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The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series

Received: 3 July 2000
Final revision received: 5 January 2001
Accepted: 7 May 2001
Published online: 14 July 2001
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Abstract Objective: To review all cases of septic shock treated with vasopressin to determine the effects on hemodynamic and renal function and to document any adverse effects.

Setting: A 14-bed mixed medical-surgical ICU of St. Paul's Hospital, a 450-bed tertiary referral hospital affiliated with the University of British Columbia.

Patients: All ICU patients who received vasopressin for treatment of severe septic shock between August 5, 1997, and March 21, 1999.

Results: We identified 50 patients: age 60 (± 14); APACHE II score 27 (± 7). Baseline data (T0) was compared to data at T4, T24 and T48 (4, 24 and 48 h) on infusion. Mean arterial pressure (MAP) increased by 18% from T0 to T4 and remained stable at T24 ($p = 0.006$) and T48 ($p = 0.008$). Systolic pulmonary artery pressure (PAP) was unchanged at 45 ± 13 mmHg. Mean cardiac in-

dex (CI) decreased by 11% at T4 ($p = 0.03$). Urine output increased 79% at T4 ($p = 0.005$) and further increases were not significant at T24 and T48. Mean pressor dosage decreased by 33% at T4 ($p = 0.001$), by 53% at T24 ($p = 0.002$) and by 48% at T48 ($p = 0.01$). Hospital mortality was 85%. There were six cardiac arrests; all but one occurred at a vasopressin dose of 0.05 U/min or more. **Conclusions:** In this group of patients with severe septic shock, vasopressin infusion increased MAP and urine output and decreased catecholamine requirements. Doses higher than 0.04 U/min were not associated with increased effectiveness and may have been associated with higher adverse effects.

Keywords Adrenergic agents · Hypotension · Septic shock · SIRS · Vasoconstrictor agents · Vasopressin

Introduction

The mortality rate of septic shock remains over 50% [1]. Early mortality is usually due to refractory hypotension, with progressive acidosis and shock which are unresponsive to fluid resuscitation and catecholamine infusions. Late mortality from septic shock usually occurs because of multiple organ failure. Effective new therapies for septic shock are lacking despite numerous multicenter trials of innovative drugs [2].

Vasopressin is emerging as a rational therapy for septic shock. Landry found that plasma levels in septic

shock patients were inappropriately low compared to patients in cardiogenic shock [3] and observed that some patients with advanced septic shock were extremely sensitive to the pressor actions of exogenous vasopressin [4]. Other small case series [5, 6, 7, 8, 9] and two small randomized controlled trials of the use of vasopressin in vasodilatory shock [10, 11] describe potential benefits of vasopressin. In all of these studies, the infusion of exogenous vasopressin resulted in a prompt increase in blood pressure and a decreased need for catecholamine infusions. These reports suggest that vasopressin holds some promise as a pharmacologic agent

Table 1 Systemic inflammatory response syndrome (SIRS) [12] is manifested by two or more of the following

Temperature	> 38 °C or < 36 °C
Heart rate	> 90 beats/min
Respiratory rate	> 20 breaths/min or PaCO ₂ < 32 torr
White cell count	12,000 cells/mm ³ , < 4000 cells/mm ³ or > 10 % immature (band) forms

for use in septic shock. What is not known from the review of this literature, however, is whether vasopressin is safe and titratable, and whether there are any adverse effects of vasopressin.

Because of the study by Landry and other reports [5, 6, 7, 8, 9], vasopressin has been used in an open label fashion in our critical care unit since 1997 as a rescue therapy for patients having severe septic shock. The purpose of this study was to review all of our cases of septic shock treated with vasopressin to determine the effects of vasopressin on hemodynamic and renal function and to document any adverse effects. We, therefore, conducted a retrospective chart review of all patients receiving vasopressin for septic shock in our ICU between August 1997 and March 1999.

Methods

Setting

This study took place in the 14-bed mixed medical-surgical ICU of St. Paul's Hospital, a 450-bed tertiary referral hospital affiliated with the University of British Columbia.

