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Effect of levosimendan on mortality in severe sepsis and septic shock: a meta-analysis of randomised trials

Wei Chang, Jian-Feng Xie, Jing-Yuan Xu, Yi Yang

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Department of Critical Care Medicine, School of Medicine, Zhongda Hospital, Southeast University, Nanjing, China

Correspondence to
Dr Yi Yang;
yiyiyang2004@163.com

ABSTRACT

Objective We aim to synthesise up-to-date randomised trials to investigate the effects of levosimendan on mortality and clinical outcomes in severe sepsis and septic shock.

Methods A collection of databases including PubMed, EMBASE, Cochrane Central Register and Web of Science were searched updated to August 2017. Randomised trials were included when they pertain to the use of levosimendan in severe sepsis or septic shock compared with any category of inotropes, or as an adjunct to standard therapy with mortality reported. The primary outcome was mortality, and the secondary outcomes were clinical performances including serum lactate, cardiac function, vasopressor requirement and fluid infusion.

Results A total of 10 studies with 1036 patients were included in this meta-analysis. The results revealed that levosimendan could not reduce mortality significantly in severe sepsis and septic shock (OR 0.89, 95% CI 0.69 to 1.16, P=0.39). Levosimendan use could reduce serum lactate more effectively, and enhance cardiac contractibility with increased cardiac index and left ventricular ejection fraction. However, its use could also increase fluid infusion but not reduce norepinephrine dose. No significant benefit in mortality could be observed of levosimendan versus dobutamine use, or in patients with proven cardiac dysfunction.

Conclusions Current evidence is not sufficient to support levosimendan as superior to dobutamine or as an optimal adjunct in severe sepsis and septic shock. More large-scale randomised trials are necessary to validate levosimendan use in sepsis.

Strengths and limitations of this study

- This article synthesised up-to-date randomised trials for quantitative analysis of the effect of levosimendan on mortality in severe sepsis and septic shock.
- Subgroup analyses were conducted to investigate the subpopulation of patients who were likely to benefit most from levosimendan use.
- Heterogeneity and biases were appraised between each study, and the optimal sample size was calculated.
- However, the trials included were of limited sample size and quality, and potentially high-biased.

BACKGROUND

Sepsis is still a great challenge to public health, and its mortality increases tremendously when severe sepsis or septic shock occurs.[1] The incidence of cardiac dysfunction in severe sepsis and septic shock remains as high as 40%–60%,[2] resulted from infectious process, cytokine storm,[3] decreased myocardial perfusion and pulmonary injuries,[4] and is associated with poor outcomes.[5 6]

Surviving Sepsis Campaign (SSC) International Guidelines (2016) recommended the usage of dobutamine infusion in patients with persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).[7] However, its effect on mortality in sepsis is still under debate,[8] and its adverse effects including increased myocardial oxygen consumption and risks of dysrhythmia could not be neglected.

Levosimendan, a calcium sensitiser that could improve myocardial contractibility in the absence of increased oxygen consumption, is regarded as a promising adjunct in the treatment of both cardiac systolic and diastolic dysfunctions,[9] and has been demonstrated to have a beneficial effect on mortality in cardiac perioperative patients and patients with advanced heart failure.[10 11]

Levosimendan was demonstrated as superior to dobutamine and milrinone in restoring cardiac function in septic animal models.[12] It could also alleviate inflammatory response by downregulating nuclear factor κB (NF-κB)-dependent transcription,[13] inhibiting inducible nitric oxide (NO) synthase promoter activity and reducing NO expression in vitro.[14]

Several meta-analyses were conducted to investigate the effect of levosimendan on mortality in sepsis, which revealed a beneficial effect, however with limited sample size.[15] In this study, we aim to perform an up-to-date

meta-analysis to investigate the effect of levosimendan on mortality in severe sepsis and septic shock.

METHODS

The manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16 17]

Eligibility criteria

We aimed to include all randomised control trials (RCT) studying levosimendan use versus any category of inotropes or as an adjunct to standard management in severe sepsis and septic shock. The articles were included in our study if they fulfilled the following criteria: (1) study population of severe sepsis or septic shock in adults, (2) randomised allocation of treatment, (3) comparison of levosimendan with any category of inotropic agents or placebo, with no restrictions on dose regimen or time limits of levosimendan infusion, and (4) data on mortality reported. The exclusion criteria were as follows: (1) duplicates, (2) paediatric subjects, (3) animal experiments or in vitro studies, (4) no sepsis population and (5) lack of data on mortality.

Information sources

Two investigators searched a collection of databases including PubMed, EMBASE, Cochrane Central Register and Web of Science updated to 1 August 2017 separately with no language restrictions. When relevant systemic reviews or meta-analyses were found, the investigators ran a backward snowballing to obtain further studies.

Search

The following keywords were used as search terms: 'levosimendan', 'simendan', 'Simdax', 'dextrosimendan', 'sepsis', 'severe sepsis', 'septicemia' and 'septic shock' (online supplementary file 1).

