The Therapeutic Role of Vasopressin on Improving lactate Clearance During and After Vasogenic Shock: Microcirculation, Is It The Black Box?

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Abstract- Arginine vasopressin as a supplementary vasopressor in septic shock restores vascular tone and mean arterial pressure, meanwhile decreases dose and exposure time to catecholamines. The objective of this study was to evaluate the effect of vasopressin on lactate and lactate clearance as markers of tissue perfusion during septic shock. In this prospective, randomized, controlled trial, 30 patients with septic shock were enrolled in two groups. One group received norepinephrine infusion (titrated to reach the target MAP of ≥65 mm Hg) and the other group in addition to norepinephrine, received vasopressin at a constant rate of 0.03 u/min. Serum lactate levels were assessed at baseline, 24 and 48 hours after randomization. Lactate clearance was estimated for each patient at 24 and 48 hours. Venous lactate was measured in both groups. Despite a tendency toward higher venous lactate at 24 and 48 hours in the norepinephrine group (3.1 vs. 2.5, *P*=0.67 and 1.7 vs. 1.1, *P*=0.47), the conflict was not statistically significant among them. While lactate clearance after 24 hours was significantly higher in vasopressin treatment group (46% vs. 20%, respectively; *P*=0.048), the 48-hour lactate clearance did not differ from statistic viewpoints despite their clinical values (66% vs. 40%, *P*=0.17). Although lactate levels did not significantly differ between treatment groups, lactate clearance at 24 hours was significantly higher in vasopressin group. This may be the effect of vasopressin effect on microcirculation and tissue hypoperfusion or its catecholamine sparing effect.

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Keywords: Vasopressin; Septic shock; Lactate clearance

Introduction

Sepsis-induced hypotension resistant to fluid resuscitation recognized as septic shock is one the most common cause of intensive care unit admission and despite all new improvements in sepsis management, it remains one of the leading causes of Intensive Care Unit (ICU) mortality (1-4).

According to the latest surviving sepsis campaign (SCC) guideline, early diagnosis and utilization of evidence-based therapy for hemodynamic support (early goal-directed therapy) in severe sepsis includes utilization of broad spectrum antibiotics, volume replacement, and vasopressors. Vasopressors are essential in sustaining perfusion pressure in severe hypotension, to reach the hemodynamic goals such as central venous pressure (CVP), mean arterial pressure (MAP) and Urine output and oxygenation (4).

Norepinephrine (NE) is the first vasopressor of choice in septic shock which is a α_1 and β_1 agonist with a potent vasoconstrictive properties (4).Vasopressin is an endogenous peptide hormone which is relatively deficient during septic shock as a result of depletion of vasopressin store and inhibition of synthesis and release from the pituitary gland (1,3). Arginine vasopressin (AVP) is not recommended as a single initial vasopressor and may be added to NE for increasing MAP or decreasing NE dose requirement in refractory hypotension (4). Recent studies have shown that continuous infusion of vasopressin restored vascular tone and mean arterial pressures via V1 receptor in the septic shock patients with the same safety profile of catecholamines. Moreover, increasing vascular response to catecholamines, which results in the catecholamine dose reduction and urine output and glomerular filtration rate improvement (1-3,5). According to a recent study,

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early initiation of AVP resulted in shorter catecholamine exposure time and better outcome (6). Since NE doses higher than 0.5 μg/kg/min or for more than three days have been proven to be an independent risk factor for death in septic shock patients (1,7), using adjunct agents to lower catecholamine dose requirements in septic shock seems justifiable.

Hypoperfusion during the early phase of sepsis exists even in the absence of hypotension as a result of vascular hyperpermeability, loss of blood volume and a decrease of vascular tone, which could lead to tachycardia, renal failure and CNS abnormalities (8). Patient blood pressure is not always an indicator of blood flow and, as a result, reaching a goal mean arterial pressure is not enough to restore perfusion pressure (9). Most widely used biomarker of perfusion is blood lactate (10). In most tissues, glucose is metabolized to pyruvate and under anaerobic condition, cells convert pyruvate to lactate. In septic shock due to hypotension, endothelial damage and disseminated intravascular coagulation (DIC), organ hypoperfusion occur which create an anaerobic condition and hyperlactatemia (10). Recent studies have shown that lactate clearance might be an alternative to ScvO2 as a marker of the effectiveness of early resuscitation in septic shock (8).

