Critical Review Form

Therapy

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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Objective: **"To evaluate whether the choice of norepinephrine over dopamine as the first-line vasopressor agent could reduce the rate of death among patients in shock". (p. 780)**

Methods: **Multicenter trial at eight hospitals in Belgium, Austria, and Spain between December 2003 and October 2007. Inclusion criteria included age > 18 years, in whom a vasopressor was used to treat shock. Shock was defined as MAP < 70 mmHg or SBP < 100 m Hg after 16 crystalloid or 500 cc colloids (unless CVP >12 mmHg or pulmonary artery wedge pressure > 14 mmHg) when signs of end-organ perfusion were present (altered mental status, mottled skin, urine output <0.5 mL/kg for one hour, serum lactate > 2 mmol/L). Exclusion criteria included age < 18 years, vasopressor therapy > 4 years before enrollment, serious arrhythmia (a fib > 160 bpm or ventricular tachycardia), or brain-dead.**

Randomization was stratified by ICU. Doses were determined by weight and could be increased by protocols (dopamine 2 µg/kg/min to maximum 20µg/kg/min, norepinephrine 0.02 µg/kg/min to a maximum of 0.19 µg/kg/min). The target BP was determined by the physician caring for each patient. If still hypotensive after the maximum vasopressor dose was attained, then open-label norepinephrine was added. Open-label dopamine was not allowed at anytime. If vasopressors were weaned, the open-label margin was weaned first then the study drug. If patients were re-admitted to the ICU within 28-days then the study drug was re-instituted first "allowing maximal exposure to the study drug" (p. 781). If an adverse event occurred, then the physician-in-charge could withdraw the patient from the study and switch the patient to open-label therapy.

The primary outcome was 28-day mortality. Secondary endpoints included death rates in the ICU, in the hospital, or at 6- and 12-months. In addition, the investigators assessed ICU length of stay, number of days without need for organ support, time to attainment of hemodynamic stability and use of dobutamine or other inotropic agents. Adverse events included arrhythmias, myocardial necrosis, skin necrosis, limb ischemia, or secondary infections. APACHE II scores and SOFA scores were calculated respectively at the time of enrollment and daily for one week (then weekly to Day 28).

Based upon previous observational data, the investigators anticipated 80% power to show 15% relative mortality difference with two-sided alpha if 765 patients were recruited in each group. However, recognizing the inaccuracy of observational trials to estimate effect size, the authors planned a sequential trial deign with two-sided alternatives to analyze the data every 100 patients and stage the trial early if one of three pre-defined situations arose: 1) NE superior to DA; 2) DA superior to NE; or 3) no difference between the two. After the first 1600 subjects were enrolled this independent statistician advised that the trial be stopped.

Data were analyzed with a Cox proportional hazards model "to evaluate the influence of potential confounding factors on the outcome" by including variables with p < 0.20 on univariate analysis. The investigators also preplanned a subset analysis of DA vs. NE on three groups of shock patients: septic, cardiogenic, and hypovolemic.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Randomization was performed in computer-generated, permuted blocks of 6 to 10, stratified according to the participating ICU". (p. 780)
2.	Was randomization concealed (blinded)?	Yes. "Treatment assignments and a five-digit reference number were placed in sealed, opaque envelopes, which were opened by the person responsible for the preparation of the trial-drug solutions. The solutions of norepinephrine or dopamine were prepared in vials or syringes according to the preference of the local ICU. Each vial or syringe was then labeled with its randomly allocated number". (p. 780).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All data were analyzed according to the intention- to-treat principle". (p. 782)

4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "There were no significant differences between the two groups with regard to most of the baseline characteristics". (p. 782). Investigators report small differences "of questionable clinical relevance" in heart rate, $PaCO_2$, SaO_2,PaO_2, and FIO_2 (Table 1, p. 785) In addition, post-randomization MAP changed similarly over time in the two treatment groups. Hydrocortisone (40% NE and 39.7% DA) and recombinant activated human protein C (18.8% DA and 19.1% NE) were used equally commonly between groups. More patients in the DA group required open-label norepinephrine at same point (26% vs. 20% $p < 0.001$).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No.
2.	Were clinicians aware of group allocation?	No. "The doctors and nurses administering the drugs, as well as the local investigators and research personnel who collected data, were unaware of the treatment assignments". (p. 780).
3.	Were outcome assessors aware of group allocation?	No. "The study statistician and investigators remained unaware of the patients' treatment assignments while they performed the final analyses". (p. 782)
4.	Was follow-up complete?	Yes. "All patients were followed to Day 28; data on the outcome during the stay in the hospital were available for 1656 patients (98.6%), data on the 6-month outcome for 1443 patients (85.9%), and data on the 12-month outcome for 1036 patients (61.7%)". (p. 782)
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 1679 patients were enrolled before the trial was halted including 62.2% septic shock, 16.7% cardiogenic shock and 15.7% hypovolemic shock. • More patients in the DA required open-label NE (26% vs. 20%), but the use of epinephrine and vasopressin was similar between the two groups. • Dobutamine was used more frequently in NE but after 12-hours the dose of Dobutamine used was higher in the DA group. • Increases in heart rate were greater in the DA group but there were no significant between group differences in cardiac index, CVP, venous oxygen saturation, or lactate levels. • There were no significant differences in 28-day mortality, ICU/hospital mortality, or longer term mortality between DA and NE via Kaplan-Meier or Cox proportional hazards analysis (adjusting for APACHIE-II score and gender). • No significant difference in ICU or days without need for organ-support. • Arrhythmias occurred in 18.4% (mostly atrial fibrillation) and were twice as common in the DA group (24% vs. 12%, $p < 0.001$). The study drug was stopped far more commonly in the DA group (6.1%) then in the NE group (1.6%, $p < 0.001$). • Although each of the point estimates favored NE, the rate of death at 28 days was significantly higher in the subset with cardiogenic shock treated with DA then with NE (Fig 3. p. 788)
2.	How precise was the estimate of the treatment effect?	The 95% CI's are fairly tight and generally around an OR of 1.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No. These were European ICU patients. Critical EP readers might wonder if these results would apply to ED patients presenting

		within the golden hour for therapy.

2.	Were all clinically important outcomes considered?	No. The investigators evaluated survival and arrhythmia/ischemia complications, but did not assess neurological or functional outcomes that patients care about.
3.	Are the likely treatment benefits worth the potential harm and costs?	There are no major cost differences between NE and DA, but if one agent adversely effects a subset of shock patients with a higher adverse event profile it makes sense to use NE as a first line agent for undifferentiated shock in the ED. Further trials will need to assess the cost-effectiveness of NE relative to other management strategies yet to be developed.

Limitations

1) **Not an ED-based study so critical readers need to ask "are there biologically plausible reasons to question this data in ED populations?"**

2) **Failure to use ED-validated MEDS score for risk stratification of the subset enrolled from the ED.**

Bottom Line

In adult sepsis patients in the ICU dopamine offers no survival advantage over norepinephrine and may increase mortality in cardiogenic shock. In undifferentiated ED patients with shock, NE is the preferred first-line vasopressor for now. Future trials should verity these findings in ED populations.