Original Article

Combination era, using combined vasopressors showed benefits in treating septic shock patients: a network meta-analysis of randomized controlled trials

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Background: Septic shock is one of the major healthcare problems, affecting millions of people around the world every year. The object of this study is to find the best kind of regimen of vasopressors treatment in septic shock.

Methods: The PubMed, and the Web of Science were used to find the included studies. Stata 15.1 was performed to this systemic review and network meta-analysis.

Results: After searching and screening the articles, finally we included articles about 31 randomized controlled trials (RCTs), 11 arms (dopamine, dopexamine, epinephrine, norepinephrine, norepinephrine + dobutamine, norepinephrine + dopexamine, norepinephrine + epinephrine, norepinephrine + vasopressin, phenylephrine, terlipressin, vasopressin) and total 5,928 patients with septic shock. Compared with dopamine, the regimens (epinephrine, norepinephrine, norepinephrine + dobutamine, and vasopressin) have significantly lower 28-day mortality. Ranking the regimens in the order of estimated probabilities of each treatment by using the network meta-analysis for 28-day mortality, the result showed that norepinephrine + dopexamine was the best one (57.3%), followed by norepinephrine + epinephrine (14.8%), norepinephrine + dobutamine (10.9%), dopexamine (11.2%), terlipressin (9.8%), norepinephrine + vasopressin (2.4%), phenylephrine (1.2%), epinephrine (1.0%), vasopressin (0.5%), norepinephrine (0.0%), and dopamine (0.0%). In addition, for the results of arrhythmia and increased heart rate, the combination regimens groups did not showed inferiority to other single regimen groups.

Conclusions: Single dopamine had significantly higher 28d mortality. Combination regimens of vasopressors accounted for the best three therapeutic regimens. In treating patients with septic shock, using combining regimens probably gets more benefits.

Keywords: Septic shock; vasopressor; norepinephrine

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Introduction

In the latest definitions for sepsis and septic shock (Sepsis-3), *Sepsis* is defined as life-threatening organ dysfunction caused by a dysregulated host response to the infection. *Septic shock* is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (1-3). Nowadays, septic shock is one of the major healthcare problems, affecting and killing millions of people around the world every year (4,5). Similar to acute myocardial infarction, or stroke, early identification and appropriate management in the initial hours after sepsis developing can improve the prognosis.

In septic shock, when volume resuscitation fails to restore mean arterial pressure (MAP), vasopressors such as dopamine, norepinephrine, epinephrine, dopexamine, will be used, either alone or in combination (6,7).

There have been some meta-analysis studies for comparing these vasopressors in 28-day mortality (8-13). The result of these studies showed that norepinephrine was probably the best regimen. The latest network meta-analysis was published in May 2019. In the meta-analysis conducted by Cheng *et al.* (14), the studies comparing levosimendan with comparators were included in their study, however, levosimendan promotes the vasodilatation (15), which is different from the vasopressors in the management of septic shock. Actually in those included studies (16-24), they not only used single levosimendan as a group [norepinephrine (16-21,23), or dopamine (22) was also added to maintain the blood pressure]. Moreover, three randomized controlled trials (RCTs) included in their study combined placebo with/using other standard therapy as a group (25-27). So in our study, we excluded the studies above, and mainly talked about "vasopressor". We did this network meta-analysis and tried to find out what kind of regimens of vasopressors could be more appropriate for treating patients with septic shock in clinical practice.

Methods

Search strategy

Two investigators independently reviewed the identified abstracts and selected articles for full reviewing, and the discrepancies were resolved by the third reviewer. The reference lists of eligible studies and relevant papers were also manually searched and reviewed. The search terms were "septic shock" and "vasopressor", etc. The search terminal date was 2019/4/22. Finally we found 2,517 articles, excluding 1,374 duplications, then we included 46 articles through reading the title and abstract, and 31 studies (28-39) were (40-58) included by reading the whole articles (*Figure 1*).

Inclusion and exclusion

Inclusions contain: (I) researched study about using vasopressors for treating septic shock; (II) outcome: 28-day mortality; (III) only be published in English.

Exclusions contain: (I) review, retrospective research, case report; (II) insufficient data in the articles.

Data elected

Two authors independently reviewed the identified abstracts and selected articles to full review. The third reviewer addressed the discrepancies. For each selected publication, the following baselines and study characteristics were extracted: first author, publication year, country, participant characteristics, total number of patients in experiment and control group, age of patients in each group, other baseline characteristics, and the treatment dose of each medication in these studies were concluded below (*Tables 1*,*S1*). Primary outcome measure was the 28-day mortality, secondary outcome measures were the incidence of arrhythmia, and increased heart rate. This study is a network meta-analysis, so it does not need ethics approval.

Risk of bias assessment

Risk of bias of trials included in this meta-analysis was assessed according to the Jadad scale, in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, and completed withdrawals and dropouts.

Statistical analysis

We pooled data and used odd ratios (OR), confidential interval (CI) for the dichotomy outcome: the 28-day mortality, incidence of arrhythmia. We used mean difference (MD), CI for the continuous outcome: heart rate. All statistical analyses were carried out with Stata 15.1.

