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Vasopressor Starting Dose and Association with Hemodynamic Goals, Renal Replacement Therapy, and Mortality

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ABSTRACT

Aim: There are no consensus recommendations for the starting dose of vasopressors in septic shock. The aim of this study was to evaluate the starting dose of vasopressors on hemodynamic, renal, and overall outcomes.

Study Design, Materials, Methods: This was a retrospective, single center cohort study from January 2016 to June 2018. The primary outcome of this study was to compare low-dose versus high-dose initial vasopressors and the impact on the attainment of MAP at 6 hours in septic shock patients. We determine groups by evaluating the per-kilogram starting dose of vasopressors (mcg/kg/min) for the entire cohort and divided the cohort into two based on the median starting dose. Low-dose was below the median starting dose and high-dose was above the median starting dose. Bivariate analysis and multivariate linear and logistic regression analysis were completed to evaluate outcomes that were significantly associated with the MAP at 6 hours, development of renal failure needing continuous renal replacement therapy, and mortality.

Results: Patients who received high-dose initial vasopressors had a significant higher average MAP at 6 hours (57.9 mmHg vs 51mmHg; P = 0.003) and a lower rate of CRRT requirements (20.7% vs. 51.7%; P = 0.014). Each 0.01 mcg/kg/min increase in starting dose led to a 0.7 mmHg increase in MAP at 6 hours (95% CI 0.037 to 1.175; P = 0.001). Every 0.01 mcg/kg/minute increase in starting vasopressor dose was associated with 1% decreased odds of needing RRT (95% CI 0.0005 to 0.98; P = 0.049). The need for CRRT was significantly associated with mortality (OR=6.1;95% CI 1.23 to 33.3; P = 0.027).

Conclusion: A higher starting dose of NE was independently associated with MAP at 6 hours and reduced risk for CRRT.

Keywords: vasopressor agents, dose, septic shock, renal replacement therapy, mean arterial pressure

Introduction

Septic shock is defined as a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities with a greater mortality compared to sepsis alone (1,2). Per the Surviving Sepsis Campaign (SSC) guidelines, timely recognition and treatment of sepsis includes the rapid initiation of effective antibiotics, early targeted fluid resuscitation for stabilization of sepsis-induced tissue hypoperfusion, and the initiation of vasopressors to reverse hypotension in those that fail to respond to fluid resuscitation (3,4). Specific vasopressor dosing is not included in the guideline treatment of septic shock. The guidelines mention that the vasopressor dose should be titrated to an end point reflecting perfusion. To avoid adverse effects, vasopressors are often initiated at a lower dose and titrated every 5–15 minutes (5,6).

While starting vasopressors at a lower dose theoretically avoids adverse effects, starting at a lower dose may also lead to a delay in restoring adequate perfusion and contribute to hypoperfusion-induced organ injury, and even mortality. Previous studies have shown the risks of a delay in reaching and/or not sustaining target mean arterial pressure (MAP). Maheshwari et al. evaluated the association of MAPs below various thresholds in septic adult patients located in the intensive care unit (ICU) ≥24 hours (7). They found a 3.6% higher in-hospital mortality for every 2 hours a patient was below a goal MAP of 65 mmHg (P<0.001) (7). Another study by Bai et al. investigated the impact of delayed initiation of norepinephrine (NE) following the onset of septic shock and its effects on in-hospital mortality (8). Their study revealed a 5.3% increased mortality rate for every hour delay in NE initiation during

the first 6 hours after septic shock onset (8). These studies emphasize the importance of achieving a goal MAP of 65 mmHg within 6 hours, if not earlier, along with the consequences of prolonged time under the MAP goal.

The current SSC guidelines recommend starting vasopressors, specifically NE, in septic shock patients that do not respond to initial fluid resuscitation. However, there is a lack of evidence to determine the optimal starting dose of NE used to reach goal MAP. The aim of this study was to retrospectively compare MAP and clinical outcomes between patients receiving low and high initial doses of NE.

