Preoperative levosimendan decreases mortality and the development of low cardiac output in high-risk patients with severe left ventricular dysfunction undergoing coronary artery bypass grafting with cardiopulmonary bypass

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BACKGROUND: The calcium sensitizer levosimendan has been used in cardiac surgery for the treatment of postoperative low cardiac output syndrome (LCOS) and difficult weaning from cardiopulmonary bypass (CPB).

OBJECTIVES: To evaluate the effects of preoperative treatment with levosimendan on 30-day mortality, the risk of developing LCOS and the requirement for inotropes, vasopressors and intra-aortic balloon pumps in patients with severe left ventricular dysfunction.

METHODS: Patient with severe left ventricular dysfunction and an ejection fraction <25% undergoing coronary artery bypass grafting with CPB were admitted 24 h before surgery and were randomly assigned to receive levosimendan (loading dose 10 µg/kg followed by a 23 h continuous infusion of 0.1µg/kg/min) or a placebo.

RESULTS: From December 1, 2002 to June 1, 2008, a total of 252 patients were enrolled (127 in the levosimendan group and 125 in the control group). Individuals treated with levosimendan exhibited a lower incidence of complicated weaning from CPB (2.4% versus 9.6%; P<0.05), decreased mortality (3.9% versus 12.8%; P<0.05) and a lower incidence of LCOS (7.1% versus 20.8%; P<0.05) compared with the control group. The levosimendan group also had a lower requirement for inotropes (7.9% versus 58.4%; P<0.05), vasopressors (14.2% versus 45.6%; P<0.05), and intra-aortic balloon pumps (6.3% versus 30.4%; P<0.05).

CONCLUSION: Patients with severe left ventricle dysfunction (ejection fraction <25%) undergoing coronary artery bypass grafting with CPB who were pretreated with levosimendan exhibited lower mortality, a decreased risk for developing LCOS and a reduced requirement for inotropes, vasopressors and intra-aortic balloon pumps. Studies with an increased number of patients are required to confirm whether these findings represent a new strategy to reduce the operative risk in this high-risk patient population.

Key Words: *Cardiac surgery; Hemodynamic optimization; Inotropic agents; Levosimendan; Postoperative low cardiac output*

Despite the reduction in perioperative mortality observed over the past two decades, the risk of performing cardiac surgery in patients with coronary artery disease (CAD) and severe left ventricular dysfunction (SLVD) remains high, especially with regard to the likelihood of developing postoperative low cardiac output syndrome (LCOS) (1-4). Concern regarding postoperative LCOS, along with an increasing number of patients with SLVD being referred for surgery, has incentivized cardiac surgery teams to propose several strategies to confront the increased risk of LCOS in this group of patients, such as the preoperative use of an intra-aortic balloon pump (IABP) or the use of off-pump coronary revascularization (5-8). The beneficial effects of the calcium sensitizer levosimendan have previously been demonstrated in LCOS patients, and its unique properties make it a potential option for preoperative treatment in this high-risk class of patients (9,10). The aim of the present study was to assess the risks of postoperative LCOS and mortality following the preoperative administration of levosimendan compared with administration of a placebo in patients with SLVD. Secondary outcomes including difficult weaning from cardiopulmonary bypass (CPB) and the requirements for inotropes, vasopressors and IABP were also evaluated.

METHODS

Patients with CAD and SLVD with an ejection fraction <25% scheduled to undergo cardiac surgery with CPB were prospectively enrolled in the present blinded study at two university hospitals. The ejection fraction was determined by ventriculography or echocardiography performed within the previous 60 days. Patients were required to have a positive stress test for ischemia (or viability) and at least two target arteries amenable to grafting. Patients were admitted to the cardiovascular intensive care unit (ICU) 24 h before surgery and were randomly assigned according to the medical record numbers (pair/unpair) to receive either a preoperative loading dose of levosimendan (10 µg/kg over 60 min) followed by a continuous 23 h infusion of 0.1 µg/kg/min (levosimendan group) or a placebo consisting of a mix of poligelin dissolved in 5% dextrose in water to mimic the colour of levosimendan (control group). The administration of the placebo was similar to levosimendan. The dose of levosimendan was chosen based on previous experience with the agent in postoperative LCOS (10).

