Preoperative levosimendan infusion in combined aortic valve and coronary bypass surgery


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Background. Cardiopulmonary bypass may have detrimental effects on intestinal function and decrease the concentrations of the active, long-acting metabolites of levosimendan, an inodilator used to improve cardiac function. The aim of this study was to evaluate the haemodynamic effects of preoperative levosimendan in patients undergoing high-risk cardiac surgery.

Methods. Twenty-four patients were randomized to receive levosimendan (12 μg bolus followed by an infusion of 0.2 μg kg⁻¹ min⁻¹) or a placebo 24 h before surgery. The inclusion criteria were left ventricular ejection fraction (LVEF) <50% or LV hypertrophy indicated by a wall thickness of >12 mm. Haemodynamics were recorded every hour for 24 h (pulmonary artery catheter) and daily until postoperative day 4 (whole-body impedance cardiography). Doppler echocardiography with tissue Doppler imaging was used to assess systolic and diastolic cardiac function.

Results. The cardiac index (CI) and stroke volume index (SI) were higher in the levosimendan group (LG) for the 4 day postoperative period (P<0.05); on the fourth postoperative day, the CI was 3.0 litre m⁻² min⁻¹ in the LG compared with 2.4 litre m⁻² min⁻¹ in the control group (CG) and the SI was 30 vs 25 ml m⁻², respectively. The LVEF measured at baseline and on the fourth postoperative morning decreased in the CG, but was maintained in the LG.

Conclusions. Levosimendan improved haemodynamics compared with a placebo in patients undergoing high-risk cardiac surgery. The concentrations of levosimendan’s metabolites were higher compared with earlier studies using perioperative dosing.

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Patients undergoing aortic valve replacement (AVR) surgery combined with coronary artery bypass grafting (CABG) are at risk for left ventricular (LV) dysfunction.1 Vasoactive therapy could be required for weaning from cardiopulmonary bypass (CPB) or to increase tissue perfusion in the perioperative period.2 Maintaining adequate cardiovascular function is essential for sufficient oxygen delivery. Adequate oxygen delivery and normal mixed venous saturation (SvO₂) values during the immediate postoperative period after cardiac surgery can decrease morbidity and, therefore, reduce the length of the hospital stay.3 Levosimendan, a calcium-sensitizing inodilator, enhances myocardial contractility and causes both coronary and peripheral vasodilatation4 without increasing the myocardial oxygen demand.5 Levosimendan is used to improve cardiac function and was used in patients suffering from congestive heart failure,6 before and after operation after CABG,7 8 and for patients in septic shock.9

Levosimendan has an intermediate metabolite OR-1855, which is further acetylated to the active metabolite OR-1896. It is formed by intestinal bacteria and its half-life is 77 (9) h.10 The metabolite OR-1896 has haemodynamic and pharmacological properties similar to the parent drug.11 12 CPB is associated with an imbalance in oxygen demand and supply in the hepatosplanchnic region,13 which may have detrimental effects on intestinal function. Patients infused with levosimendan during the perioperative period may lack the active metabolite. Our aim was to infuse levosimendan on the day before surgery to ensure the presence of OR-1896. Here, we describe the haemodynamic effects of levosimendan, compared with a placebo, in patients undergoing AVR together with CABG.
Methods

Twenty-four patients undergoing AVR with CABG were enrolled in the study. The inclusion criteria were LV ejection fraction (LVEF) <50% or LV hypertrophy, as indicated by a wall thickness of >12 mm. The exclusion criterion was a known allergy to levosimendan. The ethics committee of the hospital approved the study protocol and it was registered with EudraCT (ref: 2008-001672-70). Written informed consent was obtained from all patients before enrollment. The same surgical team performed all the operations (T.S., P.M., and K.J.).

The patients were randomized (sealed opaque envelopes) into two groups: the levosimendan group (LG) and the control group (CG). A study nurse prepared and diluted the study drugs, thereby ensuring that all personnel were blinded to the group assignment. Infusion of the study drug started the day before surgery. In the LG, patients received a levosimendan concentrate (Simdax®; Orion Pharma, Espoo, Finland) bolus 12 µg kg⁻¹ in 10 min followed by a 24 h infusion at a rate of 0.2 µg kg⁻¹ min⁻¹. In the CG, patients received a placebo bolus and infusion, which were made to look identical to levosimendan with water-soluble vitamin concentrate (Soluvit®; Fresenius Kabi, Uppsala, Sweden, 10 ml diluted in 500 ml of glucose 5%).

