Heart Surgery Forum 2023; 26(5): E609–E620
doi: 10.59958/hsf.6439

Systematic Review

Meta-Analysis of the Efficacy of Levosimendan in the Treatment of Severe Sepsis Complicated with Septic Cardiomyopathy

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Submitted: 17 July 2023 Revised: 3 September 2023 Accepted: 7 September 2023 Published: 30 October 2023

Abstract

Introduction: Sepsis is a medical condition characterized by acute organ dysfunction and uncontrolled inflammation. Organ dysfunction in sepsis is the primary cause of mortality in patients with myocardial dysfunction. Levosimendan is a vasodilating and inotropic agent used in patients with acute heart failure and has resulted in decreased morbidity and mortality in these patients. Our main objective is to examine levosimendan's efficacy in treating severe sepsis complicated with septic cardiomyopathy. **Methods**: We systematically searched five databases, PubMed, Web of Science, Embase, Cochrane Library and BioMed Central, for articles and publications from their inception to 2023. Our study adopted the PICOS approach in identifying suitable publications during the systematic search. Inclusion criteria included randomized, controlled trials utilizing levosimendan in adult patients diagnosed with septic shock or severe sepsis. We excluded non-English publications and non-randomized controlled trials. The Newcastle-Ottawa scale (NOS) scale was used to assess the methodological quality, while the risk of bias was assessed through the Cochrane Risk of bias tool. All statistical analyses were performed using RevMan version 5.4. **Results**: Eight studies met the eligibility criteria and were included in the analysis. There was a statistically significant positive effect on cardiac input in patients treated with levosimendan compared to those treated with dobutamine ($p < 0.001$). Similarly, there were positive effects on left ventricular ejection fraction (LVEF) ($p < 0.001$) and left ventricular stroke work index (LVSWI) ($p < 0.001$). We observed a significant reduction in mortality ($p < 0.01$) and serum levels of lactic acid ($p < 0.01$). **Discussion**: Levosimendan is a calcium sensitizer associated with an influx of calcium ions and activation of ATP-dependent potassium channels that increases myocardial contractility contractions, enhances vasodilation and improves oxygen supply to the cells and tissues. **Conclusion**: Levosimendan is highly efficacious and safe in the management of sepsis and sepsis-induced cardiomyopathy.

Keywords

levosimendan; sepsis; cardiomyocytes; LVEF; cardiac output

Introduction

Sepsis is a medical condition characterized by acute organ dysfunction and uncontrolled inflammation. Severe sepsis leads to high mortality rates worldwide due to cardiovascular diseases such as myocardial dysfunction and ischemic strokes [1]. Organ dysfunction in sepsis is the primary cause of mortality in patients with myocardial dysfunction [2,3]. Silvetti *et al*. [4], found that levosimendan significantly improves heart failure and cardiac dysfunction. They also observed that levosimendan improved hemodynamic effects after cardiac surgery. However, its clinical effects require further research and should be examined using high-quality RCT trials. Similarly, Conti *et al*. [5] proposed that levosimendan is an intrope that combines sensitivity to calcium by inhibiting the activity of phosphodiesterase and ATP-potassium-dependent channels. Levosimendan has a high degree of oral bioavailability and undergoes extensive metabolism before excretion as waste products.

Gonçalves *et al*. [6] suggested that levosimendan infusions in heart transplant patients decreased the incidence of heart failure and major complications. Levosimendan reduces severe effects such as arrhythmias and infections [7,8].

In sepsis, the heart undergoes a series of changes in structure and functionality based on the magnitude and severity of sepsis [9]. In the early stages of septic shock, the left ventricular ejection fraction (LVEF) is usually less than 60%, resulting in decreased contractility due to alterations in adrenaline levels. Stroke volume is typically low, accompanied by high permeability of blood vessels, inadequate cardiac preload, and decreased peripheral vascular resistance [1]. Lower stroke volumes are usually inadequate to establish and maintain required cardiac output, leading to higher levels of lactic acid and reduced blood oxygen saturation.

The development of sepsis is characterized by a reduction in LVEF and diastolic function due to low blood pressure and decreased myocardial contractility [1]. Increased inflammation due to sepsis decreases myocardium contractility by altering mitochondria function which alters adrenergic receptors, and the transport of calcium ions, leading to apoptosis. The destruction of the myocardium increases cardiac dysfunction, evidenced by elevated markers of necrosis, increased inversion of T-waves and reduction in the ST-T segments [9,10].

Levosimendan significantly affects the pathogenesis of septic cardiomyopathy through various mechanisms, such as increasing myocardial contractility, improving diastolic function, and altering hemodynamics. Chang *et al*. [11] suggested that levosimendan increases the sensitivity of cardiomyocytes to calcium by changing the structure of troponin. Changes in troponin structure increase the myocardium's contractions without affecting the intracellular concentration of calcium ions. Moreover, it does not affect the cellular oxygen requirements. Therefore, administration of levosimendan in septic patients increases the cardiac output while reducing systemic and pulmonary vascular resistance.

Pan *et al*. [12] found that levosimendan sensitizes intracellular calcium and activates ATP-potassium channels on the vascular smooth muscles responsible for vasodilation. The activation of ATP-potassium channels has a cardioprotective effect, leading to a selective inhibition of phosphodiesterase. Yang *et al*. [13] proposed that levosimendan has a critical effect in lowering the plasma levels of sICAM-1 and sVCAM-1. Levosimendan dilates the peripheral vessels and lowers the heart's preload and afterload by increasing ATP-potassium channels [13]. Therefore, levosimendan protects the heart from heart failure induced by sepsis and has a dose-dependent increase in coronary artery flow within 30 minutes of intravenous infusion.

Koca and Demirdöven [14] suggested that levosimendan has a calcium-sensitizing effect, and its inotropic effects are linked to its action on troponin C of the myocardium filaments. Furthermore, it decreases myocardial infarction injury by preventing calcium ions from influx into the cardiomyocytes. Therefore, it improves diastolic function in sepsis, and the delivery of oxygen to the myocardium and results in vasodilation of the coronary arteries. In a prospective study by Tsolaki *et al*. [15], levosimendan exhibited significant hemodynamic effects and was highly efficacious in treating patients with severe septic cardiomyopathy. Levosimendan reversed the effects of early signs cardiogenic shock and improved left ventricular function.

