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Analysis of Vasopressor Discontinuation and the Incidence of Rebound Hypotension in Patients With Septic Shock

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Abstract

Purpose: The purpose of this study was to examine the incidence of rebound hypotension in patients with septic shock requiring both norepinephrine and vasopressin infusions once discontinuation of 1 of these agents is warranted. **Methods:** A multicenter, retrospective study was conducted in 3 hospitals within a single health system between January 1, 2016, and December 31, 2017. The study population included adults, 18 years and older, diagnosed with septic shock and requiring concurrent infusions of norepinephrine and vasopressin. The primary outcome evaluated the incidence of rebound hypotension within 24 hours after the first vasopressor was discontinued. Secondary outcomes included intensive care unit length of stay, hospital length of stay, total vasopressor duration, and the time to rebound hypotension after first vasopressor discontinuation. **Results:** A total of 69 patients were included in the study, 38 in the vasopressin discontinued first group and 31 in the norepinephrine discontinued first group. Rebound hypotension occurred in 82% of patients in the vasopressin discontinued first group compared with 48% in the norepinephrine discontinued first group ($P = .004$). No differences were observed in secondary outcomes, including intensive care unit or hospital length of stay, total vasopressor duration, or the time to rebound hypotension. **Conclusions:** Discontinuation of norepinephrine before vasopressin may lead to less incidence of rebound hypotension in patients with septic shock who require concurrent norepinephrine and vasopressin infusions. Similar to previous studies, this study found no difference in secondary outcomes.

Keywords
cardiac agents, cardiovascular, critical care

Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock, a subset of sepsis, includes underlying circulatory and cellular/metabolic abnormalities that have mortality rates in excess of 40%. Per the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3), patients with septic shock are classified as having sepsis with persistent hypotension, defined as mean arterial pressure (MAP) less than 65 mm Hg despite adequate fluid resuscitation; requiring vasopressors; and having a serum lactate greater than 2 mmol/L.[1] The systemic vasodilation and cardiac dysfunction seen in septic shock lead to decreased tissue and organ perfusion and ultimately organ dysfunction.[2]

The 2016 Surviving Sepsis Campaign guidelines endorse norepinephrine as the first vasopressor to be used in septic shock and adding either epinephrine or vasopressin as a second-line vasopressor to increase a patient's MAP or vasopressin to decrease norepinephrine dose.[3] Norepinephrine provides inotropic effect via cardiac β receptors and produces vasoconstriction through stimulation of α-receptors in the peripheral vasculature. Vasopressin is an endogenous hormone synthesized in the hypothalamus and released from the posterior pituitary gland. The mechanism of interest in patients with septic shock is stimulation of V1 receptors in vascular smooth muscle, which mediates vasoconstriction via influx of intracellular calcium.[4,5] Vasopressin is often the second agent added to patients with septic shock based on this alternative mechanism of action and results of the Vasopressin and Septic Shock Trial (VASST) trial. Although the VASST trial found no difference in mortality with the

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addition of norepinephrine or vasopressin in septic shock patients already receiving norepinephrine, there was a trend toward decreased mortality in a subgroup analysis from patients with less severe septic shock.[6]

As stated, current guidelines recommend which vasopressors to initiate in patients with septic shock, but provide no guidance on the order of their discontinuation once a patient is in the recovery phase of septic shock.[3] As a general definition, the recovery phase is when vasopressors are able to be weaned due to normalization of cardiac function and vascular tone. The lack of recommendation has led to wide variability in clinical practice with some practitioners preferring to discontinue vasopressin first because of limited data for vasopressin monotherapy in septic shock. Landry and colleagues[7,8] described a vasopressin deficiency in septic shock, which could potentially influence the order in which vasopressors are discontinued. This practice is further complicated by practitioners who elect to discontinue both agents simultaneously. There are few studies that compare the incidence of rebound hypotension after discontinuation of norepinephrine or vasopressin in septic shock patients requiring both agents. Available data from retrospective studies are conflicting, with 4 studies showing an increased incidence of hypotension when vasopressin is discontinued first, but the largest study (n = 585) showing no difference between groups.[9-13] A small prospective study (n = 78), also looking at hypotension after vasopressor discontinuation, was stopped early due to a significant increase in hypotension when norepinephrine was discontinued first.[14] Finally, a recently published individual patient data meta-analysis, which included the previously mentioned studies (n = 957), found hypotension to occur more often when vasopressin was discontinued first.[15]

The purpose of this study was to examine the incidence of rebound hypotension in patients with septic shock requiring both norepinephrine and vasopressin infusions once discontinuation of 1 of these agents is warranted.

