

# Vasopressin: the preferred vasopressor in sepsis? ... not today, not yet

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Vasopressin acts as both a vasopressor and an antidiuretic hormone, and is deficient in patients with septic shock. It is therefore being increasingly considered as an alternative or additional vasopressor therapy for these patients. Small cases series and a small phase II trial<sup>1</sup> suggest it has clinical benefits, causing some clinicians to rapidly adopt vasopressin as a routine clinical therapy. Although the concept of replacing a deficiency of an endogenous vasopressor with a low therapeutic dose is appealing, we caution that all published clinical studies have been very small, that the risk–benefit ratio is unclear, and that routine clinical use in patients with septic shock is premature. The outcomes from a large international randomised trial are to be reported later in 2006.

Vasopressin is an endogenous nonapeptide, which is synthesised in the hypothalamus, stored in the posterior pituitary, and released in response to hypotension, decreased intravascular volume and hyperosmolality.<sup>2</sup> Vasopressin mediates vasoconstriction by activating V1 receptors on vascular smooth muscle, and has an antidiuretic effect by activating V2 receptors on renal collecting ducts. Vasopressin also increases plasma cortisol concentrations by nitric oxide-mediated release of corticotropin (ACTH) via central V3 receptors.<sup>3,4</sup> Interestingly, low plasma concentrations of vasopressin also mediate vasodilatation of the coronary, cerebral and pulmonary arterial circulations.<sup>5–7</sup> Vasodilatation of these key vascular beds, together with other favourable effects on the kidney (increased urine output and improved renal function despite systemic vasoconstriction) are the key reasons why vasopressin may become a useful adjunct therapy in patients with septic shock, in comparison with conventional non-selective vasoconstrictors used alone.<sup>1</sup>

In septic shock, there is an endogenous deficiency of vasopressin. Vasopressin is stored in the posterior pituitary, but only 10%–20% of the total hormonal pool can be rapidly released.<sup>2</sup> In keeping with this limited capacity for acute release, vasopressin levels are very high in early haemorrhagic and septic shock, but low in established septic and vasodilated shock. Landry and colleagues first reported inappropriately low mean vasopressin levels of 3.1 pg/mL in patients with vasodilated septic shock, compared with 4 pg/mL in normal patients, and an increase to 22.7 pg/mL in those with cardiogenic shock.<sup>8</sup> This led to the

concept of endogenous vasopressin deficiency in patients with septic shock, and to the hypothesis that vasopressin deficiency contributes to their mortality.

Potential mechanisms for vasopressin deficiency include depletion of pituitary stores, autonomic dysfunction during septic shock, and increased vascular release of nitric oxide, which may down-regulate vasopressin production in the posterior pituitary.<sup>2</sup> However, low-dose vasopressin infusions are sufficient to restore the endogenous deficiency — with intravenous infusions of 0.01 IU/min resulting in a plasma level of 30 pg/mL, and 0.04 IU/min resulting in 100 pg/mL.<sup>8</sup> Furthermore, and in keeping with clinical observations in individual cases, higher-dose infusions of vasopressin may be counterproductive.<sup>9</sup> In patients with septic shock, vasopressin infusions in doses of 0.06–1.8 IU/min were associated with decreased cardiac output, decreased oxygen delivery, and gastric mucosal ischaemia suggested by gastric tonometry.<sup>9</sup>

Not only are low infused doses sufficient to restore more “appropriate” blood vasopressin concentrations for patients with shock, but the vascular effects of infused vasopressin are also dose-dependent. In high doses, vasopressin causes non-selective vasoconstriction. In low doses, vasopressin potentiates the alpha effects of noradrenaline and adrenaline, but also causes vasodilatation of the critical vascular beds (coronary, renal, cardiac and pulmonary).

