REVIEW ARTICLE

Vasopressin versus norepinephrine as the first-line vasopressor in septic shock: A systematic review and meta-analysis

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Abstract

Background and Aim: Norepinephrine is currently the first-line vasopressor for septic shock. We conducted this meta-analysis to examine the outcomes of adult patients with septic shock who received vasopressin instead of norepinephrine.

Methods: We selected studies in adults with septic shock that compared the outcomes of patients treated with vasopressin versus norepinephrine. Cochrane ROB 2.0 and the Joanna Briggs Institute quality assessment tools were used to assess the risk of bias in RCTs and observational studies. Meta-analysis was conducted using RevMan 5.4.

Results: Eight studies were included in this meta-analysis. There were no significant differences in 28-day mortality rates (OR, 1.07; CI, 0.80–1.44) and intensive care unit (ICU) mortality (OR, 0.74; CI, 0.21–2.67) between the two groups. Similarly, length of ICU stay, length of hospital stay, mean arterial pressure at 24 h, urine output at 24 h, and serious adverse events also did not differ significantly. However, the odds of renal replacement therapy (RRT) requirement in the vasopressin group were substantially lower than in the norepinephrine group (OR, 0.68; CI, 0.47–0.98).

Conclusion: There were no differences in mortality, duration of hospitalization, and adverse effects in adults with septic shock across the two groups. However, the patients treated with vasopressin had lower chances of requiring RRT.

Relevance for Patients: Vasopressin use as the first-line vasopressor in septic shock showed a significant reduction in RRT, though there were no significant differences in terms of mortality and other adverse events. Therefore, vasopressin can be considered as a first-line vasopressor in septic shock patients with other risk factors which may contribute to renal failure requiring RRT.

1. Introduction

Septic shock is the leading cause of mortality in intensive care units (ICUs) [1,2]. In 2015, it was estimated that there were more than 230,000 cases of septic shock in the United States which directly caused more than 40,000 deaths per year [3]. Septic shock management revolves around timely source control and hemodynamic resuscitation,

ensuring end-organ perfusion. Crystalloids are used to expand the intravascular volume and catecholamine infusions, that is, norepinephrine, to provide cardiovascular support. Catecholamines, however, may reduce blood flow to end organs despite adequate perfusion pressure [4,5]. Vasopressin is an endogenously released peptide hormone that has been used as an adjunct to catecholamines for patients with septic shock not responding to fluids. Studies have shown that septic shock patients have relative vasopressin deficiency [6,7]. Vasopressin use restores vascular tone and decreases norepinephrine requirements [6,7]. Two small randomized and controlled trials (RCTs) showed that vasopressin improved mean arterial pressure (MAP) and expedited norepinephrine withdrawal [8,9]. Furthermore, vasopressin maintained glomerular filtration rate and creatinine clearance compared with norepinephrine [8,10]. The VASST trial, the largest multicenter, double-blind RCT, compared vasopressin, and norepinephrine in patients with septic shock; no mortality benefit was demonstrated in the trial [11]. In the subsequent VANISH trial, early use of vasopressin compared with norepinephrine did not improve the number of kidney failure-free days [12]. Yet, the trial mentioned that the confidence interval included a potential clinically meaningful benefit for vasopressin and the need for further large-scale trials, highlighting a persistent knowledge gap.

In light of the knowledge gap regarding the benefits of vasopressin in septic shock, we sought to conduct this systematic review and meta-analysis to appraise the available evidence fully and compare the use and benefits of vasopressin compared to norepinephrine in patients with septic shock.

1.1. Objectives

The objectives of the study are as follows:
- To compare mortality and length of stay in patients with septic shock receiving norepinephrine compared to vasopressin
- To compare MAP and urine output in patients with septic shock receiving norepinephrine compared to vasopressin
- To compare serious adverse events and renal replacement therapy (RRT) among patients with septic shock receiving norepinephrine compared to vasopressin.

2. Methods

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used for our systematic review [13]. The protocol for review was published in PROSPERO (CRD42021226012) [14].

2.1. Inclusion criteria

2.1.1. Types of studies

We included studies focusing on mortality, clinical improvement, length of hospital stays, adverse effects, mean difference of clinical improvement, and recovery among patients receiving vasopressin compared to norepinephrine for septic shock.

2.1.2. Types of participants

We included all adult patients suffering from septic shock who are more than 18 years of age who received vasopressin or norepinephrine.

2.1.3. Types of Interventions

The treatment arm consists of patients receiving vasopressin for septic shock, while the control arm consists of patients receiving norepinephrine for septic shock.

2.1.4. Types of outcome measures

For our quantitative analysis, mortality, length of stay, MAP, urine output, RRT, and serious adverse effects rates were the outcomes of interest.

2.1.5. Outcomes

We compared mortality, length of stay, MAP, urine output, RRT, and serious adverse effects among septic shock patients receiving vasopressin compared to those receiving norepinephrine.

2.2. Search strategies

PubMed, PubMed Central, Embase, and Scopus were independently searched, and the quality of the studies done in the past decade was evaluated. Finally, we filtered the studies using Covidence and extracted data for quantitative and qualitative synthesis [15]. Any potential conflict was solved by taking the final opinion of another reviewer.

2.2.1. Electronic searches

We have documented the detailed search strategy in Supplementary File 1.

2.3. Data collection and analysis

We extracted the data for quantitative synthesis through Covidence and did the analysis using RevMan5.4 [15,16]. We used a random/fixed effect to pool selected studies based on heterogeneity.

2.3.1. Selection of studies

We have included RCTs, prospective, observational studies, and cohort studies for septic shock, comparing the outcomes of those receiving vasopressin with norepinephrine. We excluded studies in the entire study population in which vasopressin was used for the treatment among the pediatric age group, pregnant women, and shock other than septic shock. In addition, we excluded meta-analyses, reviews, editorials, commentary, and the studies with no data required for quantitative analysis.

2.3.2. Data extraction and management

We evaluated the quality of studies thoroughly and considered only the outcomes in our interest.

2.3.3. Assessment of risk of bias in included studies

We used the Cochrane ROB 2.0 tool to analyze our RCTs (Figure 1) and the Joanna Briggs Institute (JBI) quality assessment

tools to assess the risk of bias in our prospective and retrospective observational studies (Table 1) [17,18]. We used RevMan 5.4 for creating a summary of biases for RCTs using the Cochrane ROB 2.0 tool.