Methods

Study Design

This was a multicenter, retrospective study of 69 patients admitted to the intensive care unit (ICU) of 3 hospitals within a health system between January 2016 and December 2017. The study protocol was approved by Sterling Institutional Review Board, and a waiver of informed consent was granted due to the retrospective nature of the study. A report was generated to identify patients receiving vasopressin during the study timeframe. There was no protocol or guideline for any vasopressor weaning or discontinuation for patients with septic shock at any institution during the study period, and thus, the decision was left to the discretion of the providers. Norepinephrine was infused in micrograms per minute and was titrated by nursing personnel. Vasopressin was infused at a set rate of 0.04 units/min and was only titratable by provider order rather than nurse titration.

Patients

Patients older than 18 years of age requiring concurrent continuous infusions of norepinephrine and vasopressin during the defined study period were included. Patients were excluded if they were not diagnosed with sepsis or septic shock; if norepinephrine and vasopressin were discontinued at the same time; if they received additional inotropic, vasopressor, or other adjuvant medications (including epinephrine, phenylephrine, dopamine, dobutamine, milrinone, and midodrine); or if they were admitted from surgery, transitioned to palliative care, or expired while receiving both vasopressin and norepinephrine.

Study Objectives

The primary objective was to examine the incidence of rebound hypotension within 24 hours based on the order of norepinephrine or vasopressin discontinuation. The term *rebound hypotension* was used, as hypotension is a potential consequence vasopressor discontinuation. Rebound hypotension was defined as a composite of (1) 2 consecutive MAP readings of $<$60 mm Hg, (2) crystalloid fluid bolus administration $>$ 500 mL, (3) increasing the dose of norepinephrine by 25% after vasopressin discontinuation, or (4) reinitiation of norepinephrine after it was discontinued. Because the third and fourth criteria are solely dependent on the order of vasopressor discontinuation, these will be reported as norepinephrine response to rebound hypotension. Multiple criteria could occur, but only 1 criterion was needed to give rise to the composite of rebound hypotension. Secondary objectives included the time to rebound hypotension after first vasopressor discontinuation, total duration of vasopressors, and both ICU and hospital length of stay.

Data Collection

Baseline demographics collected include age, sex, race, weight, and comorbidities. Additional data collected from the electronic medical record include infection source, concomitant therapies that may affect patients' hemodynamics (such as hydrocortisone, mechanical ventilation, hemodialysis, and propofol use) and vasopressor duration.

Statistical Analysis

Statistics were performed using IBM SPSS Statistics. Categorical variables were analyzed using Fisher exact tests or Pearson χ^2 as appropriate. Continuous data were analyzed using Mann-Whitney *U* test with data presented as median (interquartile range [IQR]). A *P* value of $<$.05 was defined as statistically significant.

