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

Koichi Ohsugi, Toru Kotani, Satoshi Fukuda, Yoko Sato, Satoshi Toyama, Makoto Ozaki

Abstract

**Aim of Study:** In Surviving Sepsis Campaign Guidelines 2012, noradrenaline (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

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]

From:
Department of Anesthesiology and Intensive Care Medicine, Tokyo Women's Medical University, 'Department of Anesthesiology, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence:
Dr. Koichi Ohsugi, Department of Anesthesiology and Intensive Care Medicine, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
E-mail: k.ohsugi@kpb.biglobe.ne.jp

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.[3] 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 265 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
One of the adverse effects of VP is the deterioration of organ perfusion due to the impairment of the peripheral circulation resulting from vasoconstriction.

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.

**References**

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
2. Russell JA, Walley KR, Singer J, Gordon JC, Hébert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877-87.
3. Luckner G, Dünser MW, Joehlberger S, Mayr YD, Wenzel V, Ulmer H, et al. Arginine vasopressin in 316 patients with advanced vasodilatory shock. Crit Care Med 2005;33:2659-66.
4. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
5. Russell JA, Fjell C, Hsu JL, Lee T, Boyd J, Thair S, et al. Vasopressin compared with norepinephrine augments the decline of plasma cytokine levels in septic shock. Am J Resp Crit Care Med 2013;188:356-64.
6. Bihari S, Prakash S, Bersten A. Low-dose vasopressin in addition to noradrenaline may lead to faster resolution of organ failure in patients with severe sepsis/septic shock. Anaesth Intensive Care 2014;42:671-4.
7. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, et al. Arginine vasopressin reduces permitted strong systemic vasodilation in patients with septic shock. Crit Care Med 2003;31:1752-8.
8. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiaology 2002;96:676-82.
9. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock 2009;32:35-9.
10. Hernandez G, Regueira T, Bruhn A, Castro R, Rovigno M, Fuentealba A, et al. Relationship of systemic, hepatosplanchnic, and microcirculatory perfusion parameters with 6-hour lactate clearance in hyperdynamic septic shock patients. An acute, clinical-physiological, pilot study. Ann Intensive Care 2012;2:44.
11. Nguyen HB, Rivers EP, Knoblich BP, Jacobse G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32:1637-42.
12. Jansen TC, van Bonnel J, Schoonoverbeek FJ, Skewsijk Visser SJ, van der Klooster JM, Linn AP, et al. Early lactate-guided therapy in intensive care unit patients. A multisite, open-label, randomized controlled trial. Am J Resp Crit Care Med 2010;182:752-61.
13. Srigl WI, Milner DA Jr, Sundar S, Mphantsa W, Majumdar SR. Safety and efficacy of corticosteroids for the treatment of septic shock: A systematic review and meta-analysis. Clin Infect Dis 2009;49:93-101.
14. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-24.