Chen *et al*. [16] found that levosimendan significantly reduced the serum levels of lactic acid. Similarly, Yang *et al*. [13] demonstrated levosimendan resulted in significant improvements in the levels of lactic acid and pH, which was accompanied by a decrease in systemic vascular resistance without affecting the levels of arterial blood pressure. Moreover, reducing systemic vascular resistance leads to a positive increase in cardiac index. Therefore, administering levosimendan in patients with septic cardiomyopathy resulted in improved cardiac output and LVEF which contributed to improved patient outcomes. Established guidelines recommend using noradrenaline, a potent vasoconstrictor, to manage vascular dysregulation in severe sepsis. While Levosimendan may offer benefits in cases with concurrent cardiomyopathy, it is essential to highlight that the current guidelines emphasize the prioritization of noradrenaline when cardiac complications are absent.

A study by Morelli *et al*. [17] analyzed the effect of levosimendan on hemodynamics by comparing the effects of levosimendan against dobutamine in microcirculatory systems. They found that levosimendan led to a significant improvement in blood flow in septic patients compared to dobutamine. Furthermore, there were greater changes in the flow indices of vessels in the levosimendan group compared to the dobutamine group. Similarly, a study by Meng *et al*. [18] found that levosimendan lowered the levels of biomarkers associated with septic injury in myocardial dysfunction compared to dobutamine. Moreover, levosimendan lowered the duration of mechanical ventilation and reduced the length of hospital stay in septic shock patients.

A meta-analysis by Liu *et al*. [19] using randomized controlled trials of levosimendan against traditional drugs used in treating sepsis established that levosimendan significantly reduced mortality compared to dobutamine. In contrast, a study by Vaitsis *et al*. [20] observed no effects of levosimendan on the mortality of septic patients. Differences in the co-morbidities of the patient population may explain these inconsistencies.

In this review, we performed a meta-analysis of the efficacy of levosimendan in the treatment of severe sepsis complicated with septic cardiomyopathy. Our study sought to compare the efficacy and safety of levosimendan against dobutamine and traditional drugs in treating septic cardiomyopathy.

Methods

Information Sources and Search Strategy

Our systematic review and meta-analysis was conducted based on the PRISMA guidelines and the Cochrane Handbook for systematic reviews and meta-analysis [21,22]. We systematically searched five databases, PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://clarivate.com/products/scientific-and-academic-research/research-discovery-and-workflow-solutions/webofscience-platform/), Embase (https://www.embase.com/landing?status=grey), Cochrane Library (https://www.cochranelibrary.com/) and BioMed

Central (https://www.biomedcentral.com/journals) for articles and publications from their inception to 2023. We adopted the following keywords, "sepsis", "levosimendan", "myocardial", "cardiac", "myocardium", and "heart".

Eligibility Criteria

Our study adopted the PICOS approach in identifying suitable publications during the systematic search. PICOS is an acronym for Patients, Intervention, Comparison, Outcomes and study design. Our systematic search defined patients as adults with sepsis or severe sepsis. The intervention used levosimendan, while the comparison involved inotropic therapy or dobutamine. The outcomes were divided into primary and secondary outcomes. Primary outcomes focused on the changes in the cardiac output and LVEF before and after treatment. Secondary outcomes were changes in blood lactate levels and mortality in the intensive care unit (ICU). The study design was randomized controlled trials. The following inclusion and exclusion criteria were used.

Inclusion Criteria

The inclusion criteria for this study encompassed randomized controlled trials using levosimendan in adult septic shock or severe sepsis patients, observational studies on levosimendan in septic cardiomyopathy, studies reporting primary outcomes regarding cardiac function parameters before and after levosimendan administration, and studies reporting secondary outcomes related to changes in blood lactate levels and ICU mortality rates.

Exclusion Criteria

We excluded reviews, studies with incomplete primary and secondary outcomes, conference papers and letters.

Study Selection

We used three independent reviewers to retrieve and identify relevant publications from the databases. The selected publications' references were screened with their titles and abstracts. The selection process was based on the eligibility criteria, and any differences in expert opinions were resolved by consensus. The authors of articles with incomplete data were contacted for data availability before inclusion or exclusion into the study.

Quality Assessment

Our study adopted the Newcastle-Ottawa scale (NOS) to assess the methodological quality of selected publications [23]. The NOS scale comprised eight items subdivided into selection, comparability and outcome. Studies with scores greater than six were deemed to have high methodological quality. The Cochrane risk of bias tool (version 2.0, Oxford, UK: The Cochrane Collaboration, 2003) was used to assess the risk of bias in the selected publications based on five areas: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting. The risk of bias was classified based on "low risk", "unclear risk", and "high risk". In all cases, there was support for the judgment based on the assigned risk.

Data Extraction

We used three independent reviewers to extract data from the selected publications that had passed the quality assessment. These reviewers obtained baseline information, procedures and outcomes of the selected publications. We extracted information such as sample size, intervention, study design, and outcomes. Our primary outcomes were the changes in cardiac function based on cardiac input, LVEF and left ventricular stroke work index (LVSWI). Also, we examined changes in the total fluid infused and mean arterial pressure. Our secondary outcomes were based on mortality rates in the ICU, changes in blood lactate levels and the possibility of utilizing norepinephrine during the treatment.

Statistical Analysis

Our study adopted the Review Manager (version 5.4.1 Review Manager (RevMan) [Computer program]. Oxford, UK: The Cochrane Collaboration, 2003) to conduct all statistical analyses. We analyzed binary outcomes by determining the natural logs of the risk ratios and their corresponding standard errors. In studies reporting continuous variables, we performed a meta-analysis of the standardized mean differences at 95% confidence intervals (CI). In studies reporting median values, we adopted the Cochrane Handbook for systematic reviews of intervention to estimate the means and standard deviations from the medians and quartiles based on appropriate formulas.

