META-ANALYSIS

A Meta-Analysis of the Effects of Levosimendan on Cardiac Function and Outcomes in Patients with Sepsis

Zehua Ma, MS; Hui Jin, MS; Fusheng Liu, PhD; Sumei Wang, MS; Po Huang, PhD; Xiaolei Fang, PhD

ABSTRACT

Objective • To systematically evaluate the effect of levosimendan on cardiac function and outcomes in patients with sepsis.

Method • We searched multiple databases including CNKI, VIP, WanFang Data, WOS, PubMed, EMbase, and The Cochrane Library up to February 2023. We targeted RCTs comparing levosimendan with dobutamine as a control for treating sepsis. After a rigorous screening and quality evaluation, 18 studies were selected for meta-analysis using Review Manager 5.4.

Results • Out of 18 studies involving 980 sepsis patients, the meta-analysis revealed the following for the levosimendan group compared to dobutamine: (1) A significant reduction in mortality rate (OR = 0.63, 95% CI (0.42,0.95), $P = .03$). (2) Shortened ICU stay (MD = -2.55, 95% CI (-3.12, -1.98), $P < .00001$). (3) Increased left ventricular ejection fraction (LVEF) (MD = 6.05, 95%CI (5.28, 6.81), $P < .00001$) and cardiac index (CI) (MD = 0.47, 95%CI (0.35, 0.59), $P < .00001$). (4) Decreased blood lactate (Lac) (MD = -1.31, 95%CI (-1.73, -0.90), $P < .00001$) and troponin I (TnI) levels (MD = -0.43, 95%CI (-0.66, -0.21), $P = .0002$). (5) Reduced incidence of adverse events (OR = 0.43, 95% CI (0.23,0.81), $P = .008$).

Conclusions • Compared to dobutamine, levosimendan substantially enhances cardiac function in sepsis patients, leading to improved outcomes and fewer adverse events. (*Altern Ther Health Med.* 2023;29(8):668-673).

Zehua Ma, MS; Beijing University of Chinese Medicine, Beijing, China; Department of Emergency, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China. **Hui Jin, MS;** Beijing University of Chinese Medicine, Beijing, China. **Fusheng Liu, PhD; Sumei Wang, MS; Po Huang, PhD; Xiaolei Fang, PhD;** Department of Emergency, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China.

Corresponding author: Xiaolei Fang, PhD
E-mail: fangxiaolei963@126.com

INTRODUCTION

Sepsis is one of the common fatalities in emergency departments and intensive care units, with mortality rates of up to 10% in patients with sepsis and often over 40% in patients with septic shock.[1] Sepsis is an important cause of death, but sepsis-induced cardiomyopathy or septic cardiomyopathy (SCM) is not well characterized in terms of prognosis or treatment. SCM may be defined as a decrease in intrinsic contractility due to sepsis. The prevalence of myocardial dysfunction due to sepsis is 10 - 70% in patients with sepsis.[2]

Levosimondan is a calcium sensitizer, which can be directly combined with troponin to stabilize the spatial configuration of myocardial fibrin, which is necessary for calcium-induced myocardial contraction, thereby increasing myocardial contractility, but no significant changes in heart rate and myocardial oxygen consumption. At the same time, levosimendan has a strong vasodilator effect by activating adenosine triphosphate (ATP) sensitive potassium channels to dilate peripheral veins and reduce cardiac preload, which is beneficial for treating heart failure.In simpler terms, Levosimendan improves the heart's ability to contract without increasing its oxygen demand, which can be beneficial for heart failure patients.

Therefore, this study systematically evaluated levosimendan's effect on treating patients with sepsis using Meta-analysis, using dobutamine as a control group.

MATERIALS AND METHODS

Data collection criteria

Type of study. Randomized Controlled Trial(RCT).

Study population. Patients with sepsis or septic shock of any race, region or gender and aged 18 years or over.

Interventions. Test group: Treatment with levosimendan; Control group: treated with dobutamine; the dosage form and dose of drugs used in both groups were unlimited.

