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Norepinephrine or Dopamine for Septic Shock: A Systematic Review of Randomized Clinical Trials

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Abstract

Background: There is debate as to the vasopressor agent of choice in patients with septic shock. According to current guidelines either dopamine or norepinephrine may be considered as the first-line agent for the management of refractory hypotension of septic shock. Objective: The aim of this systematic review was to evaluate randomized clinical trials which compared norepinephrine versus dopamine in critically ill patients with septic shock or in a population of critically ill patients with shock predominantly secondary to sepsis. Data Sources: MEDLINE, Embase, Scopus, Cochrane Register of Controlled Trials and citation review of relevant primary and review articles. Study Selection: Randomized clinical trials that compared norepinephrine with dopamine in critically ill adults with sepsis and reported the 28-day or in-hospital mortality. Data Extraction: We abstracted data on study design, study setting, patient population, 28-day mortality or in-hospital mortality, rate of arrhythmias, hospital length of stay, and ICU length of stay. Data Synthesis: Six studies met our inclusion criteria. These studies included a total of 2043 participants, with 995 in the norepinephrine and 1048 in the dopamine groups. There were 479 (48%) deaths in the norepinephrine group and 555 (53%) deaths in the dopamine group. There was statistically significant superiority of norepinephrine over dopamine for the outcome of in-hospital or 28-day mortality: pooled RR: 0.91 (95% CI 0.83 to 0.99; $P = .028$). We also found a statistically significant decrease in the rate of cardiac arrhythmias in the norepinephine group as compared to the dopamine group: pooled RR: 0.43 (95% CI 0.26 to 0.69; $P \leq .001$). A subgroup analysis that pooled studies in which all the randomized patients had septic shock demonstrated that norepinephrine improved in-hospital or 28-day mortality; however, the results were no longer statistically significant. Conclusions: The analysis of the pooled studies that included a critically ill population with shock predominantly secondary to sepsis showed superiority of norepinephrine over dopamine for in-hospital or 28-day mortality.

Keywords

vasopressor, norepinephrine, dopamine, septic shock, systematic review, meta-analysis

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The incidence of sepsis and septic shock is increasing in the United States and it is a common cause of mortality in the intensive care unit (ICU).[1] Sepsis is characterized by an activation of inflammation causing venous and arterial dilation, which leads to drop in systemic vascular resistance and systolic blood pressure. This drop in blood pressure and hypoperfusion to vital organs result in multiorgan failure leading to increased mortality in septic shock. Therefore, one of the early goals of resuscitation in patients with septic shock is to restore adequate organ perfusion. The initial management is to give fluid boluses. Vasopressors are added in patients who remain hypotensive despite adequate fluid resuscitation. According to the Surviving Sepsis Campaign guidelines either dopamine or norepinephrine may be considered as the first-line agent to correct hypotension of septic shock.[2]

Dopamine is a precursor of norepinephrine and acts on dopaminergic, β-adrenergic, and α-adrenergic receptor in a dose-dependent manner. It increases mean arterial pressure

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(MAP) by primarily increasing the cardiac index and to a lesser extent systemic vascular resistance (SVR). Norepinehrine is a potent α-adrenergic agent with some activity on β_1-adrenergic receptor. It increases MAP by primarily increasing the SVR.

A number of observational studies suggested that the use of dopamine in septic shock may be associated with an increased mortality.[3,4] However, a recent observational study in patients with community-acquired sepsis reported worse outcome in patients who received norepinephrine.[5] Therefore, there is a debate as to which vasopressor is associated with improved outcomes in patients' with septic shock.

The aim of this systematic review was to evaluate those randomized clinical trials that compared norepinephrine and dopamine in critically ill patients with septic shock or in a population of critically ill patients with shock predominantly secondary to sepsis.

Methods

Study Selection

We included all randomized controlled trials (RCTs) that compared norepinephrine with dopamine in critically ill adults with shock predominantly secondary to sepsis and reported the 28-day or in-hospital mortality. We did not restrict study selection based on the language of publication. However, we only included studies that enrolled adult patients. The assessment of study eligibility was performed independently in an unblinded manner by 3 reviewers. Disagreement between reviewers was resolved by consensus.