Study selection

Abstracts and titles of the articles were initially viewed separately by two investigators, and if potentially pertinent the complete articles were retrieved. Articles were assessed and selected separately by two investigators, with disagreements solved by consensus.

Data items

Information was extracted from each of the included trials on (1) characteristics of the participants (including gender, age and diagnosis); (2) interventions (including the infusion duration and dose regimen of the levosimendan or other inotropes); and (3) outcome measurements, with primary outcome determined as mortality (follow-up time was tailored at the approximate duration by the reviewers' consensus), and secondary outcomes as clinical outcomes including serum lactate level, cardiac function including cardiac index, left ventricular ejection fraction (LVEF) and left ventricular stroke work index (LVSWI), fluid infusion and vasopressor requirement.

Assessment of risk of bias

Internal validity and risks of bias were evaluated by two investigators separately following Cochrane Collaboration Methods protocols.[18] Risks of bias were assessed by scrutinising the articles and rated as 'Yes', 'No' or 'Unclear' according to the procedures taken in the articles.

Summary measures

Dichotomous outcomes were measured as proportions and calculated by OR. Continuous outcomes were described as mean±SD and calculated by mean difference or standard mean difference. The end-point and change range were both compared if the continuous variables were measured at baseline and after treatment. Missing data were imputed from other information whenever possible[19] (online supplementary file 2).

Statistical analysis

The data retrieved from the relevant articles were computerised and analysed by Review Manager V.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). We used the Mantel-Haenszel statistic method for dichotomous variable (mortality) measurements and inverse variance for continuous variables (lactate level, cardiac index, LVEF, LVSWI, fluid infusion and norepinephrine dose). Random-effects model was used for better accommodation of heterogeneity. Cochrane I^2 statistic was used for heterogeneity assessment between the studies, with a range of 0%–30% representing no or mild heterogeneity, 30%–60% as moderate heterogeneity and >60% as high heterogeneity. Publication bias was tested by visual inspection of funnel plots. As for sensitivity analysis, the data set was analysed in both fixed and randomised-effects models and the favouring directions were inspected. Each study was removed sequentially and the remaining data set reanalysed to assess the robustness of the results. Trial sequential analysis (TSA) was performed to estimate the optimal sample size for the plausible effects of levosimendan on sepsis.[20] Statistical significance was set at a two-tailed 0.05 level to establish hypothesis.

Subgroup analysis

We prespecified the subgroup analyses. Studies enrolling patients with proven cardiac dysfunction versus heterogeneous cardiac function were compared, as well as the use of levosimendan versus dobutamine and versus standard therapy. We further attempted to separate the studies enrolling patients with an average age ≥65 years vs <65 years and mortality ≥50% vs <50% in the hope of finding the subpopulation who would potentially benefit from levosimendan use.

RESULTS

Study selection

A total of 566 abstracts were retrieved from the search strategy, with 121 duplicates excluded and 199 excluded

