“Vasopressin compared to norepinephrine in septic shock: Is vasopressin more effective?”

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High-dose vasopressin is not superior to norepinephrine in septic shock

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Aim of the study

The objective of this study was to determine if high doses of arginine vasopressin were more effective when substituted for norepinephrine in septic shock, when analyzing global and hepatosplanchnic hemodynamics and oxygen transport as variables.

Patients and Methods

Klinzing and coworkers report on an experimental study of twelve septic shock patients. Patients ranged in age between 30 and 75 years-old; APACHE II scores on admission to the intensive care unit (ICU) were between 19 and 37, the underlying diagnosis varied among the patients, peritonitis being the most common, in 5 of the 12 patients. The diagnostic criteria for septic shock were taken according to the definitions of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. All studies were conducted under mechanical ventilation and under deep sedation.

Radial arterial blood pressure, central venous pressure and cardiac output were measured in all patients. Blood samples for blood gas determination of oxygen tension, pH, lactate concentration, hemoglobin and oxygen saturation were measured immediately after sampling. Gastric mucosal Pco2 gap was determined by air tonometry every 10 minutes. Pco2 gap was not available for two of the twelve patients due to technical problems. All patients were treated with H2 receptor antagonist (ranitidine), and enteral nutrition was stopped two or more hours before the measurements. Global oxygen consumption was estimated by use of a metabolic monitor. Hepatosplanchnic blood flow was evaluated by a continuous infusion of indocyanine green thru a 7.5-Fr catheter inserted into the hepatic vein via the right internal jugular vein or the right femoral vein under continuous radiographic monitoring. This technique assesses total hepatosplanchnic venous blood flow; gut and liver flow cannot be separated. Indocyanine green was assayed spectrophotometrically at 805 nm on plasma samples.

Hepatosplanchnic blood flow was calculated by the following equation:

\[
SBF = C_i / (C_a - C_{lv}) \cdot (1 - \text{hematocrit})
\]

where SBF is the splanchnic blood flow (L/min), \( C_i \) is the ICG concentration of infusate (mg/L), \( C_a \) and \( C_{lv} \) are the ICG concentrations in the radial artery and hepatic vein (mg/L) respectively. Fractional splanchnic blood flow (fSBF) was calculated by the following equation:

\[
fSBF = SBF / \text{cardiac output} \cdot 100\%
\]

Oxygen content was calculated as (hemoglobin \cdot 1.39 \cdot \text{percent saturation})+ (oxygen tension \cdot 0.0031). Total body and splanchnic oxygen delivery rates were calculated by multiplying the arterial oxygen content by the appropri-
ate flow variables. Splanchnic oxygen uptake was calculated by multiplying the hepatic venous oxygen content difference with the appropriate splanchnic blood flow.

Patients included in the study required vasoressor treatment with norepinephrine in a dose between 0.18 and 1.10 mcg·kg⁻¹·min⁻¹ to achieve a mean arterial blood pressure of 70 mmHg. All patients were treated with dobutamine (2.4-5 mcg·kg⁻¹·min⁻¹) and the infusion rate was not changed during the study period. A single measurement was made of splanchnic blood flow; and the variables that required splanchnic blood flow were calculated. Three consecutive measurements were carried out, and the results were averaged.

After the baseline period, arginine vasopressin (0.06-1.8 IU/min) was added until norepinephrine could be completely removed and the same mean arterial blood pressure of 70 mmHg was achieved. After 2 hours of stabilization, three consecutive measurements were carried out. After the second measurement series, the vasopressor infusion was stopped and norepinephrine infusion was restarted as necessary. Urine output was monitored hourly throughout the study period.

Paired data obtained before and after the vasopressor conversion were compared with nonparametric Wilcoxon rank-sign test. Significance was set at \( p<0.05 \).

**Results**

Replacement of norepinephrine (mean dose 0.56 mcg·kg⁻¹·min⁻¹, ranging from 0.18 to 1.1 mcg·kg⁻¹·min⁻¹) by arginine vasopressin (mean dose 0.47 IU/min, ranging from 0.06 to 1.8 IU/min) caused significant changes in global hemodynamics. Heart rate decreased in all patients, for the group from 96 ±14 to 80 ±16 (\( p<0.01 \)). Cardiac index decreased significantly from 3.8 ± 1 L·min⁻¹·m⁻² to 3.0 ± 1 L·min⁻¹·m⁻² (19.3 ± 18.9%, \( p<0.01 \)).

