Research Article

Does vasopressin improve the mortality of septic shock patients treated with high-dose NA

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Abstract

Aim of Study: In Surviving Sepsis Campaign Guidelines 2012, noradrenalin (NA) is recommended as a first choice vasopressor. Although vasopressin (VP) is recommended for the treatment of NA-resistant septic shock, the optimal parameters for its administration remain unclear. **Materials and Methods:** We conducted a retrospective study to evaluate the clinical outcomes of the administration of VP to adult septic shock patients who were undergoing high-dose NA (≥0.25 μg/kg/min) therapy in our Intensive Care Unit between January 2010 and December 2013. We defined high-dose NA as a dose of >0.25 μg/kg/min, based on the definition of low-dose NA as a dose of 5–14 μg/min because the average body weight of the patients in this study was 53.0 kg. **Results:** Among 29 patients who required the administration of high-dose NA, 18 patients received VP. Although the patient background physiological conditions and NA dose did not differ between the two groups, the survival rate of the VP-treated patients was significantly lower (33%) than that of the patients who were managed with a high-dose of NA-alone (82%) (P = 0.014). The lactate clearance did not change after the administration of VP, whereas it improved when in NA treatment alone. **Conclusion:** The results suggest that the administration of VP did not improve the mortality among septic shock patients when administered in addition to high-dose NA.

Keywords: Lactate clearance, noradrenalin, septic shock, vasopressin

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.178175

Quick Response Code:

Introduction

Septic shock is a form of cardiovascular failure in which decreased systemic vascular resistance, and abnormal blood distribution is induced by the production of a vasodilating substance. The Surviving Sepsis Campaign Guidelines 2012 (SSCG2012) recommended noradrenaline (NA) as the first choice of vasopressor for the treatment of septic shock.[1] Vasopressin (VP) was recommended to be added to NA with the intent of raising the blood pressure or decreasing norepinephrine dosage.[1]

The VASST study found that there was no significant difference in the mortality of patients who were treated by NA with or without VP.[2] Although a subanalysis showed that the mortality tended to be lower in patients who required 5–14 μg/min of NA,[2] the benefits of adding VP to a higher dose of NA have not been confirmed. Another report showed that VP did not improve the mortality when it was administered in combination with NA at doses of >0.6 μg/kg/min.[3]

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How to cite this article: Ohsugi K, Kotani T, Fukuda S, Sato Y, Toyama S, Ozaki M. Does vasopressin improve the mortality of septic shock patients treated with high-dose NA. Indian J Crit Care Med 2016;20:137-40.

Thus, the effects of an additional administration of VP to patients with septic shock who were treated with high-dose NA still remained unclear. Moreover, the definition of high-dose NA has not yet been established, and the details of VP administration, including the NA dose at which VP should be initiated or terminated, have not been standardized.

We therefore conducted a retrospective study to investigate the effects of the addition of VP to high-dose NA therapy in septic shock patients. We also determined the definition of high-dose NA.

Materials and Methods

After Institutional Review Board approval, a retrospective review was undertaken of the clinical records of all adult patients who were admitted to our multidisciplinary general Intensive Care Unit (ICU) between January 2010 and December 2013. All patients who were diagnosed with septic shock and received an infusion of high-dose NA were included in the analysis. We defined high-dose NA as a dose of > 0.25 μg/kg/min, based on the definition of low-dose NA as 5–14 μg/min and because the average body weight of the patients in this study was 53.0 kg.[2] There was no institutional standard regarding the timing of VP administration; thus, the administration was at the discretion of the physician in charge.

The patients who received high-dose NA were divided into two groups: Patients who were treated with NA-alone (NA-alone group) and those who were treated with NA + VP (VP group). The following data were collected: General demographic information, underlying diseases, Acute Physiology and Chronic Health Evaluation II score, Charlson's Comorbidity Index, ICU mortality, the use of low-dose steroid therapy, the dose of NA at the start of VP treatment, the duration from the start of NA infusion to VP infusion, the duration of VP infusion, the total amount of fluid, the lactate level (at ICU admission, at the initiation of NA infusion [0 h], and at 6, 12, and 24 h after the initiation of the NA infusion), and the lactate clearance. The lactate clearance was calculated by the following formula: 100 × (initial lactate − subsequent lactate)/initial lactate. The blood pressure and heart rate at ICU admission; at the initiation of NA infusion (0 h), and 6, 12, and 24 h later; at the initiation of VP infusion (0 h), and 6, 12, and 24 h later were collected.

Statistical analyses were performed using the SigmaPlot statistical software package for Windows (version 11.0; Systat, San Jose, CA, USA). The data are presented as either the means ± standard deviation or the percentages. Intergroup differences were compared using the Chi-square test, *t*-test, or a two-way repeated ANOVA as appropriate. Statistical significance was defined as $P < 0.05$.