Materials and Methods

Study Design and Patient Population

The University of Illinois at Chicago Office for Protection of Research Subjects approved this study (Protocol # 2018–1342, approved 11/6/18) under a waiver of informed consent. This was a single-center, retrospective cohort study of patients admitted between June 2016 and June 2018. Patients were identified based on the presence of International Classification of Diseases (ICD) – 10 code for septic shock. Patients identified with septic shock were cross-referenced with a list of all patients receiving vasopressors during the study period. This was done to ensure that patients received vasopressors met the definition of shock. Patients were eligible to be included if they were at least 18 years old and diagnosed with septic shock requiring at least one vasopressor for a minimum of 2 hours. Septic shock criteria were further identified by ensuring the obtainment of blood cultures (i. e., suspicion of infection), initiation of antibiotics, presence of target organ dysfunction (diagnosed by the Sequential Organ Failure Assessment [SOFA] score) (9), initiation of vasopressors (as noted above), and serum lactate of at least 2 mmol/L (1). Patients were excluded if they were without shock, transferred from an outside hospital on vasopressors, received inotropes for cardiogenic shock, had an initial MAP greater than 65 mmHg prior to starting vasopressors, were pregnant, immediate post-cardiac arrest patients, or required intermittent hemodialysis (iHD) at baseline. Only one episode of septic shock per patient was included, no further episodes during their admission or a different admission were utilized.

Patients who met inclusion criteria were then categorized into two separate groups: low-starting-dose and high-starting-dose of vasopressor. The division into low and high-dose was based on the median weight-based starting dose of vasopressor in the sample (mcg/kg/min). Weight-based doses were calculated on actual body weight (ABW) measured upon admission to the ICU. The management of sepsis at our institution is directed by institutional Septic Shock Guidelines. Our institutional guidelines include fluid (e.g., 30 mL/kg in the first 3 hours), antibiotic (e.g., administration as soon as feasible), and vasopressor recommendations (e.g., NE first-line vasopressor, goal MAP ≥65 mmHg, titrated every 5 minutes to achieve goal MAP).

Data Collection

We manually extracted data from the electronic medical record (EMR) including demographic, laboratory, and outcome data. Demographic and baseline variables included: age (years), weight (kg), height (in), past medical history, serum creatinine (mg/dL), calculated creatine clearance (by Cockcroft-Gault equation in EMR and abstracted as such) (10), respiratory status (as defined by ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio and need for mechanical ventilation at onset of septic shock), and initial SOFA score. Hemodynamic variables were collected and included baseline MAP (most recent MAP prior to the initiation of vasopressors), time to achievement of MAP ≥65 mmHg, average MAP at 6, 12, and 24 hours, change in MAP from baseline, 6, and 12 hours, amount of fluid resuscitation in mL/kg at 3-hour, 24 hours, and 48-hour timepoints. Sepsis-related variables included percent of blood cultures obtained before antibiotics, percent of positive cultures from any site, and appropriate initial antibiotics as defined by published definition for those with positive cultures (11). Vasopressor therapy information was collected on all vasopressors initiated including the starting dose (converted to NE equivalents and presented in mcg/kg/min) (12), maximum dose in NE equivalents (mcg/kg/min), duration of vasopressors (in hours), addition of multiple vasopressors (number and percent needing more than one vasopressor), and time to initiation of second vasopressor. Vasopressors were considered discontinued if not administered for greater than 2 hours. This time point was chosen as our institutional nursing policy requires discontinued agents greater than 2 hours to be reordered by a provider.

Study Outcomes

The primary outcome of this study was a comparison of MAP at 6 hours after septic shock onset between low-dose and high-dose groups. This endpoint was chosen because improved hemodynamics at 6-hours has been shown to carry clinical significance (13). The secondary outcomes were to determine variables associated with the MAP at 6 hours, requirement of continuous renal replacement therapy (CRRT), and as well as mortality before discharge.

