Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery†

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Background. The calcium sensitizer levosimendan has anti-ischaemic effects mediated via the opening of sarcolemmal and mitochondrial ATP-sensitive potassium channels. These properties suggest potential application in clinical situations where cardioprotection would be beneficial, such as cardiac surgery. We thus decided to investigate whether pharmacological pre-treatment with levosimendan reduces intensive care unit (ICU) length of stay in patients undergoing elective myocardial revascularization under cardiopulmonary bypass.

Methods. One hundred and six patients undergoing elective coronary artery bypass grafting were randomly assigned in a double-blind manner to receive levosimendan or placebo. Levosimendan (24 μg kg⁻¹) or placebo was administered as a slow i.v. bolus over a 10 min period before the initiation of bypass.

Results. Tracheal intubation time and the length of ICU stay were significantly reduced in the levosimendan group (P<0.01). The number of patients needing inotropic support for >12 h was significantly higher in the control group (18.0% vs 3.8%; P=0.021). Compared with control patients, levosimendan-treated patients had lower postoperative troponin I concentrations (P<0.0001) and a higher cardiac power index (P<0.0001).

Conclusions. Pre-treatment with levosimendan in patients undergoing surgical myocardial revascularization resulted in less myocardial injury, a reduction in tracheal intubation time, less requirement for inotropic support, and a shorter length of ICU stay.

Br J Anaesth 2009; 102: 198–204

Keywords: heart, coronary artery bypass; heart, inotropism; heart, ischaemia; surgery, cardiovascular

Accepted for publication: November 18, 2008

The myocardium has to endure periods of ischaemia and reperfusion during coronary artery bypass grafting (CABG) surgery. Despite some degree of ischaemic protection afforded by cardioplegia, which establishes electromechanical arrest and reduces myocardial oxygen consumption, myocardial contractile dysfunction is a frequent complication. This often necessitates inotropic and mechanical circulatory support and is associated with an increase in morbidity and mortality.¹ ²

Leverosimendan is a cardiovascular drug licensed for the treatment of acute decompensated heart failure.³ It has positive inotropic⁴ and anti-stunning effects mediated by calcium sensitization of contractile proteins;⁵ in addition, it has vasodilatory⁶ and anti-ischaemic effects mediated by the opening of ATP-sensitive potassium (K<sub>ATP</sub>) channels.⁷ The K<sub>ATP</sub> channel is an important mediator or end-effector of cardioprotection, thus, levosimendan may offer a beneficial approach in situations of myocardial stress.

†Trial registration: clinicaltrials.gov identifier: nCT00610350.

‡Declaration of interest. L.T., F.G., and M.S. have sat on advisory boards for levosimendan on behalf of Orion, the manufacturer, and Abbott, the distributor. They have also received honoraria for chairing/speaking at satellite symposia.
In clinical studies to date, levosimendan has improved cardiac performance in left ventricular failure\(^8\)–\(^{10}\) and in myocardial stunning after percutaneous coronary intervention.\(^{11}\) In a randomized, placebo-controlled study of 24 patients undergoing CABG, we demonstrated lower post-operative troponin I concentrations (\(P<0.05\)) and a higher cardiac index in those randomized to receive a short duration infusion of levosimendan before the initiation of cardiopulmonary bypass (CPB).\(^{12}\) This pilot study encouraged us to see whether this improvement in post-operative cardiac function would translate into clinical outcome benefit and a consequently shorter postoperative length of stay on the intensive care unit (ICU).

Methods

Between January 2005 and February 2007, we recruited adult patients with coronary artery disease undergoing elective CABG surgery into our double-blind, single-centre, prospective, randomized, placebo-controlled trial. The study was approved by the local research ethics committee, and all patients provided written informed consent. Inclusion criteria were age \(\geq 18\) yr and an intention to perform first-time multi-vessel CABG. Exclusion criteria were unstable angina, valvular disease, diabetes mellitus treated with sulphonylurea drugs, renal failure (plasma creatinine >130 \(\mu\)mol litre\(^{-1}\)), severe hepatic disease (alanine aminotransferase or aspartate aminotransferase >100 IU litre\(^{-1}\)), severe chronic obstructive pulmonary disease (forced expired volume in 1 s <50% of predicted or <2.0 litre), a history of prior CABG surgery or recent myocardial infarction (MI) within the previous month. Randomization was achieved with the use of computer-generated random numbers.

