Is levosimendan effective in paediatric heart failure and post-cardiac surgeries?

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Abstract

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was ‘do children with heart failure post-cardiac surgery undergoing treatment with levosimendan have an acceptable haemodynamic improvement?’ The use of levosimendan as a vasoactive drug is an accepted intervention for patients with altered haemodynamics post-cardiac surgeries. However, the role of levosimendan and its efficacy have been debated. Eleven relevant papers were identified, which represented the best evidence to answer the question. The author, journal, date, country of publication and relevant outcomes are tabulated. The 11 studies comprised 3 randomized trials, 2 of which compared levosimendan and milrinone. A single-centre randomized study that included 40 infants showed that cardiac output (CO) and cardiac index (CI) increased overtime in the levosimendan group compared with the milrinone group. The significant interaction for CO (P = 0.005) and CI (P = 0.007) indicated different time courses in the two groups. A similar, European randomized study undertaken on neonates (n = 63) showed better lactate levels [P = 0.015 (intensive care admission); P = 0.048 (after 6 h)] with low inotropic scores in the levosimendan group. Although the length of mechanical ventilation and mortality were less, this was statistically insignificant. A retrospective cohort analysis (n = 13) in children reported a reduced use of dobutamine and improvement in the ejection fraction from 29.8 to 40.5% (P = 0.015) with the use of levosimendan. In a questionnaire-based study from Finland, 61.1% of respondents felt that it had saved the lives of some children when the other treatments had failed. No study reported any adverse effect attributable to use of levosimendan. In conclusion, the above studies were in favour of levosimendan as a safe and feasible drug providing potential clinical benefit in low cardiac output syndrome (LCOS) and post-cardiac surgeries when other vasoactive drugs were insufficient to maintain stable haemodynamics. A small sample size was indeed a limitation in all the above studies. Furthermore, it is best used as a rescue drug on a named-patient basis. A small sample size was indeed a limitation in all the above studies. Larger, well-designed trials are required to further evaluate the efficacy and feasibility of levosimendan in paediatric heart failure and post-cardiac surgeries.

Keywords: Review • Levosimendan • Paediatric heart failure • Paediatric cardiac surgeries

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS[1].

THREE-PART QUESTION

Do [children with heart failure post cardiac surgery] undergoing [treatment with levosimendan] have an acceptable [haemodynamic profile]?

CLINICAL SCENARIO

You are on the paediatric intensive care unit and a 36-month old baby is admitted post-congenital cardiac surgery. Two hours post-operatively, the child is tachycardic with a low blood pressure and a trailing urine output. Mixed venous saturation (SvO2) is 56%, serum lactate is 12 mmol/l, left atrial pressure is 25 mmHg, and echocardiography showed reduced left ventricular function with a fractional shortening (FS) of 10%. The intensivists suggest the use of levosimendan in this situation. You are unsure of its role in the critically ill paediatric population and hence resolve to check the literature.

SEARCH STRATEGY

The MEDLINE database was searched from the date of inception to December 2012 using Medical Subject Headings (MeSH) search terms ‘levosimendan’, ‘paediatric cardiac surgery’, ‘paediatric heart failure’ and ‘congenital heart disease’. The Cochrane database of systematic reviews, EMBASE was also searched. In addition, related articles and references were screened for suitable articles.

SEARCH OUTCOME

Seventeen studies were found using the reported search. From these, eleven papers were identified that provided the best evidence to answer the question. These are presented in Table 1.
Table 1: Best evidence papers

