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Addition of Vasopressin to Norepinephrine as Independent Predictor of Mortality in Patients with Refractory Septic Shock: An Observational Study

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ABSTRACT

Objective: To identify predictors of 28-day mortality among patients with refractory septic shock treated with norepinephrine with or without vasopressin.

Design: Prospective observational cohort study.

Setting: A 1,200-bed academic medical center.

Patients: One hundred thirty-seven patients with septic shock treated with norepinephrine with or without vasopressin.

Interventions: None.

Measurements and Main Results: The 28-day mortality rate was 37.2% (n = 51). By multivariate analysis, significant predictors of death were norepinephrine plus vasopressin administration (adjusted odds ratio [AOR], 13.96; 95% confidence interval [CI] 6.47, 30.08; p = 0.001), lack of goal-directed fluid administration during initial resuscitation (AOR 15.82; 95% CI 6.16, 40.61; p = 0.003), inappropriate initial antimicrobial therapy (AOR 8.95; 95% CI 2.93, 27.33; p = 0.05), and higher Acute Physiology and Chronic Health Evaluation (APACHE) II score (AOR 1.14; 95% CI 1.07, 1.21; p = 0.033). Patients who received norepinephrine plus vasopressin (n = 68) had a significantly higher mortality rate than patients managed with norepinephrine alone (n = 69) 28 days after the initiation of vasopressors (54.4% vs. 20.3%; p < 0.001). This finding was confirmed in patients matched optimally across treatment groups.

Conclusions: Our study found an association between the use of norepinephrine plus vasopressin and 28-day mortality in refractory septic shock. In view of its known mechanism of action, vasopressin contributed to this excess mortality. Further recommendations regarding the use of vasopressin await the results of large randomized trials evaluating its efficacy and safety for septic shock.

SEVERE SEPSIS is an infection-induced syndrome resulting in a systemic inflammatory response complicated by dysfunction of at least one organ system [1]. In the United States, ap-

proximately 750,000 cases of sepsis occur each year [2,3]. The mortality rate ranges from 30% to 50%, increasing with advancing age [3,4]. The complex pathophysiology of sepsis in-

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cludes a series of interacting pathways of immune stimulation, immune suppression, hypercoagulation, and hypofibrinolysis [5,6].

Cardiovascular management plays an important role in the treatment of septic shock. Hypotension occurs secondary to failure of vasoconstriction by vascular smooth muscle, resulting in peripheral vasodilation [7,8]. When hypotension persists despite goal-directed fluid resuscitation, exogenous catecholamines are administered to increase the mean arterial pressure (MAP). Selecting the most appropriate initial vasopressor agent for the management of septic shock remains a challenge. Catecholamines (e.g., norepinephrine and dopamine) are considered first-line agents [9,10], but they often yield poor hemodynamic responses as the result of multiple mechanisms [8]. This difficulty has stimulated interest in other agents, such as vasopressin, for managing sepsis-induced hypotension.

Vasopressin is an endogenous hormone synthesized in the hypothalamus and stored in the posterior pituitary gland, from which it is secreted in response to appropriate stimuli [11–13]. In addition to its antidiuretic effects, vasopressin has potent smooth muscle vasoconstricting properties that make it useful in raising the MAP in septic shock [7,8,11,12,14]. During the early phases of septic shock, circulating vasopressin concentrations are elevated, but as hypotension persists, these concentrations decrease, and neurohypophyseal and plasma concentrations become deficient [13,15–17]. Vasopressin deficiency is one of the mechanisms involved in the development of vasodilatory shock [8], which has led to various studies showing that exogenous vasopressin increases the MAP while reducing the necessary norepinephrine dosage, and that it may improve urine output [18–22]. However, there may be negative consequences associated with administration of vasopressin to patients with septic shock, including myocardial and splanchnic ischemia [19].

The following is a description of an observational prospective study of critically ill patients with septic shock managed with norepinephrine with or without vasopressin for hemodynamic support. The purpose was to identify risk factors associated with 28-day all-

cause mortality, with a particular interest in the effects of vasopressin administration.

PATIENTS AND METHODS

Study location and patients

The study was conducted in the intensive care units (ICUs) (medical, surgical-trauma, cardiothoracic, neurologic-neurosurgical, cardiac) of a 1,200-bed academic medical center: Barnes-Jewish Hospital/Washington University Medical Center in St. Louis, MO, from December 2003 to December 2004. These ICUs are closed units employing multidisciplinary rounds directed by a physician board-certified in critical care. The study was approved by the Washington University School of Medicine Human Studies Committee. Informed consent was obtained for collection of patient data.

