Did the beneficial renal outcomes with vasopressin VANISH?

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Sepsis is the most common cause of infection-related death and is increasing in incidence. This disease state has a high mortality rate and is costly, with annual costs in the United States exceeding $24 billion (1). Therefore, optimal treatment of patients with septic shock is paramount. After aggressive fluid resuscitation, vasoactive agents are the mainstay of therapy to ensure adequate end organ perfusion. However, there are limited data regarding the optimal approach to the utilization of these agents beyond initial therapy. The 2012 Surviving Sepsis Campaign Guidelines (2) recommend norepinephrine (NE) as the first line vasoactive agent and epinephrine, vasopressin (AVP), or, in some circumstances, phenylephrine, as second line agents. However, data are not robust to guide the practitioner to the most appropriate second vasoactive agent to utilize and more information comparing outcomes between agents is needed.

The Vasopressin and Septic Shock Trial (VASST), which compared AVP to NE, is the largest study of secondary vasoactive agents in patients with septic shock (3). These investigators found that the addition of AVP (titrated to a maximum dose of 0.03 units/min) to NE compared to NE monotherapy did not significantly affect mortality. However, AVP decreased total NE requirements and there was suggestion that patients with less severe septic shock allocated to AVP had improved 28- and 90-day mortality (3). Post-hoc analyses of VASST suggest potentially beneficial effects of concomitant corticosteroids with AVP (4) and the influence of genetics on AVP clearance and outcomes (5). An additional post hoc analysis of VASST found that the addition of AVP reduced rates of progressing from acute kidney injury (AKI) risk [in the risk, injury, failure, loss and end-stage kidney disease definition (6)] to failure or loss. Additionally, in patients meeting the risk AKI category at baseline there was a reduction in the need for renal replacement therapy (RRT) and reduced mortality among those treated with AVP (7). The proposed mechanism of these beneficial renal effects with AVP are via vasopressin V1 receptor-mediated efferent renal arteriole vasoconstriction (8) and possibly vasopressin V2 receptor-mediated afferent renal arteriole vasodilation (9), which may work synergistically to increase glomerular filtration. Although these data from VASST suggested a beneficial effect of AVP on kidney function, because this was a post hoc analysis, more data were needed to confirm the findings.

In the August edition of *The Journal of the American Medical Association*, Gordon and colleagues (10) published a randomized, multi-center study of the early use of AVP compared to NE in patients with septic shock: the Vasopressin *vs*. Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial. The primary objective of this study was to determine the effect of AVP on kidney-failure free days, which was defined based on the Acute Kidney Injury Network (11) stage 3 criteria. A 2-by-2 factorial design was utilized where patients with septic shock were randomized first to either AVP (titrated to a maximum dose of 0.06 units/min) or NE (titrated to a maximum dose of 12 mcg/min); if the patient remained hypotensive after the initial blinded vasoactive therapy they were then given either hydrocortisone (50 mg dosed every 6 hours) or placebo. In the 409 patients included in the trial, there was no significant difference between AVP and NE in kidney failure-free days (difference –2.3 days; 95% CI: –13.0 to 8.5 days). However, those randomized to AVP had significantly lower use of RRT in a secondary outcome analysis (difference –9.9%; 95% CI: –19.3% to –0.6%). Additionally, the use of hydrocortisone did not significantly impact mortality rates and no interaction with AVP was

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observed (10).

VANISH is the second largest prospective evaluation of the use of AVP in patients with septic shock published to date, providing more information in this sparsely evaluated area. However, there are several nuances to the study worth discussing. First, it is important to note that in VANISH, patients could be included even if they received open-label vasopressors prior to randomization and study drug initiation. In fact, this occurred in 85% of included patients (10). Due to the emergent need to start vasoactive agents in patients with septic shock, this is understandable because preservation of organ perfusion is imperative. Even though the protocol specified that patients were to be transitioned to either study regimen AVP or NE monotherapy after randomization, a majority of patients in the AVP arm did not have open-label catecholamines titrated off until day 3 of the study. Overall, the use of open-label vasopressors in the beginning of the study has the potential to mask some of the beneficial effects of AVP, and this should be taken into consideration when extrapolating the study findings to practice.