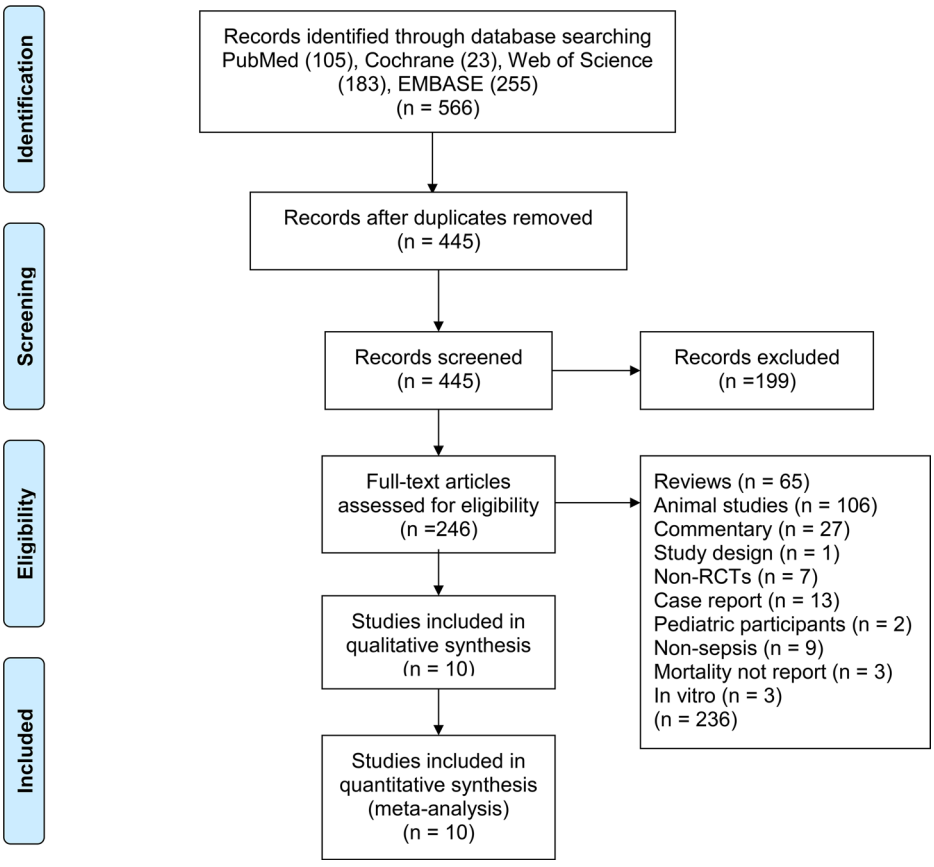


Figure 1 Flow diagram of search process and study selection. RCT, randomised control trial.

due to no eligible abstracts. Complete manuscripts of 246 abstracts were retrieved for further assessment, of which 92 were reviews or commentaries, 106 were animal experiments, 3 in vitro studies, 7 non-RCTs, 9 non-septic patients, 2 paediatric patients, 3 with mortality not reported, 13 case reports and 1 study design. A total of 10 studies were included in this meta-analysis,[21–30] 2 of which were conference abstracts[21 22] and 1 written in Chinese[26] (figure 1).

Study characteristics

Within the 10 studies enrolling 1036 patients, no differences were present in age and in the Acute Physiology and Chronic Health Evaluation II scores between the treatment and control groups at baseline. Patients diagnosed with septic shock or severe sepsis after adequate fluid resuscitation were included in the studies. Four studies set explicit criteria of cardiac dysfunctions during the patients' recruitment.[21 26 27 30] Norepinephrine was used as necessary to achieve the target mean artery pressure (MAP) ranging from 65 to 80 mm Hg during levosimendan therapy depending on the study design. Seven studies used dobutamine (dose ranged from 5 to 20 µg/kg/min) as a comparator,[21–24 26 27 30] and three used levosimendan as an adjunct to standard therapy.[25 28 29] Levosimendan was administered as continuous infusion (dose ranged from 0.05 to 2.0 µg/kg/min) over 24 hours with no bolus. Parameters reflecting cellular metabolism, microcirculation, haemodynamics, cardiac function and target organ perfusion were measured in individual studies (table 1).

Syntheses of results

The data on mortality were randomised and calculated from the 10 studies, and the final result revealed no statistical difference (total events 187/522 vs 197/514 in levosimendan and control groups, respectively; OR 0.89, 95% CI 0.69 to 1.16, P=0.39), with no evidence of heterogeneity (I^2=0%, P=0.52) (figure 2).

We conducted a series of subgroup analyses according to patients' characteristics. No statistical significance could be observed in the studies enrolling patients with proven clinical cardiac dysfunction[21 26 27 30] (OR 0.76, 95% CI 0.39 to 1.50, P=0.43) or those with heterogeneous cardiac functions[22–25 28 29] (OR 0.75, 95% CI 0.48 to 1.19, P=0.23).

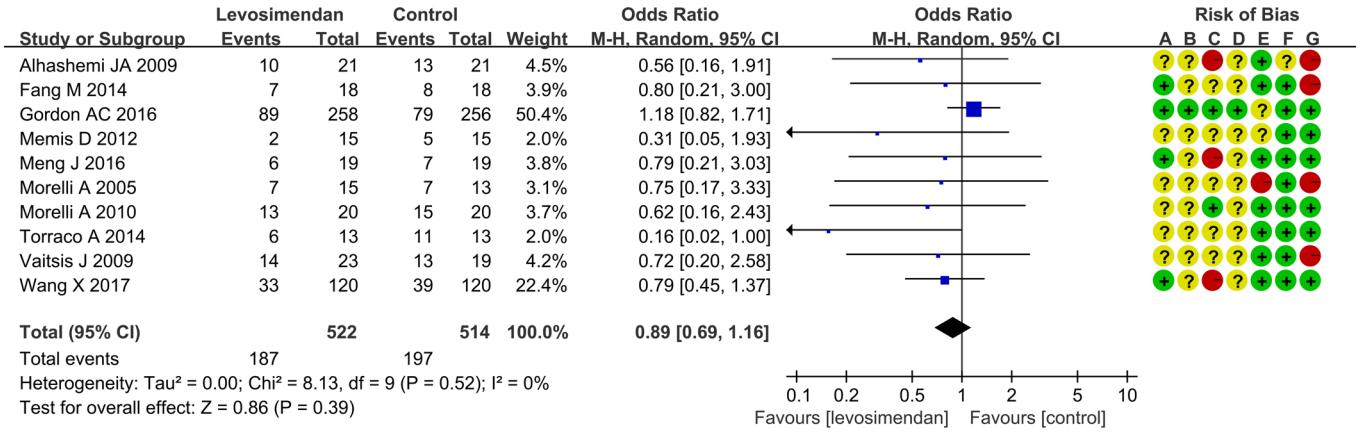
We compared the effect of levosimendan versus dobutamine on mortality in sepsis and found no statistical difference in mortality between levosimendan and dobutamine groups (OR 0.65, 95% CI 0.39 to 1.10, P=0.11),[21–24 26 27 30] and neither of levosimendan in comparison with standard therapy[25 28 29] (OR 0.82, 95% CI 0.44 to 1.55, P=0.54) (figure 3).

