Vasopressin Versus Norepinephrine for the Management of Septic Shock in Cancer Patients: The VANCS II Randomized Clinical Trial*

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Objectives: Previous trials suggest that vasopressin may improve outcomes in patients with vasodilatory shock. The aim of this study was to evaluate whether vasopressin could be superior to norepinephrine to improve outcomes in cancer patients with septic shock.

Design: Single-center, randomized, double-blind clinical trial, and meta-analysis of randomized trials.

Setting: ICU of a tertiary care hospital.

Patients: Two-hundred fifty patients 18 years old or older with cancer and septic shock.

Interventions: Patients were assigned to either vasopressin or norepinephrine as first-line vasopressor therapy. An updated meta-analysis was also conducted including randomized trials published until October 2018.

Measurements and Main Results: The primary outcome was all-cause mortality at 28 days after randomization. Prespecified secondary outcomes included 90-days all-cause mortality rate; number of days alive and free of advanced organ support at day 28; and Sequential Organ Failure Assessment score 24 hours and 96 hours after randomization. We also measure the prevalence of adverse effects in 28 days. A total of 250 patients were randomized. The primary outcome was observed in 71 patients (56.8%) in the vasopressin group and 66 patients (52.8%) in the norepinephrine group ($p = 0.52$). There were no significant differences in 90-day mortality (90 patients [72.0%] and 94 patients [75.2%], respectively; $p = 0.56$), number of days alive and free of advanced organ support, adverse events, or Sequential Organ Failure Assessment score.

Conclusions: In cancer patients with septic shock, vasopressin as first-line vasopressor therapy was not superior to norepinephrine in reducing 28-day mortality rate. (*Crit Care Med* 2019; 47:1743–1750)

Key Words: cancer; mortality; norepinephrine; randomized controlled trial; septic shock; vasopressin

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Septic shock is the most severe subset of sepsis, with mortality rates up to 50% (1, 2).

The number of patients with cancer admitted to the ICU is increasing, and cancer patients now account for up to 20% of ICU patients, and 10% of patients with sepsis (3–5). Overall,

immunocompromised patients account for about 40% of patients with septic shock (4, 6). Accordingly, research focusing on this specific subpopulation has been identified as a priority by a consensus of experts in septic shock management (5, 7).

Immunocompromised patients present high rates of mortality in septic shock, and early aggressive treatment is important in these patients (6, 8). Cancer is frequently associated with immune response defects and alteration in coagulation system and endothelial function (9, 10).

Vasopressor therapy is essential to maintain an adequate mean arterial pressure (MAP) in septic shock (11). Norepinephrine is the most commonly used drug but has significant adverse events, including potential cardiotoxicity, excessive vasoconstriction leading to bowel and peripheral ischemia, alteration of immune response, and coagulation (12–14). Notably, a substantial number of patients become refractory to norepinephrine, thus requiring increasing doses and hence increasing the risk of side effects (15, 16).

In recent years, vasopressin emerged as a potential alternative to norepinephrine as a vasopressor agent (17–20). Previous meta-analyses suggested that vasopressin administration may reduce atrial fibrillation (AF), acute kidney injury (AKI), renal replacement therapy (RRT), and duration of vasopressor therapy in vasoplegic shock patients (21–24). Vasopressin has multiple mechanisms of action, including direct vasoconstrictor effects, stimulation of V1b receptors in the anterior pituitary gland that increase adrenocorticotropic hormone-producing cortisol, in addition of effects on purinergic and oxytocin receptors, which block endothelial-mediated vasodilation (25–27).

Vasopressin mechanisms of action in septic shock may include a decrease of norepinephrine and norepinephrine adverse effects on the macro- and microcirculation, altered immunity, and a potentially beneficial interaction with corticosteroids (28).

Notably, norepinephrine has immunomodulating effects, while vasopressin may have a greater effect on reducing inflammatory cytokines compared with norepinephrine (14, 29).

