Meta-Analysis of Trials on Prophylactic Use of Levosimendan in Patients Undergoing Cardiac Surgery

Ayman Elbadawi, MD, Islam Y. Elgendy, MD, Marwan Saad, MD, PhD, Michael Megaly, MD, MS, Amgad Mentias, MD, Ahmed S. Abuzaid, MD, Hend I. Shahin, MS, Vinay Goswamy, MD, Hesham Abowali, MD, and Barry London, MD

Department of Internal Medicine, Rochester General Hospital, Rochester, New York; Department of Cardiovascular Medicine, Ain Shams University, Cairo, Egypt; Division of Cardiovascular Medicine, University of Florida, Gainesville, Florida; Department of Cardiovascular Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Division of Cardiovascular Medicine, Hennepin County Medical Center/Minneapolis Heart Institute, Abbot Northwestern Hospital, Minneapolis, Minnesota; Department of Cardiovascular Medicine, University of Iowa, Iowa City, Iowa; Sidney Kimmel Medical College at Thomas Jefferson University/ Christiana Care Health System, Newark, Delaware; and Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt, Cairo, Egypt

Background. **The role of prophylactic levosimendan in patients undergoing cardiac surgery is controversial.**

Methods. **We performed a computerized search of Medline, Embase, and Cochrane databases through September 2017 for randomized trials evaluating the prophylactic use of levosimendan in patients undergoing cardiac surgery (ie, patients without low cardiac output syndrome). The main study outcome was mortality at 30 days.**

Results. **The final analysis included 16 randomized trials with total of 2,273 patients. There was no statistically significant difference in mortality at 30 days between levosimendan and control groups (relative risk 0.68, 95% confidence interval [CI]: 0.45 to 1.03). Subgroup analysis showed no statistically significant difference in mortality at 30 days for patients with reduced left ventricular ejection fraction compared with patients having preserved left ventricular ejection fraction (p for interaction = 0.12). Further analysis suggested that levosimendan might be associated with improved mortality at 30 days when compared with active-control but not when compared with placebo (p for interaction = 0.01). The levosimendan group had a significant reduction in acute kidney injury (relative risk 0.59, 95% CI: 0.38 to 0.92), intensive care unit stay (standardized mean difference = −0.21, 95% CI: −0.29 to −0.13), and ventilation time (standardized mean difference = −0.43, 95% CI: −0.61 to −0.25), whereas it had higher rates of atrial fibrillation (relative risk 1.11, 95% CI: 1.00 to 1.24). No statistically significant differences were observed between groups in mortality beyond 30 days, postoperative dialysis, or myocardial infarction.**

Conclusions. **Prophylactic use of levosimendan does not appear to reduce the mortality at 30 days or beyond 30 days in patients undergoing cardiac surgery. This lack of benefit was noted irrespective of the LVEF.**

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In the United States and Europe, approximately 1 million cardiac surgeries using cardiopulmonary bypass are performed annually [1]. The patient population undergoing these surgeries commonly have a number of comorbidities, rendering them at a high perioperative risk [2]. Among various complications, low cardiac output syndrome complicates 3% to 14% of cardiac surgeries using cardiopulmonary bypass and is known to be associated with a significant increase in morbidity and mortality [2]. Prophylactic use of inotropic agents has been suggested to prevent low cardiac output syndrome and improve postoperative outcomes in those patients. Various inotropic agents were associated with suboptimal results due to potential increase in cardiac arrhythmias and mortality [3, 4]. Levosimendan is a calcium sensitizer that improves myocardial contractility without an increase in oxygen requirements. In prior studies, levosimendan use was promising for improvement of clinical outcomes in the setting of cardiac surgeries [4, 5]; however, two recent trials showed no benefit for levosimendan use on various clinical outcomes in patients undergoing cardiac bypass grafting

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Address correspondence to Dr Elbadawi, Department of Medicine, Rochester General Hospital, 1425 Portland Ave, Rochester, NY 14621; email: ayman.elbadawi@rochesterregional.org.

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and valvular heart surgeries [6, 7]. Hence, we conducted a meta-analysis of randomized trials on a large scale of outcomes to assess the impact of levosimendan on the individual outcomes in patients undergoing cardiac surgeries.

Patients and Methods

We performed a computerized search of Medline, Embase, and Cochrane databases without language restrictions through September 2017, using the terms "levosimendan," "cardiac surgery," and "cardiopulmonary bypass" separately and in combination to identify all randomized clinical trials that evaluated the use of levosimendan in the setting of cardiac surgeries. A similar search strategy was also done for abstracts of the major scientific sessions (American College of Cardiology, European Society of Cardiology, American Heart Association, and European Association of Cardiothoracic Anesthesiologists) to September 2017. We further screened the bibliographies of the retrieved studies, prior meta-analyses as well as clinicaltrials.gov for any relevant studies not retrieved through the initial search [4, 8–10]. The study design, baseline characteristics, intervention strategies, main outcomes, and other study characteristics were extracted by two independent investigators (A.E and M.M). Discrepancies among investigators were settled by consensus.