Because of the diminished cardiac output, global oxygen delivery decreased significantly from 891 ± 349 mL/min to 643 ± 272 mL/min (26.7 ± 14.2%, \( p<0.01 \)). Global oxygen uptake decreased significantly from 248 ± 67 to 218 ± 75 mL/min (\( p<0.05 \), 13.1 ± 10.6%). Hepatosplachnic blood flow tended to increase from 0.8 ± 0.5 L/min to 1.2 ± 1.1 L/min (not significant; or 45.5 ± 62.3%, \( p<0.10 \)). fSBF increased from 10.8 ± 7.6 to 25.9±16.6% of cardiac output (\( p<0.05 \)). Although this effect reached statistical significance, the individual data showed much variability: fSBF increased in eight patients, remained unchanged in two, and decreased in two others.

Splanchnic oxygen delivery did not increase significantly, from 101 ± 64 mL/min to 131 ± 109 mL/min (\( p>0.20 \), 32.2 ± 63.2%). Splanchnic oxygen consumption also did not increase significantly, 51 ± 40 to 79 ± 65 mL/min (62.7 ± 89.8%). Oxygen saturation in the hepatic vein tended to decrease, from 46.6 ± 16.2 to 36.1 ± 16.7% (not significant). Gastric regional Pco₂ gap increased significantly from 17.5 ± 26.6 to 36.5 ± 26.6 mmHg (\( p<0.01 \)). Replacement with arginine vasopressin caused a slight but nonsignificant increase in arterial lactate concentration from 2.3 ± 0.8 to 2.8 ± 1.5 mEq/L. There was no change in hourly urine production.

**Conclusion**

Vasopressin in doses sufficient to replace the vasopressor norepinephrine had mixed effects in septic shock patients. Hepatosplachnic blood flow was preserved during substantial reduction in cardiac output. An increased gastric Pco₂ gap suggests that the gut blood flow could have been redistributed to the disadvantage of the mucosa. Based on this limited data it does not appear beneficial to directly replace norepinephrine with vasopressin in septic shock.

**Commentary**

Sepsis and its most fatal complication, septic shock, is fairly common as reported in a recent study, over 750,000 cases of sepsis occur in the United States per year, leading to approximately 200,000 fatalities corresponding to a fatality rate of around 40% in patient that develop septic shock. [1,2] By analyzing this data we can conclude that there is significant need for improved hemodynamic control and therapy to reduce mortality rate in this group of patients.

Patients with sepsis have a markedly abnormal ventricular response to volume infusion, with a significantly smaller increase in left ventricular stroke work index (LVSWI) than controls in response to fluid challenges. Furthermore, due to the massively reduced systemic vascular resistance patients may remain hypotensive despite adequate fluid resuscitation. Should hypotension or signs of inadequate organ perfusion persist after adequate fluid resuscitation sepsis requires the use of vasoactive agents? The failure to improve tissue perfusion may lead to progressive multi-organ failure and death. However, the true risk-benefit ratio and the optimal choice of inotropic agents in patients with sepsis have yet to be determined in well-controlled clinical studies. Reluctance to optimize hemodynamics with vasopressors may stem from the traditional belief that vasopressors produce adverse vasoconstrictive effects peripherally that outweigh their posi-
tive effects on the central circulation. Nevertheless, a cornerstone of current management of septic shock is vasopressor therapy to reverse the vasodilation and refractory hypotension that characterize this condition.

Which vasopressor to use in the setting of septic shock and at what dose remains controversial. The vasodilation observed in septic shock is caused by vasoactive mediators that are released in response to the generalized inflammation process that results in endothelial changes. These mediators include nitric oxide which is believed to play an important role in the development of the vasodilatory shock. [3,4] In addition to the vasodilatory response, some studies show an impaired secretion of arginine vasopressin in the setting of septic shock when compared to other shock states.[5] This observation provides a rationale for vasopressor therapy specifically with vasopressin. Other studies have demonstrated salutary effects in the treatment of septic shock specially using relatively low doses of vasopressin [6-8].

The study reported by Klinzing and coworkers demonstrates that vasopressin in doses titrated to substitute for norepinephrine using mean arterial pressure as a target in septic shock did not appear to be beneficial with respect to global and hepatosplanchnic hemodynamics and oxygen transport.

It is important to remember that this study examined replacing norepinephrine with vasopressin and did not evaluate the combination of vasopressin and norepinephrine. At least one study has suggested a salutary effect of combination therapy. [9]

Conclusions

Vasopressin at a dose sufficient to substitute for norepinephrine in the treatment of septic shock in this study did not appear to offer any benefit over norepinephrine. The routine administration of vasopressin alone as a vasopressor agent in septic shock requires more clinical research trials. In addition, the role of vasopressin as additive therapy or for those patients refractory to more conventional vasopressor therapy needs to be defined.

References