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Levosimendan does not reduce the mortality of critically ill adult patients with sepsis and septic shock: a meta-analysis

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Abstract

Background: Previous studies on whether or not levosimendan improved the prognosis of patients with sepsis and septic shock have been inconsistent. We aimed to provide an updated analysis of the therapeutic value of levosimendan in adult patients with sepsis and septic shock, in order to provide evidence-based medical evidence for its use.

Methods: PubMed, Embase, Cochrane Library, Wanfang Data, and CNKI were searched until August 2018 without language restriction. Randomized controlled studies of levosimendan with either inotropic drugs or placebo for the treatment of sepsis or septic shock were enrolled. The primary outcome was mortality, and cardiac index and serum lactate levels were the secondary outcomes.

Results: A total of 20 randomized controlled studies were included in this meta-analysis, including 1467 patients, with 738 patients in the experimental group (levosimendan group) and 729 patients in the control group (other inotropic drugs or placebo). There were no significant differences in mortality between the levosimendan and control groups (fixed-effect relative risk [RR] = 0.90, 95% confidence interval [CI] [0.79, 1.03], $P = 0.13$). Levosimendan increased the cardiac index (VMD [weighted mean difference] = 0.51, 95% CI [0.06, 0.95], $P = 0.02$); and serum lactate levels were lower (VMD = −1.04, 95% CI [−1.47, −0.60], $P < 0.00001$).

Conclusions: Based on current clinical evidence, levosimendan does not reduce mortality in adult critically ill patients with sepsis and septic shock. Physicians should use levosimendan with caution in patients with sepsis and septic shock.

Keywords: Levosimendan; Sepsis; Septic shock; Meta-analysis

Introduction

The World Health Organization released causes of death due to disease worldwide; these showed that sepsis and septic shock surpassed acute myocardial infarction as the leading causes of death.[1] Severe infection induces the systemic inflammatory response syndrome (SIRS). SIRS further leads to septic shock. According to the definition of Sepsis 3.0, septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean artery pressure >65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.[2] Based on previous studies, nearly one-third of sepsis patients have associated left ventricular systolic dysfunction.[3] Sepsis-related myocardial dysfunction is a key factor leading to heart failure. Current studies on sepsis cardiomyopathy are in the exploratory stage, and studies have shown that the incidence of septic cardiomyopathy is as high as 40% to 60%.[4] The 2012 Surviving Sepsis Campaign guidelines[5] recommended dobutamine for patients with sepsis and disorders of left ventricular systolic function; however, whether dobutamine use reduces mortality in patients with sepsis remains unclear; on the contrary, it increases myocardial oxygen consumption and the risk of arrhythmia.[6,7] Therefore, with the increasing clinical use of levosimendan, several randomized controlled trial (RCT) studies found that levosimendan was more suitable for sepsis patients with left ventricular systolic function dysfunction.

Levosimendan, a calcium sensitizer that increases myocardial contractility without increasing myocardial oxygen consumption, is thought to be a complementary treatment for systolic and diastolic heart dysfunction.[8] Some studies have shown that it reduced mortality in patients with perioperative and progressive heart failure.[8,9]

Nevertheless, the results of previous RCTs and meta-analyses have been inconsistent with respect to mortality and other clinical data. Therefore, we designed this meta-analysis to further clarify whether the use of levosimendan in patients with sepsis and septic shock with left ventricular systolic dysfunction has an impact on mortality.

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Methods

Search strategy

PubMed, Embase, Cochrane Library, Wanfang Data, and CNKI were searched until August 2018, without language restriction. Randomized controlled studies of levosimendan with either inotropic drugs or placebo in the treatment of sepsis or septic shock were enrolled. The primary outcome was mortality, and cardiac index and serum lactate levels were the secondary outcomes.

The following keywords were used as search terms: levosimendan, sepsis, septic shock, and randomized controlled trial.

The inclusion criteria were as follows: age >18 years old, patients with sepsis and septic shock, levosimendan with either inotropic drugs or placebo in the treatment of sepsis or septic shock, including mortality data, RCT. The exclusion criteria were as follows: duplicate publications, animal research, and non-RCTs.

