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What's new in vasopressin?

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Vasopressin in septic shock

Septic shock is associated with a relative deficiency of the endogenous stress hormone vasopressin. In shock states vasopressin binds to vasopressin receptors on vascular smooth muscle, producing intense vasoconstriction with minimal osmotic effects and resulting in increased blood pressure. Two recent meta-analyses report relative risks (RR) of short-term mortality in favour of vasopressin analogues compared to noradrenaline; however, using different methodologies, one group found this difference to be statistically significant (RR = 0.87, 95 % CI 0.77–0.99) [1] and the other did not (RR = 0.91, 95 % CI 0.79–1.05) [2]. The current Surviving Sepsis Campaign guidelines recommend that vasopressin may be added as an adjunct to noradrenaline in septic shock [3]. This short review aims to give an overview of the latest clinical evidence about vasopressin.

The Vasopressin in Septic Shock Trial (VASST) compared vasopressin to noradrenaline (when added to open label vasopressors) and found no difference in 28-day mortality in the whole septic shock population [4]. However, in an a priori defined subgroup of less severe shock (noradrenaline <15 μg/min), a mortality benefit in favour of vasopressin use was present. The potential survival benefit of vasopressin in less severely shocked patients was also seen in those patients who had the lowest lactate levels [5]. The haemodynamic effects of both noradrenaline and vasopressin were similar, with no difference in cardiac or stroke volume index between the two treatment groups, although there was a greater use of inotropes in the vasopressin group [6]. Vasopressin use was associated with a significant reduction in heart rate particularly in the less severe shock subgroup, potentially due to reduced catecholamine use. This is an interesting observation in view of the recent interest in beta-blockers to treat tachycardia in septic shock [7].

Vasopressin and renal function and potential interaction with steroids

Vasopressin may have beneficial effects on renal perfusion compared to noradrenaline. Post hoc analysis of VASST data identified that vasopressin use in at "Risk" patients, according to RIFLE criteria for acute kidney injury, was associated with lower rates of progression to renal "Failure" or "Loss" and use of renal replacement therapy [8]. Further post hoc analysis of VASST data identified that a combination of vasopressin and steroids was associated with lower rates of mortality and organ dysfunction than a combination of noradrenaline and steroids [9]. Subsequently a pilot study of 61 patients with septic shock found that combining early vasopressin use with hydrocortisone reduced the duration and dose of vasopressin required, but did not alter plasma vasopressin levels [10]. Taken together all these results suggest that vasopressin may have the most benefit in septic shock when used early in less severely shocked patients, titrating up to higher doses if needed and potentially in combination with corticosteroids to prevent further

deterioration, rather than as a rescue therapy in refractory shock. However, as much of this data comes from multiple subgroup analyses we await new evidence from ongoing trials such as the Vasopressin versus Noradrenaline as Initial Therapy in Septic Shock (VANISH) trial (ISRCTN20769191) [11] to confirm or refute these recommendations.

Immune-modulating effects

There is an increasing appreciation that medications used in critical care, such as vasopressors, may have immune-modulating effects. Noradrenaline attenuates monocyte ex vivo cytokine release and inhibits macrophage migration. The immune effects of vasopressin are not fully elucidated but arginine vasopressin co-localises in human macrophages and lymphocytes [12] and may infer immune-modulating properties. It has been postulated that the aforementioned beneficial effects of vasopressin in less severe septic shock, and when used together with steroids, may reflect immune effects. It has recently been reported that patients in VASST treated with vasopressin had greater decreases of plasma concentrations of cytokines over 24 h compared with noradrenaline [13].

Adverse event and pharmacogenetics

All vasopressors can lead to serious adverse events (SAEs), primarily due to the intense vasoconstriction they induce. The prevalence of these SAEs is reported as ranging from 10 to 72 % [14], presumably reflecting the heterogeneity of patient populations, treatment regimens and SAE reporting procedures. A recent meta-analysis reported no evidence of increased SAEs when vasopressin was used to treat vasodilatory shock [2]. This is consistent with data from VASST, which reported no difference in SAEs between the treatment groups (10.3 % vasopressin vs. 10.5 % noradrenaline) [4] and specifically no difference in rates of cardiac ischaemia, assessed by more detailed examination of cardiac enzyme elevations and electrocardiograms in a subset of VASST [15].