In patients with cancer who develop septic shock, early use of vasopressin appears particularly attractive. Accordingly, we hypothesized that vasopressin was superior to norepinephrine to improve outcomes in cancer patients with septic shock, and we designed the Vasopressin versus Norepinephrine for the Management of Septic Shock in Cancer Patients (VANCS II) randomized controlled trial (RCT) to test this hypothesis. In addition, we also performed an updated systematic review focusing on vasopressin administration in cancer patients with septic shock.

MATERIALS AND METHODS

Trial Design

We performed a single-center, double-blind, RCT. The original study protocol was approved by the Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, Brazil. Patients with septic shock were randomized to receive either vasopressin or norepinephrine as first-line vasopressor therapy. Written informed consent was obtained from all participants or their legally authorized next of kin. The trial was registered before initiation (NCT01718613).

Participants

Eligible patients were adults (≥ 18 yr) with cancer admitted to ICU with a documented or strong clinical suspicion of infection, associated with greater than or equal to two criteria of the systemic inflammatory response syndrome, and with vasopressor therapy (11). The trial was performed at a quaternary hospital in Brazil. Exclusion criteria were pregnancy, Raynaud's phenomenon, systemic sclerosis, vasospastic diathesis, severe hyponatremia ($Na^+ < 130$ mmol/L), acute mesenteric ischemia, acute myocardial infarction, cardiogenic shock, ongoing use of vasopressor before randomization, enrollment in another study and refusal to consent.

Randomization and Masking

Randomization was performed with a computer-generated list in a 1:1 ratio, generated online by a web-based program that ensured allocation concealment. After informed consent, randomization was performed and the patient assigned to the intervention. The information about the intervention assignment of each patient was sent only to the ICU pharmacists. The patients, treating clinicians, and trial personnel including outcome assessors were unaware of trial-group assignment.

Intervention

Patients were randomized to receive either vasopressin or norepinephrine as first-line vasopressor therapy. Aside from vasopressor therapy, all other treatments were based on the Surviving Sepsis Campaign Guidelines (11). Vasopressin (30 international units [IUs]; BioLab Sanus Farmaceutica, São Paulo, Brazil) and norepinephrine (30 mg; Hypofarma, Ribeirão das Neves, Brazil) were prepared in identical bags of 250 mL by an unblinded pharmacist, with final concentrations of 0.12 IU/mL vasopressin and 120 µg/mL norepinephrine, labeled with the patient number only. The vasopressor infusion was titrated to maintain MAP greater than or equal to 65 mm Hg. Study-drug infusion started at 5 mL/hr and increased by 2.5 mL/hr every 10 minutes to achieve a maximum target rate of 30 mL/hr so that vasopressin doses ranged from 0.01 to 0.06 IU/min and norepinephrine doses from 10 to 60 µg/min. If the target MAP was not reached and further vasopressor support was required, open-label norepinephrine was started in addition to the study drug.

When the targeted MAP was exceeded, open-label norepinephrine was tapered first; only if open-label norepinephrine was weaned completely, tapering of the study drug was commenced.

Severe adverse events were defined as acute ST-segment elevation confirmed by a 12-lead electrocardiogram, serious or life-threatening cardiac arrhythmias, stroke, acute mesenteric ischemia, limb or skin ischemia, or hyponatremia ($Na^+ < 130$ mmol/L).

Outcomes

The primary outcome was 28 days all-cause mortality rate. The prespecified secondary outcomes were as follows: 90 days all-cause mortality; number of days alive and free of vasopressor therapy, invasive mechanical ventilation, and RRT at day 28; and Sequential Organ Failure Assessment (SOFA) score 24 and 96 hours after randomization (30). Outcomes definitions and adverse effects are described in the **Supplementary Appendix** (Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

Systematic Review and Meta-Analysis

A systematic review and meta-analysis of RCTs comparing vasopressin versus any comparator in septic shock patients with cancer was conducted in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Details on meta-analysis methodology are provided in the Supplementary Appendix (Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

Statistical Methods

The sample size was calculated for a superiority study, and it was postulated that patients of the norepinephrine group would present a prevalence of the primary outcome of 55% compared with 37% of patients of the vasopressin group. Considering a statistical power of 80% and a type 1 error (alpha) of 5%, approximately 250 patients would be required for participating in the study (21). A two-sided test was used.