Intervention measures included experimental group (levosimendan group) and the control group (other inotropic drugs or placebo). The primary outcome is mortality, and the secondary outcomes were cardiac index and serum lactate levels. We used the Cochrane risk bias assessment tool to evaluate the studies after screening. We designed a data extraction table, research data were extracted from selected studies after quality evaluation. Essential information included age, gender, title, first author, and publication date. Statistical analyses were performed using Review Manager 5.3 (Revman: The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and SPSS 21.0.

Results

Search results

A total of 553 studies were retrieved according to the search strategy. There were 253 duplicated studies, 90 reviews, 14 non-RCTs, 150 animal trials, four pediatric studies, 19 case reports, and three repeated publications [Figure 1]. Finally, 20 articles were included [Supplementary Table 1, http://links.lww.com/CM9/A42]. All these papers were RCTs. A total of 1087 patients were enrolled. Among them, 738 patients were in the experimental group (levosimendan group) and 729 were in the control group (other positive inotropic drugs or placebo).

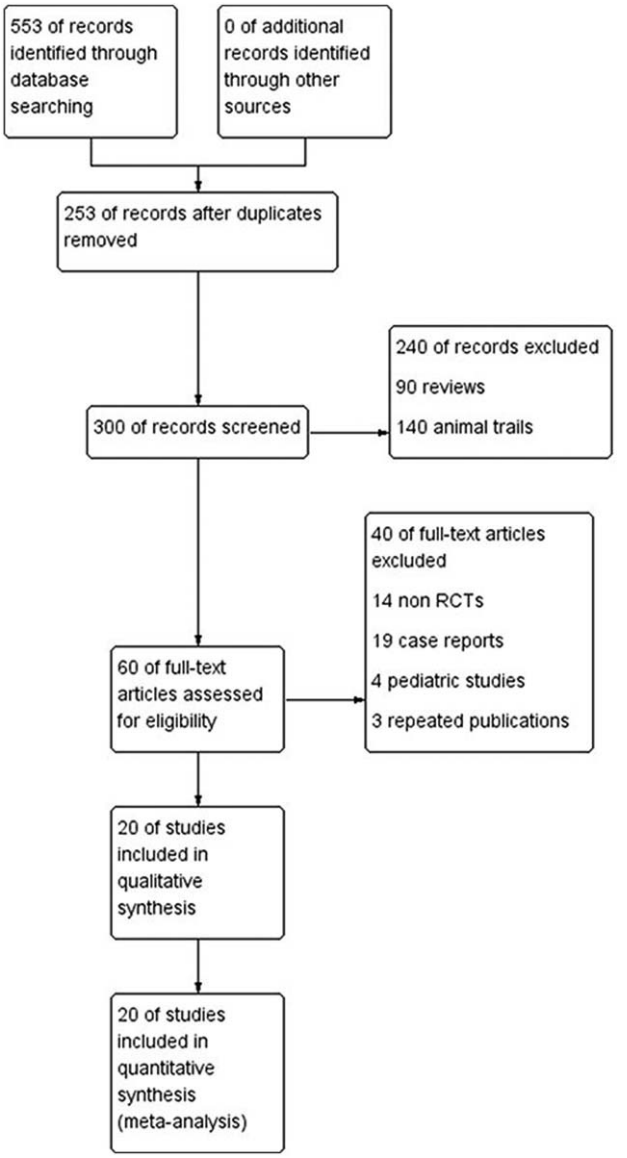

Figure 1: Flow chart. All these papers were randomized controlled trials. A total of 1087 patients were enrolled. Among them, 738 patients were in the experimental group (levosimendan group) and 729 were in the control group (other positive inotropic drugs or placebo).

Syntheses of results of outcomes

A funnel plot was drawn to test for publication bias, and visual inspection revealed no potential bias [Figure 2].

In terms of primary outcome, seven studies reported 28-day mortality, two studies reported 30-day mortality, and others were intensive care unit (ICU) mortality. The analysis showed that there was no significant difference in the mortality between the levosimendan and control groups (fixed effect RR = 0.90, 95% confidence interval [CI] [0.79, 1.03], $P = 0.13$) [Figure 3].