The purpose of this study was to evaluate the effect of early initiation of low-dose AVP (0.03 U/min) on lactate level and lactate clearance as markers of tissue perfusion in septic shock.

Materials and Methods

This survey was taken between November 2012 and April 2014 in a 20-bed general surgical and emergency, intensive care unit of a tertiary teaching hospital (Sina hospital), in Tehran, Iran. The work was approved by the Medical Ethics Committee of Tehran University of Medical Sciences (TUMS) (91-02-33-18310-63707) and written informed consent was obtained from patients' next of kin.

The survey was planned as a prospective, randomized, controlled, open-label trial. Patients older than 18 years old were admitted if they were diagnosed with septic shock within 12 hours of ICU admission. Diagnosis of septic shock was made based on the criteria defined by the American college of chest physicians/society of critical care medicine consensus conference committee (two or more of Systemic Inflammatory Response Syndrome (SIRS) criteria, infection [proven or suspected], new organ failure and hypotension) (11).

Exclusion criteria included; more than 12 hours of septic shock diagnosis have passed, previous vasopressin use, mesenteric ischemia, acute coronary syndrome, heart failure (class III or IV of NYHA), hyponatremia (Na < 130 mmol/L), pregnancy, patient with a poor prognosis (death anticipated within hours), end-stage renal failure, vasospastic diseases, recruitment in another clinical trial or unwillingness to give written informed consent.

Patients were enrolled in one of the two work groups based on a data processor-generated random number list. The first group received norepinephrine (Laboratorios Normon, Spain) infusion adjusted to MAP≥65 mm Hg. The second group received the same protocol plus vasopressin (Exir Pharmaceutical Co. Tehran, Iran) infusion at a constant rate of 0.03 u/min. Referable to the clinical status of the field, neither clinicians nor the researchers were blinded to the study groups.

NE was titrated to reach map of ≥65 mm/Hg and the addition of other vasopressors such as dopamine, epinephrine and inotropic supports (e.g., dobutamine) were entrusted to the discretion of patients' hemodynamic managements. AVP infusion discontinued the resolve of the shock or occurrence of life-threatening adverse effect (digital ischemia, mesenteric ischemia, arrhythmias, serum sodium less than 130 mEq/ml) or patient death. Vasopressors were tapered if target MAP was achieved for more than 8 hours. Crossover between study groups was not permitted during the test.

Early goal-directed therapy was started for all septic shock patients within the first 6 hours after the onset of hypotension. Volume resuscitation was done based on patient's central venous pressure. Hydrocortisone (100 mg every 8 hours) was added based on the patient's clinical condition. Intubated patients on mechanical ventilation were sedated with fentanyl infusion and midazolam. All the supportive sepsis therapies were performed according to the SCCM guideline (4).

At baseline, patients' characteristics and underlying diseases were registered. Simplified Acute Physiologic Score (SAPS) II was used for assessment of severity of illness at baseline (12), and the Sequential Organ Failure Assessment (SOFA) score as a marker of organ dysfunction (13) was calculated on a daily basis. Hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, CVP, body temperature and oxygen saturation (SpO_2) were measured continuously. Sodium, White blood cells, Platelet count, aspartate and alanine aminotransferase, total bilirubin, creatinine and ABG including pH, bicarbonate and partial pressure of O2

were collected at baseline, 24 h, and 48 h after randomization. Procalcitonin level was quantified at baseline for each patient. A 12-lead electrocardiograph was done every day. Cardiac enzymes echocardiography and other diagnostic imaging were performed whenever indicated by physical examination. Survival status of patients was recorded during ICU admission and 28 days after randomization. Adverse events were evaluated on a daily basis. NE requirements were documented during the trial.

Blood samples were collected at baseline, 24 hours and 48 hours after study initiation into heparinised tubes and were immediately centrifuged at 37°C for 10 minutes at 2000g and the plasma was stored at -80°C for later analysis of lactate level. Colorimetric measurement of serum lactate was performed on a Roche Cobas Integra 400 analyzer (Roche Diagnostics, Indianapolis, IN).

Lactate clearance calculated via equation [A]: (14)

$$\text{Lactate clearance} = \frac{\text{L1 (Initial Lactate)} - \text{L2 (Lactate more than 2 hours later)}}{\text{L1 (Initial Lactate)}} * 100$$

The primary outcomes were to compare venous lactate levels and lactate clearance (LC) in both treatment groups and the final therapeutic effect of AVP on these markers. Secondary endpoints were an evaluation of systemic hemodynamics, arterial pH, NE requirements for each group, mortality rates (ICU mortality and 28-day mortality) and organ failure (SOFA score).

