Vasopressor Discontinuation Order in the Recovery Phase of Septic Shock: A Systematic Review and Meta-Analysis

Mithi Kalayaan Zamora, MD,[1] Daniel Guevarra, MD,[2] Carla Emille Barbon, MD,[1] Roland Reuben Angeles, MD,[1] Albert Albay, MD,[2]

ABSTRACT

Background: Septic shock causes life threatening organ dysfunction needing vasopressor despite adequate fluid resuscitation. Numerous studies and meta-analysis have proven norepinephrine as the initial vasopressor of choice in septic shock with vasopressin as add-on. Although guidelines have established the goal monitoring response in septic shock, optimal approach in discontinuation of the vasopressors in the recovery phase of septic shock remains limited.

Methods: A systematic review and meta-analysis was performed on randomized controlled trials (RCTs) and non-randomized studies comparing incidence of hypotension within 24 hours of discontinuing norepinephrine first versus vasopressin. Three reviewers independently selected studies, assessed their quality, and extracted the following data: the number and characteristics of patients enrolled, inclusion and exclusion criteria for each study, the description of interventions (discontinuing norepinephrine first versus discontinuing vasopressin first) and outcomes (incidence of hypotension within 24 hours).

Results: Seven retrospective cohort studies and one prospective randomized control trial were included. Compared with norepinephrine, risk of hypotension is higher when vasopressin is discontinued first among patients in the recovery phase of septic shock (RR 2.06; 95% CI [1.11,3.82]; I^2 91%). Results were consistent in the subgroup analysis after excluding abstract-only and poor-quality studies (RR 1.73; 95% CI [0.74, 4.03]; I^2 93%). There is no difference in ICU (RR 0.97; 95% CI [0.71, 1.32]; I^2 38%) and in-hospital mortality (RR 0.88; 95% CI [0.66, 1.16]; I^2 41%) between the two vasopressor weaning strategies. Finally ICU length of stay was reported on 5 studies with no significant difference between the two strategies.

Conclusion: Based on the results, there is increased risk of hypotension when vasopressin is discontinued first versus norepinephrine.

Keywords: *systematic review and meta-analysis, vasopressor, discontinuation, septic shock, norepinephrine, vasopressin*

INTRODUCTION

Sepsis is a clinical syndrome associated with systemic inflammation due to infection. Septic shock is part of the continuum of sepsis that has circulatory, metabolic and cellular abnormalities associated with at least 40% mortality.[1,2] These patients can be identified when they fulfil the criteria for sepsis: need for vasopressors despite adequate fluid resuscitation to maintain a mean arterial pressure (MAP) of ≥ 65 and a serum lactate of > 2 mmol/L.[2]

Urgent restoration of an adequate perfusion pressure to the vital organs is of importance in the initial resuscitation of patients in septic shock. Norepinephrine (NE) is recommended as the first line vasopressor (Grade IB) in patients with septic shock[3] with vasopressin (AVP) as add

1 Medical Officer IV, Division of Pulmonary Medicine, Philippine General Hospital
2 Medical Officer IV, Division of Nephrology, Philippine General Hospital
3 Clinical Associate Professor, Division of Pulmonary Medicine, Philippine General Hospital

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Corresponding Author
Mithi Kalayaan Zamora, MD
eMail: mithikalayaanzamora@gmail.com

on in cases of refractory shock due to its vasoconstrictive effect and role in replacing AVP deficiency.[4,5]

According to the Surviving Sepsis Campaign Guidelines, norepinephrine remains the first choice of vasopressor among patients in septic shock.[2,5] Vasopressin at 0.03 units per minute has been used as an add-on in septic shock with the intent of increasing mean arterial pressure or decreasing norepinephrine usage. Vasopressin, used as a single vasopressor in septic shock or in doses higher than 0.03-0.04 units per minute has not been recommended or has been reserved as salvage therapy for refractory shock.[2,3] However, despite recommendations on the initial vasopressor of choice and recommendations regarding vasopressin as an add-on in septic shock, optimal approach in discontinuing vasopressors among patients in the recovery phase of septic shock remain scarce and no consensus exists regarding the tapering of vasopressor after shock stabilization particularly on the appropriate strategy when tapering vasopressin and norepinephrine when used simultaneously.