Outcome Measures. (1) 28-day mortality rate; (2) Blood lactate level, LAC; (3) Troponin I, TnI; (4) Left

ventricular ejection fraction, LVEF; (5) Cardiac Index, CI; (6) ICU length of stay; (7) Incidence of adverse events.

Exclusion criteria. (1) The study was conducted on children; (2) No relevant outcome indicators; (3) Data is not available or its source is unknown; (4) Data duplication in published literature.

Literature search strategy

Computer searches of databases such as CNKI, VIP, WanFang Data, Web of Science, PubMed, EMbase and The Cochrane Library were conducted using a combination of subject terms and free words. When we design the literature search strategy, the factors we consider include population, intervention,comparison,outcome and study design. Chinese search terms included: levosimendan, sepsis, septic shock, infectious shock, septic cardiomyopathy, septic myocardial suppression. English search terms include: levosimendan, septic cardiomyopathy, sepsis-induced cardiomyopathy, sepsis, severe sepsis, randomized controlled trial.

Screening and extraction of literature

Two separate researchers cross-check the selection and extraction of the literature. If there was any disagreement, a decision could be made after discussion or a third-party assessor could make a judgment. The main information collected included: (i) information required for the risk of bias assessment; (ii) literature and authors in the year of publication; (iii) age and number of patients; (iv) dose and duration of infusion; and (v) outcome indicators.

Inclusion of literature quality assessment

The 18 included publications were evaluated using the Cochrane Risk of Bias Assessment Tool, including random sequence generation, incomplete outcome data, allocation concealment, blinding (double-blinding of perpetrators and participants, blinding in outcome assessment), selective reporting of outcomes, and other biases. Judgments were made on the basis of 'low risk of bias', 'unclear' and 'high risk of bias'.

Statistical methods

The data were imported into Review Manager 5.4 software for Meta-analysis, with odds ratio (OR) as the combined effect measure for dichotomous data and mean difference (MD) as the combined effect measure for continuous data, and all statistics were expressed as 95% confidence interval (CI). Meta-analysis was conducted at $\alpha = 0.05$. Heterogeneity between studies was zanalyzed using the χ^2 test ($\alpha = 0.1$), and the magnitude of heterogeneity was determined by combining I^2, and if $I^2 < 50\%$, a fixed-effects model was used.If $I^2 > 50\%$, it indicates significant heterogeneity. Therefore, a random-effects model was used.

RESULTS

Literature screening results and basic information on the included literature

A total of 640 relevant literature were retrieved, including 91 from China Knowledge Network, 76 from Vipshop, 102 from the Wanfang database, 99 from WOS, 155 from PubMed, 88 from EMbase, and 29 from The Cochrane Library. After stratification screening, 18 papers were included in this study, including 494 cases in the trial group and 486 cases in the control group. A total of 980 patients were included in the study. The basic characteristics of literature screening and inclusion are shown in Figure 1 and Table 1.

