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Efficacy and safety of levosimendan in patients with acute right heart failure: A meta-analysis

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ABSTRACT

Aims: Right heart failure (RHF), which is caused by a variety of heart and lung diseases, has a high morbidity and mortality rate. Levosimendan is a cardiac inotropic drug and vasodilator. The effect of levosimendan on RHF remains unclear. We sought to evaluate the efficacy and safety of levosimendan in patients with acute RHF.
Materials and methods: We systematically searched PubMed, Cochrane Library, EMBASE, and ClinicalTrials.gov to identify studies reporting the efficacy and safety of levosimendan for the treatment of RHF.
Key findings: Ten trials, including 359 participants from 6 RCTs and 4 self-controlled trials, were evaluated. In the 6 RCTs, we found that patients treated with levosimendan for 24 h showed a significant increase in tricuspid annular plane systolic excursion [1.53; 95% CI (0.54, 2.53); $P = 0.002$] and ejection fraction [3.59; 95% CI (1.21, 5.98); $P = 0.003$] as well as a significant reduction in systolic pulmonary artery pressure [−6.15; 95% CI (−9.29, −3.02); $P = 0.0001$] and pulmonary vascular resistance [−39.48; 95% CI (−65.59, −13.38); $P = 0.003$], whereas changes in mean pulmonary pressure were nonsignificant. Adverse events did not significantly differ between the two groups.
Significance: Our study shows that levosimendan exhibits short-term efficacy for treating RHF in patients with a variety of heart and lung diseases. Additional strict multicentre RCTs with long follow-up times and large sample sizes are required to further validate the efficacy and safety of this treatment.

1. Introduction

Right heart failure (RHF), a clinical syndrome with multiple possible causes that results in right ventricular systolic and/or diastolic dysfunction, can eventually result in circulatory failure and death [1]. A variety of heart and lung diseases, including pulmonary hypertension (PH), left heart failure (LHF), myocardial infarction, congenital heart disease, pulmonary embolism, perioperative and chronic obstructive pulmonary disease, can lead to right ventricular pressure and/or volume overload or myocardial disease [2]. According to the US Health Center, the estimated prevalence of RHF is 5%, fairly to LHF. In addition, RHF induced by PH has a mortality rate of up to 48% in intensive care units (ICUs), which is higher than that of LHF [3]. Poor right ventricular function is an independent prognostic marker for mortality in patients with heart failure or PH [1,4,5]. Although the management of RHF has improved, the associated morbidity and mortality remain high. Additionally, published guidelines describe only a limited number of efficient treatments for RHF.

Intracellular Ca^{2+} controls numerous cellular processes via excitation-contraction coupling, and Ca^{2+}-release channels (CRCs) play important roles in the heart, skeletal muscle, and brain as well as in the processes of metabolism and aging [6]. Levosimendan, a cardiac inotropic drug and vasodilator, inhibits phosphodiesterases and promotes Ca^{2+} binding with troponin-C to improve ventricular function without increasing oxygen demand. Moreover, levosimendan activates ATP-sensitive K^{+}-channels in smooth muscle to cause vasodilation [7]. In addition, after a 24-h infusion of levosimendan, its active metabolite OR-1896, which has a long half-life (approximately 80 h), can be detected and persists for many days in human blood [8].

Evidence-based medicine has confirmed that levosimendan treatment is beneficial for patients with LHF, but its effect on patients with RHF remains unclear [9–11]. Several trials have examined this

Abbreviations: RHF, right heart failure; RV, right ventricle; PH, pulmonary hypertension; LHF, left heart failure; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; EF, ejection fraction; PVR, pulmonary vascular resistance; mPAP, mean pulmonary artery pressure; BNP, brain natriuretic peptide; SvO2, mixed venous oxygen saturation; RVEF, right ventricular ejection fraction; CO, cardiac output; CI, cardiac index; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

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relationship, but the sample sizes were small, and the results were inconclusive and even conflicting. Moreover, the molecular mechanisms of RHF are not well known [12]. Therefore, traditional therapies may be ineffective at improving RV function or survival in patients with RHF.

In this meta-analysis, we sought to evaluate the efficacy and safety of levosimendan for treating patients with RHF using Doppler echocardiography and right heart catheterization.

2. Materials and methods

2.1. Literature search

We systematically searched PubMed (from 1950 to February 2017), EMBASE (from 1966 to February 2017), the Cochrane Library database and ClinicalTrials.gov for primary literature as well as reviews of relevant articles using the keyword "levosimendan" paired with the following: "right heart or right ventricular (failure)", "pulmonary hypertension", "pulmonary embolism", "acute respiratory distress syndrome", "perioperative", "chronic obstructive pulmonary disease" or "congenital heart defect". The search was restricted to clinical trials, and no language restrictions were imposed. In addition, the references of relevant clinical trials or review articles were manually searched to identify additional relevant trials.