One hundred thirty-seven patients (73 men and 64 women) met the criteria for volume-refractory septic shock necessitating administration of either norepinephrine alone ($n = 69$) or norepinephrine plus vasopressin ($n = 68$). The mean age of the patients was 59.2 ± 15.9 years. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were 26.2 ± 6.1 and 9.4 ± 3.1 , respectively. Eighty-four patients (61.3%) were treated in medical ICUs and 53 (38.7%) in surgical ICUs.

Study entry criteria and vasopressor administration

Clinical criteria required for enrollment in the study were: (1) The presence of two or more signs of the systemic inflammatory response syndrome; (2) an infection documented by positive culture, radiographic findings consistent with infection, or a clinical syndrome associated with a high probability of infection; and (3) vasodilatory volume-refractory shock necessitating administration of norepinephrine or norepinephrine plus vasopressin for a minimum of six hours to maintain a minimum target MAP > 55 mm Hg (routine target MAP in patients without refractory shock is 60 to 65 mm Hg). In accord with the Surviving Sepsis Campaign Guidelines, vasopressin was given

to volume-refractory, norepinephrine-dependent patients at a dose of 0.04 units/min [9]. The prescription of norepinephrine alone or norepinephrine plus vasopressin was not based on specified hemodynamic cut-offs (i.e., norepinephrine dose of ≥ 0.5 mcg/kg/min or organ failure progression) but was solely at the discretion of the board-certified critical care specialist directing the patient's care. Patients given dopamine for hemodynamic stabilization were excluded from the analysis to allow a more uniform analysis. Patients with refractory shock despite appropriate vasopressor administration were included. Vasopressors were tapered by discontinuing the vasopressin infusion first, when employed, and then reducing the norepinephrine infusion by increments of 0.05 to 1.0 mcg/kg/min.

Study design and data collection

A prospective, observational cohort study design was used, segregating patients who received vasopressors according to 28-day survival to identify potential risk factors for patient death. All-cause mortality at 28 days after the initiation of vasopressors for septic shock was determined a priori to be the dependent variable of interest. Secondary analyses included a comparison of patients who received norepinephrine alone with those given norepinephrine plus vasopressin, and evaluation of cardiovascular and renal organ dysfunction or failure over time by calculating SOFA scores for each parameter.

For all study patients, the following characteristics were recorded during the first 24 h of vasopressor administration: Age, sex, weight, primary service (medical [cardiac, neurologic, and general medical patients] or surgical [cardiothoracic, neurosurgical and general surgical patients]), APACHE II score, the number of organs failing, the need for mechanical ventilation, and the use of dobutamine. Additionally, the source of infection and the presence of a positive culture (e.g., blood, respiratory specimen, urine, stool, wound specimen) were recorded on identification. Other specific process-of-care variables examined were the total volume of fluid administered in the six-hour period prior to initiation of vasopressors, the

use of invasive monitoring to guide fluid resuscitation in the first six hours after presentation, the presence or absence of appropriate initial antimicrobial treatment of the identified infection, the administration of corticosteroids or drotrecogin alfa (activated), daily renal replacement therapy, and blood glucose control.

A daily computerized list of all patients started on norepinephrine or vasopressin was generated by the Washington University School of Medicine's Medical Informatics Department, which allowed identification of study patients. One of the investigators made daily rounds on all study patients, recording relevant data from the medical records, bedside flowsheets, and the hospital's mainframe computer for reports of microbiologic studies (gram stains and cultures of blood, urine, sputum, lower respiratory tract specimens, tissue, and wounds). All pharmacotherapies administered in the emergency department, general medical or surgical ward, and ICU were evaluated using patients' medical records and the hospital's computerized bedside workstations (EMTEK Health Care Systems, Inc., Tempe, AZ, and Clinical Desktop, BJC Healthcare, St. Louis, MO).