Statistical Analysis

Descriptive statistics were used for baseline characteristics, sepsis treatment variables, vasopressor variables, and outcomes. Comparisons were made between low- and high-starting dose groups. Normal continuous data were compared with the Student T-test and described using means with standard deviations (SD) and non-normal distribution data were compared with the Mann-Whitney U test and summarized using medians and interquartile range (IQR). Categorical outcomes were compared using the Chi-Square or Fisher's Exact test and summarized using counts and proportions. We used a sample size of convenience to include the number of patients to adequately capture practice variability in starting doses across our institution. Two-way repeated measures analysis of variance (ANOVA) was used to compare the MAP at various timepoints: baseline to 6 hours, 6 hours to 12 hours, and 12–24 hours. We assessed bivariate relationships between independent variables and dependent outcomes to populate our regression models and included variables with $P<0.1$ in bivariate analyses into the models. We employed multivariate linear regression modelling for MAP at 6 hours. We created a single-step logistic regression model for CRRT and in-hospital mortality. We used variance inflation factor (VIF) to assess and exclude variables for the models if the results demonstrated collinearity. We considered $P<0.05$ to be statistically significant in the regression analyses.

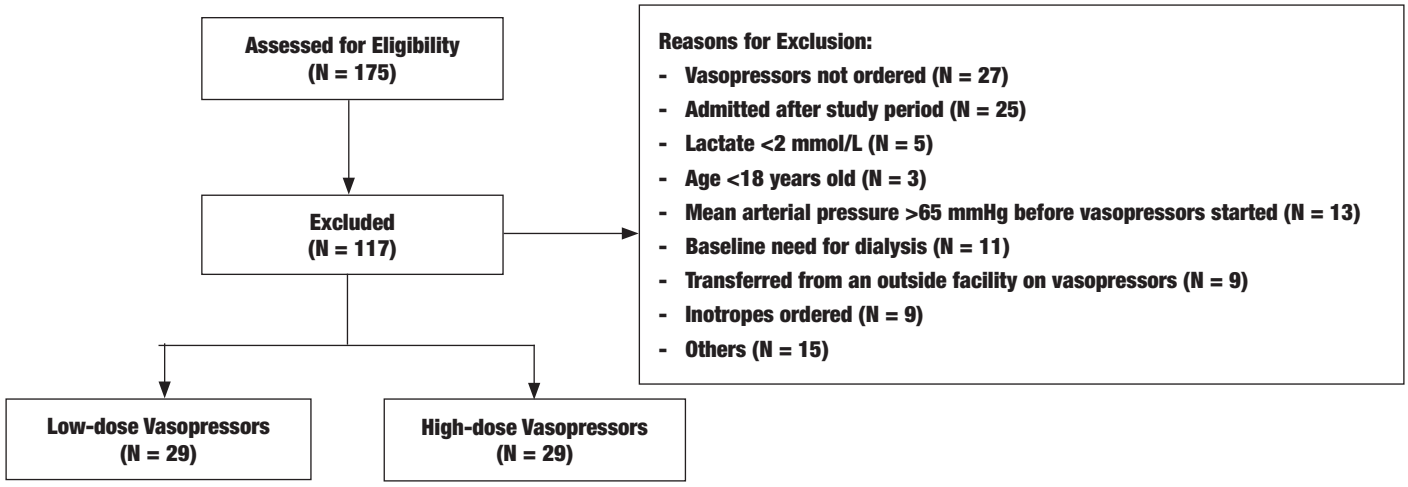

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram for patient inclusion and group assignment

Results

A total of 175 patients were evaluated with 117 excluded, leaving 58 patients included for analysis. The most common reason for exclusion was the lack of a vasopressor order meaning the patient did not fulfil septic shock criteria (Fig. 1). The baseline characteristics are presented in Table 1. Baseline characteristics were similar between the low-dose and high-dose groups. The patients' weight was significantly higher in the low dose group (99.9 kg vs 64.8 kg; P<0.001).

