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RESEARCH ARTICLE

Hemodynamic response to administration of vasopressors among patients with septic shock

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ABSTRACT

Background: Septic shock is characterized by refractory hypotension with a mortality of >50%. Early fluid resuscitation, if failed, vasopressors are recommended to maintain mean arterial pressure (MAP) of 65 mmHg to restore organ perfusion. Noradrenaline (NA) is the vasopressor of choice but can be associated with adrenergic hyposensitivity and adverse effects on prolonged high-dose treatment. Hence, the addition of arginine vasopressin (AVP) to reduce the dose of NA is recommended. In view of the paucity of data in our setup, the present observational study was undertaken. **Aims and Objectives:** The present study was conducted to analyze the hemodynamic response to vasopressors among patients in septic shock and to compare the same among patients receiving NA alone or NA + AVP. **Materials and Methods:** All consenting adult patients >18 years with septic shock receiving vasopressors were included in the study. Hemodynamic variables such as systolic and diastolic blood pressure and MAP were noted at baseline, 30 min, 1, 6, 24, and 48 h and the same was compared between patients receiving either NA alone or NA + AVP. **Results:** The median age was 45 years with male preponderance. At admission, median MAP was 63 mmHg. On administration of vasopressors, target MAP was achieved by 1-h and maintained in both the groups of patients receiving NA or NA + AVP. No significant differences were noted in terms of hemodynamic parameters among patients receiving NA alone or NA + AVP. **Conclusion:** As per the surviving sepsis guidelines 2018, vasopressor administration was initiated and the target MAP of >65 mmHg was achieved by 1 h, sustained over 48 h. No significant differences were noted among the patients receiving NA alone or NA + AVP in terms of hemodynamic variables.

KEY WORDS: Septic Shock; Mean Arterial Pressure; Noradrenaline; Arginine Vasopressin

INTRODUCTION

Septic shock is a life-threatening condition with high mortality. It is characterized by the presence of sepsis with refractory hypotension, unresponsive to crystalloid fluid challenge of 20–40 mL/kg. This results in inadequate tissue perfusion leading to multiple organ failure and, if uninterrupted, leads to death.[1] The WHO reports about 24 million cases of septic shock with a mortality rate of 50% accounting for about 6 million deaths globally.[2] A multicenter study from India reported 16.45% severe sepsis with a hospital mortality of 65.2%.[3]

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Management of septic shock as per surviving sepsis guidelines 2018 suggests administration of 30 mL/kg crystalloid for hypotension and, if no response, then vasopressors should be administered to maintain a mean arterial pressure (MAP) ≥65 mmHg within 1 h.[4] Guidelines also recommend noradrenaline (NA) as the first choice

vasopressor and vasopressin (arginine vasopressin [AVP]) can be added to NA with intent of either raising MAP or decreasing NA dosage.[4]

Longer duration of hypotension without hemodynamic support using vasopressor infusion has been shown to result in a higher mortality rate in septic shock. Hence, "Early goal-directed therapy" was developed to set early hemodynamic goals which include maintaining MAP ≥65 mmHg. At present, NA, an endogenous catecholamine, is the recommended vasopressor, regardless of the type and origin of shock. Catecholamines are mainly used as vasopressor agents for supporting arterial blood pressure and to maintain adequate organ perfusion. However, in advanced stages of shock, there could be the development of adrenergic hyposensitivity with loss of pressor effects of catecholamines. This state warrants increasing the dose of NA but is associated with serious adverse effects, leading to higher mortality.[5]

Landry *et al*. have reported that plasma level of vasopressin is low in vasodilatory shock which could be due to impaired baroreflex-mediated secretion.[6] Hence, the addition of vasopressin has been suggested to be beneficial in reversing the refractory hypotension.

To the best of our knowledge, data regarding response to vasopressors in septic shock from India are limited. Hence, the present study was undertaken with an objective to analyze the response in terms of hemodynamic parameters among patients in septic shock receiving vasopressors and also to compare the same between patients receiving NA alone or NA + AVP.

