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Incidence of Hypotension after Discontinuation of Norepinephrine or Arginine Vasopressin in Patients with Septic Shock: a Systematic Review and Meta-Analysis

Jae-Uk Song,[1*] **Jonghoo Lee**,[2*] **Hye Kyeong Park**,[3] **Gee Young Suh**,[4,5] **and Kyeongman Jeon**[4,5]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Internal Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
[4]Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ABSTRACT

Background: There has been no consensus regarding the discontinuation order of vasopressors in patients recovering from septic shock treated with concomitant norepinephrine (NE) and arginine vasopressin (AVP). The aim of this study was to compare the incidence of hypotension within 24 hours based on whether NE or AVP was discontinued first in order to determine the optimal sequence for discontinuation of vasopressors.
Methods: A systematic literature search was conducted in MEDLINE, Embase, and the Cochrane Central Register. The primary end-point was incidence of hypotension within 24 hours after discontinuation of the first vasopressor.
Results: We identified five studies comprising 930 patients, of whom 631 (67.8%) discontinued NE first and 299 (32.2%) discontinued AVP first. In pooled estimates, a random-effect model showed that discontinuation of NE first was associated with a significant reduction of the incidence of hypotension compared to discontinuing AVP first (31.8% vs. 54.8%; risk ratios, 0.35; 95% confidence interval, 0.16 to 0.76; $P = 0.008$; $I^2 = 90.7\%$). Although a substantial degree of heterogeneity existed among the trials, we could not identify the significant source of bias. In addition, there were no significant differences in intensive care unit (ICU) mortality, in-hospital mortality, 28-day mortality, or ICU length of stay between the groups.
Conclusion: Discontinuing NE prior to AVP was associated with a lower incidence of hypotension in patients recovering from septic shock. However, our results should be interpreted with caution, due to the considerable between-study heterogeneity.

Keywords: Sepsis; Hypotension; Vasoconstrictor Agents; Treatment Outcome; Meta-Analysis

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Address for Correspondence:
Kyeongman Jeon, MD, PhD
Division of Pulmonary and Critical Care Medicine, Department of Medicine, and Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
E-mail: kjeon@skku.edu

*Jae-Uk Song and Jonghoo Lee contributed equally to this work.

ORCID iDs
Jae-Uk Song
https://orcid.org/0000-0003-4597-7037
Jonghoo Lee
https://orcid.org/0000-0003-2626-7099
Hye Kyeong Park
https://orcid.org/0000-0002-4634-0401
Gee Young Suh
https://orcid.org/0000-0001-5473-1712
Kyeongman Jeon
https://orcid.org/0000-0002-4822-1772

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Song JU, Lee J, Jeon K. Formal analysis: Song JU, Lee J. Investigation: Song JU, Lee J, Park HK, Suh GY, Jeon K. Methodology: Song JU, Lee J, Park HK, Suh GY, Jeon K. Writing - original draft: Song JU, Lee J, Jeon K. Writing - review and editing: Song JU, Lee J, Park HK, Suh GY, Jeon K.

INTRODUCTION

Septic shock is a life-threatening complication of infection that has increased in incidence in the past 15 years.[1] Pathogenically, septic shock is characterized by hypovolemia and decreased vascular resistance, leading to arterial hypotension and multiple organ dysfunctions.[2] Therefore, fluid expansion and catecholamines are crucial for hemodynamic stability and adequate perfusion to vital organs.[3] However, high doses of norepinephrine (NE) often fail to reverse shock, and arginine vasopressin (AVP) can be added with the intent of either increasing mean arterial pressure (MAP) or decreasing NE dosage.[3] The rationale behind AVP use is its vasoconstrictive action and its ability to correct the deficiency of naturally occurring AVP in septic shock.[4] Given these characteristics, there has been increasing interest in early AVP treatment as an adjunct to NE,[5,6] although the evidence of a clinical benefit of AVP is weak.[3]

Once vascular tone begins to return to normal, vasopressors are gradually tapered,[7] which can decrease the adverse events from long-term use of vasopressors.[8,9] Even in the recovery phase, clinically significant hypotension after discontinuation of vasopressors has been seen[10-16] and can cause subsequent organ injury.[17] Therefore, during the discontinuation of vasopressors, clinicians should consider both the risks for adverse events from continuous infusion of vasopressors and subsequent development of hypotension from discontinuation of infused vasopressors. The current Surviving Sepsis Campaign guidelines recommend NE as the initial vasopressor of choice, with AVP as a second-line adjunct.[3] However, there has been no consensus regarding the safe discontinuation order of vasopressors in the recovery phase of septic shock.[12-16]

Therefore, we performed a systematic review of the incidence of hypotension within 24 hours based on the discontinuation order of NE and AVP in patients recovering from septic shock, and we examined, as a secondary objective, whether the discontinuation order of vasopressor influenced patients' outcomes.