The resuscitation strategies and sepsis-related characteristics were similar between the two groups (Table 2). Fluid administration volume was not statistically different between the two groups within 3, 24 and 48 hours of septic shock diagnosis (P>0.05). Additionally, the timing of appropriate antibiotics, and the use of adjunctive therapies such as stress dose hydrocortisone were similar between groups (P>0.05; Table 2). The average amount of NE started in the low-dose group was 0.04 mcg/kg/min compared to 0.08 mcg/kg/min in the high-dose group (P<0.001;

Table 1. Baseline Characteristics

	Low Dose (n=29) *	High Dose (n=29) *	p-value
Age (years) ± SD	61 (10.8)	60.7 (13.8)	0.933
Female, n (%)	16 (55.2)	12 (41.4)	0.293
Weight in kilograms ± SD	99.9 (29.7)	64.8 (14.2)	< 0.001
Hypertension, n (%)	18 (62.1)	17 (58.6)	0.788
Diabetes, n (%)	12 (41.4)	11 (37.9)	0.788
Arrhythmias, n (%)	1 (3.4)	4 (13.8)	0.352
HFrEF, n (%)	2 (6.9)	4 (13.8)	0.67
Immunocompromised, n (%)	6 (20.7)	12 (41.4)	0.089
Cirrhosis, n (%)	6 (20.7)	8 (27.6)	0.539
CKD, n (%)	6 (20.7)	4 (13.8)	0.487
CKD Stage 1 CKD Stage 2 CKD Stage 3 CKD Stage 4 CKD Stage 5	2 (33.3) 1 (16.7) 2 (33.3) 1 (16.7) 0 (0)	0 (0) 1 (25) 1 (25) 1 (25) 1 (25)	0.549
Total SOFA score, median (IQR)	10 (6.5-12.5)	8 (5-10.5)	0.2
Systemic Inflammatory Response Syndrome (SIRS) Criteria - White blood cell count (x 10^3 /mm^3), ± SD - Temperature (C), ± SD - Respiratory rate (breaths/min), ± SD - Heart rate (beats/min), ± SD	 11.3 (8.3) 38.3 (4.9) 104 (21) 23.6 (8)	 14.8 (10.8) 38 (1.1) 99.4 (19.7) 24.2 (10.1)	 0.169 0.548 0.395 0.807
Baseline SCr (mg/dL) ± SD	2.6 (1.4)	2.4 (1.3)	0.809
Baseline calculated CrCl (mL/min) ± SD	32.9 (14)	19.2 (11)	0.141
PaO_2: FiO_2 ± SD	307.8 (167.6)	267.9 (138.5)	0.614
Mechanical ventilation at onset of septic shock, n (%)	0 (0)	4 (13.8)	0.056

i. The division into low and high-dose was based on the initial vasopressor dose that was initiated based on the median weight-based starting dose of vasopressor in the sample. Weight-based doses were calculated on actual body weight (ABW) measured upon admission to the ICU
ii. CKD stages percentages were calculated only from those with CKD and were defined by eGFR as the following (28): Stage 1 = at least 90 mL/min/1.73, Stage 2 = 60-89 mL/min/1.73, Stage 3 = 30-59 mL/min/1.73, Stage 4 = 15-29 mL/min/1.73, Stage 5 = <15 mL/min/1.73
SD: Standard Deviation, **HFrEF:** Heart Failure with Reduced Ejection Fraction, **CKD:** Chronic Kidney Disease, **SOFA:** Sequential Organ Failure Assessment, **SCr:** Serum Creatinine, **CrCl:** Creatinine Clearance, **PaO_2:** Partial Pressure of Oxygen, **FiO_2:** Fraction of Inspired Oxygen