MATERIALS AND METHODS

All the adult patients fulfilling inclusion criteria admitted in intensive care unit (ICU) between November 2016 and May 2018 at Victoria Hospital attached to Bangalore Medical College and Research Institute, Bengaluru, were included in the study. The study was initiated after obtaining clearance from the Institutional Ethics Committee of Bangalore Medical College and Research Institute. Informed consent was taken from patients or their legal representatives. Sample size was estimated as 46 patients, considering proportion of survival in the treatment group as 0.71, proportion of survival in control group as 0.29, $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$, and hazards ratio of 3.78. For better validation, 50 patients were included in the study. The present study is a part of project titled "Clinical outcomes of NA and its combination with vasopressin in the management of septic shock – A prospective observational study." The sample size was calculated for the main study. All adult patients of either sex admitted in ICU who are in septic shock (defined as per Surviving Sepsis Campaign guidelines 2018) and receiving vasopressors (NA only or NA + AVP) providing informed consent (patient/legally authorized representative) were included in the study.

The vasopressor administration was not based on specified hemodynamic cutoffs (as there are no guidelines available) but was at the discretion of the critical care specialist directing the patient's care. NA was administered at 1 mg/ml and AVP was used at 1–3 units/h. The demographic, clinical, and drug data were recorded in the study pro forma. Hematological variables: Systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were recorded at baseline, 30 min, 1, 6, 12, 24, and 48 h.

Quantitative variables were expressed as mean ± standard deviation or median (25, 75 quartile) and compared using Student's *t*-test or Mann–Whitney U-tests as appropriate. Proportions are expressed as percentages and compared using Chi-square or Fisher's exact test as appropriate. All statistical analyses were performed using commercially available software, Statistical Package for the Social Sciences – 20th version.

RESULTS

Table 1 shows the baseline characteristics of the study population and also the comparison of baseline characteristics of the subgroups of the patients receiving NA alone or NA + AVP. The median age of the study population was 45 years; 60% of them were male. There was no statistically significant difference in the baseline characteristics between patients receiving NA alone or NA + AVP.

Table 2 shows the hemodynamic variables of the study population after the administration of vasopressors ($n = 50$). The median SBP in mmHg at the time of admission was 89 and after receiving vasopressors increased to 98 mmHg by 1 h and it further increased to 112 mmHg by 48 h. The median DBP in mmHg at the time of admission was 50 and after receiving vasopressors increased to 62 mmHg by 1 h and it further increased to 70 mmHg by 48 h. The median MAP in mmHg at the time of admission was 63 and after receiving vasopressors increased to 72 mmHg by 1 h and it further increased to 84 mmHg by 48 h.

Table 3 shows the hemodynamic variables of the study population receiving NA alone or NA + AVP in septic shock. No significant differences were found in the SBP or DBP between NA alone or NA + AVP at any time point. Both SBP and DBP, the groups increased and were maintained by 48 h.

Table 4 shows MAP of the study population receiving NA alone or NA + AVP in septic shock. No significant differences were found in MAP between NA alone or NA + AVP at any

Table 1: Baseline characteristics of the study population in septic shock (*n*=50) at admission along with subgroups receiving NA alone (*n*=24) or NA+AVP (*n*=26)

Variables	*n*=50	NA (*n*=24)	NA+AVP (*n*=26)
Age (years)			
Median	45	47	45
Interquartile range	36–55	38–54	32–55
Gender			
Males (%)	60	53	47
Females (%)	40	40	60
Residence			
Rural (%)	52	54	46
Urban (%)	48	42	58
Diabetes			
Present (%)	44	22	22
Absent (%)	56	26	30
Hypertension			
Present (%)	20	12	8
Absent (%)	80	36	44
SBP at admission (mmHg)			
Median	89	90	83
Interquartile range	68–110	70–103	56–110
DBP at admission (mmHg)			
Median	50	55	50
Interquartile range	40–70	42–74	41–68
MAP at admission (mmHg)			
Median	63	67	62
Interquartile range	50–83	51–83	50–81

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, h: Hours. Data analyzed by Mann–Whitney U-test between NA and NA+AVP groups. $P<0.05$ is considered significant, no variables between groups were statistically significant

time point. MAP improved in both groups by 1 h and was sustained over 48 h.

