Effects of Low Dose Vasopressin in Catecholamine Resistant Septic Shock

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Abstract

Background: Septic shock commonly leads to death in critically ill patients. Severe hypotension resistant to conventional catecholamine leads to multiorgan failure. We studied the effectiveness of low dose vasopressin in resistant septic shock.

Methods: Thirty critically ill patients with catecholamine resistant hypotension were included in the study. After adequate fluid resuscitation, infusion of norepinephrine and dobutamine was started. If the patient remained hypotensive, vasopressin was infused at a fixed rate of 0.04 unit/minute for 24 hours. Haemodynamic parameters and mortality rates were recorded.

Result: There was a significant improvement in systolic and mean arterial pressure within four hours of starting vasopressin. This improvement continued throughout the 24-hour period. In addition, it was possible to withdraw dopamine in all the patients and significantly reduce infusion rates of dobutamine and norepinephrine. No significant complication was noted.

Conclusion: Low dose vasopressin at the rate of 0.04 unit/minute is an effective vasopressor in adult patients with catecholamine resistant septic shock.

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Key Words : Severe sepsis; Septic shock; Vasopressin

Introduction

Severe sepsis and septic shock carries a high mortality and places a large burden on the health care system. Sepsis is the second leading cause of death among patients in noncoronary intensive care units and the 10th leading cause of death [1]. Despite improved knowledge of its pathophysiology and considerable advances in its treatment, mortality from septic shock exceeds 50% [2]. Most deaths are linked to refractory arterial hypotension and/or organ failure despite antibiotic therapy, fluid expansion, vasopressor and positive inotropic treatment. Recent case reports and small clinical trials suggest that low dose vasopressin may be an effective alternative to traditional high dose catecholamine therapy for increasing systemic vascular resistance and blood pressure in septic patients [3,4]. This study was undertaken to establish the role of vasopressin in treating refractory arterial hypotension in septic shock.

Material and Methods

This was a prospective study of 30 critically ill patients admitted to intensive care unit. Approval of the institutional ethics committee was obtained. Patients with septic shock were recruited if they fulfilled the diagnosis of sepsis with end-organ dysfunction unrelated to the primary septic focus. The diagnosis of septic shock was made according to the

Society of Critical Care Medicine (SCCM)/European Society of Intensive Care Medicine (ESICM)/American College of Chest Physicians (ACCP)/American Thoracic Society (ATS)/Surgical Infection Society (SIS) International Sepsis Definitions Conference [5]. These patients had persistent hypotension, systolic arterial blood pressure (systolic BP) <90 mm Hg or mean arterial pressure (MAP) < 60 mm Hg despite adequate fluid resuscitation, central venous pressure (CVP) >10 mm Hg, and / or pulmonary artery wedge pressure (PAWP) >18 mm Hg and continuous infusion of pharmacological doses of catecholamines (dopamine, dobutamine and norepinephrine). All patients were mechanically ventilated and the ventilator associated pneumonia (VAP) bundle was implemented [6]. Exclusion criteria were acute coronary artery disease or underlying cardiac problem, acute mesenteric ischemia and uncorrected shock due to blood loss.

As a part of the protocol, norepinephrine infusion was started at the rate of 0.1 µg/kg/min and subsequently increased to 0.2 µg/kg/min. After one hour if hypotension persisted, dobutamine infusion was started at the rate of 5 µg/kg/min and subsequently increased to 10 µg/kg/min. If patients were already on dopamine infusion, it was continued and norepinephrine and dobutamine added as per protocol. All patients were monitored using continuous electrocardiogram (ECG), invasive arterial pressure and pulse oximetry. If hypotension persisted after one hour of starting

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norepinephrine and dobutamine, pulmonary artery catheterization was performed, using modified pulmonary artery catheter (CCOmbo-Edwards Lifesciences) and baseline values of pulmonary artery wedge pressure were recorded. Once a pulmonary artery wedge pressure >18 mm Hg was ensured, vasopressin was infused through a central venous catheter at a fixed rate of 0.04 units/min for 24 hours.