Table 2. Septic Shock Characteristics

	Low Dose (n=29) *	High Dose (n=29) *	p-value
Amount of fluid in first 3 hours (mL/kg) ± SD	13 (10.9)	17 (16.6)	0.415
Amount of fluid in first 24 hours (mL/kg) ± SD	35 (46.4)	36.6 (38.7)	0.865
Amount of fluid in first 48 hours (mL/kg) ± SD	46.3 (53.7)	53.7 (48.5)	0.584
Blood cultures obtained before antibiotics, n (%)	27 (93.1)	26 (89.7)	0.64
On antibiotics preceding septic shock diagnosis, n (%)	11 (37.9)	13 (44.8)	0.594
Antibiotics given within 1 hour if not already on antibiotics, n (%)	13 (72) n=18	14 (88) n=16	0.271
Positive culture from suspected site, n (%)	23 (79.3)	24 (82.8)	0.738
Initial organism susceptible to initial antibiotics, n (%)	18 (78.3) n=23	18 (75) n=24	0.791
Baseline lactate (mmol/L) ± SD	6.5 (18.6)	4.8 (4.1)	0.279
6-hour lactate (mmol/L) ± SD	5.3 (3.9)	3.9 (3.3)	0.202
Stress dose steroids^, n (%)	10 (34.5)	10 (34.5)	1
High dose ascorbic acid^^, n (%)	2 (6.9)	0 (0)	0.246
High dose thiamine^^^, n (%)	2 (6.9)	0 (0)	0.246

i. The division into low and high-dose was based on the initial vasopressor dose that was initiated based on the median weight-based starting dose of vasopressor in the sample. Weight-based doses were calculated on actual body weight (ABW) measured upon admission to the ICU
^**Stress dose steroids:** at least 200 mg of hydrocortisone per day
^^**High dose ascorbic acid:** 1.5 grams, every 8 hours or three times a day
^^^**High dose thiamine:** 200 mg every 12 hours or twice a day
kg: kilogram, **mL:** milliliter, **n:** number, **SD:** standard deviation

Table 3. Hemodynamic and Clinical Outcomes

	Low Dose (n=29) *	High Dose (n=29) *	p-value
Starting dose of NE (mcg/kg/min) (IQR)	0.04 (0.033-0.054)	0.08 (0.067-0.1)	< 0.001
Max first vasopressor (mcg/kg/min) ± SD	0.25 (0.18)	0.5 (1.1)	0.22
Baseline MAP (mmHg) ± SD	54.3 (6.8)	56.8 (6.3)	0.152
Initial MAP goal (mmHg) (IQR)	65 (65-65)	65 (65-65)	1
Time to achieve MAP target after shock onset (hours) ± SD	5.8 (3.1)	5.7 (4.3)	0.901
MAP at 6 hours (mmHg) ± SD	51 (7.8)	58 (6.9)	0.003
MAP at 12 hours (mmHg) ± SD	60.4 (10.4)	61.2 (7.2)	0.726
MAP at 24 hours (mmHg) ± SD	60.7 (14.7)	60 (9.9)	0.842
MAP goal at 2 hours, n (%)	0 (0)	1 (3.4)	0.5
MAP goal at 4 hours, n (%)	11 (37.9)	14 (48.3)	0.426
MAP goal at 6 hours, n (%)	19 (65.5)	22 (75.9)	0.387
MAP goal at 8 hours, n (%)	23 (79.3)	24 (82.8)	0.738
MAP goal at 12 hours, n (%)	27 (93.1)	26 (89.7)	0.64
Additional vasopressor utilized, n (%)	17 (58.6)	13 (44.8)	0.293
Time until second vasopressor (hours) ± SD	0.5 (0.95)	0.85 (1.2)	0.375
Third vasopressor, n (%)	12 (41.4)	10 (34.5)	0.588
Fourth vasopressor, n (%)	5 (17.2)	5 (17.2)	1
Firth vasopressor, n (%)	1 (3.4)	1 (3.4)	1
Cumulative total vasopressor dose, mcg/kg/min ± SD	95 (148)	99 (171)	0.989
Duration of total vasopressors, hours ± SD	99 (99)	84 (101)	0.65
Arrhythmia, n (%) (n=55)	9 (31)	6 (20.7)	0.368
Required mechanical ventilation, n (%)	19 (65.5)	15 (51.7)	0.286
Required renal replacement therapy, n (%)	15 (51.7)	6 (20.7)	0.014
Survival, n (%)	20 (69)	18 (62.1)	0.581

i. The division into low and high-dose was based on the initial vasopressor dose that was initiated based on the median weight-based starting dose of vasopressor in the sample. Weight-based doses were calculated on actual body weight (ABW) measured upon admission to the ICU
IQR: interquartile range, **kg:** kilogram, **MAP:** mean arterial pressure, **mcg:** microgram, **min:** minute, **n:** number, **NE:** norepinephrine, **SD:** standard deviation