Patients

We used the St. Paul's Hospital pharmacy computer database of all inpatients to identify all ICU patients who received vasopressin between the dates August 5, 1997, and March 21, 1999. We then included all patients who met two out of four criteria for systemic inflammatory response syndrome (SIRS) (Table 1) [12] with a documented source of infection and who received vasopressin for a minimum of 2 h. We excluded patients receiving vasopressin for control of gastrointestinal bleeding and patients who received vasopressin for vasodilatory shock after open-heart surgery. In general, vasopressin was given to patients who were not responding adequately to moderate to high doses of norepinephrine.

Data extraction

The following data were collected on every patient: age, gender, APACHE II score 24 h prior to starting vasopressin, source of sepsis and hospital mortality. The following data were extracted only from the charts of patients receiving vasopressin infusions for 4 h or more: hemodynamic data [mean arterial pressure (MAP), systolic pulmonary arterial pressure (PAP), cardiac index (CI)], urine output hourly, dose of vasopressin used each hour and dosage of

Table 2 Demographic characteristics of 50 patients who had severe septic shock and who received vasopressin infusion (\pm SD)

Patients	50
Demographics	
Age	60 (\pm 14)
Male	31 (62 %)
APACHE II	27 (\pm 7)
Underlying comorbidity	
Immunocompromised	13 (26 %)
Hepatic failure	7 (14 %)
Renal failure	5 (10 %)
Source of infection	
Lung	24 (48 %)
Intra-abdominal	13 (26 %)
Endocarditis	3 (6 %)
Other	10 (20 %)

other vasoactive agents. We defined pressor dosage as the total units of dopamine ($\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1} \pm 3$) plus norepinephrine ($\mu\text{g}/\text{min}$) plus epinephrine ($\mu\text{g}/\text{min}$).

We compared values at baseline (before infusion) with values at 4 h, 24 h and 48 h of infusion of vasopressin. In addition, the charts were examined by two of the investigators to determine potentially serious adverse consequences of vasopressin infusion and cause of death. We defined potentially serious adverse consequences of vasopressin as ventricular arrhythmias, acute myocardial infarction or cardiac arrest.

Data analysis

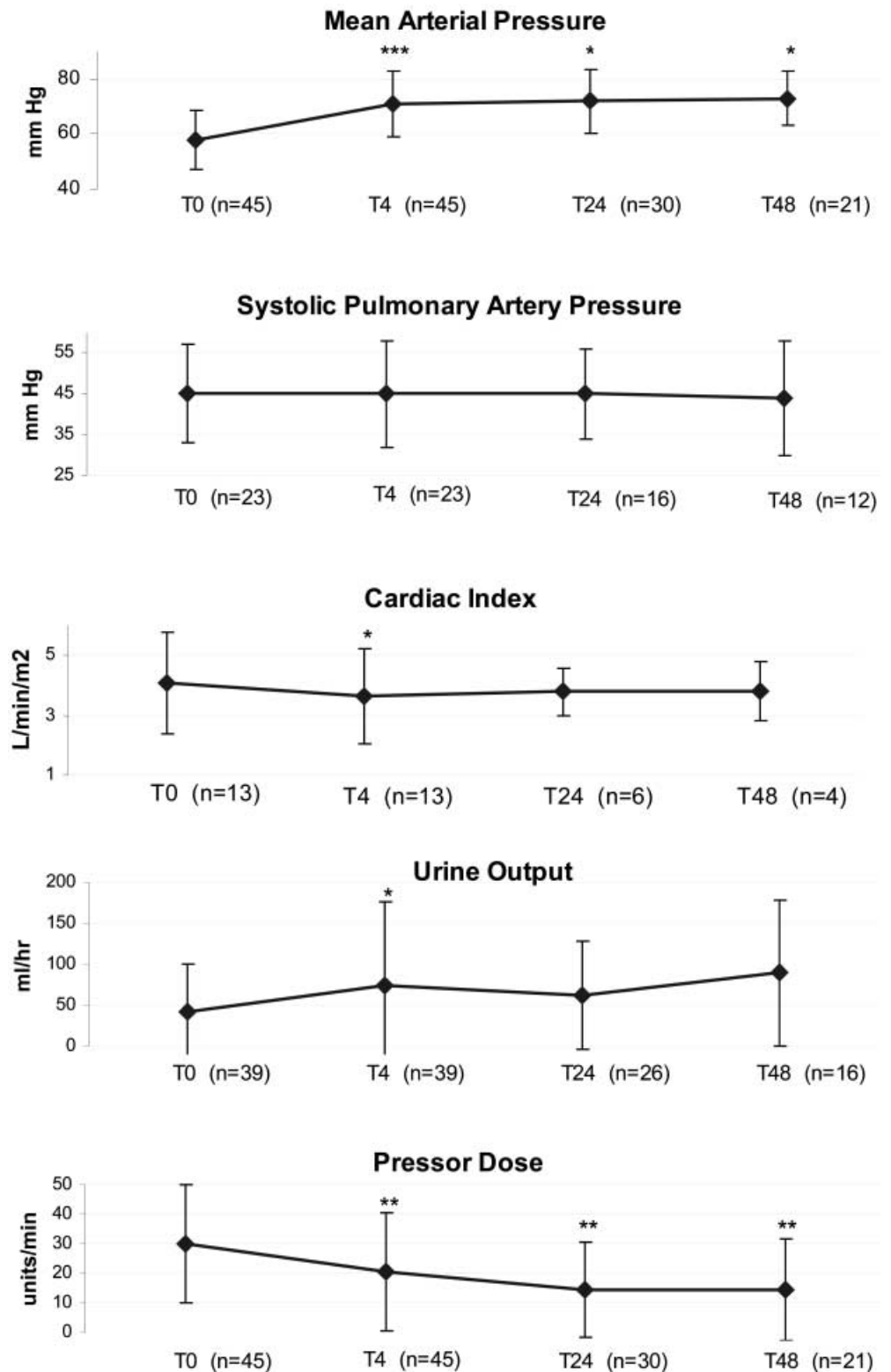
Repeated measures analysis was used to test for differences in continuous variables at baseline and 4, 24 and 48 h, choosing p less than 0.05 as significant. Univariate F tests were used to find the difference in the variables at each time point. SysStat version 5.0 (Sysstat, Evanston, Ill.) statistical software package was used.