We used the inverse variance technique in dichotomous variables based on risk ratios and corresponding 95% CI. We assessed the heterogeneity of the selected publications based on the Higgins I^2 statistic: 0 to 40% indicated low heterogeneity, 30 to 60% indicated moderate heterogeneity, and 50 to 90% indicated high heterogeneity. Heterogeneity was inferred at a statistical significance of $p < 0.01$. If heterogeneity occurred, the random effects model was used; otherwise, the fixed effects model was used. Forest plots were generated based on odds ratios alongside their 95% CI. Sub-group analysis and sensitivity analysis were also performed. The sensitivity analysis analyzed the effect of mortality rates in the ICU in studies reporting a low risk of bias based on mortality rates within 30 days. All analyses inferred statistical significance at a p-value of less than 0.05.

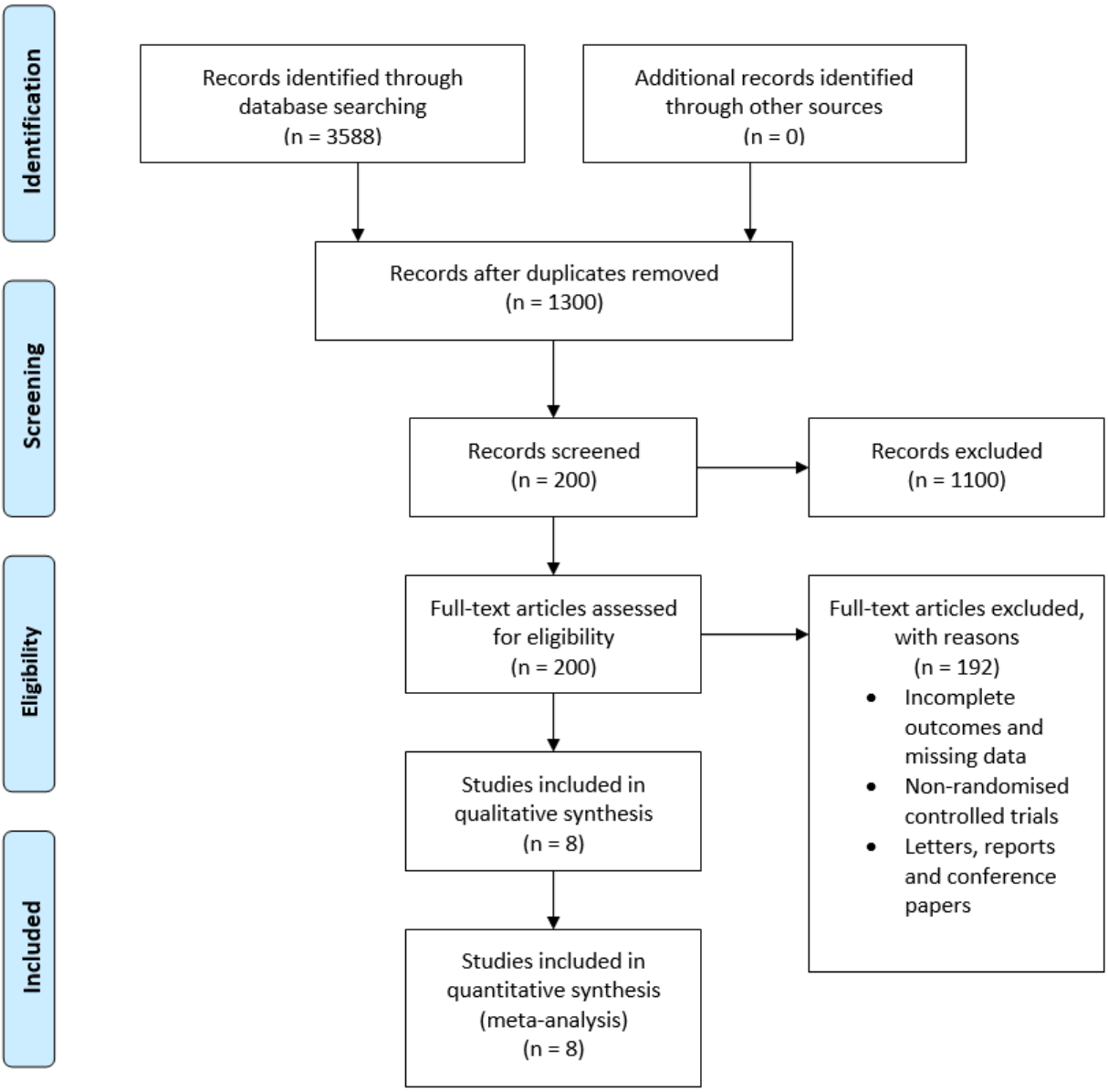

Fig. 1. PRISMA flow chart of the study selection process.

Results

Our initial literature search produced 3588 articles. After screening for duplicates, 1300 articles remained. An additional 1100 were excluded based on their titles and abstracts. After applying the eligibility criteria, 8 studies were included in the meta-analysis (see Fig. 1).

Characteristics of Included Studies

We included 8 studies (see Table 1, Ref. [17,18,20,24–28]) with a sample size of 192 patients. There were 95 in the control group treated with dobutamine and 97 in the experimental group treated with levosimendan. The sample size was relatively low, with the highest being 20 and the lowest 10. They were all randomized controlled trials reporting primary outcomes of cardiac input, LVEF and LVSWI. They also reported secondary outcomes on mortality rates in the ICU and changes in blood lactate levels.

We incorporated four studies utilizing levosimendan as an intervention in the treatment group and a combination of dobutamine and guideline therapies in the control group. In all these studies, levosimendan was constantly infused within 24 hours at a rate of 0.17 micrograms per kg per minute without the need for boluses. The mean age of participants was 63 years, 45% were females. The studies had moderate methodological quality, with five having a moderate to low risk of bias, while two studies reported a high risk of bias.