METHODS

Data sources and search strategy

The present meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] We performed a search of electronic databases, MEDLINE, Embase, and Cochrane Library. All searches for studies published in English were conducted from inception through to April 7, 2018. We used the following keywords: “vasopressors or arginine vasopressin or norepinephrine, vasoactive agents,” “discontinuation or tapering or withdrawal,” and “sepsis or septic shock.” We investigated reference lists of every article and performed a manual search of the references listed in the relevant review articles.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following inclusion criteria: 1) a randomized controlled or non-randomized cohort study that directly compared NE and AVP for discontinuation of vasopressors; 2) adult patients (i.e., 18 years or older) with a diagnosis of septic shock; 3) reported the incidence of hypotension within 24 hours after the discontinuation of one of two vasopressors; and 4) reported the risk estimates and 95% confidence intervals (CIs) or the information from which these could be calculated. We considered studies published

as full-length articles or letters in peer-reviewed English language journals. Review articles, case reports, abstracts, and commentaries were excluded. The full details of the electronic search strategy are available in the Supplementary Data 1 and 2.

Data extraction and quality assessment

Two authors independently retrieved potentially relevant studies, reviewed each study according to the predefined criteria for eligibility, and extracted data. Any discrepancies that arose during the process of study selection or data extraction were resolved by discussion. A predefined form was used to extract data from each study. We extracted all available data as outlined in the form, including characteristics of the included studies, details of the population enrolled, and outcome measures. The primary outcome was incidence of hypotension within 24 hours after discontinuation of vasopressors. Secondary outcomes were intensive care unit (ICU) mortality, in-hospital mortality, 28-day mortality, and ICU length of stay. Methodological quality and risk of bias were evaluated for each trial using the Newcastle-Ottawa quality assessment for non-randomized studies.[19] Discrepancies were resolved by consensus between the two authors.

Data synthesis and statistical analysis

All analyses were conducted using weighted frequencies for categorical variables and weighted means and ranges for continuous variables, with the weight corresponding to the sample size of each study. We extracted the risk ratios (RRs) and mean differences with associated 95% CIs for clinical outcomes after discontinuation of two vasopressors, and calculated the pooled relative risk using the Mantel-Haenszel method. Between-study statistical heterogeneity was assessed using I^2 and Cochran's Q test.[20] Heterogeneity was assessed using I^2 statistics on a scale of 0%–100%. A fixed-effects model was used unless I^2 was > 50%, indicating a substantial level of between-study heterogeneity, in which case a random-effects model was used.[20] If evidence of substantial heterogeneity was found, stratified analyses via meta-regression were performed to identify the factors that contributed to the heterogeneity.[21] When the number of enrolled studies was more than 10, publication bias for the primary outcome was assessed using Egger's regression tests.[22] The level of statistical significance for the two-tailed test of each hypothesis was 0.05. Statistical analyses were performed using Stata statistical software (version 14.2; StataCorp LLC, College Station, TX, USA) and Review Manager (version 5.3; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Subgroup analysis

Subgroup analysis was planned for the use of systemic steroid treatment in < 50% of the enrolled patients, since interaction of AVP and corticosteroid treatment should be considered.[23,24]

Ethics statement

All analyses were based on previously published studies; no ethical approval or patient consent was required.