2.3.4. Assessment of heterogeneity

The I-squared (I^2) test was used for the assessment of heterogeneity [22]. We interpreted the I-squared (I^2) test done


Figure 1. Cochrane ROB bias assessment.

based on the Cochrane Handbook for Systematic Reviews of Interventions [22].

2.3.5. Assessment of reporting biases

Reporting bias was checked by prefixed reporting of the outcome.

2.3.6. Data synthesis

Statistical analysis was performed using RevMan 5.4 software. Odds ratio (OR) was used for outcome estimation with a 95% confidence interval (CI). The fixed/random-effects model was used according to heterogeneities. Mean and standard deviation were formulated based on median and interquartile range. We used mean differences for outcomes such as the length of stay, MAP, and urine output using the mean and standard deviation values obtained from the study [23].

2.3.7. Subgroup analysis and investigation of heterogeneity

We used the random effect model in cases of heterogeneity.

2.3.8. Sensitivity analysis

Non-randomized studies were excluded for sensitivity analysis to find any alterations in the outcomes after removal.

3. Results

A total of 2442 studies were imported after a comprehensive database search. After removing duplicates, the title and abstracts of 2417 studies were screened, followed by the exclusion of 2382 studies. Thirty-five full-text studies were assessed for eligibility, and 27 studies were excluded for definite reasons. Eight studies were included in the narrative summary (Table 2), and seven studies were included in the quantitative analysis. The following is represented in the PRISMA flow diagram (Figure 2).

Table 1. JBI bias assessment.

S. No	JBI checklist for cohort studies	Russell *et al.*, 2018 [19]	Hall *et al.*, 2004 [20]	Daley *et al.*, 2013 [21]
1	Were the two groups similar and recruited from the same population?	Yes	Yes	Yes
2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes
3	Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
4	Were confounding factors identified?	No	Yes	No
5	Were strategies to deal with confounding factors stated?	No	Yes	No
6	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes
7	Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
8	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes
9	Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	Unclear	Yes	Yes
10	Were strategies to address incomplete follow-up utilized?	No	NA	NA
11	Was appropriate statistical analysis used?	Yes	Yes	Yes
	Overall appraisal	Include	Include	Include

Table 2. Narrative summary of included studies.

Study ID	Population	Intervention	Comparisons	Outcome
Patel *et al.*, 2002 [8] Prospective, double blind, randomized, and controlled trial	Patients experiencing septic shock that required high dose vasopressor support N=24 (C=11, T=13) Male: T=77% C=73% Female T=23% C=27% Value (Median, Q1, Q3D) C: 68 (58,75) T: 68 (58,70)	The starting volume of the vasopressin infusion was 7 ml/h. This corresponded to a vasopressin infusion of 0.01 units/min. The maximum rate of infusion allowed in this study protocol was 56 ml/h of blinded study drug, which corresponded to a vasopressin infusion rate of 0.08 units/min	The starting volume of the norepinephrine infusion was 7 ml/h. This corresponded to a norepinephrine infusion of 2 µg/min. The maximum rate of infusion allowed in this study protocol was 56 ml/h of blinded study drug, which corresponded to a norepinephrine infusion rate of 16 µg/min	Mean arterial pressure: Median (q1, q3) T: Baseline 69 (65,72) After 4 h 69 (65,70) mm of Hg C: Baseline 68 (65,70) After 4 h 67 (61,70) mm of Hg Urine output: Mean T: Baseline: 32.5 ml.h After 4 h: 65 ml/h C: Baseline: 25 ml/h After 4 h: 15 ml/h Cardiac index: Median (q1, q3) T: Baseline 4.8 (3.5,5.5), After 4 h: 4.4 (3.1,5.3) C: Baseline 5.0 (3.8, 5.6) After 4 h: 4.0 (3.2, 5.1) Heart rate: Median (q1, q3) T: Baseline: 102 (90, 110) bpm after 4 : 93 (91, 100) bpm C: baseline :97 (89, 110) bpm after 4 :92 (83, 100) bpm Systemic vascular ressitance index: Median (q1, q3) T: Baseline: 905 (838, 1044), After 4 hours: 948 (864,1130) C: Baseline 750 (681, 1173) After 4 hours: 781 (662, 1263)
Morelli *et al.*, 2009 [24] Prospective randomized controlled trial	Patients with septic shock with mean arterial pressure below 65 mm of Hg despite adequate volume resuscitation N=45 (T1=15/45, C=15, 45, T2=15/45) Male T1=67%, C=80%, T2=73% Female T1=33%, T2=27%, C – 20%) Value (median, Q1, Q3) Age: T1: 66 (60,74) T2: 67 (69,71) C: 64 (59,72)	T1: Vasopressin (0.03 units/min) T2: Terlipressin (1.3 µgkg^{-1}h^{-1}) All three groups received open-label norepinephrine and intravenous hydrocortisone as a continuous infusion	C: Norepinephrine (15 µg/min^{-1})	ICU mortality T1: 8/15 T2: 7/15 C: 10/15 ICU length of stay (Median, q1, q3) T1: 17 (5,27) T2: 14 (9,25), C: 17 (7, 23) Norepinephrine requirement at 48 h T1: 0.8 µgkg^{-1} min^{-1} T2: 0.2 µgkg^{-1} min^{-1} C: 1.2 µgkg^{-1} min^{-1} Urine output (ml/h) T1: Baseline: 42.3±46.9; 24 h: 42±41.6; 48 h: 43.3±58.7 T2: Baseline: 34.6±31.3; 24 h: 49.2±49.5; 48 h: 46.6±33.3 C: Baseline: 38.6±34.3; 24 h: 66±77; 48 h: 58.6±63.8 Mean arterial pressure T1: Baseline: 53±4; 24 h: 70±3; 48 h: 71±3 mmHg T2: Baseline: 53±4; 24 h: 71±3; 48 h: 71±4 mm Hg C: Baseline: 54±3; 24 h: 71±2; 48 h: 71±3 mmHg Heart rate T1: Baseline: 100±22 At 48 h: 93±25 bpm T2: Baseline: 95±16 At 48 h: 71±16 bpm C: Baseline: 97±21 At 48 h: 96±21 bpm Cardiac index T1: Baseline: 4.0±1.1 At 48 h: 4.2±1.9 L/min/m T2: Baseline: 4.0±1.0 At 48 h: 4.2±1.9 L/min/m C: Baseline: 4.0±1.0 At 48 h: 3.9±1.5 L/min/m Systemic vascular resistance index: T1: Baseline: 41±12 At 48 h: 43±12 ml/beats/m T2: Baseline: 46±13 At 48 h: 50±10 ml/beats/m C: Baseline: 4.0±1.0 At 48 h: 3.9±1.5 ml/beats/m
Lauzier *et al.*, 2006 [10] Multicenter randomized non-blinded trial	Patients with early hyperdynamic septic shock N=23 (T=13/23, C=10/23) Male T=46%, C=80% Female T=54%, C=20% Age, median (IQR): T=51.2±17.2 C=58.1±17.5	Vasopressin (0.04–0.20 Umin^{-1}) as a single agent for 48 hours	Norepinpehrine (0.1–2.8 µgkg^{-1} min^{-1}) as a single agent for 48 hours	Urine output Baseline: T: 1420±656 ml C: 1146±700 ml 24h: T: 2049±562 ml C: 1895±1292 ml 48h: T: 3051±1666 ml C: 2644±1060 ml Mean arterial pressure mean, SD Baseline: T: 72±7 C: 68±10 mm Hg 1 h: T: 74±8 C: 72±5 mm Hg 24 h: T: 81±11 C: 77±6 mm Hg 48 h: T: 78±12 C: 81±9 mm Hg Heart rate mean, SD Baseline: T: 118±16 C: 109±23 bpm 1 h: T: 105±16 C: 108±22 bpm