Figure 1. Flow chart of literature screening

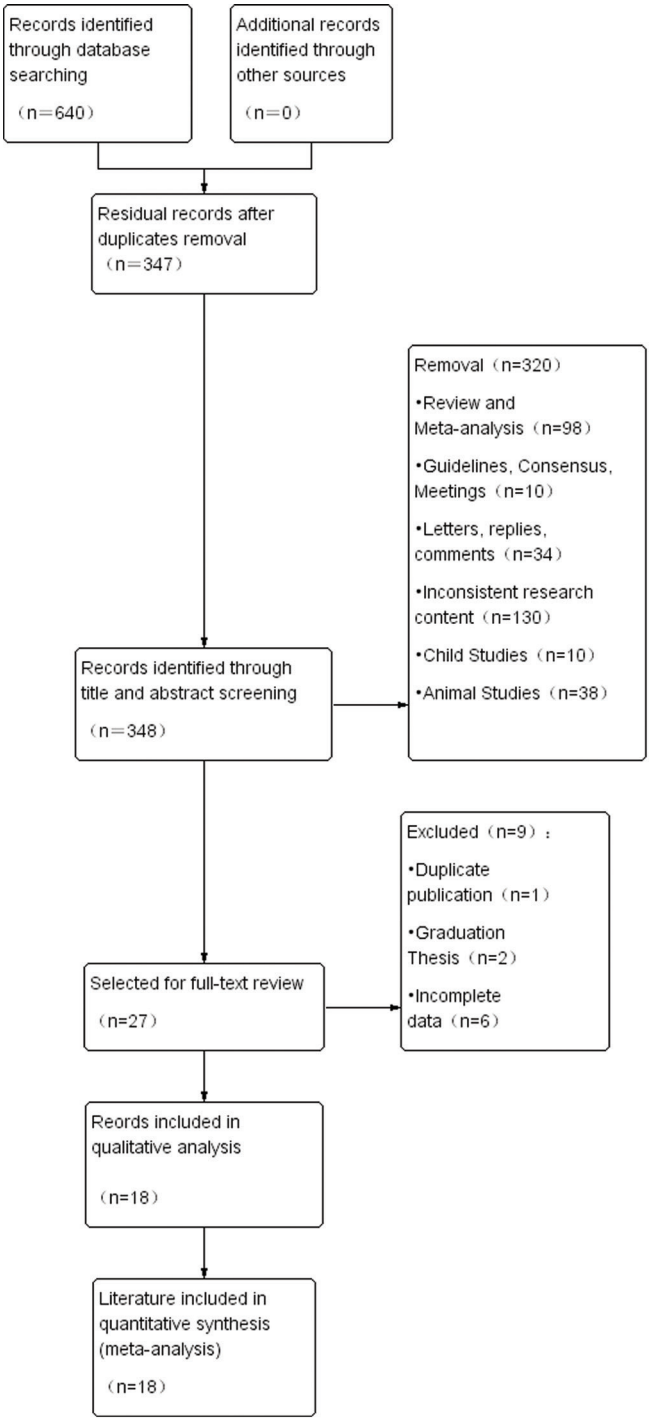


Table 1. Basic characteristics of the included studies

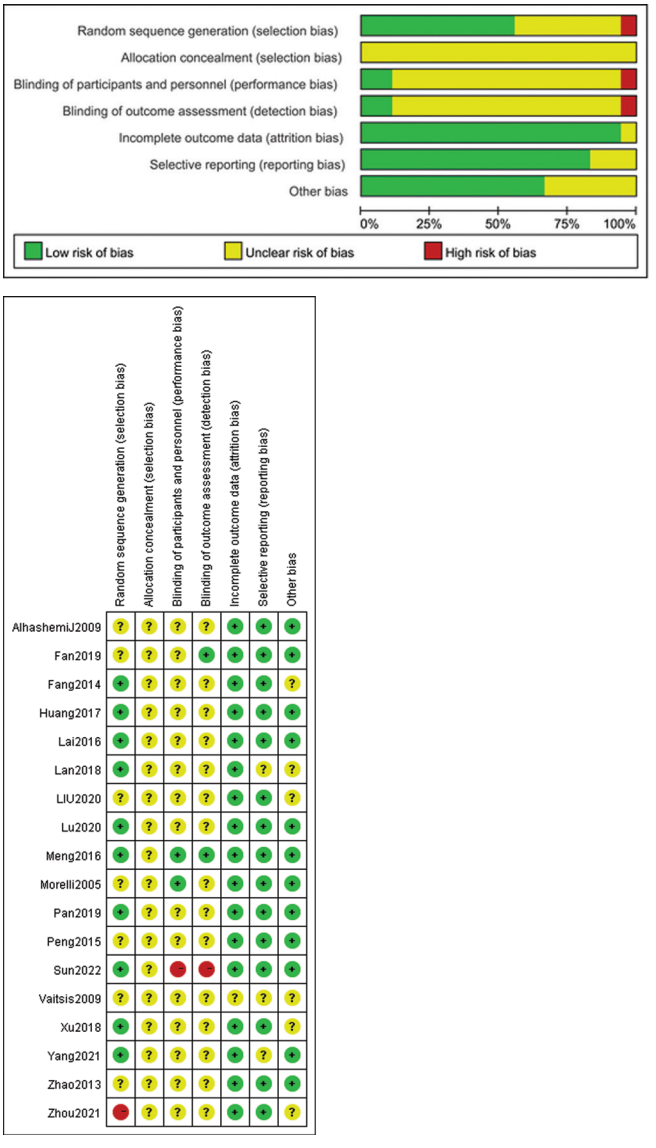
Study	Number of cases		Age		Intervention measures		Indicators
	L	D	L	D	L	D	
Alhashemi 2009[3]	21	21	NA	NA	0.05μg/ kg·min, add 0.05μg/(kg·min) every 30 minutes, maximum 0.2μg/(kg·min), 24h	5μg/(kg·min), add 5μg/(kg·min) every 30 minutes maximum 20μg/ (kg·min),7d	①④
Fan 2019[4]	63	63	63.01±6.15	62.38±6.27	6-12μg/kg, 10min 0.1μg/(kg·min), 24h	5μg/(kg·min), 3d	①②③④⑤⑥
Meng 2016[5]	19	19	55.4±17.5	50.2±13.6	0.2μg/(kg·min), 24h	5μg/(kg·min), 24h	①②③④⑥
Morelli 2005 [6]	15	13	61.5±7.0	62.4±7.3	0.2μg/(kg·min), 24h	5μg/(kg·min), 24h	①②③④⑤⑦
Sun 2022[7]	15	15	52.33±15.92	42.73±15.13	0.2μg/(kg·min), 24h	5μg/(kg·min),24h	①②③④⑤⑥
Vaitsis 2009[8]	23	19	NA	NA	0.1μg/(kg·min), 24h	5-10μg/(kg·min),24h	①③
Lan 2018[9]	22	23	70.91±14.91	72.65±16.84	12μg/kg,10 min 0.2μg/(kg·min), 24h	5-10μg/(min•kg), 24h	①②③④⑤⑥
Liu 2020[10]	60	60	63.06±7.03	62.15±6.98	6-12μkg,10 min 0.1 μg/kg/min,24h	5μg/(min•kg), 24h	①②④⑤⑥
Zhou 2021[11]	34	32	62.1±13.2	63.4±12.8	0.1μg/(kg·min), 24h	4μg/(kg·min), 24h	①④⑤⑦
Peng 2015[12]	27	25	NA	NA	12μg /kg,10 min; 0.1μg/(kg·min),24h	3μg/(kg·min), 24h	②⑦
Xu 2018[13]	15	15	87.9±8.7	88.1±6.5	0.2μg/(kg·min), 24h	5μg/(kg·min), 24h	①②④⑤⑥⑦