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lechner et al. (2012), Pediatr Crit Care Med, [2]</td>
<td>The study enrolled 40 infants comparing use of levosimendan with milrinone</td>
<td>CI (as a primary endpoint)</td>
<td>CO and CI increased overtime in the levosimendan group</td>
<td>The study group did not include pre-existing congestive cardiac failure and complex congenital heart lesions (single ventricle lesions)</td>
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<tr>
<td></td>
<td></td>
<td>Haemodynamic parameters</td>
<td>The other parameters were statistically insignificant heart rate ($P = 0.172$), systolic blood pressure ($P = 0.62$), lactate ($P = 0.80$)</td>
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<td></td>
<td></td>
<td>Inotropic score, NIRS, length of ICU stay</td>
<td>Inotropic score ($P = 0.52$), NIRS ($P = 0.42$) ICU stay ($P = 0.72$)</td>
<td></td>
</tr>
<tr>
<td>Momeni et al. (2010), J Cardiothorac Vasc Anesth, Belgium [3]</td>
<td>41 children in the age group 0–5 years were randomized in a double-blind fashion to a continuous infusion of either levosimendan or milrinone started at the onset of cardiopulmonary bypass 0.36 patients completed the study</td>
<td>Serum lactate at 4 h (as a primary endpoint)</td>
<td>Change in serum lactate was insignificant</td>
<td>Authors noted levosimendan is as efficacious as milrinone</td>
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<tr>
<td></td>
<td></td>
<td>Haemodynamic parameters</td>
<td>Lower HR (&lt;0.05) and a lower rate pressure index ($P &lt; 0.001$) were noted in the levosimendan group</td>
<td>Limitations: Heterogenous study group</td>
</tr>
<tr>
<td>Ricci et al. (2012), Intensive Care Med, Italy [4]</td>
<td>Study of levosimendan in comparison to a standard inotrope with risk stratification (RACHS 3–4)</td>
<td>Lactate levels</td>
<td>Better lactate levels ($P = 0.015$ at ICU admission; $P = 0.048$ at 6 h)</td>
<td>Levosimendan was well tolerated with benefit on haemodynamic and metabolic parameters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inotropic score</td>
<td>Better ionotropic scores in the levosimendan group ($P &lt; 0.0001$)</td>
<td>Limitations: The study was a pilot open label uncommitted trial</td>
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<tr>
<td></td>
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<td>Mixed venous saturation</td>
<td>Length of mechanical ventilation (5.9 ± 5 vs 6.9 ± 8 days, $P = 0.54$) and ICU stay (11 ± 8 vs 14 ± 14 days, $P = 0.26$) though better was not statistically significant</td>
<td>Patients with only biventricular anatomy included; RACHS 5–6 not included</td>
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<td></td>
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<td>Mortality (1 vs 3 patients, $P = 0.35$)</td>
<td>Inadequate sample size (type II error)</td>
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<td></td>
<td></td>
<td>Side effects</td>
<td>None reported</td>
<td>Conventional Inotropic score used which did not take levosimendan into consideration when calculating</td>
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<td>MAP not in the definition of LCOS was used to guide inotrope use</td>
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<td>Improved CO in 50% of the interventions and no adverse effect reported</td>
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<tr>
<td>Magliola et al. (2009), Intensive Care Med, Spain [5]</td>
<td>Open, quasiexperimental cohort involving 14 children with refractory LCOS (18 opportunities)</td>
<td>CO was the primary endpoint inotropic score</td>
<td>Successful in 9/18 ($P = 0.004$)</td>
<td>Limitations: Heterogenous sample with no risk stratification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed venous saturation</td>
<td>Ionotropic score ($P &lt; 0.01$) and A-VDO2 ($P = 0.029$) showed reduction, $SvO_2$ showed improvement ($P = 0.03$)</td>
<td></td>
</tr>
<tr>
<td>Author, date, journal and country</td>
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<td>Namachivayam et al. (2006), Pediatr Crit Care Med, Australia [6]</td>
<td>15 children aged 7 days to 18 years (median age 38 months) with severe myocardial dysfunction secondary to end-stage heart failure, or acute heart failure, who were inotrope-dependent (requiring at least one catecholamine)</td>
<td>Effect on catecholamine use</td>
<td>Reduced dose of dobutamine (from 6.4 μg/kg/min pre-levosimendan to 1.8 μg/kg/min on day 5 ( P &lt; 0.01 ))</td>
<td>Showed substantial reduction in catecolamine use</td>
</tr>
<tr>
<td>Osthaus et al. (2009), Eur J Pediatr, Germany [7]</td>
<td>Case series involving seven infants (body weight range 2.6–6.3 kg) with severe myocardial dysfunction after complex congenital heart surgery</td>
<td>Haemodynamic parameters</td>
<td>Lactate levels decreased</td>
<td>Small number of patients</td>
</tr>
<tr>
<td>Pertti et al. (2011), BMC Anesth, Finland [8]</td>
<td>Analysis of data involving 293 patients and 484 infusions (4 h 21 years age group) over 10 years</td>
<td>Need for mechanical assist device</td>
<td>70.1% successfully weaned during study period</td>
<td>No risk stratification</td>
</tr>
<tr>
<td>Bravo et al. (2011), Neonatology, Spain [9]</td>
<td>Case series study involving neonates seven neonates</td>
<td>Cerebral and peripheral intravascular oxygenation</td>
<td>NIRs showed increased intravascular oxygenation but no change in tissue oxygenation index</td>
<td>Levosimendan was used as a rescue therapy</td>
</tr>
<tr>
<td>Lobacheva et al. (2010), Anesteziol Reanimatol, Russia [10]</td>
<td>Study of 75 cases with postoperative LCOS within the age group 3 days to 2 years 10 months</td>
<td>Haemodynamic parameters</td>
<td>Increase in mean blood pressure [from 42 to 53 mmHg; ( P &lt; 0.05 )], Reduction in left atrial pressure [from 25 to 17 mmHg; ( P &lt; 0.05 )], CVP unchanged</td>
<td>Authors recommend levosimendan as an alternative to PDE III inhibitors in LCOS as well as a basic drug during extracorporeal circulation and after its cessation</td>
</tr>
</tbody>
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Continued
Lechner et al. [2] reported a lower cardiac output (CO) and cardiac index (CI) values initially in the levosimendan group compared with milrinone, and this increased at the end of 48 h. The significant interaction for CO (P = 0.005) and CI (P = 0.007) indicated different time courses of CO and CI in the two groups. However, P-values for heart rate, serum lactate, blood pressure, mixed venous saturation and near infrared spectroscopy (NIRS) were insignificant. The use of additional catecholamines, as reflected in the inotropic score did not differ between the groups (74 vs 70%).