Results

Pharmacy records identified 91 patients who received vasopressin in the ICU during the period from August 1997 to March 1999. We identified 50 patients in our ICU who received vasopressin for more than 2 h for septic shock. We excluded 41 patients from our analysis because of gastrointestinal hemorrhage ($n = 7$), post-cardiac bypass vasodilatory state ($n = 20$), other forms of shock ($n = 8$), less than 2 h infusion time ($n = 5$) and diabetes insipidus ($n = 1$).

Five of our 50 patients received infusions less than 4 h and therefore hemodynamic variables were not recorded in these five patients. The clinical characteristics of the patients included are shown in Table 2. Patients were severely ill, as evidenced by very high APACHE II (27 ± 7) and there was a high prevalence of underlying comorbid disease. The average dose of vasopressin used in the 48 h of infusion was 0.05 U/min (range 0.01–0.6 U/min). Hospital mortality was 85 %.

Fig.1 Hemodynamics, urine output and pressor dose in 45 patients who had severe septic shock and who received vasopressin infusion (n number of subjects still alive and on vasopressin infusion in whom measurements were made. Anuric patients were excluded from urine output measurements, p (see text for test used) for each time period versus baseline (TX vs T0), *pressor dose*: dopamine ($\mu\text{g}\cdot\text{kg}\cdot\text{min}$)/3+ norepinephrine ($\mu\text{g}\cdot\text{min}$) + epinephrine ($\mu\text{g}\cdot\text{min}$). * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0001$



The main results are shown in Fig. 1. MAP on infusion of vasopressin increased significantly by 18% at 4 h ($p < 0.001$) and remained at that level 24 and 48 h later ($p = 0.006$ and 0.008 , respectively). Systolic PAP remained unchanged on infusion at 45 ± 13 mmHg. Mean CI decreased by 11% at 4 h ($p = 0.03$) and did not change past that time point. Urine output compared to baseline (excluding anuric patients) increased 79% at 4 h ($p = 0.002$) and further increases were not significant for patients still alive and on vasopressin. Mean pressor dosage decreased by 33% at 4 h ($p = 0.001$), decreased by 53% at 24 h ($p = 0.002$) and decreased by 48% at 48 h ($p = 0.01$).