Complications due to pulmonary artery catheter insertion were noted. The modified pulmonary artery catheter was connected to the Edwards Life Sciences Vigilance monitor to measure continuous cardiac output and mixed venous oxygen saturation. At the time when the vasopressin infusion was initiated, systolic BP, MAP, cardiac output, mixed venous oxygen saturation (SvO_2), urine output and heart rate were recorded. These were taken as baseline 0 hour (study entry) readings and the 'study exit' was 24 hours after vasopressin infusion was initiated. These parameters were recorded every four hours for 24 hours. The total duration of vasopressin infusion, and reduction in requirement of catecholamines were recorded. Arterial and venous blood samples were drawn at study entry and every four hours to analyze blood gases, electrolytes and coagulation parameters.

The primary study end point was to evaluate the difference in haemodynamic parameters of the patients during the 24-hour observation period. Continuous cardiac output could not be recorded in a number of patients due to technical reasons. Therefore systolic and mean blood pressure, heart rate and mixed venous oxygen saturation were noted as primary indicators of haemodynamic improvements. As a secondary study end point, reduction in the requirement of catecholamines was evaluated. Results were expressed as $\pm$ standard error of mean. The changes within groups over time were compared with baseline values using a one-way analysis of variance for repeated measures (one way ANOVA). Haemodynamic variables and vasopressor dosages at 0 hour and at the end of 24 hours were compared using the students paired t test. Statistical significance was defined as $p < 0.05$.

Results

Thirty patients were enrolled in this study. The mean age was 49.7 years (range 26 - 77). There were 22 male and 8 female patients. Table 1 shows the primary diagnosis of the patients enrolled. Table 2 shows the haemodynamic variables after the initiation of vasopressin infusion at 0 hour until 24 hours at 4 hourly intervals. Fig. 1 shows the progressive changes in haemodynamic variables and SvO_2 , from 0 hour to 24 hour.

Before the initiation of the vasopressin infusion, the patients were hypotensive (systolic BP 82.7 ± 1.6 mm Hg, MAP 60.2 ± 1.3 mm Hg) despite infusions of catecholamine such as dopamine, dobutamine and norepinephrine. The mixed venous oxygen saturation was 63.3 ± 1.4 % and the heart rate 130.9 ± 2.8 beats/min. The changes in haemodynamic parameters at four hourly intervals as compared to baseline are shown in Table 3. After four hours of the initiation of vasopressin infusion, there was a significant ($p < 0.01$) increase in blood pressure (systolic BP 102.6 ± 2.8 , MAP 74.3

Table 1

Primary diagnosis of patients requiring vasopressin

Diagnosis	No. of patients (n=30)
Postoperative anastomotic leak	4
Diabetic foot	3
Necrotizing fascitis	3
Necrotizing pancreatitis	3
Polytrauma	3
Biliary peritonitis	2
Critical limb ischemia (operated)	2
Intestinal obstruction with peritonitis	2
Pyonephrosis	2
Post operative sub acute intestinal obstruction	1
Nosocomial pneumonia	1
Ruptured ovarian cyst	1
Ruptured ectopic pregnancy	1
Ovarian tumour (operated)	1
Carcinoma buccal mucosa (operated)	1

Table 2

Haemodynamic variables during first 24 hours after vasopressin infusion

Time	Systolic BP (mm Hg)	MAP (mm Hg)	SvO_2 (%)	Heart rate (beats/min)
0 h	82.7 ± 1.6	60.2 ± 1.3	63.3 ± 1.4	130.9 ± 2.8
4 h	102.6 ± 2.8	74.3 ± 2.1	66.3 ± 1.7	119.3 ± 2.9
8 h	108.6 ± 2.3	80.1 ± 1.8	70.3 ± 1.6	117.9 ± 2.9
12 h	108.4 ± 2.7	78.7 ± 2.0	70.6 ± 1.5	112.6 ± 3.1
16 h	108.0 ± 4.5	80.5 ± 2.5	71.1 ± 1.6	109.7 ± 3.2
20 h	114.1 ± 3.2	83.5 ± 2.3	73.1 ± 1.6	106.1 ± 2.9
24 h	116.8 ± 2.8	86.3 ± 1.9	74.6 ± 1.4	103.9 ± 2.6