RESULTS

Study search and characteristics and quality of included studies

A total of 128 published articles were initially identified (74 articles from MEDLINE, 20 articles from Embase, and 33 articles from the Cochrane library) (**Fig. 1**). After the literature

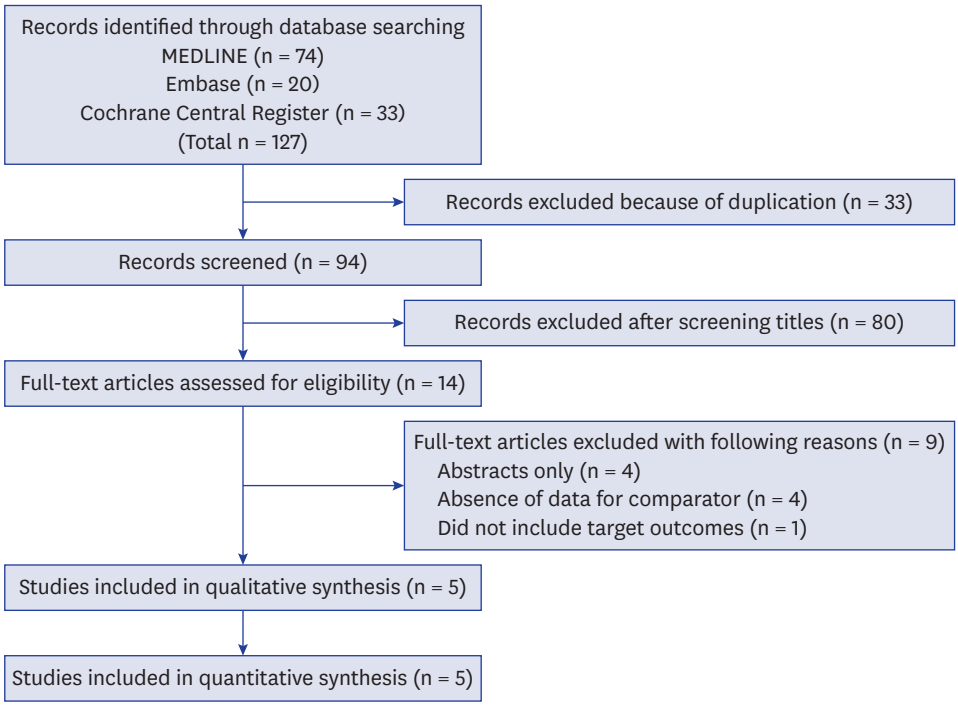

Fig. 1. Flow diagram for identification of eligible studies.

search process, five studies[12-16] were included in our final analysis. **Table 1** summarizes the features of the included studies. The total number of patients in our systematic review and meta-analysis was 930, of whom 631 (67.8%) discontinued NE first and 299 (32.2%) discontinued AVP first. All studies were single center, retrospective cohort studies and published between 2010 and 2018. Assessment of quality is presented in **Table 2**. All studies were considered to be high quality. However, publication bias could not be assessed because the number of studies was less than 10.

Primary outcome

A forest plot of primary outcome, effect of first discontinuation of NE or AVP at endpoint on incidence of hypotension, is shown in **Fig. 2**. Overall, a random effect model showed that discontinuation of NE first resulted in a significant reduction in incidence of hypotension compared with discontinuation of AVP first (31.8% vs. 54.8%; RR, 0.35; 95% CI, 0.16–0.76; $P = 0.008$; $I^2 = 90.7\%$) (**Fig. 2**). Because a substantial degree of heterogeneity existed among the trials, the meta-regression technique was used to explore heterogeneity. Specifically, we performed stratified meta-regression analyses in accordance with the study year (≥ 2015 vs. < 2015), age of the patients (≥ 60 vs. < 60 years), and use of systemic steroid treatment (≥ 50 vs. < 50% of the patients), and we did not observe any significant factor (**Table 3**).

In a subgroup analysis for the use of systemic steroid treatment in < 50% of the enrolled patients, discontinuation of NE first resulted in significant reductions in incidence of hypotension compared with discontinuation of AVP first (15.7% vs. 65.4%; RR, 0.27; 95% CI, 0.10–0.77; $P = 0.015$; $I^2 = 84.0\%$) (**Fig. 3**). On the other hand, a subgroup analysis for use of systemic steroid treatment among ≥ 50% of patients revealed that incidence of hypotension was not significantly different between two groups (36.5% vs.49.0%; RR, 0.41; 95% CI, 0.14–1.13; $P = 0.085$; $I^2 = 88.6\%$) (**Fig. 3**).

