Commentary

Choice of vasopressor in septic shock: does it matter?

Gourang P Patel and Robert A Balk

Rush Medical College, Rush University Medical Center, 1753 West Congress Parkway, Chicago, Illinois 60612, USA

Corresponding author: Robert A Balk, rbalk@rush.edu

Published: 6 November 2007
This article is online at http://ccforum.com/content/11/6/174

Critical Care 2007, **11:**174 (doi:10.1186/cc6159)

Abstract

Septic shock is a medical emergency that is associated with mortality rates of 40-70%. Prompt recognition and institution of effective therapy is required for optimal outcome. When the shock state persists after adequate fluid resuscitation, vasopressor therapy is required to improve and maintain adequate tissue/organ perfusion in an attempt to improve survival and prevent the development of multiple organ dysfunction and failure. Controversy surrounding the optimum choice of vasopressor strategy to utilize in the management of patients with septic shock continues. A recent randomized study of epinephrine compared to norepinephrine (plus dobutamine when indicated) leads to more questions than answers.

The significant economic and mortality impact of severe sepsis and septic shock has often resulted in some controversy concerning optimum management strategies, particularly in regard to choice of vasopressor support [1,2]. Annane and colleagues have recently reported on the evaluation of two vasopressor strategies in a multicenter trial of adult French septic shock patients [1]. The results of such controlled clinical trials are valuable to clinicians since septic shock has a reported mortality rate of 40-70% and currently there are no convincing data supporting the use of one vasopressor strategy over another [2]. Current consensus recommendations from 11 different societies in the Surviving Sepsis Campaign guidelines recommend either dopamine or norepinephrine as the initial vasopressor for patients with septic shock [3]. The 2004 practice parameter for hemodynamic support of sepsis in adult patients from the Society of Critical Care Medicine (SCCM) also recommends the use of dopamine or norepinephrine as the initial vasopressor(s) to use in adults with septic shock [4]. Dopamine was the traditional vasopressor choice for shock management, until recent reports of dopamine resistance and/or its potential for tachyarrhythmias resulted in norepinephrine's emergence as the preferred initial vasopressor in North America and Europe [4-6].

In an attempt to determine the optimum vasopressor to use in the management of patients with septic shock, Annane and coworkers conducted a multicenter, prospective, randomized, double-blind, controlled clinical trial evaluating epinephrine versus norepinephrine (with dobutamine, if indicated) in the management of a well-defined adult population with septic shock [1]. The trial involved patients from 19 intensive care units throughout France and was funded by the French Ministry of Health. The study enrolled adults with well-defined septic shock and evidence of organ dysfunction and/or hypoperfusion. The primary outcome parameter was 28 day all-cause mortality. Despite finding a significantly higher arterial lactate level and lower pH during the first four days of therapy in the epinephrine treated patients, there was not a significant difference in 28 day all-cause mortality or other important outcome parameters. Specifically, there was no significant difference in discharge from the intensive care unit (ICU) or hospital, hemodynamic parameters, vasopressor withdrawal or organ dysfunction between the two treatment strategies. Importantly, there was also no difference in adverse events, such as arrhythmias or cardiac, neurologic, or ischemic events [1].

As we consider these intriguing results from the study by Annane and coworkers we are impressed by the intricacies of study design and acknowledge their use of an expanded definition for early septic shock in the inclusion and exclusion criteria for study enrollment. The study was multi-centered, randomized, with a double-blind treatment algorithm. The study participants were reasonably well randomized at the start. The majority of infections were community acquired with the lung as the predominant site of infection. Given the predominance of dopamine use in North America and Europe, we were surprised investigators chose to compare epinephrine and norepinephrine [4-6]. A trial design comparing norepinephrine to dopamine, epinephrine, and possibly vasopressin or phenylephrine would have had more

ICU = intensive care unit; SCCM = Society of Critical Care Medicine.

clinical relevance for physicians in North America and Europe [4-6]. The use of epinephrine as an initial vasopressor for the management of septic shock would represent a significant paradigm shift for North America and a majority of Europe [5,6].