The anaesthesia and CPB were performed according to the hospital's clinical practice. A pulmonary artery catheter (Criticath SP5537; Becton Dickinson, Singapore) was inserted according to the hospital's clinical practice. A pulmonary artery catheter (Criticath SP5537; Becton Dickinson, Singapore) was inserted into the patient's height (cm), R the resistive part of the whole-body bioimpedance (Ω), and K the correction factor (Kᵣ₋₀₋₀=0.078, Kᵣ₋₀₋₁=0.095). Arterial blood pressure was measured non-invasively using Accutorr 4 (DatascopeCorp, Montvale, NJ, USA).

After baseline measurements, the study drug infusion was started. On the morning of surgery, the ICGWB measurements were done before the patients received their scheduled medications. Postoperative measurements were performed on the first and fourth postoperative mornings.

Echocardiography

Transthoracic echocardiography was performed by the same cardiologists (M.V. and P.L.) at baseline and on the first and fourth postoperative days. An ESAOTE S.p.A., Firenze, Italy) was used for standard measurements. The LVEF was measured from the two-dimensional echocardiography using biplane Simpson’s method. The M-mode was used to measure the LV mass and conventional cardiac dimensions. The mitral and aortic flow patterns were recorded with Doppler echocardiography and the mitral annular velocities with tissue Doppler imaging. Systolic pulmonary pressure was estimated non-invasively by adding the peak gradient of tricuspid regurgitation to the right atrial pressure estimated from the dimensions of the inferior vena cava and its decrease on deep inspiration.

Statistical methods

We calculated the sample size based on published data. Sample size was estimated as 10 patients per group, with a two-sided α level of 0.05 and a power of 0.80 to detect a 2.5 difference in SI, with an SD of 5, at the end of study. We decided to enrol 12 patients in each group in the case of drop outs. Baseline variables were tested using Student’s t-test and Fisher’s exact test for continuous and categorical variables, respectively. Normally distributed variables were tested using the analysis of variance for repeated measures (repeated) model with effects for treatment, time, and treatment × time interaction. The first measurement was used as a covariate in haemodynamic measurements. Time point-wise comparisons were done with the T-test. Cumulative doses of vasoactive medications were compared between groups using the Mann–Whitney U-test. Values are
presented as mean (SD). The analyses were carried out using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and operative data are presented in Table 1. No significant differences were detected between the treatment groups. The SI, CI, and HR measured by ICGWB are presented in Figure 1. LCWI was higher in the LG compared with the CG \((P=0.003, \text{RANOVA})\) and there was no difference in systolic or mean arterial pressure between the groups during the study period. There was a trend towards lower values for SVRI in the LG compared with the CG \((P=\text{NS})\) during the postoperative period. There was a trend towards lower values for \(E/E'\) in the LG compared with the CG \((P=0.05)\) between groups. \(E/E'\) is presented in Figure 2a. Left atrial volume indexes were also suggestive for diastolic dysfunction (39.4 ml m\(^{-2}\) in the CG and 39.9 ml m\(^{-2}\) in the LG).

The LVEFs were normal in both groups at baseline. In the postoperative period, the LVEF decreased in the CG, but was maintained in the LG (Fig. 2a). On the fourth postoperative morning, the gradient measured across the aortic valve (peak/mean) was bigger in the LG compared with the CG: [33 (8)/17 (4) mm Hg] vs [24 (7)/12 (4) mm Hg], respectively, \(P<0.05\) between groups. There was no difference in aortic valve size or in the valve type (a mechanical or biological) between the groups.

Levosimendan was rapidly absorbed and eliminated from plasma after study drug infusion ended. Twenty-four h after the start of infusion, the mean concentration was 30 (20) ng ml\(^{-1}\) and it was below the lower limit of quantification (i.e. <0.200 ng ml\(^{-1}\)) at 48 h. Both metabolites had a growing trend (Fig. 3) until 96 h after the start of the levosimendan infusion.

Fluid input was greater in the LG compared with the CG during drug infusion (from baseline to the morning of surgery) \((P=0.03)\). From the morning of surgery to the first postoperative morning, there was no difference in total fluid balance 11 631 (3291) ml in the LG vs 9620 (2789) ml in the CG \((P=0.09)\).