We attempted to divide the studies according to patients' average age (<65 years or ≥65 years) and mortality (<50% or ≥50%), and found no statistical significance between each subgroup (online supplementary figure 1).

Table 1 Characteristics of the included trials

Study	Year	Subjects (n)	Levosimendan group	Control group	Inclusion criteria	Cardiovascular criteria	Levosimendan therapy	Control therapy	Target MAP (mm Hg)	Follow-up (day)	Primary outcome
Alhashemi *et al*[22]	2009	42	21	21	Severe sepsis/septic shock	NR	0.05–2 µg/kg/min, 24 hours	Dobutamine 5–20 µg/kg/min, 7 days	≥65	ICU stay	$ScvO_2$ and serum lactate
Fang and Dong[26]	2014	36	18	18	Septic shock	LVEF ≤45%	Dobutamine 0.5 µg/kg/min for 24 hours; levosimendan 0.2 µg/kg/min 24 hours subsequently	Dobutamine 5 µg/kg/min, 48 hours	NR	28	Haemodynamics and cardiac function
Gordon *et al*[28]	2016	515	258	257*	Septic shock	MAP 60–70 mm Hg	0.05–0.2 µg/kg/min, 24 hours	Standard therapy	65–70	28	Daily SOFA score
Memiş *et al*[24]	2012	30	15	15	Septic shock	MAP ≤65 mm Hg	0.1 µg/kg/min, 24 hours	Dobutamine 10 µg/kg/min, 24 hours	>65	NR	Liver function
Meng *et al*[27]	2016	38	19	19	Septic shock	MAP ≥65 mm Hg and LVEF ≤45%	0.2 µg/kg/min, 24 hours	Dobutamine 5 µg/kg/min, 24 hours	≥65	28	Haemodynamics and myocardial injury biomarkers
Morelli *et al*[30]	2005	28	15	13†	Septic shock	MAP 70–80 mm Hg, PAOP ≥12 mm Hg and LVEF <45%	0.2 µg/kg/min, 24 hours	Dobutamine 5 µg/kg/min, 24 hours	70–80	30	Haemodynamics and cardiac function
Morelli *et al*[23]	2010	40	20	20	Septic shock	MAP ≥65 mm Hg	0.2 µg/kg/min, 24 hours	Dobutamine 5 µg/kg/min, 24 hours	70±5	ICU stay	Systemic and microvascular haemodynamics
Torraco *et al*[25]	2014	26	13	13	Septic shock	MAP ≥65 mm Hg	0.2 µg/kg/min, 24 hours	Standard therapy	65–75	28	Mitochondrial function
Vaitsis *et al*[21]	2009	42	23	19	Sepsis	CI <2.2, LVEF <35%	0.1 µg/kg/min, 24 hours	Dobutamine 5–10 µg/kg/min, 24 hours	>65	30	Mortality at 7 and 30 days
Wang and Li[29]	2017	240	120	120	Septic shock	MAP ≥65 mm Hg	0.1–0.2 µg/kg/min, 24 hours	Standard care	≥65	28	Mortality at 28 days, ICU discharge and hospital discharge

*A total of 256 patients were finally included for 28-day mortality analysis.
†Two patients in the control group failed to complete the study and were excluded.
CI, cardiac index; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MAP, mean artery pressure; NR, not reported; PAOP, pulmonary artery occlusion pressure; $ScvO_2$, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 2 Effect of levosimendan on mortality in patients with severe sepsis and septic shock. M-H, Mantel-Haenszel.

We also extracted and compared the data on lactate reduction,[22 23 26 28 30] measurements reflecting cardiac function including cardiac index,[23 25–28 30] LVEF[21 26 27 30] and LVSWI,[23 26 27 30] fluid infusion,[23 26 28 30] and norepinephrine dosage.[23 25–28 30] The results revealed that lactate was more profoundly reduced, and cardiac function significantly improved (with increased cardiac index, LVEF and LVSWI) in levosimendan group. Norepinephrine dose was reduced slightly; however, total fluid infusion over 24 hours was tremendously increased in levosimendan group (table 2, online supplementary figure 2).

Risk of bias and sensitivity analyses

The funnel plot was drawn for testing the bias, and visual inspection of the funnel plot revealed potential asymmetry (online supplementary figure 3).

