

The Interaction of Vasopressin and Corticosteroids in Septic Shock: A Pilot Randomized Controlled Trial*

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Objectives: Vasopressin and corticosteroids are both commonly used adjunctive therapies in septic shock. Retrospective analyses have suggested that there may be an interaction between these drugs, with higher circulating vasopressin levels and improved outcomes in patients treated with both vasopressin and corticosteroids. We aimed to test for an interaction between vasopressin and corticosteroids in septic shock.

Design: Prospective open-label randomized controlled pilot trial.

Setting: Four adult ICUs in London teaching hospitals.

Patients: Sixty-one adult patients who had septic shock.

Interventions: Initial vasopressin IV infusion titrated up to 0.06 U/min and then IV hydrocortisone (50 mg 6 hourly) or placebo. Plasma vasopressin levels were measured at 6–12 and 24–36 hours after hydrocortisone/placebo administration.

Measurements and Main Results: Thirty-one patients were allocated to vasopressin + hydrocortisone and 30 patients to vasopressin + placebo. The hydrocortisone group required a shorter duration of vasopressin therapy (3.1 d; 95% CI, 1.1–5.1; shorter in hydrocortisone group) and required a lower total dose of vasopressin (ratio, 0.47; 95% CI, 0.32–0.71) compared with the placebo group. Plasma vasopressin levels were not higher in the hydrocortisone group compared with the placebo group (64 pmol/L difference at 6- to 12-hour time point; 95% CI, –32 to 160 pmol/L). Early vasopressin use was well tolerated with only one serious adverse event possibly related to study drug administration reported. There were no differences in mortality rates (23% 28-day mortality in both groups) or organ failure assessments between the two treatment groups.

Conclusions: Hydrocortisone spared vasopressin requirements, reduced duration, and reduced dose, when used together in the treatment of septic shock, but it did not alter plasma vasopressin levels. Further trials are needed to assess the clinical effectiveness of vasopressin as the initial vasopressor therapy with or without corticosteroids. (*Crit Care Med* 2014; 42:1325–1333)

Key Words: adrenal cortex hormones; drug interactions; intensive care; multiple organ failure; sepsis; vasopressins

Catecholamines remain the primary vasopressors used to treat hypotension during septic shock after IV fluid resuscitation (1). Vasopressin has been proposed as an adjunctive therapy in septic shock and has been shown to increase blood pressure and reduce catecholamine requirements (2, 3). Despite some small studies suggesting a beneficial physiological effect on organ function, in particular renal function (4, 5), a large randomized controlled trial of vasopressin versus norepinephrine (Vasopressin and Septic Shock Trial, VASST) did not provide evidence of a difference in survival in the whole septic shock population (35.4% and 39.3% 28-day mortality, respectively; difference, -3.9% ; 95% CI, -10.7 to 2.9) (6).

However, there were some interesting subgroup results from this trial. First, in the *a priori* defined stratum of less severe shock (defined as patients requiring < 15 $\mu\text{g}/\text{min}$ of norepinephrine at baseline), there was a reduced mortality in the vasopressin group compared with the norepinephrine group (26.5% vs 35.7% 28-day mortality; difference, -9.2% ; 95% CI, -18.5 to 0.1) (6). In contrast, in the more severe shock stratum (≥ 15 $\mu\text{g}/\text{min}$ of norepinephrine at baseline), there was no difference in mortality between the groups (44.0% and 42.5%, respectively; difference, 1.5% ; 95% CI, -8.2 to 11.2). Further post hoc subgroup analysis suggested that vasopressin may be more effective at preventing deterioration in renal function, rather than reversing established acute kidney failure (7).

Another interesting finding in VASST was that there was evidence of an interaction between vasopressin and corticosteroid treatment (8). The combination of vasopressin and steroids led to a lower mortality compared with norepinephrine plus steroids (35.9% vs 44.7%, respectively; difference, -8.8% ; 95% CI, -16.7 to -0.9). In contrast, patients who were treated with vasopressin and did not receive corticosteroids had an increased mortality compared with patients who received norepinephrine and no corticosteroids (33.7% vs 21.3%; difference, 12.3% ; 95% CI, -0.2 to 24.9). Interestingly, patients who received corticosteroids and vasopressin had higher levels of circulating vasopressin compared with patients treated with vasopressin alone. Similar findings were observed in other retrospective analyses where plasma vasopressin levels were higher in patients on concomitant hydrocortisone (9) and also survival rates were higher in patients treated with concomitant vasopressin and hydrocortisone (10).

However, these subgroup analyses must be interpreted cautiously as many are retrospective, and even though the severity of shock strata analysis in VASST was predefined, the original hypothesis was that vasopressin would be more beneficial in the more severe stratum. The earlier use of vasopressin in septic shock and its interaction with corticosteroids needs further investigation in randomized controlled trials.