Fang 2014[14]	18	18	61.4±7.1	61.7±7.3	5μg/(kg·min), 24h	5μg/(kg·min), 48h	①②③④
Yang 2021[15]	41	41	62.5±6.4	61.8±6.9	12μg/kg, 10 min 0.1μg/(kg·min), 24h	5μg/(min•kg), 24h	①②⑤⑥
Pan 2019[16]	36	36	65.87±6.17	65.92±6.33	12μg/kg, 10 min 0.1μg / (kg·min),7d	5μg/(min•kg), 7d	②④⑥⑦
Lai 2016[17]	19	19	55±18	50±14	0.2μg/(kg·min), 24h	5μg/(kg·min), 24h	①②③④⑤⑥
Zhao 2013[18]	15	15	NA	NA	12mL/h,10min; 2mL/h, 24h	5μg/(kg·min), 24h	①④⑥⑦
Lu 2020[19]	20	20	69±8	70±6	0.2μg/(min•kg),24h	5μg/(min•kg), 24h	②③④⑤
Huang 2017[20]	31	32	63.4±6.5	62.8±6.9	6-12 μkg, 10 min, 0.1μg/(kg·min),24h	5μg/(kg·min), 24h	①②⑤

Notes: ①:mortality; ②:LVEF; ③:CI; ④:Lac; ⑤:TnI; ⑥:length of ICU stay; ⑦:Adverse event occurrence rate

Risk of bias evaluation

See Figure 2

Figure 2. Results of the risk of bias evaluation



Meta-analysis results

The comparisons of the 28-day mortality rate between two groups. A total of 9 studies reported a 28-day mortality rate,[5,7,9,10,13-15,17,20] and meta-analysis with a fixed effects model found that patients in the levosimendan group had lower mortality than those in the dobutamine group [OR = 0.63, 95% CI (0.42, 0.95), P = .03]. Six other studies also reported mortality indicators, but four of them had unclear observation time frames,[3,4,11,18] and two reported 30-day mortality[6,8] and were therefore not included in this study.