Given the lack of established guidelines and protocol-based approach in the discontinuation of AVP and NE used concurrently, this meta-analysis was conducted to evaluate the available evidence on the incidence of hypotension within 24 hours of vasopressor discontinuation among septic shock patients in the recovery phase using concomitant AVP and NE.

METHODS

The study was conducted in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All studies were identified and aggregated from a pool of available data and did not necessitate ethics approval. All references and authors were acknowledged and identified properly.

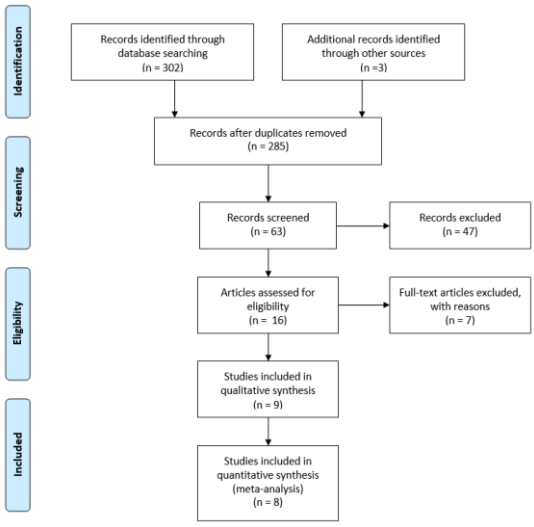

Figure 1. PRISMA Diagram of Study Selection

Search strategy and Study Selection. A comprehensive literature search of all available evidence was performed on PubMed, COCHRANE and Google Scholar to search for relevant articles comparing incidence of hypotension based on the order of removal of norepinephrine and vasopressin in patients receiving both vasopressors. The following search terms were used: "septic shock" and "vasopressin" and "norepinephrine". Articles were limited to publications in the English language.

Eligibility Criteria. All randomized and non-randomized trials were considered eligible if it included study population of adult patients who are: (1) age ≥ 18 years old hospitalized in an intensive care unit; (2) diagnosed with septic shock; (3) received concomitant norepinephrine and vasopressin; and (4) measured incidence of hypotension within 24 hours of discontinuation of one vasopressor. Studies using a vasopressor aside from norepinephrine and vasopressin were excluded in the study.

Data Extraction and Study Quality Assessment. After articles were screened based on the inclusion and exclusion criteria, the authors independently reviewed all eligible full-text articles independently. Eligibility of each study was determined by consensus and divergences were resolved via a third-party reviewer.

The Cochrane Data Extraction Template was used for data extraction of the following: characteristics of the studies (first author, year of publication, study design), patient characteristics, number of patients enrolled/ sample size, inclusion and exclusion criteria for patients of each study, interventions, and outcomes.

Three independent reviewers evaluated the quality of the studies included. Assessment of risk for bias for randomized studies was done using the Cochrane Collaboration's tool. For non-randomized studies, the Newcastle-Ottawa Scale was used. This tool was developed for evaluating observational studies for inclusion in meta-analyses. It uses a point-system with subscales on selection, comparability, and outcomes. A good quality study must have a total score of 6 with all subscales having a score of a least one.

The aggregate data from each study were summarized by entering the data in the Cochrane Review Manager Software version 5.3. Treatment effects were estimated using a random-effects model of data analysis due to the variability of patient characteristics and titration methods.