Search Strategy

We searched the PubMed, Embase, Cochrane Central Register of Controlled Trials, and Scopus databases. Three authors independently searched for relevant studies in any language from 1966 to May 2010. The search strategy was created with the assistance of a librarian using a combination of terms including vasopressor, norepinephrine or dopamine, and septic shock and randomized controlled trials. Bibliographies of all selected articles and review articles were also reviewed to identify other relevant articles. We performed this systematic review according to the guidelines proposed by the PRISMA group.[6]

Outcome Measures

Primary outcome. The primary outcome was 28-day mortality. In the absence of 28-day mortality data, we abstracted in-hospital mortality.

Secondary outcome. Secondary outcomes included the incidence of arrhythmia, hospital length of stay, and ICU length of stay.

Data Collection

Three authors independently collected data from all studies on a standardized form. Any disagreement among authors was resolved by consensus. We abstracted data on study design, study setting, patient population, 28-day mortality (or in-hospital mortality), rate of arrhythmias, hospital length of stay, and ICU length of stay. We attempted to contact the authors of the primary studies to obtain missing information.

Risk of Bias Assessment

We used the *Cochrane risk of bias tool* to assess the risk of bias.[7] Three authors independently collected information from all studies to assess the risk of bias. We obtained information on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Authors assigned "yes" or "no" to each item of *Cochrane risk of bias tool*. We assigned "unclear" to an item for which there was insufficient information in the study.

Data Analysis

We performed the meta-analysis using a fixed-effect model if no significant heterogeneity was present. To assess heterogeneity between studies, we performed a chi-square test and estimated the I^2 statistic. We considered heterogeneity to be present if the chi-square test *P* value was less than .10. Alternatively, I^2 values between 25% and 50% suggested moderate heterogeneity while a value more than 75% was indicative of severe heterogeneity. If heterogeneity were to be present, we planned a priori to explore the sources of heterogeneity and present the pooled data using a random-effects model.

Categorical data was presented as the relative risk with the 95% confidence interval. We considered a *P* value less than .05 to be statistically significant. We tested the interrater agreement of the *Cochrane risk of bias tool* using kappa statistics. We planned a priori to perform a sensitivity analyses by (1) performing the meta-analysis using the random-effects method and (2) excluding studies in which the entire study population did not have sepsis as the cause of shock. We explored the presence of a small-study effect by performing a linear regression of the standardized effect estimates against their precision. There is evidence of small-study effects if the intercept deviates significantly from zero.

Results

A search of the PubMed, Embase, Cochrane Central Register of Controlled Trials, and Scopus databases retrieved 861 articles (Figure 1). We excluded 409 duplicate articles. We reviewed the abstracts and titles of the remaining 450 articles. Ten articles were selected for detail review. Four papers were subsequently excluded as the study used an experimental drug (nitric oxide synthase inhibitor),[8] was an abstract of a study that was later published,[9] and included a crossover design.[10,11] Finally, 6 studies met the inclusion criteria for our systematic review.[12-17] These studies included a total population of 2043 participants with 995 in the norepinephrine and 1048 in

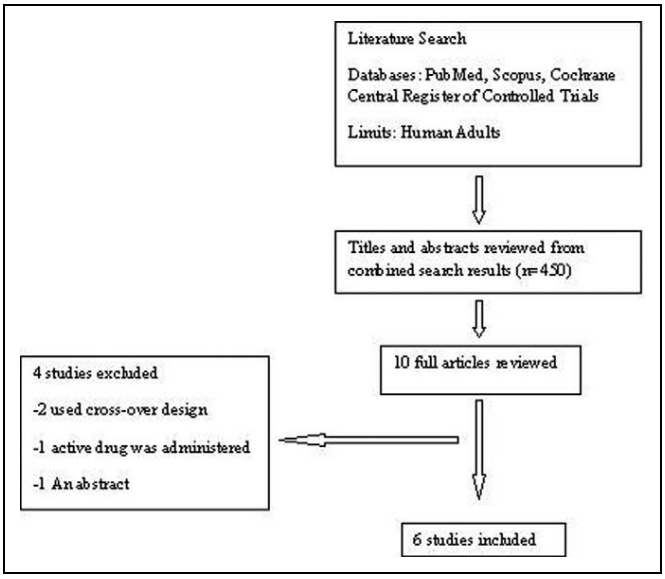

Figure 1. Flowchart of study selection for the systematic review.

the dopamine groups. Table 1 displays the characteristics of the studies. Table 2 displays the Cochrane *risk of bias tool* for all the studies. The interrater agreement for reporting the Cochrane risk of bias tool was 83.3% (kappa: 0.67).

