Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials

CRD summary
This well-conducted review found that levosimendan had cardioprotective effects that could result in a reduced postoperative mortality in patients who underwent cardiac surgery. Poor study quality should be taken into consideration when interpreting these conclusions.

Authors' objectives
To investigate the effect of levosimendan on mortality in patients undergoing cardiac surgery.

Searching
PubMed and BioMed Central were searched to January 2009 for studies in any language. Search terms were reported. References of retrieved articles and relevant reviews were examined. International experts were contacted.

Study selection
Randomised controlled trials (RCTs) of cardiac surgical patients that compared levosimendan with control and reported mortality were eligible for inclusion. There were no restrictions on dose and time of administration.

The included studies involved patients who underwent elective coronary artery bypass graft (CABG), off pump CABG, elective and non-elective cardiac surgery with cardiopulmonary bypass (CPB), CABG with CPB and aortic valve surgery. Seven studies administered a bolus and seven used continuous infusion, four after a bolus; doses ranged from 10 to 24μg/kg/min (as an intravenous bolus) and 0.1 to 0.2μg/kg (as continuous infusion). Controls were placebo, dobutamine and milrinone.

Two reviewers selected studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed by two independent reviewers in terms of randomisation, allocation concealment, blinding, concurrent treatments, reporting and other biases (not defined). Disagreements were resolved by consensus.

Data extraction
Data were extracted by four reviewers to compute odds ratios (ORs) and associated 95% confidence intervals (CIs) for categorical data or mean differences and 95% CIs for continuous data. Disagreements were resolved by consensus. Authors of primary studies were contacted for missing data.

Methods of synthesis
Pooled odds ratios, weighted mean differences (WMD) or standardised mean differences (SMD) and 95% CIs were calculated using a fixed-effect model (low or moderate levels of heterogeneity) or a random-effects model (high heterogeneity). Heterogeneity was assessed using the I² statistic (high heterogeneity was defined as I² >50%) and Cochran Q test. Funnel plots were used to investigate publication bias. Subgroup analyses were conducted for the outcome mortality in relation to type of surgery, bolus and infusion of levosimendan and type of comparator.

Results of the review
Ten RCTs were included in the review (n=440, range 24 to 137). Six RCTs reported adequate randomisation. Six trials used adequate allocation concealment. Six trials were at least single blinded. Three trials were deemed at high risk of bias, four at moderate risk and three low risk.

Levosimendan was associated with a statistically significant reduction in postoperative mortality (OR 0.35, 95% CI 0.18 to 0.71; 440 patients), atrial fibrillation (OR 0.48, 95% CI 0.29 to 0.78; 331 patients), cardiac troponin release (WMD
-2.5ng/mL, 95% CI -3.86 to -1.14; 139 patients), myocardial infarction (OR 0.26, 95% CI 0.07 to 0.97; 336 patients) and acute renal failure (OR 0.26, 95% CI 0.12 to 0.60; 228 patients) compared with control. There was no statistically significant difference between groups in time on mechanical ventilation, intensive care unit stay and postoperative hospital stay. None of these analyses except the outcome mechanical ventilation ($I^2=62.3\%$) were associated with significant heterogeneity. The results of subgroup analyses were similar to the main analyses for postoperative mortality.

The funnel plot did not suggest publication bias (based on the outcome postoperative mortality).

**Authors’ conclusions**
Levosimendan has cardioprotective effects that could result in a reduced postoperative mortality.

**CRD commentary**
The research question was supported by inclusion criteria for participants, intervention, study design and outcomes. Two databases were searched for studies in any language, which minimised the risk of language bias. It appeared that some measures were taken to identify unpublished studies. The funnel plot did not suggest publication bias, but the small number of included studies limited its reliability. Multiple reviewers were involved in study selection, quality assessment and data extraction, which reduced risks of reviewer error and bias. Study quality was assessed using appropriate criteria. Most of the included studies were at moderate or high risk of bias. The results appeared contradictory between the abstract and main body of the text.

The authors’ conclusions reflected the data presented, but poor study quality should be taken into consideration.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that a multicentre RCT powered to clinically relevant endpoints was needed to confirm the clinical advantages of levosimendan in cardiac surgery.

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