We compared baseline characteristics, follow-up measures, and clinical outcomes on an intention-to-treat basis according to the randomized study-group assignment. Continuous variables were analyzed using *t* test or Mann-Whitney *U* test, and categorical variables were compared using Pearson chi-square test, Fisher exact test, or a likelihood ratio test. Continuous data are expressed as mean with SD or median with interquartile range. The primary outcome is reported as relative risk with 95% CI. A two-sided p value of less than 0.05 was considered statistically significant. Details on statistical analysis for the meta-analysis are provided in the Supplementary Appendix (Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

The statistical analyses were performed using SPSS Version 18.0 (SPSS, Chicago, IL).

RESULTS

Between July 2014 and July 2016, a total of 250 patients were randomized (125 into the vasopressin group and 125 into the norepinephrine group). There were four protocol deviations in the vasopressin group and two in the norepinephrine group. All patients were analyzed for the primary outcome. There were no losses or exclusions after randomization (**Fig. 1**).

Baseline Characteristics

There were no significant differences regarding baseline characteristics (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/E951) between patients assigned to receive vasopressin or norepinephrine. Patients enrolled in the study were characterized by a median SOFA score of 7 in both groups. Gastrointestinal tract was the most common site of malignancy, and almost 25% of patients had received chemotherapy within the last 4 weeks before randomization.

The main sites of infection were the lungs, abdomen, and urinary tract. Approximately two-thirds of patients of both groups had a positive culture. Gram-negative microorganisms were the most common agents identified in our study. Aside from cardiovascular dysfunction, the most common organ failures at the time of randomization were respiratory failure, renal dysfunction, and neurologic dysfunction (**Table 1**).

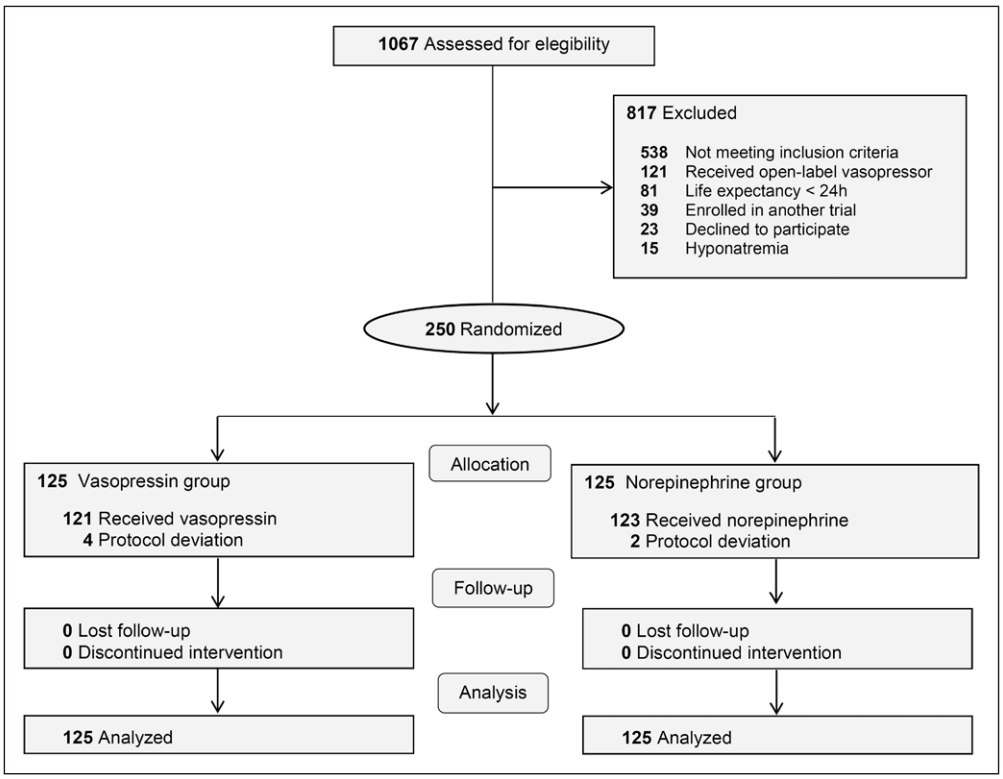

Figure 1. Study flowchart.