Momeni et al. [3] reported a lower rate pressure index, an indicator of myocardial oxygen demand, at 24 and 48 h postoperatively in the levosimendan group (P < 0.001) in comparison with the milrinone group. Although not significantly different, the troponin values in the levosimendan group were less at 1 h (median [p (25)-p (75): 20.7 (15.3–48.3) vs 34.6 (23.8–64.5) ng/ml]) and 4 h postoperatively [30.4 (17.3–59.9) vs 33.3 (25.5–76.7) ng/ml]. Lactate levels were non-significant. They concluded that levosimendan is at least as efficacious as milrinone after corrective congenital cardiac surgery in neonates and infants.

Ricci et al. [4] showed 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 paediatric cardiac intensive care unit stay (11 ± 8 vs 14 ± 14 days, P = 0.26) against a standard post-cardiopulmonary bypass inotropic infusion, with better controlled postoperative heart rate and lactate levels at admission, 6, 12 and 24 h.

Magliola et al. [5] concluded that levosimendan improved CO in 50% of the interventions with post-surgical LCOS, and no adverse effect was observed. Both inotropic score (12.1 vs 6.1, P = 0.01) and arterio-venous difference in O2-content (26.78 ± 11.5 vs 20.81 ± 7.72%, P = 0.029) showed reduction, while SvO2 improved (69.5 ± 11.4 vs 76 ± 9.29%, P = 0.03).

Namachivayam et al. [6] showed that levosimendan allowed for substantial reduction in catecholamine infusions in children with end-stage or acute heart failure and also produced an objective improvement in myocardial performance in children with acute heart failure.

Osthaus et al. [7] reported that the administration of levosimendan in seven infants with severe myocardial dysfunction was well tolerated intraoperatively. The mean arterial lactate declined. Central venous oxygen saturation increased significantly 24 and 48 h after the onset of levosimendan infusion.

Pertti et al. [8] studied 484 levosimendan infusions delivered to 293 patients over 10 years, as administered to children with cardiac surgery (72%), cardiomyopathy (14%) and with cardiac failure (14%). The most common indication for the use of levosimendan (94%) was when the other inotropic agents were insufficient to maintain stable haemodynamics. The results of a questionnaire concerning the perceptions of clinicians were also evaluated. Eighty-nine percent of the respondents believed levosimendan administration postponed the need for mechanical assist device in some children with cardiomyopathy. Furthermore, 61.1% of respondents felt that it had saved the lives of some children when the other treatments had failed, and 44% thought mechanical support was totally avoided in a few patients post-cardiac surgery after receiving levosimendan.

Bravo et al. [9] reported that levosimendan as a rescue therapy produced an increase in cerebral (P < 0.05) and peripheral (non-significant) intravascular oxygenation, a decrease in heart rate (P < 0.001) and serum lactate (P < 0.05) along with reduction in cardiovascular support. The study concluded that levosimendan

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**Table 1:** (Continued)

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<tr>
<td>Lechner et al. (2007), Pediatr Crit Care Med, Austria [11]</td>
<td>Single case report of premature 32 weeks (1.5 kg)</td>
<td>Haemodynamic parameters</td>
<td>Left atrial pressure decreased to 7 from 24 mmHg; Systolic arterial pressure increased to 60 mmHg from 40 mmHg; Serum lactate level normalized to 1.7 mmol/l from 14.8 mmol/l; Mixed venous saturation increased to 81 from 56%</td>
<td>It is difficult to extrapolate the results in a premature neonate to the haemodynamics of older infants</td>
</tr>
</tbody>
</table>

A-VDO2: arterio-venous difference in O2-content; CI: cardiac index; CO: cardiac output; CVP: central venous pressure; FS: fractional shortening; HR: heart rate; ICU: intensive care unit; LCOS: low cardiac output syndrome; LVEF: left ventricle ejection fraction; MAP: mean arterial pressure; NIRS: near infrared spectroscopy; PDE: phosphodiesterase; RACHS: risk adjustment for congenital heart surgery.
improves cerebral and systemic perfusion and oxygenation in critically ill neonates suffering from LCOS.