In terms of secondary outcomes, the cardiac index was reported in ten of the included studies; however, the measuring methods were varied. Our meta-analysis showed that levosimendan improved the cardiac index (VMD = 0.51, 95% CI [0.06, 0.95], $P = 0.02$) [Figure 4]; and 13 of all the included studies reported the serum lactate, the mean serum lactate level were lower in the levosimendan group, the synthetic analysis showed that the serum lactate level was significantly lower (VMD = −1.04, 95% CI [−1.47, −0.60], $P < 0.00001$) [Figure 5].

According to the Cochrane Handbook for Systematic Reviews of Interventions, two independent reviewers assessed methodological quality [Figure 6].

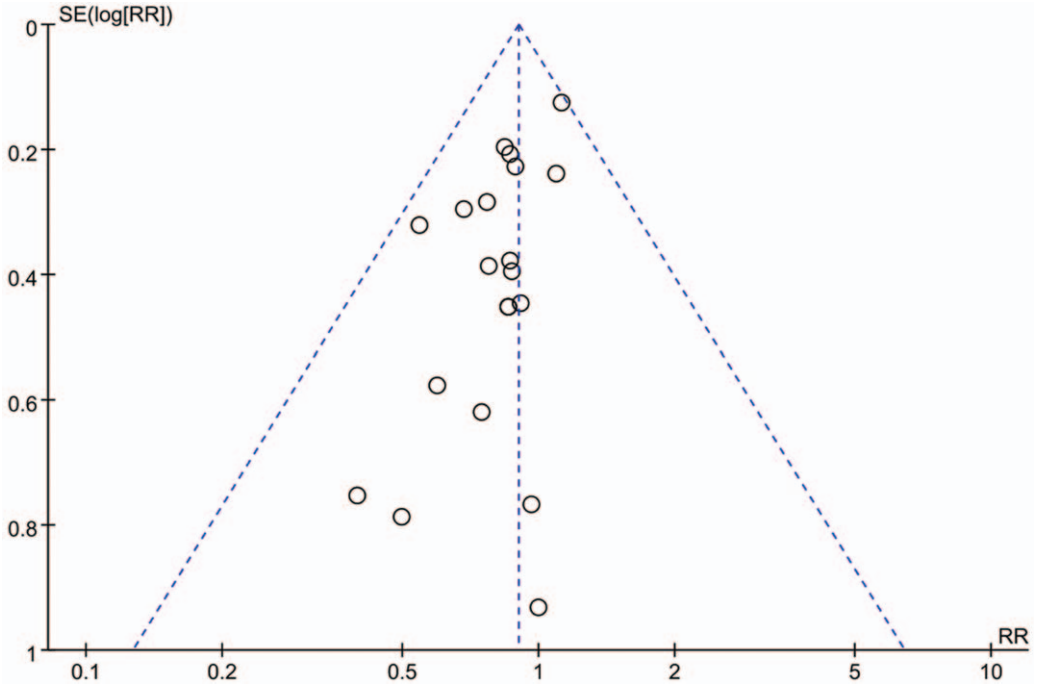

Figure 2: Funnel plot. Visual inspection revealed no potential bias.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alhashemi2009	10	21	13	21	4.7%	0.77 [0.44, 1.35]
Cai-xia Xu 2018	2	15	2	15	0.7%	1.00 [0.16, 6.20]
Fang,M2014	7	18	8	18	2.9%	0.88 [0.40, 1.90]
Fansu Meng 2013	3	10	4	10	1.5%	0.75 [0.22, 2.52]
Fansu Meng 2013-2	7	24	7	22	2.7%	0.92 [0.38, 2.20]
Gordon2016	89	258	79	257	28.8%	1.12 [0.87, 1.44]
Guan-qi Wu 2016	13	47	19	47	6.9%	0.68 [0.38, 1.22]
Hajjej 2017	3	10	5	10	1.8%	0.60 [0.19, 1.86]
He Huang 2015	3	26	3	25	1.1%	0.96 [0.21, 4.32]
Jindi Xi 2014	7	19	9	19	3.3%	0.78 [0.37, 1.66]
Memiş2012	2	15	5	15	1.8%	0.40 [0.09, 1.75]
Meng2016	6	19	7	19	2.5%	0.86 [0.35, 2.08]
Morelli2005	7	15	7	13	2.7%	0.87 [0.41, 1.81]