We undertook a pilot trial to prospectively test our primary hypothesis that there was an interaction between vasopressin and corticosteroids and secondarily to test the feasibility of vasopressin use as initial vasopressor therapy in septic shock (<http://www.controlled-trials.com/ISRCTN66727957>).

MATERIALS AND METHODS

This open-label randomized placebo-controlled parallel-group trial was conducted between October 2010 and March 2012. Recruitment was initially from the three mixed medical-surgical adult ICUs within Imperial College Healthcare NHS Trust (based at Charing Cross, Hammersmith, and St Mary's Hospitals). In addition, patients were recruited at Guy's and St Thomas' NHS Foundation Trust adult ICU from December 2011 to February 2012. Independent research ethics committee approval was obtained (10/H0604/35). In view of the emergency nature of the trial, a waiver of initial consent was granted. Patients could be enrolled into the trial without upfront consent, but then, consent was obtained from the patient or a personal or professional legal representative as soon as practically possible. In cases where a legal representative gave consent, retrospective consent was sought once the patient regained capacity.

Patients

The inclusion criteria were adult patients (≥ 16 yr) who had sepsis (2/4 systemic inflammatory response criteria due to known or suspected infection) (11) and who required vasopressors despite adequate IV fluid resuscitation. Exclusion criteria were patients who had received a previous continuous infusion of vasopressors during this hospital admission, an ongoing requirement for systemic steroid treatment (i.e., known adrenal insufficiency or regular systemic steroid therapy within the last 3 mo), end-stage renal failure, known mesenteric ischemia, Raynaud's phenomenon, systemic sclerosis or other vasospastic disease, ongoing treatment for an acute coronary syndrome, death anticipated within 24 hours or if there was a treatment limitation within place, known pregnancy, enrollment in another interventional trial that might interact with the study drugs, or hypersensitivity to any of the study drugs.

Intervention and Treatment Allocation

Enrollment, randomization, and data collection were via an online system (InForm; Oracle Corp, Redwood Shores, CA). Patients were assigned to one of two treatment groups (vasopressin and hydrocortisone or vasopressin and placebo) on a 1:1 basis with variable block randomization with two block sizes (six and four) using computer-generated random number stratified by center. The allocation sequence was prepared by an independent statistician in the Imperial Clinical Trials Unit, and it was concealed from all investigators and treating clinicians.

All patients were allocated to receive vasopressin (titrated up to 0.06 U/min) as the initial vasopressor infusion via a central venous catheter, titrated to maintain the target mean arterial pressure (MAP). A 20-unit ampoule of vasopressin (1 mL) was mixed with 49 mL 0.9% saline by the ICU bedside nurse and started at 2 mL/hr (0.013 U/min) and titrated as required to achieve the MAP target. The protocol recommended a MAP of 65 – 75 mm Hg, but this could be altered by the treating physician if clinically indicated. Once the maximum infusion rate of vasopressin was reached (0.06 U/min), patients received either

hydrocortisone phosphate (50 mg) or placebo (0.5 mL 0.9% saline) according to treatment allocation. The hydrocortisone/placebo was administered as a 50 mg IV bolus 6 hourly for 5 days, 12 hourly for 3 days, and then once daily for 3 days, as previously reported (12). It could be weaned quicker than this if the shock had already resolved. If the patient was still hypotensive after the first dose of hydrocortisone/placebo, then additional open-label catecholamine vasopressors could be administered. As the patient recovered, these additional catecholamine vasopressors were weaned first and only once they were weaned off was the vasopressin weaned, that is, vasopressin was the first vasopressor infusion to start and the last to be stopped. All other treatment was at physician discretion based on the Surviving Sepsis Campaign guidelines in place at the time (13).

Patients could present and be recruited from any part of the hospital prior to ICU admission. Although the aim was to use vasopressin as the initial vasopressor, study drugs could not be stored in multiple locations within the hospital. Therefore, in an emergency, patients could be resuscitated using “normal” clinically prescribed vasopressors. In this situation, the patient had to be enrolled into the trial within 6 hours of commencing the vasopressor infusion. As the trial vasopressin infusion was titrated up as detailed above, the initial vasopressor infusion was weaned off as quickly as possible to maximize the vasopressin infusion rate.

Data and Sample Collection

Clinical information was recorded daily while in the ICU, and the patient was followed-up to obtain day 28 and hospital discharge status. Plasma samples for vasopressin measurement were collected once the vasopressin infusion rate was at 0.06 U/min (T0) before hydrocortisone/placebo administration if possible, 6–12 hours (T1) and 24–36 hours (T2) after the first dose of hydrocortisone/placebo was administered, and then again on day 7 if still in ICU (T3). Blood was collected into chilled EDTA tubes on ice, spun, and separated immediately and the plasma stored at -80°C until analysis. Vasopressin measurement was carried out blinded to all clinical information using a radioimmunoassay (14).

