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Effects of the discontinuation sequence of norepinephrine and vasopressin on hypotension incidence in patients with septic shock: A meta-analysis☆

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ABSTRACT

Background: Although the order of vasopressor initiation in patients with septic shock is established, limited information is available on the order of vasopressor discontinuation.
Methods: We performed a meta-analysis of nine studies involving 1245 patients in whom norepinephrine ($n = 787$) or vasopressin ($n = 458$) was withdrawn first to compare the risk of hypotension.
Results: The risk of hypotension increased in patients whom vasopressin was withdrawn first (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.3–8.9; $p = 0.01$). A sensitivity analysis indicated that this effect was observed in four studies with a high risk of bias (OR, 5.4; 95%CI, 1.3–23.5; $p = 0.02$) and was not observed in five studies with a low risk of bias (OR, 2.4; 95%CI, 0.6–8.4; $p = 0.18$).
Conclusion: Our results suggest that the risk of hypotension is higher in patients with septic shock in whom vasopressin is withdrawn before norepinephrine.

Introduction

Vasodilatory shock is a common pathology among critically ill patients. The Surviving Sepsis Guidelines recommend the use of norepinephrine as the first-choice vasopressor.[1] Despite their efficacy, high doses of norepinephrine are associated with increased mortality.[2,3] This finding highlights the need for refining treatment strategies for patients with refractory shock.

The use of vasopressin as a supplementary vasopressor is an interesting option. Vasopressin is a potent vasopressor that acts on vasopressinergic receptors[4] and functions as an endogenous hormone that is involved in neuroendocrine imbalance associated with septic shock.[5] Experimental data indicate that treatment with a combination of vasopressin and norepinephrine exerts synergistic effects on the restoration of vascular tone in patients with vasodilatory septic shock.[6] Although the role of vasopressin in managing septic shock is controversial, results of subgroup analyses of randomized trials and meta-analyses suggest that the use of vasopressin is associated with improved outcomes.[7] The Surviving Sepsis Guidelines suggest the addition of vasopressin (up to 0.03 U/min) to norepinephrine to increase mean arterial pressure (MAP) to a minimal initial target level of 65 mmHg or to decrease norepinephrine dosage.[1]

However, limited information is available on vasopressor weaning. Moreover, the protocol for norepinephrine interruption has not been reported in guidelines. The use of dynamic elastance has made it possible to predict hypotension incidence during norepinephrine weaning.[10,11] Treatment weaning is challenging in patients receiving both norepinephrine and vasopressin. To our knowledge, no clear data are available on norepinephrine and vasopressin weaning in patients treated with a combination of these vasopressors.

We hypothesized that norepinephrine should be weaned only after weaning vasopressin because of the possible cardiac effect of norepinephrine. Therefore, we performed a meta-analysis to identify the discontinuation sequence of norepinephrine and vasopressin in patients with septic shock by using available data.

Methods

This meta-analysis was designed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[8] Study methods and analysis plan were

Abbreviations: MAP, mean arterial pressure; ICU, intensive care unit; OR, odd ratio

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Information sources and search strategy

Studies of interest were identified by searching electronic databases and reference lists of screened studies and review articles. Date restriction was not applied. The final search was updated in July 2018. In addition, previously published review articles on this topic were hand searched for identifying additional references. A Boolean search strategy was designed and applied to the National Library of Medicine's MEDLINE database (PubMed). The search strategy included the following medical subject headings or keywords: "(vasopressin) AND (sepsis OR severe sepsis OR septic shock) AND (hypotension OR vasodilatory OR shock)".

Eligibility criteria for studies

All comparative studies (randomized and non-randomized studies) evaluating the use of a vasopressin derivative as a vasopressor agent in adult patients with septic shock who received norepinephrine were considered eligible for inclusion in this meta-analysis. Septic shock was defined regarding surviving sepsis campaign definition.[1,9] Original studies, studies involving the use of vasopressor analogs besides arginine vasopressin (e.g., terlipressin), and studies without a specified intervention and control group or those including patients aged <18 years were excluded from the meta-analysis. The eligible studies were retrieved and combined, and duplicate studies were removed by using an Endnote reference manager.