RESULTS

Study Selection. A total of 305 unique publications were identified in the electronic database search (*Figure 1*) using the search terms. Duplicate studies were then removed resulting to 285 studies. After initial screening of the articles and limiting the studies to English publications, a total of 63 studies were included for abstract screening. Thereafter, 16 text articles were assessed for eligibility using the pre specified eligibility

Table 1. Characteristics of the Included Studies

Study	Study Design	Size (n)		Mean Age			SOFA score			Intervention	Outcome
		AVP	NE	AVP	NE	p value	AVP	NE	p value		
Jeon 2018	Prospective RCT	40	38	67	64	0.206	10	10	0.793	NE DC first versus AVP DC first	Hypotension within 1 hr of tapering first vasopressor ICU/hospital mortality, 28-day mortality
Mussalam 2018	Retrospective cohort	45	35	71.0	75.0	0.517	7.0	7.0	0.861	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC ICU mortality, ICU LOS
Sacha 2018	Retrospective cohort	155	430	63.2	60.6	0.10	11	11	0.85	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC ICU/hospital mortality
Bissell 2017	Retrospective cohort	19	42	50	60.5	0.03	-	-	-	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC Mortality, ICU LOS
Hammond 2017	Retrospective cohort	62	92	60.9	57.3	0.147	9.6	9.7	0.866	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC In-hospital mortality, 28-day mortality, ICU LOS
Bauer 2010	Retrospective cohort	18	32	61.1	61.1	0.997	11.9	11.2	0.819	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC ICU mortality, ICU LOS
Curtis 2016 (Abstract)	Retrospective cohort	32	38	-	-	-	-	-	-	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC Survival, LOS
Bredhold 2017 (Abstract)	Retrospective cohort	52	34	-	-	-	-	-	-	NE DC first versus AVP DC first	Hypotension within 24 hrs of first vasopressor DC ICU LOS

Abbreviations: AVP = vasopressin, NE = norepinephrine, DC = discontinued, LOS = length of stay

criteria leading to inclusion of six full-text articles and two abstracts in the final meta-analysis.

Study Characteristics. One study was a prospective randomized control trial of 85 patients and seven studies were retrospective cohort studies published between 2010 and 2018 with a total of 1,164 study population.[6-11] All studies used norepinephrine as the first inotrope with vasopressin as add-on vasopressor in refractory shock. Of the eight studies, two were retrospective cohort studies which were retrieved as abstracts.[12-13] Six studies were retrieved as full text articles. Of the full text articles retrieved, three studies enumerated the focus of infection for the septic shock while three did not. All studies had incidence of hypotension as the primary outcome of the study, with five of six studies measuring incidence of hypotension within 24 hours of tapering first vasopressor while one study measured hypotension within the first hour of discontinuing vasopressor. The summary characteristics of the six included studies are shown in *Table I*.

Study Quality Assessment. Overall risk of bias for the randomized study is low (*Figure 2*). Four non-randomized studies were judged to have good quality (*Table II*). Only full-text articles were scrutinized carefully for quality assessment.

Table 2: Newcastle-Ottawa Scale for non-randomized studies

Domain	Bauer 2010	Hammond 2017	Bissell 2017	Sacha 2018	Mussalam 2018
Selection	3	3	2	3	3
Comparability	1	2	0	2	2
Outcome	3	3	3	3	3
Quality	Good	Good	Poor	Good	Good

Table 3. ICU Length of Stay Across Studies

Study	ICU length of stay, median (interquartile range)		*p-value*
	AVP discontinued first	NE discontinued first	
Bissel 2017	8 (4, 15)	11 (6, 15)	0.29
Mussalam 2018	7 (5, 10.5)	12 (8, 21)	0.002
Jeon 2018	12 (8, 22)	8 (3, 12)	0.108

