Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials

CRD summary
The review found that there was no evidence of survival benefit when levosimendan was compared with placebo for treating acute severe heart failure, but that levosimendan was associated with improvement in both survival and haemodynamics when compared with dobutamine. The review was well conducted and the authors’ conclusions appear reliable.

Authors’ objectives
To compare levosimendan versus standard therapy for treating patients with acute severe heart failure.

Searching
PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the metaRegister of Controlled Trials (www.controlled-trials.com) were searched without language restrictions to June 2007. Search terms were reported. Reference lists of included studies and reviews were checked and the manufacturers of levosimendan were contacted.

Study selection
Randomised controlled trials (RCTs) that compared levosimendan for acute severe heart failure in adults versus any other therapy were eligible for inclusion. Trials were required to report mortality or change in haemodynamic parameters (ejection fraction, cardiac index and pulmonary capillary wedge pressure) and/or b-type naturetic peptide.

The mean age of patients included in the review ranged from 55 to 70 years (where reported); in most trials they were predominantly male. The included patients had various types of heart failure, including decompensated heart failure, ischaemic heart failure, cardiogenic or septic shock and low ejection fraction after heart surgery. Criteria and cut-off points for defining heart failure varied (such as ejection fraction under 30% to 45% and/or cardiac index under 2.2 to 2.5). Levosimendan was usually delivered by bolus plus infusion for 24 hours; doses varied. Control interventions included placebo, dobutamine, milrinone and prostaglandin E1, delivered over 24 hours in most cases. As well as analyses of levosimendan versus placebo or another agent, the review included analysis of dobutamine versus placebo for the outcome of mortality.

Two reviewers independently selected the studies with disagreements resolved by discussion, involving a third author if necessary.

Assessment of study quality
The following components of trial validity were assessed: allocation concealment, blinding, and use of intention-to-treat analysis. Items not clearly reported as present were deemed absent.

Two reviewers independently assessed study validity with disagreements resolved by discussion.

Data extraction
Odds ratios (ORs) were calculated for dichotomous data and mean differences for continuous data, with 95% confidence intervals (CIs). Primary trial authors were contacted for more information if required.

Two reviewers extracted the data, which were checked by a third reviewer.

Methods of synthesis
Trials were combined to calculate pooled odds ratios or weighted mean differences (WMDs) and 95% confidence intervals, using a fixed-effect model. Analyses were stratified by comparator. Heterogeneity was assessed using the $\chi^2$ and I² tests. Sensitivity analyses were conducted to investigate the effects of individual components of validity and of
using the DerSimonian-Laird random-effects model. Publication bias was assessed using a funnel plot and Egger’s statistic.

**Results of the review**

Nineteen RCTs were included (3,650 patients). Only two fulfilled all quality criteria. Five RCTs reported adequate allocation concealment, 12 used intention-to-treat analysis, and seven used blinding. Duration of follow-up ranged from one to 180 days (where reported).

There was no statistically significant difference in mortality between the levosimendan and placebo groups (six RCTs; 1,578 patients), with no substantial statistical heterogeneity.

Levosimendan was associated with significantly lower mortality than dobutamine, with some statistical heterogeneity (OR 0.75, 95% CI 0.61 to 0.92; $I^2=44.6%$, eight RCTs; 1,979 patients). Subgroup analyses showed a stronger effect in lower quality trials.

Dobutamine was associated with significantly higher mortality than placebo (OR 1.82, 95% CI 1.06 to 3.12; $I^2=0%$; three RCTs; 301 patients).

There was no significant difference in mortality between the levosimendan and milrinone groups (two RCTs).

Levosimendan improved haemodynamic parameters compared with controls. Effects were statistically significant for ejection fraction compared with placebo, and for pulmonary artery occlusion pressure and B-type natriuretic peptide compared with either placebo or dobutamine. However data were limited, with only two or three RCTs for each comparison.

There was no evidence of significant publication bias. Findings were similar when random-effects models were used.

**Authors’ conclusions**

There was no evidence of survival benefit when levosimendan was compared with placebo for treating acute severe heart failure. However, levosimendan was associated with an improvement in both survival and haemodynamics when compared with dobutamine.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies, without restriction by language or publication status. Publication bias was assessed using suitable methods. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, undertake validity assessment and extract the data.

Appropriate methods were used to combine the trials statistically and assess for statistical heterogeneity. Trial quality was taken into account in interpreting the results. The authors noted limitations in the review, including lack of fully-published data, suboptimal trial quality and variation between the trials, particularly in the duration of follow-up.

The review was well conducted and the authors’ conclusions appear reliable.

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

**Practice:** The authors stated that the results of this review give grounds for concern about the use of dobutamine other than in a well-designed RCT.

**Research:** The authors stated that high quality studies should investigate the role of inotropic medication (especially dobutamine) in patients with acute heart failure. Studies of levosimendan should be conducted in targeted populations (e.g. patients awaiting heart transplant, those with acute heart failure after cardiac surgery, those with peripartum cardiomyopathy, early graft failure after heart transplant, right heart failure, acute heart failure concurrent with beta-blocker therapy or hypotension, and patients with other potentially reversible causes of acute heart failure).

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