A dose response curve for vasopressin was not observed; that is, the degree of improvement in MAP, pressor dose and urine output was not related to dose. However, doses over 0.03 U/min were correlated significantly with decreased CI (Student's *t*-test, $p = 0.0026$).

In this case series, eight patients survived to hospital discharge. The causes of death in the remaining 42 patients were refractory shock ($n = 20$), withdrawal of care due to multiple system organ failure ($n = 19$ patients), respiratory failure later on the ward ($n = 2$) and cerebral edema due to underlying disease ($n = 1$). There were six cardiac arrests in patients who were receiving vasopressin infusion. All of these patients were in severe refractory shock. One patient had a marked decrease in CI on vasopressin infusion (0.03 U/min) and died of pulseless electrical activity. The other patients had asystole ($n = 4$) and ventricular fibrillation ($n = 1$). The doses of vasopressin at the time of cardiac arrest were more than 0.03 U/min (up to 0.6 U/min) in five patients and more than 0.05 U/min in four of these.

Discussion

To our knowledge, this is the largest clinical study of vasopressin in septic shock. Vasopressin markedly and significantly increased MAP, did not change PAP, markedly increased urine output and decreased pressor dosage significantly in this retrospective case series of patients receiving vasopressin for severe septic shock. There were six cardiac arrests on vasopressin infusion, four at relatively high dosages (≥ 0.05 U/min.).

Although vasopressin is a potent vasoconstrictor [13], it is a weak pressor in animals with an intact autonomic nervous system. This is because vasopressin resets the cardiac baroreflex to a lower pressure [14]. Very high plasma vasopressin levels (> 100 pg/ml) must be achieved before a significant increase in MAP is observed in normal humans [15]. Patients in septic shock, in contrast, are characterized by both a deficiency in vasopressin secretion and an enhanced sensitivity to the pressor effects of vasopressin [3, 4]. This may explain why we observed a marked pressor response in our pa-

tients, with consequent decreased dosage requirements for infused catecholamines.

In our patients, we observed an enhancement of the pressor effect of infused conventional catecholamines with a subsequent reduction in total pressure dosage. However, there appears to be an important, limited dose-response curve because we did not observe any enhancement of this effect at doses of vasopressin higher than 0.04 U.

Vasopressin has both direct and indirect effects on the arterial vascular system, which is dose-dependent. The direct vasoconstricting effect of vasopressin occurs at high infused doses and is due to its agonist activity at the V1 receptor causing direct activation of phospholipase C, activation of the phosphoinositide pathway and vasoconstriction of smooth muscle [16]. Vasopressin also has an indirect vasoconstrictor effect, enhancing the sensitivity of the vasculature to other pressor agents such as catecholamines [17]. In the presence of low vasopressin concentrations that do not constrict vessels to an appreciable extent, pressor responses to several other vasoconstrictors such as adrenergic agents are markedly augmented [18]. The mechanism of this enhanced pressor response is unknown and may be due to enhancement of adrenoreceptor sensitivity. These features of vasopressin make it a useful agent for the management of hypotension in patients who are refractory to infusion of catecholamines.

Vasopressin has a known vasodilatory effect on the pulmonary vasculature [19]; however, PAP did not change in our sample of patients. In the 13 patients who had pulmonary artery catheters, vasopressin infusion preceded a decrease in cardiac output at 4 h. When we examined the effect of dose of vasopressin used, doses higher than 0.03 U/min were correlated with decrease in CI, whereas doses less than these were not. Vasopressin can reset the cardiac baroreflex to a lower value [14] and it could have mediated vasoconstriction of the coronary arteries because of the high doses used. The temporal relationship between administration of high doses of vasopressin and cardiac arrest in some patients supports this speculation. Vasoconstriction of the systemic arterial vasculature could also have increased left ventricular afterload, which could have decreased cardiac output in these patients because they may have had afterload-sensitive left ventricular dysfunction.

