

Is Vasopressin Increasing or Decreasing Mortality in Patients with Septic Shock?

To the Editor:

In their prospective observational cohort study, Micek et al. investigated 137 patients with septic shock treated with norepinephrine (NE) with or without vasopressin [1]. In a multivariate subgroup analysis, the authors found additional vasopressin administration to be the most significant independent risk factor for the 28-day mortality rate. The authors also reported that vasopressin administration itself is associated with a higher mortality rate than NE alone.

Because of the study design (observational, not randomized), the results are appropriate only to generate a hypothesis that has to be tested in a randomized, controlled trial. The results of such a trial (Vasopressin and Septic Shock Trial; VASST) suggest that there is no significant difference in the overall mortality rate in patients treated with either NE alone or the combination of NE and low-dose vasopressin (max. 0.03 U/min) [2]. However, a pre-defined a priori analysis provided evidence that among the subpopulation with less severe sepsis (NE dose < 15 mcg/min), vasopressin infusion was associated with a significantly reduced 28- and 90-day mortality rate. In view of these results, vasopressin infusion in septic shock in doses not exceeding 0.03 U/min has to be regarded as a safe treatment option.

Notably, patient characteristics and process-of-care variables revealed statistically significant differences between the two subgroups. In this context, it is noteworthy that patients treated with vasopressin had higher body mass indices and more acquired organ failures, as well as a greater necessity for mechanical ventilation and treatment with drotrecogin alfa activated than the patients treated with NE only. In addition, there was a tendency toward higher Acute Physiology and Chronic Health

Evaluation (APACHE) II scores in the vasopressin group. Therefore, it is not surprising that the mortality rate was higher in the more severely ill subgroup.

Although the authors emphasized that vasopressin was administered early in the treatment algorithm, there was a great difference between the median (8 h) and mean (27.5 ± 52.8 h) duration of NE infusion prior to vasopressin administration, suggesting that the variables were not normally distributed. It therefore appears that vasopressin was used as a “last resort therapy” in a considerable number of patients. This assumption is supported by the fact that individual physicians had no definite protocol for the addition of vasopressin.

In summary, Micek et al. have not demonstrated that adding low-dose vasopressin to NE infusion increases the mortality rate of patients with septic shock. Future studies are needed to confirm the notion that low-dose vasopressin, when given in the early stage of sepsis, may actually improve survival.

REFERENCES

1. Micek ST, Shah P, Hollands JM, et al. Addition of vasopressin to norepinephrine as independent predictor of mortality in patients with refractory septic shock: An observational study. *Surg Infect* 2007;8:189–200.
2. Russel JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877–887.

Dr. Sebastian Rehberg

Dr. Christian Ertmer

Prof. Dr. Dr.h.c. Hugo Van Aken

PD Dr. Martin Westphal

*Department of Anesthesiology and Intensive Care
University of Muenster
Muenster, Germany*

Response by the Authors

To the Editor:

I thank Doctors Rehberg et al. for their interest in our paper. I agree with their important point that the findings of this study are hypothesis-generating as a result of the study design. Nonetheless, we believe many important points regarding vasopressin plus norepinephrine infusion for septic shock can be derived from this study.

First, the primary analysis focused on differences in processes of care between survivors and non-survivors. As expected, important differences in baseline characteristics and process-of-care variables were found in the two groups. To control for this potential variance, multivariable regression analysis was performed, which revealed four significant predictors of the 28-day mortality rate: Inappropriate initial antimicrobial therapy, lack of goal-directed volume resuscitation, increasing APACHE II score, and the administration of vasopressin in combination with norepinephrine.

Second, a comparison between the two vasopressor regimens was conducted. Whereas the severity of illness in the groups clearly was different, optimal bipartite graph matching was utilized to match patients receiving norepinephrine alone with the most similar patients receiving norepinephrine plus vasopressin. In the graph-matched patients, the administration of vasopressin plus norepinephrine was associated with a significantly higher 28-day mortality rate than vasopressor support with norepinephrine alone. These two modalities of controlling for confounding variables increase our confidence that vasopressin may not be a safe therapy.

*Dr. Scott Micek
Department of Medicine
Washington University
Barnes-Jewish Hospital
St. Louis, MO*