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Levosimendan use in patients with preoperative low ejection fraction undergoing cardiac surgery: A systematic review with meta-analysis and trial sequential analysis☆

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ABSTRACT

Objectives: Patients with preoperative low left ventricular ejection fraction (LVEF) are known to be associated with high morbidities and mortality in cardiac surgery. The primary aim of this review was to examine the clinical outcomes of levosimendan versus placebo in patients with preoperative low LVEF ≤ 50% undergoing cardiac surgery.

Data sources: MEDLINE, EMBASE, PubMed and CENTRAL were searched systematically from their inception until June 2018.

Review methods: All the randomised clinical trials (RCTs) were included.

Results: Twelve trials were eligible (n = 1867) for inclusion in the data synthesis. In comparison to the placebo cohort, the levosimendan cohort showed a significant reduction in mortality (TSA = inconclusive; ρ = 0.002; I^2 = 0%; FEM: OR 0.56; 95% CI 0.39, 0.80), especially in the subgroups of preoperative severe low LVEF ≤ 30% (ρ = 0.003; OR 0.33; 95% CI 0.16, 0.69), preoperative administering of levosimendan (ρ = 0.001; OR 0.46; 95% CI 0.29, 0.74) and patients who had bolus followed by infusion of levosimendan (ρ = 0.005; OR 0.50; 95% CI 0.30, 0.81). However, the effect on mortality was not significant in the subgroup analysis of high quality trials (ρ = 0.14; OR 0.73; 95% CI 0.47, 1.12). The levosimendan cohort showed a significantly lower incidence of low-cardiac-output-syndrome (ρ < 0.001; OR 0.58; 95% CI 0.46, 0.74) and lesser need for mechanical support of cardiac assist devices (ρ = 0.02; OR 0.39; 95% CI 0.18, 0.86).

Conclusions: Given the low level of evidence and inconclusive TSA, the results of this meta-analysis neither support nor oppose the use of levosimendan in cardiac patients with preoperative low LVEF ≤ 50%. Therefore, multi-centre, adequately powered, randomised controlled trials are warranted.

PROSPERO registration: CRD42017067572.

1. Introduction

Preoperative low left ventricular ejection fraction (LVEF) among cardiac surgery patients was associated with higher risk of post-operative complications, namely low-cardiac-output-syndrome (LCOS), new-onset of atrial fibrillation and acute renal failure [1–6]. All these complications caused longer duration of ventilation and hospitalisation, and subsequently significant costs to the healthcare system [3,4].

In a Bayesian network meta-analysis, levosimendan (Simdax, Orion) is ranked as the most likely inotrope to reduce mortality among cardiac surgery patients [7]. Unlike other inotropes, levosimendan (Simdax, Orion) is a non-catecholamine calcium sensitizer that stabilises troponin C to improve cardiac contractility without an increase in myocardial oxygen consumption [7–9]. It also has the properties of cardioprotection and vasodilatation that promote the haemodynamic stability of myocardium during cardiac surgery [9–11]. All these beneficial effects of levosimendan were well-supported by multiple systematic reviews based on the meta-analytic data from small studies [12–18]. However, three recent major randomised controlled trials (RCTs)-CHEETAH [19], LEVO-CTS [20], LICORN [21] reported no significant difference in mortality among adult patients undergoing cardiac surgery.

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To date, after the publication of three major RCTs, eleven meta-analyses [22–32] with different inclusion criteria were synthesised to investigate the role of levosimendan in cardiac surgery. Most of them used a non-standardized threshold to define low LVEF (< 35% [31], ≤40% [22,23,28,30] or < 50% [25,32]). Thus, some of the studies that had the inclusion criteria of preoperative LVEF < 50% were excluded from those reviews [33–37]. All the reviews were updated before December 2017 and some meta-analyses did not include the LICORN trial [25,30,31]. Thus, the efficacy and safety profile of levosimendan in improving the outcomes of cardiac surgery among patients with low preoperative LVEF (≤50%) remained unclear.

The primary aim of this review was to examine whether levosimendan affects the mortality among adult cardiac patients with low preoperative LVEF (≤50%). Secondary aims were to investigate the role of levosimendan in minimising the postoperative complications, namely author-defined LCOS, new-onset atrial fibrillation and acute renal failure.

2. Methods

This meta-analysis was conducted and reported in accordance with the 'Preferred Reporting Items for Systematic Review and Meta-analysis' (PRISMA) statement 2015 [38]. The review protocol was registered on PROSPERO (www.crd.york.ac.uk; PROSPERO ID-CRD42017067572). The research questions were formulated using a population (preoperative low LEVF ≤ 50% patients undergoing cardiac surgery), intervention (levosimendan), placebo and outcomes approach.