(Contd...)

Table 2. *(Continued).*

Study ID	Population	Intervention	Comparisons	Outcome
				6 h: T: 100±15 C: 104±22 bpm
				48 h: T: 93±21 C: 96±18 bpm
				Cardiac index mean, SD
				Baseline: T: 4.6±1.0 C: 4.4±1.4
				1 h: T: 3.6±1.1 C: 4.3±1.4
				6 h: T: 3.7±0.7 C: 4.3±1.7
				48 h: T: 3.7±0.9 C: 3.7±1.6
				Mortality ICU
				T: 2/13 C: 1/10
				Acute coronary syndrome T: 1/13 C: 1/10
Russell *et al.*, 2008 [11] Multicenter, randomized, double-blind trial	Patients older than 16 years of age who had septic shock that was resistant to fluids (as defined by lack of response to 500 ml of normal saline or a requirement for vasopressors and low-dose norepinephrine N=778 (T=396, C=382) Male: T=62%, C=59.9% Female T=38%, C=40.1% Age: T: 59.3±16.4, C=61.8±16	Blinded vasopressin infusion was started at 0.01 U per minute and titrated to a maximum of 0.03 U per minute	Blinded norepinephrine infusion was started at 5 µg per minute and titrated to a maximum of 15 µg per minute	28-day mortality Randomization: T=144/404 C=154/395 Randomization and infusion: T=140/396 C=150/382 90 day mortality Randomization T=177/400 C=194/391 Randomization and infusion T=172/392 C=188/379 Length of ICU stay median, IQR T (396) =15 (7-29); C (382) =16 (8-32) Length of Hospital stay median, IQR T (396)=27 (13-52), C (382)=26 (15-53) Serious adverse events T=41/396 C=40/382 Acute myocardial infarction T=8/396 C=7/382 Cardiac arrest T=3/396 C=8/382 Life-threatening arrhythmia T=8/396 C=6/382 Acute mesenteric ischemia T=9/396 C=13/382 Hyponatremia T=1/396 C=1/382 Digital ischemia T=8/396 C=2/382 Cerebrovascular accident T=1/396 C=1/382
Russell *et al.*, 2018 [19] Retrospective cohort study using propensity based matching SPH 1 : 2001-2007 SPH 2: 2008-2012	Patients admitted to Intensive care unit who had two of four SIRS criteria who had suspected or proven infection and who were unresponsive to fluid resuscitation and received infusion of norepinephrine or vasopressin. SPH 1: Before matching T: 165 C: 558 Age: T: 56.1±15.7 C: 60.7±16.2 Male: T: 73.3% C: 61.8% After matching T: 158 C: 158 Age: T: 56.4±15.4 C: 57.1±15.1 Male: T: 72.8% C: 67.1% SPH 2: Before matching T: 525 C: 145	Vasopressin as per local practice	Nor epinephrine as per local practice	28 day mortality SPH 1: After matching T: 96/158 C: 73/158 SPH 2: After matching T: 29/93 C: 25/93

(Contd...)

Table 2. *(Continued).*

Study ID	Population	Intervention	Comparisons	Outcome
	Age: T: 60.9±13.9 C: 61.4±16.8 Male: T: 62.4% C: 66.4% After matching T: 93 C: 93 Age: T: 60.9±13.9 C: 61.4±14.5 Male: T: 37.6% C: 30.1%			

Gordon *et al.*, 2016 [12]
Double blind, randomized clinical trial
	Adult patients (≥16 years) who had sepsis and required vasopressors despite adequate intravenous fluid resuscitation.
	N=409
	T1=101
	T2=104
	C1=101
	C2=103
	Male: T1=58%, T2=52%, C1=62%, C2=65%
	Female: T1=42%, T2=48%, C1=38%, C2=35%
	Age (median, IQR)
	T1: 66 (57-76), T2: 67 (59-77), C1: 63 (52-76), C2: 66 (54-76)
		T1=Vasopressin and hydrocortisone
		T2=Vasopressin and placebo
		T=Vasopressin with placebo or hydrocortisone
		Vasopressin (titrated upto 0.06 U/min) as the initial vasopressor infusion. Once maximum infusion rate of vasopressin was reached, either 50 mg of hydrocortisone phosphate or placebo was administered as an intravenous bolus every 6 h for 5 days, every 12 h for 3 days and then once daily for 3 days
			C1=Norepinephrine and hydrocortisone
			C2=Norepinephrine and placebo
			C=Norepinephrine with or without placebo
			Norepinephrine titrated upto 12 μg/min as the initial vasopressor infusion. Once maximum infusion rate of norepineprhine was reached, either 50 mg of hydrocortisone phosphate or placebo was administered as an intravenous bolus every 6 for 5 days, every 12 h for 3 days and then once daily for 3 days
				Hospital Mortality
				  T=68/204 C=60/204
				Requirement of RRT
				  T=52/205 C=72/204
				ICU length of stay median (IQR)
				  T=7 (3 to 11) C=5 (3 to 13)
				Hospital length of stay median (IQR)
				  T=16 (7 – 36) days C=16 (8-38) days
				Serious adverse events
				  T=22/205 C=17/204
				  Acute coronary syndrome T=7/205 C=4/204
				  Digital ischemia T=11/205 C=3/204
				  Mesenteric ischemia T=5/205 C=5/204
				  Life-threatening arrhythmia T=2/205 C=5/204
				Urine output mean, SD
				  Day 1 T (205): 737±3813 ml C (204): 1010±2455
				  Day 2 T (189): 1521±2204 ml C (198): 1628±1733
				  Day 7 T (114): 2314±1150 C (99): 1906±1363