Table 3). Despite, the difference in starting dose, no significant differences were found between the maximal dose of the first vasopressor used, the use of additional vasopressors, or duration of vasopressors between the two groups (P>0.05; Table 3). There was no difference in the incidence (n [%]) of arrhythmias between the two groups: low-dose 9 (31) vs. high-dose 6 (20.7) (P=0.368). Compared to the high-dose group, the low dose-group had a lower average (SD) MAP at 6 hours after starting vasopressors: 51.0 (7.8) mmHg vs 57.9 (6.9) mmHg (P=0.003). The average MAP did not differ between the groups at 12 or 24 hours (Table 3). The average (SD) change in MAP from baseline to 6 hours was -2.35 (-1) mmHg vs. +1 (0.6) mmHg in the low-dose vs. high-

dose groups, respectively (P=0.008). From 6 hours to 12 hours the average (SD) change in MAP was +8.6 (2.6) mmHg vs. +3.8 (0.35) mmHg and from 12 to 24 hours the average (SD) change in MAP was +0.3 (4.2) mmHg vs. -0.8 (3.2) mmHg in the low-dose and high-dose group, respectively ((P=0.052 and P=0.917, respectively). There were no differences in the percentage of patients who achieved their MAP goal at hours 2, 4, 6, 8 or 12 (P>0.05). The percentage of patients that required CRRT was higher in the low dose group (51.7% vs 20.7%; P=0.014), with no differences in survival rates (69% vs 62.1%; P=0.581).

A multivariate linear regression was calculated to predict MAP at 6 hours. Each 0.01 mcg/kg/min increase in starting dose led to a 0.7 mmHg increase in MAP at 6 hours (P=0.001; 95% CI 0.307 to 1.175). Renal disease and a history of hypertension were associated with higher MAP at 6 hours (P<0.05). The presence of cirrhosis was associated with a lower MAP at 6 hours (P<0.05). The volume of fluid resuscitation at 3 hours and SOFA score were not significant.

Logistic regression analysis for the need for CRRT revealed every 0.01 mcg/kg/minute increase in starting vasopressor dose was associated with 1% decreased odds of needing CRRT (95% CI 0.0005–0.98; P=0.049). For every increase in 1 unit of SOFA, there was 44% increased odds of needing CRRT (95% CI=1.13–1.82; P=0.003;). Treatment with an additional vasopressor agent increased the odds of needing CRRT by 4.1 times (95% CI 1.03–16.1; P=0.045).

In logistic regression for in-hospital mortality, the need for CRRT and past medical history of an immunocompromised state were significantly associated with mortality. If a patient required CRRT, they were 6.1 times more likely to die from septic shock (95% CI 1.23–33.3; P=0.027). Immunocompromised patients were 21 times more likely to die from septic shock in our sample (95% CI 3.9 to 117.6; P<0.0001). The starting dose of vasopressor was not statistically associated with increased mortality (P>0.05).

Discussion

In our analysis, we sought to compare the hemodynamic impact of starting dose of vasopressor in septic shock. Our septic shock population was similar to that of previous analyses (12–14). We found in bivariate and multivariate regression analysis, a higher starting vasopressor dose was associated with increased MAP at 6 hours. Though the magnitude of difference was small (0.7 mmHg increases in MAP per each 0.01 mcg/kg/minute of vasopressor starting dose), this change could result in significant clinical differences when extrapolated to the wide distribution in starting doses encountered in practice. Additionally, in patients receiving low-dose initial vasopressors, we observed a decrease in MAP from baseline to 6 hours as compared to an increase in MAP when high-dose initial vasopressors were used over that same time frame. Furthermore, multivariate regression analysis revealed that a higher initial vasopressor dose was associated with a decreased risk for requiring CRRT. Moreover, if a patient required initiation of an additional vasopressor, their odds of receiving CRRT substantially increased. Not surprisingly, needing CRRT was associated with an increased risk of death. Though the starting dose of vasopressor was not associated directly with mortality in multivariate regression analysis, it is possible that there is an indirect influence on morality by reducing the need for CRRT, but further study would be needed to make this association.