Primary Outcome

There were 479 (48%) deaths in the norepinephrine group and 555 (53%) deaths in the dopamine group. Meta-analysis using a fixed-effect model of the included studies showed significant superiority of norepinephrine over dopamine for the outcome of in-hospital or 28-day mortality: pooled RR: 0.91 (95% CI 0.83 to 0.99; $P = .028$). There was no evidence of statistical heterogeneity (chi-square $P = .75$; $I^2 = 0.0\%$; Figure 2).

Sensitivity Analysis

Meta-analysis for the outcome of in-hospital or 28-day mortality showed that the superiority of norepinephrine over dopamine remained statistically significant using random-effect model: pooled RR: 0.91 (95% CI 0.83 to 0.99; $P = .026$).

We also present sensitivity analysis by performing a meta-analysis using a fixed-effect model in which we removed the study with a mixed population of shock patients. The latter study is the dominant study with the largest number of patients and a weight of 81.4%. This meta-analysis showed again superiority of norepinepinephrine over dopamine; however, the results were no longer statistically significant: pooled RR: 0.84 (95% CI 0.68 to 1.02; $P = .083$).

Secondary Outcomes

Meta-analysis of 2 studies using a random-effect model showed a statistically significant decrease in arrhythmias in the norepinephine group as compared to the dopamine group: pooled RR: 0.43 (95% CI 0.26 to 0.69; $P = <.001$). However, there was evidence of statistical heterogeneity (chi-square $P = .09$; $I^2 = 65.4\%$). We did not perform meta-analysis of hospital and ICU length of stay because of lack of data (Figure 3).

Test for Small-Study Effects

Linear regression of the standard normal deviation against precision showed that the intercepts did not significantly deviate from zero ($P = .40$). There was no evidence of small-study effects, but the small number of studies limits this test.

Discussion

This systematic review suggests that norepinephrine is superior to dopamine in patients with shock predominantly due to sepsis. The use of norepinephrine was associated with a 9% decrease in the in-hospital or 28-day mortality risk when compared with dopamine. The *Cochrane Systematic Review* did not show a mortality benefit with norepinephrine as compared to dopamine.[18] However, this review included only 3 small randomized clinical trials. Our review included 3 additional randomized clinical trials that were published after 2004.

Why might norepinephrine be a better vasopressor than dopamine in patients with septic shock? There are a number of potential explanations. Firstly, norepinephrine is a more potent vasopressor than dopamine, with norepinephrine being more effective in reversing the hypotension of septic shock.[14] In patients with sepsis, norepinephrine increases blood pressure, as well as cardiac output, renal, splanchnic, cerebral blood flow, and microvascular blood flow while minimally increasing heart rate.[14,19,20] By achieving these hemodynamic goals, norepinephrine may be better than dopamine in maintaining organ perfusion. Secondly, there is a concern that dopamine may increase the risk of secondary infections. Dopamine inhibits anterior pituitary function causing a decrease in the secretion of prolactin, growth hormone, and thyroid-stimulating hormone.[21-23] Prolactin and growth hormone have immune-stimulatory properties.[24] Dopamine has also been reported to inhibit lymphocyte proliferation, immunoglobulin synthesis, cytokine production, and promote lymphocyte apoptosis.[25-28] In a murine septic shock model, dopamine was shown to decrease splenocyte proliferation and IL-2 release and was associated with an increased mortality when compared to placebo.[29] Dopamine may therefore increase the risk of infections in critically ill.[30]

The β-adrenergic properties of dopamine predominate in patients with sepsis.[12,14,31] The positive chronotropic and inotropic effects of dopamine will elevate myocardial oxygen requirements, which may not be adequately met by increased coronary flow.[10] Tachycardia and tachy-arrhythmias may therefore become the rate-limiting factor with the use of dopamine. Indeed, our review showed that septic patients treated with dopamine had a higher incidence of arrhythmias than those treated with norepinephrine. Arrhythmias have potential to impair cardiac function, leading to poor outcome.