Hall *et al.*, 2004 [20]
Retrospective cohort single center study
	Critically ill patients who were receiving continuous intravenous infusion of vasopressin, norepinephrine and dopamine
	N=50, T1=50, T2=51 and C=49
	Male:
	T1=60%, C=57% and T2=55%
	Female: T1=40%, C=43% and T2=45%
	Age: T1=67.1±17.1, T2=62.5±17.7 and C: 61.1±18.0
		T1: Fixed dosage of intravenous vasopressin 0.04 U/min
		T2: Titrated intravenous infusion of dopamine (6.7±5.5 μg/kg/min)
			C: Titrated intravenous infusion of norepinephrine (0.28±0. μg/kg/min)	28-day mortality
				  T1: 23/44 T2: 28/51 C: 30/46
				Hospital stay mean, SD
				  T1 (50): 36±34 days
				  T2 (51): 29±29 days
				  C (49): 36±40 days
				ICU length of stay mean, SD
				  T1 (50): 14±55 days
				  T2 (51): 20±26 days
				  C (49): 29±40 days
				Serious adverse events
				  T1: 36/50 T2: 36/51 C: 39/49
				  MI T1: 2/50 T2: 2/51 C: 4/49
				  ARDS T1: 10/50 T2: 12/51 CL 17/49
				  Atrial arrhythmia T1: 6/50, T2: 6/51, C=15/49
				  Acute renal insufficiency T1: 3/50, T2: 3/51, C: 3/49
				  Venous thromboembolism T1: 7/50, T2: 4/51, C=1/49
				  Peripheral vascular necrosis T1: 3/50, T2: 2/51, C=3/49
				Urine output: mean, SD
				  T1 (44): Baseline: 3437±4618, 24 h: 2898±4103
				  T2 (44): Baseline: 3215±2958 24 h: 4210±6350
				  C (43): Baseline: 2495±1960 24 h: 2810±2193
				Cardiac index mean, SD
				  T1: Baseline: 4.1±1.6; 1 h: 3.5±1.3
				  T2: 2.8±1.0; 1 h: 2.6±1.2
				  C: 3.6±1.3; 1 h: 3.3±1.0
				MAP
				  T1: Baseline: 63.3±13.3 mm Hg 1 h: 74.4±11.3 mm Hg
				  T2: Baseline: 58.7±9.5 mm Hg 1 h: 70.5±11.6 mm Hg
				  C: Baseline: 56.8±8.5 mm Hg 1 h: 72.9±8.9 mm Hg

(Contd...)

Table 2. *(Continued).*

Study ID	Population	Intervention	Comparisons	Outcome
Daley *et al.*, 2013 [21] Retrospective cohort study	Patients with septic shock with mean arterial pressure less than 65 mm Hg. N=130 T=65 C=65 Male T=52.3%, C=53.8% Female T=47.7%, C=46.2% Age mean (SD) T=61 (17.7) C=56 (17.7)	Administration of vasopressin 1 h after the onset of septic shock	Administration of norepinephrine 1 h after the onset of septic shock	Mortality T=29/65 C=32/65 Length of hospital stay (Median, Interquartile range) T=15 (8-34) C=15 (7-31) ICU length of stay: Median, Interquartile range T=7 (4-24) C=7 (3-15) Requirement of renal replacement therapy T=19/65 C=21/65 MAP mean, SD (mm Hg) T: Baseline: 57.3 (5.9), 0-6 h: 75.0 (9.6); 12-24 h: 71.7 (10.3) C: Baseline: 56.8 (6.4) 0-6 h: 76 (8.2); 12-24 h: 73.4 (11.1) Urine output mean, SD (ml/kg/h) T: 0-6 h: 0.84 (1) 6-12 h: 0.72 (0.9) 12-24 h: 0.77 (0.9) C: 0-6 h: 0.63 (1) 6-12 h: 0.66 (0.8) 12-24 h: 0.51 (0.6)
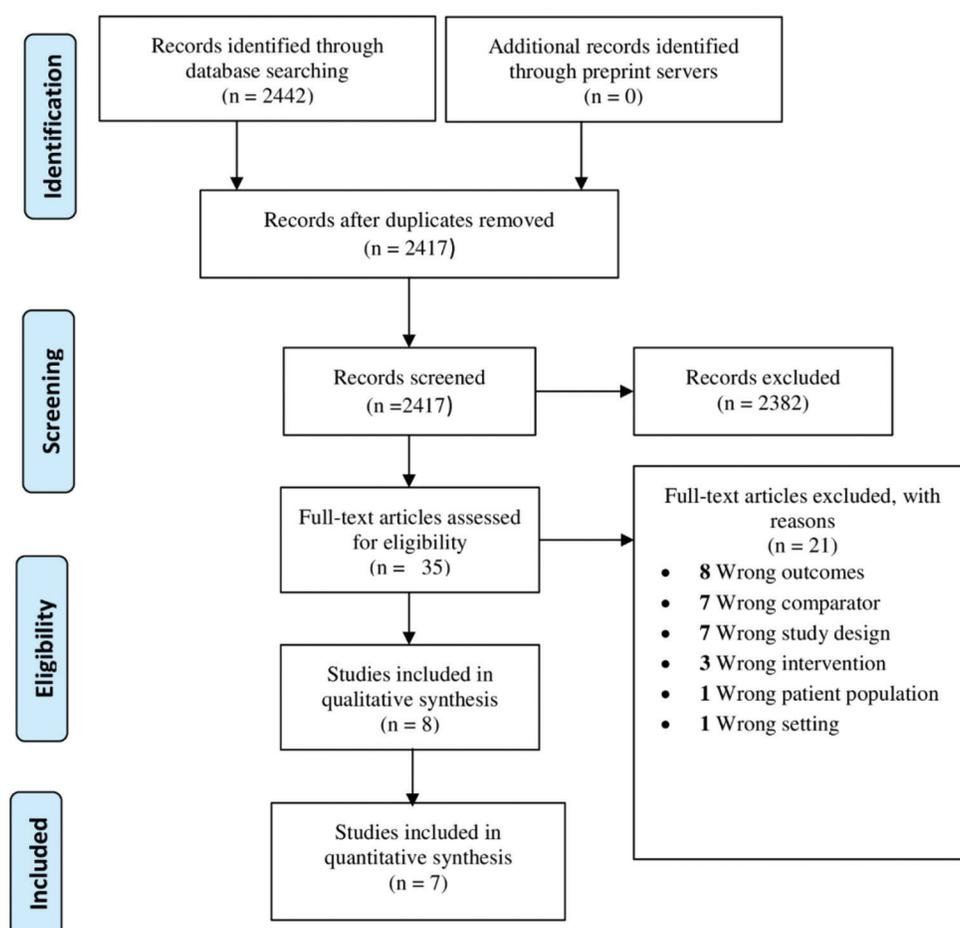
Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

3.1. Narrative summary

Three included studies were retrospective and cohort studies [19-21] and five were randomized and controlled trials [8,10-12,24].