Definitions

All definitions were selected a priori as a part of the original study design. Norepinephrine dependency was defined as the inability to wean the patient off the norepinephrine infusion during the first six hours of its administration, or the addition of a vasopressin infusion. The fluid resuscitation during the six hours immediately preceding the initiation of vasopressors was evaluated. The types of fluids administered included crystalloid solutions (0.9% sodium chloride or lactated Ringer's) or colloid solutions (fresh frozen plasma, albumin, or 6% hydroxyethyl starch). Invasive goal-directed monitoring was defined as the documentation of one or more of the following: (1) Central venous pressure to a goal of 8–12 mm Hg; (2) pulmonary artery occlusion pressure to a goal of 14–18 mm Hg; or (3) the corrected flow time (FTc) measured by esophageal Doppler probe (goal > 330 milliseconds) during the volume resuscitation phase of therapy. For the

purposes of this investigation, appropriate antimicrobial treatment was defined as the microbiologic documentation of an infection (i.e., a positive culture result) that was being treated effectively on the basis of the *in vitro* susceptibility results at the time of its identification. Corticosteroid therapy was composed of hydrocortisone 200–300 mg/day or its equivalent for seven consecutive days or until death. Patients were not required to have adrenal insufficiency on the basis of cortisol concentrations determined randomly or an adrenocorticotropic hormone (ACTH) stimulation test to receive corticosteroid. The morning blood glucose concentration was measured daily between 3:00 and 6:00 A.M. throughout the ICU stay. The average of the morning blood glucose concentrations while the patient was in the ICU was evaluated.

Calculations of APACHE II and SOFA scores were made on the basis of clinical data available for the first 24 h of vasopressor administration [24]. The definition for systemic inflammatory response syndrome was that proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [25]. The definition of organ failure was based on The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial and included one or more of the following: (1) Cardiovascular–vasopressors required to maintain the systolic blood pressure ≥ 90 mm Hg or the MAP ≥ 70 mm Hg; (2) renal–urine output < 0.5 mL/kg of body weight/h for one hour; (3) respiratory–ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($P_aO_2/F_I O_2$) ≤ 250 on mechanical ventilation; (4) hematologic–platelet count $< 80,000/\text{mm}^3$ or a decrease by 50% over the previous three days; (5) unexplained metabolic acidosis–pH ≤ 7.30 or lactate > 4 mmol/L [26]. Sequential cardiovascular and renal SOFA scores were calculated using the worst value for each parameter during each 24-h period [27].

Statistical analysis

Continuous data are reported as mean \pm standard deviation, and the Student *t*-test was employed for comparison of means between

groups. Categorical variables are reported as frequency distributions, and the chi-square or Fisher exact test was used to test whether differences existed between groups. Nonparametric data were analyzed with the Mann-Whitney U test. These data are presented as median values with 25th and 75th percentiles. After these univariate analyses, multivariable logistic regression adjusting for time at risk for the outcome event was undertaken to identify independent risk factors for in-hospital death. Risk factors significant at the 0.2 level by univariate analysis were entered in the model. Adjusted odds ratios (AORs) and their corresponding 95% confidence intervals (CIs) are reported. Kaplan-Meier curves representing the time from the start of vasopressor infusion to death up to 28 days later were compared using the log-rank test. All tests were two-tailed, and a *p* value < 0.05 was defined as statistical significance. Optimal bipartite graph matching using SAS 9.1 macros (SAS Institute, Cary, NC) was done to match patients receiving norepinephrine alone with the most similar patient receiving norepinephrine plus vasopressin [28]. Variables used in the matching are listed in Tables 1 and 2 with the exception of volume administered in the six hours prior to vasopressor administration (secondary to missing data in nine patients) and appropriate initial antimicrobial administration (not all patients had positive cultures). The paired data resulting from bipartite graph matching were compared using McNemar's test. Statistical analyses were done with the SPSS 10.1 software package (SPSS, Inc., Chicago, IL) SAS 9.1, and the MATCH macro, available from the Department of Biostatistics, Mayo Clinic, Rochester, MN.

RESULTS

The 28-day mortality rate for the entire cohort was 37.2%. The results of univariate analysis for patient characteristics according to 28-day survival status are presented in Table 1. Nonsurvivors were significantly older, had statistically greater APACHE II and SOFA scores, and also had a higher number of organs with acquired failure compared with the survivors.

