Review Article
Efficacy of norepinephrine, dopamine or vasopressor in the management of septic shock and severe sepsis: a meta-analysis

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Abstract: The aim of this study was to assess and compare the clinical efficacy of norepinephrine, dopamine, and vasopressors in severe sepsis and septic shock. A literature search of the following databases was used to identify the relevant randomized controlled trials: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov (search performed until January 15th, 2017). Data analysis was performed using Stata 14.0. Eight eligible studies out of 697 publications in the electronic databases were included in this study. The comparison of mortality between the norepinephrine and dopamine groups (RR=1.07, 95% CIs [0.96, 1.18], I^2=0.0%, P=0.884), as well as between the norepinephrine and vasopressor groups (RR=0.96, 95% CIs [0.84, 1.10], I^2=0.0%, P=0.921) indicated no statistically significant difference under the fixed-effects model. For the outcomes of changes in DO_2 (MD=86.00, 95% CIs [-142.45, 29.54], I^2=0.0%, P=0.803) and changes in VO_2 (MD=10.90, 95% CIs [-23.12, 1.33], I^2=0.0%, P=0.842) in the norepinephrine and dopamine groups, a significant difference was indicated under the fixed-effects model. Other outcomes are reported in the results section. No publication bias was observed for any of the outcomes, as evidenced by the symmetry of the funnel plots. Based on these findings, dopamine should be recommended for the treatment of severe sepsis and septic shock in adults.

Keywords: Severe sepsis, septic shock, norepinephrine, dopamine, vasopressor
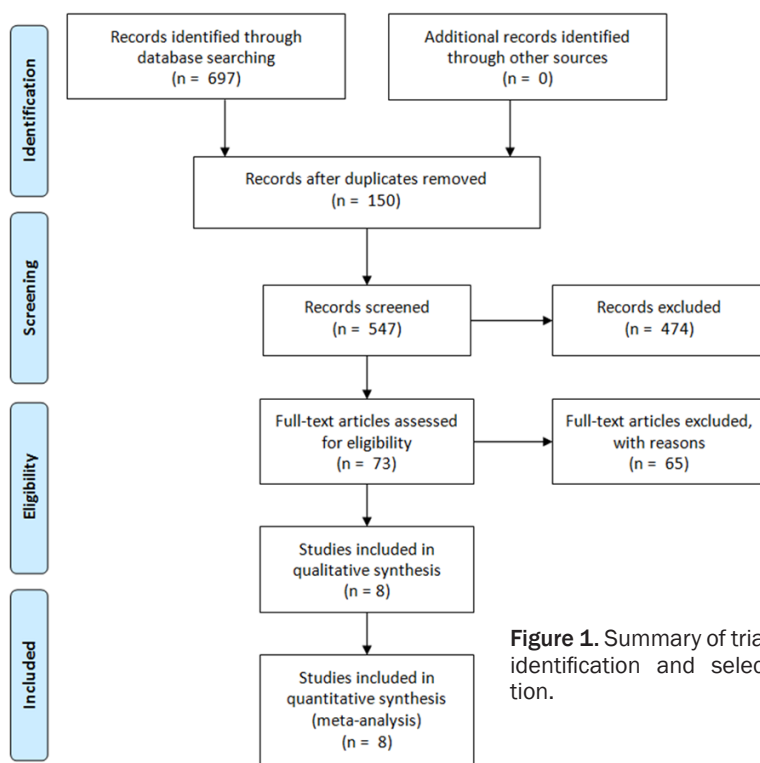
Introduction

Septic shock continues to be a significant cause of morbidity and mortality despite the use of broad-spectrum antibiotics, modern intensive care unit (ICU) management, and treatment based on specific guidelines [1-5]. Systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock. The signs of established sepsis include confusion, metabolic acidosis (which may be accompanied by faster breathing and lead to respiratory alkalosis), low blood pressure (due to decreased systemic vascular resistance), higher cardiac output, and dysfunction of blood coagulation, which may lead to clotting and organ failure [6-8]. Along this continuum, circulatory abnormaliti-

es (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock [9, 10].

Sepsis has a worldwide incidence of more than 20 million cases a year, with mortality due to septic shock reaching up to 50 percent even in industrialized countries [1, 11]. In the United States, approximately 750,000 cases of sepsis are reported each year, and at least 225,000 of these are fatal [1, 12].

While contemporary treatments have improved mortality rates, a substantial number of patients with sepsis still die [13, 14]. Improved

Figure 1. Summary of trial identification and selection.

achieve these goals. A number of studies favor norepinephrine as an effective vasopressor to maintain an adequate mean arterial pressure during septic shock [20-22].

Materials and methods

Search strategy

We conducted a search of four electronic databases, namely, PubMed, EMBASE, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov (search performed up to January 15th, 2017) for eligible randomized controlled trials (RCTs) that evaluated the effectiveness of norepinephrine versus dopamine or a vasopressor in severe sepsis and septic shock. We searched the electronic databases using the following terms: sepsis, shock, norepinephrine, noradrenaline, levarterenol, arterenol, dopamine, hydroxytyramine, Intropin, vasopressor, Pitressin, and beta-hypophamine.

Literature selection and exclusion

A thorough literature search was conducted to retrieve all randomized control trials (RCTs) testing the efficacy of norepinephrine versus dopamine or a vasopressor on patients with severe sepsis or septic shock. The included studies had to involve one or more of the following outcomes: mortality, oxygen delivery (DO_2), oxygen consumption (VO_2), cardiac index (CI), heart ratio (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), central venous pressure (CVP), or systemic vascular resistance index (SVRI). The studies were excluded in accordance with the following criteria: (1) if the study was a duplicate, (2) if the data could not be extracted or obtained through contact with the author, and (3) if the study concerned the pediatric population.