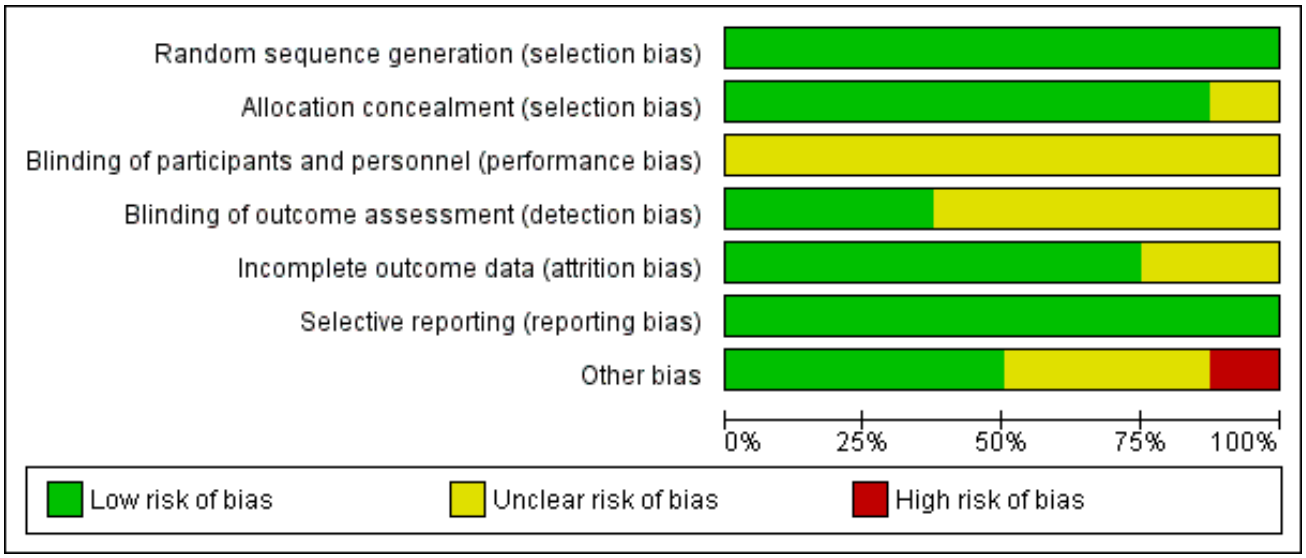

Fig. 2. Risk of bias of selected publications.

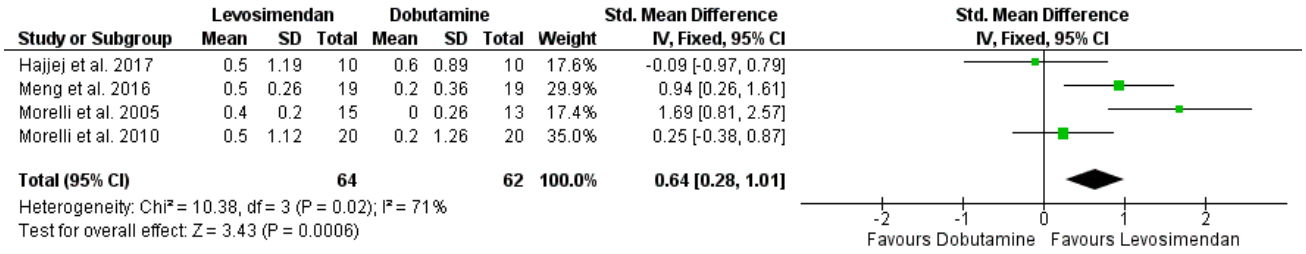

Fig. 3. Effects of levosimendan on changes in cardiac input.

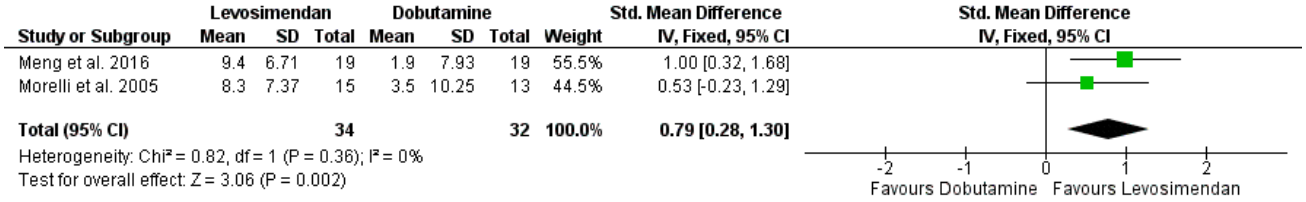

Fig. 4. Effects of levosimendan on changes in left ventricular ejection fraction (LVEF).

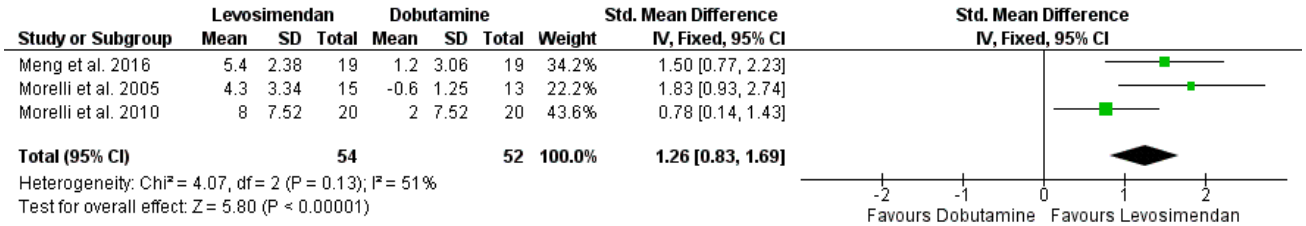

Fig. 5. Effects of levosimendan on changes in left ventricular stroke work index (LVSWI).