Study selection and data extraction

Three authors (LZ, ML, and GD) performed the literature search. In the first step, studies were screened according to their titles and abstracts, and studies that did not meet the eligibility criteria were excluded. Next, full texts of the selected studies were evaluated in detail. One author (GD) extracted the following data from all the selected studies: first author name, publication year, study design, inclusion criteria, trial arms, patient number, and primary outcome parameters.

Primary end point

The primary end point of the quantitative meta-analysis was the rate of rebound hypotension after vasopressor (vasopressin or norepinephrine) withdrawal during the first 24 h of discontinuation. In all the analyses, hypotension was defined as the decrease in MAP to below a predefined target level or as the need for fluid resuscitation, reintroduction of a previously discontinued vasopressor, or an increase in adjuvant vasopressor dose to maintain the MAP level above the target level.

Assessment of the risk of bias

The risk of bias in the included studies was evaluated using the 2016 revised Cochrane risk of bias tool for randomized trials and Newcastle–Ottawa Scale for observational studies[10,11] and by performing visual and statistical analyses of contoured funnel plots generated for the primary end point. The following domains were assessed for randomized trials: random sequence generation, allocation concealment, sequence generation blinding, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias. The following domains were assessed for observational studies using the Newcastle–Ottawa Scale Score: case and control selection, case and control comparability, and outcome assessment. Each section is granted with 1 or 2 stars it reaches quality criterion (corresponding to a low risk of bias).[11] The risk of bias was considered to be high if the criterion was unclear. The overall risk of bias for each study was classified as high if the Newcastle–Ottawa scale score of the study was under five stars over nine.

Statistical analysis

The primary end point (occurrence of rebound hypotension) was analyzed using relative risk, which was defined as the ratio of the probability of an event occurring between two groups. Fixed- and random-effects models, which account for between–study heterogeneity by weighing the studies similarly, were used. Heterogeneity was assessed using I^2 statistic, which represents the percentage of variance due to between–study factors rather than due to sampling error.[12–14] I^2 values of >50% were considered to indicate high heterogeneity. Funnel plots (i.e., plots of effect estimates against a sample size) were used to estimate the risk of bias; an asymmetry in these plots suggested the presence of publication bias in the meta–analysis.[15] The robustness of the findings was investigated by performing a sensitivity analysis by considering the risk of bias (high and low) in the studies. All analyses were performed using RevMan software version 5.3 (Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Search results and study characteristics

Study flow diagram is presented in Fig. 1. This meta-analysis included nine original articles out of 650 screened publications that were retrieved by performing the literature search.[16–24] Of the nine included studies, three were abstracts that reported the results of retrospective analyses and six were full-text articles, including five retrospective studies and one randomized clinical trial. One study reported a protocol for vasopressor weaning. In each study, the patients received vasopressin and norepinephrine continuously. The meta-analysis included 1245 patients, of which 460 patients underwent initial vasopressin weaning and 785 patients underwent initial norepinephrine weaning. The characteristics of each included study are presented in Table 1. The only prospective trial included in this meta-analysis was a randomized but unblinded trial.

Quality of the studies

Table 2 summarizes the risk of bias among the included studies according to the Newcastle–Ottawa scale. In all, four studies showed a high risk of performance bias and four studies showed a low risk of performance bias. However, all the included studies showed a risk of bias.

Primary end point

The results of the meta-analysis of the nine studies showed that the risk of rebound hypotension or the need for interventions to maintain MAP above a predefined target level increased (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.3–8.7; $p = 0.01$; I^2 = 90%) (Fig. 2) when vasopressin was tapered before norepinephrine. The associated funnel plot was reasonably symmetrical. However, the limited number of studies included in this meta-analysis did not allow for the exclusion of publication bias (Fig. 3).

