Critical Review Form
Therapy

PGY-4

Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C, Teboul JL. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care. 2010;14(4):R142.

Objectives: **To test the hypothesis that, "norepinephrine is capable of increasing cardiac output through an increase in cardiac preload…in an observational study performed in a series of septic-shock patients who early received norepinephrine to maintain perfusion in the face of life-threatening hypotension." (p. 2)**

Methods: **This prospective, observational study was conducted over a 16 month period in the medical intensive care unit (ICU) of the Bicêtre University Hospital. Patients with septic shock admitted to the ICU for < 6 hours with a MAP < 65 mmHg in whom the attending physician had decided to start a norepinephrine drip or increase its dose were eligible for inclusion. Exclusion criteria were the need for simultaneous administration of another vasoactive drug, new fluid challenge, or blood transfusion, or the need to modify the vent settings or dosage of sedation drugs.**

All patients had a baseline echocardiogram on ICU admission. The PiCCOplus device was then used to provide continuous measurements of cardiac function (including cardiac index [CI], stroke volume index [SVI], and systemic vascular resistance [SVR]) via trans pulmonary thermodilution. Hemodynamic variables were measures at two time points: before introduction or upward titration of norepinephrine and following achievement of a MAP ≥ 65, assuming the interval did not exceed 2 hours. Patients were then analyzed based on whether they achieved the median MAP value for the entire population or did not achieve this median MAP value. Patients were also analyzed based on whether their left ventricular ejection fraction (LVEF) on initial ECHO was > 45% or ≤ 45%.

There were 105 patients included in the analysis. The median age was 63 years and 68% were male. Mechanical ventilation was employed in 86% of patients and the median SAPS II score was 57. The median MAP prior to norepinephrine introduction or upward titration was 54 mmHg. Norepinephrine was initiated prior to inclusion in 57 patients (54%) but was ineffective in achieving a MAP > 65.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was an observational study,. Additionally, there really weren't two groups being compared to determine a treatment effect.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	N/A
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	N/A There were no treatment or control groups. Instead, patients were analyzed as a whole, then analyzed in subgroups based on initial LVEF and MAP response to norepinephrine.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	N/A
2.	Were clinicians aware of group allocation?	N/A
3.	Were outcome assessors aware of group allocation?	N/A
4.	Was follow-up complete?	Mostly yes. Stroke volume variation (SVV) could only be measured in those patients in whom mechanical ventilation was employed. All other outcome variables were assessed in the entire cohort.
II.	**What are the results ?**	
1.	How large was the treatment effect?	Norepinphrine introduction and titration resulted in a significant increase in CI, SVI, global end-diastolic volume index

		(GEDVI), and cardiac function index (CFI) in the cohort of patients as a whole. • CI increased from 3.2 to 3.6 ($p < 0.05$). • CFI increased from 4.7 to 5.0 ($p < 0.05$). The median MAP achieved after introduction/titration of norepinephrine was 75 mmHg. • Norepinphrine introduction and titration resulted in a significant increase in CI, SVI, GEDVI, and CFI among those whose achieved MAP was < 75 mmHg and among those whose achieved MAP was ≥ 75 mmHg. Seventy-one patients had a baseline LVEF > 45%, while 34 had an LVEF ≤ 45%. • Norepinphrine introduction and titration resulted in a significant increase in CI, SVI, GEDVI, and CFI regardless of baseline LVEF.
2.	How precise was the estimate of the treatment effect?	No measures of treatment effect were calculated and hence there were no available 95% confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Uncertain. Unfortunately, very little information regarding patients' medical history was provided. In addition, this study was conducted in the ICU rather than the emergency department, and did not evaluate the effects of treatments initiated in the ED. The median volume of saline infused in the ICU was only one liter, which is a small volume to give among patients with sepsis; the volume of saline administered prior to ICU admission was not provided.
2.	Were all clinically important outcomes considered?	No. This study only evaluated the effect of norepinephrine on surrogate outcomes, including various markers of cardiac function. Patient-centered outcomes, such as mortality, ICU/hospital LOS, need for renal replacement therapy, need for mechanical ventilation, neurologic

		outcomes, and quality of life were not evaluated.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggests that norepinephrine does not reduce cardiac function, and may in fact increase measures of cardiac function, this finding does not necessarily translate into improved outcomes. It does, however, suggest that norepinephrine use should not have an adverse effect on cardiac function when used to improve MAP in patients with septic shock.

Limitations:

1. **This was an observational study with only a single cohort; the study was not designed to compare the efficacy of two different treatments, but only to study the effect of norepinephrine on cardiac function in patients with septic shock.**

2. **Only surrogate outcomes were measured in this study, with no clear correlation with patient-centered outcomes.**

3. **Very little patient information was provided, specifically regarding past medical history.**

4. **This study was conducted in the ICU, and did not look at the effect of ED interventions (external validity).**

Bottom Line:

This small, observational study conducted in a single ICU in France found that norepinephrine initiation or upward titration increased measures of cardiac function among patients being treated for septic shock. This study did not look at the effect of norepinephrine on patient-centered outcomes, and did not compare norepinephrine to other interventions.