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Table 1. Characteristics of the studies included in the meta-analysis

Study	Design	Patients, No.		Age, yr, median		Men, %		Mean arterial pressure at vasopressor initiation, mmHg		Pneumonia, %		SOFA score at the time of first vasopressor discontinuation, median		Mechanical ventilation, %		Corticosteroid treatment, %		Total vasopressor duration before discontinuation of first vasoactive agent, hr		Primary endpoint
		NE	AVP	NE	AVP	NE	AVP	NE	AVP	NE	AVP	NE	AVP	NE	AVP	NE	AVP	NE	AVP	
Musallam et al.[16]	Single-center, retrospective chart review	35	45	75	71	60.0	42.2	52	54	40.0	44.4	NR	NR	77.1	53.3	14.3	17.8	54.4	51.3	The incidence of hypotension within 24 hours of first vasopressor discontinuation.
Sacha et al.[15]	Single-center, retrospective, observational, cohort study	430	155	61	63	53.0	49.7	NR	NR	NR	NR	11	11	NR	NR	71.4	64.5	39.3	41.7	The incidence of hypotension within 24 hours of first vasopressor discontinuation.
Bissell et al.[14]	Single-center, retrospective, observational, cohort study	42	19	61	50	61.9	42.1	62	62	NR	NR	NR	NR	NR	NR	64.2	63.2	NR	NR	The incidence of hypotension within 24 hours of first vasopressor discontinuation.
Hammond et al.[13]	Single-center, retrospective, observational, cohort study	92	62	57	61	53.3	46.8	59.1	58.4	29.3	35.5	NR	NR	NR	NR	51.1	43.5	NR	NR	The incidence of hypotension requiring intervention after first vasopressor discontinuation (did not mention the timing of the development of hypotension).
Bauer et al.[12]	Single-center, retrospective, observational, cohort study	32	18	61	61	65.6	72.2	60.2	56.4	NR	NR	11.2	11.9	75.0	83.3	93.8	66.7	50.3	47.9	The incidence of hypotension within 24 hours of first vasopressor discontinuation.

SOFA = sequential organ failure assessment, NE = norepinephrine, AVP = arginine vasopressin.

Table 2. Quality assessment for the studies included in the meta-analysis

Study	Selection of exposed and non-exposed cohorts				Comparability	Outcome of interest			Overall quality[a]
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome present at start of study	Comparability of cohorts	Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Musallam et al.[16]	★	★	★	★	★	★	★	★	High
Sacha et al.[15]	★	★	★	★	★	★	★	★	High
Bissell et al.[14]	★	★	★	★	★	★	★	★	High
Hammond et al.[13]	★	★	★	★	★	★	NR	NR	High
Bauer et al.[12]	★	★	★	★	★	★	★	★	High

NR = not reported.

[a]A study with 7 or more stars out of 8 was considered a high quality study. A study can be awarded a maximum of one star for each item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

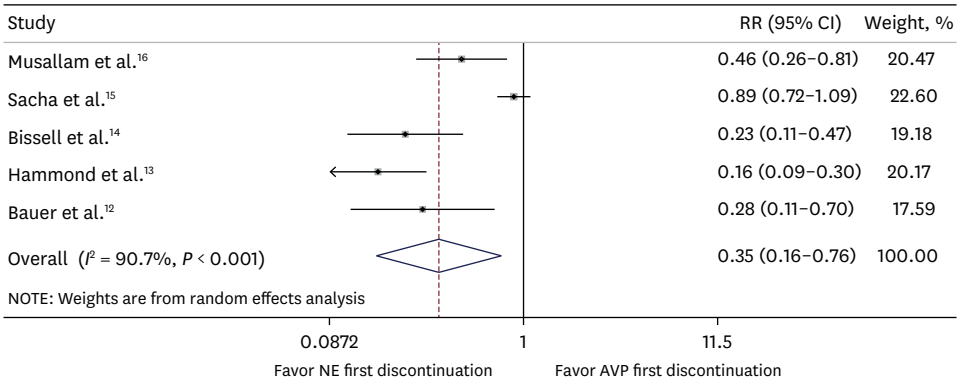

Fig. 2. Paired forest plots of RRs for the incidence of hypotension according to vasoactive agents discontinuation in patients with septic shock.
RR = risk ratio, CI = confidence interval, NE = norepinephrine, AVP = arginine vasopressin.