Results of the sensitivity analysis by considering the quality of the studies (according to the 2016 revised Cochrane risk of bias tool) showed that risk was still significant (OR, 3.4; 95% CI, 1.3–8.6; $p = 0.01$). However, this effect was only observed when the four poor-quality studies were analyzed (OR, 5.4; 95% CI, 1.3–23.5; $p = 0.02$)[17–20] and was not observed when the five high-quality studies were analyzed (OR, 2.4; 95% CI, 0.6–8.4; $p = 0.18$).[16,21–24]

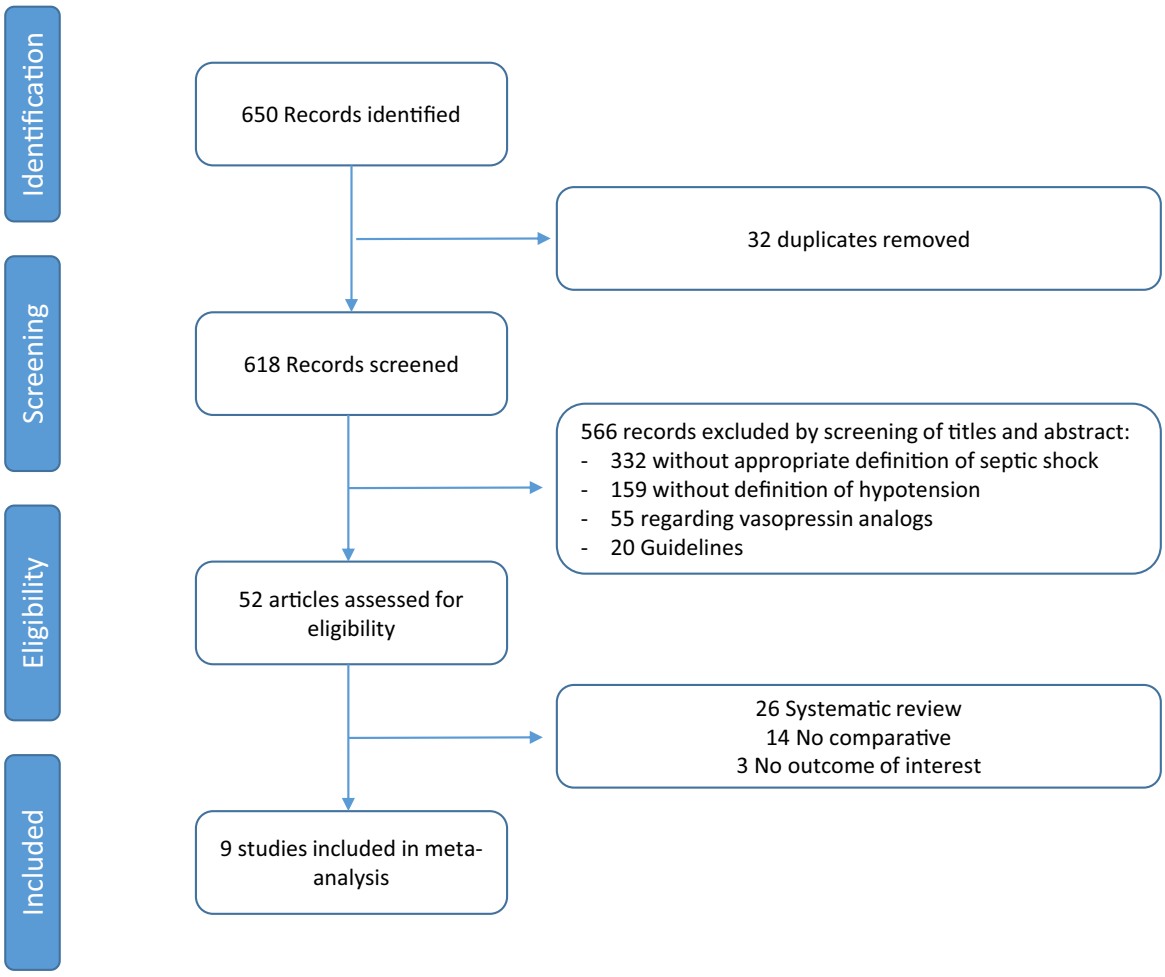

Fig. 1. Study flow diagram.