Statistics

The primary outcome was the difference in plasma vasopressin concentration between treatment groups. Based on data from the VASST study (8), to detect a 33 pmol/L difference in vasopressin levels at 6–12 hours post corticosteroid administration, assuming a SD of 45 pmol/L with a significance level of 0.05 and 80% power, 30 patients were required in each treatment group.

The difference in plasma vasopressin levels between treatment groups at T1 and T2 was analyzed on an “as treated” basis (vasopressin-corticosteroid interaction analysis). For the unadjusted analysis, the difference in mean levels at T1 is reported with a 95% CI. Adjusted analysis was carried out using regression models, with random effects incorporated to allow vasopressin levels at T1 and T2 to be jointly modeled. The secondary outcomes (clinical analyses) were analyzed on an intention-to-treat basis and include difference in vasopressin requirements between treatment groups, 28-day, ICU, and

hospital mortality rates, the onset of new organ failure, and organ failure-free days in the first 28 days.

The Sequential Organ Failure Assessment (SOFA) score (15) was used to define organ failure (score of 3 or 4 for each component) except renal failure where the Acute Kidney Injury definition of stage 3 was used (16). Last observation carried forward was used to impute any missing values as it is likely that the data were not collected because no change was expected by the clinician. The 3.6% of the SOFA component scores were imputed in this way, and these imputed values were sense checked against the patient’s other daily scores. If normal baseline creatinine values were unknown, then these were estimated using the Modification of Diet in Renal Disease equation (17) (for three patients).

All randomized patients who received the study drugs are included in the baseline table and safety data analysis and allocated to treatment group according to intention-to-treat. Continuous variables are summarized using the median and interquartile range, and dichotomous and categorical variables are presented in terms of frequencies and percentages. R software version 2.15.2 (<http://www.r-project.org>; Vienna, Austria) was used for analysis (18).

RESULTS

In total, 330 patients were screened for inclusion of whom 63 were randomized. The specific reasons for exclusion are shown in **Figure 1**; 104 patients met defined exclusion criteria, 155 patients were outside the 6-hour window of their first episode of shock, and eight patients were excluded for other reasons. Two patients were excluded by the treating physician after randomization but before receiving any study drugs because they were discovered to meet specific exclusion criteria after initial assessment (suspected mesenteric ischemia and a requirement for high-dose steroid therapy).

Of the 31 patients allocated to vasopressin + hydrocortisone treatment, 23 patients required the maximum vasopressin infusion rate (0.06 U/min) and received hydrocortisone. Among the 30 patients in the vasopressin + placebo group, 27 patients required the maximum vasopressin infusion rate and received placebo. There were six patients in the hydrocortisone group who never received any norepinephrine and two patients in the placebo group. Five patients in the placebo arm were given rescue corticosteroids for the treatment of life-threatening hypotension and were considered as crossovers. No patients were lost to follow-up.

The baseline characteristics of the patients are shown in **Table 1**. In 18 patients (30%), vasopressin was started as the initial vasopressor infusion to treat the hypotension. In the other 43 patients, norepinephrine was the most commonly used vasopressor to initially stabilize the patient in the emergency setting before being weaned off and the median time to starting the trial vasopressin infusion was less than 4 hours from the diagnosis of shock.

Plasma vasopressin levels over the first 36 hours are shown in **Figure 2** for patients who were receiving 0.06 U/min at the time of sample collection (only four patients were still