Risk of Bias

In Fig. 2, we assessed the risk of bias in selected publications based on five domains. We observed a low risk of bias in random sequence generation because we only included randomized controlled trials in our study; therefore, the selection bias was extremely low. We observed a moderate unclear risk of bias in allocation concealment because it was possible for participants to determine or influence the treatment assigned to them and alter the study's internal validity. It was impossible to determine the risk of blinding participants and personnel because in clinical trials, the

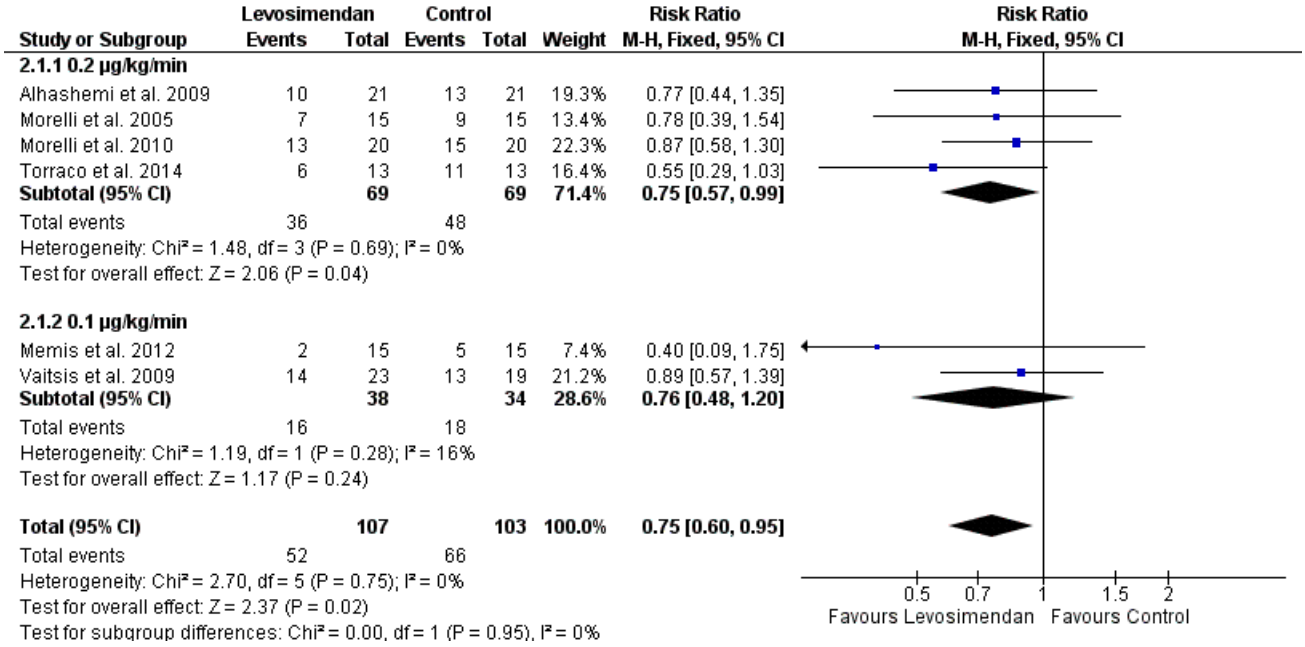

Fig. 6. Effects of levosimendan on the rates of mortality.

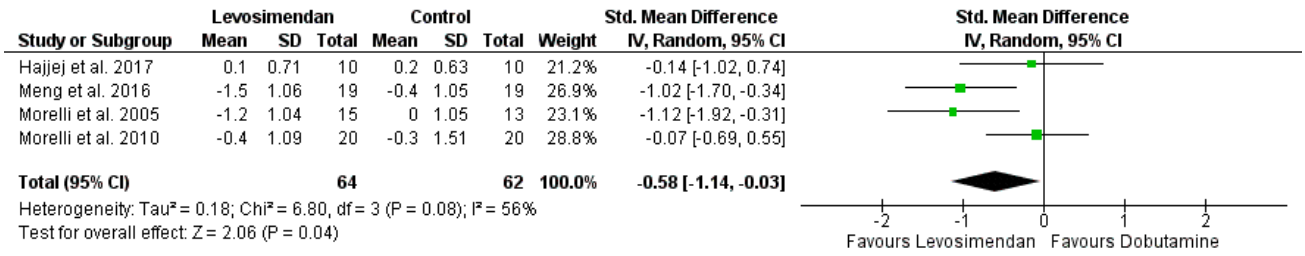

Fig. 7. Effects of levosimendan on levels of lactic acid.

