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# Comparison Of The Effects Of Low Dose Vasopressin On Haemodynamic Parameters In Septic Shock Patients At Two Different Time Intervals

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**ABSTRACT**

***Background:*** *One of the major concerns in patients with septic shock is hypotension resistant to conventional catecholamines. We studied the effects of low dose vasopressin on the hemodynamic parameters of these patients at two different time intervals.*

***Methods:*** *Patients with catecholamine resistant septic shock were included and vasopressin infusion was started at 0.04 units/min for 24 hours. Hemodynamic parameters were recorded at 0,8 and 24 hours.*

***Results****: After eight hours of the initiation of vasopressin infusion, there was a significant increase in blood pressure, and SvO2 and decrease in heart rate. There was a significant increase in hemodynamic parameters (including urine output) at the end of 24 hours.*

***Conclusion:*** *Beneficial effects of low dose vasopressin are more pronounced if continued for 24 hours.*

**KEYWORDS** : Vasopressin, Septic Shock

## Introduction

Sepsis, severe sepsis and septic shock are a common occurrence in the intensive care units (ICU) worldwide and despite significant improvements in intensive care, carry high mortality in critically ill patients. [1] One of the major concerns in treatment strategies in patients with septic shock is the development of progressive cardiovascular failure due to hypo responsiveness to catecholamines and excessive vasodilation. Norepinephrine (NE) is recommended to be used as the first choice vasopressor [2] Dopamine and Dobutamine are recommended to be used along with Norepinephrine for select patients. However a lot of patients become resistant to catecholamines even when used in high doses. In these patients Vasopressin is added to NE with intent of either raising blood pressure or decreasing NE dosage. Studies show that in most patients of septic shock, vasopressin concentrations are elevated initially but within 24-48 hours the levels decrease to normal range.[3] However in routine clinical practice we see that there is a definite improvement in clinical parameters within the first few hours of initiating vasopressin infusion and often there is a dilemma when vasopressin should be discontinued and let the routine catecholamines act now the sensitivity to catecholamines is restored with vasopressin. There is also a concern in many primary physicians that vasopressin may further contribute to decrease in urine output. We therefore thought of comparing the effects of vasopressin on the hemodynamic parameters at 8 hours and 24 hours of initiating vasopressin infusion. The aim of this study was to see the effects of low dose vasopressin on hemodynamic and oxygen utilization parameters in septic shock patients resistant to catecholamines, at 8 hours and 24 hours of initiation of infusion.

## Materials and Methods

This prospective observational study was performed at the Intensive Care Unit (ICU) of a 1000 bedded tertiary care center. Approval of the institutional ethics committee was obtained. Patients with septic shock were recruited if they fulfilled the criteria as defined by the third international consensus definitions for Sepsis and Septic Shock (Sepsis-3)[3] These patients were identified if they had a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial blood pressure(MAP) ≥ 65mmHg and had a serum lactate level > 2 mmol/L (18mg/dL) despite adequate volume resuscitation. Patients were excluded if they were pregnant, had acute coronary artery disease present or suspected, or had acute mesenteric ischemia present or suspected. Patients in shock due to hypovolemia (CVP < 7 mmHg) or underlying cardiac problem were also excluded. As per hospital protocols, norepinephrine infusion was started at the rate of 0.1µg/kg/min and subsequently increased to 0.2 µg/kg/min. If patients were already on dopamine and/or dobutamine infusion, it was continued. If hypotension persisted after one hour of starting norepinephrine, pulmonary artery catheterization was performed, using modified pulmonary artery catheter and baseline value of pulmonary artery wedge pressure (PAWP) was recorded. Once PAWP was >18 mm Hg, vasopressin infusion was started through a central venous catheter rate of 0.04 units/min for 24 hours. All patients were monitored using continuous electrocardiogram (ECG), invasive arterial pressure and pulse oximetry. Each patient had a modified pulmonary artery catheter to guide volume replacement, and to continuously monitor mixed venous oxygen saturation.

Baseline systolic blood pressure, mean arterial pressure, mixed venous oxygen saturation, urine output and heart rate were recorded at the time when vasopressin infusion was initiated and this was considered time zero. These parameters were recorded every four hours as per the ICU protocols but for the study purpose a blinded observer recorded the parameters at 0,8 and 24 hours. The primary study end point was to evaluate the difference in hemodynamic parameters of the patients at 8 hours and 24 hours. Systolic and mean blood pressure, heart rate and mixed venous oxygen saturation were noted as primary indicators of hemodynamic improvements. As a secondary study end point, reduction in the requirement of catecholamines was evaluated. Results were expressed as ± 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 at 0, 8 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 and their mean age was 49.7 years with a male predominance (22 males and 8 female

patients). Table 1 shows the mean values of the hemodynamic variables and urine output after the initiation of vasopressin infusion at 0, 8 hour until 24 hours.

On initiation of the vasopressin infusion, the systolic BP was 82.7 ± 1.6 mm Hg and MAP 60.2 ± 1.3 mm Hg despite the ongoing vasopressor infusions. 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 the end of 8 hours compared to baseline are shown in Table 2. The mean difference in these parameters was calculated with a CI of 95%. After eight hours of the initiation of vasopressin infusion, there was a significant ($p < 0.0001$) increase in blood pressure (systolic BP by 25.52 (19.61,31.42) mmHg and MAP by 19.76 (15.57, 23.95) mmHg. This was accompanied by an a significant ($p < 0.0001$) increase in mixed venous oxygen saturation by 6.59 (4.23, 8.94) % and decrease in heart rate by 13.69 (8.48, 18.90) beats/min. 4 hourly urine output also increased from baseline values by 14.31 (-14.21,42.82) ml but this increase was not statistically significant ($p = 0.3128$). This improvement continued throughout the 24-hour treatment period as we then compared the mean increase in hemodynamic parameters at 8 and 24 hours (Table 3). There was a significant increase in systolic BP ($p = 0.0414$) by 6.96 (0.29, 13.63) mmHg, MAP ($p = 0.0470$) by 4.85 (0.07, 9.63) mmHg, SvO2 ($p = 0.0006$) by 3.15 (1.49, 4.80) and 4 hourly urine output ($p = 0.0151$) by 22.32 (4.68, 39.96) ml. This was accompanied by an a significant ($p < 0.0001$) decrease in heart rate by 13.43 (8.38, 18.47) beats/min. There was a significant ($p < 0.0001$) decrease in noradrenaline infusion rate at the end of 24 hours of initiating vasopressin infusion.