All patients underwent continuous monitoring of heart rate, arterial blood pressure, pulse oximetry and measurement of hemodynamic parameters including central venous pressure, pulmonary artery occlusion pressure (PAOP), cardiac index, mixed venous saturation (SvO_2), and systemic vascular resistance with a pulmonary artery catheter. Time 0 was defined as the initial hemodynamic measurement, time 1 was recorded immediately after the levosimendan loading dose, time 2 before anesthesia induction in the operating room and time 3 on arrival back in the cardiovascular ICU following surgery. Times 4 through 7 were 6 h, 12 h, 24 h and 48 h after arrival in the cardiovascular ICU following surgery, respectively.

Anesthesia was induced with fentanyl (10 µg/kg to 20 µg/kg), midazolam (0.03 mg/kg to 0.05 mg/kg) and pancuronium to facilitate intubation and was maintained with inhalational sevofluorane and fentanyl and propofol infusions (1 mg/kg/h to 4 mg/kg/h). All procedures were performed using CPB with moderate hypothermia (32°C to 34°C). Diastolic cardiac arrest was induced with cold hyperkalemic blood

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TABLE 1
General and surgical characteristics of levosimendan versus control groups

	Levosimendan (n=127)	Control (n=125)
Age, years, mean	63.7	62.9
Female sex	33 (26)	31 (24.8)
Preoperative EF, %, mean ± SD	17.56±3.24	18.62±2.12
Hypertension	67 (52.8)	68 (54.4)
Diabetes	38 (29.9)	39 (31.2)
Previous myocardial infarct	58 (45.7)	59 (47.2)
Previous cardiac surgery	26 (20.5)	24 (19.2)
Previous angioplasty	73 (57.5)	68 (54.4)
eGFR, mL/min/1.73, median ± SD	71.42±4.23	73.55±3.66
CPB time, min, mean	108.6	114.3
Aortic clamp time, min, mean	72.5	74.3
Grafts, n	432	400
Grafts per patient, mean	3.4	3.2
Patients with arterial graft	100 (78.7)	101 (80.8)

Data presented as n (%) unless otherwise indicated. Fisher's exact test was used to assess differences between categorical variables. Differences were not statistically significant. CPB Cardiopulmonary bypass; EF Ejection fraction; eGFR Estimated glomerular filtration rate

cardioplegia with application of an aortic crossclamp. Coronary artery bypass grafts were attempted using the left internal mammary artery to the left anterior descending artery in all patients who required grafting of the left anterior descending artery, and aortocoronary vein grafts were performed to all other targets for complete revascularization. Patients undergoing an urgent, emergent, congenital, valve, aortic or combined operation were not eligible to enroll in the present study. Patients undergoing revascularization without CPB (off-pump surgeries), patients who had been treated with levosimendan within the previous three months or with other ionotropes within the previous week, and patients with a preoperative IABP were also excluded from the study.

The following postoperative complications (morbidities) were defined:

- LCOS: The presence of low cardiac index (<2.2 $L/min/m^2$), elevated PAOP (>16 mmHg), and a SO_2 $<60\%$.
- Perioperative myocardial infarction: Development of new pathological Q waves (>0.04 s) in at least two contiguous leads, an increased creatine kinase (>1000 U) and a creatine kinase-MB fraction $>10\%$.
- Vasoplegic syndrome: Systemic arterial hypotension (systolic pressure <80 mmHg) associated with reduced systemic vascular resistance (<800 dyne/s/cm^5), low filling pressures (central venous pressure <5 mmHg, PAOP <15 mmHg) with normal or elevated cardiac index, and the requirement of vasopressor agents.
- Renal failure: Elevated creatinine ($>50\%$ from baseline) with or without oliguria (urine output <0.5 ml/kg/h), or requiring dialysis.
- Prolonged ventilatory assistance: Ventilator dependence >24 h.
- Stroke: Development of a new focal neurological deficit or coma persisting >48 h, after metabolic causes have been ruled out. A neurologic change persisting <48 h was considered as a transient ischemic attack.
- Pneumonia: Presence of a new pulmonary infiltrate by radiographic imaging and clinical signs (fever, purulent sputum) or a documented pulmonary infection.
- Systemic inflammatory response syndrome: The presence of two or more of the following criteria: temperature $>38°C$ or $<36°C$, heart rate >90 beats/min, respiratory rate >20 breaths/min or PCO_2 <32 mmHg, leukocyte count $>12,000$ cells/mL, <4000 cells/mL, or $> 10\%$ immature forms.
- Sepsis: Systemic inflammatory response syndrome with documented evidence of infection.
- Adult respiratory-distress syndrome: Hypoxemia (partial pressure of arterial O_2/fraction of inspired O_2 ratio <150), reduced lung compliance, and the presence of diffuse, bilateral pulmonary infiltrates.

TABLE 2
Preoperative medications in levosimendan versus control groups

Medication	Levosimendan (n=127)	Control (n=125)
Beta blockers	105 (82.7)	108 (86.4)
ACE inhibitors	88 (69.3)	85 (68.0)
ACE blockers	19 (15.0)	14 (11.2)
Digital	39 (30.7)	36 (28.8)
Amiodarone	26 (20.5)	24 (19.2)
Hydralazine	15 (11.8)	12 (9.6)
Diuretics	121 (95.3)	122 (97.6)
Statins	27 (21.3)	24 (19.2)

Data presented as n (%). Fisher's exact test was used to assess differences between categorical variables. Differences were not statistically significant. ACE angiotensin-converting enzyme

- Postoperative mortality: Death during hospitalization or within 30 days postoperatively.

The following criteria were established for discontinuation of treatment:

- Severe hypotension: Arterial blood pressure <80 mmHg or mean arterial pressure <50 mmHg without response to a 1000 mL fluid challenge, or the requirement for high-dose vasopressors (phenylephrine >100 µg/min, norepinephrine >10 µg/min).
- Myocardial ischemia: Development of myocardial angina and/or significant ST-segment changes (>2 mm in two contiguous leads not related to increasing heart rate, pericarditis, or metabolic conditions.
- Supraventricular tachyarrhythmia: Heart rate >130 beats/min, or <130 beats/min with hemodynamic instability.
- Complex ventricular arrhythmias: Ventricular fibrillation or sustained ventricular tachycardia in the absence of electrolyte or metabolic disturbances.
- Acute mental status changes.
- Requirement for mechanical ventilation.

Adverse effects were defined as new onset nausea, vomiting, headache, supraventricular tachyarrhythmia (heart rate <130 beats/min and hemodynamically stable), simple forms of ventricular arrhythmias (premature ventricular complexes, couplets or nonsustained ventricular tachycardia) and/or mild hypotension (arterial blood pressure <80 mmHg or mean arterial pressure <50 mmHg, but responsive to a 1000 mL fluid challenge or low dose vasopressors), as well as ischemia, significant ST changes, angina and chest pain. Adverse events were recorded from the start of the levosimendan infusion until just before surgery.

The present study followed the principles of the Helsinki protocol and was approved by an internal review board. Informed consent was obtained from the patient or a relative before the initiation of any study treatment.

Statistics
Data were collected by staff who were blinded to study treatments. Analysis was performed using EPI Info 2000 software (Centres for Disease Control and Prevention, USA). Based on a predicted mortality rate of 20%, it was calculated that a minimum sample size of 200 patients would be required to detect a 50% reduction in mortality. Differences between groups were analyzed using the χ^2 test, Fisher's exact tests for categorical variables and t tests for continuous variables. The relationships between discrete variables were expressed as OR and 95% CI. Numerical variables were expressed as mean ± SD. $P<0.05$ was considered to be statistically significant based on a two-tailed t test.