The study drug (levosimendan (Abbott Pharmaceuticals, Abbott Park, IL, USA), 24 \(\mu\)g kg\(^{-1}\)) or an identical-appearing placebo prepared and labelled by the pharmacy was administered as a slow i.v. 50 ml bolus through the central venous port of a pulmonary artery catheter over the 10 min before the initiation of CPB. All patients and medical and nursing staff members remained unaware of study group assignments throughout the study period.

In the operating room, patients were connected to routine monitoring, which included five-lead ECG, radial and pulmonary artery catheters, pulse oximetry, and capnography. Anaesthesia was induced with a target-controlled infusion of propofol (site effect 1.6–1.8 \(\mu\)g mL\(^{-1}\)), sufentanil (0.35–0.5 \(\mu\)g kg\(^{-1}\)), and rocuronium (0.6 mg kg\(^{-1}\)). After tracheal intubation, the lungs were mechanically ventilated with an oxygen–air mixture (\(F_{\text{\text{O}}2}\) 40%). Anaesthesia was maintained with propofol (site effect 1.6–2.2 \(\mu\)g mL\(^{-1}\)), sufentanil (0.35 \(\mu\)g kg\(^{-1}\) h\(^{-1}\)), and supplemental boluses of rocuronium. CPB was established with the cannulation of the right atrium and ascending aorta and mild hypothermia (32°C). A retrograde coronary sinus cannula was inserted transatrially for cardioplegia infusions (cold-blood cardioplegia 6–8°C). The first cardioplegia infusion was given antegrade via an aortic root cannula for 2 min, and then retrograde cardioplegia was given for a further 2 min. The potassium concentration of the induction cardioplegia was 20 mmol litre\(^{-1}\). After each distal anastomosis, additional cardioplegic solution was delivered for 1 min. Warm-blood retrograde cardioplegia was administered at the end of cross-clamping. A standard coronary artery bypass operation was undertaken using one internal thoracic artery, and one to three peripheral vein grafts obtained from the lower limbs. After rewarming with a 37°C maximal heat-exchanger temperature, CPB was discontinued at 36–37°C nasopharyngeal temperature. Intraoperative ventricular tachyarrhythmias were treated with internal cardioversion or lidocaine (1–1.5 mg kg\(^{-1}\)). Reversal of heparin was achieved with protamine 1 mg per milligram of heparin. Inotropic support, initially with dopamine (5–10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) and secondly with epinephrine (0.02–0.15 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)), was commenced if the mean arterial pressure (MAP) was <65 mm Hg with a cardiac index (CI) \(\leq 2\) litre min\(^{-1}\) m\(^{-2}\) in the presence of a pulmonary artery wedge pressure (PAWP) of 15 mm Hg and a heart rate of 70–110 beats min\(^{-1}\). I.V. vasoconstrictors were used for a MAP <65 mm Hg, a systemic vascular resistance (SVR) <800 dyne s\(^{-1}\) cm\(^{-5}\), and a CI >3 litre min\(^{-1}\) m\(^{-2}\). Bolus phenylephrine was used until the administration of protamine, after which norepinephrine infusion was used as the vasoconstrictor agent.

While in the ICU, patients were routinely sedated with a continuous infusion of sufentanil 0.3 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) and propofol 1.5 mg kg\(^{-1}\) h\(^{-1}\) until CI exceeded 2.2 litre min\(^{-1}\) m\(^{-2}\); no significant dysrhythmias were present, temperature exceeded 36°C, haemoglobin >8 g dl\(^{-1}\) and no signs of excessive bleeding (>150 ml h\(^{-1}\)) were present. The patients were weaned from mechanical ventilation with reduction in propofol when the following criteria were met: temperature >36°C, maintained haemodynamic stability, chest tube drainage <100 ml h\(^{-1}\), and urine output >0.5 ml kg\(^{-1}\) h\(^{-1}\). After 15 min, sufentanil was titrated down at 30 min intervals. The tracheal tube was removed when the following criteria were achieved: adequate response to command, arterial oxygen saturation measured by pulse oximetry (\(S_{\text{\text{O}}2}\) )\(\geq 95\)% at a fraction of inspired oxygen (\(F_{\text{\text{O}}2}\)) \(\leq 0.5\), \(pH \geq 7.3\), arterial carbon dioxide tension (\(P_{\text{\text{CO}}2}\)) \(\leq 6.7\) kPa, and adequate respiratory effort.