Statistical Analysis

The main effects were the differences in lactate levels and LC at 24 and 48 hours between two treatment groups. Granting to the previous study (15) to detect a 1.6mmol/L difference in lactate levels at 24 and 48 hours, assuming an SD of 1.6mmol/L with a significance level of 0.05 and 80% power, each group must include at least 15 patients.

The results of the study were reported as mean ± SD or number (%).One-sample Kolmogorov-Smirnov test was used for assessment of the normality distribution of variables. For comparison of groups with normally distributed data the Student t-test was performed and for nonnormal distributed data The Mann-Whitney U-test was applied. The $\chi 2$ test was used for comparison of categorical variables. The Pearson product-moment correlation used to measure the association between two variables. IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp) was applied for statistical analysis. For all analyzes, $P<0.05$ was considered significant.

Results

The total number of 37 patients had met the inclusion criteria, of which 7 were excluded (4 patients with end-stage renal failure, 2 patients included in another trial and one patient with a poor prognosis). The remaining 30 patients randomly assigned to NE or AVP group. The patients have all entered the study within the first 12 hours of septic shock. Patients' data were all collected during the first 48 hours following registration.

Patients' demographic data are described in Table 1. Demographic and clinical variables between the two groups before randomization were not different (Table 1). In the first 48 hours of the study, 6 patients in the NE group and 2 patients in the AVP group died (*P*=0. 099). The severity of illness in both groups was high based on SAPS II score of 56.5 in the NE group and 53.4 in the AVP group. Moreover, procalcitonin levels at baseline were comparable between groups (7.9 *vs.* 5.2, *P*=0.52).

Although heart rate in AVP group was significantly lower than NE group at 24 and 48 hours, SBP and MAP were higher only after 24 hours, but not at 48 hours. CVP in both groups was comparable during the survey.

The infusion rate of AVP was constant, but NE infusion rate changed during the survey, and it was significantly lower in AVP group. At 24 hours, it was 13.1 µg/min in the NE group vs. 5.5 µg/min in AVP group (*P*<0.001) and at 48 hours it was 6.5 µg/min in the NE group vs. 3.9 µg/min in AVP group (*P*=0.045).

ICU mortality (NE vs. AVP: 53.3% vs. 46.7% days, *P*=0.456), 28-day mortality (NE vs. AVP: 46.7% vs 33.3%, *P*=0.715) and length of ICU stay (NE vs. AVP:18.3 ± 9.6 vs. 23.7 ± 7.1 days, *P*=0.14) were not significantly different between groups. Interestingly, average age of survivors and non-survivors were not different (59.8 ± 20.1 years in survivors and 63.3 ± 15.7 years in non-survivors, *P*=0.62)

Similarly, the rate of organ dysfunction between both groups were similarly based on SOFA score at 48 hours (12.8 vs. 11.4, *P*=0. 32). Renal function was not significantly different between either group. Urine output after 48 hours in the NE group was 2633± 1768 ml and in AVP group was 3530± 2022 ml (*P*=0. 29). Serum creatinine change after 48 hours was not significantly different either (NE vs. AVP: 0.67 *vs.* 0.26 mg/dL, *P*=0.15). Need for hemodialysis during the study was 40% in NE group and 26.7% in the AVP group (*P*=0.439)