Case reports and small series have reported that vasopressin infusion allows dose-sparing of other infused vasopressors (usually noradrenaline) in various groups of patients with shock, including those with septic shock.<sup>10–13</sup> For example, a retrospective series of 50 patients with septic shock in Vancouver, Canada, reported decreased noradrenaline requirements and increased urine output after varying doses of infused vasopressin.<sup>2</sup> In this series, mortality was very high (85%), perhaps because vasopressin infusions were often commenced in an attempt at salvage when death was imminent.

However, simply replacing one vasopressor with an equivalent alternative is unlikely to improve patient outcomes. The next level of support for vasopressin therapy is found in a small, prospective, phase II randomised trial in septic shock patients in Vancouver.<sup>1</sup> This

## POINTS OF VIEW

study found that a relatively low infused vasopressin dose of 0.06 IU/min was associated with decreased noradrenaline requirements and improved renal function (identified as increased urine output and improved creatinine clearance) compared with patients receiving conventional therapy. This phase II study had insufficient power to assess patient outcomes, and mortality was not reported.

Current knowledge therefore suggests that vasopressin may be beneficial in patients with septic shock by replacing a common endogenous deficiency, which occurs because vasopressin stores and release mechanisms are inadequate in many patients. Vasopressin therapy may then allow lower doses of noradrenaline to be used, reducing its toxicity, and may improve the function of key organs, specifically kidney and lung.

However, clinicians should be clear that a total of only 44 patients have received vasopressin in randomised clinical studies published to date, and that none of the potential benefits related to vasopressin have been supported by a phase III randomised clinical study. Until such results are available, there is no evidence to support the use of vasopressin at any dose as standard clinical therapy in patients with septic shock.

The Vasopressin in Septic Shock Trial (VASST) will shed new light on this intriguing therapy in the near future. VASST received Canadian federal funding to determine whether low-dose intravenous vasopressin to a maximum of 0.03 IU/min would improve patient outcomes in septic shock, without increasing adverse effects. VASST was an investigator-initiated, triple-blind, randomised trial in nearly 800 noradrenaline-dependent septic shock patients in three countries — Canada, Australia and the United States. There were five large Australian sites in three states, and the results will therefore be highly generalisable to patients in Australia and New Zealand. The results from VASST will help clinicians determine whether low-dose vasopressin should become a standard of care internationally for patients with septic shock. VASST completed patient recruitment in April 2006 and will be reporting to the investigators later in 2006.

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## References

- 1 Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002; 96: 576-82.
- 2 Holmes CL, Patel BM, Russell JA, Walley KR. Physiology of vasopressin relevant to management of septic shock. *Chest* 2001; 120: 989-1002.
- 3 Antoni FA. Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. *Front Neuroendocrinol* 1993; 14: 76-122.
- 4 Bugajski J, Gadek-Michalska A, Olowaska A, et al. Role of nitric oxide in the vasopressin-induced corticosterone secretion in rats. *J Physiol Pharmacol* 1997; 48: 805-12.
- 5 Eichinger MR, Walker BR. Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats. *Am J Physiol* 1994; 267: H2413-9.
- 6 Okamura T, Ayajiki K, Fujioka H, Toda N. Mechanisms underlying arginine vasopressin-induced relaxation in monkey isolated coronary arteries. *J Hypertens* 1999; 17: 673-8.
- 7 Russ RD, Walker BR. Role of nitric oxide in vasopressinergic pulmonary vasodilatation. *Am J Physiol* 1992; 262: H743-7.
- 8 Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95: 1122-5.
- 9 Klinzing S, Simon M, Reinhart K, et al. High-dose vasopressin is not superior to norepinephrine in septic shock. *Crit Care Med* 2003; 31: 2646-50.
- 10 Argenziano M, Choudhri AF, Oz MC, et al. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation* 1997; 96 (9 Suppl): II286-90.
- 11 Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 1998; 116: 973-80.
- 12 Malay MB, Ashton RC Jr, Landry DW, Townsend RN. Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47: 699-703.
- 13 Rosenzweig EB, Starc TJ, Chen JM, et al. Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999; 100 (9 Suppl): II182-6. □