Results

In our study, we totally included 31 RCTs with 5928

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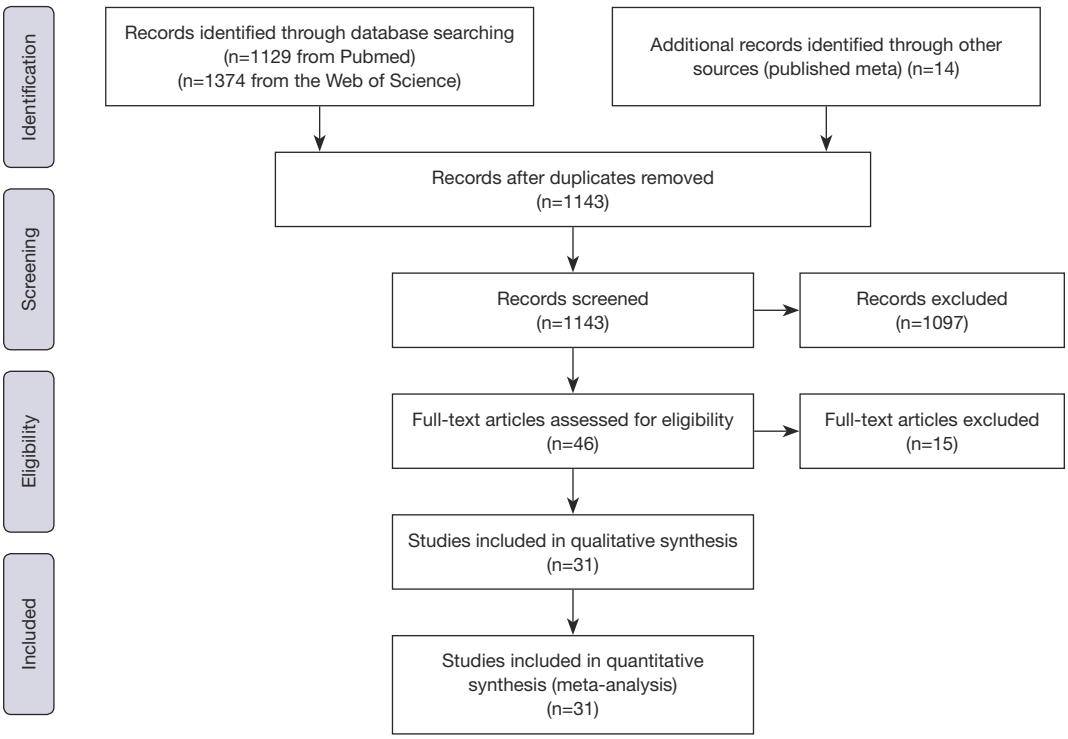

Figure 1 Flow diagram of choosing the appropriated articles.

patients about what kind of regimens of vasopressors could decrease the 28-day mortality in patients with septic shock. The quality of the article evaluations was as followed. The Jadad Scales of all included studies ranged from 2 to 7, and the studies included in our study were all well-prepared RCTs (*Table 1*).

In network meta-analysis, we didn't compare the heterogeneity in the study, but we made an inconsistency test to find out whether the data of these studies could be mixed and calculated. The inconsistency test showed that the comparison could be performed by consistency (P>0.05) (*Table 2*).

Network evidence of the comparisons for the different regimens of vasopressors was showed in *Figure 2*. Compared with dopamine, some therapeutic regimens (epinephrine (OR 0.560, 95% CI: 0.330–0.948), norepinephrine (OR 0.803, 95% CI: 0.655–0.986), norepinephrine +dobutamine (OR 0.454, 95% CI: 0.232–0.887), vasopressin (OR 0.702, 95% CI: 0.547–0.900) were more beneficial to decrease the 28d mortality, respectively. However, there was no significant difference among these therapeutic regimens (*Table 3*, *Figure 3*).

In the rank of network meta-analysis, we found that norepinephrine + dopexamine (57.3%) was the most effective therapeutic regimen to reduce the 28d mortality in these patients with septic shock, followed by norepinephrine+ epinephrine (14.8%), norepinephrine + dobutamine (10.9%), dopexamine (11.2%), terlipressin (9.8%), norepinephrine + vasopressin (2.4%), phenylephrine (1.2%), epinephrine (1.0%), vasopressin (0.5%), norepinephrine (0.0%), and dopamine (0.0%). The biggest probability means this therapeutic regimen has the greatest chance to be the best treatment (*Table 4*).

Potential publication bias of vasopressors used for treating patients with septic shock was performed and showed as funnel plot (*Figure 4*).

Supplementary data show the results of incidence of arrhythmia and increased heart rate in septic shock patients in the included studies of the network meta-analysis (*Figures S1*,*S2*, *Tables S1-S5*).

Discussion

According to the results of our study, using combination vasoactive agent (vasopressors) is prior to only one agent. In addition, for the results of arrhythmia and increased heart

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Table 1 Baseline characteristics of enrolled studies

Study	Type	Time (published)	Country	Jadad scale (randomization + concealment of allocation + double blinding + withdrawals and dropouts)	Participant	Age (A *vs.* B)	Male/total (A *vs.* B)	Total number (A *vs.* B)	Mortality (A *vs.* B)	A; B
Annane *et al.*	RCT	2007	France	1+1+1+0=3	Multi-center	–	–	161; 169	64; 58	Epinephrine; norepinephrine+ dobutamine
Baske *et al.*	RCT	2018	India	2+2+2+1=7	One center	–	14/20; 13/20	20; 20	14; 16	Epinephrine; dopamine
Choudhury *et al.*	RCT	2017	India	2+2+0+1=5	One center	46.76±12.11; 48.29±12.53	35/42; 34/42	42; 42	32; 36	Terlipressin; norepinephrine
De Backer *et al.*	RCT	2010	Spain	2+2+0+1=5	Multi-center	–	–	542; 502	291; 249	Dopamine; norepinephrine
Gordon *et al.*	RCT	2016	United Kingdom	2+2+2+1=7	Multi-center	–	111/204; 127/204	204; 204	63; 56	Vasopressin; norepinephrine
Gordon *et al.*	RCT	2010	Canada	1+1+1+1=4	Multi-center	–	–	397; 382	140; 150	Vasopressin; norepinephrine
Hammond *et al.*	RCT	2018	France	1+1+0+0=2	One center	62 [51–74]; 60 [49–68]	22/41; 18/41	41; 41	19; 18	Vasopressin + norepinephrine; norepinephrine
Hua *et al.*	RCT	2013	China	2+1+0+0=3	One center	52.2±14.0; 56.6±16.4	8/16; 10/16	16; 16	8; 7	Dopamine; terlipressin
Jain *et al.*	RCT	2010	India	2+1+2+0=5	One center	42.88±5.39; 45.29±7.41	15/27; 13/27	27; 27	15; 16	Norepinephrine; phenylephrine
Levy *et al.*	RCT	1997	France	1+1+0+0=2	One center	54±10; 56±9	10/15; 11/15	15; 15	9; 8	Epinephrine; norepinephrine+ dobutamine
Lauzier *et al.*	RCT	2006	Canada	2+2+0+0=4	Two centers	58.1±17.5; 51.2±17.2	8/10; 6/13	10; 13	3; 3	Norepinephrine; vasopressin
Luckner *et al.*	RCT	2006	Austria	1+1+0+0=2	One center	–	–	10; 8	8; 7	Vasopressin + norepinephrine; norepinephrine
Marik *et al.*	RCT	1994	–	–	One center	–	–	10; 10	5; 6	Norepinephrine; dopamine
Mathur *et al.*	RCT	2007	–	–	One center	–	–	25; 25	14; 19	Norepinephrine; dopamine
Martin *et al.*	RCT	1993	–	–	One center	–	–	16; 16	7; 10	Norepinephrine; dopamine
Morelli *et al.*	RCT	2008	Italy	2+1+0+1=4	One center	70 [53–74]; 70 [59–74]	11/14; 13/19	16; 16	10; 9	Phenylephrine; norepinephrine
Morelli *et al.*	RCT	2008	Italy	1+1+0+1=3	One center	66 [28–84]; 67 [29–83]	13/19; 14/20	19; 20	12; 14	Terlipressin; norepinephrine