Table 3. Meta-regression analysis performed using the model weighted by the inverse of the variance

Covariates	Coefficient	Standard error	95% CI	*P* value[a]
Study year ≥ 2015	0.592	0.473	−5.423–6.608	0.429
Age ≥ 60 years	0.497	0.286	−3.140–4.134	0.333
Systemic steroid treatment ≥ 50%	0.322	0.261	−2.999–3.641	0.434

CI = confidence interval.
[a]*P* values from random effect meta-regression using restricted maximum likelihood.

Secondary outcome

Three trials with a total of 715 patients compared ICU mortality between NE first and AVP first discontinuation group in patients with septic shock.[12,15,16] In pooled estimates, ICU mortality was 50.1% and 49.5% in the NE-first and the AVP-first groups, respectively. The pooled estimates using a random effect model demonstrated that ICU mortality was not significantly different between the two groups (RR, 1.11; 95% CI, 0.79–1.56; P = 0.555; I^2 = 50.1%) (**Fig. 4A**). Also, no significant difference was found between the NE first and the AVP first group in in-hospital mortality (48.0% vs. 43.2%; RR, 1.22; 95% CI, 0.86–1.74; P = 0.266; I^2 = 57.5%) (**Fig. 4B**).[13-15] We

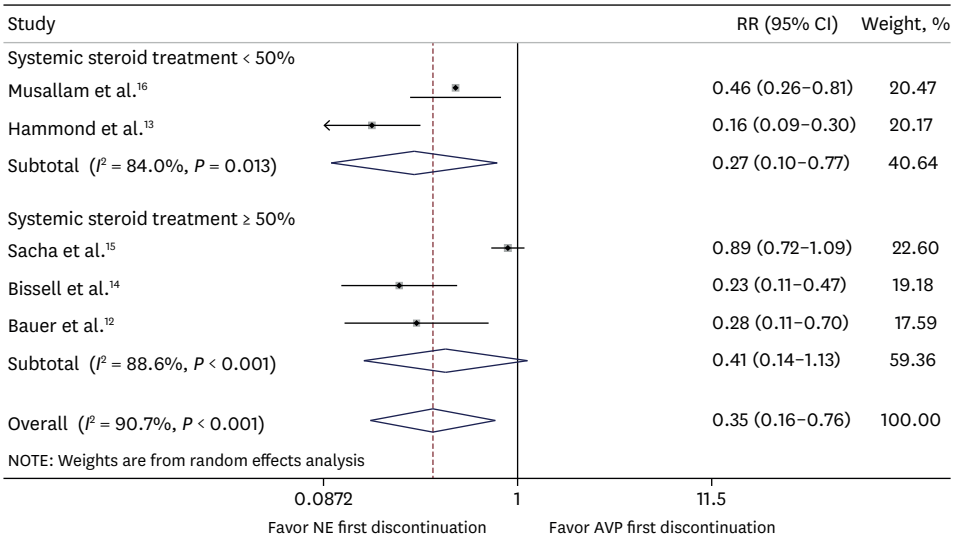

Fig. 3. Paired forest plots of RRs for the incidence of hypotension by steroid treatment for septic shock.
RR = risk ratio, CI = confidence interval, NE = norepinephrine, AVP = arginine vasopressin.