Table 1. Demographic information and baseline characteristics of patients

		NE (n=15)	AVP (n=15)	*P.* value
Age (year)		62.8 ± 15	65.2 ± 21.3	0.73
Male sex n (%)		9 (60)	10 (66.7)	0.7
	CAD	6 (40)	4 (26.7)	0.439
	CHF	2 (13.3)	3 (20)	0.624
	HTN	10 (66.7)	8 (53.3)	0.456
	COPD	1 (6.7)	3 (20)	0.283
Preexisting conditions n (%)	**CKD**	4 (26.7)	3 (20)	0.666
	Diabetes	2 (13.3)	2 (13.3)	1
	CLD	1 (6.7)	0 (0)	0.309
	IDU	1 (6.7)	2 (13.3)	0.543
	Cancer	1 (6.7)	1 (6.7)	1
	SOT	0 (0)	1 (6.7)	0.309
Admission type n (%)	**History of corticosteroid use**	1 (6.7)	2 (13.3)	0.543
	Medical	7 (46.7)	3 (20)	0.296
	Elective surgical	3 (20)	4 (26.7)	--
	Emergency surgical	5 (33.3)	8 (53.3)	--
New organ failure at randomization n(%)	**Cardiovascular**	15 (100)	15 (100)	1
	Respiratory	13 (86.7)	14 (93.3)	0.543
	Renal	7 (46.7)	4 (26.7)	0.256
	Hematologic and coagulation	4 (26.7)	3 (20)	0.666
	Neurologic	-	-	-
The source of infection	**Lung**	7 (46.7)	6 (40)	0.713
	Abdomen	4 (26.7)	5 (33.3)	0.690
	Urinary	1 (6.7)	2 (13.3)	0.543
	Other	3 (20)	1 (6.7)	0.283
SIRS criteria	**SAPS II**	56.5 ± 10.3	53.4 ± 19.3	0.58
	SOFA	12 ± 2.6	11.9 ± 3.5	0.9
	Procalcitonin	7.9 ± 13.8	5.2 ± 8.6	0.52
	Temperature (°C)	37.7 ± 0.9	37.4 ± 1.6	0.58
	Heart rate (bpm)	87 ± 18	90 ± 19	0.77
	Mechanically ventilated n (%)	13 (86.7)	14 (93.3)	0.543
	Leucocyte count (×10^9/L)	10.4 ± 8.8	16.1 ± 11.1	0.134
Tissue hypoperfusion/organ dysfunction	**PaO2/FiO2 (mm Hg)**	286 ± 240	211 ± 138	0.3
	Urinary output (mL/24 h)	2013 ± 1215	1909 ± 1391	0.8
	Lactate (mg/dL)	35.9 ± 19.5	41.8 ± 17.3	0.46
	pH	7.32 ± 0.07	7.3 ± 0.1	0.53
	Platelet counts (×10^9/L)	137 ± 88	161 ± 87	0.45
	GCS	6.7 ± 0.7	7.4 ± 2.9	0.36
	Time from onset of shock to randomization (hr)	6.8 ± 2.4	7.4 ± 3.4	0.58
	norepinephrine dose at randomization (µg/min)	12.1 ± 4.5	12.5 ± 4.3	0.8
Vasoactive drugs n (%)	**Dopamine**	6 (40)	4 (26.7)	0.439
	Epinephrine	2 (13.3)	3 (20)	0.624
	Dobutamine	3 (20)	2 (13.3)	0.624
Hydrocortisone use n (%)		6 (40)	9 (60)	0.273

NE norepinephrine, AVP Arginine vasopressin, CAD Coronary artery disease, CHF Congestive Heart Failure, HTN Hypertension, COPD Chronic Obstructive Pulmonary Disease, CKD Chronic Kidney Disease, CLD Chronic Liver Disease, IDU Injection Drug User, SOT Solid-Organ Transplant, SAPS II Simplified Acute Physiology Score II, SOFA Sepsis-related Organ Failure Assessment, SIRS systemic inflammatory response syndrome, PaO2 Partial Pressure of Oxygen, FIO2 Fraction of Inspired Oxygen, GCS Glasgow Coma Score

Even though there was a trend toward higher ALT (217 vs 38 IU/L), AST (392 vs 26 IU/L) and total bilirubin (5.1 vs 3.1 mg/dL) in NE group vs. AVP group, but the difference was not statistically significant. PaO2/FiO2 was also comparable between groups.

SOFA score was comparable at baseline, 24 hours and 48 hours. Adverse effects in both groups were assessed on a daily basis, which were as follows cardiac

arrest (NE vs. AVP; 3 vs. 1), arrhythmias (NE vs. AVP; 3 vs. 1), two instances of hyponatremia in AVP group (129 mEq/l and 132 mEq/l), one case of digital ischemia in AVP group, 2 cases of hypertension in AVP group (SBP 149 mmHg, 173 mmHg) (Table 2).