Table 1 (*continued*)

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Table 1 (*continued*)

Study	Type	Time (published)	Country	Jadad scale (randomization + concealment of allocation + double blinding + withdrawals and dropouts)	Participant	Age (A *vs.* B)	Male/total (A *vs.* B)	Total number (A *vs.* B)	Mortality (A *vs.* B)	A; B
Morelli *et al.*	RCT	2009	Italy	2+1+0+1=4	One center	67 [60–71]; 66 [60–74]; 64 [59–72]	11/15; 10/15; 12/10	15; 15; 15	7; 8; 10	Terlipressin; vasopressin; norepinephrine
Myburgh *et al.*	RCT	2008	Australia	2+2+2+1=7	Mult-center	59.4±15.9; 60.4±14.8	10/64; 7/63	64; 63	15; 17	Epinephrine; norepinephrine
Mahmoud *et al.*	RCT	2012	Egypt	2+2+2+0=6	One center	52.4±4.5; 50.3±6.5	16/30; 15/30	30; 30	15; 16	Norepinephrine + dobutamine; norepinephrin + epinephrine
Mehta *et al.*	RCT	2013	Canada	1+1+1+1=4	9 centers	62.9 [51.2–73.6]; 65.5 [50.8–76.1]	43/65; 42/56	65; 56	27; 24	Vasopressin; norepinephrine
Patel *et al.*	RCT	2010	USA	1+1+0+0=2	One center	–	64/134; 52/118	134; 118	67; 51	Dopamine; norepinephrine
Ruokonen *et al.*	RCT	1993	Finland	1+1+0+0=2	One center	18-76; 39–53	–	5; 5	4; 3	Norepinephrine; dopamine
Ramaswamy *et al.*	RCT	2016	India	2+2+2+1=7	One center	7 [1–11]; 4 [0.8–8]	15/29; 15/31	29; 31	14; 18	Epinephrine; dopamine
Russell *et al.*	RCT	2009	Australia	1+1+1+1=4	Mult-center	–	–	396; 382	140; 150	Vasopressin; norepinephrine
Russell *et al.*	RCT	2008	Canada	2+2+2+1=7	Mult-center	59.3±16.4; 61.8±16	246/396; 229/382	396; 382	140; 150	Vasopressin; norepinephrine
Russell *et al.*	RCT	2013	Canada	1+1+1+0=3	Multi-center	60.7±16.7; 60.0±15.7	121/191; 112/203	191; 203	65; 60	Norepinephrine; vasopressin
Schmoelz *et al.*	RCT	2006	Germany	2+1+2+0=2	One center	49.24±19.03; 56.7±18.5	14/22; 10/21	22; 21	4; 5	Dopamine; dopexamine
Seguin *et al.*	RCT	2002	France	1+1+0+0=2	One center	65±12; 70±13	6/10; 6/11	10; 11	4; 5	Epinephrine; norepinephrine+ dobutamine
Seguin *et al.*	RCT	2006	France	1+1+0+0=2	One center	67±13; 65±10	–	10; 12	3; 2	Epinephrine; dopexamine + norepinephrine
Ventura *et al.*	RCT	2015	Brazil	2+2+2+1=7	One center	39.6±46.3 months; 56.9±58.2 months	35/63; 35/57	63; 57	13; 4	Dopamine; epinephrine

RCT, randomized controlled trial.

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Table 2 Network meta inconsistency test

Variable	Direct		Indirect		Differ		P
	Coef	Std. Err	Coef	Std. Err	Coef	Std. Err	
AB	–	–	–	–	–	–	–
AC	−0.706	0.348	−0.396	0.423	−0.310	0.548	0.572
AD	−0.216	0.107	−0.268	0.446	0.052	0.458	0.910
AJ	−0.251	0.710	−0.758	0.376	0.507	0.804	0.528
CD	0.188	0.409	0.498	0.364	−0.310	0.548	0.572
CE	−0.210	0.212	0.789	496.336	−1.000	496.336	0.998
CF	−0.762	1.037	1.152	1,537.021	−1.914	1,537.021	0.999
DH	0.032	0.421	0.414	1,001.855	−0.381	1,001.855	1.000
DI	0.191	0.438	0.440	885.914	−0.248	885.914	1.000
DJ	−0.580	0.378	−0.015	0.627	−0.565	0.735	0.442
DK	−0.136	0.072	0.333	1.482	−0.469	1.484	0.752
EG	0.134	0.517	1.261	1,270.869	−1.127	1,270.869	0.999
JK	0.267	0.732	0.300	0.368	−0.033	0.819	0.968

A, dopamine; B, dopexamine; C, epinephrine; D, norepinephrine; E, norepinephrine + dobutamine; F, norepinephrine + dopexamine; G, norepinephrine + epinephrine; H, norepinephrine + vasopressin; I, phenylephrine; J, terlipressin; K, vasopressin.

