CRITICAL CARE

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Epinephrine: Is it really the black sheep of vasoactive agents?

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Expanded abstract

Citation

Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C, Troche G, Ricard JD, Nitenberg G, Papazian L, Azoulay E, Bellissant E: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet* 370:676-684 [1].

Background

International guidelines for management of septic shock recommend that dopamine or norepinephrine are preferable to epinephrine. However, no large comparative trial has yet been done.

Methods

Objective: To compare the efficacy and safety of norepinephrine plus dobutamine (whenever needed) with those of epinephrine alone in septic shock.
Design: Prospective, multicenter, randomized, double-blind study.
Setting: 19 participating intensive care units in France.
Subjects: 330 adult patients with septic shock. Inclusion criteria were the presence for less than 7 days of: evidence of infection; at least 2 of the 4 criteria of systemic inflammatory response syndrome (SIRS); and at least two signs of tissue hypoperfusion or organ dysfunction. Additionally, subjects had to have had to meet the three following criteria for less than 24 hours: systolic blood pressure less than 90 mm Hg or mean BP less than 70 mm Hg; administration of fluid bolus of at least 1000 mL or capillary wedge pressure between 12 and 18 mm Hg; and need for more than 15 μg per kg bodyweight per min of dopamine or any dose of epinephrine or norepinephrine. Specific exclusion criteria were established to ensure other causes of shock were excluded.
Intervention: Participants were assigned to receive epinephrine (n=161) or norepinephrine plus dobutamine (n=169), which were titrated to maintain mean blood pressure at 70 mm Hg or more.
Outcomes: The primary outcome was 28-day all-cause mortality. The secondary outcomes were survival distribution from randomization to day 90; mortality rates at day 7, 14, at discharge from intensive care and from hospital, and at day 90; systemic hemodynamics; arterial pH and lactate; SOFA score; time to hemodynamic success and time to vaspressor withdrawal. Analyses were by intention to treat.

Results

There were no patients lost to follow-up; one patient withdrew consent after 3 days. At day 28, there were 64 (40%) deaths in the epinephrine group and 58 (34%) deaths in the norepinephrine plus dobutamine group (p=0.31; relative risk 0.86, 95% CI 0.65-1.14). There was no significant difference between the two groups in mortality rates at discharge from intensive care (75 [47%] deaths vs. 75 [44%] deaths, p=0.69), at hospital discharge (84 [52%] vs. 82 [49%], p=0.51), and by day 90 (84 [52%] vs. 85 [50%], p=0.73), time to hemodynamic success (log-rank p=0.67), time to vasopressor withdrawal (log-rank p=0.09), and time course of SOFA score. Rates of serious adverse events were also similar.

Conclusions

There is no evidence for a difference in efficacy and safety between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock. (ClinicalTrials.gov number, NCT00148278).

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Commentary

Surviving sepsis campaign guidelines recommend norepinephrine or dopamine as the first line vasoactive agents for the management of hypotension in septic shock. In contrast, epinephrine is relegated to second or third-line therapy due to adverse effects, including hyperlacatemia, arrhythmias, and decrease in splanchnic circulation. In porcine models, epinephrine has been shown to cause a significant reduction in intestinal mucosal pH along with significant mucosal damage as early as the first three hours [2]. Similarly, in human studies, epinephrine has been shown to decrease fractional splanchnic blood flow [3], increase splanchnic oxygen utilization and CO_2 production, and alter acid base balance. In view of the important role of the integrity of the intestinal epithelium in development of multiple organ dysfunction syndrome and the effects of epinephrine on splanchnic circulation, epinephrine was not considered first-line therapy [4]. However, some studies have suggested that these effects are transient [5]. Previously, no large comparative trial had been performed.

Annane and colleagues conducted a double-blind randomized controlled trial to compare epinephrine to norepinephrine and dobutamine (whenever needed) in septic shock [1]. Theirs was a moderate-sized, well-designed study with clinically important endpoints. The two treatment groups were well balanced at baseline except that the median age was slightly higher in the epinephrine group than in the norepinephrine plus dobutamine group. Unfortunately, no differences were seen in short- or long-term mortality, hemodynamic stabilization, resolution of organ dysfunction, or adverse events. In addition, epinephrine did not induce excessive cardiovascular adverse effects, including arrhythmias, stroke, or acute coronary events, as compared to norepinephrine.

A few weaknesses of the study merit consideration. First, the study was powered to demonstrate an absolute risk reduction in 28-day mortality of 20%. Very few interventions in critical care reduce mortality by this magnitude. Instead, this study demonstrated a non-significant 6% difference in mortality (34% for subjects receiving norepinephrine and dobutamine compared to 40% for subjects receiving epinephrine), similar to mortality reduction seen with activated protein C. Second, a large number of subjects (1261/1591) screened for the study were not enrolled, thereby limiting the generalizability of the study. Third, by design, all subjects had some exposure to vasopressors prior to enrollment, including >15 μg/kg/min of dopamine or any dose of epinephrine or norepinephrine. This exposure, though less than 24 hours, may have confounded the effects of vasoactive agents and the ability to detect a difference in outcomes.

Recommendation

In conclusion, this study is unlikely to change current recommendations for use of vasoactive agents in septic shock. Although cardiovascular adverse effects were similar for epinephrine and norepinephrine with dobutamine, the study was not adequately powered to assess small differences in mortality. The non-significantly higher mortality for subjects receiving epinephrine highlights the need to conduct larger studies before considering epinephrine as a first line agent for management of septic shock.

Competing interests
The authors declare no competing interests.

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