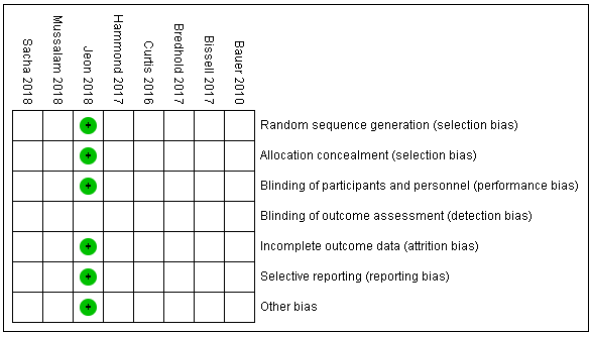

Figure 2. Risk of Bias Summary

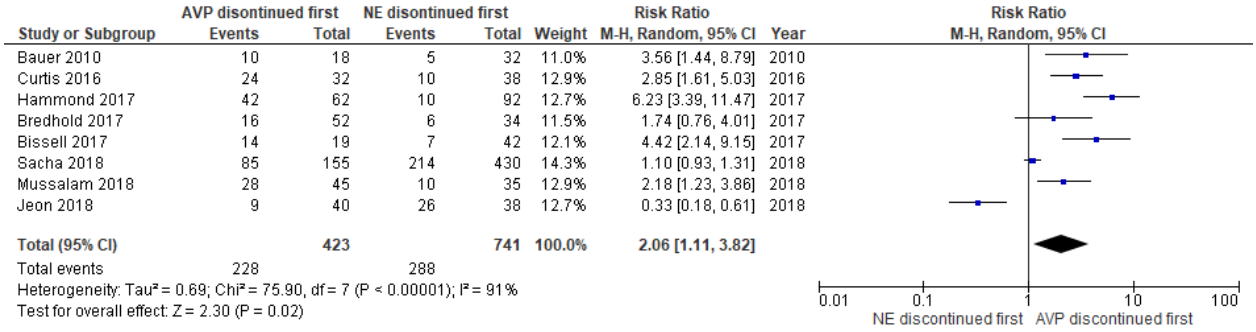

Figure 3. Incidence of Hypotension on Discontinuing AVP vs NE first

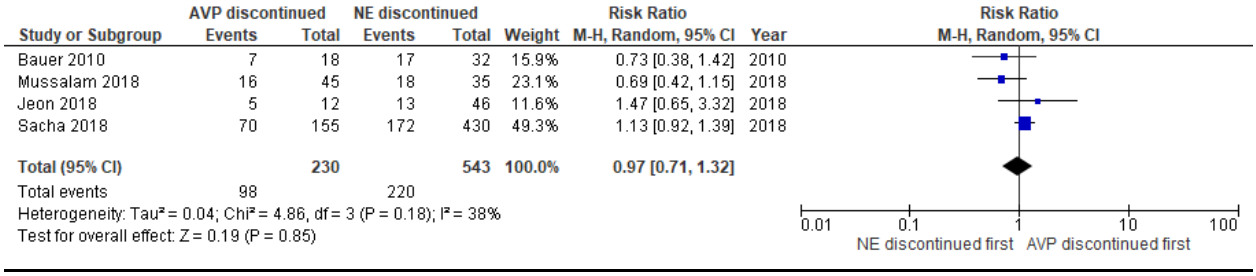

Figure 4. ICU Mortality on Discontinuing AVP vs NE first

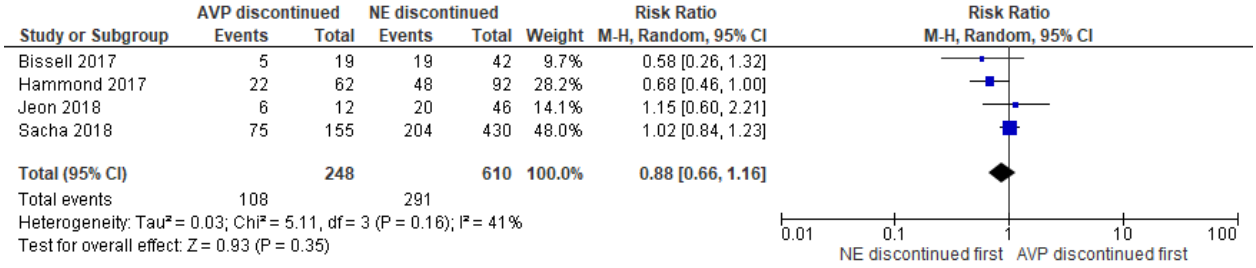

Figure 5. Hospital Mortality on Discontinuing AVP vs NE first

Incidence of hypotension after discontinuing AVP versus NE first. Seven of the eight included studies showed increased risk of hypotension upon discontinuation of AVP first versus NE (Figure 3). Only the study by Jeon et al (2018) showed that discontinuing NE first lead to an increased risk of hypotension upon earlier discontinuation. In a random-effects meta-analysis, discontinuing AVP first leads to an increased risk of hypotension (RR 2.06; 95% CI [1.11, 3.82]; I^2 91%). However substantial heterogeneity was observed. Even after excluding the abstract-only and poor quality studies[10-13], the heterogeneity persists (RR 1.73; 95% CI [0.74, 4.03]; I^2 93%).

Four studies look into ICU mortality as a secondary outcome (*Figure 4*). The studies however exhibited inconsistent results. Analysis of pooled data showed no significant difference in ICU mortality between the two vasopressor weaning strategies (RR 0.97; 95% CI: 0.71 - 1.32; I^2 38%).

In a random-effects meta-analysis, there is a trend toward higher hospital mortality when norepinephrine is discontinued first (RR 0.88; 95% CI: 0.66 - 1.16, I^2 41%). However, this did not reach statistical significance.

ICU length of stay. Five studies reported outcomes on ICU length of stay. Two studies reported means and standard deviations, while three studies reported medians and interquartile ranges.[6,7,9,10,11] Pooled analysis of the two studies showed no significant difference in ICU length of stay between the two strategies (*Figure 6*).

Of the three other studies, only Mussalam et al (2018) reported a significant difference in ICU length of stay favoring the discontinuation of AVP first (*Table III*).

DISCUSSION

Based on the results, the risk of hypotension is greater with the earlier discontinuation of vasopressin compared

