CJEM Journal Club

Dopamine versus norepinephrine in the treatment of shock

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Clinical question
Which vasopressor agent, norepinephrine or dopamine, is superior in the treatment of shock?
Article chosen
De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779-89.
Study objective
The authors of this study set out to compare 28-day mortality in patients with shock who were treated with either dopamine or norepinephrine as initial vasopressor therapy. The authors' secondary outcome measures included mortality beyond 28 days and adverse events associated with each agent.

BACKGROUND

Physicians have several options to choose from when instituting vasopressor therapy for patients in shock.[1] Among these choices, norepinephrine and dopamine are the two most frequently initiated as first-line therapy. For instance, in the septic shock subset, use of either of these agents is recommended as first-line treatment in the Surviving Sepsis Campaign.[2] Physiologic models have been proposed to suggest the superiority of one over the other, but neither has consistently been shown to be advantageous. Nonrandomized clinical studies have shown the benefit of both dopamine and norepinephrine.[3,4] However, few randomized studies have explicitly addressed the question of whether one vasopressor produces better outcomes over the other when used in the treatment of shock.

STUDY DESIGN

This double-blind, randomized, controlled study was conducted in eight intensive care units (ICUs) in Belgium, Austria, and Spain. A total of 1,679 patients judged to require a vasopressor agent were randomized to receive either dopamine, which could be increased incrementally to a maximum dose of 20 μg/kg/min, or norepinephrine, which could be increased to a maximum dose of 0.19 μg/kg/min. The dopamine and norepinephrine solutions were administered from preprepared vials to maintain blinding for the treating doctors and nurses. If, despite receiving the maximum dose of the study drug, the patient remained in shock, open-label norepinephrine was added. If the decision was made to reduce the amount of vasopressor therapy, the open-label norepinephrine was withdrawn first, before the study drug.

POPULATION INCLUDED AND STUDIED

Patients were included in the study if they met the following criteria:

1. 18 years of age or greater
2. Shock, of any etiology, defined as mean arterial pressure (MAP) $<$ 70 mm Hg or systolic blood pressure (SBP) $<$ 100 mm Hg and signs of tissue hypoperfusion (altered mental status, mottled skin, urine output $<$ 0.5 mL/kg or lactate $>$ 2 mmol/L)

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despite a minimum of 1 L of intravenous crystalloid or 500 mL of colloid administered

Patients were excluded from the study if they had

1. Already received a vasopressor agent for more than 4 hours during the current episode of shock
2. A serious arrhythmia
3. Been declared brain dead

OUTCOMES MEASURED

The primary outcome measured was the mortality rate at 28 days. Several secondary end points were also examined. Among the most clinically important were mortality in the ICU, in the hospital, and at 6 and 12 months and adverse effects, including the rate of arrhythmias (ventricular tachycardia, ventricular fibrillation, or atrial fibrillation).

RESULTS

After 1,600 patients, study enrolment was halted because of a predefined stopping rule that met the criterion for futility (a lack of difference between the two study drugs for the primary end point of 28-day mortality). The 28-day mortality in the dopamine group was 52.5%, compared to 48.5% in the norepinephrine group ($p = 0.10$). No significant difference was found in mortality rates in the ICU, in the hospital, or at 6 or 12 months (Table 1).

The baseline characteristics of the two groups were similar. The majority of patients enrolled had sepsis as the etiology of their shock (62%). The other two defined subgroups were cardiogenic and hypovolemic shock. An a priori defined subgroup analysis was conducted on these three groups. Although the authors did not stratify the randomization of the subgroups, the baseline characteristics listed among each of the subgroups appear to be similar. No analysis was conducted to ensure that two potentially important confounding treatment variables, initiation time of antibiotics for patients with septic shock and the rates of use of thrombolytics for patients with acute myocardial infarction, were similar between treatment arms. Accepting these limitations, those patients with cardiogenic shock had an increased rate of death if randomized to the dopamine group ($p = 0.03$).

