Levosimendan reduces cardiac troponin release after cardiac surgery: a meta-analysis of randomized controlled studies


CRD summary
This review investigated the effects of levosimendan in cardiac surgery. The authors found that levosimendan has cardioprotective effects that resulted in reduced postoperative cardiac troponin release. This review was generally well-conducted, but small study size and suboptimal quality made the reliability of the authors' conclusions unclear.

Authors' objectives
To investigate the effects of levosimendan in cardiac surgery.

Searching
BioMed Central and PubMed were searched to September 2007 for studies in any language. Search terms were reported. Proceedings of five conferences were searched (2002 to 2006). References of retrieved articles and reviews were scanned. International experts were contacted to identify further studies.

Study selection
Randomised controlled trials (RCTs) that reported outcome data of levosimendan in cardiac surgical patients were eligible for inclusion. There was no restriction on dose or time of administration. Primary review outcomes were postoperative release of cardiac troponin, myocardial infarction and hospital mortality.

Included studies used levosimendan in cardiac surgery with cardiopulmonary bypass or in off-pump coronary artery bypass (OFCAB) graft surgery. Levosimendan was administered as a bolus before surgery in most studies and after surgery in one study; continuous infusion was used in some of the studies. The dose ranged from 12 to 24μg/kg (as an intravenous bolus) or between 0.1 and 0.2μg/kg/min (as a continuous infusion). Control was either placebo or milrinone.

Studies were selected independently by four reviewers and disagreements resolved by consensus. Two reviewers then assessed adherence to inclusion criteria. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed by two independent reviewers according to The Cochrane Collaboration methods (studies assessed in terms of sequence generation, allocation concealment, blinding, outcome data, similarity of therapies and bias). Disagreements were resolved by consensus.

Data extraction
Means and standard deviations (SDs) or odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated for individual studies. Authors were contacted for missing data.

Four reviewers independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Pooled odds ratios and weighted mean differences (WMDs) with 95% CIs were calculated for categorical outcomes (ORs) and continuous outcomes (WMDs). Statistical heterogeneity was evaluated using Cochrane Q tests and the I² statistic. Where there was evidence of low statistical heterogeneity (I² ≤ 25%) the Peto fixed-effect method was used; otherwise a random-effect model was used. Publication bias was assessed using funnel plots. Sensitivity analyses were performed to assess the effects of study population and baseline risk.

Results of the review
Five RCTs were included in the review (139 patients, range 24 to 31). Most studies were reported to be of suboptimal quality. Overall risk of bias was reported as low in one study, moderate for three studies and high for one study.
Levosimendan was associated with a significant decrease in cardiac troponin peak release (WMD 2.5ng/dL, 95% CI -3.86 to -1.14; 139 patients) and time to hospital discharge (WMD -1.38 days, 95% CI -2.78 to 0.03; 79 patients). There was no significant difference between levosimendan and control for mortality (n=139), myocardial infarction (139 patients), atrial fibrillation (84 patients), intensive care unit stay (109 patients) and time on mechanical ventilation (139 patients). Myocardial infarction, intensive care unit stay and time on mechanical ventilation were associated with moderate to high statistical heterogeneity ($I^2$=45.7 to 62.3%).

Sensitivity analyses showed similar results. No evidence of publication bias was found.

**Authors' conclusions**

Levosimendan had cardioprotective effects that resulted in reduced postoperative cardiac troponin release.

**CRD commentary**

The research question was supported by inclusion criteria for study design, participants, intervention and outcomes. All languages were searched, which reduced the possibility of language bias. It appeared that there were limited attempts to identify unpublished studies by contacting authors. Publication bias was not suggested; few studies were included, which may have limited the worth of using funnel plots to determine this. Review processes were performed in duplicate, which reduced the risk of error and bias. Validity was assessed using appropriate criteria and this was taken into account in the analysis. Meta-analysis appeared to be appropriate and sources of statistical heterogeneity were investigated. This review was generally well-conducted, but small study size and suboptimal quality made the reliability of the authors’ conclusions unclear.

**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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