Editorial

Attempting to define and refine vasopressin use in septic shock: the VANISH trial

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Severe sepsis and septic shock are medical emergencies affecting almost 230,000 Americans every year with almost 40,000 deaths with an estimated cost of almost 25 billion dollars (1,2). About 50% of patients with septic shock will develop acute kidney injury (AKI), and the mortality associated with sepsis induced AKI renal failure is as high as 70% (3,4). The prevention and management of renal failure in the septic patient is therefore an active area of interest and research in the critical care community.

In severe septic shock there is a certain degree of vasoplegia that may be resistant to vasopressors necessitating the initiation of a second line agent to maintain mean arterial pressure (MAP) (5). Both vasopressin and norepinephrine (NE) have good response characteristics in all major vascular beds with vasopressin having a slightly better response in the splanchnic circulation (5). Vasopressin acts on an entire family of receptors which include the V1a, V1b and V2 receptors. The receptor of primary interest in raising blood pressure in septic shock is the V1a receptor located primarily on the vascular endothelium. The V2 receptor is linked to osmotic effects and maintaining fluid balance, and is located primarily in the kidneys. The V1b receptor is located in the pituitary and activates release of adrenocorticotrophic hormone (ACTH) (6). Corticosteroids in septic shock seem to reverse the cytokine mediated down-regulation of V1 receptors located in the vascular endothelium and when combined with vasopressin could produce a synergistic effect in maintaining the MAP (7). Plasma vasopressin levels increase rapidly in early septic shock but may become depressed as shock the state continues suspected due to exhaustion of stores in the posterior pituitary and an inability to synthesize and release adequate amounts (8). As a result in severe septic shock there is a relative deficiency of vasopressin since vasopressin levels should be elevated in a shock state and frequently are not (9). Low dose vasopressin (≤0.04 units/min as traditionally described) in septic shock is hence more of a replacement dose to restore expected physiological levels of vasopressin.

Vasopressin is a pure vasopressor and at higher doses has been associated with coronary, digital, and splenic ischemia. In the 1970's esophageal variceal bleeders, prior to endoscopic treatment techniques and octreotide, were often treated with higher doses of vasopressin to decrease splanchnic blood flow and consequentially lower the pressure head in the portal venous system that was driving the esophageal variceal hemorrhage. Vasopressin may increase risk of splanchnic vasoconstriction compared to other vasopressors and at higher doses raises concerns of clinically significant mesenteric ischemia. Vasopressin is a pure vasopressor and decreases cardiac output via vasoconstriction, decrease in heart rate and lack of any inotropic effect. Low cardiac output states would therefore increase the risk of ischemic complications of vasopressin.

Based on rationale for physiologic replacement of vasopressin and studies that supported a potential renal protective effect of vasopressin the vasopressin versus NE

infusion in patients with septic shock (VAAST) trial was performed (10,11). The VASST trial compared NE alone *vs.* NE plus the addition of 0.03 units/min of vasopressin in patients with septic shock (12). No difference in outcome was observed in this trial although it demonstrated the safety of 0.03 units/min vasopressin when added to NE. Following the VAAST trial the Surviving Sepsis Campaign (SSC) in 2008 adopted the recommendation of the option of titrating vasopressin to a max dose of 0.03 units/min either as a second pressor when NE failed to achieve MAP target or added to any dose of NE as a NE sparer potentially restoring expected physiologic levels of vasopressin (13). Of interest two meta analyses comparing vasopressin to other vasopressors produced conflicting results as to preference of vasopressin (14,15).

The rational for the design of the Effect of Early Vasopressin *vs.* Norepinephrine on Kidney Failure in Patients with Septic Shock (VANISH) randomized control trial was based on two sub-group analyses from the VAAST trial (16-18). Vasopressin when added early to subjects enrolled in this VAAST trial (within 12 hours of onset of shock) was associated with improved renal function (17). In addition when hydrocortisone was also used in the vasopressin treatment group there appeared to be a clinical outcome benefit (18). However as this was not the primary outcome of the study it was only hypothesis generating. A secondary analysis of the VAAST trial suggested that in less severe septic shock (NE dose <15 mcg/min), vasopressin along with a corticosteroid seemed to confer both a survival benefit and renal protective ability. In the VAAST trial, corticosteroids when compared to placebo were linked to increased plasma levels of vasopressin in septic shock patients on similar doses of vasopressin.

The VANISH trial was designed to test the hypothesis that vasopressin when used as initial vasopressor up to a dose of 0.06 units/min would decrease renal failure when compared to NE as primary vasopressor therapy. The VANISH trial was conducted in tertiary care ICUs in the UK with the aim to determine if early titratable dose vasopressin was superior to NE in decreasing the number of renal failure free days in patients with septic shock. Patients were evaluated and randomized within 6 hours of onset of septic shock and trial drug was initiated. This allowed for maximal effect of vasopressin hopefully prior to the onset of kidney dysfunction. The trial results showed no difference in the number of kidney failure free days at the 28th day which was the primary study outcome. There was a signal detected as to decreased need for renal replacement therapy (RRT) in the vasopressin group which was consistent with the results of the VAAST trial. A two × two factorial method was used to study both the potential renal protection of early vasopressin administration and the potential synergy of steroids when combined with vasopressin. Patients were randomized to vasopressin with/without hydrocortisone *vs.* NE with/without hydrocortisone with roughly 100 patients per intervention group (four groups). All groups had similar baseline characteristics. The rates of kidney failure and mortality were as expected and per initial statistical calculations. The intervention drug was started within 3.5 hours of the onset of septic shock and both groups achieved their targeted MAPs. The double blinded nature and use of a single company for creation and labelling of all study drugs facilitated blinding and integrity of the trial.

It is disappointing to note that vasopressin did not confer any advantage over NE in decreasing the total number of renal failure free days. Cox regression analysis did not demonstrate any interaction between hydrocortisone and vasopressin. There was no effect on mortality. There was a non-statistically different increase in urine output (UOP) and slightly lower serum creatinine in the vasopressin group. The decrease in the need for RRT in the vasopressin group as compared to the NE group gives the increase UOP and decreased creatinine more credibility. Hydrocortisone compared to placebo did not seem to confer any advantage with respect to either mortality or number of kidney failure free days.

The decision to add hydrocortisone as an additional intervention to create a two × two factorial design is potentially problematic when considering the trial design characteristics and power. A two × two factorial design is typically used to study two unrelated potential interventions in a certain disease. The trial design was linked to the Surviving Sepsis Campaign recommendation to use hydrocortisone only in septic shock patients who remained unstable despite fluid therapy and vasopressor. Therefore, steroids or placebo were only added to study vasopressor when either 0.06 units/min vasopressin or NE at 12 μg/min dosing was achieved and MAP continued to remained below target. Therefore not all patients got steroid or placebo and the power of the study may not have allowed this interaction to be tested adequately. The VANISH trial was interestingly designed and asked good questions but was likely underpowered. There is insufficient evidence in the VANISH trial data to recommend any changes to the current usage for vasopressin as outlined in the 2008 and 2012 SSC guidelines. The decreased need for RRT is

consistent with the VAAST trial and deserves further study. This study offers no additional help in the difficult decision on when to add steroids to the treatment of septic shock.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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