### Table 1 Patient characteristics and operative data. Results are expressed as mean (SD) or numbers. ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 12)</th>
<th>Levosimendan (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>75 (8)</td>
<td>76 (10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (12)</td>
<td>84 (13)</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>1.88 (0.20)</td>
<td>1.97 (0.18)</td>
</tr>
<tr>
<td>Preoperative (\beta)-blocker</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Preoperative ACE inhibitor</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Preoperative Ca-channel blocker</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Preoperative statin</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Preoperative LVEF (%)</td>
<td>69 (9)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Preoperative aortic valve gradient (mm Hg) peak</td>
<td>78 (12)</td>
<td>89 (22)</td>
</tr>
<tr>
<td>Mean</td>
<td>47 (8)</td>
<td>56 (17)</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>220 (48)</td>
<td>240 (40)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>125 (29)</td>
<td>133 (21)</td>
</tr>
</tbody>
</table>

**Fig 1** (a) SI, (b) CI, and (c) HR at baseline (-1), on the morning of surgery (0), and on the first (1) and fourth (4) postoperative mornings, measured by whole-body impedance cardiography. Results are expressed as mean (confidence intervals). *\(P<0.05\) between the groups and # the significant difference between the groups from the first postoperative morning to the morning before surgery.
fluid input (crystalloids, colloids, and blood products) and output was comparable between the groups. ECW was comparable between the groups before operation, but it was significantly higher in the LG, compared with the CG, during the postoperative period ($P = 0.008$ RANOVA; Fig. 4).

The LG required more norepinephrine during surgery and in the ICU compared with the CG [1.87 (1.23) vs 0.37 (0.57) mg, $P = 0.001$ and 1.22 (0.99) vs 0.18 (0.30) mg, $P = 0.001$, respectively]. Norepinephrine infusion was discontinued in all patients by the first postoperative morning. Otherwise, the need for vasoactive medication did not differ between the groups. At baseline, NT-proBNP was elevated in 10 patients in the LG compared with eight patients in the CG; 2088 (2541) vs 1232 (1010) ng litre$^{-1}$, $P = 0.29$, respectively. After operation, NT-proBNP increased in both groups on the fourth postoperative morning; 3329 (2662) ng litre$^{-1}$ in the LG vs 3298 (1933) ng litre$^{-1}$ in the CG ($P = NS$). P-CK-MB and systemic lactate values were comparable between the groups throughout the study period. Myocardial injury was described using a strict criterion of P-CK-MB. In two patients in both groups, P-CK-MB exceeded 75 U litre$^{-1}$ in the first postoperative morning. By the second postoperative morning, P-CK-MB was above 75 U litre$^{-1}$ in one patient in the LG. The mechanical ventilation time did not differ between the groups: 586 (615) min in the LG vs 340 (88) min in the CG ($P = 0.20$). The length of stay in the ICU was 25.3 (9.7) h in the LG vs 25.6 (10.1) h in the CG and in the hospital 8.6 (3.3) days in the LG vs 8.8 (5.6) days in the CG ($P = NS$). One patient in the LG died on the first postoperative morning. The death was not related to study drug infusion.

**Discussion**

In this prospective randomized study, 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.
Peak concentrations of the levosimendan metabolites have been observed at 2–4 days in heart failure patients, whereas the concentration peaked at day 6 in cardiac surgery patients studied by Eriksson and colleagues. In our study, the concentrations of metabolites showed an increasing trend until day 4. The concentrations on day 4 were higher than the peak concentration in the study by Eriksson and colleagues; the mean concentration of OR-1855 was 8.4 (3.3) ng ml\(^{-1}\) compared with the peak value of 6.6 (4.9) ng ml\(^{-1}\) reported by Eriksson and colleagues on day 6. Similarly, the mean concentration of OR-1896 was 8.8 (4.9) ng ml\(^{-1}\) compared with 7.7 (6.3) ng ml\(^{-1}\). This supports our hypothesis that the formation of the metabolites is not disturbed by possible hypoperfusion caused by CPB, when levosimendan is started before operation. Eriksson and colleagues also showed the concentration of levosimendan peaked ~2 h after infusion began. In our study, patients underwent surgery 24 h after starting the study drug infusion. The patients received the beneficial effects of levosimendan before operation and the metabolites were starting to increase early in the postoperative phase. The lowest concentration of OR-1896 that enhances cardiac output; enhancements of other inotropes; however, no differences were found in the requirements for inotropic support between the two study groups.

On the fourth postoperative morning, the gradient measured across the aortic valve was higher in the LG compared with the CG. The implanted valves were comparable in both groups. Higher values in the LG were likely due to the increased SI. Diastolic dysfunction was suggested by Doppler and tissue Doppler imaging. The diastolic function was assessed with \(E'/E\), which combines the influence of transmialdriving pressure and myocardial relaxation. De Luca and colleagues have shown a decrease in LV filling pressure, assessed by \(E'/E\), after levosimendan treatment.