TABLE 1. PATIENT CHARACTERISTICS

	28-day survivors (n = 86)	28-day nonsurvivors (n = 51)	P value	Norepinephrine (n = 69)	Norepinephrine plus vasopressin (n = 68)	P value
Age (yrs)	57.1 ± 16.4	62.9 ± 14.8	0.040	60.2 ± 14.2	58.3 ± 17.7	0.477
No. (%) male	49 (57.0)	23 (45.1)	0.178	36 (52.2)	36 (52.9)	0.928
Weight (kg)	85.5 ± 35.1	84.5 ± 36.2	0.884	78.4 ± 21.5	91.9 ± 44.5	0.025
No. (%) patient type						
Medical	48 (55.8)	36 (70.6)	0.086	43 (62.3)	41 (60.3)	0.808
Surgical	38 (44.1)	15 (29.4)		26 (37.7)	26 (39.7)	
APACHE II score	24.5 ± 5.5	28.9 ± 6.3	<0.001	25.3 ± 6.4	27.1 ± 5.8	0.086
SOFA score	8.8 ± 2.9	10.5 ± 3.1	0.001	9.1 ± 3.2	9.8 ± 3.0	0.174
No. (%) having mechanical ventilation	71 (82.6)	47 (92.2)	0.116	53 (75.4)	66 (97.1)	<0.001
No. of acquired organ failures	2.5 ± 0.9	3.1 ± 0.9	0.001	2.5 ± 0.90	3.1 ± 0.9	<0.001
Reason for ICU admission						
Post-op (non-trauma)	23 (26.7)	10 (19.6)	0.100	17 (24.6)	14 (20.6)	0.448
Post-op (trauma)	5 (5.8)	0		1 (1.4)	4 (5.9)	
ARDS	10 (11.6)	7 (13.7)		7 (10.1)	10 (14.7)	
Sepsis	37 (43.0)	27 (52.9)		33 (47.8)	28 (41.2)	
Acute MI	9 (10.5)	6 (11.8)		9 (13.0)	6 (8.8)	
Other	2 (2.3)	1 (1.9)		2 (2.9)	6 (8.8)	
Infection source						
Lung	40 (46.5)	21 (41.2)	0.774	32 (45.7)	31 (46.3)	0.554
Abdomen	30 (34.9)	22 (43.1)		24 (34.3)	26 (38.8)	
Urine	7 (8.1)	2 (3.9)		6 (8.6)	2 (3.0)	
Other	9 (10.5)	6 (11.8)		8 (11.3)	8 (11.9)	
No. (%) positive cultures	66 (76.7)	34 (66.7)	0.199	54 (78.3)	46 (67.6)	0.162
No. (%) positive blood cultures	27 (31.4)	20 (39.2)	0.351	25 (36.3)	22 (32.4)	0.633

APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment Score; ICU = intensive care unit; ARDS = acute respiratory distress syndrome; MI = myocardial infarction.

Table 2 displays the univariate analysis for the process-of-care variables. The administration of vasopressin and corticosteroids, as well as the lack of goal-targeted fluid administration during initial resuscitation, occurred significantly more often in the nonsurvivors than in the survivors.

Independent risk factors for 28-day mortality, as compiled by multiple logistic regression analysis, are shown in Table 3. The administration of vasopressin, the lack of goal-directed volume resuscitation, higher APACHE II scores, and inappropriate antimicrobial therapy were independently associated with 28-day mortality. Twenty-eight-day survivors had significantly longer median durations of intensive care (12.5 days; interquartile range [IQR] 6 to 30 days vs. 9 days, IQR 6 to 12.5 days; $p = 0.002$) and hospital lengths of stay (33 days; IQR 15 to 53 days vs. 12 days, IQR 7.5 to 19 days; $p < 0.001$) compared with nonsurvivors.

A comparison of patients who received norepinephrine with those receiving norepinephrine plus vasopressin revealed several differences in baseline characteristics and process-of-care variables. Patients who received norepinephrine plus vasopressin had a statistically greater body mass, number of acquired organ system derangements, and mechanical ventilation requirement and were significantly more likely to be given drotrecogin alfa (activated) than those who received norepinephrine alone (Tables 1 and 2). Twenty-eight days after the start of vasopressor administration, 14 of 69 patients (20.3%) managed with norepinephrine alone and 37 of 68 (54.4%) treated with norepinephrine plus vasopressin had died ($p < 0.001$). A Kaplan-Meier analysis of survival at 28 days yielded similar results ($p < 0.001$) (Fig. 1). Additionally, the administration of vasopressin in combination with norepinephrine in graph-matched patients was associated with a