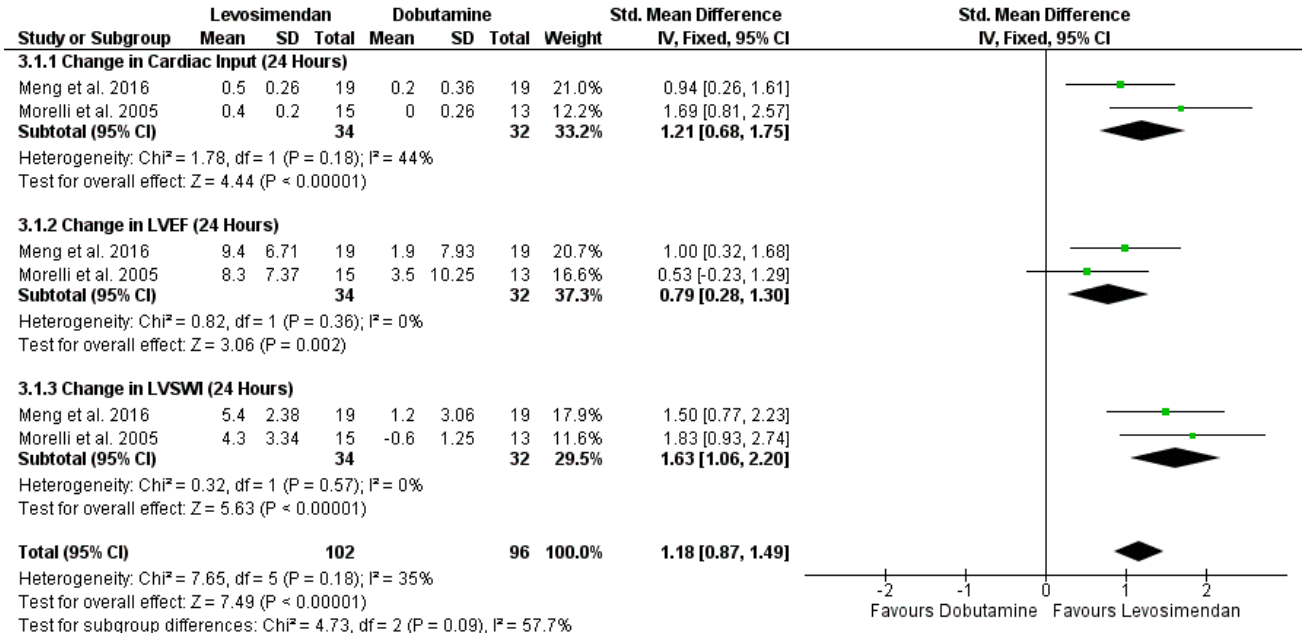

Fig. 8. Sensitivity analysis of the primary outcomes.

clinical professionals have exposure to the patient and are informed of the required treatment. Hence, there was an unclear risk of bias since most studies did not report on the blinding technique used for patients and professionals. Similarly, there was a relatively moderate unclear risk of bias in the detection bias. There was a low risk of bias in reporting bias and attrition bias.

Analysis of Primary Outcomes

Effects of Levosimendan on Changes in Cardiac Input

In Fig. 3, there was a statistically significant positive effect on cardiac input of patients treated with levosimendan compared to those treated with dobutamine (SMD = 0.64, $p < 0.001$, 95% CI [0.28, 1.01]). In this analysis, we reported a moderate to high heterogeneity in the selected publications ($I^2 = 71\%$, $p = 0.02$); nonetheless, we adopted the fixed effects model because the heterogeneity was not statistically significant. Furthermore, we conducted a sensitivity analysis to examine the effects of excluding these studies on the primary outcomes.

Effects of Levosimendan on Changes in LVEF

In Fig. 4, there was a statistically significant effect of an increase in LVEF after treatment with levosimendan compared to dobutamine (SMD = 0.79, $p < 0.01$, 95% CI [0.28, 1.30]). We adopted the fixed effects model because there was no significant heterogeneity in the studies ($I^2 = 0\%$, $p = 0.36$).

Effects of Levosimendan on Changes in LVSWI

In Fig. 5, there was a statistically significant effect of an increase in LVSWI after 24-hour treatment with levosimendan compared to dobutamine (SMD = 1.26, $p < 0.01$, 95% CI [0.83, 1.69]). We adopted the fixed effects model because there was no significant heterogeneity in the selected studies ($I^2 = 51\%$, $p = 0.13$).

Analysis of Secondary Outcomes

Effects of Levosimendan on the Rates of Mortality

In Fig. 6, there was a statistically significant effect in the reduction in mortality rates in the ICU in patients who were treated with levosimendan at an infusion dose of 0.2 µg/kg/min compared to the control group (RR = 0.75, 95% CI [0.57, 0.99], $p = 0.04$). Additionally, the sub-group analysis of patients treated with levosimendan at an infusion dose of 0.1 µg/kg/min reported a non-significant reduction in mortality rates (RR = 0.76, 95% CI [0.48, 1.20], $p = 0.24$). All the selected publications had a low level of heterogeneity ($I^2 = 0\%$, $p = 0.75$).

Effects of Levosimendan on Levels of Lactic Acid

In Fig. 7, we observed a statistically significant effect in the reduction of levels of serum lactic acid after 24-hour treatment with levosimendan compared to dobutamine (SMD = –0.58, 95% CI [–1.14, –0.03], $p = 0.04$). The selected studies had a moderate level of heterogeneity ($I^2 = 56\%$, $p = 0.08$) which was not statistically significant.

Sensitivity Analysis

We conducted a sensitivity analysis by excluding studies reporting a high and unclear risk of bias in the primary outcomes. Moreover, these studies had moderate to high levels of heterogeneity; hence, they were excluded from the sensitivity analysis. Particularly, a high level of heterogeneity was observed in the studies reporting outcomes of changes in cardiac input and the serum levels of lactic acid.

In Fig. 8, after eliminating studies with high heterogeneity, we adopted the fixed effects model to examine the effects of levosimendan on these parameters. Our sensitivity analyses reported positive outcomes and benefits of 24-hour treatment with levosimendan compared to dobutamine. However, we observed significant differences in the techniques used in measuring the primary outcomes in the selected studies, which could have led to the heterogeneity that still exists. Nonetheless, the sensitivity analysis showed that our study is highly stable and consistent ($p < 0.001$).

Discussion

Our meta-analysis has examined the effects of 24-hour treatment with levosimendan compared to dobutamine in septic or severe sepsis myocardial dysfunction. We observed positive benefits of increased cardiac input, LVEF and LVSWI after treatment with levosimendan compared to the control groups. Furthermore, there was a statistically significant reduction in the serum levels of lactic acid and mortality rates in the ICU. Our sub-group analysis of mortality rates suggested a dose-dependent effect of levosimendan on mortality rates in patients with severe sepsis and septic cardiomyopathy. The statistically significant reduction in mortality at the higher dose of 0.2 µg/kg/min indicates a potential benefit. The non-significant reduction at the lower dose of 0.1 µg/kg/min highlights the need for further investigation and potentially a larger sample size. Moreover, we propose that levosimendan is highly efficacious at an infusion dose of 0.2 µg/kg/min or higher.

Our findings were consistent with Legrand *et al.* [29], who observed that dobutamine selectively increases microvascular perfusion in some patients but not others. Furthermore, they showed that in post bypass patients, the mean arterial pressure increased from 65 mmHg to 75

mmHg. Combining dobutamine with norepinephrine significantly increases blood flow in the renal blood vessels and the rate of glomerular filtration. Dubin *et al*. [30] proposed that dobutamine only affects systolic function and leads to positive outcomes in patients with systolic dysfunction. However, dobutamine worsens diastolic dysfunction, acute stress cardiomyopathy, and dynamic left intraventricular obstruction. Hence, treatment with dobutamine in myocardial dysfunction or septic cardiomyopathy does not lead to positive outcomes in cardiac input, LVEF and LVSWI. Therefore, there is a heterogenous response to dobutamine in patients with septic shock.

