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Original Article

Vasopressin and its analog terlipressin versus norepinephrine in the treatment of septic shock: a meta-analysis

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Abstract: Purpose: To compare the effectiveness and safety of vasopressin and its analog terlipressin with norepinephrine treatment in adult patients with septic shock and to explore the most effective and safe protocol. Materials and Methods: This study was based on Cochrane methodology for conducting meta-analysis. Only randomized controlled trials were eligible for this study. The participants were adults who had septic shock. The Review Manager Database (RevMan version 5.1, The Cochrane Collaboration 2011) was used to analyze selected studies. Results: Eleven randomized controlled trial involving 2273 patients were included. The mortality rate was significantly lower in the vasopressin/terlipressin group (relative risk 0.87). The pulmonary artery occlusion pressure was higher in the vasopressin/terlipressin group (mean difference 1.51, 95% CI 0.84 to 2.17). Subgroup analysis showed the mortality rate, heart rate and cardiac index were significantly lower in the vasopressin group compared with the norepinephrine group. Conclusions: Compared with norepinephrine, vasopressin and its analog terlipressin could significantly reduce mortality rate of adult septic shock patients. The combination of low-dose vasopressin and corticosteroids was associated with decreased mortality, heart rate and cardiac index compared with conjoint use of norepinephrine and corticosteroids.

Keywords: Vasopressin, norepinephrine, terlipressin, septic shock, meta-analysis

Introduction

Septic shock is a common illness presenting to the emergency and critical care medicine (CCM) department, with a mortality rate ranging from 30% to 60% [1-4]. After adequate volume resuscitation, vasoactive medications are typically used to treat persistent hypotension. Catecholamines such as dopamine and norepinephrine are often preferred agents. However, some adverse effects can occur, including arrhythmias, myocardial ischemia, decreased cardiac output, increased tissue oxygen consumption, and pulmonary hypertension [5, 6]. Besides, its effect on patient-relevant outcomes remains controversial. Thus, a more safe and potent vasoactive agent is desirable.

Vasopressin, also known as antidiuretic hormone (ADH), is crucial for osmoregulation, cardiovascular control and homeostasis. Over the past several decades, vasopressin and its analog terlipressin have been extensively employed to treat upper gastrointestinal bleeding, central diabetes insipidus and bleeding disorders. In recent years, many studies have reported positive outcomes and high safety profiles of these two agents in the treatment of septic shock [7-9]. However, no consensus has been made regarding the optimal vasoactive medication in such condition. The aim of this study is to compare the effectiveness and safety of vasopressin and its analog terlipressin with norepinephrine treatment in adult patients with septic shock and to explore the most effective and safe protocol.

Materials and methods

This study was based on Cochrane methodology for conducting meta-analysis [10].

Search strategy

The published literature was searched using the electronic databases MEDLINE (1950 to

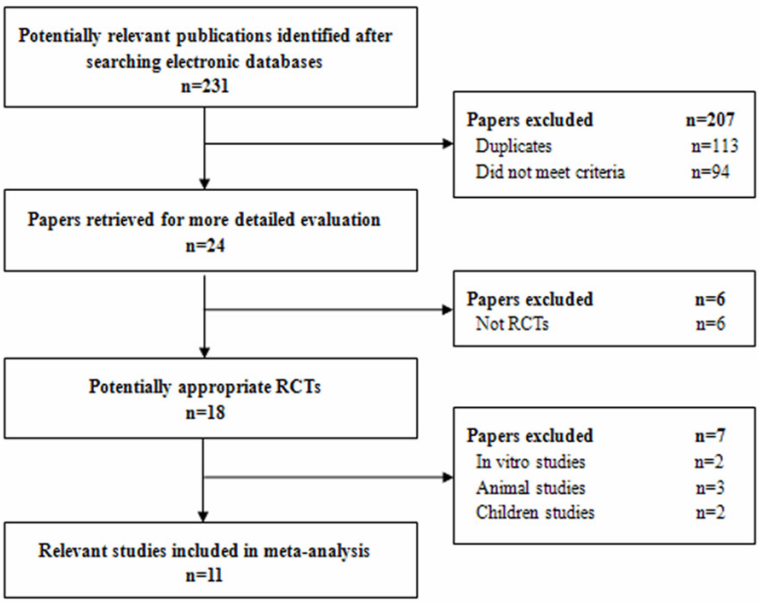

Figure 1. Flowchart of the study selection. RCT = randomized controlled trial; n = number of papers.