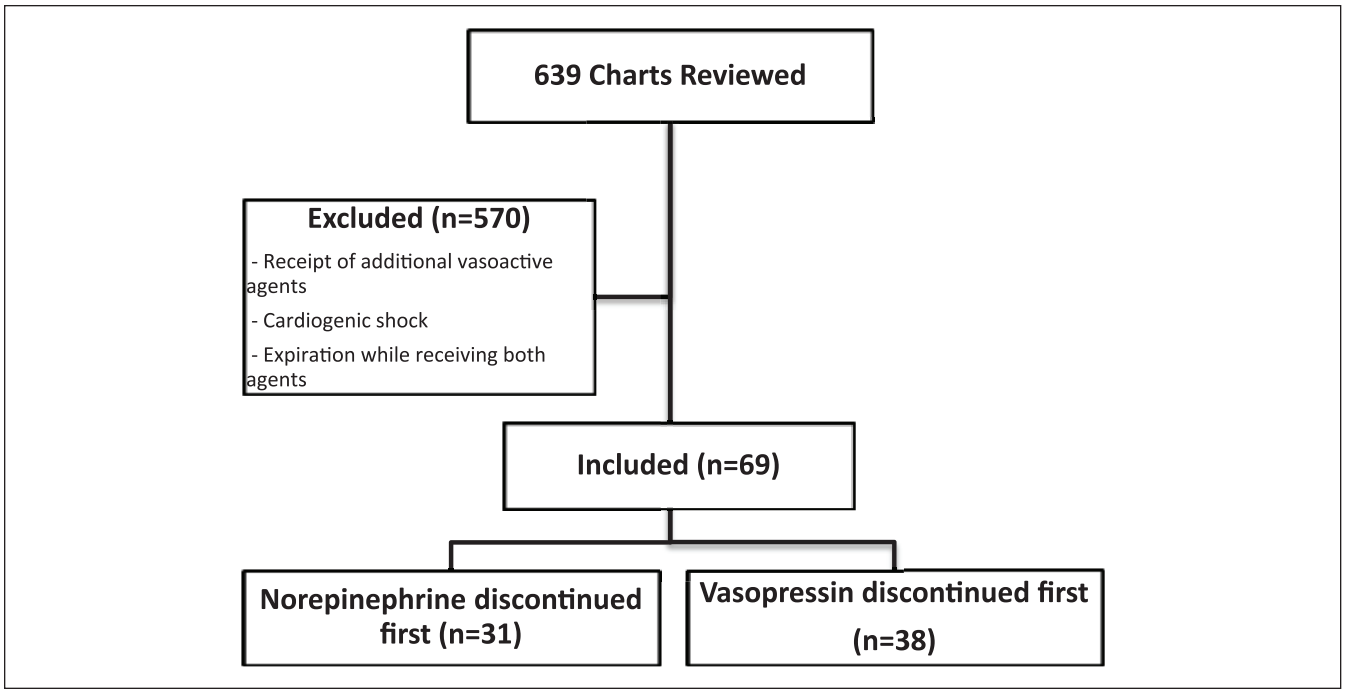

Figure 1. Patient inclusion and exclusion. In total, 639 charts were reviewed, of which 570 patients were excluded and 69 patients were included. Of the 69 patients included, 31 patients had norepinephrine discontinued first and 38 patients had vasopressin discontinued first.

Results

A total of 639 charts were reviewed for study inclusion. Of these, 570 patients met exclusion criteria, with the most common reasons for exclusion being no diagnosis of septic shock, receipt of any additional vasoactive medications, and expiration while receiving both norepinephrine and vasopressin infusions. This resulted in 69 patients included for evaluation. Of 69 patients, 38 had vasopressin discontinued before norepinephrine and 31 had norepinephrine discontinued before vasopressin (Figure 1). Baseline characteristics were similar between the 2 groups, with the exception that patients who had vasopressin discontinued first had significantly higher median age (64 vs 55, $P = .012$). The overall population was predominately Caucasian, but past medical histories and potential treatments known to affect MAP both were similar between groups. Infection sources were also similar between groups with pneumonia being the most prevalent source, followed by urinary tract, intra-abdominal, and other infections (Table 1).

For the primary outcome of rebound hypotension, discontinuation of vasopressin first was associated with a statistically significant increase in rebound hypotension compared with when norepinephrine was discontinued first (82% vs 48%; $P < .004$; Table 2). The criteria that triggered hypotension resulted from a significantly higher number of patients with 2 consecutive MAPs < 60 mm Hg (47% vs 16%, $P = .006$), 25% dose increase in norepinephrine after vasopressin discontinuation (55% vs 0%, $P = .000001$), and re-initiation of norepinephrine (0% vs 42%, $P = .00001$) for the vasopressin discontinued first group versus the norepinephrine discontinued first group, respectively. There was no significant difference in fluid bolus administration between groups. No statistical differences were observed for secondary end points (Table 3). Total vasopressor duration was similar between the vasopressin and norepinephrine groups (89.6 vs 89.4 hours, $P = .655$). Intensive care unit (7.5 vs 7 days, $P = .961$) and hospital length of stay (16 vs 16 days, $P = .638$) were nearly identical between groups, respectively. Our study also did not find a significant difference in the time to rebound hypotension between groups (6 vs 4.3 hours, $P = .453$) as reported in previous studies.[9,11]