Table 1
Characterization of selected studies

	VP first		NE first		Total VP 1st	Total NE 1st	VP first	NE first
Reference	Hypotension	No hypo	Hypotension	No hypo			Hypotension	Hypotension
Sacha et al. Pharmacotherapy. 2018	86	69	215	215	155	430	55%	50%
Bauer et al. J Crit Care. 2010	10	8	5	27	18	32	56%	16%
Hammond et al. Journal of Intensive Care Medicine 2017	42	20	10	82	62	92	68%	11%
Bredhold et al. (Abstract) Crit Care Med. 2018	16	36	6	28	52	34	31%	18%
Payne et al. (Abstract) Crit Care Med. 2018	14	23	6	38	37	44	38%	14%
Mussalam et al. Annals of Pharmacotherapy 2018	28	17	10	25	45	35	62%	29%
Bissell et al. Journal of Intensive Care Medicine 2017	14	5	7	35	19	42	74%	17%
Curtis et al. (Abstract) Crit Care Med. 2016	24	8	10	28	32	38	75%	26%
Jeong et al. Crit Care 2018	9	29	26	14	38	40	24%	65%
Total	243	215	295	492	458	787	53%	37%

NE: Norepinephrine; VP: Vasopressine.

Discussion

The results of our meta-analysis suggest that the risk of rebound hypotension increases in patients with septic shock in whom vasopressin is weaned before norepinephrine. This finding suggests that a weaning strategy involving the discontinuation of norepinephrine before that of vasopressin could provide an optimum outcome among patients with septic shock receiving the combination of these vasopressors. The strength of our study lies in is its large sample size. In addition, a consistent result was observed among all the retrospective studies. However, the only randomized clinical trial included in this meta-analysis showed that the rate of rebound hypotension increased when norepinephrine was tapered before vasopressin (hazard ratio, 2.2; 95% CI 1.1–4.4; $p = 0.02$).[24] The maximum dose of vasopressin was 0.03 UI/min in the clinical trial and the mean dose of vasopressin was 0.04 or 0.05 UI/min in the other studies,[16,19,21,23] suggesting that a dose effect interfered with the choice of drugs used.

Our results showed that hypotension developed in 55% patients in whom vasopressin was tapered before norepinephrine and in 36% patients in whom norepinephrine was tapered before vasopressin. To our knowledge, no data are available on the effect of rebound hypotension during recovery from septic shock. Jeon at al. did not observe

Table 2
Assessment of risk of bias in cohort studies using the Newcastle–Ottawa Scale tool

Risk of bias	Musalam 2018	Sacha 2017	Hammond 2017	Bissel 2017	Payne 2017	Bredhold 2017	Curtis 2016	Bauer 2010
Selection bias	1*	2*	3*	1*	0*	0*	0*	2*
Case definition adequation	+	+	+	–	–	–	?	+
Representativeness of exposed cohort	–	–	+	–	?	?	?	–
Selection of non exposed cohort	–	+	+	+	?	?	?	+
Definition of controls	–	–	–	–	–	–	–	–
Comparability bias	1*	2*	2*	0	0*	0*	2*	1*
Age	+	+	+	–	?	?	+	+
Comorbidities	–	+	+	–	?	?	+	–
Outcome bias	3*	3*	3*	3*	1*	2*	1*	3*
Assessment of outcome	+	+	+	+	+	+	?	+
Follow Up long enough	+	+	+	+	?	+	+	+
Adequacy of follow up	+	+	+	+	?	?	?	+
Total	5*/9	7*/9	8*/9	4*/9	1*/9	2*/9	3*/9	6*/9

Data not available from Curtis 2016, Bredhold 2017 and Payne 2017 abstracts are notified with an ? sign.