In regard to the study results, it is remarkable that the 28 day all-cause mortality rate was 40% in the epinephrine and 34% in the norepinephrine patients [1]. This impressive mortality rate is lower than typical reports of 40-70% for septic shock patients and raises questions regarding the reason for the improvement in 28 day all-cause mortality rate [2]. This observation is even more curious in light of the increased arterial lactate and lower pH in the epinephrine group over the first few days of management. Even though there was recovery of this metabolic derangement by the fourth study day, there did not appear to be any adverse sequelae. The finding that epinephrine can produce exaggerated aerobic glycolysis within muscles, decrease splanchnic and hepatic blood flow, and may increase oxygen consumption, despite an increase in oxygen delivery to the tissues likely explains the increased arterial lactate and reduced pH [4,7,8]. Lactate has been an important surrogate marker for assessing tissue hypoperfusion [9]. Its measurement and prognostic implications have resulted in its incorporation into sepsis bundles which have been widely adopted to guide initial sepsis management [10,11]. Rivers and colleagues also reported a distinct correlation between lactate clearance and outcome in septic shock [9,12]. Increased lactate formation and delayed clearance of lactate have been associated with increased mortality rates in septic shock patients [9]. However, these results demonstrate a survival benefit irregardless of the early increases in lactate formation and presumed decrease in clearance. The explanation for the positive survival benefits could be related to the potential impact of the high prevalence of steroid use (approximately 80% of all patients) in this study. This percent of patients managed with corticosteroid replacement therapy is higher that the typical sepsis trial and represents yet another controversial area of sepsis management [5]. Finally, it is noteworthy that adverse events reported during this trial were similar. The authors also evaluated the patients for significant ischemic events involving the cardiac, neurologic, or peripheral circulation and again there were no significant differences between the two groups, supporting the safety of epinephrine in this study population.

We applaud the efforts of the French investigators to determine if there is a preferred vasopressor to use in septic shock. The current study was particularly well-done, but unfortunately, did not answer the question and raised additional questions for the practicing intensivists. The excellent survival results of this current trial (approximately 60%) for both epinephrine and norepinephrine treated patients raises the question of whether the excellent outcome was reflective of the vasopressor strategy, increased corticosteroid use, or another variable. The epinephrine outcomes were even more impressive in light of the initial increase in arterial lactate and decrease in pH observed in these patients compared to the norepinephrine treatment. To help answer these questions and determine if there is a "best vasopressor" we need another large, multicenter, prospective, randomized, controlled trial to compare norepinephrine, dopamine, and epinephrine. Until this data becomes available, it appears that there is no clear "best vasopressor" to use in the management of adults with septic shock.

Competing interests

The authors declare that they have no competing interests.

References

1. Annane D, Vignon P, Renault A, Bollaert EP, Charpentier C, Martin C, Troche G, Ricard JD, Nitenberg GN, Papazian L, Azoulay E, Bellissant E, for the CATS Study Group: **Norepinephrine plus dobutamine versus epinephrine alone for the management of septic shock: A randomized trial**. *Lancet* 2007, **370:**676-684.
2. Russel JA: **Management of sepsis**. *N Engl J Med* 2006, **355**: 1699-1713.
3. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, *et al*.: **Surviving Sepsis Campaign Guidelines for the management of patients with sepsis and septic shock**. *Crit Care Med* 2004, **32:**858-873.
4. Hollenberg SM, Ahrens TS, Annane D, *et al*.: **Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update**. *Crit Care Med* 2004, **32:**1928-1948
5. Levy B, Dusang B, Annane D, Annane D, Gibot S, Bollaert PE, and the College Interregional Des Reanimateurs du Nord-Est: **Cardiovascular response to dopamine and early prediction of outcome in septic shock: A prospective multiple-center study**. *Crit Care Med* 2005, **33:**2172-2177.
6. Sakr Y, Reinhart K, Vincent JL, Spring CL, Moreno R, Ranieri M, De Backer D, Payen D: **Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study**. *Crit Care Med* 2006, **34:**589-597.
7. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, Nabet P, Larcan A: **Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study**. *Intes Care Med* 1997, **23**:282-287.
8. Seguin P, Bellissant E, Le Tulzo Y, Laviolle B, Lessard Y, Thomas R, Malledant Y: **Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock**. *Clin Pharm Ther* 2002, **71**:381-388.
9. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, for the Early Goal-Directed Therapy Collaborative Group: **Early-goal directed therapy in the treatment of severe sepsis and septic shock**. *N Engl J Med* 2001, **345:**1368-1377.
10. Levy MM, Pronovost PJ, Dellinger RP, Townsend S, Resar RK, Clemmer TP, Ramsay G: **Sepsis change bundles: Converting guidelines into meaningful change in behavior and clinical outcome**. *Crit Care Med* 2004, **32**:S595-S597.
11. Kortgen A, Niederprum P, Bauer M: **Implementation of an evidenced-based "standard operating procedure" and outcome in septic shock** *Crit Care Med* 2006 **34**:943-949.
12. Nguyen HB, Rivers EP, Knobloch BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC: **Early lactate clearance is associated with improved outcome in severe sepsis and septic shock**. *Crit Care Med* 2004, **32**:1637-1642.