In the present study, the difference between the groups was not significant despite a decreasing trend in the LG and an increasing trend in the CG. This may be due to the haemodynamic treatment protocol, which aimed at standardized filling pressures. The LG needed more fluids to achieve pre-set filling pressure. Statistically significant changes were not seen in any other measurements concerning diastolic function. The left atrial volume index, peak Doppler velocities of early (\(E\)) and late diastolic (\(A\)) flow, deceleration time of \(E\)-wave, and \(E'/A\) ratio were not significantly different between treatment groups at any time point. Still, the SI increased, the LVEF remained constant, and diastolic function assessed with \(E'/E\) showed an increasing trend in the LG compared with the CG.

There was no significant difference in the NT-proBNP or P-CK-MB between the groups. This is in the NT-proBNP probably because, in our treatment protocol, fluids were infused to meet the PCWP goal; therefore, we were unable to see the decrease in filling pressures. A recent meta-analysis suggests that levosimendan is associated with a reduction in cardiac troponin release in cardiac surgery patients. The release of the injury marker we used did not confirm this finding.

Tasouli and colleagues investigated starting the levosimendan infusion at different time points. In their study, patients were randomized to receive a continuous infusion of levosimendan (0.1 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) started either intraoperatively or after operation in the ICU. The earlier start was associated with a shorter ICU and hospital stay. In our study, the length of the ICU or hospital stay did not differ between the groups, which may be due to small sample size.

ICG\(\text{WB}\) is reportedly a reliable method of measuring cardiac output; comparisons with a bolus and continuous thermodilution and direct Fick methods showed that ICG\(\text{WB}\) measures cardiac output accurately in different conditions (in the supine position, during head-up tilt, after induction of anaesthesia, and CABG). Differences in cardiac output values between the ICG\(\text{WB}\) and thermodilution methods were comparable with those between direct Fick and thermodilution methods. The repeatability of ICG\(\text{WB}\) was nearly twice as good as that of thermodilution. Therefore, ICG\(\text{WB}\) is an adequate method to estimate cardiac output and its changes.

The exact volume of ECW in man is unknown. In invasive diagnostics, the distribution space of substances used for ECW volume estimation ranges from 15% (inulin and mannitol) to 23% (ions such as bromide and chloride) of body weight. The ICG\(\text{WB}\) device calculates ECW volume on the basis of the equation derived by Kolesnikov and colleagues, which is fitted to thiosulphate space giving ECW values around 16% of body weight. The decrease in systemic vascular resistance caused by levosimendan resulted in changes in the fluid distribution from the central to peripheral vasculature. We do not believe this would significantly influence the measured \(R\) in the equation, and thereby increase the calculated ECW. The higher ECW values measured after
operation in the LG were probably due to the increased need for fluids in the preoperative phase.

Levosimendan may exert cardioprotective effects by the activation of K\textsubscript{ATP} channels.\textsuperscript{37,38} The authors made an effort to minimize confounding factors by selecting total i.v. anaesthesia. Volatile anaesthetics are known to affect K\textsubscript{ATP} channel opening on reperfusion.\textsuperscript{39} We also tried to minimize other confounding factors; two surgeons performed all the operations and one anaesthesiologist was responsible for the anaesthesia and CPB. The elective patients received the levosimendan bolus under continuous haemodynamic monitoring. In order to maintain adequate blood pressure, the patients in the LG needed volume loading. None of the patients needed norepinephrine. We suggest that in this patient group, the bolus is given with caution.

A limitation of this study is the small sample size. The sample size was calculated based on differences in stroke index. The study was not designed and powered to detect differences in other variables, for example, diastolic function or hospital stay. Another limitation in the present study is that the metabolites of levosimendan were only measured for 4 days and the peak concentrations were probably not seen. The cardiac surgery patients usually are transferred from our hospital to other hospitals on the fourth or fifth postoperative day; therefore, we were not able to take samples after the fourth day. The patients were invited to the hospital 3 h earlier than they normally would have been. If this can be done in the clinical practice, the preoperative infusion of levosimendan is not adding costs beyond the price of the drug.

In conclusion, the present study shows that CI and SI are enhanced for four postoperative days when levosimendan is infused before operation. The formation of levosimendan’s metabolites also seems more efficient compared with perioperative dosing.

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Conflict of interest

H.L. and L.L. have lectured for Orion, the manufacturer.

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