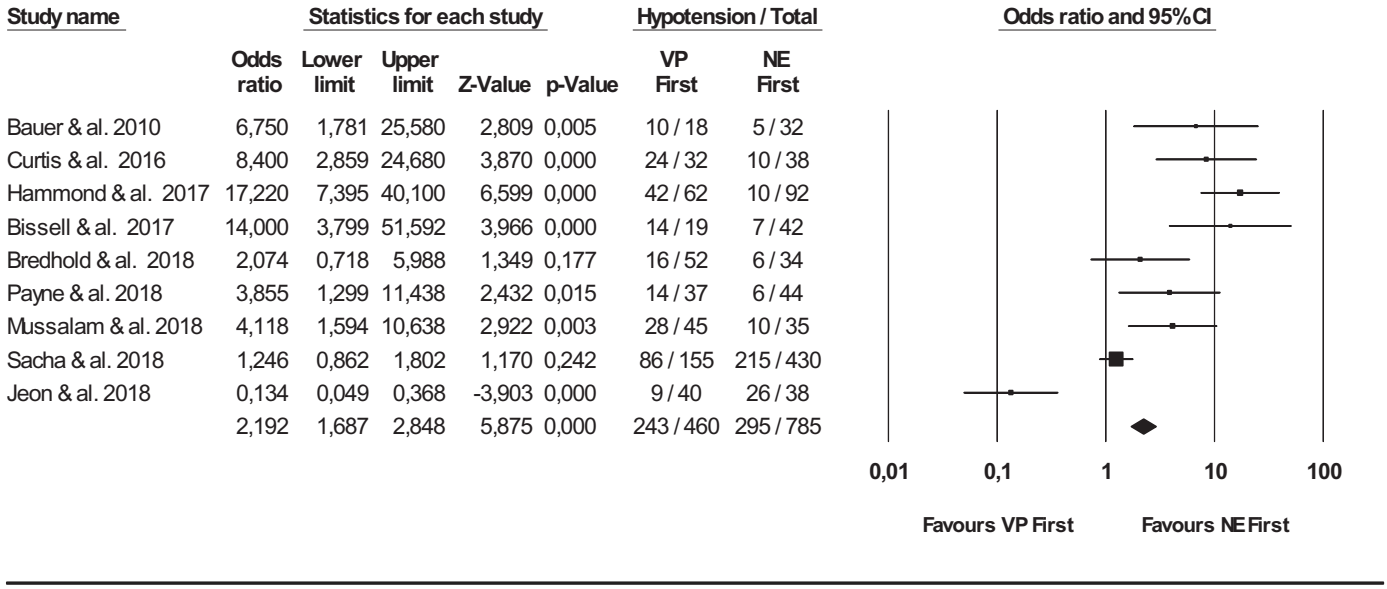

Fig. 2. Pooled odd ratio of hypotension after weaning of vasopressor.

any difference between patients who developed hypotension and those who did not develop hypotension.[24] Hypotension is associated with a poor outcome if it occurs early during the course of septic shock.[25] Notably, this is not consistently observed in intensive care unit (ICU) patients.[26] However, it has been suggested that the occurrence of hypotension should be prevented in ICU patients because its effect on the outcomes of these patients are unclear.

Some physiological theories may explain the results of our study. Vasopressin level is specifically decreased during septic shock with a relative vasopressin deficiency as shock last longer than few hours. The lack of physiological response secondary to vasoplegia remains unexplained but makes vasopressin a potential therapeutic key.[27,28] Furthermore, the half-life of vasopressin (16–24 min) is longer than that of norepinephrine (2–3 min), which may partly explain these results.[5,29,30] This suggests that vasopressin discontinuation has a lingering effect compared with norepinephrine discontinuation, which has an immediate effect. Moreover, this effect can be aggravated in patients requiring ICU in whom the clearance of drugs may be delayed because of renal or liver dysfunction.