Discussion

The Surviving Sepsis Campaign provides no recommendations on the order of vasopressor discontinuation in patients recovering from septic shock.[3] At the study institutions, there is no consensus approach to vasopressor discontinuation order. Likewise, landmark clinical trials evaluating norepinephrine and vasopressin, such as VASST and Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH), differed in their methods for discontinuing these vasopressors.[6,16] In the VASST trial, patients were first weaned off of open-label norepinephrine before the study drugs (norepinephrine or vasopressin); therefore, in patients

Table 1. Baseline Characteristics.

	AVP discontinued first (n = 38)	NE discontinued first (n = 31)	*P* value
Age, y, median (IQR)	64 (49.8-75.3)	55 (46-63)	.012
Gender, male, n (%)	21 (55)	12 (39)	.171
Caucasian race, n (%)	33 (87)	29 (94)	.446
Weight, kg, median (IQR)	79.1 (67.6-94.8)	86.1 (67.5-105)	.228
Hypertension, n (%)	26 (68)	23 (74)	.771
Heart failure, n (%)	11 (29)	4 (13)	.108
Diabetes, n (%)	12 (32)	11 (35)	.732
Chronic kidney disease, n (%)	4 (11)	2 (6)	1
End-stage renal disease, n (%)	1 (3)	0 (0)	1
Chronic obstructive pulmonary disease, n (%)	27 (71)	21 (68)	.766
Liver disease, n (%)	3 (8)	2 (6)	1
Pneumonia, n (%)	20 (53)	18 (61)	.652
Urinary tract, n (%)	7 (18)	3 (10)	.494
Intra-abdominal, n (%)	5 (13)	3 (10)	.722
Bacteremia, n (%)	1 (3)	2 (6)	.584
Other, n (%)[a]	5 (13)	3 (10)	.722
Propofol use, n (%)	22 (58)	17 (55)	.535
Hydrocortisone use, n (%)	12 (32)	11 (35)	.218
Hemodialysis, n (%)	5 (13)	4 (13)	.745
Mechanical ventilation, n (%)	26 (68)	20 (65)	.599

Note. AVP = vasopressin; NE = norepinephrine; IQR = interquartile range.
[a]Includes unknown origin, endocarditis, meningitis, skin and soft tissue, osteomyelitis.

Table 2. Primary Outcome.

	AVP discontinued first (n = 38)	NE discontinued first (n = 31)	*P* value
Rebound hypotension, n (%)	31 (82)	15 (48)	.004
Two consecutive MAPs <60 mm Hg, n (%)	18 (47)	5 (16)	.006
≥500 mL fluid bolus, n (%)	10 (26)	5 (16)	.308
Norepinephrine response to rebound hypotension,[a] n (%)	21 (55)	13 (42)	—

Note. AVP = vasopressin; NE = norepinephrine; MAP = mean arterial pressure.
[a]Includes 25% increased dose of norepinephrine after vasopressin discontinuation, or re-initiation of norepinephrine after it was first discontinued.

Table 3. Secondary Outcomes.