October 2015), AMED (1985 to October 2015), EMBASE (1974 to October 2015), CINHAL (1982 to October 2015), Cochrane Library (2015), CNKI (1994 to October 2015), Scopus and Biomed Central. No language or date restrictions were applied. The Medical Subject Headings (MeSH) and keyword search adopted was "septic shock" AND "vasopressin" OR "terlipressin" OR "norepinephrine". The unpublished literature was searched using the electronic databases OpenSIGLE (System for Information on Grey Literature in Europe), the WHO International Clinical Trials Registry Platform, Current Controlled Trials, UKCRN Portfolio Database and National Technical Information Service from their inception to 1st October 2015. Finally, the reference lists of all full text papers identified as pertinent to the study were reviewed for any unidentified studies.

Inclusion and eligibility criteria

Only randomized controlled trials (RCTs) were eligible for this study, with an experimental group that used vasopressin or terlipressin, and a control group that received norepinephrine. The participants were adults who had septic shock. Subgroup analysis was performed for patients with different characteristics.

Study selection

Two authors (JXT, HC) independently applied the search strategy to selected references from these databases. The titles and abstracts of those articles were reviewed independently. When there was a doubt, the full text was retrieved for further scrutiny. Those two authors independently assessed each full study report to see whether it met the review's inclusion criteria, and authors were contacted for more information and clarification of data as necessary. Any disagreement was discussed with the senior authors (DZ, FH), and when consensus could not be reached, that study was excluded. A list of all pertinent papers satisfying these criteria was then constructed by each reviewer, to compile an agreed list of studies.

Data abstraction

A data extraction form was designed and agreed by the authors, and a pilot test of five articles was performed to ensure its consistency. Initially, two authors (JXT, HC) independently extracted the data, which was later reviewed jointly to produce agreed accurate data. Disagreements were resolved by consensus or consultation with the senior authors. Data extracted included: sample size, study design, subject age, gender, interventions, prognostic index, mean arterial pressure (MAP) target value, results, and follow-up period.

Outcome

The outcome measures were the mortality, intensive care unit (ICU) length of stay, heart rate (HR), MAP, arterial pH, lactate, urinary output, cardiac index (CI), stroke volume index (SVI), left and right ventricular stroke work indices (LVSWI, RVSWI), mean pulmonary arterial pressure (MPAP), pulmonary artery occlusion pressure (PAOP), pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), systemic oxygen delivery index (DO_2I), oxygen consumption index (VO_2I) and adverse events.

Quality assessment

In order to assess the methodological quality of included studies, review authors (JXT, HC) used

Table 1. Characteristics of the included studies

Author	Groups	Number	Age	Interventions	MAP target value	Prognostic index	Combine with Corticosteroids	Year	Jadad
Russell [12]	VP	203	60.0±15.7	0.01-0.03 U/min	65-75 mmHg	26.5±7.7 (APACHE II)	Yes	2013	5
	NE	191	60.7±16.7	5-15 μg/min		27.2±7.0 (APACHE II)			
Mehta [13]	VP	65	62.9	0.01-0.03 U/min	65-75 mmHg	28.1±8.0 (APACHE II)	Yes	2013	5
	NE	56	65.5	5-15 μg/min		29.2±7.3 (APACHE II)			
Gordon [14]	VP	123	NA	0.01-0.03 U/min	65-75 mmHg	NA	Yes	2012	5
	NE	118	NA	5-15 μg/min		NA			
Gordon [15]	VP	373	59.1	0.01-0.03 U/min	65-75 mmHg	26.7 (APACHE II)	NA	2010	5
	NE	357	61.9	≥5 μg/min		27.0 (APACHE II)			
Russell [16]	VP	295	59.0±16.2	0.01-0.03 U/min	65-75 mmHg	27.4±7.2 (APACHE II)	Yes	2009	5
	NE	293	61.4±15.7	5-15 μg/min		27.9±6.7 (APACHE II)			
Morelli [17]	VP	15	66	0.03 U/min	65-75 mmHg	60 (SAPS II)	NA	2009	3
	TP	15	67	1.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$		62 (SAPS II)			
	NE	15	64	15 μg/min		58 (SAPS II)			
Morelli [18]	TP	19	66	1 mg	65-75 mmHg	60±12 (SAPS II)	NA	2008	5
	NE	20	67	0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$		59±10 (SAPS II)			
Lauzier [19]	VP	13	51.2±17.2	0.04-0.20 U/min	≥70 mmHg	22.8±3.4 (APACHE II)	Yes	2006	3
	NE	10	58.1±17.5	0.1-2.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$		23.5±4.2 (APACHE II)			
Albanese [20]	TP	10	66	0.03-0.04 U/min	65-75 mmHg	28 (APACHE II)	No	2005	2
	NE	10	65	0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$		29 (APACHE II)			
Dunser [21]	VP	24	68±9.4	4 U/h	≥70 mmHg	51.6±16.8 (SAPS II)	NA	2003	2
	NE	24	68±13.5	0.5-2.26 $\mu g \cdot kg^{-1} \cdot min^{-1}$		49.7±18.3 (SAPS II)			
Patel [22]	VP	13	68	0.05-0.06 U/min	NA	22 (APACHE II)	NA	2002	3
	NE	11	68	12-29.9 μg/min		24 (APACHE II)			

