Commentary

Nephroprotective strategies in septic shock: the VANISH trial

Sophia Kwon[1,2], George Crowley[1], Syed Hissam Haider[1], Liqun Zhang[1,3], Anna Nolan[1,4]

[1]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, New York University, School of Medicine, New York, USA; [2]Department of Medicine, Hackensack University Medical Center-Palisades, North Bergen, New Jersey, USA; [3]Department of Respiratory Medicine, PLA, Army General Hospital, Beijing 100853, China; [4]Department of Environmental Medicine, New York University, School of Medicine, New York, USA

Correspondence to: Anna Nolan, MD, MS. Assistant Professor of Medicine and Environmental Medicine, NYU School of Medicine, Division of Pulmonary, Critical Care and Sleep, New Bellevue, 7N Room 24, 462 1st Avenue, New York, NY 10016, USA. Email: anna.nolan@med.nyu.edu.

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Overview of the VANISH trial

In the August issue of *JAMA*, Gordon and colleagues compared the outcomes of renal failure in septic shock between early vasopressin and norepinephrine treatment (1). The investigators utilized a randomized factorial (2×2), double blinded study and recruited subjects from 18 adult intensive care units in the United Kingdom over a 2-year period. Subjects were enrolled if they were within 6 hours of septic shock diagnosis and required vasopressors even after fluid resuscitation, were randomized to (I) vasopressin and hydrocortisone; (II) vasopressin and placebo; (III) norepinephrine and hydrocortisone; or (IV) norepinephrine and placebo. The investigators chose kidney-failure-free days as the primary outcome. Secondary outcomes included use of renal replacement therapy, survival, and serious adverse events. Known side effects of vasopressin use including renal hypoperfusion, intestinal hypoperfusion, and myocardial ischemia were monitored. In the current investigation, significant complications were not seen. It was found that early use of vasopressin, compared to norepinephrine, did not improve the number of kidney-failure-free days. Although the study's findings did not support the use of vasopressin as initial treatment, the investigators posited that "confidence intervals included a potentially important benefit for vasopressin and larger trials may be warranted to assess this further."

Sepsis is a public health concern

The incidence of sepsis is increasing, the Center for Disease Control (CDC) has recently spotlighted sepsis as a medical emergency, and its treatment accounts for at least 5% (20 billion US dollars) of hospital costs in the US (2-5). Optimizing treatment of sepsis and septic shock continues to be a significant focus of critical care research; the sepsis treatment guidelines have recently been updated to improve recognition and optimize treatment (6-10). Organ dysfunction remains a significant component of the severity grading of sepsis. Specifically renal impairment is common and carries a higher risk for mortality (11). The degree of renal impairment is a component of the Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA), which is a metric utilized in the new sepsis definitions and guidelines (12). Current guidelines recommend the use of norepinephrine as first line vasopressor therapy after adequate fluid resuscitation. Several studies have advocated for the use of vasopressin as an adjunct or as first line therapy.

Vasopressin in sepsis therapy

Sepsis and it associated end-organ dysfunction is a complex multifactorial disease state. Studies have focused on identifying deficiencies or key mediators that have been attenuated in hopes of providing a therapeutic advantage and effecting a survival benefit. Vasopressin is an endogenously released hormone and hypotension is a significant trigger of its release in the early septic shock. The levels of vasopressin have been reported to decline by 36 hours after the onset of shock (13). Specifically in septic shock there has been a reported depletion of vasopressin when compared to shock due to cardiogenic causes (14). Vasopressin therapy in severe sepsis and shock may improve

vascular tone, has catecholamine-sparing effects, improve short-term urine output, and creatinine clearance (15). Several studies have already been undertaken that study vasopressin as an adjuvant in the treatment in severe sepsis/shock and some have focused on its nephroprotective abilities (16-18). In one of the largest studies to date, the Vasopressin and Septic Shock Trial (VASST), trial over 700 subjects were randomized to receive low dose vasopressin (0.01–0.03 U/min) or norepinephrine (5–15 micrograms/min) and were also allowed to receive open label vasopressors (19). Although they found that there was no significant difference in overall mortality they did identify a lower 28-day mortality (based on promising confidence intervals) in the vasopressin treated group with less severe sepsis. This finding was one of the key inspirations of VANISH (19).

Vasopressin and the kidney

The renoprotective effects of vasopressin have been evaluated in several, smaller studies (20,21). In a post hoc analysis of VASST, the investigators found that although there was a significant decrement in renal risk as assessed by glomerular filtration rate and urine output, this significance was lost when the models were adjusted for confounders in a multivariate regression analysis.

Global comments and future directions

The VANISH group tried to answer some key questions that have arisen from prior investigations. The dosing of vasopressin has been examined in several studies. The VASST investigators dosed vasopressin at half of that used in the current study (18). The VANISH trial used 0.06 U/min titration of vasopressin up to target MAP of 65–75 mmHg, which allowed for flexibility toward clinical indications by the treating physician. Other studies that show a nephroprotective effect with as high as 0.2 U/min of vasopressin spark concern for adverse effects such as ischemia from excessive vasoconstriction. Although in VANISH the investigators found that doubling the dose of vasopressin, compared to that used in VASST, did not lead to a significantly increased number of adverse effects, there was no clear nephroprotective effect identified. There is a need to increase sample size to confirm or refute the trend toward the efficacy of vasopressin in decreasing kidney-failure-free days identified in the current study. Expanded studies may consider investigating a higher dose of vasopressin in evaluation for nephroprotective effects.

Vasopressin, in the context of co-treatment with corticosteroids, has been the focus of many studies (22-25). Several hypotheses for the potential biophysiological interaction between corticosteroids and vasopressin have been offered. Vasopressin binds to V1b receptors in the anterior pituitary, leading to ACTH release, and corticosteroids may restore cytokine-mediated down-regulation of vasopressin receptors. The VASST investigators chose to include hydrocortisone co-treatment arms for both norepinephrine and vasopressin, finding vasopressin and corticosteroid co-treatment had decreased mortality rates compared to those treated with norepinephrine and corticosteroids. In VANISH, although corticosteroids reduced the need for vasopressin requirement, it was not adequately powered to study the effects of hydrocortisone or placebo alone. This important trend should be a focus of future studies investigating the interaction between corticosteroids and vasopressin use. Other factors warranting further investigation include timing of both renal replacement therapy and infusion of vasopressin. The level of hemodynamic monitoring provided and time to sepsis diagnosis and treatment may vary at different centers. In addition, it may be worthwhile to incorporate outpatient medication usage and comorbidities in the assessment, as these confounders may significantly alter outcomes. Finally, studies should include more diverse populations and positive findings will need to be validated in other populations. The VANISH investigators have provided us with food for thought, that will fuel our continuing search for an understanding of the optimal way to incorporate vasopressin in the care of our septic patients.

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Footnote

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