RESULTS
Between December 1, 2002 and June 1, 2008, a total of 252 patients were enrolled in the present study, with 127 randomly assigned to receive preoperative levosimendan and 125 randomly assigned to the control group. General and preoperative characteristics were comparable between groups (Table 1). Preoperative medications were also similar between treatment groups (Table 2). During the three

TABLE 3
Adverse events during the 24 h preoperative infusion

	Levosimendan (n=127)	Control (n=125)
Hypotension	9 (7.1)	7 (5.6)
Mild	9 (7.1)	7 (5.6)
Severe	0 (0)	0 (0)
Need for vasopressors	2 (1.6)	2 (1.6)
Headache	4 (3.1)	3 (2.4)
Nausea	1 (0.8)	1 (0.8)
Vomiting	1 (0.8)	1 (0.8)

Fisher's exact test was used to assess differences between categorical variables. Differences were not statistically significant.

months before enrolling in the present study, 88 patients (34.9%) had experienced at least one hospitalization due to heart failure, 67 (26.6%) had been treated with at least one inotropic agent and 173 (68.5%) were evaluated as potential candidates for heart transplantation.

The preoperative infusion of levosimendan was successfully completed in all cases. A total of 16 patients (6.3%) developed mild hypotension that resolved with fluid infusions (nine [7.1%] in the levosimendan group compared with seven [5.6%] in the control group). Two patients (1.6%) in each group required the temporary use of low-dose vasopressors. Table 3 lists the adverse effects observed during the 24 h levosimendan infusion.

Hemodynamic data demonstrate a rapid improvement in cardiac index (Figure 1), SvO_2 (Figure 2) and PAOP (Figure 3) in patients receiving levosimendan. These effects persisted during the intraoperative period and the early postoperative period, and the differences were significant between the levosimendan and control groups at all timepoints ($P>0.05$). Three (2.4%) patients treated with levosimendan and 12 (9.6%) in the control group required more than one attempt at weaning from CPB ($P<0.05$).

The overall mortality rate was 8.2% (21 patients: five [3.9%] in the levosimendan group versus 16 [12.8%] in the control group; $P<0.05$). Thirty-five (13.9%) patients developed postoperative LCOS (nine [7.1%] in the levosimendan group compared with 26 [20.8%] in the control group; $P<0.05$).

Fewer patients required the addition of inotropic agents (10 [7.9%] versus 73 [58.4%]; $P<0.05$) and vasopressors (18 [14.2%] versus 57 [45.6%]; $P<0.05$) in the levosimendan group compared with the control group. Eight (6.3%) patients treated with levosimendan received an IABP compared with 38 (30.4%) in the control group ($P<0.05$). Of the patients requiring an IABP in the control group, four (3.2%) also required a more complex form of circulatory support, while none of the patients requiring an IABP in the levosimendan group required complex circulatory support. In general, there were fewer major postoperative complications in the levosimendan group than in the control group (Table 4).