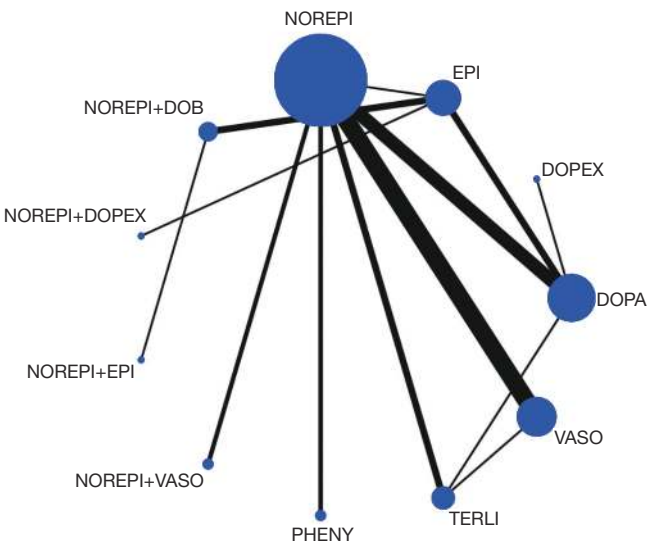

Figure 2 Network evidence of the comparisons for the different vasopressors regimens.

rate, the combination regimens groups did not showed inferiority to other single regimen groups.

Why using combination is more beneficial to patients with septic shock? The reasons should be derived from the composition of every combination regimen. We found out that every combination regimen contain norepinephrine, which mainly plays a role in the alpha adrenergic receptor in peripheral blood vessels, and some agents (epinephrine, dopexamine, dobutamine) increase the heart rate and stroke volume.

On the one hand, in pathophysiology, septic shock is a kind of distributive shock; the hypotension results from peripheral vasodilation and low systemic vascular resistance (59). Septic shock not only injures the vessel, making the body fluid flow from blood vessel to tissue, but also damages the cardiac function by secreting bacterial toxin (60,61).

On the other hand, single vasopressor regimens have many adverse events. For example, epinephrine induces higher heart rate, cardiac output, oxygen delivery, and more oxygen consumption than the combinations by stimulating the beta-1 adrenergic receptors (6); dopamine increases MAP mostly due to increment of stroke volume and heart rate; Norepinephrine also has limitations, as it increases MAP by means of the vasoconstrictive effects, with little improvement of cardiac function, changing heart rate and increasing strike volume less; In recent studies, low dose of

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Table 3 Odd ratio of comparisons for the different vasopressors regimens

Variable	A	B	C	D	E	F	G	H	I	J	K
A	–										
B	1.406 (0.321–6.160)	–									
C	0.560 (0.330–0.948)	0.398 (0.083–1.910)	–								
D	0.803 (0.655–0.986)	0.571 (0.129–2.538)	1.435 (0.842–2.446)	–							
E	0.454 (0.232–0.887)	0.323 (0.064–1.634)	0.810 (0.535–1.228)	0.565 (0.287–1.110)	–						
F	0.261 (0.032–2.134)	0.186 (0.014–2.421)	0.467 (0.061–3.565)	0.325 (0.040–2.661)	0.576 (0.072–4.588)	–					
G	0.518 (0.154–1.747)	0.369 (0.054–2.496)	0.926 (0.310–2.769)	0.645 (0.191–2.181)	1.143 (0.415–3.148)	1.984 (0.197–19.981)	–				
H	0.830 (0.355–1.942)	0.590 (0.107–3.245)	1.483 (0.555–3.961)	1.384 (0.453–2.358)	1.830 (0.630–5.317)	3.177 (0.332–30.394)	1.601 (0.368–6.972)	–			
I	0.973 (0.403–2.350)	0.692 (0.124–3.865)	1.738 (0.633–4.773)	1.211 (0.513–2.856)	2.145 (0.720–6.394)	3.724 (0.385–36.062)	1.876 (0.423–8.326)	1.172 (0.356–3.855)	–		
J	0.524 (0.273–1.005)	0.372 (0.074–1.872)	0.514 (0.412–2.127)	0.652 (0.346–1.227)	1.155 (0.460–2.898)	2.005 (0.224–17.967)	1.010 (0.257–3.971)	0.631 (0.223–1.785)	0.538 (0.185–1.564)	–	
K	0.702 (0.547–0.900)	0.499 (0.112–2.233)	1.254 (0.722–2.178)	0.874 (0.758–1.008)	1.548 (0.776–3.088)	2.688 (0.327–22.099)	1.354 (0.397–4.616)	0.846 (0.366–1.955)	0.722 (0.302–1.723)	1.341 (0.704–2.553)	–

A, dopamine; B, dopexamine; C, epinephrine; D, norepinephrine; E, norepinephrine + dobutamine; F, norepinephrine + dopexamine; G, norepinephrine + epinephrine; H, norepinephrine + vasopressin; I, phenylephrine; J, terlipressin; K, vasopressin.

vasopressin is probably effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits.

In addition, combination regimens probably have synergistic effects on decreasing the dosage and adverse events of one agent.