Table 2.Changes in the hemodynamic response and laboratory parameters

	Baseline	*P*-value	24 hr	*P*.value	48 hr	*P*-value
HR beats/min						
NE	87.2±18	0.663	105.4±10.1	0.003	104.8±7.8	0.0001
AVP	90.2±19.2		86.9±18.9		85.1±11.1	
SBP, mm Hg						
NE	75.1±11.1	0.295	101.8±27.6	0.032	123.5±19.4	0.790
AVP	80.±14		121.9±20.3		121.5±15.6	
MAP, mm Hg						
NE	62.2±6.5	0.613	79.5±10.4	0.044	82.1±16.3	0.671
AVP	65.4±6.4		87.6±10.4		85.1±16	
CVP mm Hg H2O						
NE	11.5±11.2	0.41	17.3±6.2	0.86	11.1±9.8	0.16
AVP	15.4±4.9		16.9±5.3		16.9±4.9	
PaO2/FIO2						
NE	286±240	0.30	247±182	0.73	265±192	0.17
AVP	211±138		227±139		179±96	
pH						
NE	7.32±0.07	0.602	7.29±0.14	0.909	7.32±0.09	0.673
AVP	7.30±0.10		7.28±0.10		7.30±0.07	
Lactate, mg/dL						
NE	35.9±19.5	0.398	28.4±23.3	0.673	15.8±9.6	0.472
AVP	41.8±17.3		23.1±15.4		10.3±.5.1	
Creatinine, mg/dL						
NE	1.4±0.5	0.550	1.7±0.4	0.268	2±0.9	0.222
AVP	1.3±0.6		1.4±0.6		1.5±0.7	
Urine output ml/hr						
NE	2013±1215	0.830	2646±928	0.592	2633±1768	0.295
AVP	1909±1391		2980±2174		3530±2022	
Platelets, g/L						
NE	137066±87632	0.452	130666±87742	0.622	149777±91146	0.746
AVP	161333±86663		146933±91056		137246±85597	
AST, IU/L						
NE	81.7±54.1	0.946	392.7±944.6	0.468	192.6±225.6	0.550
AVP	84.7±73.2		26±17		7±6.2	
ALT, IU/L						
NE	66.2±16.2	0.677	217.8±506.2	0.507	273.6±410.9	0.645
HR, beats/min						
	82.1±71.2		38.2±55.9		19±11.2	
Total Bilirubin, mg/dL						
NE	5.1±6.4	0.334	5.1±6.4	0.345	5.5±7.8	0.193
AVP	3.1±6.4		3.1±4.6		2.3±2.8	
NE, µg/min						
NE	12.1±4.4	0.806	13.1±5.5	0.0001	6.5±2.6	0.045
AVP	12.5±4.3		5.4±3.7		3.9±2.9	
SOFA score						
NE	12±2.6	0.399	11.8±3	0.327	12.8±4.1	0.329
AVP	11±3.3		10.9±2		11.4±2.4	

NE norepinephrine, AVP Arginine vasopressin, HR Heart Rate, SBP Systolic Blood Pressure, MAP Mean Arterial Pressure, CVP Central Venous Pressure, PaO2 Partial Pressure of Oxygen, FIO2 Fraction of Inspired Oxygen.

Lactate in both groups was assessed from the venous line. There was a trend toward higher venous lactate at 24 and 48 hours in the NE group than in the AVP group (28.4 vs. 23.1, *P*=0.67 and 15.8 vs. 10.3, *P*=0.47; respectively). However, lactate clearance (LC) calculated from equation [A] was significantly different between groups. Lactate clearance after 24 hours (LC24) were 21% with NE and 46% with AVP, *P*=0.048. Although lactate clearance after 48 hours (LC48) were

higher in AVP group, but it did not quite arrive at a statistically significant level (40% with NE and 66% with AVP, *P*=0.17).

There was a significant correlation between NE dose at 24 and 48 hours with lactate clearance at the same times. (NE dose and LC24 had a Pearson correlation coefficient of -0.56, *P*=0.002 and NE dose and LC48 had a Pearson correlation coefficient of -0.46, *P*=0.034). Nevertheless, no other significant correlation between NE dose and other parameters such as heart rate, systolic blood pressure or urine output were found. Of note, there was a correlation between baseline lactate and 28-day mortality (Pearson correlation coefficient of 0.458, *P*=0.013) (Figures 1, 2).