Study Outcomes

All-cause mortality at 28 days was 56.8% in the vasopressin group and 52.8% in the norepinephrine group ($p = 0.52$) (**Table 2** and **Fig. 2**).

TABLE 1. Characteristics of Infection

Variable	Vasopressin, *n* = 125, *n* (%)	Norepinephrine, *n* = 125, *n* (%)	*p*
Infection site			
Lung	71 (56.8)	67 (53.6)	0.836[a]
Abdomen	24 (19.2)	22 (17.6)	
Urinary tract	13 (10.4)	12 (9.6)	
Bloodstream	4 (3.2)	6 (4.8)	
Others	13 (10.4)	18 (14.4)	
Cultures			
Positive cultures	63 (51.2)	77 (61.6)	0.099[a]
Gram-positive	33 (26.4)	37 (29.6)	0.573[a]
Gram-negative	33 (26.4)	50 (40)	0.022[a]
Fungi	17 (13.6)	17 (13.6)	1.000[a]
Multi-drug resistant	10 (8)	23 (18.4)	0.015[a]
Organ dysfunction at ICU admission			
Cardiovascular	125 (100)	125 (100)	1.00
Respiratory	64 (51.2)	62 (49.6)	0.800[a]
Renal	53 (42.4)	52 (41.6)	0.898[a]
Neurologic	27 (21.6)	31 (24.8)	0.549[a]
Hematologic	26 (20.8)	32 (25.6)	0.369[a]
Hepatic	10 (8)	6 (4.8)	0.301[a]

[a]Pearson's chi square test.

All-cause mortality rate at 90 days was also similar between groups. There was no significant difference between groups in SOFA score within the first 24 and 96 hours after randomization (Table 2). We did not observe significant difference in the number of days alive and free of vasopressor therapy, invasive mechanical ventilation, and RRT. ICU readmission rate, length of ICU stay, and length of hospital stay were also similar between groups. No difference was observed between groups regarding the prevalence of AKI and requirement of RRT (Table 2).

Vasopressor Therapy and Hemodynamic Variables

The duration of the vasopressor therapy was similar between groups; nevertheless, more patients in the vasopressin group had persistent hypotension requiring rescue open-label norepinephrine (Table 2). No significant difference was observed regarding MAP, heart rate, and central venous oxygen saturation between groups (**eTable 2** and **eFigs. 1–3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E951). A similar urinary output during the period of intervention was observed (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E951). Also, there were no significant differences between groups in perfusion markers such as arterial lactate, pH, and base excess (**eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

The daily dose of norepinephrine and vasopressin administered from randomization to day 7 is presented in eTable 4 and **eFigs. 4** and **5** (Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

Adverse Events

A total of 59 patients (47.2%) of the vasopressin group and 58 patients (46.4%) of the group norepinephrine presented greater than or equal to one adverse event ($p = 0.420$). Cardiac arrhythmia was the most common adverse event in both groups. There were no significant differences between groups regarding the prevalence of limb or skin ischemia, stroke, myocardial infarction, ventricular and supraventricular arrhythmia, and mesenteric ischemia. No significant difference was observed in the prevalence of hyponatremia between groups (Table 2).