Similarly, the meta-analysis conducted by Zhou *et al.* (10) also showed the priority to combination regimens. However, the guideline (62) only demonstrated that norepinepherine was more useful than dopamine, and 'adding either vasopressin or epinephrine' to norepinepherine was suggested. Nowadays, in clinical practice, combinations only appear when single vasopressor treatment could not appropriately control the MAP.

The limitations of our study were showed as followed: Firstly, the studies included were only published in English, so we might lose some excellent studies published in other languages. Secondly, although the result showed that the probably best combination was norepinephrine and dopexamine. This finding was based on a single study

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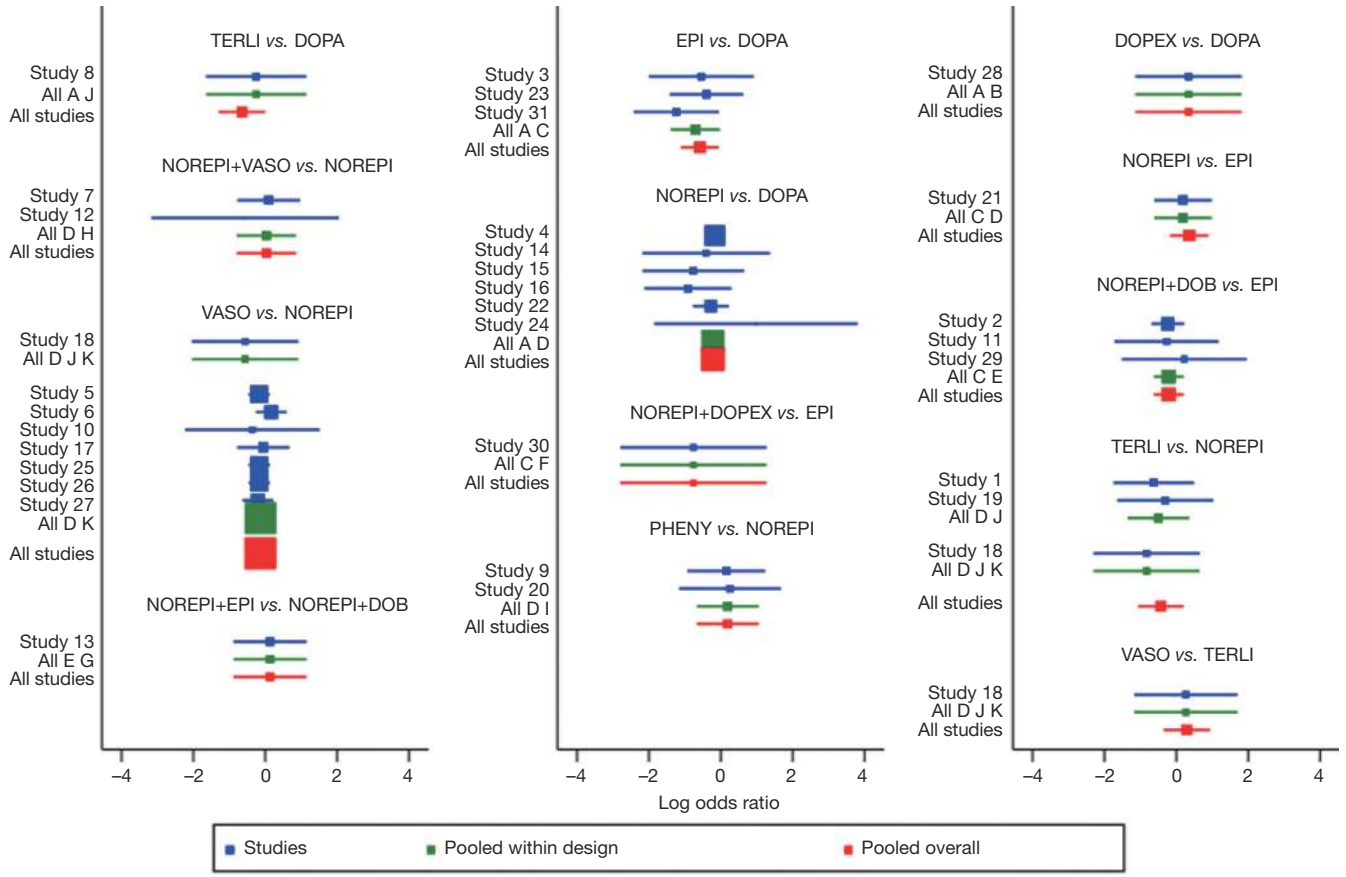

Test of consistency: chi2 (4) =1.04, P=0.904

Figure 3 Forest plots of the comparisons for the different vasopressor regimens.

Table 4 Estimated probabilities (%) of each treatment being the best

Treatment	DOPA	DOPEX	EPI	NOREPI	NOREPI + DOB	NOREPI + DOPEX	NOREPI + EPI	NOREPI + VASO	PHENY	TERLI	VASO
Outcome	0.0	11.2	1.0	0.0	10.9	57.3	14.8	2.4	1.2	9.8	0.5

DOPA, dopamine; DOPEX, dopexamine; EPI, epinephrine; NOREPI, norepinephrine; NOREPI + DOB, norepinephrine + dobutamine; NOREPI + DOPEX, norepinephrine + dopexamine; NOREPI + EPI, norepinephrine + epinephrine; NOREPI + VASO, norepinephrine + vasopressin; PHENY, phenylephrine; TERLI, terlipressin; VASO, vasopressin.

comparing this combination to epinephrine. Further, dopexamine is not available in many countries and has fallen out of favor. But according to our study, the results gave clinical practitioners the reference that the combination treatment could be better in downing 28-day mortality.

Conclusions

All in all, single dopamine showed significantly higher 28d mortality, as well as combination regimens of vasopressors accounted for the best three therapeutic regimens. In treating patients with septic shock, using combining regimens probably gets more benefits.