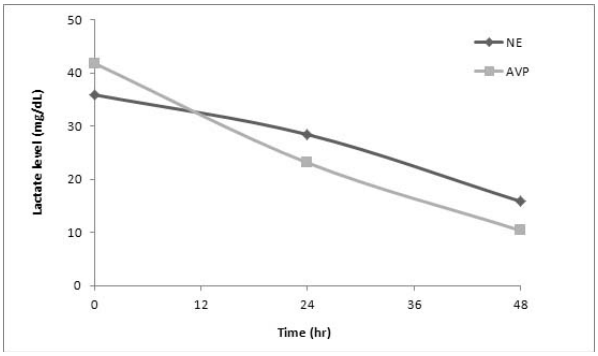

Figure 1. Mean lactate at baseline, 24 hours and 48 hours after randomization in each treatment group

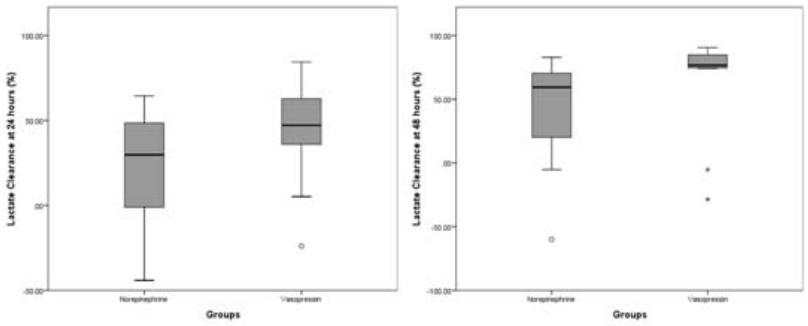

Figure 2. Percentage of lactate clearance at 24 and 48 hours after randomization in each treatment group

Discussion

In this randomized trial, AVP effects on septic shock patients were assessed. Consistent with previous trials, vasopressin when added to NE, the need for NE was decreased, and there were a higher MAP and lower heart rate in this group of patients. Overall, serious adverse effects were comparable in both groups (6,16-23). ICU mortality and 28-day mortality were not different between groups.

In this study, venous lactate was measured, as shown in previous studies, there is a strong agreement between arterial and venous lactate levels in sepsis and septic shock patients, but venous lactate values are little higher (24). Although the venous lactate level did not differ between groups, but lactate clearance was higher in the AVP group at 24 and 48 hours, though only at 24 hours LC was significantly different. This has confirmed our hypothesis that low-dose AVP could increase LC and lead to improved tissue perfusion. In most studies, AVP reduced lactate levels during the study, but it was not significantly different from NE groups in these studies (16,17,21,25,26).

In the early phase of sepsis, lactate is probably a byproduct of anaerobic metabolism originating from tissue hypoperfusion, which is a result of a macro and microcirculatory dysfunction, hypermetabolic state and mitochondrial dysfunction (27). High initial lactate is an independent predictor of a higher mortality rate in sepsis (28). A small increase in lactate levels (lactate > 1mmol/L) even in the absence of hypotension could be a manifestation of organ hypoperfusion (8). To normalize the lactate level, the balance between production and consumption should be established. This is only feasible by adequate perfusion pressure, normal mitochondrial function and sufficient hepatic clearance (29).

ACC guideline recommends normalization of ScvO2 and lactates via resuscitation in patients with hyperlactatemia as markers of tissue hypoperfusion. As spectrophotometric catheters to monitor ScvO2 may not be available in every center, lactate is a feasible alternative (4).

Wacharasint *et al*., retrospectively evaluate the lactate level of two previous studies comparing NE and AVP in septic shock patients (30). The results showed that lactate could play the role of a biomarker of response to vasopressin in septic shock patients. Although SCC guideline uses a cut-off of 4.0 mmol/L for diagnosis of severe septic shock, some studies argue that the cut-off should be lower (30). As previously shown in other studies, 45% of patients were in the normal range of lactate during septic shock, which make lactate less useful as a sole marker of severity in these patients (31). Therefore, utilization of lactate clearance (LC) which was originally an assessment tool in trauma patients appears to be more practical. Low lactate clearance is correlated with increased procalcitonin and IL-6 and also is a predictor of higher mortality in severe sepsis (10). So far, LC is utilized more like a resuscitation endpoint in studies (28).

However, there is a debate about the final goal of LC in septic shock patients at different time points. Nguyen *et al*., in a cohort of patients with severe sepsis and septic shock showed that LC after 6 hours was an independent predictor of survival and best cut-off point for this predictor was 10% (14). Craig *et al*., in a retrospective study in patients with severe sepsis and septic shock showed that optimal cut-off values for LC were 36% for 6 hours, significantly higher than previous reports (28). Jansen *et al*., target LC of 20% at 2 hours interval in patients with lactate higher than 3 mEq/L. LC group had a significantly lower mortality rate (32). In a study by Tian *et al*., patients with the target LC of 30% at 6 hours showed a significant decrease in APACHE II score after 48 hours, shorter ICU stay and lower 28-day mortality, compared to patients with the target LC of 10% (33). In another multicenter study by Nguyen *et al*., the addition of goal LC to the resuscitation bundle recommended by the SCC guideline improved outcome (34). As LC demonstrates the quality of resuscitation, patients with higher LC have better outcomes (28).