DISCUSSION

Septic shock is a life-threatening condition characterized by refractory hypotension. Vasopressors are recommended if the hypotension remains refractory to intravenous fluid therapy to maintain MAP of >65 mmHg.

The present study was conducted to analyze the response in terms of hemodynamic parameters to vasopressors in patients with septic shock and compared the same among patients receiving NA alone or NA + AVP. The results showed that vasopressors were administered to increase MAP to the target level of ≥65 mmHg which was achieved by 1 h. No statistically significant differences were noted among the groups receiving NA alone or NA + AVP.

The median age of the study population in the present study was 45 years, of them, 60% were male and 40% were female and 52% of patients were from rural areas and 48% from urban areas. A multicentric study in India by Todi *et al*. reported that the mean age of the study population was 58.17 years with male preponderance of 57%.[3] An observational study done by Micek *et al*. shows that the mean age of the patients was 59.2 ± 15.9 years.[7]

The crucial step in the management of patients with septic shock is to increase systemic and regional/microcirculatory flow. Administration of vasopressors will increase the arterial blood pressure and thereby improves the input pressure driving organ perfusion. Nevertheless, NA is regarded as the first-choice vasopressor in the management of hypotension in septic shock, but no clear guidelines on the choice of additional vasopressors have been reported.

NA is being used as the first-choice vasopressor in our study setting also. The same is in line with surviving sepsis guidelines and the reports of many systematic reviews and meta-analysis.

A recent survey of 839 physicians from 82 countries in 2019, by the European Society of Intensive Care Medicine reported that the physicians opined that the leading reasons for vasopressor use were low MAP and reduced response to initial fluid resuscitation (83%). NA was the first-choice vasopressor (97%) to achieve target MAP of >60–65 mmHg (70%). They also recommended that NA should be started early and not to delay until fluid resuscitation is completed.[8]

Avni *et al.* in a systematic review of many vasopressors (NA, AVP, terlipressin, epinephrine, etc.) have reported that no vasopressor had a statistically significant effect on the MAP at any measurement point as compared to other vasopressors. They added that NA had more benefits as compared to other vasopressors in terms of decreasing lactate levels and increasing central venous pressure and urine output.[9]

Recently, a Phase 2 randomized controlled trial, early use of norepinephrine in septic shock resuscitation[10] has been reported by Permpikul *et al.*, on early low-dose norepinephrine (NE) versus placebo in septic shock. The primary outcome was control of shock defined by a composite of MAP >65 mmHg plus either urine output >0.5 ml/kg/h or 10% decline in lactate from baseline. The above-mentioned target was achieved in 76% of patients on early NE infusion versus 48% in placebo group. The authors reported that early NA administration may reduce organ injury, prevent downregulation of adrenergic receptors, and reduce the need for sustained high-dose NA infusion.

Table 2: Hemodynamic variables of the study population after administration of vasopressors (*n*=50)

Time	SBP (mmHg)		DBP (mmHg)		MAP (mmHg)	
	Median	IQR	Median	IQR	Median	IQR
30 min	80	60–90	50	40–58	58	49–71
1 h	98	76–110	62	48–75	72	59–84
6 h	117	100–130	68	60–83	84	73–98
12 h	110	98–117	68	60–79	80	69–88
24 h	108	100–118	69	60–76	82	74–86
48 h	112	100–123	70	59–82	84	74–94

IQR: Interquartile range, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, Min: Minutes, h: Hours

Table 3: Hemodynamic variables of the study population receiving NA alone or NA+AVP in septic shock (*n*=50)

Time	SBP (mmHg)		SBP (mmHg)		DBP (mmHg)		DBP (mmHg)	
	NA only		NA+AVP		NA only		NA+AVP	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
30 min	81	70–95	73	44–88	50	42–61	49	25–53
1 h	96	72–107	99	81–120	59	49–73	66	49–76
6 h	117	100–125	118	96–133	70	60–80	68	61–82
12 h	107	89–114	109	99–118	68	62–75	70	60–83
24 h	109	106–116	113	96–133	70	65–76	70	60–86
48 h	121	110–162	110	98–128	83	67–120	79	58–79

Data analyzed by Mann–Whitney U-test. IQR: Interquartile range, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, NA: Noradrenaline, AVP: Arginine vasopressin. $P<0.05$ is considered significant, no variables at any time point between groups were statistically significant