This VASST data was combined with data from a non-blinded hospital patient cohort (receiving vasopressin and/or noradrenaline) to determine the frequency, risk factors and outcomes of SAEs [14]. As might be expected this study reported that patients with SAEs had a higher adjusted mortality than those without. There was no evidence that SAEs were related to vasopressin levels, as a similar area under the plasma vasopressin concentration curve was reported for those patients with and without SAEs. A specific genotype (AA) of a single nucleotide polymorphism (SNP), rs28418396 in the 5′ untranslated region of the *AVPR1b* gene, was associated with higher SAE rates in both vasopressin- and noradrenaline-treated patients. The mechanism behind this potential effect is unknown but binding of vasopressin to V1b receptors in the anterior pituitary normally results in adrenocorticotropin hormone release. The same investigators have also reported that another SNP, rs4869317 in the leucyl/cystinyl aminopeptidase gene (also known as vasopressinase), was associated with vasopressin clearance and 28-day mortality rates in these same two cohorts [16].

Selepressin, a selective V1a agonist

Vasopressin binds to all subtypes of the vasopressin receptor V1a, V1b and V2 (Table 1). Vasoconstriction is mediated through V1a receptors with other potentially less desirable effects (in the context of septic shock), mediated through V2 receptors including selective vasodilation, pro-thrombotic and osmotic effects. Because of this it has been suggested that selective V1a agonists such as selepressin may be preferable to vasopressin in septic shock. In an ovine model of pneumonia, selepressin maintained mean arterial pressure, whilst preventing microvascular leak and a net-positive fluid balance [17]. Although early restoration of intravascular volume is an

Table 1 Distribution of vasopressin receptors and associated effects in the management of shock

Receptor subtype	Location	Effect mediated
V1a	Vascular smooth muscle	Vasoconstriction
	Platelets	Platelet aggregation
	Brain	Baroreflex control
	Adrenal cortex	Increased cortisol
	Hepatocytes	Glycogenolysis and glycolysis
V1b	Anterior pituitary	ACTH release
		Prolactin release
	Adrenal medulla	Catecholamine secretion
V2	Collecting duct	Aquaporin 2 synthesis and insertion—water reabsorption
	Vascular endothelium	Selective vasodilatation
		Release of factor VIII and von Willebrand factor

important part of resuscitation in sepsis, avoiding excessive positive fluid balances may be associated with improved outcomes. It will be interesting to see the effect of selepressin in future clinical trials.

Vasopressin use in non-septic states

Vasopressin use has been investigated in a number of other non-septic conditions. Vasopressin either in addition to or instead of adrenaline has been proposed for cardiac arrest. A recent multi-centre randomised controlled trial reported that combined vasopressin–adrenaline and methylprednisolone resulted in improved hospital survival with favourable neurological status compared to adrenaline/placebo (odds ratio 3.28, 95 % CI 1.17–9.20) in patients requiring vasopressors after in-hospital cardiac arrest [18].

Data from the Vasopressin versus Noradrenaline for the Management of Shock After Cardiac Surgery (VaNCS) study (NCT01505231) suggests that vasopressin may improve outcomes in patients with vasoplegic shock after cardiac surgery [19]. In patients randomised to vasopressin there was a lower incidence of acute kidney injury, less use of dialysis, and lower rates of atrial fibrillation.

Finally a review of animal data [20] reported that vasopressin was more effective than other treatments in refractory haemorrhagic shock. The recently completed (but currently unreported) Vasopressin in Traumatic Haemorrhagic Shock (VITRIS) trial (NCT00379522) may provide further information for its use in this context.

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