Patel *et al.* randomized patients to vasopressin to norepinephrine infusion for 4 h [8]. In the study, vasopressin decreased the catecholamine use in septic shock and achieved significantly higher urine output and creatinine clearance than norepinephrine. However, since Patel *et al.* were a short duration study, the outcomes were not reported beyond 4 h, and it could not be included in the quantitative synthesis.

Lauzier *et al.* randomized patients to high-dose vasopressin or norepinephrine in early septic shock [10]. Vasopressin in the

high dose (o.2U/min) could not attain Map in all the patients in the study and required d additional epinephrine. However, the patients achieved less modified sofa in the vasopressin arm than norepinephrine arm at 48 h.

Russell *et al*. (VASST) were the largest RCT with 778 patients, which randomized patients to vasopressin or norepinephrine in septic shock [11]. The primary endpoint of the study was death at 28 days. There was no difference in mortality at 28 days and severe adverse effects in both arms. However, in the patients with less severe septic shock (those who required NE <15 ug/min), vasopressin provided a mortality benefit compared to norepinephrine. Gordon *et al*. (VANISH trial) were conducted to study the renal effects of vasopressin versus norepinephrine in patients with septic shock [12]. The primary endpoint was the number of kidney-free days. Vasopressin did not increase the number of kidney-free days in septic shock compared to norepinephrine.

The TERLIVAP study (Morelli *et al*.) was a randomized control trial with three arms: A continuous terlipressin arm, a continuous vasopressin arm, and a fixed-dose norepinephrine arm [24]. The primary endpoint was the additional requirement of norepinephrine. Terlipressin required lower norepinephrine as compared to the vasopressin arm. There was no difference in hemodynamic differences achieved by vasopressin, norepinephrine, and terlipressin.

3.2. Quantitative analysis

A total of seven studies were included in the meta-analysis (four RCTs and three cohorts).

3.2.1. Mortality outcome

Five studies reported 28-day/hospital mortality. Pooling the data using random-effect model, there was no difference in odds of mortality between vasopressin and norepinephrine group among septic shock patients (OR, 1.07; 95% CI, 0.80–1.44; n=1929; I^2=51%). Similarly, two studies reported ICU mortality outcome which was not different across two groups (OR, 0.74; 95% CI, 0.21–2.67; n=53; I^2=0%) (Figure 3). Further,

no significant differences were seen while analyzing the 28-day mortality outcome after excluding non-randomized studies (Supplementary File 2, Figure 1).

3.2.2. Length of Stay

Length of ICU stays outcome was reported by five studies. Pooling of results using the mean difference in length of ICU stay in days showed some reduction in length in the vasopressin group; however, it did not reach the level of significance (MD, −0.24; 95% CI, −1.35–0.86; n=1445; I^2=41%). Similarly, length of hospital stay was reported in four studies and there was no significant difference across two groups (MD, −0.49; 95% CI, −3.12–2.14; n=1415; I^2=0%) (Figure 4). Further, no significant differences were seen while analyzing for ICU-LOS and LOHS after excluding non-randomized studies (Supplementary File 2, Figure 2).

3.2.3. MAP

Pooling data for MAP (mmHg) showed no significant difference in mean of baseline MAP (MD, 0.08; 95% CI, −1.51–1.66; n=183; I^2=0%); MAP at 24 h (MD, −0.88; 95% CI, −2.47–0.72; n=183; I^2=3%); and MAP at 48 h (MD, −0.18; 95% CI, −2.26–1.91; n=53; I^2=0%) (Figure 5).

3.2.4. Urine output

There was no significant difference in urine output in terms of mean of baseline urine output (MD, 10.91; 95% CI, −6.65–28.46; n=140; I^2=0%); urine output at 24 h (MD, −7.47; 95% CI, −25.46–10.52; n=549; I^2=0%); and urine output at 48 h (MD, −3.55; 95% CI, −18.21–11.12; n=440; I^2=0%) (Figure 6). Further, no significant differences were seen while analyzing for urine output after excluding non-randomized studies (Supplementary File 2, Figure 3).