2.2. Inclusion criteria

The main inclusion criteria were the following:

1) Patients with RHF or overload who were diagnosed according to the Canadian Cardiovascular Society Consensus Conference guidelines for heart failure, update 2009: Diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials [13].
2) Patients with New York Heart Association (NYHA) class III to IV symptoms or severe PH with mPAP ≥ 60 mm Hg at baseline.
3) Patients who received intravenous infusion of levosimendan (with a specified treatment dose and duration) at 0.1 μg/kg/min to 0.2 μg/kg/min for 24 h and a control group that received conventional therapies including placebo, dobutamine, etc.
4) Patients whose outcomes were evaluated using Doppler echocardiography and/or right heart catheterization.

2.3. Exclusion criteria

We excluded non-human studies, case reports, reviews, letters, and commentaries.

2.4. Quality assessment

Each study was assessed using the Jadad scale for quality. Trials scored one point for each area addressed, with an overall possible score between 0 and 5 (highest level of quality). A score ≤ 2 indicates low quality, and a score ≥ 3 indicates high quality [14]. In addition, we also used the Cochrane Collaboration tool to assess the risk of bias among the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias [15]. Each reference study was judged by two authors as being low risk, high risk or unclear.

2.5. Data extraction

Two authors (JYQ and LJ) independently screened titles and abstracts to assess trials according to the inclusion and exclusion criteria. Disagreements were identified computationally. Each manuscript was checked independently. Ten studies that met our inclusion criteria were added; data were extracted using a predefined pilot-tested data extraction form. When actual data were not presented in the studies, two authors (JYQ and LJ) directly contacted the corresponding authors for the data. A third researcher was involved in decision making in cases of disagreement between the first two researchers. The extracted data included the following study characteristics: (1) first author; (2) publication year; (3) sample size (male and female); (4) intervention strategy and study duration; (5) study design; (6) adverse events and (7) baseline and final index or net changes in tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (sPAP), ejection fraction (EF), pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), etc.

2.6. Data synthesis and analysis

For each study's data, we calculated the changes from baseline following treatment in the levosimendan group and the control group. The mean and standard deviation (SD) of changes in ten studies were reported. The missing SD values for the remainder of the studies were input based on the mean and SD of changes reported in the ten studies described above. A correlation coefficient (r) of 0.5 was calculated. The meta-analysis was conducted using Stata software (version 12.0; Stata Corporation, College Station, TX) and RevMan software (version 5.3; Cochrane Collaboration, Oxford, United Kingdom). The mean difference (MD) and 95% confidence interval (CI) were used as summary statistics. A P value of <0.05 was considered statistically significant. Heterogeneity was assessed using Cochran's Q-test ($P<0.1$) and the I^2 test. The I^2 index was used to assess the heterogeneity of the pooled effect. I^2 values ≥ 50% represented significant heterogeneity, and a random effects model was used in such cases; otherwise, a fixed effects model was used. Potential publication bias was assessed using a funnel plot.

3. Results

3.1. Results of the literature search

A total of 1399 studies were identified through the database search. However, most studies were excluded because they were not relevant to the purpose of this meta-analysis or they were non-human studies, cross-sectional studies, reviews, commentaries, letters or case reports.

Ultimately, 10 observational articles (10 trials; 359 patients) satisfied our inclusion criteria [16–25]. Of these, 5 trials evaluated right ventricular function using Doppler echocardiography [16–20], and 5 trials used right heart catheterization [21–25]. The selection procedure is shown in Fig. 1.

3.2. Study characteristics and quality assessment

The study characteristics are shown in Table 1.

All studies were conducted between 2006 and 2016; study locations included Germany (n = 3), Turkey (n = 5), Austria (n = 1) and Greece (n = 1) [16–25]. The trials varied in sample size from 20 to 63 subjects (for a total of 359 subjects). Among the trials reporting the study participants' gender and age, 72.2% of the population was male (242/335), 27.8% was female (93/335), and the age range was 38–77 years. The gender distribution of the remaining 25 participants (from one self-controlled trial) is unknown. The study subjects all had class III or IV NYHA cardiac function.

All subjects were intravenously administered levosimendan as the intervention. Either an initial treatment dose of 6–12 μg/kg over 10 min followed by continuous infusion of 0.1–0.2 μg/kg/min for 24 h or a continuous intravenous infusion without an initial loading dose was used. End-points were detected by Doppler echocardiography or right heart catheterization. Quality assessments are detailed in Table 1.

The included trials consisted of six randomized controlled trials (RCTs) and four self-controlled trials. The quality of these trials varied