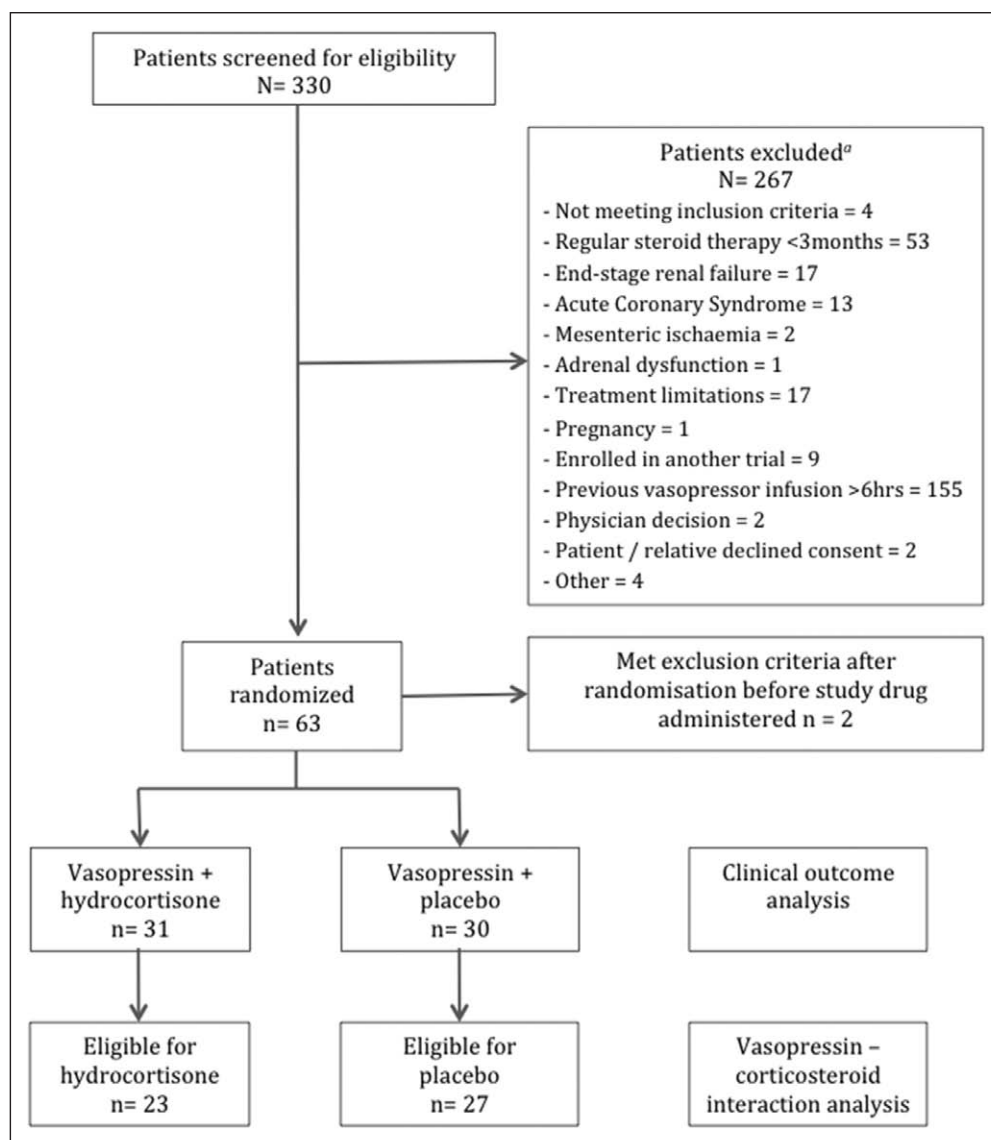


Figure 1. Patient flow diagram. All patients are included in the clinical outcome analysis, but only patients who required the maximum vasopressin infusion rate and then received the hydrocortisone or placebo were included in the vasopressin-corticosteroid interaction analysis. *Patients may have more than one exclusion criteria.

receiving a vasopressin infusion at day 7, and therefore, this time point has not been included). The median time from vasopressin infusion starting and first sample collection (T₀), once the maximum infusion rate was reached and before the second study drug was administered, was similar in both groups (145 min in the hydrocortisone group and 120 min in the placebo group). There was no convincing evidence of a difference in plasma vasopressin levels at any of the time points, and similar results were obtained reanalyzing the data as “intention-to-treat” and with crossovers excluded. As part of a sensitivity analysis, regression models were used to analyze these data with adjustment for baseline vasopressin levels and/or body weight. Adjusting the analyses for either or both of these variables did not change the result.

The MAP over time was similar in both treatment groups (Fig. 3). However, the patients in the hydrocortisone group were weaned off the vasopressin infusion more quickly than those in

the placebo group. This resulted in a 3.1 day (95% CI, 1.1–5.1 d; $p = 0.001$) shorter duration of vasopressin infusion (Fig. 4A) in the hydrocortisone group and a halving of the total dose (ratio, 0.47; 95% CI, 0.32–0.71; $p = 0.001$) of vasopressin required compared with the placebo group (Fig. 4B). The duration and doses of additional norepinephrine infusion rates are shown in Supplement Figures 1 and 2 (Supplemental Digital Content 1, <http://links.lww.com/CCM/A840>). The duration of additional norepinephrine infusion was 2.0 days (95% CI, –7.0 to 0.0 d; $p = 0.015$) shorter in the hydrocortisone group compared with the placebo group. There was no difference in IV fluid administration, total fluid balance, or lactate clearance between treatment groups (Supplement Figs. 3 and 4, Supplemental Digital Content 1, <http://links.lww.com/CCM/A840>).

There was no difference in mortality rates, onset of new organ dysfunction, or organ failure-free days between the two treatment groups (Table 2). In total, there were 14 adverse events reported, of which four were defined as serious adverse events. Only one serious adverse event was assessed

by the treating physician as possibly related to the study drugs (extension of a preexisting recent ischemic cerebral infarct). Of the five minor adverse events (potentially related), three were for cool/mottled peripheries, one rise in serum lactate, and one rise in troponin.