	AVP discontinued first (n = 38)	NE discontinued first (n = 31)	*P* value
Duration of NE, h, median (IQR)	37.8 (21.2-63)	40.8 (28.8-72.7)	.072
Duration of AVP, h, median (IQR)	27.3 (13.8-45.6)	58 (39-103)	.052
Total vasopressor duration, h, median (IQR)	89.6 (48.9-132.9)	89.4 (52.9-151.5)	.655
Time to HOTN, h, median (IQR)	6 (1.3-13.2)	4.3 (1.5-6.2)	.453
ICU LOS, d, median (IQR)	7.5 (5-13)	7 (5-12)	.961
Hospital LOS, d, median (IQR)	16 (9.8-18)	16 (9-24)	.638

Note. AVP = vasopressin; NE = norepinephrine; IQR = interquartile range; HOTN = hypotension; ICU = intensive care unit; LOS = length of stay.

who were randomized to norepinephrine plus vasopressin, norepinephrine was the first vasopressor discontinued. In this protocol, vasopressin was weaned at a rate of 0.005 units/h.[6] Similarly, in the VANISH trial, open-label vasopressors were weaned prior to the study drugs.[16] In the prospective trial from Jeon et al,[14] vasopressin was tapered at a rate of 0.01 units/min every hour, while norepinephrine was tapered by 0.1 μg/kg/min every hour.

Data evaluating the discontinuation order of vasopressors in patients with septic shock remain limited. Bauer et al[9] first

evaluated the incidence of hypotension within 24 hours of norepinephrine or vasopressin discontinuation among 50 patients with septic shock. This retrospective study demonstrated a higher incidence of hypotension when vasopressin was discontinued first compared with norepinephrine (55.6% vs 15.6%, $P = .008$), and after multivariate analysis, discontinuation of vasopressin first was associated with a nearly 6-fold increase in incidence of hypotension. Hammond et al[10] and Bissell et al[11] both conducted retrospective, observational studies that revealed similar results. The former evaluated 154 patients with septic shock and found that hypotension occurred more frequently in patients who had vasopressin discontinued first (67.8% vs 10.8%, $P < .001$) and had a 13.8 times higher incidence of hypotension after multivariate analysis. The latter evaluated 61 patients with septic shock and found that hypotension occurred in 73.6% of patients who had vasopressin discontinued first compared with 16.7% of patients when norepinephrine was discontinued first ($P < .0001$). The authors performed a subgroup analysis that evaluated the incidence of hypotension following vasopressor discontinuation based on total vasopressin duration. Interestingly, this subgroup analysis found no difference in the incidence of hypotension based on discontinuation order when patients received vasopressin >48 hours. When patients received vasopressin ≤48 hours, discontinuation of vasopressin first was associated with a statistically significant higher incidence of hypotension ($P < .0001$). The most recent retrospective study to date, Musallam et al,[13] included 80 patients with septic shock to be evaluated. The investigators found similar results to previous studies, in which patients had a significantly higher incidence of hypotension when vasopressin was discontinued first compared with when norepinephrine was discontinued first (62.6% vs 28.6%) and had a 7.2 times increased incidence of hypotension after multivariate analysis.

In the largest retrospective study to date, Sacha et al[12] evaluated 585 patients with septic shock. In contrast to previous studies, the investigators noted no significant difference in the incidence of hypotension when vasopressin was discontinued first compared with when norepinephrine was discontinued first (54.8% vs 49.8%, $P = .28$). The authors do note since the publication from Bauer and colleagues, which originated from the same institution, there was an effort to discontinue norepinephrine prior to vasopressin. This is seen in their distribution of patient between groups, with 155 patients in the vasopressin discontinued first group versus 430 patients in the norepinephrine discontinued first group and could potentially introduce selection bias. In opposition to these previous studies, the prospective, randomized trial from Jeon et al[14] found an increased incidence of hypotension in the first hour after discontinuation of norepinephrine first compared with the reverse order (68.4% vs 22.5%, $P < .001$). As described recently,[15] the much higher norepinephrine dose when vasopressin was first discontinued could potentially be the reason for the difference in findings among the prospective and retrospective studies. In the recently published individual patient data meta-analysis, which included all previous studies,[9-14] patients had a higher incidence of hypotension when vasopressin was discontinued first compared with when norepinephrine was discontinued first (60.7% vs 43.3%). After adjustment, the norepinephrine discontinued first group had lower odds of developing hypotension (odds ratio = 0.22, 95% confidence interval = 0.07-0.68).[15] More importantly from this study, there was no difference in mortality, intensive care length of stay, or hospital length of stay, further strengthening the results from previous and current studies.