It has been established from previous literature that a longer time to reach goal MAP and failure to maintain it leads to worsening clinical outcomes, including acute renal failure and mortality (15,16). This is theorized to be due to compromised perfusion to vital organs secondary to a lack of driving arterial pressure. Further, it has also been shown that septic shock patients lack vascular smooth muscle tone which may lead to a decreased effect of exogenous vasopressors (17). Therefore, the patients in our study with a higher initial dose of vasopressors may have exhibited an improved exogenous vasopressor response secondary to receiving a more effective dose to target this relatively "hyporesponsive" state. The improved response would be expected to result in an improvement of MAP for those patients receiving higher initial doses, as observed in our study. In the earliest phase of vasopressor use in our study (baseline to 6 hours), the MAP increased in the high-dose group rather than decreasing in the low-dose group. It was not until 12 hours that the MAP "equalized" between groups. This critical early time at lower MAP could have been enough to lead to target organ hypoperfusion. The pharmacokinetics of NE (the predominant vasopressor in our analysis) demonstrates a linear profile (18). This would support the notion that higher starting NE doses should lead to a greater dose-response as measured by higher MAP, decreasing time to goal MAP, providing earlier restoration of end organ perfusion, and improved clinical outcomes. In our analysis, higher starting doses of vasopressor were associated with a greater increase in MAP at 6 hours and decreased usage of CRRT which may serve as a surrogate for target organ perfusion but had no effect on survival. Given the small sample size, our study is likely underpowered to observe differences in mortality, but additional studies may better answer this important question.

Higher starting doses of NE may raise potential concerns. Increased doses of NE are typically avoided due to the possibility of adverse effects. Of note, we did not observe an increased incidence of arrhythmias in our study population. Additionally, there has been data to suggest that the short-term use of high-dose vasopressors may be safe. A retrospective study evaluated 1178 ICU patients requiring NE and found that patients receiving high doses of NE (>1 mcg/kg/min) for up to 5 hours had no ill effects on survival (19). It is important to note that the duration of this study was shorter than our study. Notably, the average duration of vasopressors was 99±99 and 84±101 hours in our low-dose and high-dose groups respectively. Conversely, retrospective data have found a correlation between increased vasopressor exposure and worse patient outcomes, namely cardiac events, AKI, and mortality (7,20–22). However, these studies measured the effects of cumulative dose and total exposure in the setting of refractory septic shock and did not assess the consequences of "front loading" vasopressors and its effect on attainment of goal MAP, potentially leading to faster resolution of hypotension. It should be noted that the patients in our study receiving higher starting doses of vasopressors ultimately had an equal total vasopressors exposure.

Perhaps the risks associated with high-dose vasopressors are more a function of the time-dependent area under the curve of total exposure.