DISCUSSION

In this randomized controlled trial of vasopressin and corticosteroids compared with vasopressin and placebo, there was evidence of a clinical interaction between vasopressin and corticosteroids. The vasopressin requirements of patients randomized to receive corticosteroids were halved, but there was no difference in plasma vasopressin levels.

Vasopressin has consistently been shown to act as a vasoconstrictor in septic shock (3–5, 9, 19–22). However, despite its ability to increase blood pressure and to reduce norepinephrine requirements, vasopressin is often used in refractory shock as a

TABLE 1. Demographics and Baseline Characteristics of Patients

Variable	Vasopressin + Hydrocortisone	Vasopressin + Placebo
Age (yr)	61 (54, 68)	60 (48, 76)
Male sex (%)	18 (58)	18 (60)
Weight (kg)	72 (60, 82)	77 (65, 85)
Body mass index (kg/m ²) ^a	25 (23, 29)	26 (24, 32)
Caucasian ethnicity (%)	20 (65)	26 (87)
Recent surgical history (%)	12 (39)	6 (20)
Acute Physiology and Chronic Health Evaluation II score	19 (14, 22)	20 (17, 25)
Preexisting conditions (%)		
Ischemic heart disease	2 (6)	1 (3)
Severe chronic obstructive pulmonary disease	2 (6)	2 (7)
Chronic renal failure	1 (3)	3 (10)
Cirrhosis	2 (6)	3 (10)
Cancer	9 (29)	3 (10)
Immunocompromised	3 (10)	1 (3)
Diabetes	3 (10)	3 (10)
Organ failure (%) ^b		
Respiratory	14 (45)	19 (63)
Renal	5 (16)	6 (20)
Liver	2 (6)	0 (0)
Hematological	3 (10)	1 (3)
Neurological ^a	3 (10)	3 (10)
Physiological variables		
Mean arterial pressure (mm Hg) ^a	72 (63, 80)	66 (60, 74)
Heart rate (beats/min)	105 (84, 125)	106 (92, 124)
Central venous pressure (mm Hg) ^a	14 (9, 17)	10 (8, 16)
Lactate (mmol/L) ^a	2.1 (1.4, 5.0)	1.8 (1.3, 2.7)
Pao ₂ /Fio ₂ (Torr)	225 (146, 344)	152 (90, 228)
(kPa)	30 (19, 46)	20 (12, 30)
Creatinine (μmol/L)	85 (66, 129)	97 (54, 199)
Bilirubin (μmol/L)	12 (10, 32)	16 (8, 32)
Platelets (× 10 ⁹ /L)	162 (106, 218)	204 (136, 267)
Glasgow Coma Scale ^a	15 (15, 15)	15 (15, 15)
Mechanical ventilation (%)	23 (74)	25 (83)
Renal replacement therapy (%)	2 (6)	2 (7)
Volume of IV fluid in previous 4 hr (mL)	1,392 (1,064, 1,922)	1,240 (1,000, 1,760)
Patients receiving other vasopressor at randomization (%)	21 (68)	22 (73)
Time from onset of shock to randomization (hr)	3.5 (0.4, 5.3)	4.0 (1.4, 5.9)
Norepinephrine dose at randomization (μg/kg/min) ^c	0.16 (0.12, 0.25)	0.18 (0.08, 0.30)

(Continued)

TABLE 1. (Continued). Demographics and Baseline Characteristics of Patients

Variable	Vasopressin + Hydrocortisone	Vasopressin + Placebo
Source of infection (%)		
Lung	12 (39)	17 (57)
Abdomen	9 (29)	6 (20)
Soft tissue or catheter	2 (6)	3 (10)
Other	8 (26)	4 (13)

^aVariables with missing data are as follows: body mass index (hydrocortisone, 2); Glasgow Coma Scale (hydrocortisone, 1); mean arterial pressure (hydrocortisone, 1); central venous pressure (hydrocortisone, 11; placebo, 14); lactate (hydrocortisone, 1).
^bRenal failure is defined as having acute kidney injury stage 3 (urine output criteria omitted as data unavailable); other organ failures defined as having a Sequential Organ Failure Assessment score of ≥ 3 .
^cBased on patients receiving norepinephrine (hydrocortisone, 21; placebo, 22).
Median (lower quartile, upper quartile) for continuous variables and *n* (%) for dichotomous and categorical variables.

last resort. In the largest trial of vasopressin in septic shock to date (6), this was the hypothesis tested in the planned subgroup analysis, that is, that patients who had more severe shock would obtain the most benefit from vasopressin treatment. However, no benefit was seen in this group of patients, and if there was any benefit, it appeared to be confined to patients who had less severe shock (defined by norepinephrine requirements $< 15 \mu\text{g}/\text{min}$). Further exploratory work from the VASST study demonstrated improved outcomes (reduced progression of renal failure, reduced renal replacement therapy, and reduced mortality) in patients treated using vasopressin who only had mild forms of acute kidney injury at inclusion (“Risk” category according to Risk of renal dysfunction, Injury to the kidney, Failure of

kidney function, Loss of kidney function and End-stage kidney disease criteria) (7). In contrast, there was no difference in outcomes in patients who had already sustained more severe kidney injury before receiving vasopressin. However, it remains to be tested in prospective trials if vasopressin improves outcome compared with norepinephrine if used as initial vasopressor therapy. The 2012 Surviving Sepsis Campaign guidelines do not recommend vasopressin as the single initial vasopressor for treatment of sepsis-induced hypotension (23).

