Sepsis

Levosimendan reduces mortality in patients with severe sepsis and septic shock: A meta-analysis of randomized trials[☆,☆☆]

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ARTICLE INFO

ABSTRACT

Purpose: There is controversy about the use of inotropes in the treatment of severe sepsis and septic shock. The objective of this study was to evaluate if levosimendan, as compared with standard inotropic therapy (eg, dobutamine), reduces mortality in septic patients.
Materials and Methods: BioMedCentral, PubMed, EMBASE, and the Cochrane Central Register were searched for pertinent studies, up to 1st May 2015. Randomized trials on the use of levosimendan in patients with severe sepsis and septic shock were included if reporting mortality data. The primary outcome was mortality, whereas secondary outcomes were blood lactate, cardiac index, total fluid infused, norepinephrine dosage, and mean arterial pressure.
Results: Seven studies for a total of 246 patients were included in the analysis. Levosimendan was associated with significantly reduced mortality compared with standard inotropic therapy (59/125 [47%] in the levosimendan group and 74/121 [61%] in the control group; risk difference $= -0.14$, risk ratio $= 0.79$ [0.63-0.98], P for effect $= .03$, $I^2 = 0\%$, numbers needed to treat $= 7$). Blood lactate was significantly reduced in the levosimendan group, whereas cardiac index and total fluid infused were significantly higher in the levosimendan group. No difference in mean arterial pressure and norepinephrine usage was noted.
Conclusions: In patients with severe sepsis and septic shock, levosimendan is associated with a significant reduction in mortality compared with standard inotropic therapy. A large ongoing multicenter randomized trial will have to confirm these findings.

1. Introduction

Acute organ dysfunction due to severe infection is associated with a high mortality rate [1]. The mortality rate of patients with septic shock is decreasing [2,3], but still remains high, despite widespread adoption of international sepsis guidelines [4]. There are still several doubts about medical therapy in septic patients. For example, a recent randomized controlled trial showed that protocol-based resuscitation of patients in septic shock does not improve outcomes [5]. Further studies are needed to evaluate new therapeutic approaches to decrease mortality and morbidity of septic patients.

Hypotension associated with septic shock is predominantly due to a vasodilatory state secondary to infection and inflammatory response. In addition, the perfusion deficit may be worsened by new-onset cardiac dysfunction, a well-known manifestation of organ dysfunction in sepsis. This occurs in 40% to 50% of patients with prolonged septic shock and is associated with a higher mortality [6–8]. Nowadays, whether the addition of an inotropic agent improves clinical outcomes in septic shock remains unresolved. Current guidelines recommend a trial of dobutamine in case of myocardial dysfunction or tissue hypoperfusion [4].

Another inotropic agent is levosimendan [9], a calcium-sensitizer agent [10] with vasodilatory properties [11], exerting beneficial effects particularly in cardiac surgery, a setting where it recently showed a survival benefit when compared with dobutamine [12]. The absence of increase in myocardial oxygen consumption likely brings to a myocardial protective effect [13]. Furthermore, novel available data suggest that levosimendan can be useful in patients with renal impairment [9,14].

Experimental studies in septic animal models showed that levosimendan improves myocardial function [15], attenuates intestinal dysfunction [16], improves microvascular oxygenation [17], protects against endotoxemic acute renal failure [18], and exerts immunomodulatory effects [19–21]. However, results are still controversial [17,22–25].

In humans, several case series [26–29] and small single-center randomized control clinical trials [30–36] provide good evidence to sustain the hypothesis that levosimendan might be a promising therapy in severe sepsis and septic shock. However, in 2 subanalyses of a meta-analysis regarding levosimendan administration in critical care setting, investigators failed to find a significant difference in mortality in the septic group [37,38].

Because new randomized articles have been recently published [30–32,34,36], we decided to perform an updated meta-analysis of all the randomized clinical trials published so far to determine the impact of levosimendan on mortality in patients with severe sepsis and septic shock.

2. Materials and methods

2.1. Search strategy

Appropriate studies were independently searched in BioMedCentral, PubMed, EMBASE, and the Cochrane Central Register of clinical trials (updated 1st May 2015) by 3 trained investigators. The full PubMed search strategy is available in the supplementary material (Supplementary Material 1). We decided to use a basic search strategy in order to make the strategy as sensitive as possible.