Results

A total of 2723 patients who were treated during the study period were screened. Treatment for septic shock was performed according to the SSCG2008.[4] Seventy-six patients were diagnosed with septic shock and 54 patients (71%) survived [Table 1]. Twenty-nine patients required the administration of high-dose NA, 18 (62%) of whom received VP. The NA infusion rate was equivalent to 0.25 μg/kg/min or greater in the study population. The mean blood pressure was maintained at ≥65 mmHg within 6 h after the start of treatment in the ICU. An initial VP dose of 2 U/h was maintained without change until the end of the administration in all patients.

There were 9 (82%) and 6 (33%) survivors in the NA-alone and VP groups, respectively, which was significantly different ($P = 0.014$). No difference was observed in the background characteristics of the two groups with the exception of weight and body mass index [Table 2]. Low-dose steroid therapy was used to treat septic shock in seven patients [Table 3]. The NA dose was reduced in 10 patients by >30% in comparison to before VP infusion; however, only three of these patients survived. The lactate levels in the NA-alone group peaked at the start of NA treatment and gradually decreased over time. The lactate level remained at approximately 5 mmol/L in the VP group, whereas a greater improvement in the lactate values and clearance were observed in the NA-alone group. The difference, however, was not significant [Table 4].

Discussion

We found that VP infusion did not improve the mortality when it was added to an NA dose of 0.25 μg/kg/min or higher. There were no clinical data to show that VP improved the prognosis of septic shock patients who had already received a high-dose of NA.

A recent randomized clinical trial showed that survivors of septic shock had greater decreases in cytokines than nonsurvivors, and VP decreased the 24-h serum cytokine levels compared to NA.[5] Low-dose VP administered within the first 24 h of ICU admission in addition to low-dose NA in sepsis/septic shock patients led to earlier resolution of organ failure.[6] VP infusion is

Table 1: Baseline demographic date and characteristics of all patients

Age (y)	64.2 (12.7)
Females	15 (52)
Weight (kg)	53.0 (10.6)
Body mass index	21.0 (3.1)
Survivors	15 (52)
APACHE II score	28 (11)
Charlson comobidity index	5 (3)
Preexisting conditions	
Diabetes	6 (21)
Chronic renal failure	6 (21)
Immunosuppression	16 (55)
Dose NA, max (μg/kg/min)	0.56 (0.33)
Co-treatment	
VP	18 (62)
Low dose steroids	7 (24)
CRRT	10 (34)
Lactate at admission (mmol/L)	5.2 (3.8)
Blood culture positive	8 (28)

Date are presented as mean (SD) or number (proportion). BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; NA: Noradrenaline; VP: Vasopressin; CRRT: Continuous Renal Replacement Therapy

Table 2: Baseline demographic date and characteristics in noradrenalin group or vasopressin group

	NA group (*n*=11)	VP group (*n*=18)	*P* value
Age (y)	67 (10)	62 (14)	0.265
Females	5 (45.5)	10 (55.6)	0.622
Weight (kg)	48 (7)	56 (11)	0.037
Body mass index	19 (2)	22 (3)	0.012
APACHE II score	29 (14)	28 (9)	0.795
Charlson comorbidity index	4 (3)	5 (3)	0.268
Comorbid diagnosis			
Diabetes	3 (27.3)	4 (22.2)	0.851
Chronic renal failure	3 (27.3)	3 (16.6)	0.493
Immunosuppression	5 (45.5)	11 (61.1)	0.092
Hemodynamic state at ICU admission			
Systric blood pressure (mmHg)	82 (54-162)	96 (60-146)	0.149
Mean blood pressure (mmHg)	60 (38-114)	70 (40-119)	0.293
Diastolic blood pressure (mmHg)	46 (29-90)	56 (30-106)	0.286
Heart rate (beats/minute)	100 (66-140)	124 (60-160)	0.143
Lactate (mmol/L)	4.0 (0.8-9.5)	4.4 (1.5-16)	0.243
Blood culture positive	5 (45.5)	6 (33.3)	0.513
Mortality	9 (81.8)	6 (33.3)	0.014

Date are presented as mean (SD), number (proportion) or median (range)

recommended if the plasma level of VP decreases due to the worsening of a patient's pathological condition.[7] The addition of VP has also been recommended to maintain the blood pressure or to reduce the dose of NA when catecholamine resistance is observed.[8] Thus, as shown in the *post hoc* comparisons of the VASST study, earlier addition of VP probably benefits the patients with septic shock in terms of avoiding high-dose NA infusion and improving mortality.

One of the adverse effects of VP is the deterioration of organ perfusion due to the impairment of the peripheral circulation resulting from vasoconstriction.