This study demonstrates that it is feasible to use vasopressin as first-line therapy for treatment of septic shock. Although the logistics of a clinical trial in an emergency situation prevented all patients receiving vasopressin as the very initial vasopressor, 30% of patients did receive it as initial vasopressor infusion and half of all patients received vasopressin within 4 hours of the onset of shock. Furthermore, 18% of patients did not require the maximum vasopressin infusion rate ($0.06 \text{ U}/\text{min}$) to maintain blood pressure, and eight patients (13%) received no catecholamines at any time, demonstrating that it is feasible to use vasopressin early and to avoid additional exogenous catecholamine infusions in some septic shock cases. In view

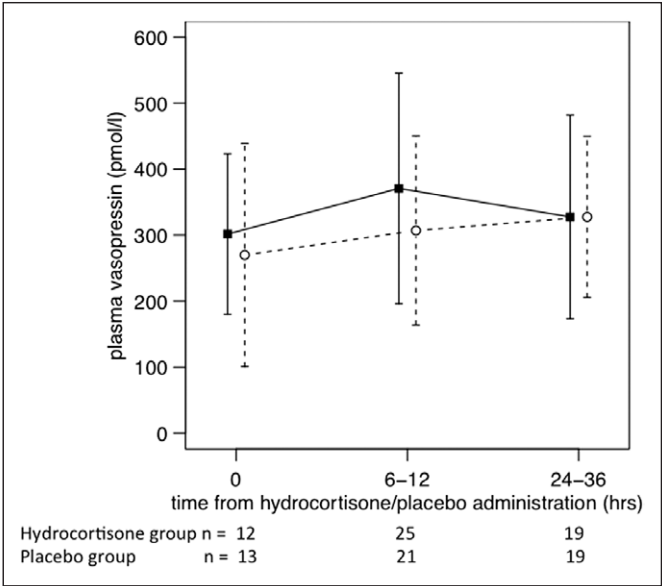


Figure 2. Plasma vasopressin levels over time. Black squares and solid line are vasopressin and hydrocortisone; open circles and dashed line are vasopressin and placebo. Symbols show mean and the vertical lines indicate ± 1 sd. Difference in vasopressin levels at the 6- to 12-hour time point was $64 \text{ pmol}/\text{L}$ (95% CI, -32 to $160 \text{ pmol}/\text{L}$). The mean (± 1 sd) in the hydrocortisone and placebo groups, respectively, at each time point are T0 $302 (\pm 122)$ vs $270 (\pm 169) \text{ pmol}/\text{L}$, $p = 0.59$; T1 $371 (\pm 175)$ vs $307 (143) \text{ pmol}/\text{L}$, $p = 0.18$; T2 $328 (\pm 154)$ vs $327 (\pm 122) \text{ pmol}/\text{L}$, $p = 1.00$.

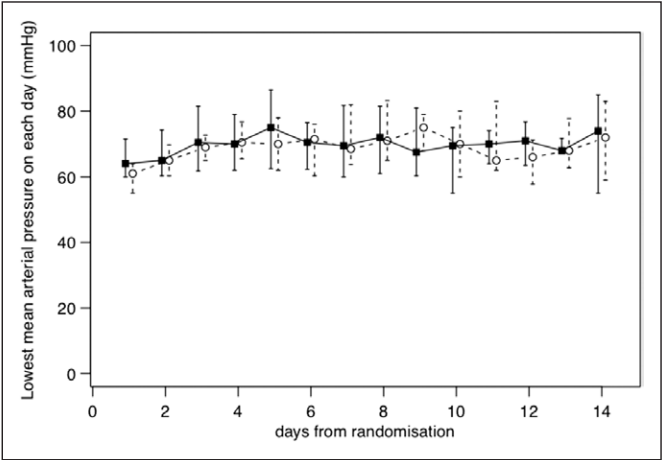


Figure 3. Lowest mean arterial pressure (MAP) recorded on each day. Black squares and solid lines are median MAP for vasopressin and hydrocortisone; open circles and dashed line are median MAP for vasopressin and placebo. Vertical lines indicate the interquartile ranges.