It should be noted that while early MAP (e.g., 6-hours) was higher in the high-dose group, both groups average MAP over the first 24 hours fell short of the SSC guideline recommendation of MAP ≥65 mmHg. While the SSC guidelines recommend the goal MAP ≥65 mmHg, there is also data to support different MAP targets. In fact, numerous analyses in septic shock patients have found a variety of MAP goals ranging from 50–70 mmHg to be adequate for organ perfusion (16,23). Additionally, numerous studies demonstrate that specific patient populations (e.g., chronically hypertensive or cirrhotic patients) may require individualized and reconsidered MAP goals (24–27). The MAP at the 6-hour time point observed in our study (55 +/– 7.9) was significantly less than the SSC guideline recommended MAP ≥65 mmHg. However, overall mortality rate was consistent with those seen in other analyses with a similar severity of illness (12,13,19,24–27). There is a potential concern that starting at a higher dose of vasopressors could result in higher MAP values and adverse effects from vasopressors. However, in a study intentionally targeting a higher MAP goal (e.g., 80–85 mmHg), the authors found an increased risk of atrial fibrillation but a decreased rate of AKI in the subset of patients with chronic hypertension (24). In our analysis, the rates of arrhythmias were not greater with higher starting doses, and we did not observe excessive MAP. Although there may be benefits of individualized MAP goals for specific patient populations that differ from the SSC guidelines, considering the available evidence, it appears that starting at higher vasopressor doses does not lead to overcorrecting or excessive MAP.

Limitations

This study has several limitations to consider. First, the study was a retrospective, single-center study design. This could limit external validity at institutions providing care for a different septic shock population. In addition, given the retrospective nature of the study, the study investigators could not influence the resuscitation strategies. This is of particular importance given the relative lack of early fluid administration observed in our cohort. Per SSC guideline recommendations, patients should receive 30 mL/kg of crystalloid fluid resuscitation in the first 3 hours of diagnosis. Our patients received only 15 mL/kg on average at the 3-hour mark. It should be noted that within the first 24 hours, patents ultimately did receive the recommended amount. Fortunately, the resuscitation strategies were similar across the study population making the comparison between groups valid. Second, we used chart review to manually collect data. This manual process is reliant on accurate chart documentation and would have risk of recall bias and transcription errors. We used a consistent data collector to ameliorate this limitation. Third, we did not have pre-hospitalization data and limited access to other medical centers' records. We thus, had to rely on hospital admission information to populate baseline characteristics. Further, though we used ICD-10 diagnostic criteria to identify our patients, we cannot exclude the use of specific modalities for particular indications. For example, we did not capture if the use of CRRT was for indications other than AKI such as intoxications. Though relatively unlikely, this could be a confounder and thus remains a limitation. Furthermore, we included patients in the study over a 48-month period which could introduce bias from practice changes over that period. Fortunately, guidelines for septic shock management did not undergo any significant changes during our study period, making this limitation theoretical. Additionally, our study population was one of convenience and determined by stratification based on the median dose of the sample. Given the weight-based doses were calculated by actual body weight, this study is unable to speak toward the best dosing weight to utilize for institutions that use body weight dosing of vasopressors. Further, given the large number of obese patients receiving lower doses, a specific dose recommendation is unable to be determined specifically for obese versus non-obese patients. Lastly, as a pilot study, we utilized a relatively small sample size and results need to be interpreted cautiously. Despite the described limitations, we did observe statistical and clinical differences with higher starting doses of vasopressors being associated with increased MAP at 6 hours and decreased usage of CRRT.

Conclusion

We found that a higher starting dose of NE in septic shock patients was associated with an increased MAP at 6 hours a reduced risk of continuous renal replacement during septic shock resuscitation. Future large, randomized controlled trials are needed to determine if increasing the starting dose of NE would lead to positive clinical outcomes.

Acknowledgements

This work in part was presented as a research poster presentation at the Society of Critical Care Annual Meeting in 2020.

Key Messages

A higher dose of norepinephrine was associated with higher blood pressure at 6 hours and a reduced risk of renal replacement during septic shock resuscitation. Further investigation is needed to determine optimal starting dose of vasopressors in septic shock.

AUTHOR CONTRIBUTIONS:

Concept: SB, JM; **Design:** SB, JM; **Supervision:** SB, PB; **Data Collection and/or Processing:** JM, SB; **Analysis and/or Interpretation**: SB, JM, PB; **Literature Search:** SB, JM, PB; **Writing Manuscript**: SB, JM, PB; **Critical Review:** SB, JM, PB.

Ethics Committee Approval: The University of Illinois at Chicago Office for Protection of Research Subjects approved this research study.

Peer-review: Externally peer-reviewed.

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