In a prospective echocardiographic study by Razazi *et al*. [31], dobutamine led to a significant increase in the contractions of the myocardium in both ventricles with a further increase in diastolic function at the lateral mitral annulus. However, dobutamine was discontinued due to poor tolerance in about 70% of patients, regardless of the dose. Moreover, increased lactic acidosis led to vasodilation, increased vasoplegia and low survival outcomes.

Rhodes *et al*. [32] proposed that the international guidelines of 2016 recommend the utilization of dobutamine in the treatment of myocardial dysfunction; however, during the development of these guidelines, the standards and definitions of sepsis have evolved with the emergence of new treatment techniques such as levosimendan. Therefore, these recommendations should be interpreted cautiously because they do not reflect modern guiding principles for medical professionals. Dobutamine has a positive inotropic effect, and its mechanisms in sepsis-induced cardiomyopathy are based on increasing heart contractions, vasodilation, heart rate and oxygen supply to the tissues [1]. The primary action of dobutamine in myocardium contractility involves activating the beta-1 adrenergic receptors, which leads to an influx of calcium ions into the cardiomyocytes. An influx of calcium ions positively affects the myocardium's contractions and the heart's capacity to pump blood [33]. Additionally, activating beta-2 adrenergic receptors through vasodilation reduces systemic vascular resistance and increases blood flow within the capillaries and veins. Increased blood flow lowers the workload on the heart and increases cardiac output.

Our findings suggest that levosimendan is highly efficacious and safe in treating and managing septic cardiomyopathy. These findings were consistent with Weiss *et al*. [34], who proposed that levosimendan requires minimal amounts of oxygen in the tissues and positively lowers the occurrence of arrhythmias and the production of catecholamines. Moreover, levosimendan is a calcium sensitizer whose inotropic mechanism of action is independent of the release of cyclic adenosine monophosphate. The inotropic mechanism of levosimendan has the clinical benefit of inhibiting septic-induced cardiomyopathy by increasing the potential of ATP potassium channels. Our findings were consistent with Hu *et al*. [35], who observed a positive effect of levosimendan on septic cardiomyopathy. These positive effects were related to vasodilation and inotropic effects; however, they did not observe significant effects on the functions of the right heart. Levosimendan has a dual pharmacological action; first, it has a positive effect of binding to cardiac troponin C and increases the sensitivity of cardiomyocytes to calcium. Secondly, it has a vasodilation effect by regulating the opening of the ATP-dependent potassium channels within the pulmonary artery vascular system.

Our study was consistent with Rysz *et al*. [36], who examined the effects of levosimendan in swine models and found that it increased and restored spontaneous circulation. Moreover, the rates of survival were increased. The administration of levosimendan within 24 hours of resuscitation increases cardiac output and alleviates severe symptoms of septic cardiomyopathy. However, it is advised to use a constant intravenous administration of levosimendan compared to loading doses at a constant rate of 0.2 µg/kg/min. The intravenous administration of levosimendan lowers mean arterial pressure and improves the left ventricular system and ejection fraction. The reduction in mean arterial pressure is attributed to the vasodilatory effects of levosimendan through the opening of adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle cells. This leads to relaxation of the smooth muscle and subsequent vasodilation, decreasing peripheral vascular resistance. The reduction in systemic vascular resistance can lead to a lowering of mean arterial pressure. Interestingly, despite its vasodilatory properties, established guidelines recommend using noradrenaline, a potent vasoconstrictor, to manage vascular dysregulation in severe sepsis. While Levosimendan may offer benefits in cases with concurrent cardiomyopathy, it is important to highlight that the current guidelines emphasize the prioritization of noradrenaline when cardiac complications are absent.

Our analysis of secondary outcomes revealed a significant reduction in serum lactic acid levels in the intervention group compared to the control group. However, we do not suggest that levosimendan increased the perfusion of tissues due to the administration of extra fluid compared to the controls. Fluid resuscitation in septic cardiomyopathy is critical in protecting the organs and limiting the spread of infections to surrounding tissues and cells [37]. Fluid resuscitation is crucial in managing septic cardiomyopathy by supporting hemodynamic stability and optimizing tissue perfusion. In sepsis, fluid resuscitation aims to restore intravascular volume, improve cardiac output, and maintain adequate organ perfusion [37]. Additionally, fluid resuscitation helps to increase preload, which improves ventricular filling and stroke volume. By expanding the intravascular volume, fluid resuscitation enhances cardiac output and helps maintain blood pressure, which is vital for adequate tissue perfusion [37].

Table 1. Characteristics of Included Studies.

Author's surname	Year of publication	Country	Study design	Sample size	Gender	Age	Outcomes
Morelli *et al*. [24]	2005	Italy	Randomized Controlled Trial	28	21 Males and 7 Females	Intervention group: 62.4 years. Control group: 61.5 years	The intervention group was treated with levosimendan at an infusion dose of 0.2 µg/kg/min, while the control group was treated with dobutamine at an infusion dose of 5 µg/kg/min.
Morelli *et al*. [17]	2010	Italy	Randomized Controlled Trial	40	30 Males and 10 Females	Intervention group: 68 years. Control group: 66 years	The intervention group was treated with levosimendan at an infusion dose of 0.2 µg/kg/min, while the control group was treated with dobutamine at an infusion dose of 5 µg/kg/min.
Meng *et al*. [18]	2016	China	Randomized Controlled Trial	38	24 Males and 14 Females	Intervention group: 55.4 years. Control group: 50.2 years	The intervention group was treated with levosimendan, while the control group was treated with dobutamine.
Hajjej *et al*. [25]	2017	Tunisia	Randomized Controlled Trial	20	17 Males and 3 Females	Intervention group: 51.0 years. Control group: 61.0 years	The intervention group was treated with levosimendan, while the control group was treated with dobutamine.
Vaitsis *et al*. [20]	2009	Greece	Randomized Controlled Trial	42	24 Males and 18 females	Mean age of 66.1 $\pm$ 7.54 years	The intervention group was treated with levosimendan at an infusion dose of 0.1 µg/kg/min, while the control group was treated with dobutamine at an infusion dose of 5 µg/kg/min.
Torraco *et al*. [26]	2014	Italy	Randomized Controlled Trial	26	85% of males in the intervention group and 62% of males in the control group	Intervention group: 70 years. Control group: 68 years	The intervention group was treated with levosimendan at an infusion dose of 0.2 µg/kg/min, while the control group was treated with standard therapy.
Memiş *et al*. [27]	2012	Turkey	Randomized Controlled Trial	30	7 males and 8 females in both intervention and control groups	Intervention group: 56.27 years. Control group: 54.93 years.	The intervention group was treated with levosimendan at an infusion dose of 0.1 µg/kg/min, while the control group was treated with dobutamine at an infusion dose of 10 µg/kg/min.
Alhashemi *et al*. [28]	2009	Saudi Arabia	Randomized Controlled Trial	42	Not reported	Not reported	The intervention group was treated with levosimendan at an infusion dose of 0.2 µg/kg/min, while the control group was treated with dobutamine at an infusion dose of 5 µg/kg/min.