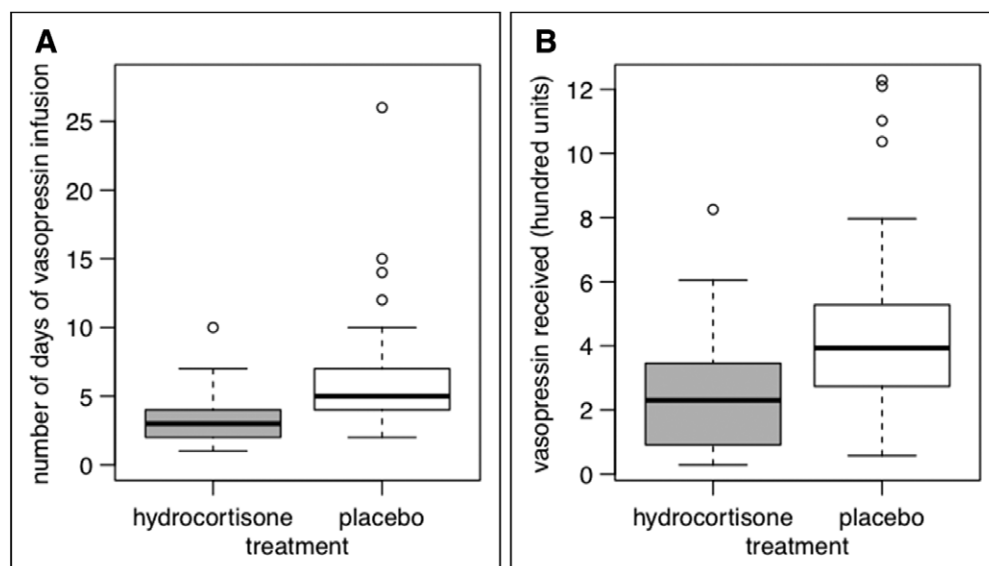


Figure 4. Duration of vasopressin infusion (**A**) and total dose of vasopressin infused (**B**) in the hydrocortisone and placebo groups. In both comparisons, $p = 0.001$ using a Mann-Whitney test. Line = median, box = interquartile range, whiskers = extremes of the data ($\times 1.5$ the interquartile range), and circles = very extreme outliers.

of the concern about adverse effects of catecholamines, this is an important clinical finding (24). The 23% mortality in this study compares favorably to local historical mortality rates (28% 28-day mortality in 2009–2010) and is similar to the 24% 28-day mortality rate in the placebo group of a recent septic shock trial (25). However, as all patients in this trial received early vasopressin infusions, no comparison of effectiveness to catecholamines can be made.

As well as acting as a pilot study for a larger double-blind controlled trial, the primary objective of this study was to test for an interaction between vasopressin and corticosteroids. Both vasopressin and corticosteroids are commonly used as adjuncts to catecholamines in septic shock, and there are complex interactions between the hypothalamic-pituitary-adrenal axis and the hypothalamic-posterior pituitary-vasopressin axis. Vasopressin binds to V3 receptors located in the anterior pituitary and may increase adrenocorticotrophin hormone production and secretion (26) and may also directly stimulate adrenal glucocorticoid production (27). Norepinephrine is known to inhibit the antidiuretic effect of vasopressin in the kidney but requires cortisol (28). Similarly corticosteroids have been reported to increase vasopressin messenger RNA (29), but other studies have found that corticosteroids do not change vasopressin levels (30) and others have suggested that corticosteroids may actually delay vasopressin release (31) and suppress vasopressin gene expression (32). In two previous trials of vasopressin therapy, circulating levels of vasopressin have been found to be higher in patients given corticosteroids (8, 9). Although these results both came from controlled trials, the use of corticosteroids was not controlled. Furthermore, it should be noted that circulating vasopressin levels did not differ in patients not administered exogenous vasopressin, suggesting there was little or no effect on vasopressin secretion (8). Therefore, we undertook this study to randomize patients prospectively to receive exogenous vasopressin and either

corticosteroids or placebo treatment and then compare plasma vasopressin levels between the two groups. We found no difference in plasma vasopressin levels at any time point, and although the analysis was complicated by a few crossovers, the results were similar when the analyses were carried out as intention-to-treat, as treated, crossovers excluded, or adjusting for baseline levels.

