PGY-2

Critical Review Form
Therapy

Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial. Am J Respir Crit Care Med. 2019 May 1;199(9):1097-1105.

Objectives: **"to examine the hypothesis that administering low-dose norepinephrine at the beginning of sepsis-induced hypotension resuscitation accelerates shock control." (p. 1098)**

Methods: **This double-blind, randomized controlled trial was conducted in the emergency department (ED) of Siriraj Hospital, Mahidol University in Bangkok, Thailand between October 2013 and March 2017. Adults (18 years or older) presenting to the ED who met criteria for sepsis and a mean arterial blood pressure (MAP) < 65 mmHg were eligible for enrollment. Exclusion criteria included presence of septic shock criteria for more than one hour prior to randomization, acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active cardiac dysrhythmia, active gastrointestinal hemorrhage, pregnancy, seizure, drug overdose, burn injury, trauma, need for immediate surgery, or advanced-stage cancer.**

Patients were randomized in a 1:1 fashion to either receive a norepinephrine infusion (0.05 µg/kg/min) or to receive a placebo infusion for 24 hours without titration. Infusions were given either peripherally or centrally. All patients received care according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012**. The primary outcome was shock control rate by 6 hours, defined as sustained MAP ≥ 65 with evidence of adequate tissue perfusion. Secondary outcomes were 28-day mortality, hospital mortality, need for mechanical ventilatory support, need for renal replacement therapy, and number of organ support-free days to day 28.**

During the study period, 456 patients were screened, of whom 320 were randomized. After excluding 10 patients who withdrew consent, there were 310 patients in the final analysis, with 155 patients in each group. The median age in the norepinephrine and control groups was 65 and 68, respectively, and 45.8% and 49.7% were male. The median MAP was 56 mmHg and median lactate was 2.8 mmol/L.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion to either a norepinephrine infusion or placebo, along with standard sepsis care and fluid resuscitation.
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?	Yes. "Randomization was performed using a computer-generated randomization table derived from www.randomization.com. This process was performed by an investigator (S.T.) who had no other role in patient enrollment or management." (p. 1099) This should be sufficient to prevent subversion of the randomization process (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All primary and secondary outcomes analyses were based on the intention-to-treat principle." (p. 1099) The authors make no mention of crossover between the groups.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, APACHE II score, the presence of medical comorbidities, infectious source, identified pathogens, and physiologic parameters (including MAP at presentation).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "The other investigators, the patients, the patients' relatives, the attending physicians, and the nurses were all blinded to the study assignment." (p. 1099)
2.	Were clinicians aware of group allocation?	No. See above. It would not be possible, however, to hide the effects of norepinephrine on blood pressure, and clinicians would likely have been able, in many cases, to determine which group the patient was allocated to.
3.	Were outcome assessors aware of group allocation?	No. "The outcome evaluation, data management, and analysis were conducted by

		the principal investigator and a statistician, both of whom were blinded to the patient enrollment and treatment process." (p. 1098)
4.	Was follow-up complete?	Yes. Follow-up information was available for all patients in the final analysis.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• Median time from ED arrival to norepinephrine administration was significantly shorter in the early norepinephrine group than in the standard treatment group (93 min vs. 192 min; P < 0.001). • Shock control at 6 hours occurred more frequently in the early norepinephrine group than in the control group: 76.1% vs. 48.4%, OR 3.4 (95% CI 2.09 to 5.53). • Median time from diagnosis to a MAP ≥ 65 was shorter in the early norepinephrine group than the control group: 3:30 hours vs 4:45 hours, p < 0.001. • Patients in the two group received similar volumes of fluid at every time period. • There was a trend toward lower mortality at 28 days in the norepinephrine group: 15.5% vs. 21.9%, RR 0.79 (95% CI 0.53 to 1.11). There was no difference in hospital mortality. • There was no difference in need for mechanical ventilation or renal replacement therapy between the two groups, and no difference in organ support-free days to day 28.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	

1.	Were the study patients similar to my patient?	Uncertain. While this study was conducted in Thailand, the admitting hospital was a large urban center, and the patients met strict criteria for sepsis with hypotension. Patients had a fairly high rate of medical comorbidities (nearly half with hypertension, a third with diabetes, and a quarter with malignancy) which would likely be similar to what is seen in our patient population. There may be some differences in medical care between our institutions that could affect the outcomes. For example, nearly half of the patients in this study were admitted to the medical ward rather than the ICU, while in the US, most patients with this degree of sepsis (particularly if they might be receiving a norepinephrine infusion) would be admitted to the ICU. Overall, it seems reasonable to apply the results of this study to our patient populations (external validity).
2.	Were all clinically important outcomes considered?	Yes. While the primary outcome was somewhat of a surrogate outcome, the authors did also consider several patient-centered outcomes, including mortality, need for mechanical ventilation, need for renal replacement therapy, and organ support-free days. They did not look at ICU or hospital length of stay or duration of antibiotic therapy.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. Based on this single-center study, an infusion of low-dose norepinephrine initiated early in the management of sepsis with hypotension resulted in resolution of shock more quickly, with a trend toward lower mortality. Further studies will be needed to validate these results and potentially show a difference in more patient-centered outcomes.

Limitations:

1. **There was some differences in the way patients in this study were managed compared to management our institution (external validity):**
    a. **Not all patients were treated in the ICU: after initial resuscitation in the emergency room, patients who required endotracheal intubation for mechanical ventilation, required initiation of renal**

replacement therapy, and/or required invasive hemodynamic monitoring were transferred to the medical ICU.

b. Nurse to patient ratio was 1:1 in ICU and 1:3 in general medical ward, compared to lower nurse to patient ratios at our institution.

2. The primary outcome in this study was a surrogate outcome. Although patient-centered outcomes were also evaluated, the study was underpowered to detect a potentially clinically significant difference in mortality.

3. This is a single-center study, and the results will need to be validated prior to generalization of these findings.

Bottom Line:

This single-center, double-blinded, randomized controlled trial found that early administration of a low-dose norepinephrine drip for patients with sepsis and initial hypotension resulted in higher rates of shock control at 6 hours OR 3.4 (95% CI 2.09 to 5.53) compared with standard care. While there was a trend toward decreased mortality, this result did not achieve statistical significance.