Data extraction

The relevant information, including study design, patient characteristics, interventions, comparisons, and outcomes, was independent-

outcomes are mainly ascribed to earlier identification and improvements in the process of sepsis care rather than to specific pharmacologic interventions [5, 13, 15]. The use of immunosuppressive therapy, an aging population, improved survival of individuals with debilitating illnesses, and invasive medical procedures are thought to have contributed to this increase in sepsis cases. Despite initial optimism, antiendotoxin and anticytokine therapies appear to have little role in the treatment of sepsis [16]. Broad-spectrum antibiotics and fluid resuscitation therefore remain the cornerstone of treatment in patients with septic syndrome and septic shock [17]. However, despite adequate fluid resuscitation, many sepsis patients remain hypertensive and have evidence of inadequate tissue oxygen utilization. Inotropic agents are usually used in this situation to increase blood pressure and improve tissue oxygen delivery [4, 16]. Effective cardiovascular support plays an essential role in the management of patients with septic shock [18, 19]. Oxygen delivery must be maintained above a critical threshold, and arterial pressure must exceed a level that allows appropriate distribution of cardiac output for adequate regional perfusion. Combinations of catecholamines, including norepinephrine, epinephrine, dopamine, and dobutamine, are currently used to

Table 1. Characteristics of the included studies

Study	Year	Country	Population	Gender (Female %)	Age	Sample (I/C)	Mean APACHE II Score	Interventions I	C	Outcomes
Ruokonen [26]	1993	Finland	①②④	NA	45.1±16.6/54.8±7.9	10/11	13.3±3.9	Norepinephrine 2.0 µg/kg/min	Dopamine 2.0 µg/kg/min	1-6, 8, 9
Marik [27]	1994	USA	②⑤	40/50	46±7/46±4	10/10	18±1/17±2	Norepinephrine 0.18 µg/kg/min	Dopamine 26 µg/kg/min	1-7, 9
Lauzier [28]	2006	Canada	②③⑤	20/53.8	58.1±17.5/51.2±17.2	10/13	23.5±4.2/22.8±3.4	Norepinephrine 0.1-2.8 µg/kg/min	Arginine-vasopressin (AVP) 0.004-0.20 U/min	1, 4-9
Mathur [33]	2007	India	①②	40/32	52.76±10.41/54.60±10.92	25/25	25.60±2.31/24.56±2.90	Norepinephrine 0.5-2.5 mcg/kg/min	Dopamine 10-25 mcg/kg/min	1-5, 9
Russell [29]	2008	Canada	NA	40.1/38	61.8±16/59.3±16.4	382/397	27.1±6.9/27.0±7.7	Norepinephrine 5.0-15.0 µg/kg/min	Vasopressin 0.01-0.03 U/min	1
Morelli [30]	2009	Germany	⑤	20/33	64/66	15/15	NA	Norepinephrine 15.0 µg/kg/min	Vasopressin 0.03 U/min	1, 6, 7, 9
De Backer [31]	2010	Belgium	①⑤	45.3/40.9	67/68	821/858	20/20	Norepinephrine 0.19 µg/kg/min	Dopamine 20 µg/kg/min	1
Patel [32]	2010	USA	①⑤	55.9/52.2	> 18	118/134	27±6.1/28±6.7	Norepinephrine 5-20 mcg/kg/min	Dopamine 5-20 mcg/kg/min	1

I: Intervention group; C: Control group; NA: Not obtainable; Population: ① Systolic blood pressure < 90 mm Hg; ② Cardiac index > 3.0 L/min/m²; ③ Arterial blood lactate levels > 2.5 mmol/L; ④ Bacteremia or a verified source of infection; ⑤ Mean arterial pressure < 60 mmHg; Outcomes: 1 mortality, 2 oxygen delivery, 3 oxygen consumption, 4 cardiac index, 5 heart ratio, 6 mean arterial pressure, 7 mean pulmonary arterial pressure, 8 central venous pressure, 9 systemic vascular resistance index.
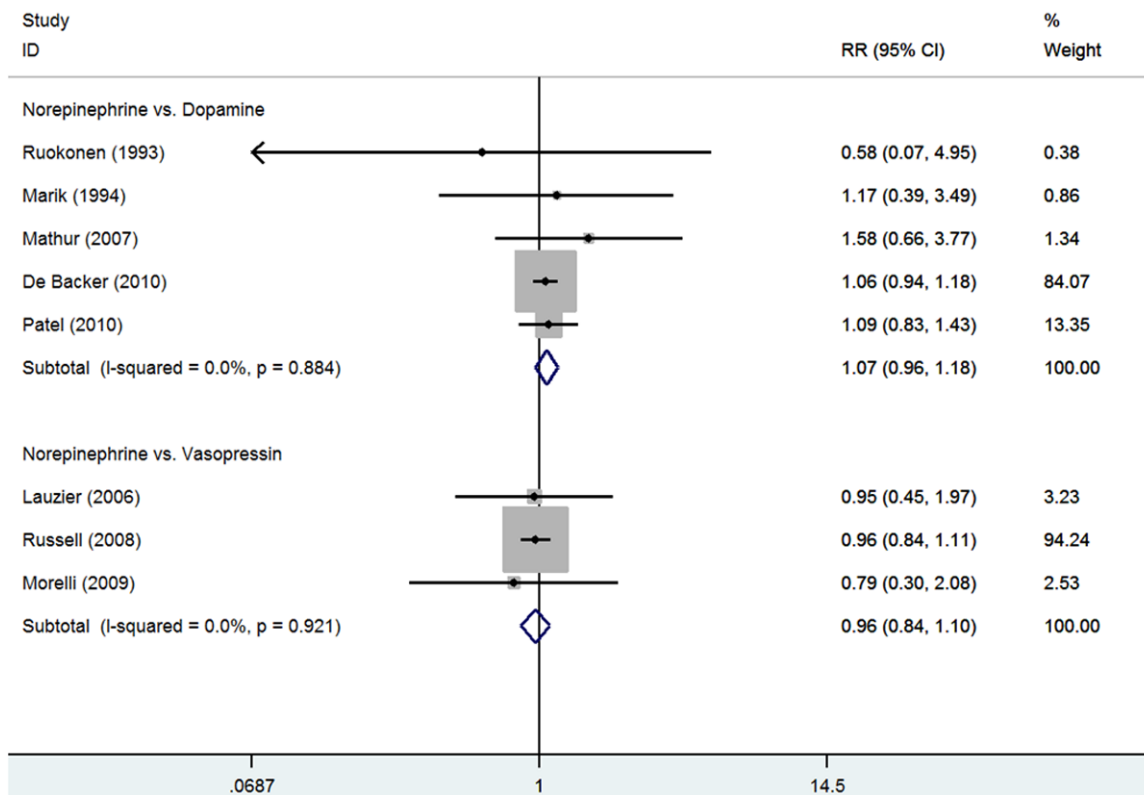
Figure 2. Forest plot of mortality compared to dopamine or vasopressor.