Fig. 1: Changes in haemodynamic variables and SvO_2 from 0 hour to 24 hours

± 2.1 mm Hg). This was accompanied by an increase in mixed venous oxygen saturation (66.3 ± 1.7 %) and decrease in heart rate (119.3 ± 2.9 beats/min). The changes in SvO_2 and heart rate in the first four hours were not statistically significant (though clinically, these parameters showed improvement). This improvement continued throughout the 24-hour treatment period. The parameters showed significant improvement ($p < 0.01$) by the end of the 24-hour study period. Systolic BP, MAP and SvO_2 increased to 116.8 ± 2.8 mm Hg (37%), 86.3 ± 1.9 mm Hg (38%) and 74.6 ± 1.4 % (12%)

Table 3

Changes in haemodynamic parameters from baseline value at four hourly intervals

Time from 0h	Increase in systolic BP (mm Hg)	Increase in MAP (mm Hg)	Increase in SvO ₂ (%)	Decrease in heart rate (beats/min)
4 h	19.9**	14.1**	3.0 ^{ns}	11.6 ^{ns}
8 h	25.9**	19.8**	7.0*	13.0
12 h	25.7**	18.4**	7.3*	18.4**
16 h	25.3**	20.2**	8.4**	21.2**
20 h	30.4**	23.4**	9.8**	24.8**
24 h	34.1**	26.0**	11.3**	27.0**

*p < 0.05, **p < 0.01, ^{ns} not significant p > 0.05

respectively. Heart rate had decreased to 103.9 ± 2.6 beats/min (20%).

It was observed that systolic BP, MAP and SvO₂ increased substantially in the first eight hours of starting vasopressin, after which these parameters stabilized and continued to be at more or less the values reached at 8 hours. At the time when vasopressin infusion was initiated, the average dopamine, dobutamine and norepinephrine infusion rates were 2.6 ± 0.79 µg/kg/min, 9.28 ± 0.53 µg/kg/min and 0.2 ± 0.004 µg/kg/min respectively. At the end of 24 hours, there was a significant decrease ($p < 0.01$) in the infusion rates of the conventional vasopressors. Dopamine, if started was completely withdrawn in all the cases. It was possible to reduce the infusion rates of dobutamine (3.0 ± 0.63 µg/kg/min) and norepinephrine (0.09 ± 0.01 µg/kg/min) at the end of the 24 hour study period significantly. At the end of 24 hours, there was a reduction in dobutamine requirements by 68% and that of norepinephrine by 55% as shown in Table 4.

It was possible to stop vasopressin at the end of 24 hours in 11 patients. In the rest (n=19), attempts to discontinue vasopressin resulted in a decline in the systolic BP and MAP. Vasopressin was continued in these patients and attempts to decrease the vasopressin infusion were repeated every hour until the patients tolerated tapering off and discontinuation of the drug without a decrease in systolic BP < 90 mmHg. Four patients did not survive the 24-hour study period. As a result, the duration of vasopressin infusion ranged from 4 to 68 hours, the average duration being 33.06 hours. Patients were followed up for two weeks. Out of the 30 patients in whom vasopressin was given, 19 (63.3%) patients survived and 11 (33.7%) patients died within two weeks. Of these 11 patients, four (13.3%) patients remained hypotensive despite administration of the vasopressin infusion and did not survive the 24 hour study period. These patients received additional fluid boluses and increases in the rate of the norepinephrine and dobutamine infusions. The remaining seven patients showed improvement in haemodynamic parameters initially but eventually died from multiple organ failure that occurred over a 14 day period.