Post Hoc Analyses

Post hoc subgroup analysis of rates for the main outcome of all-cause mortality at 28 days, no difference was observed between vasopressin group and norepinephrine group according to age, gender, metastatic disease, corticosteroid use, site of infection, AKI at the time of randomization, and mechanical ventilation at the time of randomization (**Fig. 3**). Since patients in the norepinephrine group had a higher baseline prevalence of multidrug-resistant (MDR) infections, we performed a post hoc multiple logistic regression analysis adjusted for MDR which showed no difference in 28-day mortality (**eTable 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/E951). Association between lactate levels and outcomes is reported in **eTable 6** and **eFigure 6** (Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

Meta-Analysis

Our search identified seven RCTs comparing vasopressin versus any comparator in septic shock patients (9, 10, 31–35) in addition to the present VANCS II trial. Data on cancer patients were available only for two RCTs. Trials characteristics are presented in **eTable 7** and **eFigs. 7** and **8** (Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

Vasopressin was superior to control in reducing the need for RRT (14/150 [9.3%] vs 26/147 [17.7%]; relative risk, 0.46; 95% CI, 0.23–0.93; $p = 0.03$; p for heterogeneity = 0.39; $I^2 = 0\%$; two included trials; **eFig. 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

There were no differences between vasopressin and comparator in any of the other outcomes (Supplementary Appendix, Supplemental Digital Content 1, http://links.lww.com/CCM/E951).

DISCUSSION

The main finding of this RCT is that among cancer patients with septic shock, vasopressin was not superior to norepinephrine in reducing 28-day mortality or improving other major outcomes. In addition, adverse effects rate, including mesenteric and digital ischemia, was not different between groups.

TABLE 2. Outcomes

Variable	Vasopressin, *n* = 125	Norepinephrine, *n* = 125	Absolute Difference (95% CI)	*p*
Primary outcome, n (%)				
28-d mortality	71 (56.8)	66 (52.8)	4.0 (−8.2 to 16.1)	0.525[a]
Secondary outcomes				
90-d mortality, *n* (%)	90 (72.0)	94 (75.2)	−3.2 (−14.0 to 7.7)	0.566[a]
Days alive and free of mechanical ventilation, median (IQR)	20 (6–28)	22 (7–28)		0.748[b]
Days alive and free of vasopressor agent, median (IQR)	10 (1–23)	12 (1–24)		0.669[b]
Days alive and free of dialysis, median (IQR)	20 (7–28)	21 (7–28)		0.819[b]
SOFA 24 hr, median (IQR)	8 (5–11)	7 (5–10)		0.425[b]
SOFA 96 hr, median (IQR)	7 (2–12)	7 (3–12)		0.825[b]
Other outcomes				
Norepinephrine use "open label," *n* (%)	67 (53.6)	51 (40.8)	12.8 (0.4–24.6)	0.043[a]
Days of norepinephrine "open label," median (IQR)	2 (2–5)	2 (1–3)		0.009[b]
Acute kidney injury, *n* (%)	53 (42.4)	52 (41.6)	0.80 (−11.3 vs 12.9)	0.898[a]
Renal replacement therapy, *n* (%)	10 (8.0)	17 (13.6)	−5.60 (−13.6 to 2.25)	0.154[a]
Delirium, *n* (%)	40 (32.0)	40 (32.0)	0 (−11.44 to 11.44)	1.000[a]
ICU readmission, *n* (%)	8 (6.4)	11 (8.8)	−2.40 (−9.41 to 4.48)	0.474[a]
ICU length of stay (d), median (IQR)	7 (4–12)	6 (4–12)		0.520[b]
Hospital length of stay (d), median (IQR)	11 (6–23)	12 (6–22)		0.835[b]
Adverse events, *n* (%)				
Arrhythmia	34 (27.2)	40 (32.0)	−4.80 (−15.92 to 6.48)	0.406[a]
Hyponatremia	31 (24.8)	20 (16.0)	8.80 (−1.23 to 18.66)	0.084[a]
Cerebral ischemia	6 (4.8)	1 (0.8)	4.00 (−0.42 to 9.32)	0.120[c]
Acute myocardial infarction	3 (2.4)	7 (5.6)	−3.2 (−8.93 to 2.06)	0.197[a]
Digital ischemia	0 (0)	2 (1.6	−1.60 (−5.65 to 1.60)	0.498[c]
Mesenteric ischemia	0 (0)	0 (0)		–
Number of adverse events				
0	66 (52.8)	67 (53.6)		0.420[d]
1	46 (36.8)	46 (36.8)		
2	11 (8.8)	12 (9.6)		
3	2 (1.6)	0 (0)		

[a]Pearson's chi square test.
[b]Mann-Whitney test.
[c]Likelihood ratio test.
[d]Fisher exact test.

