The Effect of Early Vasopressin Use on Patients With Septic Shock: A Systematic Review and Meta-analysis

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Research

Keywords: early, Vasopressin initiation, Septic shock, Systematic review, Meta-analysis

Posted Date: November 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-99744/v1>

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Version of Record: A version of this preprint was published at The American Journal of Emergency Medicine on October 1st, 2021. See the published version at <https://doi.org/10.1016/j.ajem.2021.05.007>.

Abstract

Background: The effect of early vasopressin initiation on clinical outcomes in patients with septic shock is uncertain. A systematic review and meta-analysis was performed to evaluate the impact of early start of vasopressin support within 6 hours after the diagnosis on clinical outcomes in septic shock patients.

Methods: We searched the PubMed, Cochrane, and Embase databases for randomized controlled trials (RCTs) and cohort studies from inception to the 1st of October 2020. We included studies involving adult patients (> 16 years) with septic shock. All authors reported our primary outcome of short-term mortality and in the experimental group patients in the studies receiving vasopressin infusion within 6 hours after diagnosis of septic shock and in the control group patients in the studies receiving no vasopressin infusion or vasopressin infusion 6 hours after diagnosis of septic shock, clearly comparing with clinically relevant secondary outcomes (use of renal replacement therapy (RRT), new onset arrhythmias, ICU length of stay and length of hospitalization). Results were expressed as odds ratio (OR) and mean difference (MD) with accompanying 95% confidence interval (CI).

Results: Five studies including 788 patients were included. The primary outcome of this meta-analysis showed that short-term mortality between the two groups was no difference (odds ratio [OR] = 1.09; 95% CI, 0.8 to 1.48; $P = 0.6$; $\chi^2 = 0.83$; $I^2 = 0\%$). Secondary outcomes demonstrated that the use of RRT was less in the experimental group than that of the control group (OR = 0.63; 95% CI, 0.44 to 0.88; $P = 0.007$; $\chi^2 = 3.15$; $I^2 = 36\%$). The new onset arrhythmias between the two groups was no statistically significant difference (OR = 0.59; 95% CI, 0.31 to 1.1; $P = 0.10$; $\chi^2 = 4.7$; $I^2 = 36\%$). There was no statistically significant difference in the ICU length of stay (mean difference = 0.16; 95% CI, -0.91 to 1.22; $P = 0.77$; $\chi^2 = 6.08$; $I^2 = 34\%$) and length of hospitalization (mean difference = -2.41; 95% CI, -6.61 to 1.78; $P = 0.26$; $\chi^2 = 8.57$; $I^2 = 53\%$) between the two groups.

Conclusions: Early initiation of vasopressin in patients within 6 hours of septic shock onset was not associated with decreased short-term mortality, new onset arrhythmias, shorter ICU length of stay and length of hospitalization, but can reduce the use of RRT. Further large-scale RCTs are still needed to evaluate the benefit of starting vasopressin in the early phase of septic shock.

Introduction

Septic shock, which is characterized by severe hemodynamic failure, remains a major challenge associated with 30% to 40% hospital mortality, even though important therapeutic advances have been made over the past decades[1]. The essential step in the management of patients with septic shock is to increase systemic and regional/microcirculatory flow. Increasing arterial blood pressure with vasopressors when patients are hypotensive is used to improve the input pressure driving organ perfusion. The Surviving Sepsis Campaign (SSC) guidelines recommend norepinephrine as the first-line vasoactive agent in patients presenting with septic shock[2]. Vasopressin is recommended as a second-line vasopressor by the SSC[2].

This is a weak recommendation[2], owing significantly to the lack of improvement in mortality when vasopressin was added to norepinephrine in patients experiencing septic shock in a large randomized trial of vasopressin versus norepinephrine in patients with septic shock (VASST) [3]. However, vasopressin was not initiated until almost 12 hours after study criteria were met, which may have adversely affected its potential impact on patient outcomes. Pilot studies have more recently evaluated earlier initiation of vasopressin with or not with norepinephrine, and observed encouraging findings[4-6], including improvements of renal function[5] and sequential organ failure assessment (SOFA) scores[6] at 48 and 72 hours after admission and fewer episodes of new-onset arrhythmias[4]. Studies from Wu et al[7] and Bauer SR. et al [8] observed no difference in the time to achieve target mean arterial pressure MAP but a benefit in mortality[7] if delay in the start of vasopressin. A large interventional study did not find a benefit in kidney failure-free days or mortality with earlier use of vasopressin[9].