Morelli2010	13	20	15	20	5.5%	0.87 [0.58, 1.30]
Torraco2014	6	13	11	13	4.0%	0.55 [0.29, 1.03]
Vaitsis2009	14	23	13	19	5.2%	0.89 [0.57, 1.39]
Wang,X2017	33	120	39	120	14.2%	0.85 [0.57, 1.25]
Yong-guang Huang 2017	17	31	16	32	5.7%	1.10 [0.68, 1.76]
Zhanyuan Zhao 2013	2	15	4	15	1.5%	0.50 [0.11, 2.33]
Zhi-zhen Lai 2016	6	19	7	19	2.5%	0.86 [0.35, 2.08]
Total (95% CI)		**738**		**729**	**100.0%**	**0.90 [0.79, 1.03]**
Total events	250		273			

Heterogeneity: Chi² = 9.92, df = 19 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)

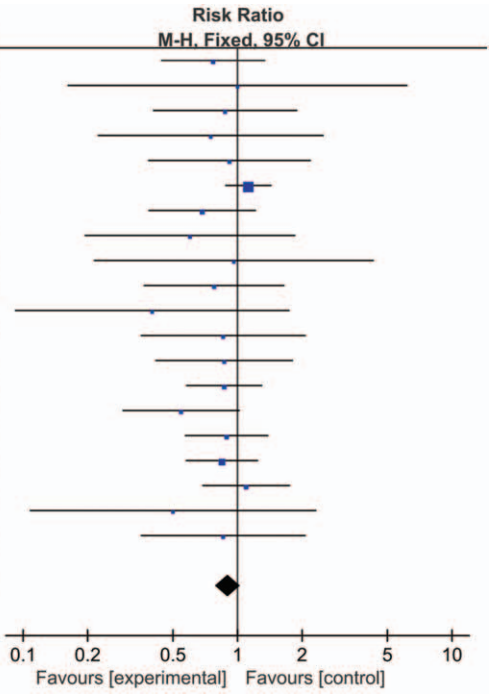

Figure 3: Forest of mortality. Seven studies reported 28-day mortality, two studies reported 30-day mortality, and others were ICU mortality. The analysis showed that there was no significant difference in the mortality between the levosimendan and control groups. ICU: Intensive care unit.

Discussion

The main results of this meta-analysis suggested that levosimendan did not reduce mortality in patients with sepsis and septic shock; however, it increased the cardiac index and reduced serum lactate levels.

Nevertheless, after further analysis, we observed that one study suggested that increased cardiac index might be due to the vasodilatory effects of dobutamine; therefore, one would have to bolus more fluid to maintain mean arterial pressure, and the more fluid infused, the greater the risk of pulmonary and peripheral edema, ultimately leading to