ly extracted and entered into a database by two investigators. When relevant research information was missing, particularly study design or outcome information, we contacted the original authors for clarifications.

Statistical analysis

To describe the dichotomous data [23], we used relative risk (RR) 95% confidence intervals (CIs) and *P* values. Weighted mean differences (MD), 95% CIs, and *P* values were employed for continuous data [24]. All the outcome data were processed using STATA 14.0 software, and the Mantel-Haenszel method was employed for summarizing the statistical effects. We performed a statistical test for heterogeneity and adopted an I^2 of greater than 50% as evidence for heterogeneity according to the Cochrane Handbook [24]. The symmetry of a funnel plot was used to qualitatively determine whether there was publication bias [24, 25]. In the funnel plot, larger studies that provided a more precise estimate of an intervention's effect formed the spout of the funnel, whereas smaller studies with less precision

formed the cone end of the funnel. Asymmetry in the funnel plot indicated a potential publication bias.

Results

Literature search outcome

We identified 697 relevant publications in the electronic databases (**Figure 1**). Employing the selection criteria summarized in the materials and methods section, we obtained quantitative data for our meta-analysis after reading all the titles, abstracts, and full texts. Eight eligible studies [26-33] were included in our final analysis (**Table 1**).

Mortality

A comparison of the mortality between the norepinephrine and dopamine groups (RR=1.07, 95% CIs [0.96, 1.18], I^2=0.0%, P=0.884), as well as the norepinephrine and vasopressor groups (RR=0.96, 95% CIs [0.84, 1.10], I^2= 0.0%, P=0.921), is shown in **Figure 2**, and there was no statistically significant difference under the fixed-effects model.
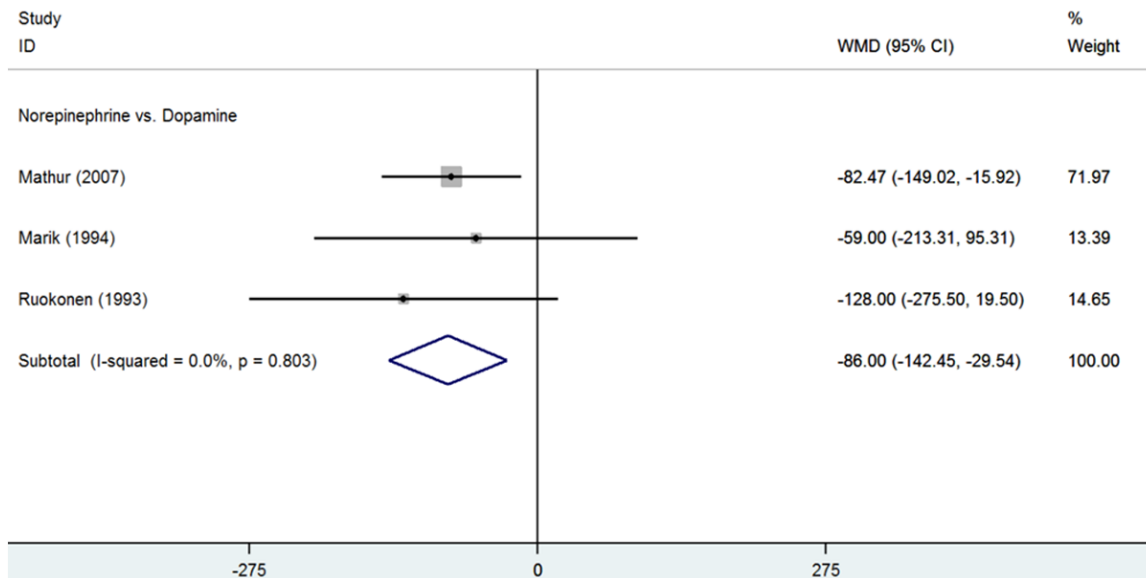
Figure 3. Forest plot of change in oxygen delivery for norepinephrine compared with dopamine.
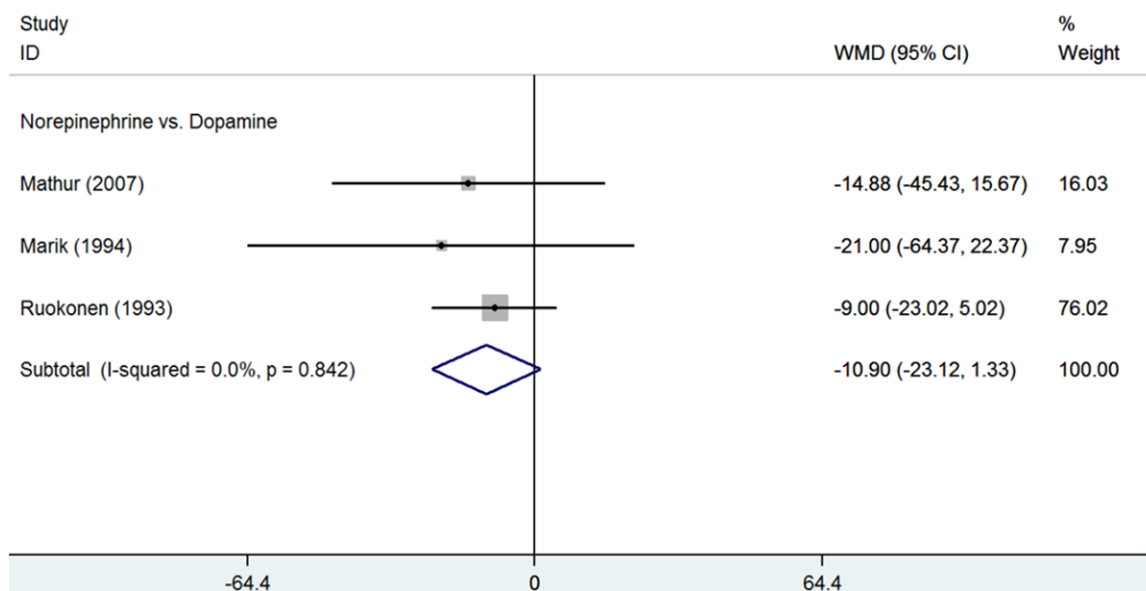
Figure 4. Forest plot of change in oxygen consumption for norepinephrine compared to dopamine.

Changes in DO$_2$

A comparison of changes in DO$_2$ in the norepinephrine and dopamine groups, shown in **Figure 3**, indicated a significant difference (MD=-86.00, 95% CIs [-142.45, 29.54], I^2= 0.0%, P=0.803) under the fixed-effects model.
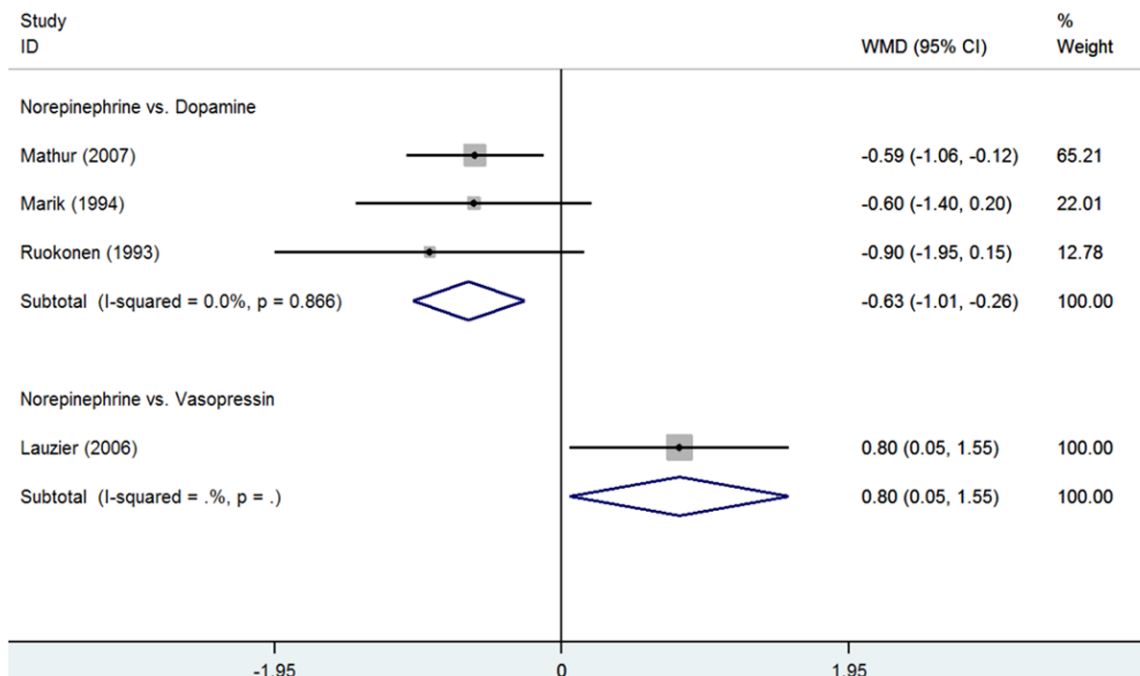
Changes in VO$_2$