Table 1. Randomized Control Trials Comparing Norepinephrine With Dopamine in Patients With Septic Shock: Baseline Characteristics of Studies Included in the Meta-Analysis

Author	Year	Population	Country	Number (NE)	Deaths (NE)	Arrhythmia (NE)	Number (DA)	Deaths (DA)	Arrhythmia (DA)	Mean Age (NE)	Mean age (DA)	Male (NE)	Male (DA)	APACHE II (NE)	APACHE II (DA)
Martin[12]	1993	Septic Shock	France	16	7	NR	16	10	NR	52 ± 12	53 ± 19	12	12	31 ±1.3	30 ± 1.2
Ruokoacn[13]	1993	Septic Shock	USA Finland	5	4	NR	5	3	NR	42.2 ± 28	44.6 ± 6	NR	NR	NR	NR
Marik[14]	1994	Septic Shock	USA	10	5	NR	10	6	NR	46 ± 22	46 ± 13	6	5	18 ± 3	17 ± 6
Mathur[15]	2007	Septic Shock	India	25	14	NR	25	19	NR	52.8 ± 10.4	54.6 ± 10.9	15	17	25.6 ± 2.3	24.5 ± 2.9
Paid[16]	2010	Septic Shock	USA	118	51	14	134	67	51	NR	NR	52	64	27 ± 6.1	28 ± 6.7
Dc Backer[17]	2010	Shock	Europe	821	393	102	838	450	207	67[a]	68[a]	449	507	20[a]	20[a]

Abbreviations: NE, Norepinephrine; DA, Dopamine; NR, not reported.
[a] Median.

Table 2. Cochrane Risk of Bias in Included Studies

Author	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Assessed	Free of Selective Outcome Reporting	Free of Other Biases
Martin	Yes	Unclear	Yes	Yes	Yes	Yes
Ruokonen	Yes	No	Unclear	Yes	Yes	Yes
Marik	Yes	Unclear	Unclear	Yes	Yes	No
Mathur	Unclear	Unclear	Yes	Yes	Yes	No
Patel	No	No	No	Yes	Yes	No
Debacker	Yes	Yes	Yes	Yes	No	No

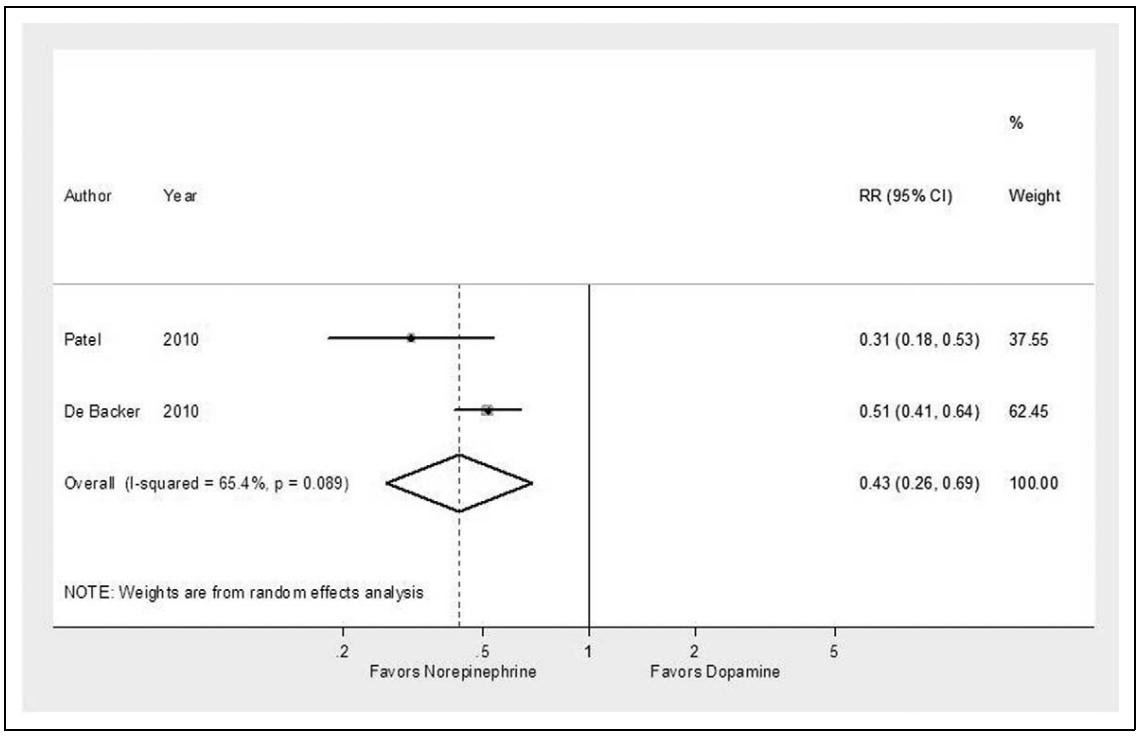

Figure 2. Comparison of mortality between norepinephrine and dopamine in patients with septic shock.