TABLE 2. PROCESS-OF-CARE VARIABLES

	28-day survivors (n = 86)	28-day nonsurvivors (n = 51)	P value	Norepinephrine (n = 69)	Norepinephrine plus vasopressin (n = 68)	P value
No. (%) appropriate initial antimicrobial treatment	62 (93.9)	30 (88.2)	0.188	50 (94.3)	42 (91.3)	0.557
Volume administration (mL) ^a	2549 ± 1791	2159 ± 1540	0.220	2321 ± 1767	2515 ± 1654	0.523
Volume administration (mL/kg) ^a	31.2 ± 21.1	28.9 ± 25.1	0.575	29.1 ± 19.9	31.8 ± 25.2	0.503
No. (%) goal-directed fluid administration	34 (39.5)	10 (19.6)	0.016	20 (29.0)	24 (35.3)	0.429
Type of goal-directed hemodynamic monitoring, n (%)						
Central venous pressure	31	7	0.005	18	20	0.664
Pulmonary capillary wedge pressure	2	1	0.888	0	3	0.078
Esophageal Doppler probe	5	2	0.335	3	4	0.683
No. (%) vasopressin	31 (36.0)	37 (72.5)	<0.001	—	—	
No. (%) dobutamine	9 (10.5)	10 (19.6)	0.134	7 (10.1)	12 (17.6)	0.204
No. (%) corticosteroids	46 (53.5)	36 (70.6)	0.048	40 (58.0)	42 (61.8)	0.651
No. (%) drotrecogin alfa (activated)	19 (22.1)	16 (31.3)	0.229	10 (14.5)	25 (36.7)	0.003
No. (%) renal replacement therapy	16 (18.6)	12 (23.5)	0.490	12 (17.4)	16 (23.5)	0.373
Blood glucose (mg/dL)	145.4 ± 36.0	152.7 ± 47.2	0.310	146.5 ± 45.1	149.7 ± 35.4	0.645

^aTotal intravenous fluid administration in the six-hour time window prior to initiation of vasopressors.

significantly higher 28-day mortality rate than vasopressor support with norepinephrine alone ($p < 0.001$). The median duration of intensive care (9 days; IQR 6–16 days vs. 11 days, IQR 6–22 days; $p = 0.310$) and hospital length of stay (20 days; IQR 6–30 days vs. 19 days, IQR 11–39 days; $p = 0.356$) was not statistically different in patients receiving norepinephrine alone vs. norepinephrine plus vasopressin, respectively.

Figure 2 displays the norepinephrine dose and duration of infusion when vasopressin was added for management of shock. The median dose of norepinephrine when vasopressin was added was 0.3 mcg/kg/min (IQR 0.16–0.56

mcg/kg/min; mean ± SD 0.39 ± 0.28 mcg/kg/min), and the median time on norepinephrine before vasopressin was initiated was 8 h (IQR 3.75–19.5 h; mean ± SD 27.5 ± 52.8 h). There was no statistical correlation between the dose and time on norepinephrine when vasopressin was initiated (Spearman coefficient -0.119 ; $p = 0.339$). The median dose of norepinephrine when vasopressin was added for hemodynamic support did not differ between survivors and nonsurvivors (0.23 mcg/kg/min; IQR 0.14–0.53 mcg/kg/min vs. 0.38 mcg/kg/min; IQR 0.25–0.57 mcg/kg/min; $p = 0.138$). Similarly, the median amount of time patients were managed with norepinephrine

TABLE 3. MULTIVARIABLE ANALYSIS OF INDEPENDENT RISK FACTORS FOR 28-DAY MORTALITY

	Adjusted odds ratio	95% CI	P value
Norepinephrine plus vasopressin administration	13.96	6.47, 30.08	0.001
Lack of goal-directed volume resuscitation	15.82	6.16, 40.61	0.003
Increasing APACHE II score, per point	1.14	1.07, 1.21	0.033
Inappropriate initial antimicrobial therapy	8.95	2.93, 27.33	0.050

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval.

Covariates not included in table had p value ≥ 0.05 . These were corticosteroid administration, patient type (medical or surgical), mechanical ventilation, amount of intravenous fluid administered six hours prior to initiation of vasopressors, use of dobutamine, and administration of drotrecogin alfa (activated). Hosmer-Lemeshow goodness of fit test $p = 0.47$.