DISCUSSION

The main findings of the present study demonstrate that in patients with coronary artery disease and SLVD, the preoperative use of levosimendan reduced postoperative mortality, the development of LCOS, the incidence of difficult weaning from CPB, and the requirement for inotropes, vasopressors, IABP and other forms of complex circulatory support. Using our hospital's protocol for infusion, levosimendan was well-tolerated, with a low incidence of adverse effects, none of which required study withdrawal. Although improvements in hemodynamic effects were observed in both treatment groups, the beneficial hemodynamic effects in the levosimendan group were larger than in the control group, and were observed early in the preoperative period and persisted throughout the intraoperative and early postoperative period. The resulting hemodyamic optimization correlates with the observed improvements in patient outcome. These hemodynamic effects are consistent with the unique properties
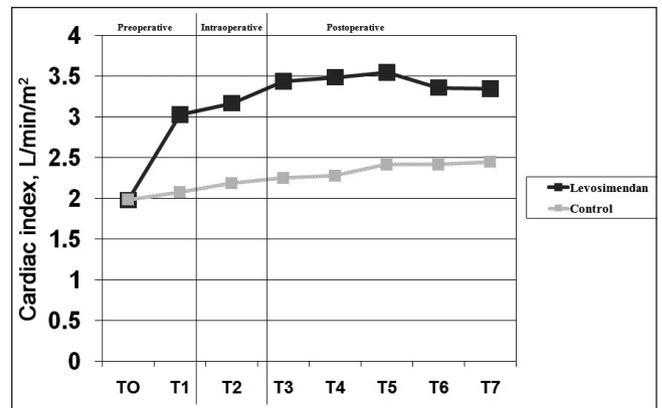

Figure 1) *An improvement in the cardiac index was observed immediately following administration of the levosimendan loading dose and was sustained for 48 h postoperatively. T0 Time 0, defined as the initial hemodynamic measurement; T1 Time 1, recorded immediately after the levosimendan loading dose; T2 Time 2, before anesthesia induction in the operating room; T3 Time 3, on arrival back in the cardiovascular intensive care unit following surgery; T4 to T7 Time 4 to Time 7, representing 6 h, 12 h, 24 h and 48 h after arrival back in the cardiovascular intensive care unit, respectively*
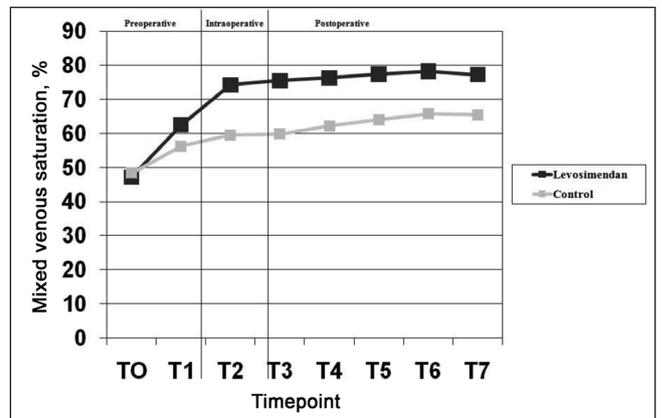

Figure 2) *A rapid improvement in the mixed venous pressure was observed in the levosimendan group following administration of the loading dose and was sustained for 48 h postoperatively. T0 Time 0, defined as the initial hemodynamic measurement; T1 Time 1, recorded immediately after the levosimendan loading dose; T2 Time 2, before anesthesia induction in the operating room; T3 Time 3, on arrival back in the cardiovascular intensive care unit following surgery; T4 to T7 Time 4 to Time 7, representing 6 h, 12 h, 24 h and 48 h after arrival back in the cardiovascular intensive care unit, respectively*

of levosimendan, which also make it particularly appropriate for preoperative use in this high-risk class of patients (11-13).

The multiple and complementary mechanisms of action of levosimendan are illustrated in Figure 4. This agent possesses calcium sensitizing activity, which is associated with a positive inotropic effect and increased myocardial contractility. However, in contrast to other inotropes, it accomplishes this without an elevation in intracellular calcium levels or an increase in cyclic AMP. As a result, there is no associated increase in myocardial O_2 consumption, which would seem particularly beneficial to patients with a limited myocardial reserve who are under conditions of stress from undergoing cardiac surgery. The stunned myocardium observed in the perioperative scenario exhibits, among other defects, a loss of calcium sensitivity which is favourably modified by levosimendan binding to cardiac troponin C, thereby increasing myocardial contraction at a low energy cost.