3.2.5. Serious adverse effect

Three studies reported serious adverse events. Pooling of the data showed no significant differences in its occurrence across two
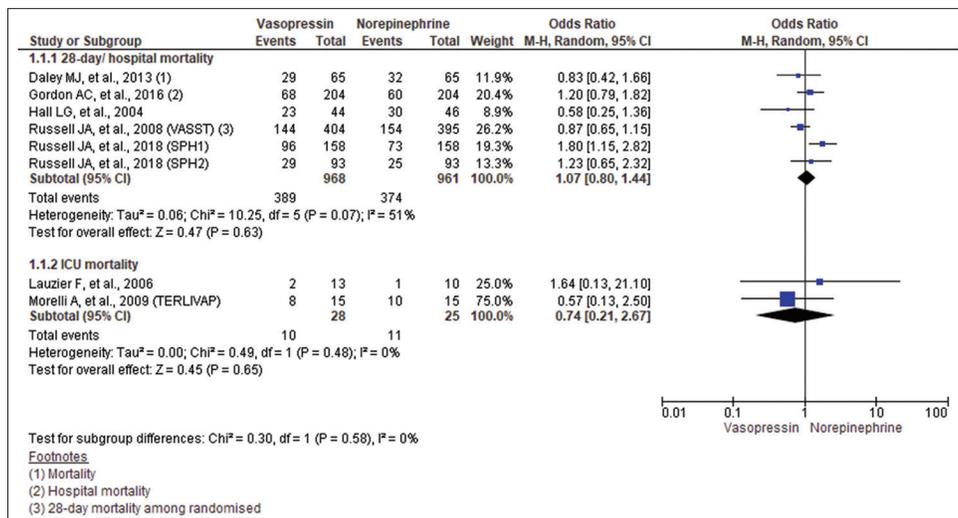
Figure 3. Forest plot comparing mortality outcome across vasopressin and norepinephrine in septic shock patients.
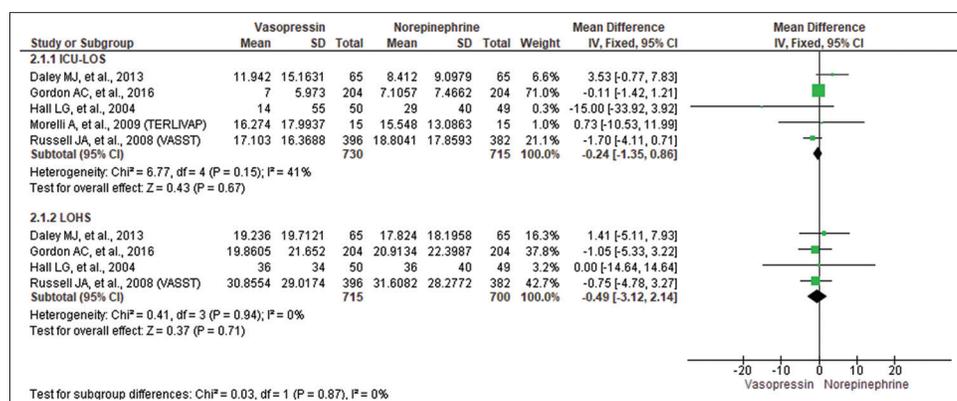
Figure 4. Forest plot comparing the length of intensive care unit stay and hospital stay across vasopressin and norepinephrine in septic shock patients.
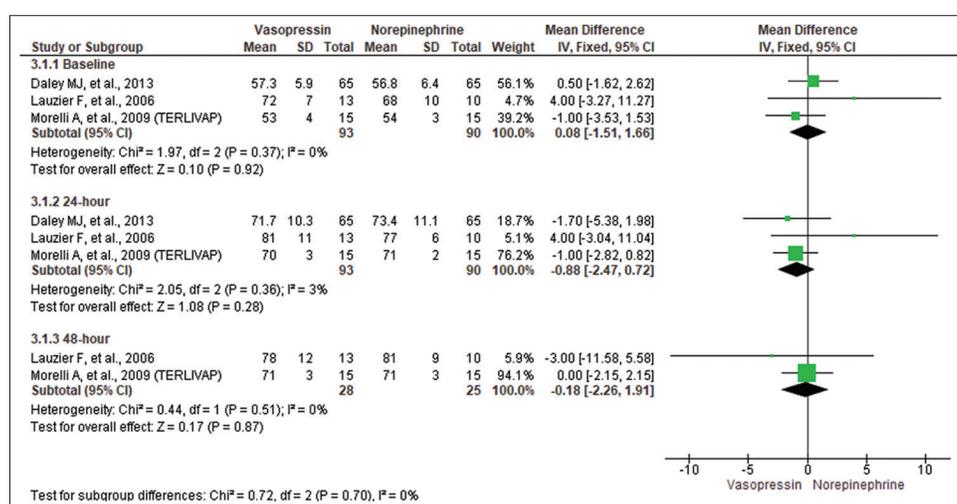
Figure 5. Forest plot comparing mean arterial pressure across vasopressin and norepinephrine in septic shock patients.

groups (OR, 1.01; 95% CI, 0.71–1.43; n=1286; I^2=0%) (Figure 7).

3.2.6. RRT

Pooling data from two studies reporting requirement of RRT, the odds for requirement of RRT in vasopressin group were lowered significantly (OR, 0.68; 95% CI, 0.47–0.98; n=539; I^2=0%) (Figure 8).

4. Discussion

We analyzed eight studies in our study. When both medications were compared, neither showed survival benefit over the other. Furthermore, no statistical difference was found between norepinephrine and vasopressin in terms of length of ICU stay, MAP, severe adverse effects, and urine output. Norepinephrine was the first-choice vasopressor for managing hypotension in septic shock. In contrast, vasopressin has been used as one of the first add-on vasopressors to norepinephrine to attain the target MAP or decrease the norepinephrine dosage [25]. Our study found no significant difference between hospital mortality and 28-day mortality among patients treated with either medication. This finding is consistent with other meta-analyses, which have also compared the mortality outcome [26,27]. Similarly, there was no significant difference in the length of ICU stay among the patients. A previous meta-analysis had also reached a similar conclusion [28].