VP = vasopressin; NE = norepinephrine; TP = terlipressin; MAP = mean arterial pressure; NA = not available.

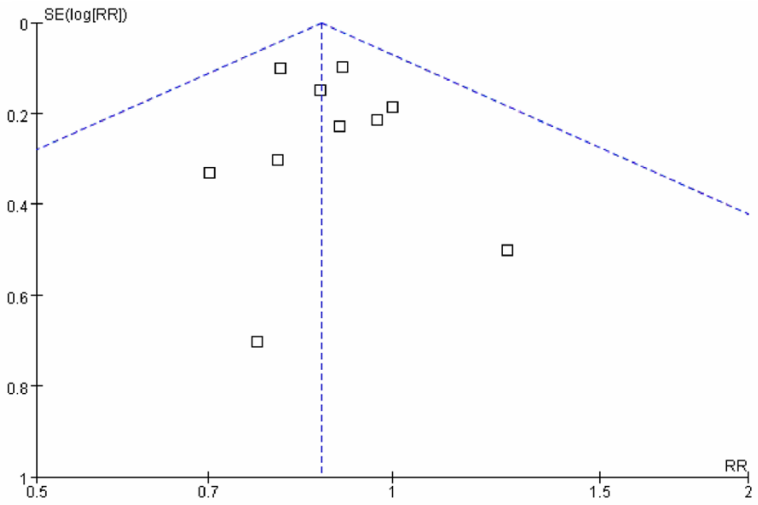

Figure 2. Trials of vasopressin/terlipressin *vs* norepinephrine: funnel plot of mortality. SE = standard error; RR = relative risk.

the Jadad score [11], including the proper conduct of randomization, concealment of treatment allocation, similarity of treatment groups at baseline, clinician blinding, and the description of withdrawals and dropouts. The methodological quality of each trial was scored and ranged from 0 to 5. Any disagreement was resolved by the senior authors.

Statistical analysis

The Review Manager Database (RevMan version 5.1, The Cochrane Collaboration 2011) was used to analyze selected studies. Continuous data for each arm in a particular study were expressed as mean and standard deviation (SD), and the treatment effect as mean differences. Dichotomous data for each arm in a particular study were expressed as proportions or risks, and the treatment effect as relative risk (RR). Missing data were sought from the authors. When this was not possible or data were missing through loss to follow-up, intention-to-treat principles were used. Statistical heterogeneity was assessed using the value of I^2 and the result of the chi-squared test. A p-value of < 0.1