We included randomized clinical trials that evaluated the preoperative, intraoperative, or postoperative prophylactic use of levosimendan for patients undergoing cardiac surgery irrespective of the type of surgery (ie, coronary artery bypass graft or valve surgeries), and reported clinical endpoints for the levosimendan group versus no levosimendan (control) group. We excluded nonrandomized studies and studies including patients already having low cardiac output syndrome.

The primary outcome of the study was mortality at 30 days. The secondary outcomes included mortality beyond 30 days, perioperative myocardial infarction (MI) as defined per each individual study, use of mechanical assist devices, use of additional inotropic agents, postoperative acute kidney injury, dialysis, postoperative atrial fibrillation, and postoperative cerebrovascular accident. Mean duration of intensive care unit stay and mean ventilation time were also assessed.

All aspects of this meta-analysis were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. Statistical analysis was conducted using STATA version 14 software (StataCorp, College Station, TX). Descriptive analyses were conducted using frequencies for categoric variables and standardized means with standard deviations for continuous variables. We pooled our data mainly using the random-effect DerSimonian and Laird model, as we expected considerable heterogeneity. For estimating the effect of each outcome, we reported the relative risk (RR) and the 95% confidence interval (CI). The p values were two-tailed and considered statistically significant if less than 0.05.

The quality of included trials was assessed on basis of adequate description of treatment allocation, blinded outcome assessment, and description of losses to follow-up [12]. Accordingly, the methodologic quality of each study was classified into "low risk" (low risk of bias for each criteria), "high risk" (at least one criterion at high risk of bias), or "unclear risk." Publication bias was assessed using Egger's test [13]. Statistical heterogeneity across trials was assessed by I^2 statistics, with I^2 statistic values less than 25%, 25% to 50%, and more than 50% considered as low, moderate, and high degree of heterogeneity, respectively [14, 15].

Subgroup analyses were performed for the primary outcome in patients with reduced left ventricular ejection fraction (LVEF) of less than 40% versus those with preserved LVEF of 40% or greater, placebo-controlled versus active-controlled studies, and preoperative versus postoperative use of levosimendan. Meta-regression analyses were prespecified for the primary outcome according to age, sex, prior MI, preoperative use of β-blockers, preoperative use of angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers, cross-clamp time, and total bypass time to evaluate for any modification in the outcome with baseline characteristics.

Results

Study selection process is described in the flow diagram (Fig 1). Our final analysis included 16 studies with a total of 2,273 patients [5–7, 15–27] (Supplemental Tables 1 and 2). Data from the study by Eriksson and colleagues [19, 28] was retrieved from the initially published article and a subsequent article reporting impact of levosimendan on renal function. The baseline characteristics of the included studies are described in Table 1. Quality of the included studies is outlined in Table 2. All included studies were classified as low risk of bias.

Our main study outcome of mortality at 30 days was analyzed in 13 of 16 studies. There was no statistically significant difference between the levosimendan group and control groups in mortality at 30 days (RR 0.68, 95% CI: 0.45 to 1.03, $p = 0.070$, $I^2 = 14.8\%$). No publication bias was observed by Egger's test ($p = 0.53$; Fig 2). In a subgroup analysis by LVEF, there was no statistically significant difference in mortality at 30 days among patients with reduced LVEF (RR 0.57, 95% CI: 0.34 to 0.93, $p = 0.026$; $I^2 = 21\%$), compared with patients having preserved LVEF (RR 1.17, 95% CI: 0.54 to 2.54, $p = 0.696$, $I^2 = 0\%$; p for interaction = 0.12). Another subgroup analysis by the type of control group revealed that the mortality at 30 days benefit was mainly observed when levosimendan was compared with the active-control group (RR 0.32, 95% CI: 0.16 to 0.66, $p = 0.002$, $I^2 = 0\%$), but not when compared with the placebo-control group (RR 0.91, 95% CI: 0.60 to 1.39, $p = 0.677$, $I^2 = 0\%$; p for interaction = 0.01; Supplemental Fig 1). Further subgroup analysis by the timing of levosimendan use demonstrated no subgroup interaction between patients who received levosimendan before aortic clamping (RR 0.76, 95% CI: 0.49 to 1.18, $p = 0.224$, $I^2 = 14\%$) versus after aortic clamping (RR 0.35, 95% CI: 0.13 to 0.98, $p = 0.047$, $I^2 = 0\%$; p for interaction = 0.18). Meta-regression analysis did not