Table 4: Mean arterial pressure of the study population receiving NA alone or NA+AVP in septic shock (*n*=50)

Time	MAP (mmHg)		MAP (mmHg)		*P* value
	NA only		NA+AVP		
	Median	IQR	Median	IQR	
30 min	61	50–74	57	28–71	0.251
1 h	71	56–84	73	62–92	0.372
6 h	84	74–99	88	74–99	0.954
12 h	82	75–89	80	68–90	0.694
24 h	82	79–86	83	69–87	0.489
48 h	89	80–95	81	71–91	0.261

Data analyzed by Mann–Whitney U-test. IQR: Interquartile range, MAP: Mean arterial pressure, NA: Noradrenaline, AVP: Arginine vasopressin. $P<0.05$ is considered significant, no variables at any time point between groups were statistically significant

A Cochrane systematic review evaluated the effects of various vasopressors in the management of shock informed that high-quality evidence was available to conclude that dopamine increases the risk of arrhythmia compared with NE and might increase mortality. It further concluded that evidence to identify significant differences among other vasopressors including AVP was insufficient.[11]

The other most common vasopressor added to NA was AVP in our study setup. The use of AVP also has been recommended by surviving sepsis guidelines and many clinical trials. Landry *et al*. were the first to show that vasopressin was in appropriately low in vasodilatory septic shock. In 19 patients with vasodilatory septic shock, vasopressin level was 3.1 pg/ml with systolic arterial pressure (SAP) of 92 mmHg. After the administration of vasopressin infusion at 0.04 IU/min, SAP increased from 92 to 146 mmHg, but decreased when vasopressin was withdrawn.[6]

The present study did not record any significant differences in the hemodynamic parameters of patients receiving NA alone or NA + AVP. The same has been reported by many clinical trials.[12-14]

The landmark vanish (vasopressin vs. NE as initial therapy in septic shock) trial evaluated the effect of early vasopressin versus NE on kidney failure in patients with septic shock. The trial reported that MAP in all treatment groups was similar at baseline and over the first 7 days. Vasopressin demonstrated NA-sparing effect by reducing the total dose of NA required to maintain the blood pressure.[12]

Another important vasopressin and septic shock trial by Russel *et al*. conducted in 778 adult patients with vasodilatory septic shock, evaluated the clinical outcomes in NA versus NA + AVP. The trial did not find a significant difference in both groups in terms of blood pressure and MAP which is concurrent with the results of the present study. The study had few limitations that AVP levels were not measured and the MAP at admission was around 70 which does not quantify that the patients are in shock, instead the trial evaluated the catecholamine sparing effect of AVP.[13]

Fernandez *et al*. conducted a cohort study to report the effects of NA versus NA + AVP in refractory septic shock among children noted that MAP was maintained in both the groups at 1, 2, and 3 h. The study concluded that MAP was sustained over the time regardless of the medication.[14]

Recently, Chawla *et al.*[15] have suggested the concept of "broad-spectrum vasopressors," in which the patients in septic shock should be started on multiple vasopressors with different mechanisms of action and once the responsiveness is assessed; then, the de-escalation can be initiated. This is because it has been shown that critically ill patients who are non-responders to high-dose catecholamines have a fatal outcome and patients have a variable response to vasopressin and angiotensin II. The authors believe that this approach will improve the responsiveness of the patients and survival in septic shock.

Evidence on the response to vasopressors in septic shock is inadequate and inconclusive. The present study was conducted in a real-life environment and hence provides pragmatic results. The limitations of the study are that it was a short-term observational study and conducted in a single center. The sample size was small and no defined criteria for the addition of vasopressin to NE were followed, mainly due to the lack of guidelines. In the future, newer therapeutic agents with better clinical trial designs and execution are required to reduce the high mortality associated with septic shock.

CONCLUSION

Thus, from the present study, it can be concluded that as per surviving sepsis guidelines, vasopressors were initiated to maintain target MAP by 1 h. However, no significant differences were noted among patients receiving NA or NA + AVP in terms of hemodynamic parameters. Long-term outcomes of these groups are awaited.

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