Levosimendan reduces mortality in critically ill patients: a meta-analysis of randomized controlled studies

CRD summary
This review concluded that levosimendan had cardioprotective effects that could result in reduced mortality in critically ill patients who required inotropic support. The synthesis did not take into account the level of clinical heterogeneity among the included studies, particularly with respect to comparators, which made the reliability of the conclusions unclear. The recommendations for research appeared appropriate.

Authors' objectives
To determine the impact of levosimendan on mortality in critically ill patients.

Searching
BioMed Central, PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to November 2008 without language restrictions. The search strategy was reported. References of identified studies and relevant reviews were checked and experts were contacted.

Study selection
Randomised controlled trials (RCTs) that compared levosimendan to a control condition and reported mortality as an outcome were eligible for inclusion. Secondary outcomes were hypotension, in-hospital myocardial infarction and acute renal failure.

About half of the included trials enrolled patients with decompensated heart failure; most other trials enrolled those undergoing cardiac surgery and some trials assessed it in interventional cardiology, vascular surgery and sepsis. Most studies used both a bolus and continuous infusion. Duration of continuous infusions ranged from four to over 24 hours. Doses ranged from 0.05 to 0.6mg/kg/minute. Bolus doses ranged from 3μg/kg to 36μg/kg. Controls received no treatment, placebo, dobutamine, milrinone or prostaglandin E1.

Four independent reviewers assessed abstracts for inclusion in the review. Full papers were selected by two reviewers.

Assessment of study quality
Two independent reviewers assessed study validity using the Cochrane Risk of Bias tool of randomisation, allocation concealment, comparability of concurrent therapy, completeness of outcome data, use of uniform and explicit outcome definition, selectiveness of outcome reporting and other forms of bias. The overall risk of bias was classified as high, moderate or low.

Data extraction
Four independent reviewers extracted data to enable calculation of odds ratios (OR) with 95% confidence intervals (CI) for dichotomous variables and mean differences with 95% CI for continuous variables.

Methods of synthesis
Studies were combined using fixed-effect meta-analysis to calculate Peto odds ratios with 95% CI for dichotomous variables where statistical heterogeneity was low and a random-effects model where statistical heterogeneity was considered moderate to high. Weighted mean differences (WMD) with 95% CI were calculated for continuous variables; a fixed-effect model was used except where significant heterogeneity was detected. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. The authors stated that they undertook sensitivity analyses, but no details were provided. Publication bias was assessed through funnel plot analysis.

Results of the review
Twenty-seven RCTs (3,350 participants) were included in the review. Trial quality was variable. Only seven trials were considered to be at low risk of bias and many others did not report details critical to an appraisal of their
methodological strength. Follow-up ranged from the end of hospitalisation to 18 months.

There were statistically significant reductions in mortality (OR 0.74, 95% CI 0.62 to 0.89, I²=11.3%; 27 RCTs) and myocardial infarction (OR 0.20, 95% CI 0.06 to 0.64, I²=0%; 14 RCTs) in groups treated with levosimendan compared with control. There was no significant difference in the incidence of acute renal failure between the groups. There was a statistically significant increase in hypotension in levosimendan groups (OR 1.38, 95% CI 1.06 to 1.80, I²=37.7%).

There was no evidence of publication bias.

Authors' conclusions
Levosimendan had cardioprotective effects that could result in reduced mortality in critically-ill patients who required inotropic support.

CRD commentary
The review question and inclusion criteria were clear. Several relevant databases and other sources were searched without restrictions, which reduced the chance that relevant studies were omitted from the review and reduced the risk that selection bias was introduced. The authors reported that they used methods designed to reduce bias and error at all stages of the review process. Validity of the included studies was assessed using appropriate criteria and the results were used to inform the synthesis. The use of meta-analysis did not take into account that both placebo-control and active-control trials were included and (although statistical heterogeneity was not high) it was unclear whether this was appropriate.

It is not clear how reliable the conclusions are, although the recommendations for further research appear strong.

Implications of the review for practice and research
Practice: The authors stated that, primarily for economic reasons, it was unclear whether levosimendan should be used as a first drug or as an adjunct. The dose of levosimendan should be titrated according to the haemodynamic conditions of the patients.

Research: The authors stated that a multicentre RCT with adequate power for outcomes such as mortality was needed to confirm the clinical advantages of levosimendan in critically ill patients who required inotropic support.

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