Patients were eligible for transfer out of the ICU when the following criteria were met: \(S_{\text{\text{O}}2} \geq 90\%\) at an \(F_{\text{\text{O}}2} \leq 0.5\) by facemask, adequate cardiac stability with no haemodynamically significant arrhythmia, chest tube drainage <50 ml h\(^{-1}\), urine output >0.5 ml kg\(^{-1}\) h\(^{-1}\), no i.v. inotropic or vasopressor therapy, and no seizure activity. The criteria for eligibility for hospital discharge were haemodynamic and cardiac rhythm stability, the presence of clean and dry incisions, no pyrexia, the ability to void and move bowels and independent ambulation and feeding.
Haemodynamic data [MAP, PAWP, CI, cardiac power index (CPI) and systemic vascular resistance normalized for body surface area (SVRI)] were recorded just before the start of surgery, on admission to the ICU, and at 6 and 24 h later. CPI is a novel haemodynamic measure, which is the product of simultaneously measured CI and MAP.13 Cardiac output was measured using the bolus thermodilution method by injecting 10 ml cold saline at end-expiration. Three measurements within 10% of each other were averaged. Blood samples for cardiac troponin I (cTnI) were drawn at baseline, on arrival in the ICU and at 6, 24 and 48 h after operation. The limit of quantification of cTnI determination was 0.04 ng ml\(^{-1}\). When values below the detection limit were reported, zero was used as the value. The coefficient of variation for this assay is 15% for TnI values up to 0.08 ng ml\(^{-1}\), 6% for values between 0.47 and 1.44 ng ml\(^{-1}\) and 5% for values above 1.44 ng ml\(^{-1}\). Standard 12-lead ECG recordings were obtained before operation and on postoperative days 1 and 4.

The primary endpoint of the study was the length of ICU stay. Secondary endpoints included the length of hospital stay, tracheal intubation time and reduction in inotropic support over the first 7 days. Additional postoperative data specifically collected included number of deaths, number of acute MIs, incidence of atrial fibrillation, any type of adverse event, and serum creatinine concentrations. The definition of acute MI was as follows: new Q-wave or new persistent ST-segment or T-wave changes accompanied by a creatine kinase MB isoenzyme level $>50$ units litre\(^{-1}\) and a creatine kinase-MB/creatine kinase ratio $>5\%$ or a troponin I level $>10\, \mu$g litre\(^{-1}\).

A sample size of 100 subjects was estimated to provide a 90% power (with a two-sided $\alpha=0.05$) to detect a decrease of at least 11 h (i.e. 24 vs 35 h) in the median ICU length of stay in the levosimendan arm. To account for the skewed distribution of the primary endpoint, sample size estimation was performed using non-parametric methods based on bootstrap simulation. A pilot study data set,\(^{12}\) from which the ICU length of stay empirical distribution had been estimated, was used for the bootstrap resampling.\(^{14}\) One hundred and forty patients were screened for eligibility, anticipating a 40% rate of potential dropouts, either for non-willingness to participate or lack of eligibility.

Patients’ baseline characteristics in treated and control groups are reported as mean (SD), median (range), or frequencies and percentages. Differences were assessed using $\chi^2$ or the Fisher exact test for categorical variables and the Mann–Whitney U-test for continuous ones. Owing to the non-normal distribution of ICU and hospital stay, the Mann–Whitney U-test was also used to assess differences in the main endpoints between the treatment group and controls. As secondary outcomes, cTnI and haemodynamic data (i.e. MAP, PAWP, CI, SVRI and CPI) were analysed with a hierarchical linear model for repeated measurements to assess differences over time between treatment and control groups.\(^{15, 16}\) An unstructured correlation type was used to account for unequally spaced time occasions during follow-up. $P$-values $<0.05$ were considered statistically significant. All analyses were performed using SAS Statistical Package Release 9.1 (SAS Institute, Cary, NC, USA).

### Results

One hundred and forty patients were assessed for eligibility, of whom 106 were randomly assigned to levosimendan ($n=53$) or placebo ($n=53$). One patient in the levosimendan group and three in the placebo group were withdrawn after randomization because their surgery was cancelled (Fig. 1).