After including the results of this RCT in an meta-analysis, we confirmed that in septic shock patients with cancer, vasopressin decreases significantly the need for RRT, with no effect on other major outcomes.

Reducing the use of catecholamines is desirable in septic shock patients. High doses catecholamine may produce excessive chronotropic effect leading to tachyarrhythmias, impaired diastolic function, myocardial ischemia,

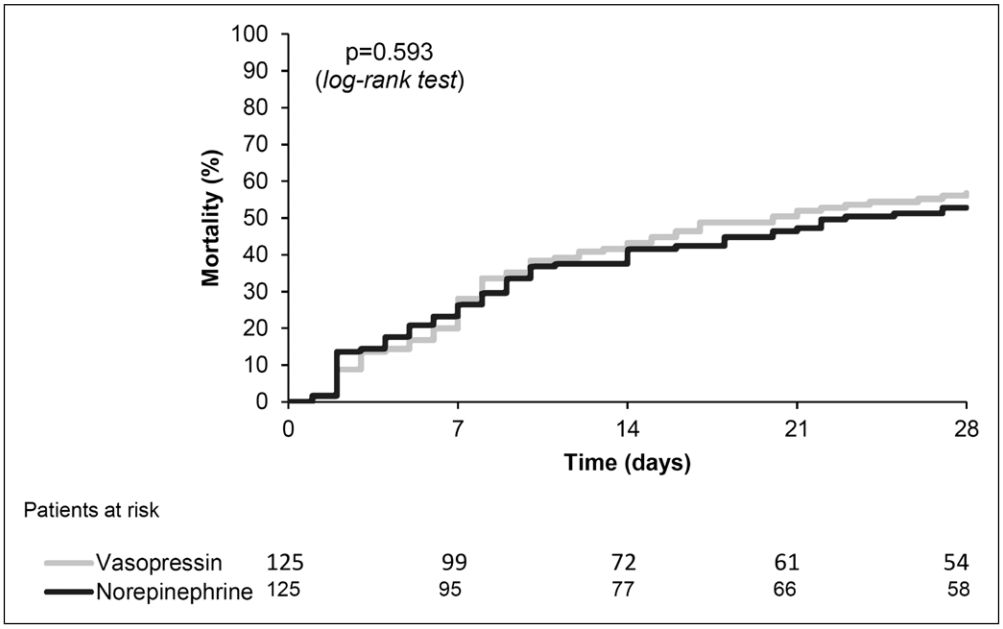

Figure 2. Kaplan-Meier probability for 28 d mortality using the log-rank test.

immunosuppression, pulmonary edema, hypercoagulability and gut ischemia, and consequently might increase morbidity and mortality (4, 7, 14).

Adding vasopressin to norepinephrine is an effective way of reducing catecholamines (20). Few large RCTs were performed aiming to compare vasopressin with norepinephrine in patients with septic shock (17, 18). Russell et al (17), in the Vasopressin and Septic Shock Trial (VASST), studied 778 patients with septic shock who received low-dose vasopressin (0.01–0.03 IU/min) or norepinephrine (5–15 μg/min) in addition to open-label vasopressors. Although no difference was observed regarding 28-day mortality, patients with less severe septic shock presented a lower 28-day mortality rate in the vasopressin group. In a post hoc analysis of the VASST trial, vasopressin reduced progression to AKI and mortality in patients with septic shock at risk of kidney injury (36).

In a more recent RCT, Gordon et al (18) randomized 409 patients with septic shock to receive vasopressin or norepinephrine. Vasopressin was associated with a reduced use of RRT, without affecting mortality rates. The Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial was the first published RCT to compare head to head norepinephrine with vasopressin (titrated up to 0.06 IU/min) in septic shock.