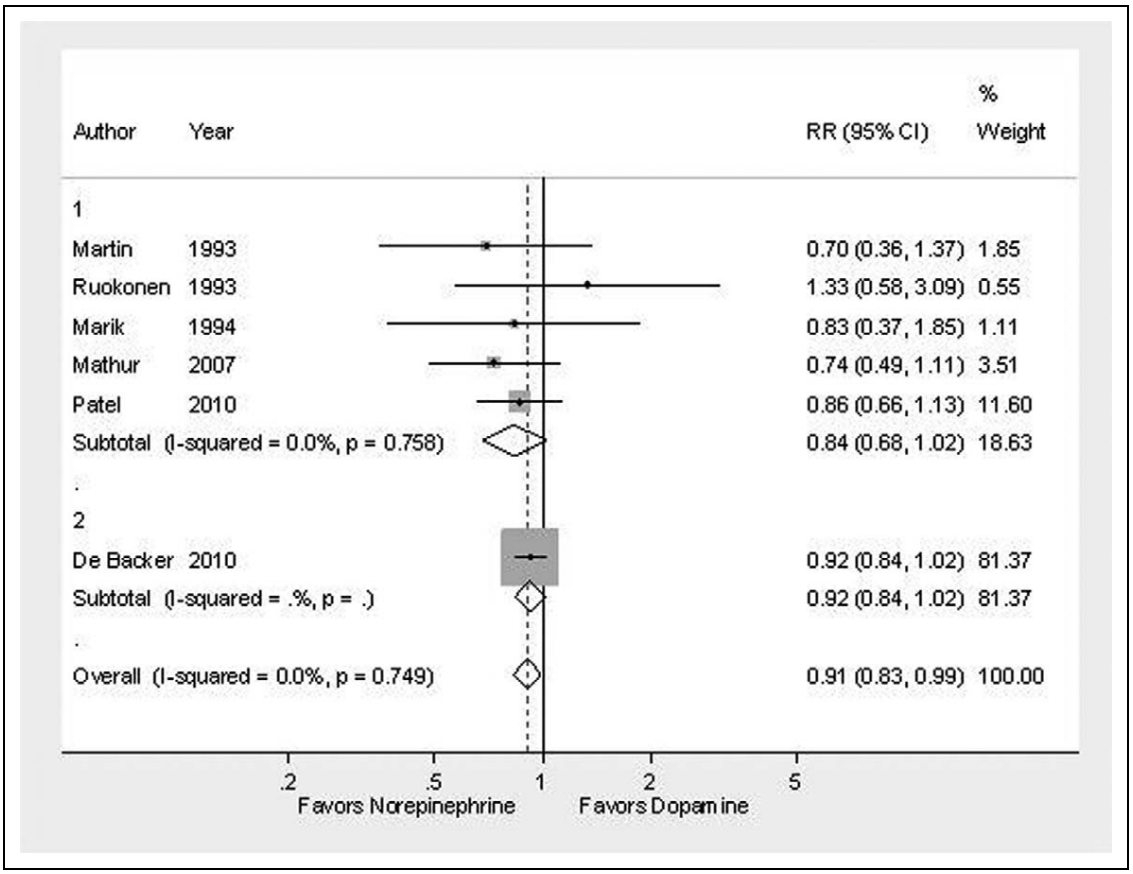

Figure 3. Rate of cardiac arrhythmia (comparison between norepinephrine and dopamine).

Our review has several strengths; we used an exhaustive search strategy and included only relevant randomized clinical trials. Furthermore, we followed the guidelines recently proposed by PRISMA and used *Cochrane's risk of bias tool* to assess the quality of studies.[6,7] The main limitation of our meta-analysis is that it is dominated by the study of De Backer and colleagues.[17] This study included patients' with cardiogenic, septic, and hypovolemic shock; however, the majority of the patients had sepsis as the etiology of shock. We were unable to obtain subgroup data from the authors.

In conclusion, our meta-analysis demonstrated the superiority of norepinephrine over dopamine in a critically ill population of patients with shock in which sepsis was the predominant etiology. Additionally, dopamine was associated with an increased risk of arrhythmias.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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