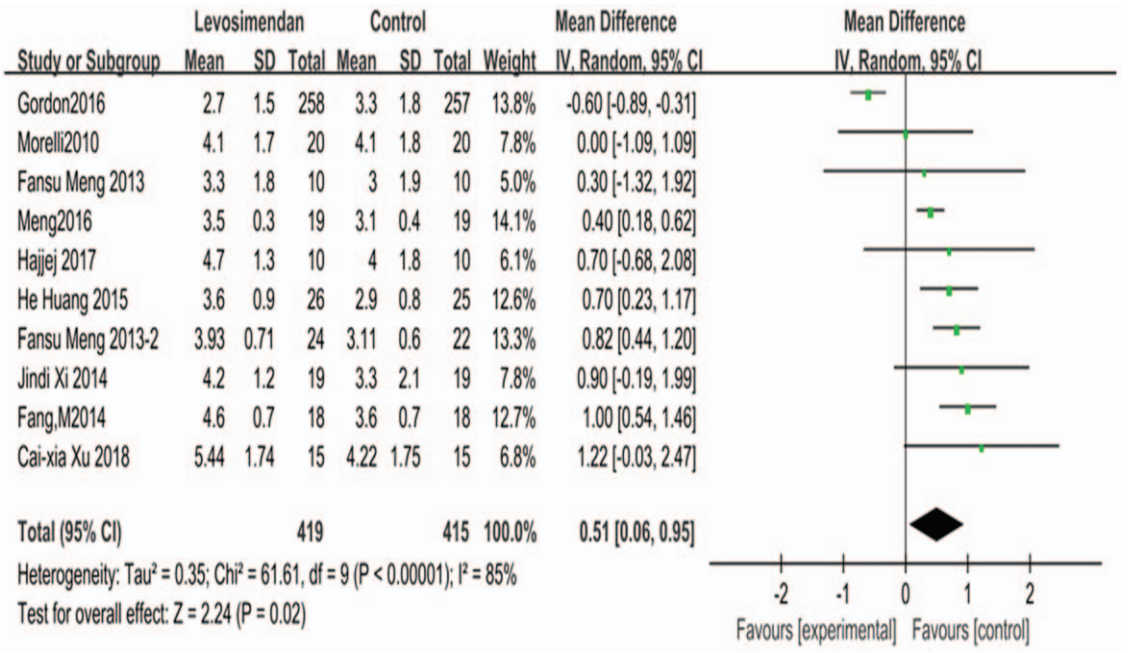

Figure 4: Forest of cardiac index. The cardiac index was reported in ten of the included studies; however, the measuring methods were varied. Our meta-analysis showed that levosimendan improved the cardiac index.

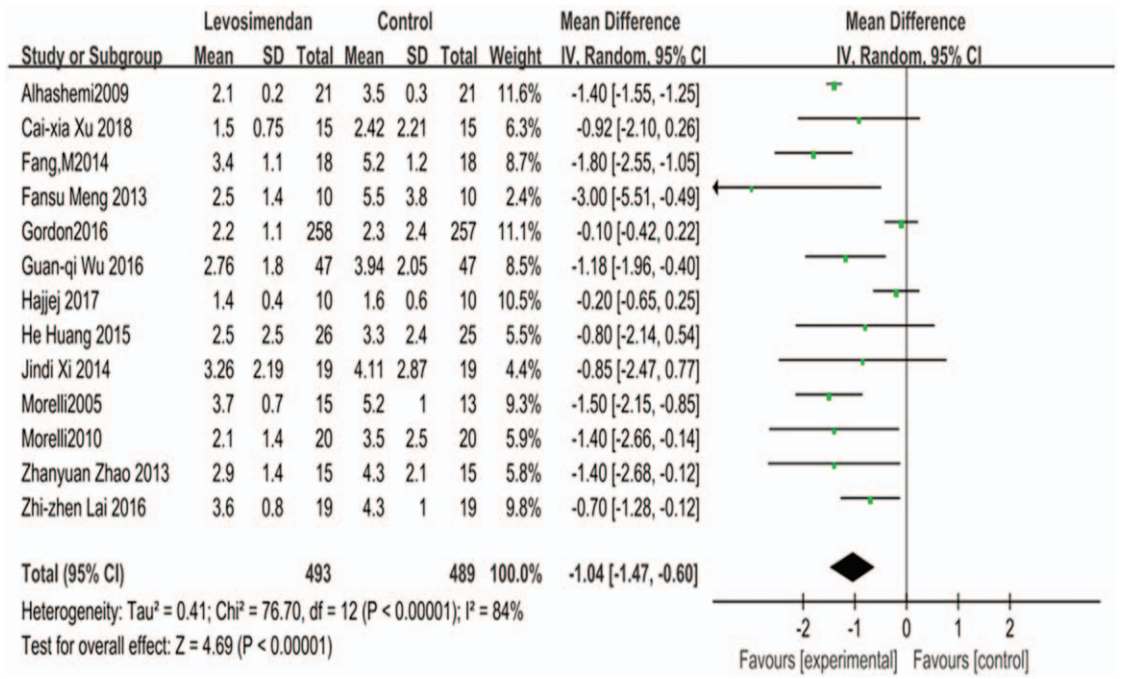

Figure 5: Forest of lactic acid. Thirteen of all the included studies reported the serum lactate, the mean serum lactate level was lower in the levosimendan group, the synthetic analysis showed that the serum lactate level was significantly lower.