Labacheva et al. [10] observed that during levosimendan infusion, there was a significant increment in mean blood pressure and a reduction in left atrial pressure. The left ventricular ejection fraction significantly rose by 6%. The major adverse reaction noted was a tendency towards systemic hypotension within the first hour of levosimendan infusion.

Lechner et al. [11] reported a premature infant postnatal switch operation in heart failure. Administration of levosimendan when conventional inotropes failed resulted in the increase in systemic pressure, decrease in left atrial pressure with improvement of left ventricular function and fractional shortening.

Braun et al. [12] published that a breakthrough in treatment was achieved in a two-month old baby by using levosimendan to improve left ventricular function and to decrease vascular resistance.

CLINICAL BOTTOM LINE

The current best evidence suggests that levosimendan is beneficial in improving cardiac performance and reducing the left ventricular afterload. In addition, it may be effective in reducing the need for catecholamine and the duration of critical care. Furthermore, it is safe and well tolerated. It is promising as a rescue drug on the named-patient basis for a potential clinical benefit in low-CO syndrome and post-cardiac surgeries. No data are available to validate its role with regard to its cost effectiveness in comparison with milrinone. These encouraging results need to be evaluated by larger, well-designed clinical trials and its indications further elucidated. However, the present evidence may not be enough to recommend it to change the current practice in paediatrics.

Conflict of interest: none declared.

REFERENCES


eComment. Preoperative levosimendan administration in cardiac surgery patients

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According to its dual mode of action, levosimendan is both a calcium sensitizer, hence enhancing myocardial contractility without increasing the concentration of intracellular calcium, and a potassium adenosine triphosphate (ATP)-dependent channel opener, leading to vasodilatation, which reduces left ventricular afterload and improves blood flow to vital organs [1]. Levosimendan exerts vasodilatory and possible anti-ischaeamic and cardioprotective effects by opening of the ATP-dependent potassium-channel. Levosimendan may facilitate weaning from cardiopulmonary bypass (CPB) by both its inotropic and lusitropic properties. It enhances both systolic and diastolic left and right ventricular performance [1].

Levosimendan has a half-life of 1 hour, meaning that it is quickly eliminated from plasma. However, it has an active metabolite (OR-1896), which is formed by intestinal bacteria. OR-1896 has a similar haemodynamic profile to its parent compound, but a longer half-life of 70–80 hours. These pharmacokinetic features provide plausible explanations for the prolonged haemodynamic effects of levosimendan metabolites, which last for up to 7–9 days after discontinuation of a 24-h infusion of levosimendan [2].

We read with great interest the paper by Angadi et al. [3], regarding levosimendan use in paediatric cardiac surgery patients. They suggest that levosimendan is beneficial in improving cardiac performance and reducing the left ventricular afterload. It is promising as a rescue drug on the named-patient basis for a potential clinical benefit in low cardiac output syndrome (LCOS) and postcardiac surgeries. We agree with their implications and also would like to add a short comment on preoperative levosimendan administration.

Currently, the use of levosimendan in cardiac surgery has gradually increased and is studied more in adults than in children. In cardiac surgery patients, candidates to receive levosimendan include low preoperative left ventricular ejection fraction (LVEF)<35%, high-risk patients (emergency operation, decompensated heart failure), weaning failure from CPB, scheduled for mechanical assist device (intra-aortic balloon pump/left ventricular assist device), or postoperative LCOS [1]. Levosimendan is often used to improve peri- and postoperative haemodynamics to reduce morbidity and hospital stay.

Levosimendan may be administered preoperatively, intraoperatively (before, during, or after CPB), or postoperatively. The timing depends on the logistic utilities of the hospital and the haemodynamic target [1]. Current dosing regimes use levosimendan perioperatively. However, during CPB, there is hyperperfusion in the hepato-splenic region, which may affect intestinal function. Thus, patients receiving levosimendan perioperatively may not have the active metabolite OR-1896.

In our retrospective study [4] we reported early results of 18 patients receiving preoperative levosimendan that underwent coronary artery bypass grafting (CABG) with LVEF of 35% or less. Levosimendan infusion was given at a rate of 0.2 microgram/kg/min without a loading dose. It started 12 h before surgery. There was no in-hospital mortality. Levosimendan infusion was tolerated well in all patients. There were significant amelioration in haemodynamic parameters and diuresis. All patients showed no stormy postoperative recovery.

In the prospective randomized study by Leppikangas et al. [5], levosimendan improved haemodynamics during the 4 day postoperative period, when infused a day before surgery. The formation of metabolites was documented for this 4 day postoperative period.

We think that preoperative levosimendan administration may improve haemodynamic function and clinical outcome in patients with poor left ventricular function undergoing CABG.

Conflict of interest: none declared.