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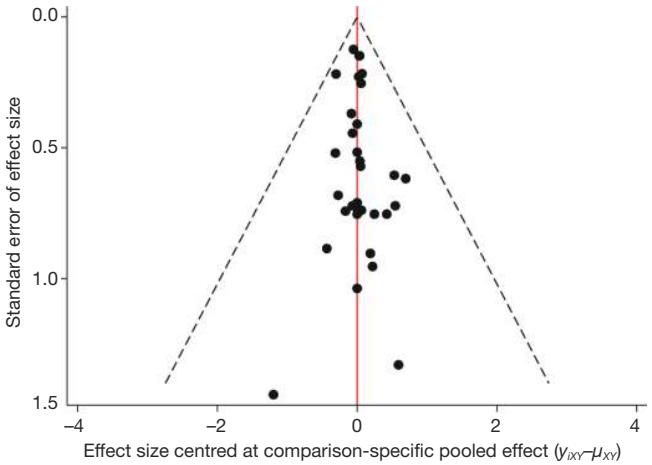

Figure 4 Funnel plot.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study is a network meta-analysis, which does not need ethics approval. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 The treatment doses of drugs in these studies

Author	Treatment dose of drug	Arrhythmia	Heart rate
Annane 2007	Norepinephrine was titrated at 0.2 μg/kg/min + dobutamine 5 μg/kg/min; epinephrine was titrated at 0.2 μg/kg/min; two groups maintain mean blood pressure of 70 mmHg or more	Epinephrine: 31/161; norepinephrine + dobutamine: 30/169	NA
Baske 2018	Epinephrine or dopamine was initiated at 0.2 or 10 μg/kg/min; after 15 min if shock persisted, epinephrine or dopamine was increased to 0.3 or 15 μg/kg/min, and thereafter to 0.4 or 20 μg/kg/min	NA	Epinephrine: 162±25; dopamine: 156±27
Choudhury 2016	Terlipressin was titrated and infused at a rate of 1.3 to 5.2 μg/min i.e., 2–8 mg over 24 hours; noradrenaline at a rate of 7.5 μg/min and gradually increased to maximum dose of 60 μg/min	Atrial fibrillation + ventricular tachycardia. terlipressin: 1/42; noradrenaline: 4/42	NA
De Backer 2010	Doses of dopamine could be increased or decreased by 2 μg/kg/min and doses of norepinephrine by 0.02 μg/kg/min. Maximum dose for dopamine: 20 μg/kg/min; Maximum dose for norepinephrine: 0.19 μg/kg/min	Only total shock data. Dopamine: 207/858; norepinephrine: 102/821	NA
Gordon 2016	Received either vasopressin (titrated up to 0.06 U/min) or norepinephrine (titrated up to 12 μg/min) to maintain a target mean arterial pressure (MAP) of 65–75 mmHg	Vasopressin: 2/205; norepinephrine: 5/204	Vasopressin: 96.66±18.01; norepinephrine: 97.33±20.66
Gordon 2010	Either low-dose vasopressin (0.01–0.03 U/min) or norepinephrine (5–15 μg/min)	NA	NA
Hammond 2018	Norepinephrine monotherapy at 5 μg/min; the dosage of norepinephrine reached 15 μg/min but the MAP had not achieved target	Norepinephrine + vasopressin: 6/41; norepinephrine: 3/41	NA
Hua 2013	Terlipressin: 1.3 μg/kg/h. Dopamine: up to 20 μg/kg/h to maintain a mean arterial pressure of 70±5 mmHg for 48 h	No tachyarrhythmia was observed during the first 48 h	Vasopressin: 93±21; norepinephrine :96±18
Jain 2010	Either norepinephrine or phenylephrine infusion titrated to achieve a target of SBP >90 mmHg, MAP >75 mmHg, SVRI >1,100 dynes.s/cm5m2, CI >2.8 L/min/m^2, DO2I >550 mL/min/m^2, and VO2I >150 mL/min/m^2 for continuous 6 h	NA	Norepinephrine: 115.66±7.46; phenylephrine: 150.48±12.72
Levy 1997	Epinephrine and Norepinephrine infusions were started at 0.3 μg/kg/min and dobutamine was infused at a fixed dose of 5 μg/kg/min to obtain an MAP greater than 80 mmHg with a stable or increased CI	Non-arrhythmia happened (0 *vs.* 0)	Epinephrine: 108±19; norepinephrine-dobutamine: 120±15
Lauzier 2006	Vasopressin (0.04–0.2 U/min); Norepinephrine (0.1–2.8 μg/kg/min) for 48 h to achieve MAP at or above 70 mmHg	NA	Vasopressin: 93±21; norepinephrine: 96±18
Luckner 2006	Group 1: Vasopressin (4 IU/h), norepinephrine was adjusted for achieving 65 mmHg; Group 2: norepinephrine was adjusted for achieving 65 mmHg	NA	NA
Marik 1994	Randomized to receive an infusion of either dopamine or norepinephrine titrated to increase the MAP to greater than 75 mmHg	NA	Dopamine:139±3; norepinephrine: 102±3
Mathur 2007	Dopamine: dosage range 10–25 mcg/kg/min and with increments of 2.5 mcg/kg/min; norepinephrine: dosage range 0.5–2.5 mcg/kg/min with increments of 0.25 mcg/kg/min	NA	Dopamine: 141.64±8.67; norepnephrine:129.08±5.86
Martin 1993	Received either dopamine (2.5 to 25 μg/kg/min) or norepinephrine (0.5 to 5.0 μg/kg/min)	NA	NA
Morelli 2008	Either norepinephrine or phenylephrine infusion titration to achieve a mean arterial pressure between 65 to 75 mmHg	New-onset tachyarrhythmias. Phenylephrine: 2/16; norepinephrine: 1/16	NA
Morelli 2008	Norepinephrine: a continuous infusion to maintain MAP at 70 mmHg. Terlipressin: 1 mg	NA	NA
Morelli 2009	Vasopressin: 0.03 U; norepinephrine: 15 μg/min; terlipressin: 1.3 μg/kg/h for 48 h	New-onset tachyarrhythmias (i.e., atrial fibrillation). Vasopressin: 1/15; terlipressin: 0/15; norepinephrine: 4/15	Vasopressin: 93±25; norepinephrine 96±21; terlipressin 71±16
Myburgh 2008	To achieve a MAP ≥70 mmHg	NA	NA
Mahmoud 2012	Started at norepinephrine: 0.05 μg/kg/min and increased gradually up to 0.1 μg/kg/min. Group 1: continued on norepinephrine and dobutamine was added at a starting dose of 3 μg/kg/min and increased in increments of 2 up to 20 μg/kg/min. Group 2: continued on norepinephrine and epinephrine was added in a starting dose of 0.05 μg/kg/min and increased in increments of 0.03 up to 0.3 μg/kg/min	Norepinephrine + dobutamine: 4/30; norepinephrine + epinephrine: 6/30	Norepinephrine + dobutamine: 105±5; norepinephrine + epinephrine: 120±7
Mehta 2013	Low-dose vasopressin (0.01–0.03 U/min) or NE (5–15 μg/min), titrated to maintain a mean blood pressure of 65–75 mmHg	Vasopressin: 4/65; norepinephrine: 8/56	NA
Patel 2010	Dopamine (5–20 μg/kg/min); norepinephrine (5–20 μg/min)	Dopamine: 51/134; norepinephrine: 14/118	NA
Ruokonen 1993	The goal of the treatment was to correct the hypotension (MAP >70 mmHg)	NA	Norepinephrine: 113±18; dopamine: 114±24
Ramaswamy 2016	Randomized to receive either dopamine (in incremental doses, 10 to 15 to 20 μg/kg/min) or epinephrine (0.1 to 0.2 to 0.3 μg/kg/min)	Epinephrine: 1/29; dopamine: 3/31	NA
Russell 2009	Vasopressin (0.01–0.03 U/min); norepinephrine (5–15 μg/min)	Life-threatening arrhythmia. Vasopressin: 7/397; norepinephrine: 6/382	NA
Russell 2008	Randomized receiving a minimum of 5 μg of norepinephrine/min to receive either low-dose vasopressin (0.01 to 0.03 U/min) or norepinephrine (5–15 μg/min)	NA	NA
Russell 2013	Vasopressin (0.01–0.03 U/min) or norepinephrine (5–15 μg/min) that were titrated and weaned to maintain a mean arterial pressure of 65–75 mmHg	NA	NA
Schmoelz 2006	Dopexamine (2 μg/kg/min); dopamine (3 μg/kg/min)	NA	Dopexamine: 97.5±19.54; dopamine: 83.57±19.37; placebo: 84.85±22.90
Seguin 2002	Epinephrine or norepinephrine from 0.1 μg/kg/min with 0.2 μg/kg/min increases every 5 min; dobutamine continuously infused at 5 μg/kg/min; doses of epinephrine and norepinephrine were 0.3±0.2 and 0.9±0.4 μg/kg/min	NA	Epinephrine: 113±20; dobutamine-norepinephrine: 110±27
Seguin 2006	Epinephrine and norepinephrine: 0.2 μg/kg/min with 0.2 μg/kg/min increments every 3 minutes; dopexamine: 0.5 μg/kg/min with 0.5 μg/kg/min increments every 3 minutes	NA	Epinephrine + norepinephrine: 115±14; dopexamine + epinephrine: 109±18
Ventura 2015	Dopamine (5–10 μg/kg/min); epinephrine (0.1–0.3 μg/kg/min)	NA	Dopamine: 142±26; epinephrine: 140±23