A comparison of changes in VO$_2$ in the norepinephrine and dopamine groups, shown in **Figure 4**, indicated no significant difference (MD=-10.90, 95% CIs [-23.12, 1.33], I^2=0.0%, P=0.842) under the fixed-effects model.
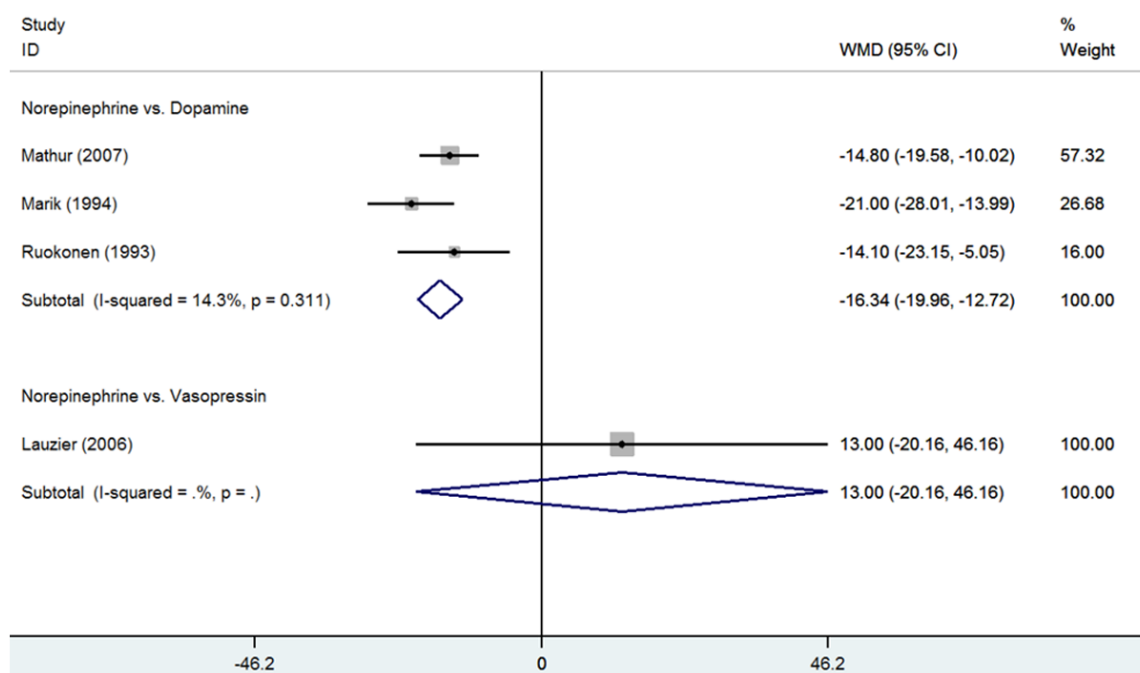
Changes in CI

A comparison of changes in CI in the norepinephrine and dopamine groups (MD=-0.63, 95% CIs [-1.01, -0.26], I^2=0.0%, P=0.866), as well as in the norepinephrine and vasopressor groups (MD=0.80, 95% CIs [0.05, 1.55], I^2=NA, P=NA), shown in **Figure 5**, indicated significant differences under the fixed-effects model.

Figure 5. Forest plot of change in cardiac index for norepinephrine compared to dopamine or vasopressor.

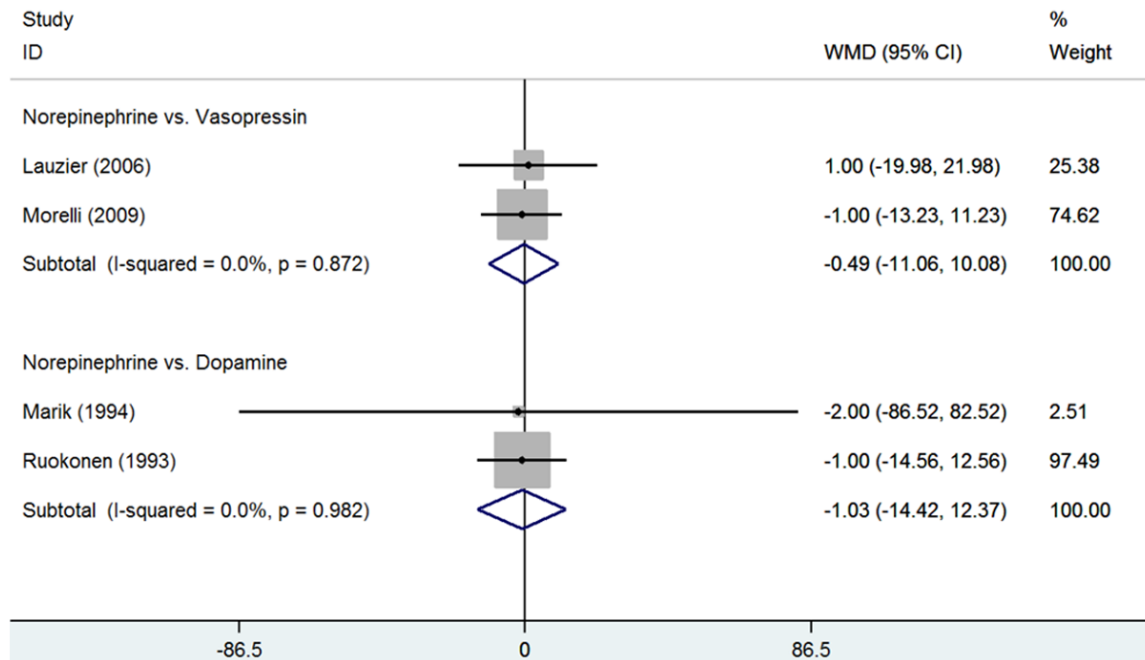
Figure 6. Forest plot of change in heart ratio for norepinephrine compared to dopamine or vasopressor.

