatory effects on the pulmonary vascular bed. A review by Zamanian et al. [26] of different management strategies for patients with raised pulmonary artery pressure in the ICU revealed dobutamine, milrinone, inhaled nitric oxide, and prostacyclin were the agents most widely used, according to the literature. Levosimendan undergoes calcium-dependent binding to the N-terminal domain of

cardiac troponin C (TnC), with greater affinity at high calcium concentrations and a lower affinity at low calcium concentrations, stabilizing the calcium–TnC complex, inhibiting the effect of troponin I, and prolonging the rate of actin–myosin cross-bridge association. The positive inotropic effect of levosimendan is obtained without increasing intracellular calcium concentration and without significantly increasing myocardial oxygen demand, which is usually seen with other inotropes [5, 27]. Levosimendan causes vasodilatation [7], thus reducing both preload and afterload, and increases coronary and other organ blood flow [28].

One of the limitations we faced in this study was the high cost of levosimendan, which prevents us from investigating a larger number of patients. Therefore, the cost and benefit of use of levosimendan should be borne in mind if a decision is taken to use it. That is to say, use of levosimendan is recommended in cases of severe pulmonary hypertension. Additionally, there should be a large comparative study including most of the inotropes and dilators used for pediatric cardiac patients with high pulmonary artery pressure. This should reveal the most effective drug in reducing pulmonary artery pressure, with minimum hemodynamic effects. Another limitation was that no placebo group was used; it may, however, be regarded as ethically unacceptable to use a placebo for pediatric cardiac patients with severe pulmonary hypertension. It should also be remarked that the decrease in PAP might be related to closure of the septal defect [29]. In this study, Talwar et al. concluded that surgical repair of the ventricular septal defect by use of a unidirectional valved patch might have been involved in reducing pulmonary artery pressure in the postoperative period. Power analysis in our study was based on percentage improvement in pulmonary artery pressure (PAP) resulting from use of dobutamine and levosimendan, with 25 cases in each group. We found that the mean percentage improvement of PAP at T2 between the 2 study groups was 3.4 %. If the true difference between dobutamine and levosimendan was similar to our calculated difference, we are able to reject the null hypothesis with 60 % power. Similarly, we reported that the difference at T3, T4, and T5 was 9.4, 13.7, and 13 % respectively, resulting in power of >99 %. In all calculations, we used the SD of the levosimendan group, which was the higher one. Student's *t* test was used in the analysis with type I error probability equal to 0.05. Calculations were performed by use of PS Power and Sample Size Calculations Software, version 2.1.30 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

In conclusion, levosimendan significantly reduced pulmonary artery pressure more than dobutamine for pediatric patients undergoing cardiac surgery.

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