Our findings support the data from VANISH study, showing that in a head to head comparison, the use of vasopressin (dose up to 0.06 IU/min) is not superior to norepinephrine alone in reducing septic shock mortality. In addition, in cancer

28-day mortality	Vasopressin	Norepinephrine	OR (95%CI)	P#
Age, *n* (%)				
≤60 years	22/45 (48.9%)	29/53 (54.7%)	1.26 (0.57 - 2.80)	0.565
>60 years	49/80 (61.3%)	37/72 (51.4%)	0.67 (0.35 - 1.27)	0.221
Gender, *n* (%)				
Male	31/57 (54.4%)	30/56 (53.6%)	0.97 (0.46 - 2.03)	0.931
Female	40/68 (58.8%)	36/69 (52.2%)	0.76 (0.39 - 1.5)	0.434
Metastasis, *n* (%)				
No	17/32 (53.1%)	15/34 (44.1%)	0.69 (0.26 - 1.84)	0.465
Yes	52/89 (58.4%)	48/86 (55.8%)	0.89 (0.49 – 1.63)	0.765
Infection site, *n* (%)				
Pulmonary	46/71 (64.8%)	35/67 (52.2%)	0.59 (0.30 - 1.18)	0.136
Abdominal	12/24 (50.0%)	13/22 (59.1%)	1.44 (0.45 - 4.64)	0.537
Others	13/30 (43.3%)	18/36 (50.0%)	1.31 (0.49 - 3.46)	0.589
AKI at admission, *n* (%)				
No	36/70 (51.4%)	39/76 (51.3%)	1.00 (0.52 - 1.91)	0.989
Yes	31/51 (60.8%)	27/49 (55.1%)	0.79 (0.36 - 1.75)	0.565
MV at admission, *n* (%)				
No	51/96 (53.1%)	49/97 (50.5%)	0.90 (0.51 - 1.58)	0.717
Yes	20/29 (69.0%)	17/28 (60.7%)	0.70 (0.23 - 2.07)	0.515
Corticostheroids, *n* (%)				
No	19/40 (47.5%)	18/41 (43.9%)	0.86 (0.36 - 2.07)	0.745
Yes	52/85 (61.2%)	48/84 (57.1%)	0.85 (0.46 - 1.56)	0.594

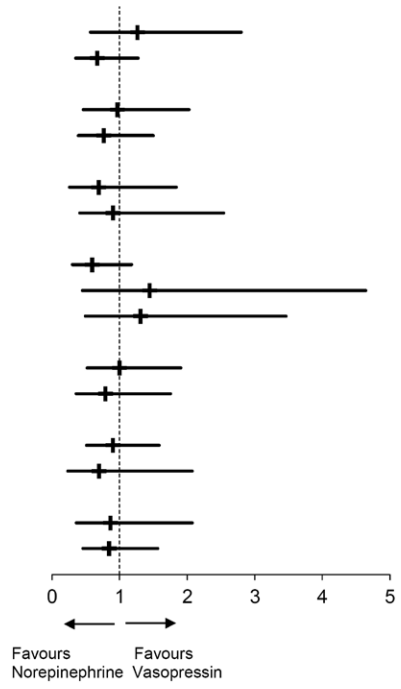

Figure 3. Subgroup analyses. AKI = acute kidney injury, MV = mechanical ventilation, OR = odds ratio.

patients with septic shock, vasopressin did not exert renal protective effect. Our data showed that more patients of the vasopressin group needed open-label norepinephrine. This could be explained because there may be a subset of patients who have vasopressin resistance and also because some patients with septic shock may present more benefit from a multimodal therapy, with different action vasopressors (37).

Previous meta-analyses showed benefits of vasopressin in comparison with norepinephrine in reducing AF and AKI in vasodilatory shock (21–23, 37). These published systematic reviews included both septic shock and vasoplegic shock after cardiac surgery (21–23, 38).