Second, there are many differences in how AVP and corticosteroids were intended to be utilized in VANISH and how they are typically used in practice. In the VANISH protocol, AVP was intended to be initiated as monotherapy, early in septic shock presentation, an approach not currently recommended by guidelines (2). However, as discussed above, due to the frequent use of open-label vasopressors at study drug initiation, patients did not receive initial AVP monotherapy and the population in VANISH was therefore similar to that studied in VASST. Additionally, in VANISH, corticosteroids were started in the early stages of shock, when the MAP goal was not achieved with a relatively low dose of NE (12 mcg/min) or blinded AVP. This design element was implemented because of a potential beneficial interaction between AVP and corticosteroids (which was not demonstrated), and resembles that of a study where corticosteroids were not found beneficial (12). In practice, corticosteroids are often started later in shock at higher vasopressor doses. In addition, significantly more patients in the AVP arm received the second blinded drug (hydrocortisone or placebo) due to persistent hypotension (82% *vs.* 65%; P<0.001). This indicates that although there were no significant outcome differences, the blood pressure effects of AVP were not equivalent to NE at the doses used in the protocol. This finding is consistent with previous studies, which found that AVP doses of 0.15–0.47 units/min were needed to replace NE as the sole vasoactive agent in patients

with septic shock (13,14). Despite promising retrospective data (15,16), monotherapy or early initiation of AVP at doses up to 0.06 units/min appears unlikely to be sufficient to achieve a goal blood pressure in patients with septic shock and adjunctive vasoactive therapy will be needed, which may mask the potential renal benefits of AVP.

The authors mention in the manuscript that although there was no significant difference in kidney failure free days, the spread of the confidence interval does not rule out a clinically significant benefit with AVP. Because the absolute difference in kidney failure-free days between AVP and NE was –4 (95% CI: –11 to 5), the authors are correct in that the confidence interval suggests that there may be up to a five day difference in favor of AVP. However, this interpretation ignores the point estimate of the difference favoring NE and overlooks the possibility of an 11 day difference in favor of NE. Therefore, this statement should be applied cautiously moving forward.

One potentially impactful finding of this study was the reduction in RRT utilization, but this outcome was driven by a difference only in non-survivors. Similar to a previous study (17), those treated with AVP had lower serum creatinine values and higher urine output compared to the NE group. This could have impacted the clinicians' decision to initiate RRT in the AVP group, a decision which was not dictated by the study protocol. Since the lower need for RRT with AVP was not consistent between survivors and non-survivors the clinical implications are unclear. Instead of the drastic improvement in renal outcomes that was hypothesized based on the results of VASST, the renal outcome findings in VANISH were mixed, leaving uncertainties of the true effect of AVP on renal function.

The VANISH trial adds to the slowly growing body of literature regarding AVP's role in septic shock patients, but still leaves many questions. Prior studies have shown a positive effect of AVP use on kidney function (3,7,17) and a positive interaction between AVP and corticosteroid use (4,18), both findings which were not corroborated in VANISH. There are many differences in the prior trials and VANISH, including how AVP was utilized and the timing of corticosteroid initiation. Yet, the difference that led to the discrepancy in results is unknown. Perhaps, there is no true clinical effect of AVP on kidney function, leading to questions about the drug's overall benefit and indication for use. However, despite the investigators' best efforts with the study design, VANISH does not allow for firm conclusions in this regard. Pairing this with the recent, drastic rise in cost of AVP in the United States, maybe use

of AVP should be limited. However, if cost weren't an issue, the VANISH trial seems unlikely to have a large impact on clinical practice. Regardless, randomized trials indicating an outcome benefit and niche for AVP's use are lacking. Unless the appropriate patient population benefiting from AVP use is identified, and because of the cost implications, an argument could be made to begin scaling back AVP use in patients with septic shock.

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Footnote

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