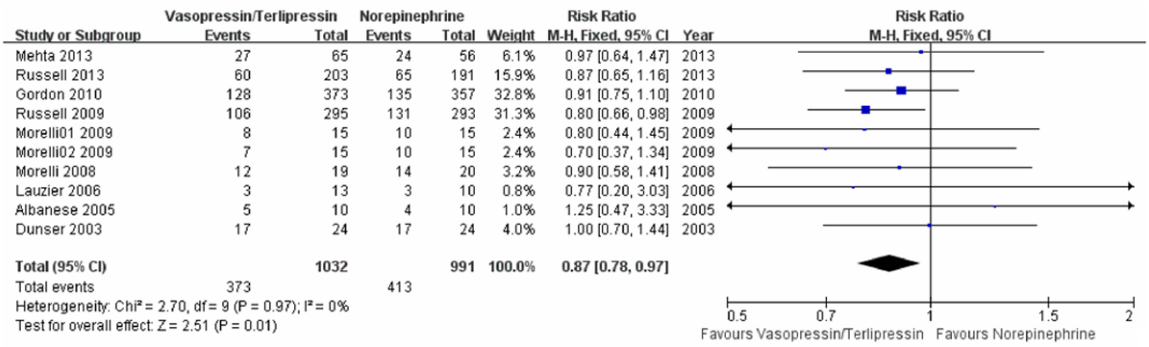

Figure 3. Trials of vasopressin/terlipressin *vs* norepinephrine: Forest-plot of mortality rate. M-H = Mantel-Haenszel; CI = confidence interval; % = percentage. Morelli01 = vasopressin group vs. norepinephrine group; Morelli02 = terlipressin group vs. norepinephrine group.

Table 2. Summary of other analysis results of vasopressin/terlipressin *vs* norepinephrine

Other analysis	Studies (n)	Patients (n)	Mean difference [95% CI]	Heterogeneity
ICU stay	5	138/130	3.40 [-1.62, 8.43]; P=0.18	I^2=0%; P=0.47
HR	7	213/203	-3.91 [-7.83, 0.02]; P=0.05	I^2=0%; P=0.52
MAP	8	232/223	1.92 [-0.95, 4.78]; P=0.19	I^2=78%; P=0.0004
pH	6	206/202	0.00 [-0.02, 0.02]; P=0.89	I^2=0%; P=0.70
Lactate	4	166/158	-0.22 [-1.20, 0.76]; P=0.66	I^2=0%; P=0.97
Urinary output	4	62/60	8.64 [-14.45, 30.87]; P=0.48	I^2=6%; P=0.36
CI	7	213/203	-0.23 [-0.48, 0.02]; P=0.08	I^2=24%; P=0.26
SVI	6	200/192	-1.76 [-4.35, 0.83]; P=0.18	I^2=0%; P=0.71
LVSWI	5	187/182	-1.16 [-3.57, 1.25]; P=0.35	I^2=24%; P=0.27
RVSWI	4	59/60	-0.78 [-2.12, 0.55]; P=0.25	I^2=0%; P=0.83
MPAP	7	219/212	0.21 [-1.05, 1.48]; P=0.74	I^2=0%; P=0.89
PAOP	6	195/188	1.51 [0.84, 2.17]; P<0.00001	I^2=0%; P=0.79
PVRI	5	72/70	-10.72 [-54.43, 32.98]; P=0.63	I^2=0%; P=0.50
SVRI	5	77/74	32.78 [-112.64, 178.20]; P=0.66	I^2=0%; P=0.65
DO_2I	5	77/74	3.78 [-53.23, 60.78]; P=0.90	I^2=5%; P=0.37
VO_2I	5	86/84	7.55 [-13.71, 28.82]; P=0.49	I^2=58%; P=0.05

ICU = intensive care unit; HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SVI = stroke volume index; LVSWI = left ventricular stroke work indices; RVSWI = right ventricular stroke work indices; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index; DO_2I = systemic oxygen delivery index; VO_2I = oxygen consumption index.

and an I^2 value > 50% were considered suggestive of statistical heterogeneity, prompting a random effects modeling estimate. Otherwise, a fixed effects approach was used. Conversely, a non-significant chi-squared test result (a *p*-value ≥ 0.1 and an I^2 value ≤ 50%) only suggested that there was no evidence of heterogeneity: it did not imply that there was necessarily homogeneity, as there may have been insufficient power to be able to detect heterogeneity. When the data allowed, we performed subgroup analysis of the trials according to the different vasoactive medications of the experimental group and whether or not combined with corticosteroids.

Results

A total of 231 abstracts and titles were reviewed. Of these 11 satisfied the eligibility criteria and were included in the meta-analysis [12-22]. There was an article containing two experimental groups (vasopressin and terlipressin) [17]. A flowchart is provided in **Figure 1**. The number of patients included in these randomized controlled trials ranged from 20 to

Table 3. Subgroup analysis of different vasoactive medications of the experimental group *vs* norepinephrine