Septic shock is a state of relative vasopressin deficiency attributed to impaired baroreceptor-mediated vasopressin secretion [29]. However, all the clinical implications of the relative deficiency state are not known. A short-term study has shown that the microcirculation effects of vasopressin in patients are dependent on the baseline norepinephrine dose [30]. Regarding the hemodynamic parameters, many hemodynamic parameters were not reported in the studies; however, they were reported with inconsistent time duration. We compared the effect of vasopressin versus norepinephrine on MAP, on which a significant difference could not be found. The previous meta-analysis has reported multiple hemodynamic parameters and MAP, such as heart rate, cardiac index, systemic vascular resistance index, and oxygen consumption, which have no significant differences [26]. The study found no significant difference in the occurrence of major side effects. While vasopressin may increase the incidence of digital ischemia, prior meta-analyses have shown no increase in the incidence of major adverse effects [28,31,32].
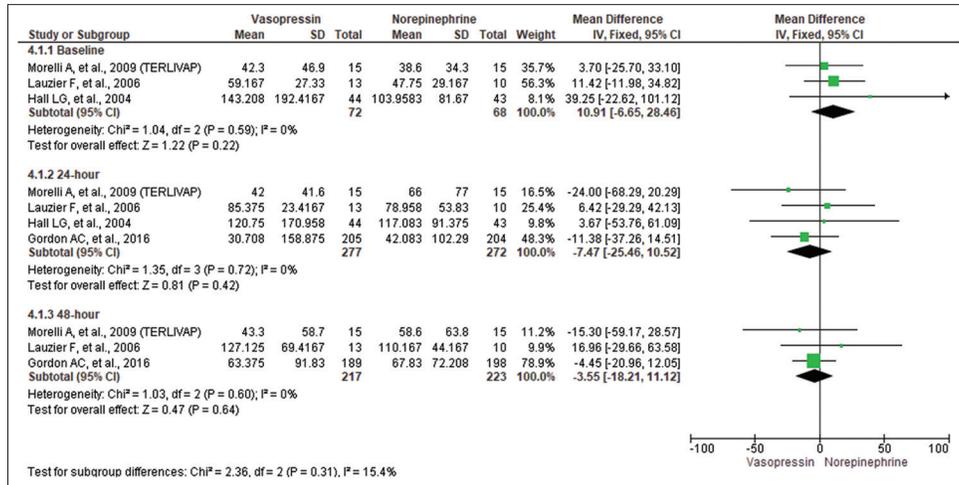
Figure 6. Forest plot comparing urine output (ml/h) across vasopressin and norepinephrine in septic shock patients.
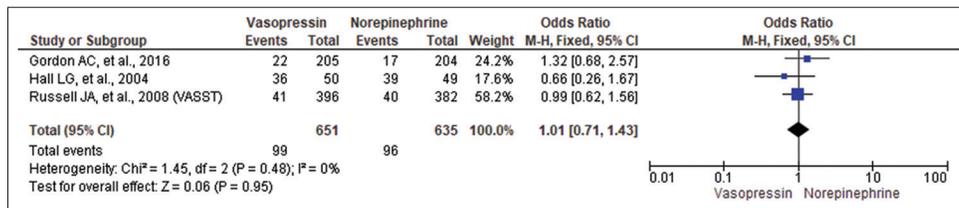
Figure 7. Forest plot comparing SAE across vasopressin and norepinephrine in septic shock patients.
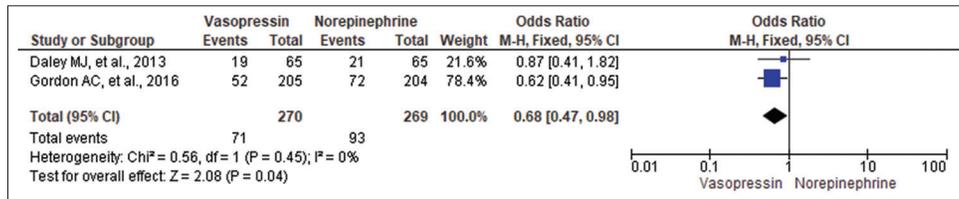
Figure 8. Forest plot comparing requirement of renal replacement therapy across vasopressin and norepinephrine in septic shock patients.

Patel *et al*. have shown that vasopressin increases urine output and decreases serum creatinine compared to norepinephrine in the early hours of administration [8]. However, there seems to be no difference in kidney failure-free days in patients treated with vasopressin than norepinephrine. Although we did not find any significant difference in urine output in our study, there were lower odds of RRT with vasopressin. Our findings of the decreased requirement for RRT align with the findings of prior clinical studies that have found improvement in glomerular filtration rate and creatinine clearance in the vasopressin group compared to norepinephrine [8,10]. Further studies are necessary to evaluate the implications of possible renal benefits seen with vasopressin compared to norepinephrine.

4.1. Limitations

Our meta-analysis has several limitations, including the small number of available studies and the heterogeneity of study designs and demographics. Included studies have their inherent limitations. The included studies have been conducted from 2002

to 2018 and represent a contemporary cohort of septic shock patients. Treatment protocol, formulations, and drug dosage are comparable and offer granularity of data in assessing individual influence. The presence of organ dysfunction and comorbidities could have influenced the clinical outcomes [33]. We could only report adverse effects and the need for RRT based on a few studies. We could not report various other parameters of interest as there was wide variation in reporting among studies.

Furthermore, we have only included studies published in English, which could have excluded studies published in other languages. Further studies are warranted to uncover the pathophysiology of vasopressin in septic shock and its potential role in therapeutics.

5. Conclusion

This comprehensive meta-analysis reports no mortality benefit when comparing vasopressin to norepinephrine in septic shock patients. Yet, the need for RRT was significantly lower in the vasopressin group. In addition, we found no difference in adverse

events and duration of hospitalization in septic shock patients receiving vasopressin compared to norepinephrine. Therefore, further large-scale randomized clinical trials are required to uncover the renal benefit of vasopressin in septic shock.

Conflict of Interest

The authors declare that they have no competing interests.

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REVIEW ARTICLE

Supplementary: Vasopressin versus norepinephrine as the first-line vasopressor in septic shock: A systematic review and meta-analysis

Supplementary File 1. Electronic search details

Embase

Search: ("vasopressin"/exp OR vasopressin) AND ("nor adrenaline" OR "nor epinephrine") AND ("septic shock"/exp OR "septic shock" OR (septic AND ("shock"/exp OR shock)) OR "sepsis"/exp OR sepsis)
Link: https://www.embase.com/#advancedSearch/resultspage/history.13/page.1/25.items/orderby.date/source.
Total hits: 4

PubMed

Search: ((Vasopressin) AND (Nor-adrenaline or Nor-epinephrine)) AND (Septic shock or sepsis)
Link: https://pubmed.ncbi.nlm.nih.gov/?term=%28%28Vasopressin%29+AND+%28Nor-adrenaline+or+Nor-epinephrine%29%29+AND+%28Septic+shock+or+sepsis%29&sort=date
Total hits: 354

PubMed Central

Search: ((Vasopressin) AND (Nor-adrenaline or Nor-epinephrine)) AND (Septic shock or sepsis)
Link: https://www.ncbi.nlm.nih.gov/pmc/?term=((Vasopressin)+AND+(Nor-adrenaline+or+Nor-epinephrine))+AND+(Septic+shock+or+sepsis)
Total hits: 2363
Cochrane Library
No findings

Scopus

Search: "Vasopressin" AND ("Nor-adrenaline" or "Nor-epinephrine") AND ("Septic shock" or "sepsis")
Link:https://www.scopus.com/results/results.uri?numberOfFields=0&src=s&clickedLink=&edit=&editSaveSearch=&origin=searchbasic&authorTab=&affiliationTab=&advancedTab=&scint=1&menu=search&tablin=&searchterm1=+%22Vasopressin%22+AND+%28%22Nor-adrenaline%22+or+%22Nor-epinephrine%22%29+AND+%28%22Septic+shock%22+or+%22sepsis%22%29&field1=TITLE_ABS_KEY&dateType=Publication_Date_Type&yearFrom=Before+1960&yearTo=Present&loadDate=7&documenttype=All&resetFormLink=&st1=+%22Vasopressin%22+AND+%28%22Nor-adrenaline%22+or+%22Nor-epinephrine%22%29+ AND+%28%22Septic+shock%22+or+%22sepsis%22%29&st2=&sot=b&sdt=b&sl=106&s=TITLE-ABS-KEY%28+%22Vasopressin%22+AND+%28%22Nor-adrenaline%22+or+%22Nor-epinephrine%22%29+AND+%28%22Septic+shock%22+or+%22sepsis%22%29%29&sid=98b53e3b530215da51c640cd717903d4&searchId=98b53e3b530215da51c640cd717903d4&txGid= c6cb180e933f7eaea68f5605edc8353d&sort=plf-f&originationType=b&rr=
Hits: 1