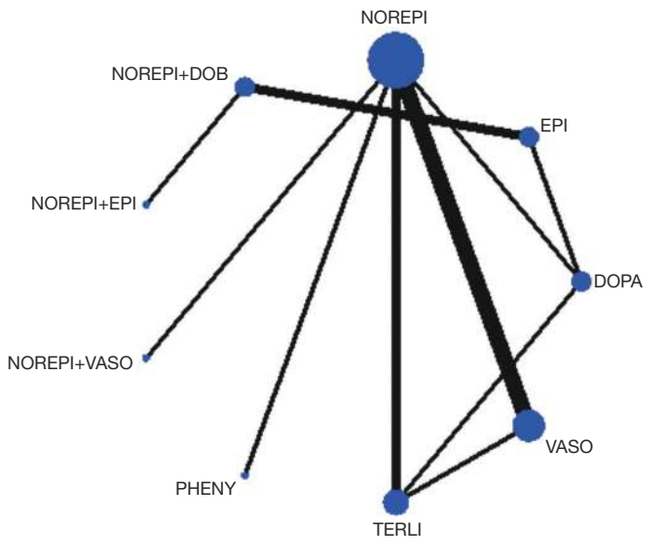

Figure S1 Network evidence of the comparisons for the different vasopressors regimens in arrhythmia.

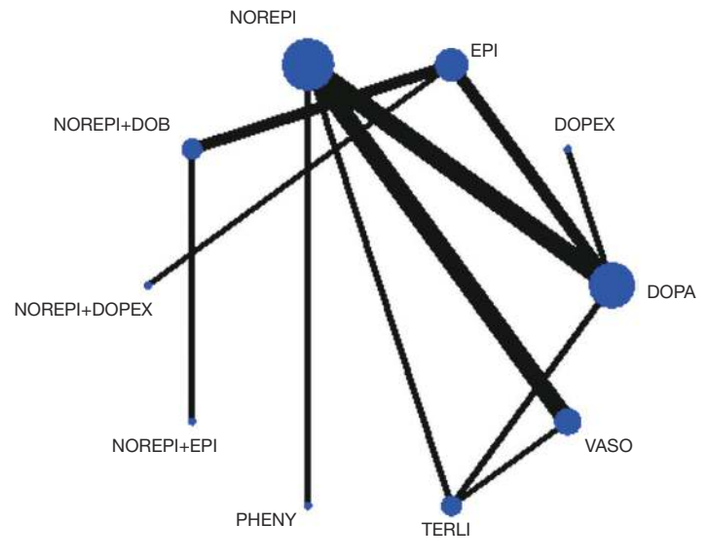

Figure S2 Network evidence of the comparisons for the different vasopressors regimens in heart rate.