Patients in the dopamine group were found to have a significantly increased risk of developing arrhythmias compared to the norepinephrine group (24.1 % v. 12.4%; $p < 0.001$). As well, more people were vasopressor support free at 28 days in the norepinephrine group than in the dopamine group ($p = 0.01$).

STUDY CONCLUSION

Despite there being no significant difference in the primary end point, death at 28 days, the authors concluded that "serious concerns" were raised about dopamine therapy because of the increased rate of arrhythmias in the dopamine group and increased mortality in the subgroup with cardiogenic shock.

COMMENTARY

Shock is frequently encountered in the emergency department and is associated with high rates of mortality and morbidity. Hemodynamic treatment priorities include fluid resuscitation followed by administration of vasopressors to improve blood pressure and tissue perfusion, even though there is no evidence that the use of vasopressors improves patient outcomes. The choice of vasopressor agent until this point has largely depended on physician or institution preference, guided by physiologic models and observational evidence. Prior to this study, 62 patients had

Table 1. Mortality rates

	Dopamine (%)	Norepinephrine (%)	*p* Value
In the intensive care unit	50.2	45.9	0.07
During the hospital stay	59.4	56.6	0.24
At 28 days	52.5	48.5	0.10
At 6 months	63.8	62.9	0.71
At 12 months	65.9	63.0	0.34

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been enrolled in randomized trials involving these agents.[5]

The study's primary end point, death at 28 days, failed to identify a superior agent. However, in subgroup analysis, those patients with cardiogenic shock in the dopamine group had a higher mortality than patients in the norepinephrine group. This finding is counter to published guidelines, including those of the American Heart Association (AHA), which recommend dopamine in patients with shock secondary to an acute myocardial infarction.[6] It is recognized that the AHA recommendation is based on low-level evidence and expert consensus.

Another potential advantage of norepinephrine over dopamine in this study was a lower incidence of arrhythmias, although this had no impact on rates of survival. A prospective study conducted by Patel and colleagues also found a significantly greater incidence of arrhythmias with dopamine compared to norepinephrine (dopamine, 19.4%; norepinephrine, 3.4%; $p < 0.0001$).[7] In the De Baker and colleagues study, this difference did not result in mortality benefit, as shown in the primary end point.[8]

There are a few concerns with this study's design. Shock was defined as MAP $<$ 70 mm Hg or SBP $<$ 100 mm Hg despite adequate fluid resuscitation, defined as 1 L of crystalloids or 500 mL of colloids. Previous literature[9] and general opinion suggest that this may be inadequate fluid resuscitation.[10] Certainly, a "one size fits all" model does not apply as some patients are more fluid depleted than others. It is difficult to assess how this may have impacted the comparison between dopamine and norepinephrine. It should be noted that in the supplementary appendix, Figure 4, panel G shows that patients in both groups received an average of 4 to 4.5 L of fluid on day 1 in both arms of the study.

A second concern is the issue of equipotency between 0.19 μg/kg/min of norepinephrine and 20 μg/kg/min of dopamine.[10] Although expert opinion may support these doses, there is no convincing evidence to support this claim.

CONCLUSION

This pragmatic study was generally well designed, and the potential concerns listed above do not diminish the conclusions of the study. There was no significant difference in mortality between dopamine and norepinephrine in the treatment of shock. Although fewer arrhythmias were associated with norepinephrine than with dopamine, this had no impact on outcomes. As well, outcomes were improved in the subgroup analysis of patients with cardiogenic shock who received norepinephrine. Given the lack of superiority of one agent in the primary outcome, it may well be important that the next large randomized trial include a placebo arm to determine if vasopressors offer any outcome benefit to patients in shock. Subgroup analysis suggests that previous AHA recommendations that supported the use of dopamine in cardiogenic shock should be reconsidered.

Competing interests: None declared.

Keywords: dopamine, norepinephrine, review

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