It is possible that the decrease in cardiac output that we observed in some patients is a signal of a beneficial effect. Vasopressin may actually improve tissue oxygenation by aligning oxygen availability with areas of oxygen need, abrogating the need for an increase in flow. Patients who had a decrease in CI might have had improved tissue oxygenation, which could be indicated by an increase in mixed venous oxygen saturation. Unfortunately, due to the retrospective nature of this study,

we do not have data to support this, as mixed venous oxygen saturation was not measured routinely in these patients. As the explanation for a decrease in CI remains unclear, we recommend that vasopressin should be used cautiously, if at all, in patients with symptomatic coronary artery disease, and not at doses above 0.03 U/min. Future prospective randomized studies could address this question in the subset of patients who have a pulmonary artery catheter in place.

Urine output significantly increased at 4 h, but this effect was not sustained at 24 and 48 h. The paradoxical diuretic effect of vasopressin has been observed in patients with hepatorenal syndrome and congestive heart failure [20], yet the mechanisms remain unexplained. There are three possible explanations for vasopressin's diuretic effect. Firstly, the renal vasculature seems to be relatively resistant to the vasoconstrictor effects of vasopressin [21]. At low doses, there is some renal efferent arteriolar vasoconstriction, relatively sparing the afferent renal arterioles, which therefore increases renal perfusion pressure [22]. A vasodilatory effect of vasopressin on the renal vasculature is present at low doses (0.02 U/min) which can be blocked by L-NAME [23], suggesting that the effect is mediated by nitric oxide. Secondly, oxytocin has a natriuretic and diuretic effect, due to inhibition of sodium reabsorption at the proximal and distal tubules [24]. Vasopressin may be directly activating oxytocin receptors, causing natriuresis and diuresis. Thirdly, vasopressin releases atrial natriuretic peptide [25], which may be an indirect mechanism of its diuretic effect. Although the diuretic effect of vasopressin in severe septic shock is appealing, it is not known whether there is an improvement in renal function. We did not note a change in creatinine over the 48-h period of this study. Importantly, there was no evidence of a dose-response curve; patients receiving doses higher than 0.04 U/min did not have a significantly higher urine output than patients receiving lower doses. Therefore, high-dose vasopressin should be avoided because this constricts the renal vasculature [26, 27] and because we did not see a benefit at doses over 0.04 U/min.

We observed very high mortality (85%) in our sample of patients who had severe septic shock. Vasopressin was used in our ICU as "rescue therapy" in patients who appeared to be dying of refractory hypotension. Be-

cause this is not a matched cohort study, we cannot draw any conclusions regarding the effect of vasopressin on mortality in severe septic shock.

There are several limitations to this study. Firstly, this is a retrospective case series; therefore, we could not control for progression of underlying disease or co-interventions such as fluid therapy and steroid use that could also alter the outcome variables. Furthermore, timing of entry into the study was not standardized (i.e. duration of septic shock varied). Secondly, patients did not receive vasopressin according to strict guidelines, so patients could have been at different stages of septic shock at the onset of vasopressin infusion. The strength of this study is that it is the largest unselected series of patients having septic shock who received vasopressin.

This study identifies interesting questions for future research. The effect of vasopressin on regional circulations in sepsis remains unknown. Future studies could be designed to assess the effect of vasopressin on renal and splanchnic perfusion and the effect of vasopressin on tissue oxygenation in human septic shock. Finally, a well-conducted, randomized controlled trial powered to assess clinically important outcomes such as the effect of vasopressin on resolution of organ failure and survival in septic shock is needed.

In conclusion, in this retrospective case series of patients receiving vasopressin for severe septic shock vasopressin infusion increased MAP, decreased catecholamine requirements and increased urine output. There were six cardiac arrests and five patients were on vasopressin infusions higher than 0.03 U/min. Vasopressin should be used in severe septic shock at a fixed low dosage, i.e. 0.01–0.04 U/min, because beneficial effects are achieved at doses of 0.04 U/min or less and adverse effects are more likely at higher doses. As this was not a matched cohort study, we cannot determine whether vasopressin has any advantage over conventional catecholamines on end points such as organ failure and mortality. This question can only be answered by a prospective, randomized, controlled trial of vasopressin in septic shock.

Acknowledgements The authors wish to thank Mary-Jo Race for her diligence in data collection, design of the case report form and assistance in data entry.

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