The data set was analysed both in the fixed and random-effects models for sensitivity analysis, and the result revealed no shift of favouring directions (online supplementary figure 4). Each trial was removed and the remaining data set reanalysed subsequently, and the result indicated that the statistical significance was obscured only when the trial by Gordon *et al*[28] was put into analysis (online supplementary figure 5).

Trial sequential analysis

TSA was performed to determine the optimal information size. We estimated a 26% mortality based on the recent epidemiological data on severe sepsis,[31] and assumed an average of 20% relative risk reduction in reference to the effect of levosimendan on overall mortality reduction in hospitalised patients,[32] with 80% power and two-sided α=0.05. The calculation indicated an optimal information size of 2082 patients for detection of the plausible treatment effect of levosimendan in sepsis. The Lan-DeMets sequential monitoring boundary constructed by the optimal information size did not cross, indicating that the cumulative evidence was not conclusive and reliable (figure 4).

DISCUSSION

The main finding of this study was that levosimendan could not significantly reduce mortality in severe sepsis and septic shock. Levosimendan could reduce serum lactate level more effectively and improve cardiac function. However, no change in norepinephrine dose but profound increase in fluid infusion could be observed.

We noticed that, although cardiac function was improved after levosimendan use, more fluid was infused for maintenance of the target MAP probably due to the vasodilatory effect of levosimendan, which could exacerbate pulmonary and peripheral oedema and potentially impede oxygen uptake and exchange. The use of levosimendan was also suggested to be accompanied with higher incidence of life-threatening arrhythmias like supraventricular tachyarrhythmia, which could cause haemodynamic instability and bring risks to the patients.[28]

The previous study by Zangrillo *et al*[15] enrolling a series of RCTs yielded a significantly reduced mortality in levosimendan group in septic shock. However, it should be noted that, in our study, statistical significance was obscured after a large, multicentre RCT with a sample size of 514 patients by Gordon *et al*[28] was included.

We thought that there may be several reasons for this. The percentage of patients in the trial by Gordon *et al* who underwent cardiac function assessment was rather low (30%), so Gordon and coworkers might have enrolled patients with heterogeneous cardiac functions.[33] Although the prevalence of septic cardiomyopathy is high (40%–60%), the discriminative enrolment could still