Changes in HR

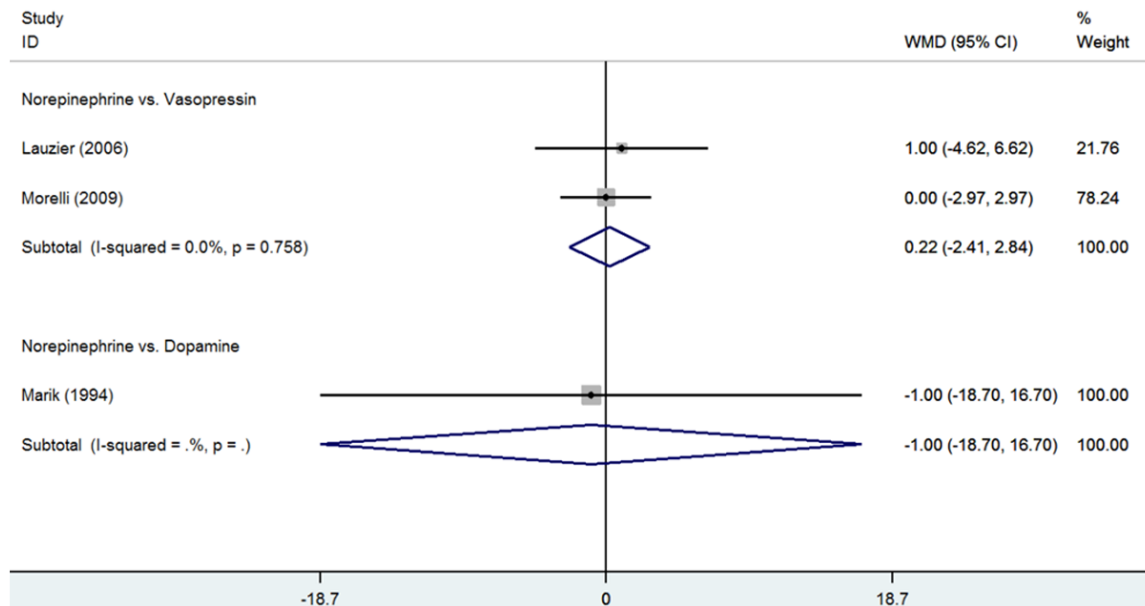A comparison of changes in HR in the norepinephrine and dopamine groups (MD=-16.34, 95% CIs [-19.96, -12.72], I^2=14.3%, P=0.311), shown in **Figure 6**, indicated a significant difference under the fixed-effects model. Comparison of changes in HR in the norepinephrine and vasopressor groups (MD=13.00, 95% CIs [-20.16, 46.16], I^2=NA, P=NA) indicated no significant difference under the fixed-effects model.

Figure 7. Forest plot of change in mean arterial pressure for norepinephrine compared to dopamine or vasopressor.

Figure 8. Forest plot of change in mean pulmonary arterial pressure for norepinephrine compared to dopamine or vasopressor.

Changes in MAP

A comparison of changes in MAP in the norepinephrine and dopamine groups (MD=-0.49, 95% CIs [-11.06, 10.08], I^2=0.0%, P=0.872), as well as in the norepinephrine and vasopressor groups (MD=-1.03, 95% CIs [-14.42, 12.37], I^2=0.0%, P=0.982), shown in **Figure 7**, indicat-

ed no significant difference under the fixed-effects model.

Changes in MPAP

A comparison of changes in MPAP in the norepinephrine and dopamine groups (MD=-1.00, 95% CIs [-18.70, 16.70], I^2=NA, P=NA), as well

Figure 9. Forest plot of change in central venous pressure for norepinephrine compared to dopamine or vasopressor.

as in the norepinephrine and vasopressor groups (MD=0.22, 95% CIs [-2.41, 2.84], I^2=0.0%, P=0.758), shown in **Figure 8**, indicated no significant difference under the fixed-effects model.
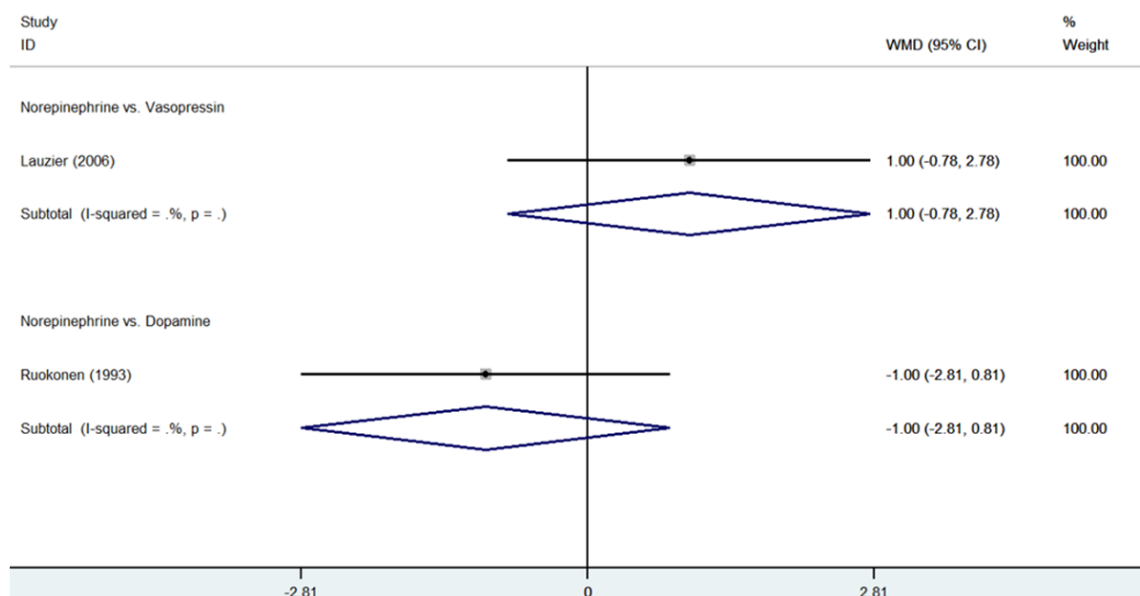
Changes in CVP