On the contrary, vasopressin seems to be superior to norepinephrine in vasodilatory shock after cardiac surgery (19,23), mainly exerting benefits in reducing the occurrence of AKI, AF, requirement for RRT, decreasing length of hospital stay and facilitating the weaning of vasoactive drugs. In the largest trial performed in the setting of cardiac surgery, the Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS), 330 patients with postoperative vasodilatory shock were randomized to receive vasopressin (up to 0.06 IU/min) or norepinephrine (up to 60 μg/min) as first-line vasopressor therapy (19). Patients randomized to vasopressin had a lower prevalence of major complications, driven by a reduction in AKI prevalence. Furthermore, length of ICU and hospital stay was significantly lower in the vasopressin group. The protocol for vasopressor administration was similar to that used in the present trial. However, the population enrolled in the VANCS trial was different, as also reflected by the lower 30-day mortality (23% vs 55%). In addition, we hypothesize that in the pathophysiology of cardiac-surgery associated vasoplegic shock, there might be a more significant reduction in vasopressin levels when compared with septic shock. However, it should be noted that data on vasopressin use in cardiac surgery derive from single-centers RCTs only, which carry a higher risk of bias when compared with multicenter RCTs (39).

The renal protective effect of vasopressin is not clearly established. There is experimental evidence showing a preferential binding of norepinephrine to the α-1 receptors of renal afferent arterioles, while vasopressin binds preferentially to arginine vasopressin receptor 1A receptors on glomerular efferent arterioles, thus increasing glomerular perfusion pressure and filtration (40). Renal protection related to reduced activation of the renin-aldosterone-angiotensin system is one of the hypothesized benefits of vasopressin in distributive shock; creatinine clearance has been shown to improve when vasopressin was started early after the onset of distributive shock (32).

However, Post et al (41) demonstrated in an ovine model of fecal peritonitis that norepinephrine and vasopressin may have different effects on renal autoregulation.

Our study is limited by its single-center design, but this may also increase the intrinsic value of the study reducing heterogeneity. Furthermore, we did not measure plasma vasopressin levels, as we did in the VANCS trial (19). Maybe we have underestimated the sample size based in the hypothesis that vasopressin would reduce mortality when compared with norepinephrine. However, the overall 28-day mortality observed in the trial was 55%, as hypothesized during sample size calculation, with comparable mortality rates in the two groups. The absence of even a hint of survival benefit from vasopressin administration, supported by the results of the meta-analysis, suggest that it is unlikely that a larger sample size would have yielded different results. Interestingly, observed mortality was higher than predicted by SOFA score, suggesting that SOFA may be inaccurate in a subpopulation of patients with malignancy. Patients randomized to norepinephrine presented a high baseline prevalence of MDR bacteria that could have contributed to worse outcomes in these patients. However, in an adjusted model, the results were similar. The exclusion of patients with hyponatremia might limit the generalizability of the results. However, only 15 patients were excluded due to this reason. Finally, patients in the vasopressin group required more open-label norepinephrine administration. This might be related to the study design, with use of vasopressin different from that recommended by current guidelines, and to the relatively long half-life of the drug, that may hinder adequate dose titration. However, previous trials showed that vasopressin can be used successfully as first-line vasopressor therapy (also in double-blind trial) and the dose titrated to blood pressure targets (18, 42). Results of our meta-analysis are limited by the low number of data on cancer patients available from published trials.

Considering that septic shock has a multifactorial pathophysiology and different clinical presentations, a single intervention such as therapy with only one vasopressor may not influence mortality. There is the possibility that the best therapy to improve results in septic shock would be the combination of multiple drugs with a different mechanism of action simultaneously in lower doses than usual, such as low doses of norepinephrine, low doses of vasopressin, angiotensin, steroids and, possibly, vitamin C and thiamine supplementation (43–45) Once the vasopressor sensitivities are assessed, the vasopressors are deescalated accordingly (46). Further trials are needed with low doses of multiple vasopressors such as norepinephrine, vasopressin, and angiotensin II in septic shock patients, addressing multiple defects in the pathophysiology of shock, and simultaneously avoiding adverse effects of high doses of the drugs. In a near future, the choice of vasopressors for septic shock treatment may be guided by predictive biomarkers, such as copeptin or vasopressinase (leucyl/cystinyl aminopeptidase).

CONCLUSIONS

In conclusion, in cancer patients with septic shock, vasopressin did not reduce 28-day mortality.

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