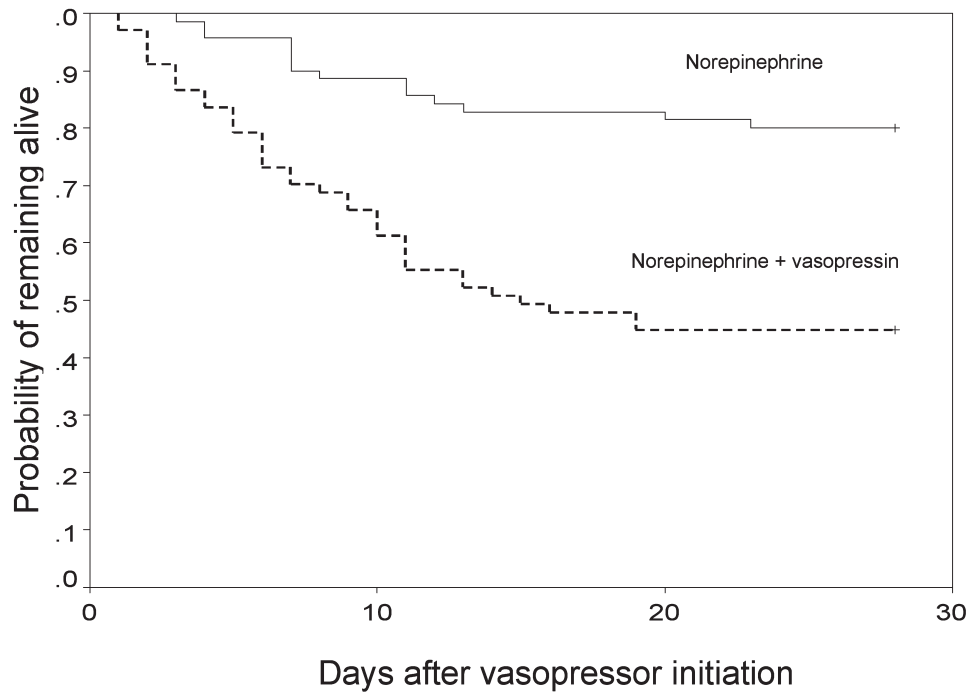


FIG. 1. Kaplan-Meier curves comparing probability of survival at day 28 for patients treated with norepinephrine alone and those receiving norepinephrine plus vasopressin ($p < 0.001$; log-rank test).

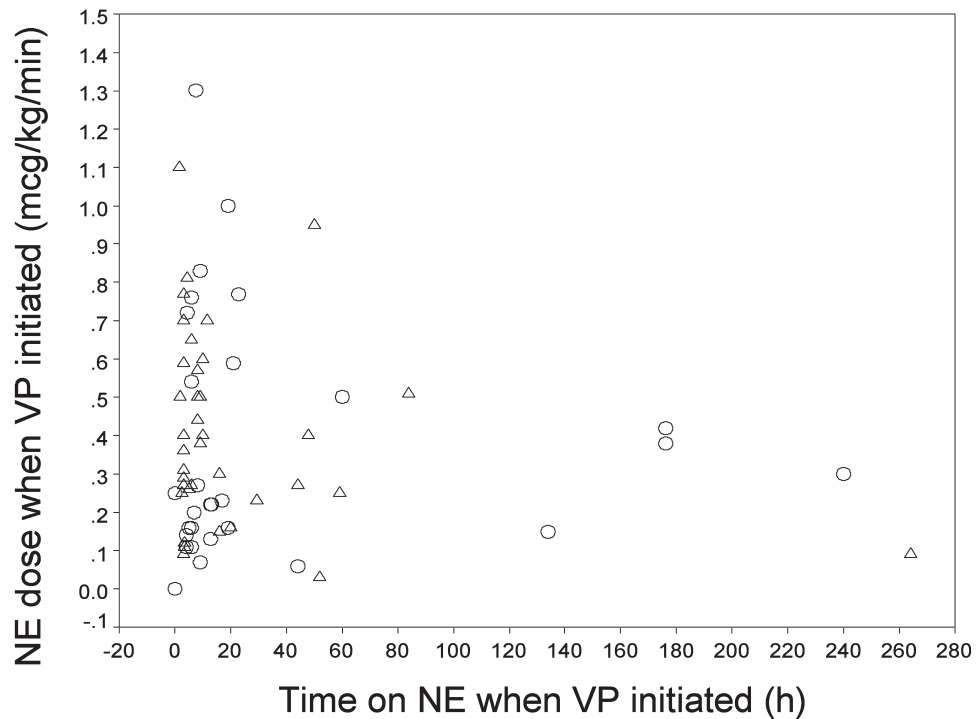


FIG. 2. Scatter plot of norepinephrine (NE) dose and infusion duration when vasopressin (VP) was initiated. Open triangles represent nonsurvivors and open circles survivors at day 28 after initiation of vasopressors. (Spearman coefficient -0.119 ; $p = 0.339$).

before vasopressin was initiated did not differ between survivors and nonsurvivors (9 h; IQR 6–21 h vs. 8 h; IQR 3–16 h; $p = 0.204$). The overall duration of norepinephrine infusion for survivors and nonsurvivors was not statistically different (4.8 ± 4.1 vs. 5.1 ± 2.8 days; $p = 0.681$). Conversely, patients who received vasopressin had statistically longer durations of norepinephrine infusion than those who did not (5.7 ± 4.0 vs. 4.2 ± 3.2 days; $p = 0.024$).

