Early low-dose norepinephrine in patients with septic shock

Kenneth Nugent MD, Camilo Pena MD

Permpikul and co-authors published the results from the CENSER trial (Early Use of Norepinephrine in Septic Shock Resuscitation) in the May issue of the *American Journal of Respiratory and Critical Care Medicine*.[1] These authors randomized 310 patients into an early low-dose norepinephrine arm and into a placebo arm. All patients received conventional standard therapy, including antibiotics, fluid resuscitation, and open label norepinephrine when needed. The endpoint in this trial was the control of shock within six hours of diagnosis based on a mean arterial blood pressure greater than 65 mmHg for two consecutive readings, improvement in renal function based on urine output greater than 0.5 ml/kg/hr for 2 consecutive hours, and a decrease in serum lactate by greater than 10 % from baseline. Patients in the treatment group received norepinephrine within 93 minutes after diagnosis at a rate of 0.05 µg/kg/minute for 24 hours. Shock control was significantly higher in the early norepinephrine treatment group (76.1%) than in the control group (48.4%). There were no differences in the fluid administered in the first hour, the first 6 hours, the first day, or the first 3 days in the 2 groups. There were no differences in mortality (15.5% early norepinephrine vs 21.9% control), the requirement for renal replacement therapy (12.3% norepinephrine vs. 14.8% control), or mechanical ventilation (37.4% norepinephrine vs. 38.1% control) between the two groups. Patients in the early norepinephrine group were less likely to develop cardiogenic pulmonary edema (14.4% norepinephrine vs. 27.7% control) or a new onset arrhythmia (11% norepinephrine vs. 20% control). The maximum dose of norepinephrine used in both groups was 0.1 µg /kg/minute. The patients in the early norepinephrine group received vasopressors for 2 days; patients in the control or standard treatment group received vasopressors for 3 days. These investigators did not use vasopressin in this trial.

Corresponding author: **Kenneth Nugent**
Contact Information: Kenneth.nugent@ttuhsc.edu
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This management strategy provided better shock control within six hours without important effects on fluid requirements, renal replacement requirements, mechanical ventilation, or mortality. How can we explain these drug effects, and are these effects important? The answer depends on the effect of sepsis on the macrovascular circulation, the microvascular circulation, and cellular metabolism and will need to consider the heterogeneity of tissue involvement in sepsis and the timeframe in the disease course at the initiation of evaluation and management of the patient with sepsis. Analysis will also depend on drug pharmacology with consideration of both the dose and the duration of drug treatment. Norepinephrine has alpha-1, beta-1, and beta-2 adrenergic activity and can cause vasoconstriction, increased cardiac contractility, and some metabolic effects (hyperglycemia and increased lactate production), and these effects likely contribute to improved short-term outcomes.

The normal physiology of blood flow to specific tissues depends on metabolic demand, and the arterial blood pressure selectively regulates perfusion and flow to each organ system as these requirements change. With systemic hypotension, the flow to all tissues will be decreased, and the regulatory capacity becomes aberrant due to the inability to adjust the appropriate flow based on metabolic demand. It is well known that the critical closing pressure of the major vital organs is lower than a mean arterial pressure (MAP) of 60 mmHg which means that a MAP between 50- 60 mmHg will be adequate to maintain patent blood vessels.[2] But during some episodes of hypotension the autoregulatory capacity of vessels can be lost and then blood flow in the (some) microcirculations will not be adequate. In addition, during distributive shock, patients develop relative hypovolemia as a result of an increase in vascular compliance with a subsequent decrease in venous return and as a result of capillary leak and loss of fluid into

interstitial spaces. Optimal volume administration, a critical part of the sepsis bundles used in hospitals, should increase the intravascular volume available for distribution to tissues. However, with increased and abnormal compliance of the vasculature, there will be maldistribution of the flow from the inability to adequately regulate the intravascular blood flow based on metabolic demand. This explains the increase in SVO_2 in some patients, indicating an augmented return of oxygen to the central circulation as its extraction has been compromised by an inability to deliver the appropriate flow to the specific organ in need or by impaired intracellular metabolism, and indicates that the SVO_2 may be a poor guide to resuscitation.