Through the impact of vasopressin or analogs use remains unclear, guidelines support their use in daily practice in case of refractory shock.[1] Vail and colleagues analyzed the use of vasopressin in septic shock is united states.[31] Among 584,421 patients with septic shock in 532 hospitals, 100,923 (17.2%) received vasopressin between July 2008 and June 2013.[31] A total of 6.1% of patients received vasopressin alone, and 93.9% received vasopressin in combination with other vasopressors with a trend of increasing use during the study period (14–19%).[31]

Recent data support that a combined early use of vasopressor may improve outcome during septic shock. We explored the use of an early perfusion of terlipressin in association with norepinephrine regarding a SOFA outcome after 72 h of treatment.[32] Hammond and colleagues found equivalent results using an early perfusion of vasopressin in association of norepinephrine.[33] This trend of early association between vasopressors is supported by physio pathological hypothesis and editorials but needs to be confirmed by randomized clinical trials.[34] To confirm these findings, we initiated a RCT (NCT03336814) to evaluate the effect of terlipressin infusion versus placebo in the early stage of septic shock in patients with no heart failure.

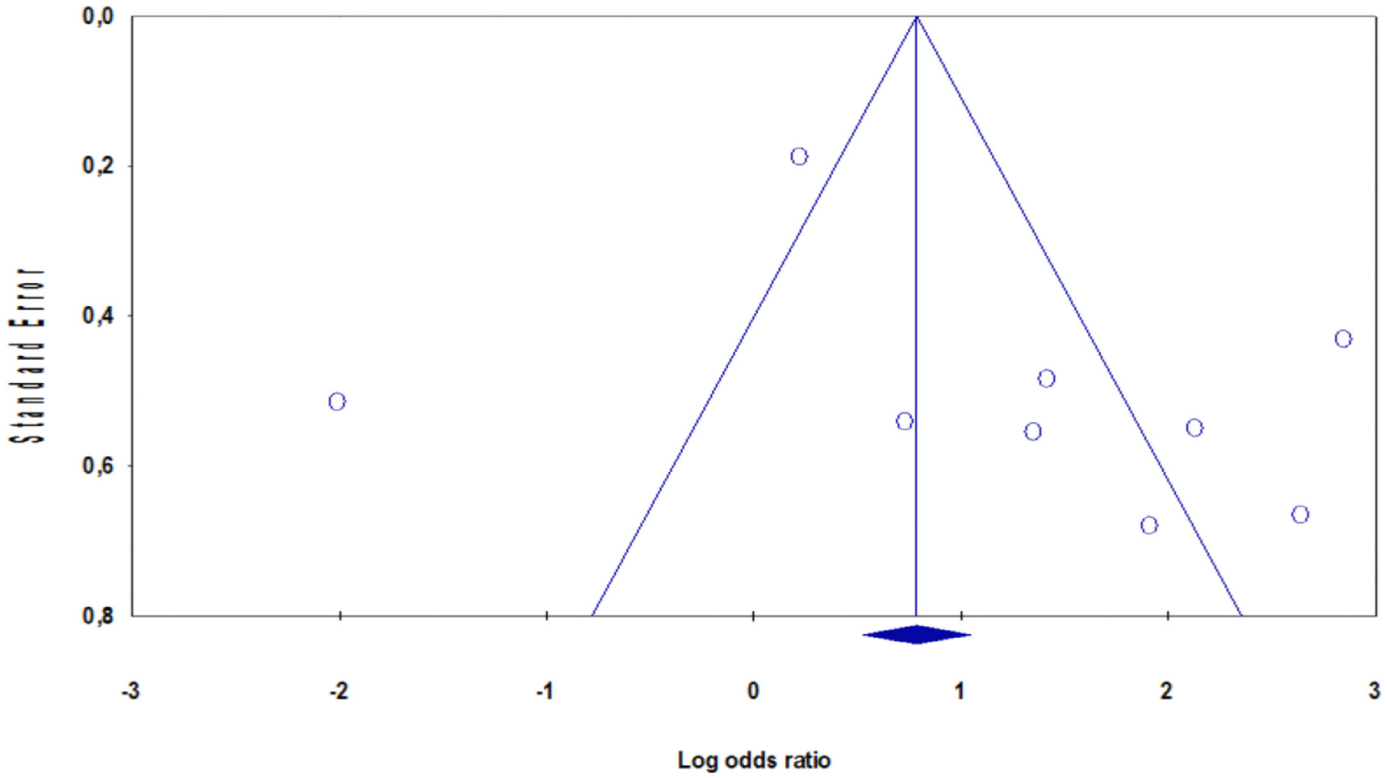

Fig. 3. Funnel plot of standard error by log odds ratio.