An increase in cardiac work without an elevation of myocardial O_2 consumption has been defined as external mechanical efficiency, and

TABLE 4
Postoperative complications within 48 h in the levosimendan versus control groups

Complication	Levosimendan (n=127)	Control (n=125)	P
Mortality	5 (3.9)	16 (12.8)	<0.05
Complicated weaning	3 (2.4)	12 (9.6)	<0.05
Low cardiac output syndrome	9 (7.1)	26 (20.8)	<0.05
New renal failure	7 (5.5)	18 (14.4)	<0.05
Dialysis	3 (2.4)	8 (6.4)	NS
Prolonged stay on ventilator	7 (5.5)	21 (16.8)	<0.05
Postoperative myocardial infarct	1 (0.8)	8 (6.4)	<0.05
Vasoplegic syndrome	3 (2.4)	12 (9.6)	<0.05
Atrial fibrillation	18 (14.2)	40 (32.0)	<0.05
Ventricular arrhythmia	8 (6.3)	19 (15.2)	<0.05
Systemic inflammatory response syndrome	4 (3.1)	15 (12.0)	<0.05
Sepsis	2 (1.6)	10 (8.0)	<0.05
Transitory ischemic attack	2 (1.6)	2 (1.6)	NS
Cerebrovascular accident	2 (1.6)	2 (1.6)	NS

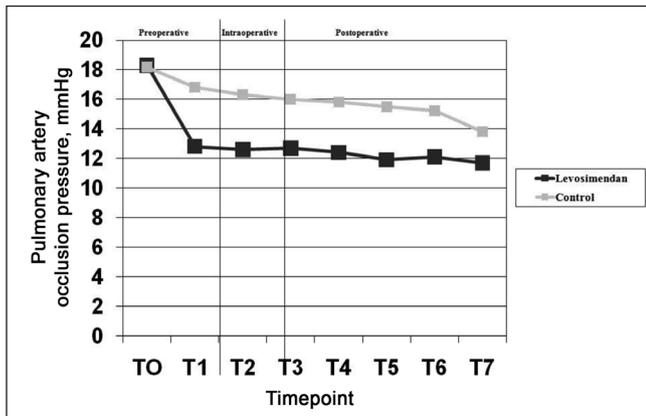*Data presented as n (%) unless otherwise indicated. NS Not statistically significant*

Figure 3) *An improvement in the pulmonary artery occlusion pressure was observed immediately following administration of the levosimendan loading dose and was sustained for 48 h postoperatively. T0 Time 0, defined as the initial hemodynamic measurement; T1 Time 1, recorded immediately after the levosimendan loading dose; T2 Time 2, before anesthesia induction in the operating room; T3 Time 3, on arrival back in the cardiovascular intensive care unit following surgery; T4 to T7, Time 4 to Time 7, representing 6, 12, 24 and 48 h after arrival back in the cardiovascular intensive care unit, respectively*

has been studied in the context of levosimendan treatment by Meyer et al (14,15). The authors demonstrated that myocyte function was preserved after ischemia-reperfusion injury in specimens pretreated with levosimendan. This phenomenon was particularly effective in hearts with severe dysfunction, even in individuals who were previously refractory to epinephrine.

Furthermore, by the same calcium sensitizing effect, levosimendan has positive lusitropic effects, preserving or improving diastolic properties. This has been demonstrated experimentally and also in clinical heart failure patients (16,17).

Levosimendan also acts on the mitochondrial ATP-sensitive potassium (KATP) channels, as well as KATP channels in vascular smooth muscle cells. Levosimendan develops pharmacological preconditioning effects through the activation of KATP channels localized at the mitochondrial level, leading to cardioprotection against ischemia-reperfusion conditions (eg, cardiac surgery), or at least limiting myocardial injury. The lower incidence of perioperative myocardial infarction in the present study supports this theory, and is consistent
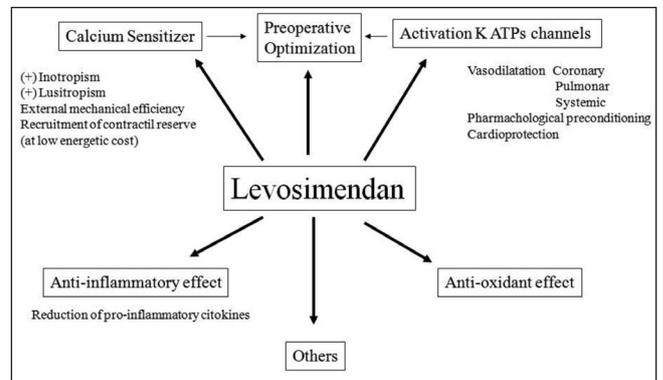