The comparisons of LVEF levels between two groups. A total of 14 studies reported changes in LVEF levels,[4-7,9-10,12017,19-20] and the results of Meta-analysis using a fixed effects model showed that patients in the test group had significantly higher LVEF levels compared to controls [MD = 6.05, 95% CI (5.28, 6.81), P < .00001].

The comparisons of CI levels between two groups. A total of 9 studies reported CI changes[4-8,9,14,17,19]; the results of the Meta-analysis with a fixed effects model showed that patients in the test group had significantly higher levels of CI compared to the control group [MD = 0.39, 95% CI (0.33, 0.44), P < .00001].

The comparisons of Lac levels between two groups. A total of 14 studies reported Lac changes[3-7,9-11,13-14,16-19]; results of Meta-analysis using a random effects model showed that the test group was more effective in reducing Lac in patients compared to the control group [MD = -1.31, 95% CI (-1.73, -0.90), P < .00001].

The comparisons of TnI levels between two groups. A total of nine studies reported changes in TnI[4,6-7,9-11,15,17,20]; results of Meta-analysis with a random effects model showed that patients in the test group had a more significant decrease in TnI levels compared to the control group [MD = -0.43, 95% CI (-0.66, -0.21), P = .0002].

Figure 3. Meta-analysis of 28-day mortality in the levosimendan group compared with the dobutamine group

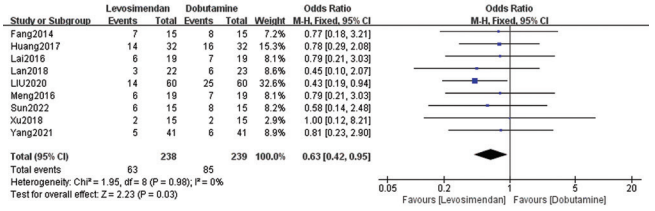


Figure 4. Meta-analysis of LVEF in the levosimendan group compared with the dobutamine group

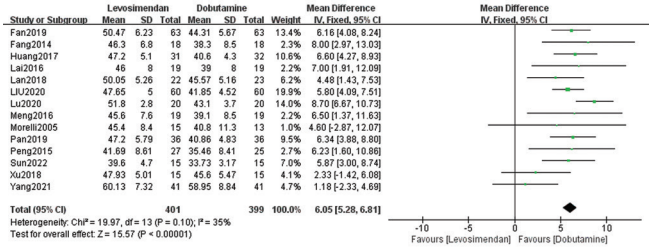


Figure 5. Meta-analysis of CI in the levosimendan group compared with the dobutamine group

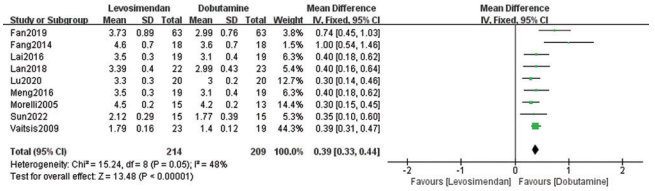
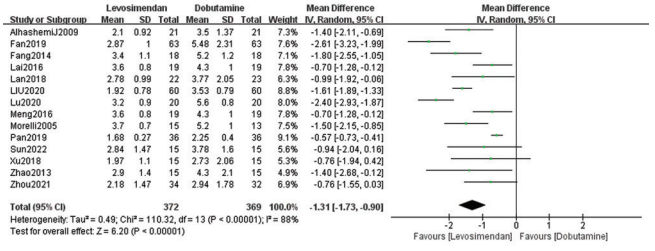


Figure 6. Meta-analysis of Lac in the levosimendan group compared with the dobutamine group



The comparisons of ICU length of stay levels between two groups. A total of 10 studies reported on ICU length of stay[4-5,7,9-10,13,15-18] and the results of Meta-analysis with a random effects model showed that patients in the levosimendan group had a significantly shorter ICU stay compared to the dobutamine group [MD = -2.29, 95% CI (-3.51, -1.07), *P* = .0002].