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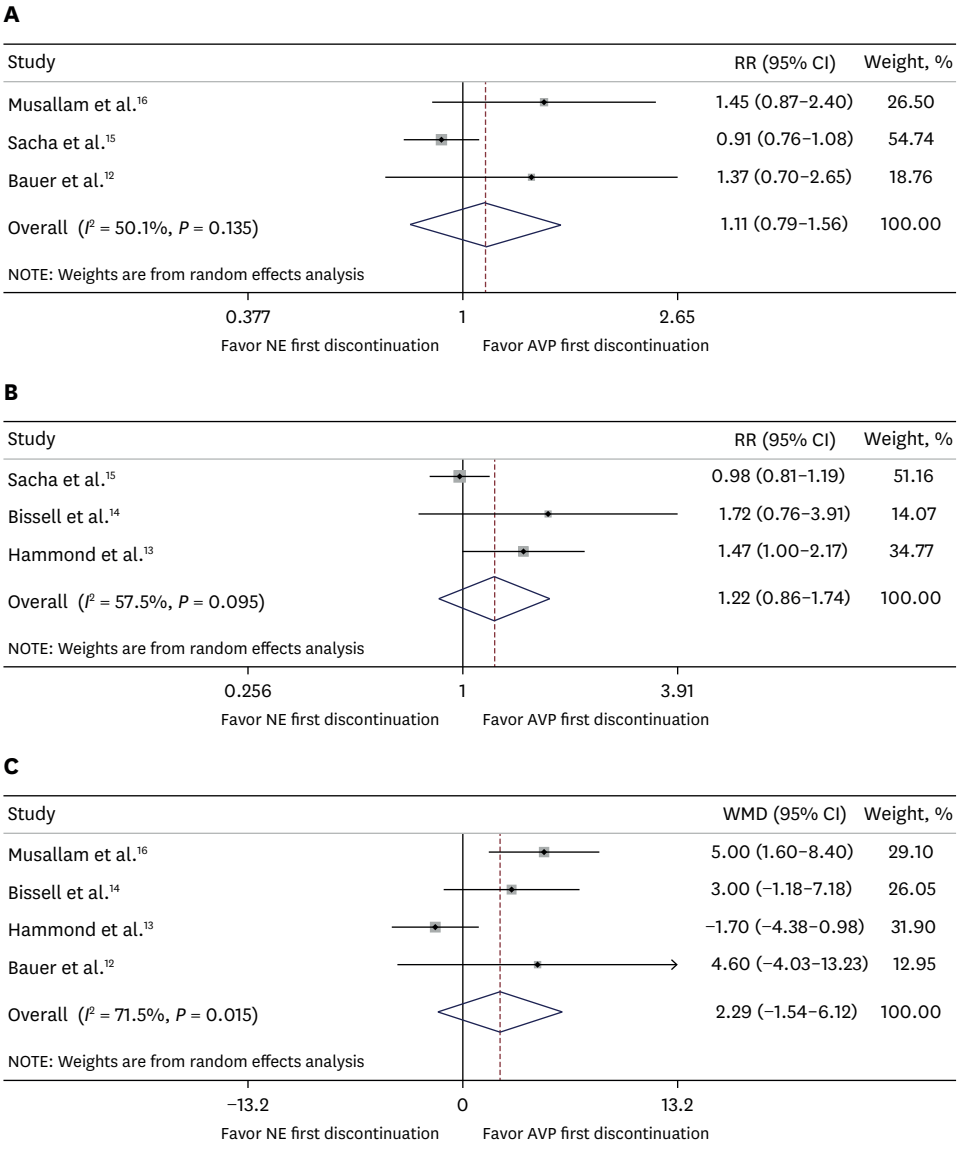

Fig. 4. Paired forest plots of RRs for clinical outcomes according to vasoactive agent discontinuation in patients with septic shock; (**A**) ICU mortality, (**B**) in-hospital mortality, and (**C**) the mean difference (day) in ICU length of stay.
RR = risk ratio, CI = confidence interval, NE = norepinephrine, AVP = arginine vasopressin, WMD = weighted mean difference, ICU = intensive care unit.

retrieved data concerning ICU length-of-stay according to two strategies from four studies,[12-14,16] and there was no significant difference in ICU length-of-stay between the NE-first group and the AVP-first group (mean difference, 2.29 days; 95% CI, −1.54–6.12; P = 0.241; I^2 = 71.5%) (**Fig. 4C**).

DISCUSSION

In the present study, we found that discontinuing NE before AVP led to a lower incidence of hypotension in patients recovering from septic shock on concomitant NE and AVP. However, a substantial degree of heterogeneity existed among the trials. Although we conducted a meta-regression to explore heterogeneity, we did not observe any specific significant factors of bias.