Figure 4) *Levosimendan's unique properties are attributed to its multiple and complementary mechanisms of action*

with previous reports examining postoperative LCOS by other authors (10,18). The reduction of difficult weaning from CPB and the persistence of the optimized hemodynamic parameters also appear to be part of this protective effect (10,19,20). These effects on KATP channels in vascular smooth muscle cells also cause coronary, pulmonary and systemic vasodilation, increasing the coronary perfusion and reducing the afterload, and improving the myocardial supply while reducing its demands. This creates a beneficial environment for affording a critical cardiac condition (21). Protein-bound active metabolites of levisomendan (OR 1855 and OR 1896) may exert clinical effects for up to one week. It is, therefore, possible that the favourable hemodynamic effects observed with levosimendan treatment may be sustained for longer periods of time than with other agents (eg, dobutamine and milrinone). This represents a desirable characteristic for a strategy of myocardial protection that is initiated in the preoperative period and persists during the critical intra- and postoperative periods.

Another remarkable property of levosimendan is its anti-inflammatory effects, reducing the level of proinflammatory cytokines and markers of oxidative stress. Parissis et al (22) and Paraskevaidas et al (23) have reported that levosimendan caused a marked reduction of interleukin-6 and a slight decrease in tumour necrosis factor-alpha levels in patients with advanced heart failure. Avgeropoulou et al (24) observed a reduction in the levels of malondialdehyde, a product of lipid peroxidation, indicating an antioxidant effect of levosimendan. Liu et al (25) presented an association between the use of levosimendan, lower levels of inflammatory response markers and reduction of postoperative atrial fibrillation (which was also observed in the present study). Although we did not measure these markers, the lower incidence of systemic inflammatory response syndrome, vasoplegia and atrial fibrillation in the present study appear to support these findings.

Two recent meta-analyses suggest a beneficial effect of levosimendan on mortality. A small meta-analysis of 10 studies involving 440 patients randomly assigned to levosimendan (n=235) or control (n=205) demonstrated that the perioperative use of levosimendan is associated with a reduction in postoperative mortality after cardiac surgery (26). The overall analysis showed a 65% reduction in postoperative mortality in the levosimendan group versus the control group (OR 0.35 [95% CI 0.18 to 0.71]; P=0.003), as well as a 52% reduction in the rate of atrial fibrillation in the levosimendan group versus the control group (OR 0.48 [95% CI 0.29 to 0.78]; P=0.003). The authors also conducted subgroup analyses that confirmed the reduction in the rate of mortality in patients treated with levosimendan versus control patients within the following groups: a 62% reduction in patients undergoing cardiac surgery with cardiopulmonary bypass; a 56% reduction in patients receiving both an intravenous bolus and a continuous infusion of levosimendan; a 60% in mortality with levosimendan compared with dobutamine; and an 80% reduction in mortality with levosimendan compared with milrinone.

A second meta-analysis by Maharaj and Metaxa (27) of 14 levosimendan studies including 729 patients undergoing percutaneous coronary revascularization or cardiac surgery demonstrated a 60% reduction in mortality and a 46% reduction in atrial fibrillation. Improvements in cardiac index, cardiac enzyme levels and length of stay were also observed in the levosimendan group compared with control groups. Although this meta-analysis was not powered to determine statistical significance for mortality in the cardiac surgery subgroup, many small pilot studies suggest a beneficial effect of levosimendan on postoperative mortality and morbidity. The present study of the preoperative use of levosimendan in 252 patients with SLVD is consistent with and contributes to the evidence for reduced mortality with levosimendan reported in both of these meta-analyses.

