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BRIEF COMMUNICATION

# Levosimendan Following Cardiac Surgery

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A best evidence topic was written to address if perioperative levosimendan improves mortality following cardiac surgery. Fourteen papers represented the best available evidence. An older meta-analysis summarising 11 of these trials concluded that there were fewer deaths in the levosimendan group compared to the control group (OR 0.41, $p < 0.001$) however, this was driven by the results of three included trials by the same author. Three larger and more recent randomised controlled trials failed to demonstrate significant differences in mortality. We conclude that levosimendan lacks robust evidence to substantiate claims of mortality benefit in cardiac surgery patients and should not be used routinely in such patients.

**Keywords** Review • Levosimendan • Cardiac surgery • Perioperative

## Introduction

In adult patients undergoing a cardiac surgery, is perioperative pressure support with levosimendan superior in terms of postoperative mortality? A best evidence topic was constructed according to a structured protocol [1].

## Search Strategy and Outcome

A total of 157 papers were found searching Medline 1950 to January 2018 using Ovid interface and by hand-searching of references. [cardiac surgery.mp OR exp Thoracic Surgery/] AND [levosimendan.mp OR levosimendan/]. Trials with adult patients including mortality as an endpoint were included. From these, 14 papers (one meta-analysis encompassing the results of 11 of the trials found and three recent randomised control trials (RCT)) papers were identified that provided the best evidence to answer the question.

## Results

Zhou [2] conducted a meta-analysis investigating rates of acute kidney injury and need for dialysis among adult cardiac surgery patients. The results of 13 trials were included, of which 11, representing 1,315 patients, included mortality as an endpoint. Nine of the trials used placebo as control, two used milrinone, and two used dobutamine. The authors found that 35 of 658 patients died in the levosimendan group vs 94 of 657 patients in the control/placebo group (OR, 0.41; 95% CI 0.27–0.62; $p < 0.001$; $I2 = 0.0\%$), a significantly reduced 30-day mortality for the levosimendan group. However, this result was driven by three papers by the same author (Levin) all of which considered a similar patient group, therefore significantly biasing the finding.

Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) [3] compared 24-hour preoperative levosimendan infusion to placebo in adult patients with impaired left ventricular ejection fraction (35% or less) undergoing cardiac surgery on cardiopulmonary bypass. Patients received 0.2 μg/kg/min for the first hour and 0.1 μg/kg/min for the remaining 24 hours. Their four-component composite primary endpoint of 30-day mortality, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of a mechanical cardiac assist device through day 5 occurred in

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105 of 428 patients (24.5%) in the levosimendan group and 103 of 421 (24.5%) in the placebo group (OR 1.00; 99% CI 0.66–1.54; p = 0.98). The two-component composite primary endpoints of 30-day mortality or use of a mechanical cardiac assist device through day 5 occurred in 56 patients (13.1%) in the levosimendan group and 48 (11.4%) of the placebo group (OR 1.18; 96% CI 0.76–1.82; p = 0.45). Adverse events did not differ between the two groups. Lower rates of low cardiac output syndrome and secondary inotrope use occurred among in the levosimendan group. Mortality, recorded at 30-days in the primary outcome (15 (3.5%) vs 19 (4.5%), OR 0.77, p = 0.45) and 90-days as a safety outcome (20 (4.7%) vs 30 (7.1%), OR 0.64, p = 0.12) did not differ significantly, however the authors cited that an adequately powered trial to examine mortality as the primary endpoint would require 3,000 patients.

Levosimendan in High Risk Patients Undergoing Cardiac Surgery (CHEETAH) [4] compared levosimendan infusion to placebo in adult patients requiring haemodynamic support following cardiac surgery. Initiating haemodynamic support was at the discretion of the attending physician but suggested criteria were mean arterial pressure $< 70$ mmHg and cardiac index $<2.2$L/min/m$^2$. Randomisation took place when patients required high doses of inotropes for bypass weaning. Stopped for futility at n = 506, the authors found no statistical difference in 30-day mortality (32/248 (12.9%) vs 33/258 (12.8%); absolute risk difference 0.1%; 95% CI −5.7–5.9; p = 0.97), duration of mechanical ventilation (median 19 vs 21 hours; median difference −2 hours; 95% CI −5–1; p = 0.48), length of ICU stay (median 72 vs 84 hours; median difference −12 hours; 95% CI −21–2; p = 0.09), and length of hospital stay (median 14 vs 14 days; median difference 0 days; 95% CI −1–2; p = 0.39). Adverse events did not differ between the two groups. The mean dose was 0.07 μg/kg/min.

Preoperative Levosimendan in CABG Patients With Poor LV Function (LICORN) [5] compared prophylactic 24-hour levosimendan infusion (0.1 μg/kg/min) to placebo in 336 adults scheduled to receive isolated or combined coronary artery bypass graft (CABG) with cardiopulmonary bypass. There was no significant difference between the groups for the composite primary endpoint of: need for catecholamine-infusion 48 hours after study drug initiation, left ventricular mechanical assist device (or failure to wean from it at 96 hours after study drug initiation if inserted preoperatively), or renal replacement therapy at any time postoperatively (87 (52%) vs. 101 (61%), p = 0.15). Mortality, a secondary outcome, was not significantly different in terms of in-hospital (10 (6%) vs. 12 (7%), p = 0.59), 28-day (12 (7%) vs. 9 (5%), p = 0.39), or day-180 (14 (8%) vs. 16 (10%), p = 0.59).

## Clinical Bottom Line

Although there is a suggestion from smaller trials that levosimendan may confer survival benefit among cardiac surgery patients, larger, more recent randomised trials have failed to replicate this, in part due to the study size required to demonstrate significance as well as lack of higher-dose levosimendan groups. The rationale for lower dose infusions is the higher rates of hypotension and arrhythmias with higher dose (≥0.2 μg/kg/min) infusions in several, non-cardiac surgery-related trials [6]. Evaluation of larger cohorts is required, as well as those investigating dose, length of follow-up, timing of randomisation, and indications for therapy, to enrich our understanding of its effects on mortality in cardiac surgery patients. At this point, evidence for mortality benefit is lacking and our recommendation is that routine levosimendan should not be used as prophylactic therapy in cardiac surgery patients.

## Conflict of Interest

None declared.

## Sources of Funding

No funding provided.

## Ethics

This trial violates no ethical principles.

## References

[1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. Interact CardioVasc Thorac Surg 2003;2:405–9.
[2] Zhou C, Gong J, Chen D, Weipeng W, Mingzheng L, Liu B. Levosimendan for prevention of acute kidney injury after cardiac surgery: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2016;67(3):408–16.
[3] Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med 2017;376:2032–42.
[4] Landoni G, Lomivorotov VV, Alvaro G, Lobreglio R, Pisano A, Guarracino F, et al. Levosimendan for hemodynamic support after cardiac surgery. N Engl J Med 2017;376:2021–31.
[5] Cholley B, Caruba T, Grosjean S, Amour J, Ouattara A, Villacorta J, et al. Effect of levosimendan on low cardiac output syndrome in patients with low ejection fraction undergoing coronary artery bypass grafting with cardiopulmonary bypass: the LICORN randomized clinical trial. JAMA 2017;318(6):548–56.
[6] Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, et al. Effects of levosimendan on mortality and hospitalization: a meta-analysis of randomized controlled studies. Crit Care Med 2012;40:634–46.