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Possible explanations for potential sources of bias may be considered, such as the following. The first is the timing to discontinuation of vasopressors considering the onset of an AVP deficiency. Patients who were included in a retrospective large cohort experienced a shorter time to discontinuation of vasopressors compared to other studies.[15] That study reported no significant difference in the incidence of hypotension based on discontinuation order of vasopressors.[15] In contrast, the remaining four retrospective studies demonstrated that discontinuing AVP first led to a higher incidence of hypotension.[12-14,16] These conflicting results could be explained by the onset time of the AVP deficiency in septic shock. An AVP deficiency contributes to a decreased response to hypotension and enhanced sensitivity to infused AVP.[10,25] These characteristics of AVP in septic shock may be more beneficial than NE for hemodynamic stabilization, especially in patients with AVP deficiencies. Theoretically, during AVP deficiency, endogenous AVP production and function are muted. Before AVP deficiency is restored, discontinuation of exogenous AVP may result in hypotension.[26,27] However, the exact onset time of AVP deficiency has not been clearly determined.[27,28] According to previous studies, plasma AVP levels was increased during the first 24–36 hours of septic shock,[8,27,28] and most patients exhibit a relative AVP deficiency after 36 hours following onset of shock.[27] In this regard, discontinuation of AVP first could be associated with an increased risk of hypotension with a time-varying effect that decreases over time.[14,15] Therefore, AVP discontinuation after 36 hours of septic shock onset could be extremely sensitive to the development of hypotension.

In subgroup analysis for the use of systemic steroid treatment ≥ 50% of the patients, the effect of the discontinuation order of NE and AVP were suppressed. Corticosteroids increase AVP messenger RNA[29] and plasma level of AVP.[23] This might be associated with the primary outcome between the two groups, especially in the NE discontinuation first group. Therefore, interaction of AVP and corticosteroid treatment should be considered.[23,24,29]

Finally, there is the speed of discontinuation of vasopressors. Discontinuation practice in which vasopressors are titrated or ceased was inconsistent between study institutions. Although the practice for discontinuation of vasopressors was difficult to elucidate, AVP is most frequently ceased without tapering and is sometimes decreased to half of the dose for a short period of time and then discontinued, as opposed to NE, which is gradually reduced. This potentially dramatic adjustment in AVP may have led to a higher incidence of hypotension after discontinuation of AVP, despite the longer effective half-life of AVP (10–20 minutes) compared to NE (2–2.5 minutes).[30] Moreover, in the five retrospective studies, the incidence of hypotension was markedly different in patients who discontinued NE first (11%–50%) than in those who discontinued AVP first (55%–74%).[12-16] This difference was likely caused by center-specific variations in the rate of NE titration. This could also affect the difference in the primary outcome between studies. Therefore, we believe that these center-specific practice variations with vasopressors could be one of the reasons why the incidence of hypotension after discontinuation was different among studies. Considering the variations in discontinuing method of vasopressors, we suggest a future randomized controlled trial on the incidence of hypotension with vasopressor discontinuation.

In contrast to the findings from these observational studies, a recent prospective randomized controlled study (DOVSS) on the incidence of hypotension during vasopressor tapering showed that NE tapering more likely led to hypotension than did AVP tapering.[31] However, the primary endpoint of the DOVSS study was the incidence of hypotension within one hour of tapering the first vasopressor from the predefined dose of both NE (0.3 mcg/kg/min)

and AVP (0.03 U/min). As the study protocol, NE was titrated first to 0.3 mcg/kg/min in all participants. In addition, hypotension developed during vasopressor tapering was included in the study. Therefore, we did not include the DOVSS study in our meta-analysis on the incidence of hypotension within 24 hours after discontinuation of NE or AVP.

Our results add useful information regarding discontinuation of vasopressors in the recovery phase of septic shock. However, the potential limitations of our study should be considered. First, our meta-analysis was performed with a small number of trials, which limits the generalizations of our findings. Therefore, current results should be interpreted with caution, and further large-scale randomized controlled trials should be conducted to substantiate our findings. Second, there was statistically significant heterogeneity in the selected studies. Although we explored the heterogeneity using stratified meta-regression, we failed to identify the source of bias. Third, although our literature search procedures were extensive, other trials may have appeared or may not have been published, which could have affected the findings. Finally, myocardial dysfunction was not considered in our study. Because myocardial dysfunction is a very common and severe complication of septic shock, this factor may influence our results.[32] Therefore, further studies using advanced monitoring for cardiac function are needed.

In conclusion, our study demonstrated that discontinuing NE before AVP led to a lower incidence of hypotension within 24 hours in patients recovering from septic shock, although between-study heterogeneity was high in the current study. In addition, there were no differences in ICU mortality, in-hospital mortality, and ICU length-of-stay between the two groups.

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