**Table 1: Mean values of parameters at 8 and 24 hours**

| | 0 hr | 8 hr | 24 hr |
|---|---|---|---|
| Mean SBP (mmHg) | 82.7 ± 1.6 | 108.4 ± 2.3 | 116.8 ± 2.8 |
| Mean MAP (mmHg) | 60.2 ± 1.3 | 80.1 ± 1.8 | 86.3 ± 1.9 |
| Mean HR (beats/min) | 130.9 ± 2.8 | 117.9 ± 2.9 | 103.9 ± 2.6 |
| Mean Venous Oxygen saturation (SvO2)(%) | 63.3 ± 1.4 | 70.3 ± 1.6 | 74.6 ± 1.4 |
| Mean Urine output (ml/ 4 hours) | 125.66 ± 18.44 | 143.96 ± 14.55 | 165.35 ± 17.45 |

**Table 2 Mean difference in parameters at 8 hrs after initiation of therapy**

| | Mean (95% CI) | P value |
|---|---|---|
| Increase in SBP (mmHg) | 25.52 (19.61,31.42) | <0.0001 |
| Increase in MAP (mmHg) | 19.76 (15.57, 23.95) | <0.0001 |
| Decrease in HR (beats/min) | 13.69 (8.48, 18.90) | <0.0001 |
| Increase in SvO2 (%) | 6.59 (4.23, 8.94) | <0.0001 |
| Increase in Urine output (ml/4hr) | 14.31 (-14.21,42.82) | 0.3128 |

**Table 3 Mean difference in parameters between 8 hrs and 24 hrs after initiation of therapy**

| | Mean Difference (95% CI) | P value |
|---|---|---|
| Increase in SBP (mmHg) | 6.96 (0.29, 13.63) | 0.0414 |
| Increase in MAP (mmHg) | 4.85 (0.07, 9.63) | 0.0470 |
| Decrease in HR (beats/min) | 13.43 (8.38, 18.47) | < 0.0001 |
| Increase in SvO2 (%) | 3.15 (1.49, 4.80) | 0.0006 |
| Increase in Urine output (ml/4hr) | 22.32 (4.68, 39.96) | 0.0151 |

**Discussion**

In the last two decades, several studies and case reports have been published about the effects of low dose vasopressin in patients with septic shock. There is evidence for both a deficiency and an exquisite sensitivity to vasopressin, which has mechanistic and therapeutic implications [4]. In most patients of septic shock, vasopressin concentrations are elevated initially but within 24-48 hour, the levels decrease to normal range. This has been called relative vasopressin deficiency because in the presence of hypotension, vasopressin is expected to be elevated [5].

Noradrenaline is recommended to be used as the first line vasopressor in patients with septic shock [2]. Low dose vasopressin infusion may be considered similar to hormonal replacement therapy as opposed to pharmacotherapy using vasopressors titrated to a blood pressure endpoint. In these patients, thre baroreceptor reflexes are impaired and the pressor activity of vasopressin is greatly enhanced. Moreover it also sensitizes the body to the vasopressors to which the patients had earlier become resistant to in terms of correction of hypotension. We therefore studied the effects of low dose vasopressin at 8 hours and 24 hours to see whether the improvement was due to vasopressin per say or due to the restored sensitivity to vasopressors after initially starting vasopressin.

Our study demonstrates that low dose vasopressin infusion produces a clinically significant increase in blood pressure (systolic BP and MAP) and mixed venous oxygen saturation and decrease in heart rate at the end of eight hours. However the increase I urine output was not statistically significant. However as time passed these hemodynamic parameters continued to improve which were both clinically and statistically significant. At the end of 24 hours there was a significant improvement in all parameters including urine output. This is in accordance to similar studies done earlier. [8,9,10]. Therefore it would be prudent to continue vasopressin infusion for at least 24 hours since the beneficial effects continue even after 24 hours. Short-term vasopressin infusions up to 8 hours do improve the hemodynamic parameters but without any significant improvement in urine output which is also an important aspect.

As in earlier studies [6, 7], a placebo group was not possible in our study too because all the patients were sufficiently hypotensive and vasopressin infusion was warranted to augment the vasopressor therapy.

We did not observe any major side effects, which could be attributed to vasopressin. This is in accordance to the landmark Vasopressin and Septic Shock Trial (VASST), which included 778 patients. It did not demonstrate any differences between vasopressin and noradrenaline in the overall rates of serious adverse events [11].

The study had several limitations. Firstly the number of patients studied was very small where we focused on improvement in hemodynamic parameters at two arbitrary time intervals. We did not study the effects on overall mortality of the patients. Secondly, we didn't take into account the demographic factors, which may have been confounding the effect on hemodynamic parameters. However, the present study demonstrates that low dose vasopressin does have beneficial effects on hemodynamic parameters in patients with septic shock. Though these beneficial effects are seen even after short-term usage, but the overall beneficial effects are certainly more pronounced if continued for 24 hours.

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