The purpose of this meta-analysis was to evaluate the impact of early start of vasopressin support within 6 hours after the diagnosis on clinical outcomes in septic shock patients.

Methods

The present meta-analysis was performed and reported according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10]

Registration and protocol

This meta-analysis was registered on PROSPERO (CRD42020206103)

Data source and literature search

We searched the PubMed, Cochrane, and Embase databases for studies from inception to the 1st of October 2020 using the following search terms: timing, time, early, earlier, delay, late, initiation, start, vasopressin, and septic shock. The search was slightly adjusted according to the requirements of the different databases. All of the review articles and cross-referenced studies from the retrieved articles were screened for pertinent information. The flow chart of the search strategies is summarized in Fig.1.

Types of outcome measures

The primary outcome was short-term mortality; short-term mortality included hospital mortality, 28-day mortality. The secondary endpoints included use of renal replacement therapy (RRT), new onset arrhythmias, ICU length of stay and length of hospitalization,

Study selection and data extraction

The inclusion criteria were as follows: (1) adult patients (> 16 years) with septic shock, septic shock was classified according to the current Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis3.0), which considers the presence of suspected infection accompanying organ dysfunction, the use of vasopressors, MAP < 65 mmHg, and lactate levels > 2 mmol/L [11]; (2) RCTs as well as prospective and retrospective cohort studies comparing adult septic shock patients receiving vasopressin infusion within 6 hours after diagnosis of septic shock compared with patients receiving no vasopressin infusion or vasopressin infusion 6 hours after diagnosis of septic shock; (3) all authors reported our primary outcome of short-term mortality; patients in the studies receiving vasopressin infusion within 6 hours after diagnosis of septic shock in the experimental group and receiving no vasopressin infusion or vasopressin infusion 6 hours after diagnosis of septic shock in the control group, clearly comparing with clinically relevant secondary outcomes. We excluded review or conference abstract articles and studies about pediatric or animal.

Study quality evaluation

Two reviewers independently performed quality assessment. The quality of studies was assessed using the Cochrane Collaboration's tool for RCTs [12] and the Newcastle Ottawa Scale (NOS) was used for cohort studies [13]. The risk of bias summary for included RCT is presented in Fig.2; the risk of bias graph for included RCT is presented in Fig.3.

NOS allocates a maximum of 9 points according to the quality of the selection, comparability, and outcomes of the cohort study populations. Study quality was defined as poor (0–3), fair (4–6), or good (7–9). The quality of the included cohort studies is presented in Table 1.

Statistical analysis

Statistical analyses were performed using Review Manager version 5.3 (RevMan, The Cochrane Collaboration, Oxford, UK). Odds ratio (OR) with 95% confidence intervals (CI) was calculated for dichotomous variables. As to the continuous variables, mean difference (MD) and 95% CI were estimated as the effect result. A random effects model was used to pool studies with significant heterogeneity, as determined by the chi-squared test ($P < 0.10$) and inconsistency index ($I^2 \geq 50\%$) [14]. Some of the selected continuous variables were represented by the median (interquartile range). We calculated their mean and standard deviation according to the sample size with a calculator [15] and then performed a meta-analysis. A P value < 0.05 was set as the threshold of statistical significance.

Results

Study characteristics

The search strategy identified 876 studies, and the data were from 1 RCT and 4 cohort studies comprising 788 patients (Table 2) [4, 9, 16–18]. The characteristics of the included studies are shown in Table 2. A total of 5 eligible studies were published between 2013 and 2019. Among these studies, one study was conducted in UK, all other studies were conducted in the USA. In addition to a multicenter randomized controlled study, the other four studies were single center prospective or retrospective cohort studies.

Primary outcome

A total of five studies including 788 patients were included, and the short-term mortality was about 38.3% (154/394 in the experimental group and 148/394 in the control group). There was no difference in short-term mortality between the two groups (odds ratio [OR] = 1.09; 95% CI, 0.8 to 1.48; $P = 0.6$; $\chi^2 = 0.83$; $I^2 = 0\%$) (Fig. 4). A funnel plot was used to assess the publication bias (Fig. 5).