A growing body of evidence supports the use of 'early' use of levosimendan in cardiac surgery. A pilot study of 24 patients by Tritapepe et al (28) reported the release of troponin I was lower and the postoperative cardiac index higher among 12 patients treated with levosimendan before starting CPB compared with a control group. In a population of 30 patients with an ejection fraction <30%, De Hert et al (29) compared the intraoperative administration of levosimendan versus milrinone immediately after release of the aortic cross clamp (all patients received dobutamine). Patients treated with levosimendan exhibited improved postoperative stroke volume, required lower doses of dobutamine and norepinephrine for shorter periods of time, and required less time on the ventilator. The authors conclude, in agreement with our hypothesis, that the early use of levosimendan before or early during the ischemic insult has cardioprotective effects that avoid or limit the degree of postoperative stunning of the myocardium in patients with SVD *(SLVD?)*.

Tasouli et al (30) analyzed 45 patients with an ejection fraction <35% treated with levosimendan in addition to standard therapies (dobutamine, epinephrine, IABP), and compared early intraoperative use with postoperative utilization. Intraoperative use of levosimendan led to a reduction in the need for reintubation, a shorter length of stay in the ICU and in the hospital, a lower incidence of sepsis (none in patients receiving early administration of levosimendan) and a lower mortality rate compared with postoperative use.

A second placebo-controlled study by Tritapepe et al (18) involving 106 patients reported lower myocardial injury, decreased time on the ventilator, lower inotropic requirements and a shorter length of stay in the ICU. These studies, while presenting levosimendan treatment defined as 'early', included an infusion started in the operating room after the anesthetic induction. Not all cases underwent coronary revascularization and the left ventricular function differed but was higher in all cases than the population in the present study.

In the present study, infusion occurred one day before surgery, and resulted in significant and persistent hemodynamic benefits. This 'hemodynamic optimization', along with the cardioprotective effects of levosimendan, may increase tolerance of surgical injury. The concept is associated with the idea that early modifications of unfavourable hemodynamic conditions in critical patients will produce better outcomes, as was suggested 30 years previously by Schoemaker et al (31). In a different clinical scenario (sepsis), Rivers et al (32) also demonstrated that early hemodynamic interventions are associated with improved outcomes. In that analogy, our 'golden hours' would seem to be in the preoperative period.

Limitations

Although the present study represents one of the larger cardiac surgery studies with levosimendan, the number of patients is still limited. At least two issues warrant discussion: first, the need for a loading dose, and second, the appropriate time to start a preoperative infusion. Previous research involving LCOS patients has demonstrated the safety of using a bolus dose, consistent with the findings of the present study. Several studies have suggested an association between the cardioprotective effects of levosimendan and the use of a loading dose, as discussed in the meta-analysis performed by Zangrillo et al (33). This meta-analysis demonstrated that there was a smaller elevation of troponin I levels in patients receiving a levosimendan bolus. Research by De Santis et al (34) supports the same point.

Considering the most appropriate time to start treatment, it would appear that some point between the day before surgery and the induction of anesthesia may be the optimal time. Evidence suggests that patients with worse clinical conditions, as in the present study, would benefit from an earlier hemodynamic optimization.

Beyond these controversies, the reduction of mortality in patients with CAD and SLVD represents a remarkable finding, which will facilitate future research on this strategy, especially given the increasing number of patients in this category.

CONCLUSIONS

In patients with SLVD undergoing surgical coronary revascularization under CPB, the preoperative use of the calcium sensitizer levosimendan decreased mortality and the incidence of postoperative LCOS. Requirements o inotropic and vasopressor agents as well as the need for IABP were also reduced. Studies involving a larger number of patients are necessary to confirm the validity of this strategy.

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