In our study, the high lactate clearance in AVP group may be the result of AVP effects on microcirculation and tissue perfusion. Although AVP is known for its vasoconstrictive properties, activation of endothelial V1, V2 and oxytocin receptors in some vascular beds such as pulmonary, renal, mesenteric, coronary and cerebral arteries may cause vasodilation via the Nitric Oxide (NO) release by the endothelium (3,5). However, other *hypotheses also can be* considered [1] AVP decreases NE dose requirement and as a result, decrease vasoconstriction due to a high dose of NE. This NE sparing effect results in a better tissue perfusion. [2] Lactate release from skeletal muscle is stimulated by catecholamine's effect on Na+, K+-ATPase. The resultant lactate will offer a fuel substrate for organs such as brain, liver and heart (9,10,35). This means that high-dose catecholamines increase the lactate level despite sufficient perfusion pressure (3) The Liver is in charge of main lactate clearance by oxidizing it or converting it back to glucose. As a result, liver dysfunction as a common organ failure in sepsis may cause hyperlactatemia even with adequate perfusion pressure (10). So a trend toward higher AST (NE vs. AVP: 392 vs. 26), ALT (NE vs. AVP: 217 vs. 38) and total bilirubin (NE vs. AVP: 5.1 vs. 3.1), may indicate a higher rate of liver failure in NE group and lead to lower LC in NE group in our study.

Despite significantly higher LC at 24 hours in AVP group (P=0.048), LC at 48 hours (P=0.17) was not significantly different. One explanation might be the development of tachyphylaxis against the vasoconstrictive effect of AVP (36). Constant AVP dose of 0.03 u/min which was used in this study may become less effective after 48 hours due to the tachyphylaxis. Another reason for this result might be the lower chosen dosing of AVP. In our study, we use 0.03 u/min vasopressin as was recommended by the SSCM guideline (4) and VAAST trial (16). However, the optimum dose of AVP in septic shock is still unclear. Although some studies propose that higher dose of AVP (0.067u/min) may be more effective in septic shock (17, 19), hypoperfusion and higher rate of adverse events resulted from high dose AVP in some studies (23,37-39) persuade researchers to use low dose AVP which in conjunction with volume resuscitation and NE, showed a favourable effect on microcirculation and organ dysfunction (16, 40). Luckner *et al*., in a retrospective, controlled study of patients with vasodilatory shock compare supplementary infusion of AVP at 0.033 and 0.067 IU/min. The results showed that AVP dosages of 0.067 IU/min reduced lactate level more than 0.033IU/min (22 vs. 37 mg/dL, P<0.001) (19). It can be hypothesized that utilization of low-dose AVP in our study might be the reason of less lactate clearance after 48 hours.

Of note, in the largest trial of vasopressin in septic shock (VASST), lactate levels were similar between

treatment groups (16). This might be the result of the later initiation of AVP (12 hours) for shock rescue. In our study, AVP administered earlier (6.8 ± 2.4 hours) which may result in better lactate clearance. Therefore, earlier initiation and a higher dose of AVP in septic shock patients may lead to lower lactate levels and a better outcome.

The limitations of our trial include; smaller sample size, the study was not blinded due to clinical condition, cancer patients may bias the results and should have been excluded, AVP dose was not adjusted for body weight (41), and the infusion rate was fixed. Arterial lactate level could not be measured, and venous lactate was measured instead. Lactate level was measured after 24 and 48 hours of study initiation and early lactate level (6 hours) was not available.

In summary, we have investigated the effect of low-dose AVP (0.03 U/min) infusion added to NE in septic shock patients. Patients in AVP group had lower NE requirements, higher MAP, and lower heart rate. Even though lactate levels were comparable between groups, but LC was significantly higher at 24 hours after study initiation, which might be the sign of enhanced microvascular blood flow and tissue perfusion in this group of patients. Future trials with a larger sample size and the shorter time interval of lactate measurement are needed to evaluate AVP effect on LC in septic shock patients.

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