Table 3: Characteristics after Intensive Care Unit admission in noradrenalin group or vasopressin group

	NA group (*n*=11)	VP group (*n*=18)	*P* value
NA administration	67 (10)	62 (14)	0.265
Length of time from ICU admission to NA administration (hour)	5 (45.5)	10 (55.6)	0.622
Maximum dose of NA (μg/kg/min)	48 (7)	56 (11)	0.037
VP administration	19 (2)	22 (3)	0.012
Length of time from admission to VP administration (hour)	29 (14)	28 (9)	0.795
Co-treatment			0.268
Low dose steroids	2 (18.2)	5 (27.8)	0.558
CRRT	5 (45.5)	10 (55.6)	0.597
Fluid therapy (ml)			
6 hour after ICU admission	2885 (300-6270)	3722 (280-11500)	0.391
12 hour after ICU admission	4782 (860-8927)	4170 (1920-12710)	0.720
24 hour after ICU admission	6134 (1800-13699)	6640 (2970-14630)	0.702
Hemodynamic state at 6 hour after ICU admission			
Systric blood pressure (mmHg)	110 (90-140)	102 (86-156)	0.856
Mean blood pressure (mmHg)	80 (61-100)	76 (58-97)	0.719
Diastolic blood pressure (mmHg)	60 (46-90)	60 (44-74)	0.819

Date are presented as mean (SD), number (proportion) or median (range)

Table 4: Lactate and lactate clearance after Intensive Care Unit admission in noradrenalin group or vasopressin group

	NA group (*n*=11)	VP group (*n*=18)	*P* value
Lactate (mmol/L)			
At ICU admission	4.0 (0.8-9.5)	4.4 (1.5-16)	0.243
At 6 hour after ICU admission	2.3 (0.6-9.1)	4.0 (0.9-14.6)	0.126
At 12 hour after ICU admission	2.2 (0.6-10.9)	5.0 (1.0-17.8)	0.104
At 24 hour after ICU admission	1.6 (0.5-13)	5.5 (0.8-17.8)	0.100
Lactate clearance (%)			
At 6 hour after ICU admission	−12.5 (−42.2-85.0)	2.3 (−166.0-78.6)	0.539
At 12 hour after ICU admission	0.0 (−29.8-36.5)	0.0 (−33.8-53.7)	0.504
At 24 hour after ICU admission	20.0 (−54.8-42.9)	−1.5 (−160.0-41.0)	0.107

Date are presented as median (range)

Prolonged hyperlactatemia and lactic acidosis observed in nonsurvivors in this study were consistent with the deterioration of organ perfusion. Since VP did not decrease the mortality in the patients whose NA dose could be decreased by VP, the potential explanations for prolonged hyperlactatemia include VP-induced lactate production, impairment of lactate clearance, or both.

The lactate clearance indicated the occurrence of tissue hypoxia and/or hypoperfusion during the treatment of septic shock;[9] a value of <10% reflects a decrease in the intrahepatic blood flow.[10] A previous study reported that a 10% increase in the lactate clearance was associated with an 11% decrease in the likelihood of mortality.[11] Patients with hyperlactatemia due to septic shock who underwent early lactate clearance-guided therapy tended to show an improved mortality in comparison to those who underwent early goal-directed therapy.[12] In this study, the lactate levels of the VP group showed no improvement, whereas the NA group tended to improve. These results indicate that hypoperfusion undoubtedly existed under VP plus high-dose NA, even though the initial treatment goal (mean blood pressure ≥65 mmHg) was achieved according to the SSCG2008.[4]

The optimal blood pressure to maintain tissue perfusion in patients with septic shock remains unknown. The SSCG2012 proposed that the optimal average blood pressure should be determined on an individual basis by evaluating systemic or local perfusion indicated by the lactate level, skin perfusion, consciousness level, or urine output.[13] Our results suggest that it is important to monitor not only the blood pressure but also tissue perfusion, to prevent worsening of the prognosis by the administration of VP for patients who have already received treatment with high-dose NA and that a serial measurement of the lactate value and lactate clearance would benefit these patients.

There are several potential limitations associated with this study. This was a single-center, retrospective, case-series study. The sample size was small, and the results may have been influenced by the patients' underlying diseases/conditions, which included immunosuppression. Furthermore, the course of the treatment for sepsis before ICU admission was not taken into account. Low-dose steroid therapy was recommended for patients with septic shock;[14] however, we had to use higher doses in most patients because they were on long-term steroid therapy.

Conclusion

Our results show that VP did not improve the mortality associated with septic shock in this cohort study when added to high-dose NA (≥0.25 μg/kg/min). Monitoring of the lactate clearance, as well as measuring of the lactate levels, would therefore be useful to understand the indications for the administration of VP.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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