Subgroup analysis	Studies (n)	Patients (n)	Results [95% CI]	Heterogeneity
Mortality				
Vasopressin	7	988/946	0.87 [0.78, 0.97]; P=0.02	I^2=0%; P=0.94
Terlipressin	3	44/45	0.88 [0.62, 1.25]; P=0.47	I^2=0%; P=0.61
MAP				
Vasopressin	5	188/178	-0.01 [-2.24, 5.99]; P=0.37	I^2=80%; P=0.002
Terlipressin	3	44/45	2.36 [-2.53, 7.26]; P=0.34	I^2=81%; P=0.02
pH				
Vasopressin	4	162/157	-0.00 [-0.03, 0.02]; P=0.87	I^2=0%; P=0.78
Terlipressin	3	44/45	0.010 [-0.03, 0.05]; P=0.58	I^2=30%; P=0.23
Urinary output				
Vasopressin	2	28/25	-1.82 [-29.11, 25.48]; P=0.90	I^2=0%; P=0.48
Terlipressin	2	34/35	30.41 [-10.21, 71.04]; P=0.14	I^2=2%; P=0.31
MPAP				
Vasopressin	4	175/167	0.64 [-0.83, 2.11]; P=0.40	I^2=0%; P=0.93
Terlipressin	3	44/45	-1.00 [-3.49, 1.49]; P=0.43	I^2=0%; P=1.00
PVRI				
Vasopressin	2	28/25	-18.70 [-85.53, 48.12]; P=0.58	I^2=0%; P=0.82
Terlipressin	3	44/45	-4.76 [-62.53, 53.02]; P=0.87	I^2=54%; P=0.14
VO_2I				
Vasopressin	3	52/49	1.73 [-29.18, 32.65]; P=0.91	I^2=57%; P=0.10
Terlipressin	2	34/35	14.82 [-26.27, 55.92]; P=0.48	I^2=78%; P=0.03
PAOP				
Vasopressin	3	151/143	1.58 [0.65, 2.51]; P=0.0009	I^2=0%; P=0.74
Terlipressin	3	44/45	1.43 [0.49, 2.38]; P=0.003	I^2=6%; P=0.30

MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; VO_2I = oxygen consumption index; PAOP = pulmonary artery occlusion pressure.

730. A total of 2273 patients were enrolled in the randomized controlled trials. The details are shown in **Table 1**. These studies were relatively well designed and the quality assessment score was high in most of them, with a mode of 5, the highest possible score and a range of 2 to 5. Only two studies had a score less than 3. A funnel plot based on the most frequently cited outcome was broadly symmetrical, indicating minimal publication bias (**Figure 2**).

Mortality

In all, 10 trials including 2023 patients provided mortality information (**Figure 3**). Mortality of septic shock adult patients was 373 of 1032 and 413 of 991 patients in vasopressin/terlipressin and norepinephrine groups, respectively. The mortality rate was significantly lower in the vasopressin/terlipressin group (RR, 0.87 [95% CI, 0.78 to 0.97]; P = 0.01).

Other outcomes

Except the PAOP was higher in the vasopressin/terlipressin group (mean difference 1.51, 95% CI 0.84 to 2.17; P < 0.00001), the other 15 outcomes were not significantly different (**Table 2**). Significant heterogeneity was found in two outcomes (MAP and VO_2I). Besides, the authors of this paper compared all reported adverse events among the groups. However, there was no sufficient data to analyze the outcome.

Subgroup analysis

There were nine trials using vasopressin [12-17, 19, 21-22] and three using terlipressin [17, 18, 20]. Compared with norepinephrine, vasopressin (1934 patients) could significantly reduce the mortality rate (RR, 0.87 [95% CI, 0.78 to 0.97]; P = 0.02), however, it turns out that terli-