The addition of vasopressin to norepinephrine did not result in better cardiovascular or renal function when evaluated by SOFA scores over a 14-day period (Fig. 3). The mean cardiovascular SOFA scores representing the norepinephrine dose requirement were statistically higher in patients managed with the combination of norepinephrine and vasopressin on days 2, 3, 5, and 7 of vasopressor therapy than in those treated with norepinephrine alone. There were no observed differences in kidney function over 14 days when comparing renal SOFA scores for patients who received vasopressin with those who did not.

A subgroup analysis of 28-day survivors and nonsurvivors was performed comparing baseline characteristics and process-of-care variables in patients treated with both norepinephrine and vasopressin ($n = 68$). Significant differences in baseline characteristics between survivors and nonsurvivors included age (51.9 ± 18.3 years vs. 63.6 ± 15.5 years; $p = 0.006$), APACHE II score (25.2 ± 4.1 vs. $28.6 \pm$

6.6 ; $p = 0.014$), and having a positive blood culture (19.4% vs. 43.2%; $p = 0.036$). Significant differences in process-of-care variables between survivors and nonsurvivors included the use of goal-directed fluid administration during the initial phase of resuscitation (54.8% vs. 18.9%; $p = 0.002$) and the administration of corticosteroids (48.4% vs. 73.0%; $p = 0.038$).

DISCUSSION

Our study found patients with septic shock who were initially volume resuscitated without goal-directed invasive hemodynamic monitoring and those who received inappropriate initial antimicrobial therapy to be at higher risk of death by 28 days. This study also substantiated our previous finding that vasopressin in doses up to 0.04 units/min administered in combination with norepinephrine for hemodynamic support is an independent predictor of 28-day mortality.

Previous studies have shown that vasopressin may have beneficial short-term, organ-sparing effects in patients with septic shock. However, because of the lack of clinical outcome data, vasopressin has been recommended for use only in patients who are volume-refractory and require norepinephrine in doses exceeding 0.5 mcg/kg/min [9,20]. As a result of numerous investigations that have found vasopressin to have catecholamine-sparing ef-

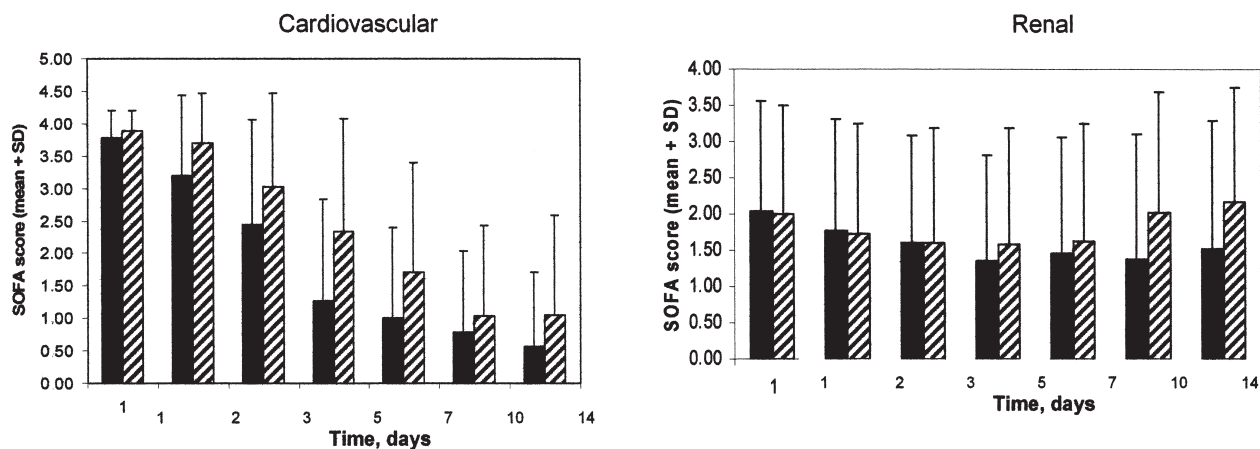


FIG. 3. Mean SOFA scores for cardiovascular and renal organ systems in patients receiving norepinephrine alone (solid bars) and norepinephrine plus vasopressin (striped bars). Difference between mean scores was significant for cardiovascular system on days 2, 3, 5, and 7 ($p < 0.05$).