to norepinephrine. Recommendations regarding the first vasopressor to start has been established, however, when weaning from vasopressors, recommendations regarding the vasopressor to remove first remain scarce. The meta-analysis show that discontinuing norepinephrine before vasopressin appears safer translating to fewer hypotensive episodes among patients in the recovery phase of septic shock.

Substantial heterogeneity was present in the analysis of the available studies. Reasons for the high heterogeneity of the pooled analysis comes from the quality of included studies and small sample sizes. Majority of the included studies are retrospective cohorts without allocation concealment and lack of blinding. In addition, the small sample sizes of the included studies provided insufficient power to reliably examine the treatment effect and increasing the risk of bias.

In the assessment of ICU and hospital mortality and ICU length of stay as an outcome for patients weaned off from vasopressin versus norepinephrine, there appears to be no significant difference between the two vasopressors. All studies crossed the line of no effect. Reasons for the lack of difference may include the heterogeneity of cases, severity of the admitted cases and prognosis of the patients at the ICU.

CONCLUSION

The quality of the included studies, heterogeneity of the population and the high risk of bias were the main limitations of the study. However, with the current available evidence and the consistent conclusion of decreased hypotensive episodes with analysis of all studies and the subgroup analysis of low risk of bias studies, there seems a trend towards benefit in weaning patients first on norepinephrine before vasopressin. Hence, removing norepinephrine first should be considered as a weaning strategy among patients recovering from septic shock. Further studies using a randomized control trial to eliminate potential biases, including a larger sample size and including surrogate outcomes – acute kidney injury, serum lactate and other secondary outcomes – number of hospital days, ICU admission days can be included in further studies to improve available evidence and come up with protocols and strategies in removing vasopressors among patients in the recovery phase of septic shock.

Declaration of Conflicts of Interest

The authors declare no conflict of interest or funding sources for the development and writing of this work and output.

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