The comparisons of the incidence of adverse events between two groups. Six of these papers reported on the incidence of adverse events[6,11-13,16,18] Meta-analysis was performed with a fixed effects model, and as a result, patients in the levosimendan group had a lower incidence of adverse events compared to the dobutamine group [OR = 0.43, 95% CI (0.23, 0.81), *P* = .008].

Figure 7. Meta-analysis of TnI in the levosimendan group compared with the dobutamine group

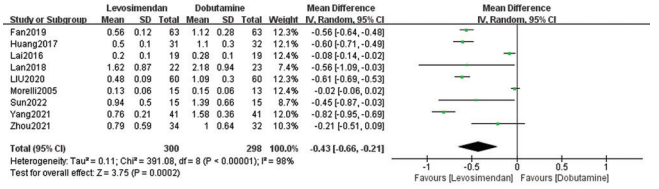


Figure 8. Meta-analysis of the duration of ICU stay in the levosimendan group compared to the dobutamine group

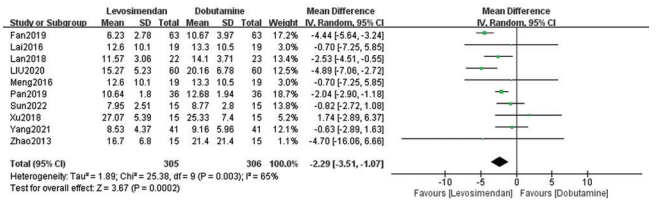


Figure 9. Comparison of the incidence of adverse events between the two groups

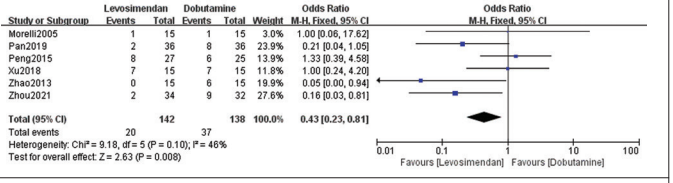


Table 2. Meta-analysis results for each outcome indicator

Outcome indicators	Number of included studies	Heterogeneity test		Model	Meta-analysis	
		P value	I^2		OR/MD (95%CI)	*P* value
28-day mortality rate	15	.98	0	Fixed	0.63(0.42, 0.95)	.03
Lac	14	<.00001	0.88	Random	-1.31(-1.73,-0.90)	<.00001
TnI	10	<.00001	0.98	Random	-0.43(-0.66,-0.21)	.0002
LVEF	14	.1	0.35	Fixed	6.05(5.28,6.81)	<.00001
CI	9	.05	0.48	Fixed	0.39(0.33,0.44)	<.00001
length of ICU stay	6	.003	0.65	Random	-2.29(-3.51,-1.07)	.0002
Adverse event occurrence rate	10	.1	0.46	Fixed	0.43(0.23,0.81)	.008

Sensitivity analysis

Sensitivity analyses were performed using a case-by-case exclusion method for some of the heterogeneous outcome indicators, where the heterogeneity of the combined results was significantly reduced when Fan 2019[4] was excluded for the analysis of ICU length of stay, suggesting that this article may be the main reason for the greater heterogeneity. Meta-analysis after exclusion of the above studies then showed that patients in the levosimendan group still had a significantly lower length of ICU stay than those in the dobutamine group [MD = -2, 95% CI (-2.65, -1.35), *P* < .00001]. The heterogeneity of the remaining outcome indicators and the combined results did not change significantly, suggesting that the Meta-analysis results were more stable.

Publication bias analysis

Inverted funnel plots were drawn using 28-day mortality and adverse event rates as indicators, as detailed in Figures 10 and 11. The results found that there was less potential for bias in this study and fewer scattered distribution studies.