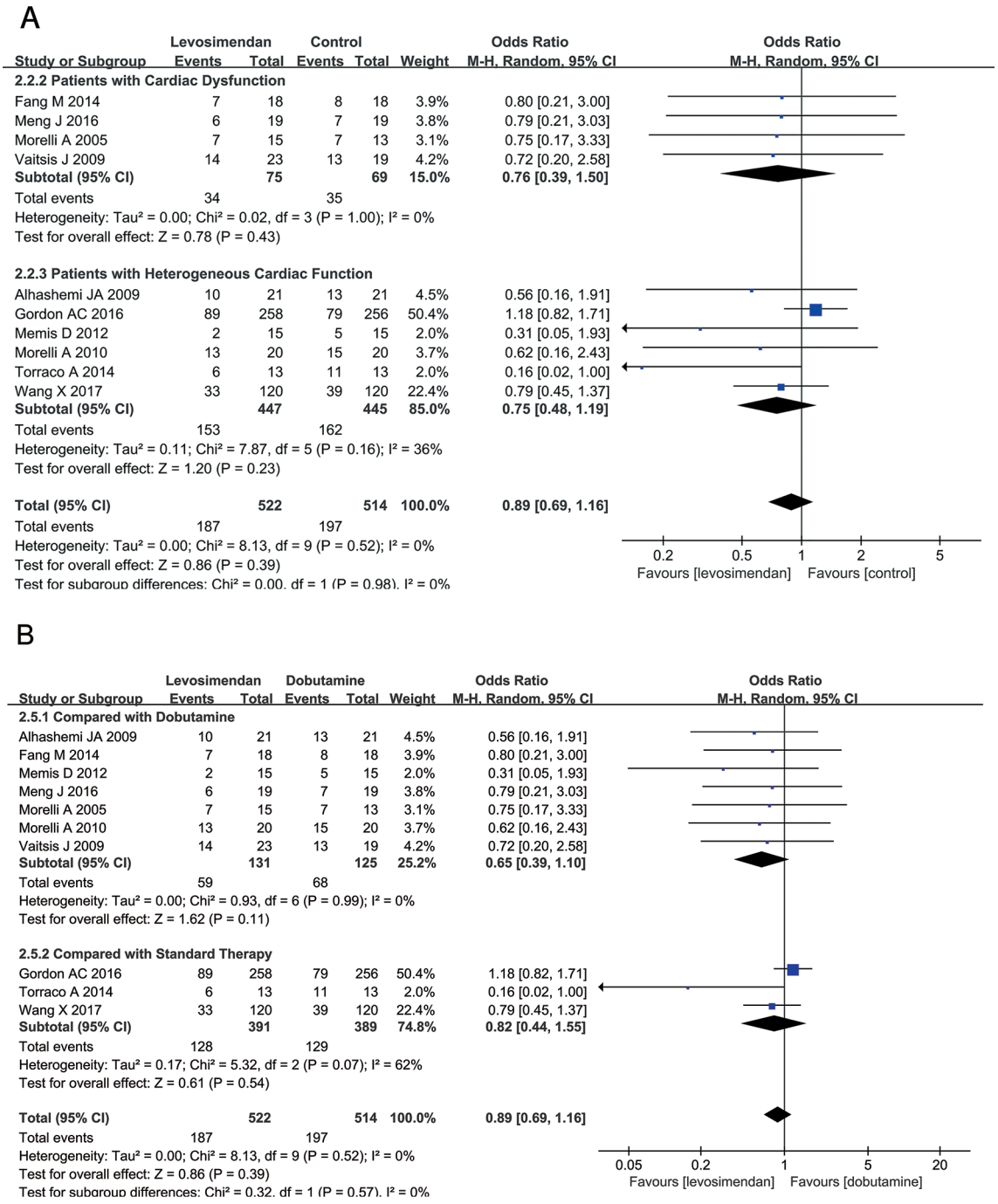


Figure 3 Subgroup analysis. (A) Levosimendan in patients with proven cardiac dysfunction versus patients with heterogeneous cardiac function (OR 0.76, 95% CI 0.39 to 1.50, P=0.43 vs OR 0.75, 95% CI 0.48 to 1.19, P=0.23). (B) Levosimendan versus dobutamine (OR 0.65, 95% CI 0.39 to 1.10, P=0.11) or standard therapy (OR 0.82, 95% CI 0.44 to 1.55, P=0.54).

mask the potential benefit of levosimendan, considering that there might be patients recruited who did not have cardiac dysfunction, and may not benefit from inotropic use as indicated by the SSC International Guidelines (2016) in which the increase of cardiac function to supranormal level is discouraged.[7]

We attempted to synthesise the studies with patients who had proven cardiac dysfunction; however, the result revealed no statistical significance (OR 0.76, 95% CI 0.39 to 1.50, P=0.43). We then performed a TSA and yielded an optimal sample size of 1719, suggesting that more trials focusing on patients with cardiac dysfunction are probably needed to determine the plausible effects of levosimendan on sepsis.

The patients enrolled in the trial by Gordon *et al* might be relatively at low risk (with the 28-day mortality of 31%).[33 34] In the study by Zangrillo *et al*, the mortality decreased from 61% to 47% after levosimendan use,[15] and in that study the baseline mortality was very high (61% in control group), suggesting that patients at 'extremely' high risk may benefit the most from levosimendan use.

Table 2 Clinical outcomes after randomisation

Outcomes	References	Subjects (n)	MD (95% CI)	P for overall effect	P for heterogeneity	I^2 (%)
$Lactate_{TRT}$	22 23 26–28 30	656	−0.89 (−1.48 to −0.29)	0.003	<0.00001	87
ΔLactate	23 26–28 30	614	−0.80 (−1.41 to −0.20)	0.009	0.0002	82
CI_{TRT}	23 26–28 30	277	0.39 (0.17 to 0.62)	0.0005	0.05	59
ΔCI	21 23 26–28 30	319	0.46 (0.30 to 0.63)	<0.00001	0.01	66
$LVSWI_{TRT}$	26 27 30	102	3.73 (0.49 to 6.98)	0.02	0.0009	86
ΔLVSWI	23 26 27 30	142	5.00 (3.95 to 6.06)	<0.00001	0.83	0
$LVEF_{TRT}$	26 27 30	102	6.76 (3.53 to 10.00)	<0.0001	0.75	0
ΔLVEF	21 26 27 30	144	4.98 (0.75 to 9.21)	0.02	0.001	81
$Norepinephrine\ dose_{TRT}$	23 26–28 30	547	−0.04 (−0.16 to 0.09)	0.58	<0.00001	96
ΔNE dose	23 25 27 28 30	537	−0.06 (−0.13 to 0.01)	0.08	0.006	72
Fluid infusion in 24 hours	23 26 28 30	581	2.72 (0.75 to 4.69)*	0.007	<0.00001	97

Note: Subscript TRT stands for outcomes after treatment; Δ stands for change range of outcomes.
*Standard mean difference is used in this case due to large difference in means (MD 1048.74, 95% CI 303.21 to 1794.27).
CI, cardiac index; LVEF, left ventricular ejection fraction; LVSWI, left ventricular stroke work index; MD, mean difference; NE, norepinephrine.

We also attempted to synthesise the studies by dividing the studies with patients at high (≥50%) or low (<50%) risks and found an OR of 0.55 (95% CI 0.30 to 1.03) and 0.99 (95% CI 0.74 to 1.32), respectively. Although no statistical significance could be observed, we found the group of studies with high-risk patients were more likely to benefit from levosimendan use. Still, more trials are definitely needed.