fects [19,20,29], administration of this agent to patients requiring low-dose norepinephrine has been reported [22] and tested at many medical centers. The best example of the catecholamine-sparing effect was demonstrated in a randomized, double-blind study conducted by Patel et al. [21], in which patients requiring norepinephrine for septic shock were randomized to additional norepinephrine or vasopressin in doses up to 0.08 units/min. Four hours after the additional vasopressors were added, the norepinephrine dose was significantly lower than the baseline value in patients randomized to vasopressin, with no statistically significant change observed in the norepinephrine-only group. Similar dose-reducing effects have been observed when vasopressin is added to dopamine infusions [22]. Interestingly, the opposite effect was seen in our study in that patients who received vasopressin plus norepinephrine had statistically higher mean cardiovascular SOFA scores and thus a higher norepinephrine dose requirement over the first seven days of vasopressor therapy. Another potential benefit of the addition of vasopressin to norepinephrine is the increases in glomerular filtration and urine output as a result of selective constriction of the glomerular efferent arteriole when the drug is administered to patients with acute renal failure and septic shock [30]. This effect has been observed clinically in a number of trials; however, there are no data to support this result beyond the first 24 h of vasopressin infusion [18,19,21,29,31]. Again, we found no difference in renal function, as measured by SOFA scores, over the course of 14 days in patients who received vasopressin and those who did not.

This is the second study that has associated vasopressin with negative clinical outcomes. We previously found vasopressin to be an independent predictor of in-hospital death in a cohort of patients who received drotrecogin alfa (activated) [23]. The explanation for this finding may be related to end-organ ischemia induced by vasopressin, manifested most obviously by ischemic skin lesions [32–34]. Low-dose vasopressin administration also has been associated with increased splanchnic hypoperfusion [35–37] and a lower cardiac index when added to norepinephrine [19,29]. These reports

suggest taking a more cautionary stance to the use of vasopressin in septic shock until the results of large randomized clinical trials examining its value become available.

Our investigation has several important limitations. First, it was performed in a single hospital, and the results may not be generalizable to other treatment settings. Second, there were no defined criteria for the addition of vasopressin to norepinephrine, partly because of the lack of conclusive studies indicating which patients may benefit. Third, we did not measure pre-treatment vasopressin concentrations or determine which patients had vasopressin deficiency. Most patients received vasopressin within 48 h of presenting with septic shock and beginning the norepinephrine infusion (Fig. 2), suggesting that most of the vasopressin infusions were begun prior to overt vasopressin deficiency [13]. Fourth, patients receiving norepinephrine plus vasopressin appeared to have a greater severity of illness, more organ derangements, and a greater likelihood of receiving drotrecogin alfa (activated). Although we cannot discount the possibility that these baseline differences accounted for the greater mortality rate in this group, we applied two methods to control for potential variance. In both the logistic regression and bipartite graph-matched analyses, patients who received vasopressin in combination with norepinephrine had a statistically higher mortality rate than those who did not. Therefore, the administration of vasopressin was associated with a higher mortality rate independent of baseline comorbidities included in the statistical models. Finally, we did not evaluate the role of other potential therapies, hemodynamic status, or sequential organ dysfunction that could interact specifically with vasopressin to influence clinical outcomes. One example of this is the adequacy of initial volume resuscitation. However, our subgroup analysis evaluating only the patients receiving vasopressin found no differences in initial resuscitation volumes between survivors and nonsurvivors, making this an unlikely explanation for the excess mortality associated with vasopressin administration.

In summary, our study found an association between the use of vasopressin for refractory septic shock and 28-day mortality. Prospective

studies are needed to determine the role of vasopressin as a treatment for septic shock. In view of its mechanism of action, there is the possibility that vasopressin contributed directly to this excess mortality. Therefore, clinicians should be cautious about using vasopressin in patients with volume-refractory and norepinephrine-dependent septic shock. Further recommendations regarding the use of vasopressin await the results of large randomized trials.

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