Abstracts from recent international conferences were searched for additional relevant studies. In addition, we used backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews). The search strategy aimed to include any randomized study ever performed with levosimendan administration in severe sepsis and septic shock in adult humans. *Severe sepsis* was defined as an acute organ dysfunction secondary to documented or suspected infection, and *septic shock* was defined as severe sepsis with hypotension not reversed with fluid resuscitation [4]. No language restriction was enforced.

2.2. Study selection

References obtained from searches were first independently examined at an abstract level by 3 investigators and then, if potentially relevant, collected as complete articles. If the complete article was not available in the database, the corresponding author was contacted for further material.

The following inclusion criteria were used for potentially relevant studies: administration of levosimendan in patients with severe sepsis or septic shock, random allocation to treatment, comparison of levosimendan vs control, and mortality data availability. There were no restrictions on dose or time of administration. The exclusion criteria were as follows: duplicate publications, pediatric studies, and nonintravenous administration of levosimendan. Three investigators independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences finally resolved by consensus.

If the article did not include appropriate data for the meta-analysis (eg, lack of data on mortality), the corresponding author was contacted.

2.3. Data abstraction and study characteristics

Three trained investigators abstracted baseline, procedural, and outcome data using a data-recording form developed for this purpose. In details, we collected potential sources of significant clinical heterogeneity, such as study design, sample size, clinical setting, inclusion and exclusion criteria, levosimendan dose and length, control treatment, mean arterial pressure (MAP) target, follow-up duration, and authors' conflicts of interests, as well as primary study end point and other secondary end points.

The primary end point of the present review was mortality at the longest follow-up available. The secondary end points were blood lactate, cardiac index (CI), total fluid infused, norepinephrine requirement, and MAP, after randomization. The time points of the collection of these variables followed what reported by the authors.

2.4. Internal validity and risk of bias assessment

The internal validity of each trial included in this review was critically evaluated for bias according to The Cochrane Collaboration methods [39]. We assessed the risk of bias associated with the sequence generation method, allocation concealment, blinding of participants and personnel, similarity of the concurrent therapy, completeness of outcome data, free of selective reporting, and free of other bias. We rated the risk of bias by applying a rating of "Yes," "No," or "Unclear" to determine whether adequate measures were taken to protect against each potential source of bias in each study. The overall risk of bias was expressed as low, moderate, or high.

2.5. Data analysis and synthesis

To analyze the binary outcome, we calculated the natural logarithms (ln) of risk ratios (RRs) and its SD. Standardized mean difference (SMD) and 95% confidence intervals were computed for continuous variables. Furthermore, we calculate risk difference and numbers needed to treat. To assess the between-study heterogeneity, we used Cochran Q statistic and the I^2 statistic ($I^2 > 25\%$ was used as a threshold indicating significant heterogeneity). We pooled the study-specific estimate using the inverse variance method and a fixed-effect model in case of low statistical inconsistency ($I^2 < 25\%$) or with random-effect model (which better accommodates clinical and statistical variations) in case of moderate or high statistical inconsistency ($I^2 > 25\%$). Publication bias was assessed by visually inspecting funnel plots of the primary outcome, by analytical appraisal based on the Begg adjusted-rank correlation test, and on Egger linear regression test (a 2-sided P value of .10 or less was regarded as significant).

Sensitivity analyses were done to quantify the effect on mortality when restricted to trials with low risk of bias and to trials reporting 30-day mortality. We also investigated the influence of a single study on the overall risk, estimated by sequentially removing the studies to test the robustness of the main results. To explore the influence of length of follow-up and year of publication on mortality, we performed univariate meta-regression analyses of log-risk against these variables.

Statistical significance was set at the 2-tailed .05 level for hypothesis testing. Data analysis was performed using STATA 11.0 Software (StataCorp LP, College Station, Tex). The present systematic review was conducted in keeping with Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [40,41].

3. Results

3.1. Literature search

The search strategy yielded 106 abstracts (Fig. 1). Twenty-five studies were reviewed in complete form. Major exclusions were due to lack of mortality data (n = 2) [42,43] or of a randomized design (n = 14) [29,27,44–47,28,48–53,21,54,55]. Finally, 7 articles (246 participants) were included in the meta-analysis [30–36] (Table 1).

3.2. Study characteristics

The characteristics of the 7 selected studies are shown in Tables 1 and 2. Six studies had dobutamine as comparator [31–36], whereas 1