2.1. Search strategy

We adopted the cut-offs of LVEF ≤30% and 30–50% as severe and borderline low LVEF, respectively from the guideline of the European Society of Cardiology [39]. Databases of MEDLINE, EMBASE, PubMed and CENTRAL were systematically searched from inception until June 2018.

The inclusion criteria set for the subjects were:

1. Adults (≥18 years old)
2. Undergoing cardiac surgery
3. Preoperative low LVEF ≤50% (measured with echocardiogram)
4. Receiving levosimendan or placebo/no treatment given
5. RCTs only.

Observational studies, case reports, case series, non-systematic reviews and trials published as abstracts, studies comparing levosimendan with other comparators, namely dobutamine, milrinone and intra-aortic balloon pump (IABP) were excluded. The search strategy and terminology used are provided in eTable 1. Though the language was not a criterion for exclusion, only the literature written in English was assessed in this review. The bibliographies of the included papers and relevant systematic reviews were scrutinized to find more papers for inclusion in this study.

2.2. Outcomes

The primary outcome was all-cause mortality based on the analysis of the longest follow-up data (30 days, 90 days and 180 days). Secondary outcomes were the incidence of new-onset postoperative atrial fibrillation, acute renal failure, author-defined LCOS, hypotension, the need for mechanical cardiac assist devices (IABP, extracorporeal membrane oxygenation and ventricular assist device), the length of stay in a hospital or intensive care unit (ICU) stay, and the duration of ventilation. The criteria for author-defined LCOS were low cardiac index ≤2.2 L/min/m^2, elevated pulmonary capillary wedge pressure > 16 mm Hg, arterial partial pressure of oxygen < 60 mm Hg, the use of inotropes or mechanical cardiac assist devices in the postoperative period [20,21,36,37,40,41].

2.3. Study selection and data extraction

Titles and abstracts were independently screened against eligibility criteria by two authors (WT and XC). The same two reviewers independently screened the full texts of qualifying papers. Any disagreements at any of the two stages were resolved by the third author (KN). All the included RCTs were assessed for the risk of bias using the Cochrane Collaboration Risk of Bias Assessment Tool (https://handbook.cochrane.org). In addition to the measures of outcomes, the following fields, namely citation, year of publication, study design, country, population, sample size and dosage of levosimendan were extracted. When the LVEF was presented as the median (interquartile range), it was converted to mean (± standard deviation) [42].

The GRADE assessments of the evidence was performed and the summary of findings were compiled independently by the two authors (KN and XC) using the GRADEpro/GDT software (https://gradepro.org/). Based on the Cochrane handbook, we downgraded the starting rating of "high quality" evidence of RCT based on the five criteria (risk of bias, inconsistency, indirectness, imprecision and publication bias) by one level for serious concern and by two levels for very serious concerns [43]. Any disagreements were resolved by the third author (CW).

2.4. Statistical analyses

Statistical analyses were undertaken using RevMan Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). I^2 test was used to assess the heterogeneity of studies. The values of < 40%, 40–60% and > 60% were used to determine low, moderate and substantial heterogeneity, respectively [43]. A two-sided ρ-value of < 0·05 was used to denote the statistical significance of heterogeneity. If substantial heterogeneity was absent, a fixed-effects model (FEM) analysis (Mantel–Haenszel method) was used to pool the estimates. If substantial heterogeneity (I^2 > 50%) was found, a random-effects model (REM) analysis (DerSimonian–Laird method) was used. Findings were reported as odds ratios (OR) or mean difference (MD) with 95% confidence intervals (CI). For measured outcomes with zero event in either arms, we adhered to the guidance of the Cochrane Handbook (16.9.3) by using OR-based method because it excludes those studies that show reporting bias whether or not they are published [44]. We performed subgroup analyses for all the outcomes based on the quality of studies (high risk vs low risk of bias). For primary outcome (mortality), subgroup analyses were conducted based on the severity of LVEF (severe vs borderline LVEF), different timing (preoperative-before the induction of general anaesthesia vs intraoperative-after the induction of general anaesthesia vs postoperative- after the cardiac surgery) and the regimes of administering levosimendan (bolus only vs bolus followed by continuous infusion respectively).

To prevent the risk of random error and multiplicity phenomenon due to repeated significant testing in meta-analyses, trial sequential analysis (TSA) with the Law of the Iterated Logarithm was performed on the primary outcome using the TSA viewer version 0.9.5.5 Beta (Copenhagen Trial Unit, 2016) [45]. The calculations of the required meta-analysis information size and the adjusted significance thresholds were based on a two-sided TSA-adjusted fixed effects model with 5% risk of type 1 error and power 80%.

3. Results

The results of the literature search and study selection process are outlined in the PRISMA flow chart (Fig. 1). The titles and abstracts of 1477 non-duplicate articles were screened. Of these, 41 articles were retrieved. After applying the inclusion and exclusion criteria, twelve