reduced oxygenation.[10] Dobutamine can also lead to life-threatening risks due to potential arrhythmias as side-effects.[11]

It should be noted that our meta-analysis included the study of Gordon *et al*,[10] which enrolled 516 patients, contributing 50% of patients in our meta-analysis; therefore, different results emerged. We believe that a possible reason for the contrary result is that the percentage of patients in their study who underwent cardiac function assessment was extremely low (30%); in other words, the researchers included heterogeneous groups, on account of the fact that patients with poor heart function may benefit from positive inotropic drugs (whether levosimendan or other positive inotropic drugs); therefore, there was no significant difference in mortality

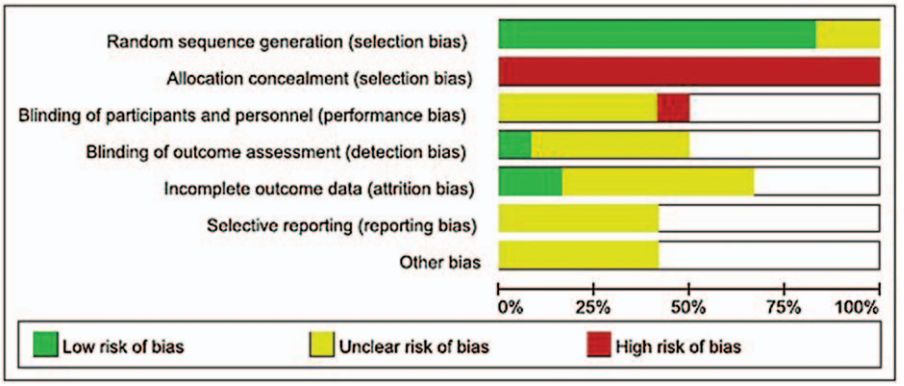

Figure 6: Methodological quality graph. The following criterions were evaluated: random sequence generation, allocation concealment, blind experimental design of participants and personnel, blind outcome assessment, incomplete outcome data, selective reporting, and other biases.

between groups. Due to its large sample size, we found no significant difference in mortality in our meta-analysis.

The pharmacological effect of levosimendan[12] is such that it does not act in the same way as drugs do such as dobutamine. Levosimendan increases cardiac systolic function without affecting diastolic function by increasing the sensitivity of cardiac myocytes to calcium ions. Furthermore, levosimendan does not increase oxygen consumption in cardiac myocytes, possibly an advantage over other positive inotropic drugs.[13] The half-life of levosimendan is up to 80 h, that is to say, if the drug is given for 24 h straight, the effect of the drug can last for about 1 week.[14] Because of this feature, the use of levosimendan allows most patients with sepsis and septic shock to successfully transition to hemodynamic stability.

This meta-analysis has the following limitations. First, the included studies' sample sizes were generally small, and one of the enrolled studies contributed 50% of patients; the other 11 studies contributed 50%, possibly leading to bias between the final synthesis results and the actual clinical situation. Furthermore, studies varied as to descriptions of mortality. For example, some studies used 28-day mortality, while others used 30-day mortality, hospital mortality or ICU mortality. Various expressions may lead to deviation of the results. Second, there were various types of positive inotropic drugs used in the control group, usually including dobutamine, milrinone or standard therapy recommended according to guidelines. Because of various mechanisms of drugs, various conclusions may be drawn. Third, the methods of obtaining the cardiac index varied; for example, some of the included studies used Swan-Ganz catheterization, and some studies used ultrasound measurements or PiCCO. These limitations may result in bias. Therefore, large samples, homogeneity, and multi-center clinical randomized trials are needed to further clarify the value of levosimendan in patients with sepsis and septic shock.[15-17]

In conclusion, compared with traditional positive inotropic drugs, there was no significant difference in mortality between the levosimendan and the control groups. Physicians should use levosimendan with caution in patients with sepsis and septic shock.

Conflicts of interest

None.

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