Several studies over the last 10 years, including the ProCESS, ARISE and ProMISe trials, have shown that focusing our efforts mainly on intravenous fluid administration does not change the outcomes compared to the current standard of care and suggest that the benefits from current management strategies have plateaued.[3] This suggests that we need for better tools to evaluate and manage patients and that we need to review fluid administration goals in individual patients and avoid fixed formulas during the initial resuscitation. The early administration of norepinephrine or other vasoactive medications might improve outcomes, and these considerations led to the CENSER trial. This study used a composite outcome to assess the "control" of shock but was not powered to assess mortality. It does provide a new approach to management of circulatory failure in one of the most common diagnoses and supports the need for larger randomized controlled trials.

This trial demonstrated that the early use of norepinephrine reversed shock in the majority of patients (76%) within 6 hours.[1] However, this outcome depends on the measurement of arterial blood pressures at a single vascular site in patients, and this pressure probably does not reflect the pressures in all organs in patients with sepsis. In addition, this single blood pressure does not reflect the distribution of blood flow to these tissues. This trial also demonstrated norepinephrine increased urine output to the target level within 6 hours in 69% of patients. This provides information about tissue level drug effect which presumably reflects improvement in the microvascular circulation, at least in part. But, this outcome likely overestimates the real renal benefit, as many of these patients developed acute kidney injury, and it is well known that urine output in an injured kidney becomes an unreliable measure of intravascular volume and restored blood flow. Finally, norepinephrine decreased a lactate levels in these patients. This could reflect decreased production of lactate secondary to better perfusion of tissues or to improved cellular function or it could reflect increased lactate clearance.

Do studies in the literature support these possibilities? Miranda and colleagues reviewed microcirculatory dysfunction in sepsis and emphasized the heterogeneity of dysfunction in the microcirculation and the complexity of events in patients with sepsis.[4] Vellinga and colleagues reported an analysis of the relationship between central venous pressure (CVP) measurements and microcirculatory blood flow based on sublingual imaging.[5] This study included 70 patients and demonstrated that patients with higher CVPs had significant reductions in microcirculatory blood flow, and these authors suggested that the elevated CVP may act as an outflow obstruction of organ perfusion. Veenstra and colleagues measured total vessel density using *in vivo* microscopy.[6] They noted that microvessel density increased with fluid administration in both cardiac surgery patients and patients with sepsis but that there was a poor correlation between the fluid volume administered and the change in total vessel density in sepsis patients. Thooft reported that norepinephrine increased cardiac output, increased peripheral vessel density, and decreased lactate.[7] Hernandez et al noted that the requirement for high levels of norepinephrine associated with high lactate levels in septic patients was associated with decreased microvessel density.[8] Harrois et al reviewed the complexity of mitochondrial function in sepsis and suggested that peroxynitrate was an important factor in the development of mitochondrial dysfunction.[9] Regueira demonstrated that norepinephrine increased blood pressure and improved hepatic mitochondrial function in an experimental sepsis model using endotoxin in pigs.[10] Hamzaoui et al reviewed the use of norepinephrine

septic shock and discussed the best timeframe for its administration and the optimal dose.[11] These investigators concluded that a low diastolic arterial pressure was a good marker for depressed vascular tone and that the early use of norepinephrine in these patients was appropriate. They suggested the addition of vasopressin in cases with refractory hypotension. Lesur reviewed the literature on hemodynamic support in the early phase of septic shock and reached a final conclusion that "unresolved questions are bigger than the quality of evidence."[12]

In this summary, the management of patients with sepsis requires rapid evaluation and treatment. Fluid administration is crucial but should be individualized according to the clinical profile of each patient. The best tools to assess the circulatory volume and blood flow are still missing. Several recent trials have proven that a minimalistic approach to sepsis based on correcting one variable at the time does not change the outcomes; by addressing key hemodynamic abnormalities early in treatment we may be approaching a new era of sepsis management. Early use of norepinephrine may improve outcomes.[1] Patients with refractory shock and high norepinephrine requirements probably benefit from the use of vasopressin and hydrocortisone.[11]

Keywords: norepinephrine, sepsis, shock, randomized controlled trial

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