There were no major complications due to insertion of pulmonary artery catheter except transient supraventricular arrhythmias seen during catheter insertion in some patients. However, recording pulmonary artery pressures were difficult

Table 4

Catecholamine requirements

Catecholamines	Infusion rate at study entry (0 h)	Infusion rate at study exit (24 h)
Dopamine (µg/kg/min)	2.6 ± 0.79	0
Dobutamine (µg/kg/min)	9.28 ± 0.53	3.0 ± 0.63
Noradrenaline (µg/kg/min)	0.2 ± 0.004	0.09 ± 0.01
Vasopressin (units/min)	0.04 ± 0.00	0.02 ± 0.00

in spontaneously breathing patients. The ability to consistently record cardiac output with the device was highly variable, which led us to abandon its use. Pulmonary artery catheter was removed after 48 to 72 hours.

Discussion

Cardiovascular dysfunction contributes to the high mortality rate (40-70%) of septic shock. Catecholamines have been the primary vasopressors used in septic shock to maintain venous tone and mean arterial pressure. Vasopressin is an alternative agent [7] that has recently been used in septic and distributive shock [3,8]. Landry et al [9], discovered that patients in vasodilatory septic shock are deficient in vasopressin because of a defect in the baroreflex-mediated secretion of the hormone. Further administration of low doses of the exogenous hormone yielded a hypersensitive pressor response [3]. This retrospective study formed the basis for the present study. Activation of vasopressin (V₁) receptors on vascular smooth muscle is responsible for vasoconstriction and increased systemic vascular resistance. When baroreceptor reflexes are impaired, during septic shock [3], the pressor activity of vasopressin is greatly enhanced. We consider low dose vasopressin infusion during septic shock similar to hormonal replacement therapy as opposed to pharmacotherapy using catecholamines titrated to a blood pressure endpoint.

The present study demonstrates that low dose vasopressin infusions produce clinically important increase in blood pressure (systolic BP and MAP), increase in mixed venous oxygen saturation and decrease in tachycardia in hypotensive patients with vasodilatory septic shock. After initiation of the vasopressin infusion, the increase in blood pressure was sufficient in the majority of these patients so that no further increase in any of the other pressor was necessary. As in earlier studies [3,9], an untreated (placebo) group was not possible because all the patients were sufficiently hypotensive to warrant pressor therapy. However, the haemodynamic responses after discontinuing the vasopressin infusion after the 24 hour study period (the systolic BP and MAP) provided evidence that vasopressin infusion was responsible for the increase in blood pressure observed. Indeed, in these

19 patients blood pressure returned to pre treatment levels when the vasopressin infusion was discontinued and returned to post treatment levels when the vasopressin infusion was resumed, suggesting that vasopressin infusion was responsible for the effects on blood pressure, mixed venous oxygen tension and heart rate.

The results of the present study are in agreement with other studies [3,4,9-11], on the effectiveness of low-dose vasopressin infusion in patients with vasodilatory septic shock. The present study shows that vasopressin infusion spared use of conventional catecholamines. Impairment in the release of vasopressin possibly explains this pressor sensitivity to such small doses of the hormone. It has been reported that endogenous vasopressin levels are inappropriately low in clinically septic patients [9]. Finally, desensitization of the catecholamine α -1 adrenergic receptors may develop during septic shock, which explains the development of hypotension refractory to standard catecholamine vasopressors. Although both vasopressin and the catecholamines use the same phosphatidylinositol second-messenger system, different receptors mediate vascular vasoconstriction and concomitantly increase the arterial blood pressure.

We did not observe evidence of myocardial ischemia in any of the patients during the 24 hour study period, which is in accordance with other studies [12]. Ischaemic skin lesions have been reported in patients receiving vasopressin treatment [13,14]. However, we did not observe any skin lesion in this study. A recent study by Rivers et al [15] has emphasized the role of low dose vasopressin in the initial resuscitation of septic shock. The Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock also advocate the use of low dose vasopressin [16].

The limitations were the brief study duration, where we focused on indices of haemodynamic stability and measures of oxygen delivery and consumption rather than mortality. Secondly, confounding factors such as age, sex, severity of underlying illness, and cause for septic shock were not taken into account that could affect the outcome. We did not compare vasopressin versus another agent in septic shock (norepinephrine/placebo) as in many studies. However, the present study with its limitation demonstrates that low dose vasopressin has potentially important physiologic benefits as compared to the conventional catecholamines.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

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