A comparison of changes in CVP in the norepinephrine and dopamine groups (MD=1.00, 95% CIs [-2.81, 0.81], I^2=NA, P=NA), as well as in the norepinephrine and vasopressor groups (MD=1.00, 95% CIs [-0.78, 2.78], I^2=NA, P=NA), shown in **Figure 9**, indicated no significant difference under the fixed-effects model.

Changes in SVRI

A comparison of changes in SVRI in the norepinephrine and dopamine groups (MD=-119.43, 95% CIs [-192.88, -45.99], I^2=0.0%, P=0.699), shown in **Figure 10**, indicated a significant difference under the fixed-effects model. A comparison of changes in SVRI in the norepinephrine and vasopressor groups (MD=14.75, 95% CIs [-211.25, 240.74], I^2=12.5%, P=0.285) indicated no significant difference under the fixed-effects model.

Publication bias

No publication bias was observed for any of the outcomes, as evidenced by the symmetry of the funnel plots.

Discussion

Consensus guidelines for the management of sepsis have recently been published [34]. There are many ways to treat severe sepsis, such as early goal-directed therapy, ventilation, broad-spectrum antibiotics, and activated protein C. Early recognition and focused management may improve outcomes in sepsis. Current professional recommendations include a number of actions ("bundles") to be followed as soon as possible after diagnosis. Within the first three hours, individuals with sepsis should receive antibiotics and intravenous fluids if there is evidence of either low blood pressure or inadequate blood supply to organs (as evidenced by an increased lactate level). Blood cultures also should be obtained within this time period. After six hours, blood pressure should be adequate, and close monitoring of blood pressure and the blood supply to organs should be performed. Furthermore, lactate should be measured again if the initial level was high [35]. A related bundle, the "Sepsis Six", is in widespread use in the United Kingdom; it requires the administration of antibiotics within an hour of recognition, blood cultures, lactate and hemoglobin determination, urine output monitoring, high-flow oxygen, and intravenous fluids [36]. The cornerstone of emergency management of sepsis is early goal-directed therapy [37, 38] plus lung-protective ventilation, broad-spectrum antibiotics, and,
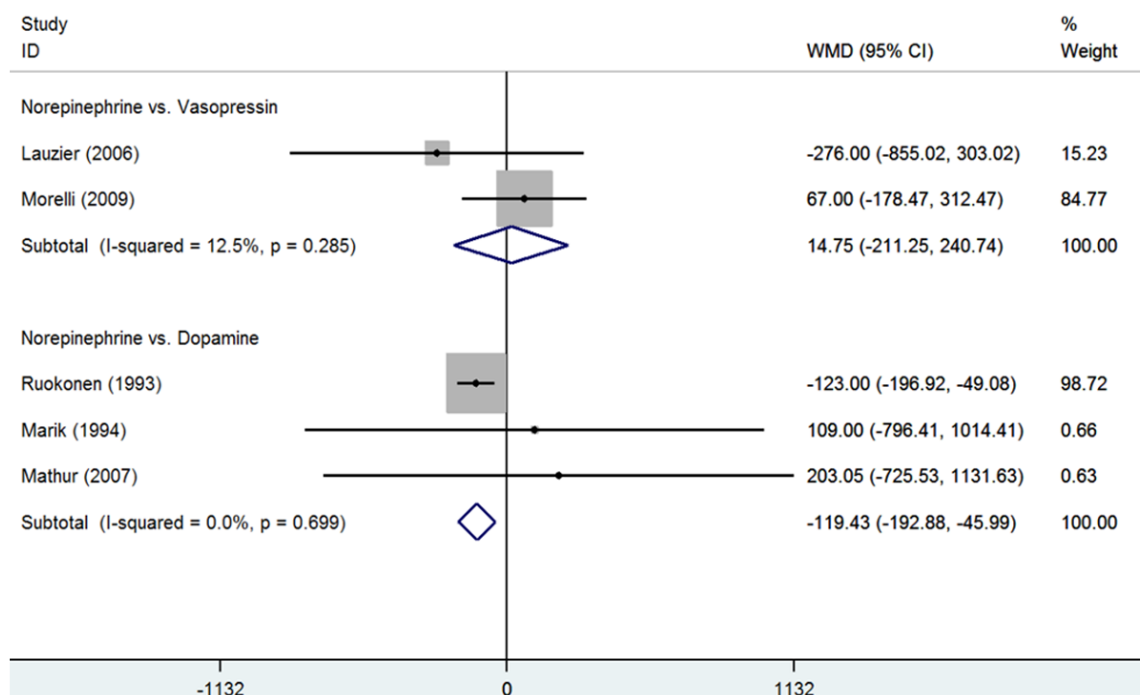
Figure 10. Forest plot of change in systemic vascular resistance index for norepinephrine compared to dopamine or vasopressor.