Early synergy use of vasopressors in patients with septic shock may increase in the future. This highlight the need of data regarding their weaning order to prevent adverse effect.[35] Literature, at this moment, cannot afford a reliable answer.

Our meta-analysis has several limitations. First, eight out of the nine studies included in this meta-analysis were retrospective studies with discrepancy in the amount of patients included in each studies.[16–23] Indeed, Sacha et al. study represents more than 50% of the patients included in the norepinephrine group, with no difference between groups. We attempted to reduce this risk of bias with the sensitivity analysis. Second, three studies were published only in the form of abstracts, with few variables, and can lead to omission bias by full data lacking.[17–19] Third, we observed a discrepancy between the retrospective studies and the randomized clinical trial, suggesting that our major finding was obtained from poor-quality studies. Finally, the definition of rebound hypotension differed among the included studies, with a variation in cut-off level (from 60 to 65 mmHg), interventions used (fluid bolus, increased vasopressor rate, etc.), and study duration. These variations may be responsible for the difference in the results of the randomized clinical trial and the retrospective studies.

Conclusions

The results of our meta-analysis suggest that the risk of rebound hypotension increases in patients with septic shock or severe sepsis in whom vasopressin is tapered before norepinephrine. However, additional studies should be performed to determine the impact of these observations on the recovery of organ dysfunction in and survival of these patients.

Declarations

Ethics approval and consent to participate: not applicable.

Consent for publication: not applicable.

Availability of data and materials all the data generated or analyzed during this study are included in this published article (and its supplementary information files).

Competing interest: ML received lecture fees from MSD, Pfizer, LFB, Amomed, Baxter, and Aguettant

Funding: No funding was received for the design of the study, the collection,

analysis or interpretation of the data or for writing this manuscript.

Author's contribution

Conception and Design: G.D., K.B. and M.L.
Provision of study materials: M.D. and M.L.
Data analysis and interpretation: K.B., G.D., L.Z. and M.L.
Manuscript writing and final approval: all authors.

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Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.05.007.

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377.
2. Auchet T, Regnier M-A, Girerd N, Levy B. Outcome of patients with septic shock and high-dose vasopressor therapy. *Ann Intensive Care*. 2017;7(1):43.
3. Martin C, Medam S, Antonini F, Alingrin J, Haddam M, Hammad E, et al. Norepinephrine: not too much, too long. *Shock Augusta Ga*. 2015;44(4):305–309.

