The role of vasopressin in the management of sepsis

With mortality rates approaching 40%, septic shock is one of the most common causes of death on intensive care units. Vasodilatation, myocardial depression and fluid loss as a result of increased capillary permeability result in hypotension and impaired organ perfusion. Multiple organ failure as a consequence of organ hypoperfusion results in death. Initial therapeutic strategies involve fluid resuscitation and pharmacological means to increase mean arterial pressure. The catecholamines dopamine, noradrenaline and adrenaline are the predominant pharmacological agents used.

Antidiuretic hormone, or vasopressin, is produced in the supraoptic and paraventricular nuclei and released from the posterior pituitary in response to numerous stimuli including hypotension. Plasma vasopressin levels are typically significantly raised during the initial period of septic shock. As demonstrated by Sharshar et al (2001), during the later stages, vasopressin levels are often inappropriately low either as a result of depleted stores, impaired production or secretion.

Exogenous vasopressin can be used to increase the systemic vascular resistance where hypotension is the result of vasodilatation. Low plasma levels of vasopressin activate V2 receptors resulting in the formation of aquaporin channels in the renal collecting duct. Increasing systemic plasma levels of vasopressin result in the activation of V1 receptors, ultimately increasing intracellular levels of inositol triphosphate and calcium, with the resultant effect of vasoconstriction. The preferential site of action of vasopressin on the human vasculature has been variably reported.

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Vasopressin is often used when catecholamine requirements are escalating significantly or when a state of catecholamine resistant shock develops. When should we be using vasopressin in the management of septic shock, if at all?

Discussion

Numerous case reports and case series have demonstrated a beneficial effect of vasopressin in various forms of shock. However, few randomized trials have been undertaken in adult patients with septic shock.

Russell et al (2008) undertook the largest trial to date, the Vasopressin and Septic Shock Trial (VASST), which investigated the use of vasopressin as a substitute vasopressor therapy in various severities of septic shock. A blinded randomized multicentre trial with over 750 patients, it failed to demonstrate a mortality benefit of vasopressin at 28 and 90 days. However, because of the study design this was in effect a trial of vasopressin as noradrenaline-sparing therapy. Subgroup analysis by Gordon et al (2010) suggested a survival benefit in those with acute kidney injury on institution of therapy.

Further work by Russell et al (2009) on those co-administered vasopressin and corticosteroids has suggested a beneficial effect. Of greatest interest is the subgroup analysis undertaken in the original study which indicated a potential mortality benefit of vasopressin in less severe septic shock, defined as a noradrenaline requirement of 5–14 μg/min. If this were confirmed in an adequately powered large trial, it would alter the way we currently use vasopressin dramatically.

Dünser et al (2003) undertook the only trial investigating the use of vasopressin in catecholamine-resistant shock, which was a single centre randomized trial of vasopressin in patients requiring in excess of 0.5 μg/kg/min of noradrenaline. Unsurprisingly the addition of vasopressin increased mean arterial pressure while decreasing noradrenaline requirements, but no mortality benefit was seen in the vasopressin group. In comparison with the control group, those treated with vasopressin had a significantly reduced incidence of new tachyarrhythmias, decreased incidence of cardiac arrest and an improvement in cardiac function as determined by a pulmonary artery catheter.

Despite concerns among intensive care physicians regarding the deleterious effects of vasopressin, these do not appear to be reflected in the two randomized trials mentioned above. Such concerns predominantly relate to the effect of an unopposed potent vasoconstrictor on cardiac output, in particular reduced splanchnic flow and the risk of myocardial ischaemia.

Conclusions

Vasopressin is likely to have a role when catecholamines have little effect upon the peripheral vasculature, despite the addition of steroids. The potential role of vasopressin in early sepsis, as hypothesized by the subgroup analysis of those patients in the VASST trial, needs to be delineated by further larger randomized controlled trials. BJHM

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