Table S2 Estimated probabilities (%) of each treatment being the best to occur arrhythmia

Treatment	DOPA	EPI	NOREPI	NOREPI + DOB	NOREPI + EPI	NOREPI + VASO	PHENY	TERLI	VASO
Outcome	0.0	4.1	0.3	8.3	5.6	1.4	6.2	58.9	15.2

DOPA, dopamine; EPI, epinephrine; NOREPI, norepinephrine; NOREPI + DOB, norepinephrine + dobutamine; NOREPI + EPI, norepinephrine + epinephrine; NOREPI + VASO, norepinephrine + vasopressin; PHENY, phenylephrine; TERLI, terlipressin; VASO, vasopressin.

Table S3 Estimated probabilities (%) of each treatment being the best to increase heart rate

Treatment	DOPA	DOPEX	EPI	NOREPI	NOREPI + DOB	NOREPI + DOPEX	NOREPI + EPI	PHENY	TERLI	VASO
Outcome	0.3	18.8	0.3	0.0	2.5	3.0	39.8	5.2	0.0	0.1

DOPA, dopamine; DOPEX, dopexamine; EPI, epinephrine; NOREPI, norepinephrine; NOREPI + DOB, norepinephrine + dobutamine; NOREPI + DOPEX, norepinephrine + dopexamine; NOREPI + EPI, norepinephrine + epinephrine; PHENY, phenylephrine; TERLI, terlipressin; VASO, vasopressin.

Table S4 Odd ratios of arrhythmia in different groups

Variable	A	B	C	D	E	F	G	H	I
A	–								
B	0.33 (0.03–3.44)	–							
C	0.24 (0.11–0.53)	0.71 (0.06–8.40)	–						
D	0.30 (0.03–3.37)	0.91 (0.50–1.65)	1.27 (0.10–16.05)	–					
E	0.49 (0.03–7.98)	1.47 (0.32–6.76)	2.07 (0.11–37.45)	1.63 (0.40–6.60)	–				
F	0.52 (0.10–2.77)	1.55 (0.09–27.47)	2.17 (0.49–9.53)	1.71 (0.09–32.14)	1.05 (0.04–27.16)	–			
G	0.51 (0.04–7.15)	1.53 (0.04–51.92)	2.14 (0.17–26.62)	1.68 (0.05–60.10)	1.04 (0.02–48.20)	0.99 (0.05–18.33)	–		
H	0.07 (0.01–0.42)	0.21 (0.01–3.97)	0.30 (0.06–1.53)	0.23 (0.01–4.64)	0.14 (0.01–3.90)	0.14 (0.01–1.24)	0.14 (0.01–2.79)	–	
I	0.14 (0.05–0.37)	0.41 (0.03–5.22)	0.58 (0.28–1.21)	0.45 (0.03–6.16)	0.28 (0.01–5.39)	0.27 (0.05–1.39)	0.27 (0.02–3.72)	1.95 (0.33–11.48)	–

A, dopamine; B, dopexamine; C, epinephrine; D, norepinephrine; E, norepinephrine + dobutamine; F, norepinephrine + dopexamine; G, norepinephrine + epinephrine; H, norepinephrine + vasopressin; I, phenylephrine.

Table S5 Mean difference of heart rate in different groups

Variable	A	B	C	D	E	F	G	H	I	J
A	–									
B	13.93 (–15.99–43.85)	–								
C	1.60 (–19.84–23.05)	–12.33 (–49.14–24.49)	–							
D	–13.60 (–29.88–2.67)	–27.53 (–61.60–6.53)	–15.21 (–42.09–11.68)	–						
E	7.04 (–24.13–38.20)	–6.89 (–50.10–36.31)	5.43 (–17.20–28.06)	20.64 (–14.55–55.83)	–					
F	–4.40 (–41.80–33.01)	–18.33 (–66.22–29.57)	–6.00 (–36.64–24.64)	9.21 (–31.56–49.98)	–11.43 (–49.53–26.66)	–				
G	22.04 (–19.69–63.76)	8.11 (–43.24–59.45)	20.43 (–15.37–56.23)	35.64 (–9.17–80.45)	15.00 (–12.74–42.74)	26.43(–20.69–73.56)	–			
H	21.22 (–11.28–53.71)	7.29 (–36.89–51.46)	19.61 (–19.30–58.52)	34.82 (6.70–62.94)	14.18 (–30.87–59.23)	25.61 (–23.92–75.14)	–0.82 (–53.72–52.08)	–		
I	–22.32 (–44.81–0.16)	–36.25 (–73.68–1.17)	–23.93 (–54.98–7.12)	–8.72 (–30.60–13.16)	–29.36 (–67.81–9.09)	–17.93 (–61.55–25.70)	–44.36 (–91.77–3.05)	–43.54 (–79.17––7.91)	–	
J	–12.67 (–35.41–10.08)	–26.60 (–64.18–10.99)	–14.27 (–45.50–16.96)	0.94 (–16.31–18.19)	–19.70 (–58.31–18.91)	–8.27 (–52.02–35.48)	–34.70 (–82.24–12.84)	–33.88 (–66.87–0.89)	9.66 (–14.72–34. 03)	–

A, dopamine; B, dopexamine; C, epinephrine; D, norepinephrine; E, norepinephrine + dobutamine; F, norepinephrine + dopexamine; G, norepinephrine + epinephrine; H, norepinephrine + vasopressin; I, phenylephrine; J, terlipressin.