Preoperative patient characteristics are summarized in Table 1. The ICU length of stay (time meeting fit-for-discharge criteria) and duration of tracheal intubation were significantly lower in the levosimendan group ($P=0.002$ and $P=0.02$, respectively), although the hospital length of stay showed no difference between the groups (Table 2). Troponin I increased transiently in both groups (Fig. 2), but this increase was significantly lower in the levosimendan group (treatment-by-time interaction $P=0.0001$).

Haemodynamic data are presented in Figure 3. After operation, there were significantly higher values of MAP, CI and CPI (all treatment-by-time $P<0.007$) and a lower SVRI ($P=0.005$) in those treated with levosimendan. Four patients in the levosimendan group developed hypotension, which was successfully treated with phenylephrine.

In the first 7 days after surgery, 34% ($17/50$) of the patients in the placebo group vs 17.3% ($9/52$) of the levosimendan patients ($P=0.053$) received inotropic support with dopamine $5\, \mu$g kg\(^{-1}\) min\(^{-1}\) (Table 2). The number of patients requiring inotropic support for $>12$ h was significantly higher in the control group (18.0% vs 3.8%; $P=0.02$). The groups were similar with respect to frequency of atrial fibrillation, MI and postoperative serum creatinine $>130\, \mu$mol litre\(^{-1}\), and mortality (Table 2).

### Discussion

Variable degrees of postoperative myocardial stunning occur after cardiac surgery, and these may result in transient myocardial dysfunction. Different cardioprotective strategies have been tested to reduce myocardial injury during cardiac surgery, including short-term preconditioning using ischaemia,\(^{17}\) volatile anaesthetic agents\(^{18–20}\) and opiates.\(^{21}\) To our knowledge, the current study using a short-term infusion of levosimendan before CPB in patients undergoing first-time surgical myocardial revascularization is the first to demonstrate a reduction in the ICU stay in addition to reduced tracheal intubation time and inotropic support requirements.
A considerable body of experimental and clinical evidence indicates that levosimendan pre-treatment induces protection against subsequent ischaemic stress through its KATP channel-opening properties. The opening of mitochondrial KATP channel protects the heart against ischaemia–reperfusion damage. The increased potassium influx associated with mitochondrial KATP channel opening is sufficient to protect/preserve mitochondrial function, perhaps via the normalization of matrix and intermembrane space volumes, in situations of distress such as ischaemia or reperfusion.

Previous studies have demonstrated improved survival with post hoc treatment with levosimendan after MI. The study flow diagram is shown in Figure 1.

Table 1: Baseline characteristics. Data are reported as mean (range) for age, mean (SD), median (range) or frequencies and percentages. P-values refer to χ² or the Fisher exact test for categorical variables and Mann–Whitney U-test for continuous ones.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>66.5 (54.0–87.0)</td>
<td>64.0 (54.0–86.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Sex: male, n (%)</td>
<td>39 (78.0)</td>
<td>43 (82.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Body mass index, kg m⁻²</td>
<td>28.8 (2.3)</td>
<td>28.1 (2.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>3.5 (1.0–7.0)</td>
<td>2.5 (1.0–7.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>44.1 (9.8)</td>
<td>41.6 (10.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td>53.6 (7.1)</td>
<td>54.6 (6.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>83.2 (12.4)</td>
<td>85.8 (10.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Number of bypasses</td>
<td>3.0 (2.0–4.0)</td>
<td>3.0 (2.0–4.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>ACE-inhibitor, n (%)</td>
<td>20 (40.0)</td>
<td>17 (32.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>40 (80.0)</td>
<td>43 (82.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>17 (34.0)</td>
<td>16 (30.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Antiarrhythmic drugs, n (%)</td>
<td>5 (10.0)</td>
<td>4 (7.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>10 (20.0)</td>
<td>9 (17.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Nitrates, n (%)</td>
<td>18 (36.0)</td>
<td>16 (31.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Platelet inhibitor therapy, n (%)</td>
<td>24 (48.0)</td>
<td>26 (51.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>39 (78)</td>
<td>41 (79)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 2: Postoperative results. Data are reported as mean (SD), or frequencies and percentages. P-values refer to χ² or the Fisher exact test for categorical variables and Mann–Whitney U-test for continuous ones.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirty-day mortality</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>MI, n</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>10 (20.0)</td>
<td>12 (23.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Time on ventilator, h</td>
<td>13.6 (4.5)</td>
<td>11.3 (2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Received inotropes, n (%)</td>
<td>17 (34.0)</td>
<td>9 (17.3)</td>
<td>0.053</td>
</tr>
<tr>
<td>Received inotropes &gt;12 h, n (%)</td>
<td>9 (18.0)</td>
<td>2 (3.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Postoperative serum creatinine &gt;130 μmol litre⁻¹, n (%)</td>
<td>4 (8)</td>
<td>2 (3.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>ICU stay, h</td>
<td>32.7 (12.9)</td>
<td>24.8 (7.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospital stay, days</td>
<td>12.0 (2.5)</td>
<td>11.1 (2.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Re-admission to ICU, n (%)</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Re-exploration for bleeding, n (%)</td>
<td>1 (2.0)</td>
<td>1 (1.9)</td>
<td>0.9</td>
</tr>
</tbody>
</table>
and in one of the two multi-centre studies of patients with acute decompensation of chronic heart failure. To our knowledge, this study is the first to confirm improved cardiac function (haemodynamics, and inotropic requirements), reduced myocardial damage (postoperative cTnI concentrations) and outcome benefit (reduced ICU length of stay) with the use of levosimendan pre-treatment.