Figure 10. 28-day mortality funnel chart

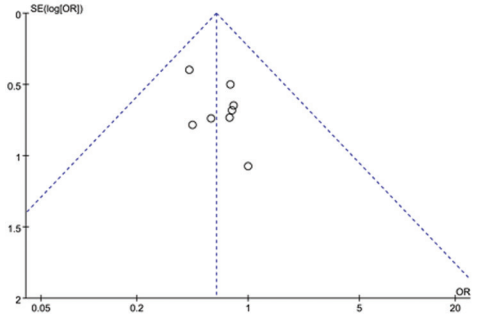
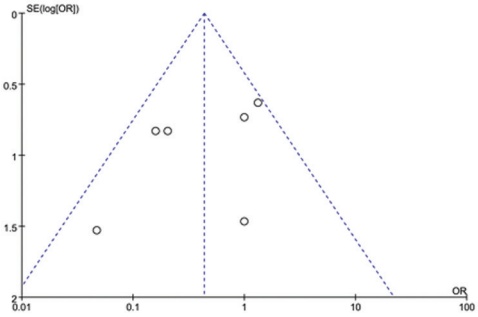


Figure 11. Funnel chart of adverse event rates



To sum up, compared with dobutamine group,the mortality rate of patients with sepsis in the levosimendan group was significantly improved, the length of stay in ICU was significantly shortened, and the LVEF was significantly reduced, LVEF and CI were significantly increased,and Lac and TnI levels were significantly reduced,and the incidence of adverse events was lower.

DISCUSSION

Myocardial injury resulting from sepsis has a multifaceted pathogenesis, including factors such as myocardial inhibitory components, oxidative stress, altered metabolic pathways, mitochondrial dysfunction, and cardiomyocyte apoptosis.[21] These factors interplay in various ways.

Levosimendan enhances cardiac function by stabilizing myocardial fibronectin's structure via direct troponin C binding. This not only augments myocardial contractility and cardiac output but also preserves myocardial cell electrophysiology and diastolic function. Its other benefits include the activation of ATP-sensitive potassium channels and vasodilation, improving myocardial oxygenation without raising oxygen consumption

The results of this study showed that the clinical application of levosimendan for sepsis patients had a lower 28-day mortality rate and reduced ICU length of stay compared to the control group, while cardiac function indicators LVEF and CI were significantly higher and Lac levels and TnI, an indicator of myocardial injury, were lower. Zangrillo et al.[23] conducted a Meta-analysis of RCTs of levosimendan compared with conventional positive inotropic agents for sepsis and septic shock and concluded that levosimendan was associated with a significant reduction in mortality, as well as an increase in CI and a decrease in Lac levels. However, a meta-analysis published by Liu et al[24] found that levosimendan significantly improved CI and Lac levels in patients with sepsis but did not affect mortality or LVEF levels. Thus, there has been considerable controversy regarding the effect of levosimendan on cardiac function and prognosis in patients with sepsis admitted to the ICU. Our research contributes to this ongoing debate by providing fresh insights and data on levosimendan's impacts.The reasons for the different conclusions may be related to factors such as the control of primary infection and underlying disease in sepsis patients, the wide range of literature included in this Meta-analysis, which involves 12 Chinese and 6 English literature, and differences in statistical analysis methods.

A large RCT showed that for cardiac arrhythmias, levosimendan infusion was associated with an increased incidence of atrial fibrillation compared with dobutamine.[25] However, unlike other cardiac drugs, levosimendan does not lead to increased intracellular Ca^{2+} concentrations and myocardial oxygen consumption, meaning that ventricular arrhythmias are unlikely to occur during levosimendan treatment.[26] The same conclusion was reached in the present Meta-analysis, where the incidence of adverse events during treatment was significantly lower in the levosimendan group than in the dobutamine group, suggesting that levosimendan has the advantage of a higher safety profile, with the main adverse effects being hypokalemia, atrial fibrillation, and tachycardia.

In summary, this study found that levosimendan was superior to dobutamine in improving cardiac function and prognosis in patients with sepsis. However, there are some limitations to the results: (1) the number of Chinese literature included in the systematic analysis is large and the results may be one-sided; (2) the sample size of the included studies is limited and the results obtained cannot be ruled out by chance; (3) the random method and blinding method of some studies are unclear and there is a risk of bias. Given these limitations, there's a pressing need for further, more comprehensive research to solidify our understanding of levosimendan's role in septic patients.

FUNDING

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