Sepsis can lead to widespread vasodilation and maldistribution of blood flow, resulting in inadequate tissue perfusion. Fluid resuscitation helps restore perfusion to vital organs, such as the heart, brain, kidneys, and liver. Adequate tissue perfusion is essential to meet oxygen and nutrient demands, remove metabolic waste products, and prevent organ dysfunction [37]. Early initiation of appropriate antibiotic therapy is crucial in sepsis. Fluid resuscitation can help optimize antibiotic delivery by improving blood flow and facilitating drug distribution to infected tissues. Adequate fluid volume also enhances the clearance of microbial toxins and inflammatory mediators, promoting the resolution of infection. Fluid resuscitation is a key aspect of septic cardiomyopathy; the approach should be tailored to the patient's condition and hemodynamic response [37]. Excessive fluid administration can lead to fluid overload, impaired oxygenation, and worsening cardiac function. Therefore, closely monitoring clinical signs, hemodynamic parameters, and perfusion markers is essential to guide fluid therapy and ensure optimal resuscitation.

The reduction in serum levels of lactic acid is attributed to a positive effect of increased cardiac output and vasodilation. Increased cardiac output is associated with increased stroke volumes and myocardial contractility, ensuring adequate perfusion in tissues and oxygen delivery [38]. Sufficient tissue perfusion and increased delivery of oxygen to the cells and tissues eliminates anaerobic respiration and, consequently, the production of lactic acid. Additionally, vasodilation has a positive effect on the rate of tissue perfusion and supply of oxygen to the cardiomyocytes. Thus, vasodilation eliminates hypoxic conditions associated with lactic acidosis [38].

Levosimendan has the positive effect of increasing LVEF. LVEF is determined by echocardiography and is a critical indicator of left ventricular systolic function [39]. Previous studies have reported high heterogeneity in the measurement techniques for LVEF, with major disagreements between the Simpson and Teichholz techniques [40]. In our study, only three trials reported using the Simpson technique while the other studies did not report the measurement used for LVEF.

Our findings observed positive effects of levosimendan on the LVSWI. LVSWI is an important parameter implicated in cardiac function [41]. The increase in LVSWI is due to increased myocardium contractions by calcium sensitization of the myofilaments. Increased calcium sensitization enhances the rate of calcium binding to troponin, which is associated with increased activity of the myofilaments. Consequently, positive interactions between myosin and actin increase the myocardium contractility.

We observed that levosimendan positively increases vasodilation of the arteries and veins by opening the ATP-dependent potassium channels of the smooth muscles. This effect is essential in reducing the afterload and preload on the heart, thereby increasing LVSWI. Moreover, the opening of the ATP channels protects against injuries due to ischemic reperfusion. Maintaining the integrity of the mitochondria increases the production of energy in the cardiomyocytes, thereby maintaining contractility.

Other studies [42,43] have suggested that levosimendan has an anti-inflammatory response that limits the production of chemokines and inflammatory cytokines. The anti-inflammatory effect prevents the activation and recruitment of immune cells during sepsis. An abnormal activation of neutrophils and macrophages enhances sepsis by compromising the immune system, leading to organ dysfunction. However, the exact mechanisms of levosimendan are different in every patient due to variations in individual features such as age and the presence of secondary infections.

Limitations

Our study was limited by the quality of the trials used, with some studies having a higher clinical heterogeneity. Additionally, the studies consisted of a smaller sample size, and further studies should be based on data from multiple centers with larger sample sizes. The patients in ICUs could be suffering from secondary infections that exacerbate sepsis and septic shock, leading to higher levels of heterogeneity. We observed a non-uniform duration of follow-up in the selected publications, with some studies reporting 28 days to 30 days while others did not report follow-up.

Conclusion

Our study has demonstrated that levosimendan is highly efficacious and safe in managing sepsis and sepsis-induced cardiomyopathy. We observed a significant improvement in cardiac output changes in LVEF and LVSWI upon administration of levosimendan within 24 hours. Furthermore, there were significant effects in reducing the rates of mortality in the ICU and the serum levels of lactic acid. Interestingly, despite its vasodilatory properties, established guidelines recommend using noradrenaline, a potent vasoconstrictor, to manage vascular dysregulation in severe sepsis. While Levosimendan may offer benefits in cases with concurrent cardiomyopathy, it is important to highlight that the current guidelines emphasize the prioritization of noradrenaline when cardiac complications are absent.

Due to the high heterogeneity in the selected studies examining cardiac output, our findings should be interpreted cautiously because the included studies adopted different techniques of assessing and measuring the primary outcomes.

Author Contributions

XZ conceptualized and designed the work. QG, CZ, BL, DH, AL and JQ acquired data and performed analysis. QG and XZ drafted the work. DH and JQ reveiwed intellectual content. QG and CZ contributed to editorial changes in the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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