4. Delmas A, Leone M, Rousseau S, Albanèse J, Martin C. Clinical review: vasopressin and terlipressin in septic shock patients. *Crit Care Lond Engl*. 2005;9(2):212–222.
5. Russell JA. Vasopressin in vasodilatory and septic shock. *Curr Opin Crit Care*. 2007;13(4):383–391.
6. Leone M, Boyle WA. Decreased vasopressin responsiveness in vasodilatory septic shock-like conditions. *Crit Care Med*. 2006;34(4):1126–1130.
7. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the vanish randomized clinical trial. *JAMA*. 2016;316(5):509–518. 02.
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.
9. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165–228.
10. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
11. Ottawa Hospital Research Institute [Internet]. [cited 2018 Sep 24]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22(4):719–748.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
15. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97–111.
16. Bauer SR, Aloi JJ, Ahrens CL, Yeh J-Y, Culver DA, Reddy AJ. Discontinuation of vasopressin before norepinephrine increases the incidence of hypotension in patients recovering from septic shock: a retrospective cohort study. *J Crit Care*. 2010;25(2):362. e7-362.e11.
17. Curtis J. 1386: discontinuation of vasopressors in septic shock patients weaning from norepinephrine and vasopressin. *Crit Care Med*. 2016;44(12):422.
18. Bredhold B, Winters S, Allen L, Callison J, Heidel E, Hamilton L. 1496: impact of the sequence of norepinephrine and vasopressin discontinuation post-septic shock. *Crit Care Med*. 2018;46(1):732.
19. Payne S, Herr D, Wilson S, Pajoumand M, Yeung SYA. 978: characterization of vasopressin use for shock states. *Crit Care Med*. 2018;46(1):472.
20. Bissell BD, Magee C, Moran P, Bastin MLT, Flannery AH. Hemodynamic instability secondary to vasopressin withdrawal in septic shock. *J Intensive Care Med*. 2017:885066617716396.
21. Hammond DA, McCain K, Painter JT, Clem OA, Cullen J, Brotherton AL, et al. Discontinuation of vasopressin before norepinephrine in the recovery phase of septic shock. *J Intensive Care Med*. 2017:885066617714209.
22. Sacha GL, Lam SW, Duggal A, Torbic H, Reddy AJ, Bauer SR. Hypotension risk based on vasoactive agent discontinuation order in patients in the recovery phase of septic shock. *Pharmacotherapy*. 2018;38(3):319–326.
23. Musallam N, Altshuler D, Merchan C, Zakhary B, Aberle C, Papadopoulos J. Evaluating vasopressor discontinuation strategies in patients with septic shock on concomitant norepinephrine and vasopressin infusions. *Ann Pharmacother*. 2018;52(8):733–739.
24. Jeon K, Song J-U, Chung CR, Yang JH, Suh GY. Incidence of hypotension according to the discontinuation order of vasopressors in the management of septic shock: a prospective randomized trial (DOVSS). *Crit Care Lond Engl*. 2018 May;22(1):131.
25. Jones AE, Yiannibas V, Johnson C, Kline JA. Emergency department hypotension predicts sudden unexpected in-hospital mortality: a prospective cohort study. *Chest*. 2006;130(4):941–946.
26. Patel JJ, Kurman JS, Biesboer A, Taha H, Katz M, Szabo A, et al. Impact of duration of hypotension prior to norepinephrine initiation in medical intensive care unit patients with septic shock: a prospective observational study. *J Crit Care*. 2017;40:178–183.
27. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D. Circulating vasopressin levels in septic shock. *Crit Care Med*. 2003;31(6):1752–1758.
28. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA*. 2000;283(8):1038–1045.
29. Martin C, Viviand X, Arnaud S, Vialet R, Rougnon T. Effects of norepinephrine plus dobutamine or norepinephrine alone on left ventricular performance of septic shock patients. *Crit Care Med*. 1999;27(9):1708–1713.
30. Albanèse J, Leone M, Delmas A, Martin C. Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. *Crit Care Med*. 2005;33(9):1897–1902.
31. Vail EA, Gershengorn HB, Hua M, Walkey AJ, Wunsch H. Epidemiology of vasopressin use for adults with septic shock. *Ann Am Thorac Soc*. 2016;13(10):1760–1767.
32. Duclos G, Cantaloube M, Medam S, Resseguier N, Leone M. Preliminary results of synergy between norepinephrine and terlipressin during septic shock. *Intensive Care Med*. 2019;45(5):730–732.
33. Hammond DA, Cullen J, Painter JT, McCain K, Clem OA, Brotherton AL, et al. Efficacy and Safety of the Early Addition of Vasopressin to Norepinephrine in Septic Shock. *J Intensive Care Med*. 2017:885066617725255.
34. Martensson J, Gordon AC. Terlipressin or norepinephrine, or both in septic shock? *Intensive Care Med*. 2018;44(11):1964–1966.
35. Bissell BD, Flannery AH. Hemodynamic instability secondary to vasopressin withdrawal in septic shock. *J Intensive Care Med*. 2019;34(1):79–80.