possibly, activated protein C [39-41]. Early goal-directed therapy is a stepwise approach, with the physiologic goal of optimizing cardiac preload, afterload, and contractility [38]. This therapy involves the administration of early antibiotics. Furthermore, it involves the monitoring of hemodynamic parameters and specific interventions to achieve key resuscitation targets, which include maintaining a central venous pressure of 8-12 mmHg, a mean arterial pressure of 65-90 mmHg, a central venous oxygen saturation (ScvO$_2$) greater than 70%, and a urine output greater than 0.5 ml/kg/hour. The goal is to optimize oxygen delivery to tissues and achieve a balance between systemic oxygen delivery and demand. An appropriate decrease in serum lactate may be equivalent to ScvO$_2$ and is an easier measurement to obtain [38, 42]. The mechanisms of the benefits of early goal-directed therapy are unknown but may include reversal of tissue hypoxia and decreases in inflammation and coagulation defects [43]. Once early goal-directed therapy has been initiated, lung-protective ventilation should be considered. Acute lung injury often complicates sepsis, and lung-protective ventilation (i.e., the use of relatively low tidal volumes) is thus another important aspect of manage-

ment. It is recommended that the head of the bed be raised if possible to improve ventilation. Paralytic agents should be avoided unless acute respiratory distress syndrome (ARDS) is suspected [35]. Furthermore, lung-protective ventilation decreases mortality and is beneficial in septic acute lung injury [44]. Because the site of infection and the causative microorganisms are usually not known initially in a patient with sepsis, cultures should be obtained, and intravenous broad-spectrum antibiotics should be administered expeditiously while the patient's immune status is ascertained. In severe sepsis and septic shock, broad-spectrum antibiotics (usually two antibiotics or a β-lactam antibiotic with broad coverage) are recommended [35, 45]. Observational studies indicate that the outcomes of sepsis and septic shock are worse if the causative microorganisms are not sensitive to the initial antibiotic regimen [40, 46]. Some recommend that antibiotics be given within one hour of making the diagnosis and state that for every hour of delay in the administration of antibiotics, there is an associated 6% rise in mortality [45, 47]. Several factors determine the most appropriate choice for the initial antibiotic regimen [47]. These include local patterns of bac-

terial sensitivity to antibiotics, whether the infection is thought to be a hospital or community-acquired infection, and which organ systems are thought to be infected [8]. Antibiotic regimens should be reassessed daily and narrowed if appropriate. The treatment duration is typically 7-10 days, and the type of antibiotic used is directed by the results of cultures. Administering antibiotics continuously may be better than administering them intermittently [48]. Once goal-directed therapy, lung-protective ventilation, and antibiotic therapy have been initiated, the use of activated protein C should be considered. Therapy with activated protein C (24 µg/kg/hour for 96 hours) has been reported to decrease mortality and ameliorate organ dysfunction in patients with severe sepsis [49, 50].

Currently, choosing the optimum vasopressor agent for patients with septic shock remains an area of controversy [4, 17]. Although almost all agree that vasopressor therapy should not be started until there has been adequate volume resuscitation, which is currently defined American Standards Association (ASA) central venous pressure (CVP) of 8 to 12 mmHg measurement, there is no consensus as to which drug is the "best vasopressor" drug. In 2004, the Society of Critical Care Medicine published consensus guidelines for hemodynamic support in septic shock [51]. These guidelines recommended initiation of either dopamine or norepinephrine. If further hemodynamic support is necessary, the recommendation is to add norepinephrine (if not initially started), a fixed, low-dose vasopressor (0.01-0.04 U/min), phenylephrine, or epinephrine [52, 53].

In this meta-analysis, we evaluated 8 clinical trials that included 2854 sepsis patients older than 18 years of age. In this study, compared with norepinephrine, dopamine was associated with a statistically significant difference in the changes in DO_2, HR, CI, and SVRI. However, in terms of other hemodynamic indices, vasopressor therapy was not superior to norepinephrine or dopamine. This indicates that when choosing drugs to control and treat severe sepsis and severe shock, dopamine should be recommended, and vasopressors should be used with caution.

Some limitations of our study should be addressed. First, only a few clinical trials met the inclusion and exclusion criteria; therefore, more clinical studies are required to confirm our results [24]. Second, some clinical trials had missing data on basic characteristics, possibly falsely increasing heterogeneity due to the failure to perform a meta-regression for confounding factors [54]. Finally, although all the included studies were randomized controlled trials or parallel-group clinical trials, not all of them adequately implemented allocation concealment, blinding of participants, blinding of personnel and blinding of outcome assessment; therefore, the overall quality of the included studies could have resulted in limitations in this study [55].

Conclusions

This study evaluated and compared the effectiveness of norepinephrine, dopamine, and vasopressors in sepsis patients via a meta-analysis of published studies. Our results indicated that dopamine therapy had greater effectiveness and ability to change DO_2, HR, CI, and SVRI than norepinephrine and vasopressors. Based on these findings, dopamine should be recommended for the treatment of severe sepsis and septic shock in adults.

Disclosure of conflict of interest

None.

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