Postoperative serum cTnI concentrations, indicative of myocardial damage, have been shown to increase to some extent in all patients undergoing cardiac surgery, even in the absence of postoperative MI. This may be influenced by the type of surgery, the choice of cardioplegic solution and its mode of delivery. However, after accounting for the complexity of the surgery and other potential confounding factors, cTnI levels at 24 h remain independent predictors of short, medium, and long-term outcome. An increased cTnI (>13 ng/ml) in adults undergoing cardiac surgery is associated with major postoperative complications with delayed extubation and a prolonged length of ICU stay. On the basis of published literature, including our previous pilot study findings, we predicted that greater preservation of cardiac function immediately after CPB would result in a better recovery after cardiac surgery. Our results are indeed consistent with these findings. We did not find any significant difference in 30 day mortality, likely because of the low perioperative risk profile of the patients enrolled. Further studies are required to determine whether benefit can be achieved in high-risk patients. Larger outcome effects may be achieved, though potentially, at the risk of more adverse events such as hypotension. We also did not perform any cost–benefit analysis arising from a shorter ICU stay.

The duration of tracheal intubation in the current study is comparable with what has been reported in other studies that did not use fast-rack anaesthesia protocols. The length of stay in our ICU and that in hospital are longer than those reported by North American centres but reflect typical practice in Italy and other countries, where there is less economic pressure for earlier discharge.

CPI is a relatively novel haemodynamic parameter, which was the strongest haemodynamic correlate of in-hospital mortality in patients admitted with cardiogenic
In our study, levosimendan treatment led to a significant postoperative increase in both CI and CPI. The increase in CPI indicates that increased myocardial contractility contributes to the increase in CI, rather than a reduction in SVRI alone. Reported kinetics for levosimendan would exclude the haemodynamic benefit being derived from its calcium-sensitizing effect. We thus feel the observed effect is more likely to be related to a cardioprotective effect that persists after drug elimination. The dosage used and the mode of administration in our study would achieve neither a minimum effective concentration nor appreciable amounts of its active metabolite, OR-1896. Kinetic models have not yet considered the potential influences of hypothermia or CPB; however, we feel this low dose of levosimendan (and its metabolite) is very unlikely to exert any haemodynamic effect after operation.

Owing to its K_{ATP} channel-opening properties, levosimendan will produce vasodilatation and, potentially, significant hypotension. In our study, we observed mild hypotension (MAP<65 mm Hg) in four patients treated with levosimendan during CPB. This was transient (<10 min) and easily managed by titrated doses of phenylephrine.

In conclusion, short pre-treatment with levosimendan in patients undergoing myocardial revascularization resulted in a reduction of tracheal intubation time, decreased requirement for inotropic support and thus a shorter duration of ICU stay. Further studies should investigate patients undergoing high-risk cardiac surgery and procedures where myocardial stress is likely, for example invasive aortic–iliac vascular surgery requiring vessel cross-clamping.

Funding

This study was funded by an independent research grant from the Department of Anesthesiology and Intensive Care of the ‘Sapienza’ University of Rome.

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