Supplementary File 2. Additional analysis

1. Morality

 Sensitivity analysis for 28-day mortality outcome conducted by excluding non-randomized studies (Hall *et al.*, 2004, and Russell *et al.*, 2018) also could not show significant differences across two groups (OR, 0.95; 95% CI, 0.76–1.18; n=1337; I^2=0%) (Figure 1).
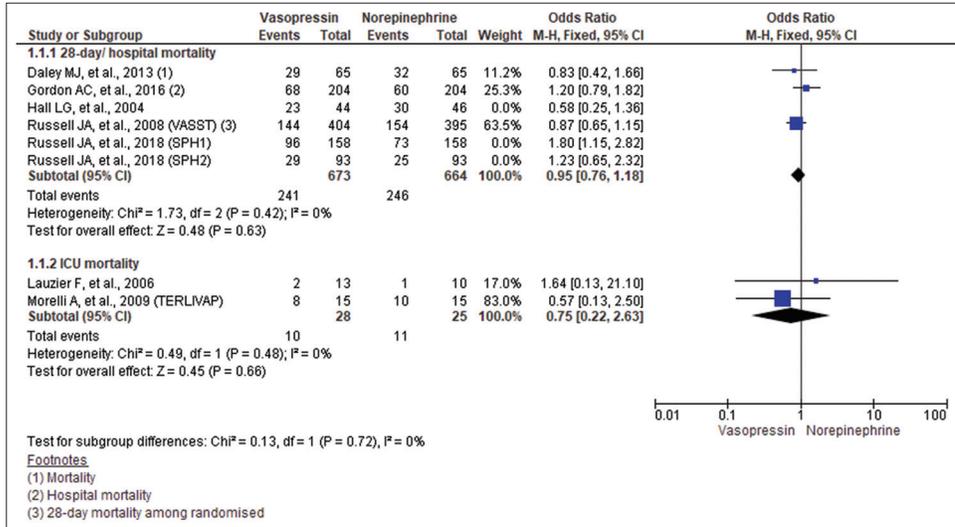
Figure 1. Forest plot showing mortality outcome after excluding non-randomized study.

2. LOS

 Excluding non-randomized study (Hall *et al.*) also could not make significant difference in overall ICU (MD, −0.19; 95% CI, −1.30–0.91; n=1346; I^2=32%), and length of hospital stay (MD, −0.51; 95% CI, −3.18–2.17; n=1316; I^2=0%) (Figure 2).
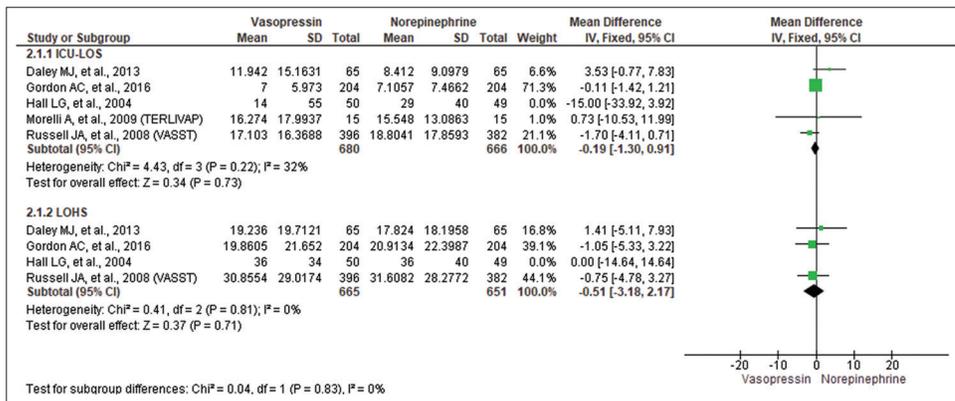
Figure 2. Forest plot showing LOS outcome after excluding non-randomized study.

3. Urine output

Excluding non-randomized study (Hall *et al.*) also could not make significant difference in baseline urine output (MD, 8.42; 95% CI, −9.88–26.73; *n*=53; I2=0%), and 24-h urine output MD, −8.68; 95% CI, −27.62–10.27; *n*=462; I^2=0%) (Figure 3).
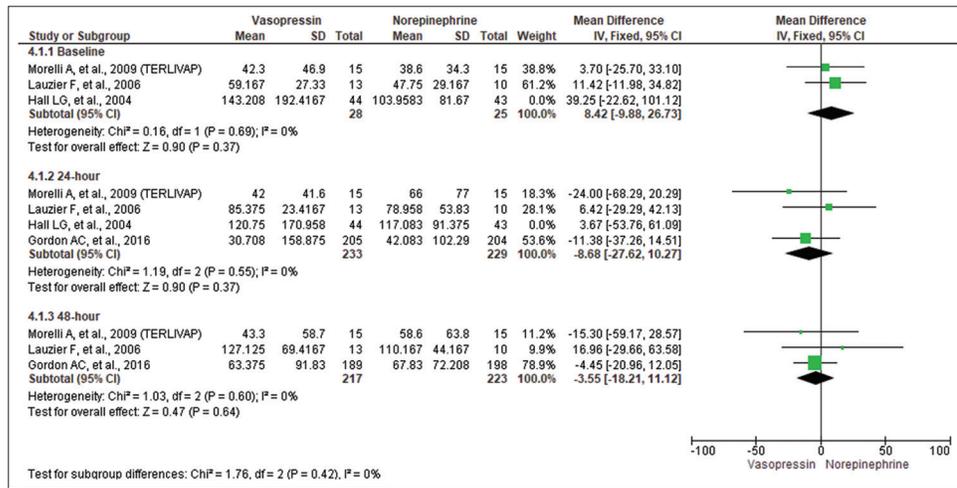
Figure 3. Forest plot showing urine output after excluding non-randomized study.