Secondary outcomes

Use of RRT

Three of the included studies were analyzed to assess the use of RRT. the use of RRT was less in the experimental group than that of the control group (OR = 0.63; 95% CI, 0.44 to 0.88; $P = 0.007$; $\chi^2 = 3.15$; $I^2 = 36\%$) (Fig. 6).

New onset arrhythmias

Four of the included studies were analyzed to assess the new onset arrhythmias. The new onset arrhythmias between the two groups was no statistically significant difference (OR = 0.59; 95% CI, 0.31 to 1.1; $P = 0.10$; $\chi^2 = 4.7$; $I^2 = 36\%$) (Fig. 7).

ICU length of stay

All of included studies were analyzed to assess the ICU length of stay (day).

There was no statistically significant difference in the ICU length of stay between the two groups (MD = 0.16; 95% CI, -0.91 to 1.22; $P = 0.77$; $\chi^2 = 6.08$; $I^2 = 34\%$) (Fig. 8).

Length of hospitalization

All of included studies were analyzed to assess the length of hospitalization (day). There was no statistically significant difference in the length of hospitalization between the two groups (MD = -2.41; 95% CI, -6.61 to 1.78; P = 0.26; $\chi^2 = 8.57$; $I^2 = 53\%$) (Fig. 9). The result of the study by Reardon[4] was different from the other studies. A sensitive analysis was performed by removing the study by Reardon, the combined MD was - 3.75 (95% CI -7.81 to -0.31; P= 0.07; $I^2 = 39\%$).

Discussion

This systematic review and meta-analysis of five studies including 788 patients evaluated the impact of early start of vasopressin support on clinical outcomes in septic shock patients within 6 hours after the diagnosis. We found that the overall short-term mortality was about 38.3%, there were no statistically significant difference in the short-term mortality, new onset arrhythmias, ICU length of stay and length of hospitalization between the experimental group and control group, the use of RRT was lower in the experimental group.

Vasopressin is a neurohypophyseal hormone with diverse actions mediated by tissue-specific receptors. The rationale for using vasopressin is the development of relative vasopressin deficiency in patients with septic shock and the observation that low dose vasopressin infusion improves blood pressure, decreases requirements for catecholamines and improves renal function[19]. From a retrospective cohort study [20], it revealed that 17.2% of patients with septic shock in United States hospitals received vasopressin. In the ADRENAL trial[21], which included patients from Australia, the United Kingdom, New Zealand, Saudi Arabia, and Denmark, usage was similar with 16.8% of patients receiving vasopressin at baseline.

Vasopressin levels vary during the different stages of septic shock[22], therefore, timing of vasopressin initiation could play a critical role in septic shock management.

In the VASST trial[3], vasopressin was not associated with improved mortality as compared with norepinephrine but when mortality rates were stratified into patients who received early vasopressin (≤ 12 h), rates were higher in the norepinephrine group (40.5% vs. 33.2%, P = 0.12), initiation of vasopressin within 12 hours could have been delayed because plasma vasopressin levels were extremely low as early as 6 hours[22]. In this meta-analysis, we do not find improved short-term mortality when vasopressin initiated within 6 hours of septic shock onset. Though early initiation of vasopressin in patients with septic shock may achieve and maintain goal MAP sooner[16, 18], surrogate end points evaluated, such as time to goal MAP, failed to translate to a mortality benefit.

Acute kidney injury (AKI) is a common complication of sepsis and septic shock. a post hoc analysis of VASST [23] demonstrated that patients at risk for AKI development according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria, who received vasopressin within 12 hours of shock onset had a lower rate of progression to renal failure or loss categories (21% vs 40%, respectively; P = 0.03) and a lower need for RRT (17% vs 38%, P = 0.02). In the VANISH trial[9], the early use of vasopressin compared with norepinephrine did not improve the number of kidney failure-free days, Patients in the vasopressin group were less likely to receive RRT compared with the norepinephrine group (25% vs 35%, P = 0.03). In our meta-analysis we found the use of RRT was less in the experimental group than that of the control group. A recent meta-analysis [24] focused on renal outcomes in distributive shock patients who received vasopressin or terlipressin, demonstrated patients who received vasopressin or terlipressin had reduced need for RRT and lower incidence of AKI. However, significant heterogeneity in the studies existed, and the lower incidence of AKI and use of RRT with vasopressin analogues was lost in the septic shock patients.