In this retrospective, observational, multicenter study, patients who had vasopressin discontinued first observed a significantly higher incidence of rebound hypotension within the first 24 hours of discontinuation compared with patients with norepinephrine discontinued first. This resulted in an absolute risk difference of 34%, which is consistent with previous studies with similar outcomes (33%-57%).[9-11,13] When the composite definition of rebound hypotension is examined, the most common indicator of rebound hypotension was 2 consecutive MAPs less than 60 mm Hg, which occurred significantly more often when vasopressin was discontinued first. In norepinephrine response to rebound hypotension, norepinephrine dose was more likely to be increased by 25% when vasopressin was discontinued first and norepinephrine was more likely to be restarted if it was first discontinued. This is likely due to the inability to titrate vasopressin at the study institutions as well as the ease of titrating norepinephrine to goal MAP. It should be noted that although the authors expected improved clinical outcomes with a decrease in rebound hypotension, in the current study, there were no significant differences in clinical secondary outcomes which included ICU and hospital length of stay. Patients who had norepinephrine discontinued first received vasopressin for a longer period of time compared with those who had vasopressin discontinued first. When factoring in the recent price increase in vasopressin, patients who had norepinephrine discontinued first would likely have higher costs. This could potentially be a factor when deciding order of vasopressor discontinuation and may lead to more vasopressin being discontinued first.

To our knowledge, this is the first study to evaluate incidence of rebound hypotension in patients with septic shock across multiple centers. Previously referenced studies included various combinations of vasoactive agents, including epinephrine, phenylephrine, dobutamine, milrinone, and midodrine. Although the previous studies tapered off the additional vasoactive medications before inclusion into their respective studies, our decision to excluded additional vasoactive medications further strengthens our data and limits the ability to confound results. These potential confounders were mitigated by including only patients who received norepinephrine and vasopressin while excluding patients that received other vasoactive agents. Additional

strengths of this study include the similarity of baseline characteristics and inclusion of therapies that could be regarded as confounders such as such as hydrocortisone use, mechanical ventilation, hemodialysis, and propofol use. Inclusion of these additional therapies also makes our study more generalizable as many patients with septic shock are mechanically ventilated on propofol and may require hemodialysis. Similar to previous studies, our definition of rebound hypotension was broad and included multiple interventions to characterize hypotension.

Our study is not without limitations. Our health system's practice of infusing vasopressin at a rate of 0.04 units/min is greater than the 2016 Surviving Sepsis Campaign guideline recommended dose of 0.03 units/min. Furthermore, the appropriateness of antibiotics was not accounted for. Because of the retrospective nature of this study, the rationale for order of vasopressor discontinuation could not be determined. Although discontinuation strategies exist, a standardized process of discontinuing vasopressin has not been adopted at our health system, leading to most patients having vasopressin infusions turned off rather than titrated down. This is important, as the half-life of vasopressin is ≤10 minutes and could therefore expect rebound hypotension within 1 to 2 hours as vasopressin is cleared.[17] Due to the rigorous exclusion criteria, only a small number of patients were included in this multicenter study; however, a statistically significant difference existed and post hoc power analysis revealed the power of the current study was 85% at an α of .05. In addition, most patients were Caucasian, which could limit the applicability of our findings.

Conclusions

There is a paucity of data and lack of standardization regarding the order in which to discontinue vasopressors in patients with septic shock requiring concomitant norepinephrine and vasopressin infusions. This study contributes to the current literature that proposes discontinuation of vasopressin first may lead to a higher incidence of rebound hypotension compared with when norepinephrine is discontinued first. This study is also consistent with previous literature that despite the physiologic rationale for discontinuing vasopressin last, the vasopressor discontinuation order does not affect clinical outcomes. A large, prospective, randomized controlled clinical trial powered to assess mortality, length of stay, and total vasopressor duration is essential to further evaluate these findings.

Authors' Note

Christopher T. Buckley is currently affiliated with Union University College of Pharmacy, Jackson, TN, USA.

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