Commentary

Vasopressin versus noradrenaline as initial therapy in septic shock. Is vasopressin-related renal protection doomed to "vanish" in the haze?

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Gordon *et al*. recently reported the results of the multicenter Vasopressin *vs*. Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial comparing the effect of these two potent vasopressors on kidney failure in adult patients with septic shock (1). Rationale for this study was the landmark Vasopressin and Septic Shock Trial (VASST) which found an association between low-dose (0.01 to 0.03 U per minute) vasopressin and decreased mortality in less severe septic shock but no difference between vasopressin and noradrenaline on global mortality or organ dysfunction rates (2). Post-hoc analysis of the VASST study suggested that vasopressin treatment was associated with a trend to reduced progression to renal failure or loss, less need for renal replacement therapy, and reduced mortality in septic shock patients at risk of kidney injury (3). This concurred with earlier small clinical studies demonstrating an improvement in creatinine clearance in vasopressin-treated patients (4,5). Unfortunately, the VANISH study did not find a difference in the number of kidney failure-free days in surviving patients receiving vasopressin or noradrenaline. The observation that, in the vasopressin group, fewer renal replacement therapy was required and that those who did not survive and/or experienced renal failure had less kidney failure-free days procured only some meagre scientific solace (1).

What could be the reasons behind this primary outcome "failure"? Vasopressin adheres to and subsequently stimulates a family of specific receptors located at vascular, pituitary, and renal level. Occupation of the renal receptor produces antidiuretic, vasodilating, and pro-coagulating effects (6) which are clearly not warranted during the course of septic shock! However, these effects occur at low (<10 pmol/L) plasma levels of vasopressin. Septic shock initially generates manifold higher vasopressin concentrations in response to hypotension which then rapidly decline. Low-dose vasopressin infusion in the VASST trial maintained median plasma vasopressin levels above 50 pmol/L throughout therapy (6). Plasma concentrations in the VANISH study were probably even higher since vasopressin was titrated up to a twice higher dose (1). Thus, renal protective effects of vasopressin in septic shock primarily depend upon its ability to maintain global renal and glomerular perfusion pressure in the presence of adequate volume resuscitation (6,7). However, sepsis-induced acute kidney injury (SAKI) is no longer cut down to a classic paradigm of hypoperfusion/ischemia. SAKI can occur in the presence of normal or even increased renal blood flow (8). An intact renal blood flow does not guarantee adequate microvascular perfusion (9). Intrarenal blood flow may also considerably differ between medulla and cortex area (10). Restoring adequate global kidney blood flow and oxygenation often fails to influence corticomedullar blood flow maldistribution nor does it avoid evolution to SAKI (11,12). In addition, sepsis exposes the kidneys to a multitude of intrinsic (systemic inflammation, oxidative stress, microvascular dysfunction, intracellular reactions including mitochondrial damage and apoptosis…) and extrinsic (nephrotoxic drugs and infusions) malefactors (13).

Ample fluid resuscitation is highly recommended before initiating vasopressor therapy. However, an unrestrained preload increase may adversely affect the kidneys by enhancing venous congestion and blocking venous outflow (14). Such augmentation in kidney "afterload"

was found to be associated with an increased incidence and mortality of SAKI (15,16). Being encapsulated, the kidneys are also extremely vulnerable to compression by evolving edema. The VASST study reported no significant differences in fluid volume, fluid balance, or diuretic use during the first 4 days between vasopressin- and noradrenaline-treated patients at risk for SAKI (3). However, no data on baseline or serial preload measurement were provided. It is noteworthy that baseline central venous pressure measurement was not performed in 43% of patients enrolled in the VANISH study (1). Subsequent preload monitoring was omitted, type of resuscitation fluid was not specified, and information on the use of diuretics or potential concomitant nephrotoxic medication was lacking. Moreover, vasopressin-treated patients received more fluid and had lower urinary output than noradrenaline-treated subjects during the crucial first 48 hours of treatment, resulting in a mean total excess fluid of approximately 500 mL. Thus, a negative impact of a higher preload and fluid charge on kidney function in the vasopressin group cannot be excluded.

Finally, the VANISH study results may be clouded by the concomitant corticosteroid treatment. Corticosteroids interact with many relevant signalling pathways involved in human sepsis. A 200–300 mg daily "stress" dose of hydrocortisone is often added to support cardiovascular function in patients with septic shock refractory to fluid and catecholamine infusion (17). Corticosteroids reduce severity and duration of shock which both are meaningful for improving organ perfusion and function. This is illustrated by a post-hoc analysis of the CORTICUS trial which showed a significantly greater likelihood of renal recovery in patients with septic AKI who received steroids (18). Combination of vasopressin with corticosteroids restores receptor responsiveness for vasopressin and enhances anti-inflammatory effects. Hydrocortisone does not alter plasma vasopressin levels but spared vasopressin requirements in the treatment of septic shock (19). Extent, duration and possible individual patient variations of steroid/vasopressin interactions are unknown. Patients treated with low-dose vasopressin plus corticosteroids had lower 28-day mortality compared with noradrenaline plus corticosteroids (35.9% *vs.* 44.7%, P=0.03) and also less organ dysfunction as shown by more days alive and free from shock, ventilation, and renal failure. In contrast, the pattern of organ dysfunction in the vasopressin group was directionally opposite for all these organ failures in corticosteroid-naive patients (20). The interplay between vasopressin and corticosteroid treatment in septic shock definitely requires further study.

The VANISH investigators deserve all respect for endeavouring to demonstrate that conscious use of vasopressin might prevent or attenuate SAKI. Their efforts highlight the inherent complexity of SAKI and underscore that future clinical research on the use of vasopressin in septic shock should take into account potential bias induced by common recommendations on fluid and corticosteroid treatment.

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Footnote

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

Comment on: Gordon AC, Mason AJ, Thirunavukkarasu N, *et al*. Effect of Early Vasopressin *vs.* Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA 2016;316:509-18.

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