Table 4. Subgroup analysis of corticosteroids *vs* Non-corticosteroids group

Subgroup analysis	Studies (n)	Patients (n)	Results [95% CI]	Heterogeneity
Mortality				
Corticosteroids	4	576/550	0.84 [0.72, 0.98]; P=0.03	I^2=0%; P=0.87
Non-Corticosteroids	6	456/441	0.91 [0.78, 1.06]; P=0.21	I^2=0%; P=0.92
HR				
Corticosteroids	2	136/128	-5.75 [-10.11, -1.04]; P=0.02	I^2=0%; P=0.73
Non-Corticosteroids	5	77/75	0.27 [-6.82, 7.36]; P=0.94	I^2=0%; P=0.55
MAP				
Corticosteroids	2	136/128	-1.40 [-3.61, 0.82]; P=0.22	I^2=47%; P=0.17
Non-Corticosteroids	6	96/95	1.68 [0.14, 3.21]; P=0.03	I^2=81%; P<0.001
CI				
Corticosteroids	2	136/128	-0.44 [-0.75, -0.12]; P=0.007	I^2=0%; P=0.61
Non-Corticosteroids	5	77/75	0.15 [-0.28, 0.58]; P=0.49	I^2=0%; P=0.86
SVI				
Corticosteroids	2	136/128	-2.95 [-6.10, 0.19]; P=0.07	I^2=0%; P=0.64
Non-Corticosteroids	4	64/64	0.74 [-3.82, 5.31]; P=0.75	I^2=0%; P=0.90
MPAP				
Corticosteroids	2	136/128	0.64 [-1.12, 2.40]; P=0.47	I^2=0%; P=0.57
Non-Corticosteroids	4	83/84	-0.25 [-2.07, 1.57]; P=0.79	I^2=0%; P=0.83
PAOP				
Corticosteroids	2	136/128	1.27 [0.04, 2.50]; P=0.04	I^2=0%; P=0.88
Non-Corticosteroids	4	59/60	1.61 [0.82, 2.39]; P<0.0001	I^2=0%; P=0.48

HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SVI = stroke volume index; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure.

pressin didn't have this advantage (RR, 0.88 [95% CI, 0.62 to 1.25]; P = 0.47) (**Table 3**).

Corticosteroids have been used simultaneously with vasoactive agents [12-14, 16, 19]. Subgroup analysis showed the mortality rate, HR and CI were significantly lower in the vasopressin group compared with the norepinephrine group (**Table 4**). However, in non-corticosteroids group, no significant difference existed.

Discussion

Although norepinephrine is the recommended agent for the treatment of hypotension in volume-resuscitated hyperdynamic septic shock (1), its effectiveness and safety remains controversial. Therefore, vasopressin and its analog terlipressin, a neurohypophyseal hormone with diverse actions mediated by tissue-specific receptors, have been utilized by many emergency and CCM doctors to decrease mortality rate of septic shock patients.

According to our analysis results, the use of vasopressin and terlipressin could effectively reduce mortality rate than norepinephrine in adult septic shock patients. This is not consistent with results of previous meta-analyses by Serpa Neto [23] and Polito [24]. Possible reasons for this diversity include relatively small sample sizes in previous studies, inclusion of non-RCTs, children and different control groups.

Subgroup analysis demonstrated that vasopressin significantly reduced the mortality rate, while terlipressin was not as effective as its analogue. However, since only 3 studies (89 patients) reported the mortality of terlipressin, maybe it's too early to get the conclusion that terlipressin is not of promise. Previous studies have shown that corticosteroids, compared with placebo, decreased mortality in septic shock patients [16, 25]. Similarly, subgroup analysis of this study showed the mortality rate, HR and CI were significantly lower when vasopressin was used conjointly with corticosteroids. Russell et al [16] and Ertmer et al [26] reported that the potential mechanisms of this benefit could be increased vasopressin levels induced by corticosteroids, enhanced responsiveness to vasopressin conferred by cortico-

steroids and more potent anti-inflammatory effects of the combination of vasopressin and corticosteroids.

In this meta-analysis only RCTs were eligible and only data of one experimental group that used vasopressin or terlipressin and of control group that received norepinephrine were extracted from multi-group comparison study. Significant heterogeneity among different studies have been demonstrated when MAP and VO_2I were evaluated. This phenomenon could not be well explained by the difference of treatment protocol, MAP target value, prognostic index or administration regimen in each study. Rather, we believed that the sample size difference, patient characteristics variation, inclusion and exclusion criteria diversity, difference of management protocols and logistics between treating centres, as well as different strategies for measuring outcomes should be responsible for such heterogeneity.

Limitations of this meta-analysis include the small sample size of each study and the significant heterogeneity in MAP and VO_2I. Besides, no sufficient data is available to support our intention to analyze adverse events, other organ function or plasma cytokine levels.

Conclusion

Compared with norepinephrine, vasopressin and its analog terlipressin could significantly reduce mortality rate of adult septic shock patients. The combination of low-dose vasopressin and corticosteroids was associated with decreased mortality, HR and CI compared with conjoint use of norepinephrine and corticosteroids.

Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the study: J.T. X.C. F.H.; Selected references and extracted data: J.T. H.C.; Analyzed and interpreted the data: J.T. D.Z. F.H.; Wrote the paper: J.T. H.C.; Provided critical revisions: X.C. D.Z. F.H.; Approved the final version of the manuscript: J.T. H.C. X.C. D.Z. F.H.

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