Limitations

Our study had several limitations. The randomised trials included in this meta-analysis were of limited sample size, 8 out of 10 studies included less than 50 patients,[21–27 30] and were potentially high-biased. Follow-up duration was not reported in one study[24]; only intensive care unit mortality was reported in two studies,[22 23] and the inconsistency in follow-up duration could potentially bring bias

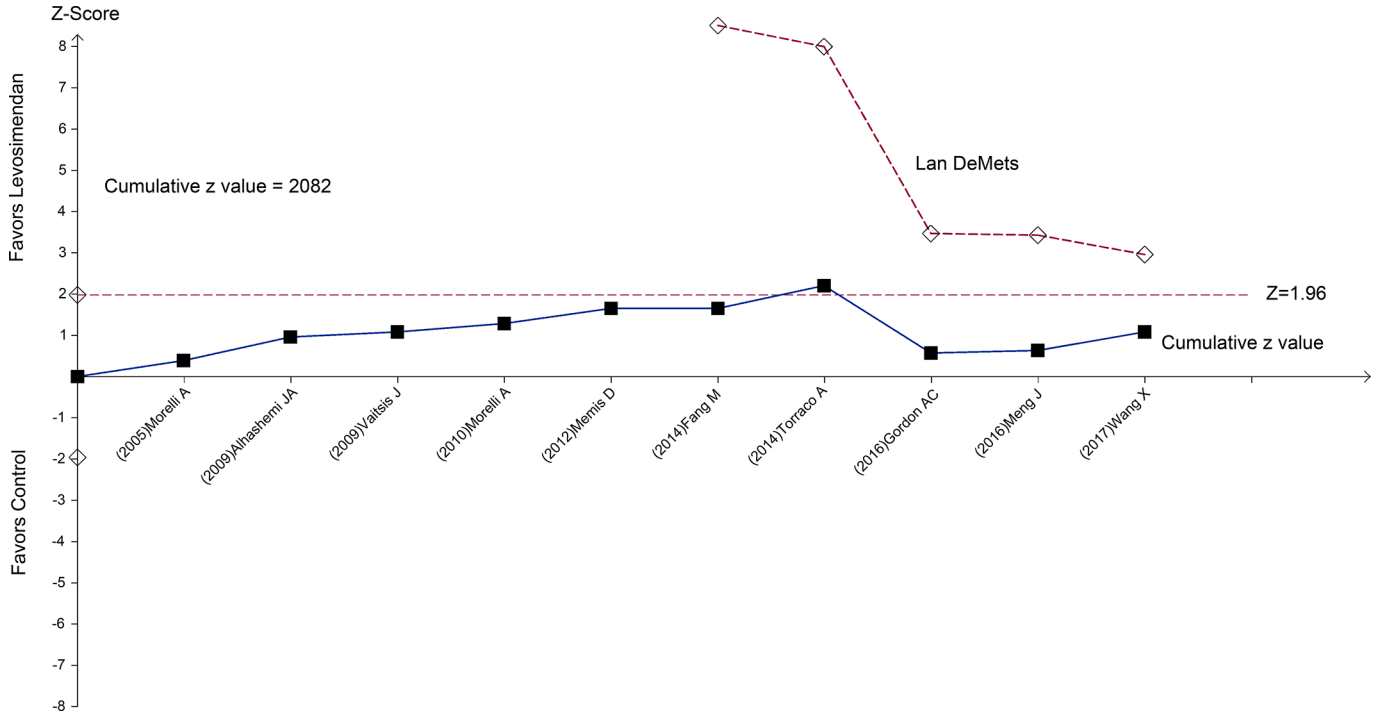


Figure 4 Trial sequential analysis. The optimal information size of 2082 patients for detection of the plausible treatment effect of levosimendan in sepsis and the Lan-DeMets sequential monitoring boundary constructed by the optimal information size did not cross.

to the results. Also, the dose regimen of levosimendan varied from 0.05 to 0.2 µg/kg/min, which could cause different haemodynamic effects to the patients.

CONCLUSION

Although levosimendan could improve clinical outcomes including cardiac function and tissue perfusion compared with dobutamine or standard therapy, it also increased fluid infusion but did not reduce vasopressor requirements. Still, it failed to bring significant benefit to mortality in sepsis. More RCTs are necessary to further elucidate the effects of levosimendan on sepsis, particularly in those with cardiac dysfunctions.

Contributors WC carried out the analysis and interpretation of data, and participated in drafting, editing and submitting the manuscript. The articles were reviewed by two reviewers (WC and J-FX) independently in accordance with the inclusion criteria. Disagreements were resolved and by consensus and discussion including a third reviewer (J-YX). The quality of the articles was assessed by WC and J-FX independently, with disagreements resolved by consulting a third reviewer (J-YX). YY was responsible for conception, design and coordination of the study, and revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data sets used and/or analysed during the study are available from the corresponding author on reasonable request.