However, despite no difference in measured plasma vasopressin levels, there was a marked difference in vasopressin infusion requirements between the two groups. Patients randomized to vasopressin and corticosteroids required a vasopressin infusion for three fewer days and also

received less than half the total vasopressin dose compared with patients randomized to vasopressin and placebo. This is the first time that the vasopressin-sparing effect of corticosteroids has been demonstrated in clinical studies. As plasma vasopressin levels did not change, the mechanism behind this effect remains uncertain. Corticosteroid treatment may have improved vascular responsiveness. In animal models of sepsis, cytokine-mediated down-regulation of vasopressin (V1a) receptors has been demonstrated (33) and this hyporesponsiveness was reversed by high-dose glucocorticoid treatment (34). These findings are consistent with the effects seen in this study. The clinical implications of this corticosteroid effect remain uncertain. There was also a reduced requirement for additional norepinephrine in the hydrocortisone group in this study. Previous trials of corticosteroids in septic shock have demonstrated more rapid shock resolution (35), but this did not improve outcome (12). Furthermore, recent studies have suggested that cortisol levels are elevated in septic shock, and there is an impairment of cortisol metabolism (36).

It should be noted that the dose of vasopressin infusion used in this trial (0.06 U/min) is higher than that recommended in the Surviving Sepsis Guidelines (23). The optimum dose of vasopressin in septic shock remains unknown, although the dose of 0.067 U/min was more effective than 0.033 U/min at restoring cardiovascular function in a previous randomized controlled trial (9). In that trial, as well as this current trial, circulating vasopressin levels were significantly higher than physiological levels seen in shock states. As vasopressin stimulates both V1a and V2 receptors, it is possible that a selective V1a agonist might produce the same vasopressor effect and avoid the potential unwanted effect of V2 stimulation, such as release of von Willebrand factor (37).

Limitations of this trial should be considered. It was prospectively powered to detect a difference in plasma vasopressin

TABLE 2. Clinical Outcomes Comparing Hydrocortisone and Placebo Groups

Variable	Vasopressin + Hydrocortisone	Vasopressin + Placebo	Difference ^a (95% CI)
28-day mortality (%)	7/31 (23)	7/30 (23)	-0.01 (-0.22, 0.20)
ICU mortality (%)	7/31 (23)	8/30 (27)	-0.04 (-0.26, 0.18)
Hospital mortality (%)	8/31 (26)	9/30 (30)	-0.04 (-0.27, 0.18)
Survivors without new organ dysfunction (%)			
Respiration	7/17 (41)	4/11 (36)	0.05 (-0.32, 0.42)
Hematological	17/28 (61)	21/29 (72)	-0.12 (-0.36, 0.13)
Liver	21/29 (72)	20/30 (67)	0.06 (-0.18, 0.29)
Renal	16/26 (62)	14/24 (58)	0.03 (-0.24, 0.30)
Organ failure-free days (excluding survivors without organ failure) ^b			
Cardiovascular	24 (12, 26)	20 (6, 24)	4 (-2, 12)
Respiration	20 (5, 24)	18 (8, 23)	2 (-12, 8)
Hematological	11 (2, 23)	13 (4, 23)	-2 (-21, 16)
Liver	6 (2, 16)	17 (4, 24)	-10 (-22, 6)
Renal	9 (2, 23)	15 (9, 22)	-6 (-18, 7)

^aDifference in proportions: (vasopressin + hydrocortisone) – (vasopressin + placebo).

^bMedian (lower quartile, upper quartile) and 95% CI of difference between medians calculated using bootstrap methods.

levels at a single time point after reaching maximum rate of vasopressin infusion and corticosteroid administration. However, not all patients reached the maximum vasopressin infusion rate even though additional existing catecholamines were weaned off quickly, thus reducing the sample size and potential power in the analysis of plasma levels. However, this slight reduction in power was somewhat offset by additional information from another vasopressin measurement at a second time point (T2), as well as further analyses examining changes from baseline between the two groups. There were also five crossovers from the placebo group to the corticosteroid group due to refractory shock. However, the results remained unchanged independent of how these crossovers were handled in the analyses, supporting the robustness of the results. A trial of 61 patients has limited power to detect differences in clinical outcomes measures, and we saw no difference in mortality rates or organ failure assessments between the two groups. This contrasts to a larger previous study that demonstrated a greater improvement in liver failure and cardiovascular failure in patients randomized to hydrocortisone treatment (35), but this may simply reflect that our trial was not powered to detect differences in clinical outcomes. Also the adverse events appear typical of other recent vasopressor therapy trials in septic shock (38, 39). Thus, it would seem appropriate to use a similar trial design in a subsequent larger randomized controlled trial.

CONCLUSIONS

In this randomized controlled trial of hydrocortisone versus placebo added to initial vasopressor therapy for the treatment of septic shock, there was a significant clinical interaction between vasopressin and corticosteroids. Hydrocortisone therapy

reduced vasopressin requirements but did not alter plasma vasopressin levels. It is feasible to use vasopressin as initial vasopressor therapy in septic shock. A multicenter double-blind randomized controlled trial of vasopressin compared with norepinephrine as initial vasopressor therapy in septic shock, including an interaction with corticosteroids, is now underway (<http://www.controlled-trials.com/ISRCTN20769191>). The results of this and other trials are needed before early use of vasopressin can be recommended in routine clinical practice.

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