Catecholamine use has been linked to both an increased incidence of arrhythmias and increased cardiac ischemia[25]. In our meta-analysis we found no reduced new onset arrhythmias when vasopressin initiated within 6 hours of septic shock onset. However, the definition of arrhythmias of the included studies was different, which might render an unsolvable bias. In addition, our meta-analysis showed that there was no statistically significant difference in the ICU length of stay and length of hospitalization between the two groups.

Several limitations should be taken into consideration when interpreting our findings. Firstly, by the nature of meta-analysis in general, the results of this paper were dependent on the quality of available studies. There are only one RCT study included, other four included studies were small-scale single center cohort studies. The results and conclusions should therefore be interpreted with caution. Second, we did not perform a subgroup analysis of RCT and cohort studies, very heterogeneous populations were included in both randomized and observational studies. Third, mean arterial pressure and organ dysfunction is also a very important clinical outcome. However, few included studies had shown this data. In addition, inclusion/exclusion criteria and vasopressin dosage were widely different among included studies which supposed a limitation to interpret results. Therefore, our findings should be interpreted with caution.

Conclusion

Early initiation of vasopressin in patients within 6 hours of septic shock onset was not associated with decreased short-term mortality, new onset arrhythmias, shorter ICU length of stay and length of hospitalization, but can reduce the use of RRT. Further large-scale RCTs are still needed to evaluate the benefit of starting vasopressin in the early phase of septic shock.

List Of Abbreviations

MAP: Mean arterial pressure

SSC: Surviving Sepsis Campaign

RCTs: Randomized controlled trials

ICU: Intensive care unit

SOFA: Sequential organ failure assessment

RRT: Renal replacement therapy

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

NOS: Newcastle-Ottawa Scale

OR: Odds ratio

MD: Mean difference

CI: Confidence interval

AKI: Acute kidney injury

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no any conflict of interests.

Funding

This work was supported by Zhejiang Traditional Chinese Medicine Science and Technology Project(NO. 2020ZA046)

Authors' contributions

Haijun Huang and Wei Mao carried out the studies, participated in collecting data, and drafted the manuscript. Chenxia Wu and Qinkang Shen performed the statistical analysis and participated in its design. Yixin Fang and Hua Xu helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

None.

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Tables

Table 1 Quality of the included cohort studies (The Newcastle-Ottawa Scale)

Study	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Daley 2013	□	□	□	□	□ □	□	□	□	9
Reardon 2014	□	□	□	□	□ □	□	□	□	9
Hammond 2018	□	□	□	□	□ □	□	□	□	9
Hammond 2019	□	□	□	□	□ □	□	□	□	9

Table 2. The basic characteristics of studies included in the meta-analysis

Trial	Year	Country	Study design	Sample size	Study period	Experimental group	Control group
Daley 2013	2013	USA	Single center retrospective cohort	130	May 2008-Sep.2009	vasopressin	norepinephrine
Reardon 2014	2014	USA	Single center retrospective cohort	71	Jan. 2010 - Dec. 2011	early vasopressin and catecholamines	later vasopressin and catecholamines
Gordon 2016	2016	UK	multicenter RCT	409	Feb. 2013 - May 2015	vasopressin	norepinephrine
Hammond 2018	2018	USA	Single center prospective cohort	82	Nov.2015-Jun. 2016	vasopressin and norepinephrine	norepinephrine
Hammond 2019	2019	USA	Single center retrospective cohort	96	May 2014- Oct. 2015	vasopressin and norepinephrine	norepinephrine

Figures

Figure 1

Flow chart of literature selection.

Figure 2

The risk of bias summary for included RCT .

Figure 3

The risk of bias graph for included RCT.

Figure 4

Forest plot for short-term mortality.

Figure 5

Funnel plot for short-term mortality.

Figure 6

Forest plot for use of RRT.

Figure 7

Forest plot for new onset arrhythmias.

Figure 8

Forest plot for ICU length of stay.

Figure 9

Forest plot for length of hospitalization.