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REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, *et al*. Surviving sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165–228.
2. Pang D, Aneja RK. Levosimendan for septic myocardial dysfunction: not yet ready for prime time. *Crit Care Med* 2015;43:2522–3.
3. Sato R, Nasu M. A review of sepsis-induced cardiomyopathy. *J Intensive Care* 2015;3:48.
4. Aneman A, Vieillard-Baron A. Cardiac dysfunction in sepsis. *Intensive Care Med* 2016;42:2073–6.
5. Landesberg G, Gilon D, Meroz Y, *et al*. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J* 2012;33:895–903.
6. Gonzalez C, Begot E, Dalmay F, *et al*. Prognostic impact of left ventricular diastolic function in patients with septic shock. *Ann Intensive Care* 2016;6:36.
7. Rhodes A, Evans LE, Alhazzani W, *et al*. Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43:304–77.
8. Annane D, Vignon P, Renault A, *et al*. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet* 2007;370:676–84.
9. Pollesello P, Papp Z, Papp JG. Calcium sensitizers: what have we learned over the last 25 years? *Int J Cardiol* 2016;203:543–8.
10. Belletti A, Castro ML, Silvetti S, *et al*. The Effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials. *Br J Anaesth* 2015;115:656–75.
11. Pollesello P, Parissis J, Kivikko M, *et al*. Levosimendan meta-analyses: is there a pattern in the effect on mortality? *Int J Cardiol* 2016;209:77–83.
12. Barraud D, Faivre V, Damy T, *et al*. Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide-treated rabbits: comparison with dobutamine and milrinone. *Crit Care Med* 2007;35:1376–82.
13. Wang Q, Yokoo H, Takashina M, *et al*. Anti-inflammatory profile of levosimendan in cecal ligation-induced septic mice and in lipopolysaccharide-stimulated macrophages. *Crit Care Med* 2015;43:e508–20.
14. Sareila O, Korhonen R, Auvinen H, *et al*. Effects of levo- and dextrosimendan on NF-kappaB-mediated transcription, iNOS expression and NO production in response to inflammatory stimuli. *Br J Pharmacol* 2008;155:884–95.
15. Zangrillo A, Putzu A, Monaco F, *et al*. Levosimendan reduces mortality in patients with severe sepsis and septic shock: a meta-analysis of randomized trials. *J Crit Care* 2015;30:908–13.
16. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
17. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
18. Higgins JP, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
19. Wiebe N, Vandermeer B, Platt RW, *et al*. A systematic review identifies a lack of standardization in methods for handling missing variance data. *J Clin Epidemiol* 2006;59:342–53.
20. Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials* 1997;18:580–93. discussion 661-6.
21. Vaitsis J, Michalopoulou H, Thomopoulos C, *et al*. Use of levosimendan in myocardial dysfunction due to sepsis. *Critical Care* 2009;13(Suppl 1):P165.
22. Alhashemi JA, Alotaibi QA, Abdullah GM, *et al*. Levosimendan vs dobutamine in septic shock. *J Crit Care* 2009;24:e14–15.
23. Morelli A, Donati A, Ertmer C, *et al*. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. *Crit Care* 2010;14:R232.
24. Memiş D, Inal MT, Sut N. The effects of levosimendan vs dobutamine added to dopamine on liver functions assessed with noninvasive liver function monitoring in patients with septic shock. *J Crit Care* 2012;27:318.e1–6.
25. Torraco A, Carrozzo R, Piemonte F, *et al*. Effects of levosimendan on mitochondrial function in patients with septic shock: a randomized trial. *Biochimie* 2014;102:166–73.
26. Fang M, Dong S. [Effects of levosimendan on hemodynamics and cardiac function in patients with septic shock]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2014;26:692–6.
27. Meng JB, Hu MH, Lai ZZ, *et al*. Levosimendan versus dobutamine in myocardial injury patients with septic shock: a randomized controlled trial. *Med Sci Monit* 2016;22:1486–96.
28. Gordon AC, Perkins GD, Singer M, *et al*. Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med* 2016;375:1638–48.
29. Wang X, Li S. Effect of small-dose levosimendan on mortality rates and organ functions in Chinese elderly patients with sepsis. *Clin Interv Aging* 2017;12:917–21.
30. Morelli A, De Castro S, Teboul JL, *et al*. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med* 2005;31:638–44.
31. Fleischmann C, Scherag A, Adhikari NK, *et al*. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016;193:259–72.
32. Landoni G, Biondi-Zoccai G, Greco M, *et al*. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. *Crit Care Med* 2012;40:634–46.
33. Groesdonk HH, Sander M, Heringlake M, *et alN Engl J Med* 2017;376:798.
34. Landoni G, Belletti A, Putzu A, *et al*. Prevention of organ dysfunction in septic shock: still looking for an effective treatment. *J Thorac Dis* 2016;8:E1715–E1718.