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Effect of Very Low-Dose Hydrocortisone on Shock Reversal in Patients With Septic Shock

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Objectives: In patients with septic shock, hydrocortisone 200–400 mg/d has been shown to reverse shock compared with placebo. Lower doses of hydrocortisone have not previously been studied, and there are no previous studies comparing two different doses of hydrocortisone. At our institution, some clinicians routinely prescribe doses less than 200 mg/d. This study aims to compare the effect of lower doses of hydrocortisone to standard doses on shock reversal and adverse events in septic shock.

Design: Retrospective cohort study.

Setting: Single-center medical ICU.

Subjects: Patients who received hydrocortisone for septic shock.

Interventions: Electronic chart review.

Measurements and Main Results: Patients were divided into low-dose hydrocortisone (75–150 mg/d) and standard-dose hydrocortisone (200–400 mg/d) cohorts based on initial prescribed hydrocortisone dose. Rates of shock reversal and adverse events in the two cohorts were compared. Two-hundred thirteen patients were included–41 in low-dose and 172 in standard-dose cohorts. Baseline characteristics including initial vasopressor requirement and Sequential Organ Failure Assessment scores were similar. Average rates of change in vasopressor needs, conditional hazard rate for vasopressor withdrawal, and cumulative probability for vasopressor withdrawal were all quantitatively similar for low-dose and standard-dose hydrocortisone. Insulin requirement (particularly in those with diabetes mellitus), blood glucose in those with diabetes mellitus, and frequency of secondary infections seemed to be lower in the low-dose hydrocortisone cohort. Mortality and other secondary outcomes were similar.

Conclusions: In septic shock, hydrocortisone dosed 75–150 mg/d appears to reverse shock as effectively 200–400 mg/d and may cause a lower frequency of adverse events.

Key Words: corticosteroid; glucocorticoid; hydrocortisone; sepsis; septic shock

Septic shock is a life-threatening condition, with mortality rates that can exceed 30% (1, 2) Corticosteroids are commonly used as an adjunctive treatment in septic shock, and their use in this context has been the subject of intensive investigation in dozens of clinical trials. In the vast majority of randomized studies, no change in overall mortality is observed with the use of corticosteroids, although recent meta-analyses suggest a possible very small reduction in risk of death (3, 4). However, faster resolution of shock is consistently observed with hydrocortisone dosed 200–400 mg/d compared with placebo (5–8). In addition, some studies noted increases in adverse events related to corticosteroids such as hypernatremia, hyperglycemia, gastrointestinal bleeding, and secondary infections (3).

Although corticosteroids clearly promote faster resolution of shock than placebo, the optimal dosage needed for hemodynamic support in septic shock is not known. Recent trials have studied predominantly hydrocortisone. The lowest initial dose of hydrocortisone for adults with septic shock studied in randomized trials is 200 mg/d. However, several early studies of patients undergoing major surgery estimate daily cortisol production under this stress at approximately 75–150 mg/d, rarely exceeding 200 mg/d (9). Thus, even in patients with low endogenous cortisol production the effective dose of hydrocortisone in septic shock might be lower than 200 mg/d. Current guidelines make weakly graded recommendations suggesting use of hydrocortisone for shock reversal in septic shock with moderate to high vasopressor requirements despite adequate volume resuscitation. One guideline recommends initial dose of 200 mg/d, while another suggests no more than 400 mg/d but does not specify the lowest acceptable dose. Recommendations vary for duration and tapering (2, 10).

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To date, no trials exist that directly compare different doses of hydrocortisone in septic shock, and the effect of doses less than 200 mg/d on shock reversal and other outcomes has not been studied. At our institution, some clinicians routinely prescribe hydrocortisone at starting doses less than 200 mg/d due to clinical equipoise on the lowest effective dose and concerns regarding side effects related to treatment. Hydrocortisone is tapered based on clinical judgment. This retrospective study seeks to compare the effect on shock reversal of "low-dose" (75–150 mg/d) versus "standard-dose" (200–400 mg/d) hydrocortisone in patients with septic shock.

MATERIALS AND METHODS

The study was approved by the institutional review board. We conducted a retrospective study of patients admitted to the ICU at a tertiary care academic center who were prescribed hydrocortisone for septic shock. Inclusion criteria were age greater than or equal to 18 years; inpatient admission to the ICU between June 2014 and October 2017; prescription of IV hydrocortisone 75–400 mg/d for at least 24 hours; a diagnosis of sepsis with prescription of systemic antibiotics for documented or suspected infection at time of hydrocortisone initiation; shock as defined by hypotension requiring administration of IV vasopressors at a dose of 0.07 to 0.7 μg/kg/min norepinephrine equivalents at time of hydrocortisone initiation (using conversion factors from the The Angiotensin II for the treatment of high-output Shock-3 (ATHOS-3) trial [11]); and Sequential Organ Failure Assessment (SOFA) score of at least 6. The lower vasopressor threshold (0.07 μg/kg/min) was chosen in order to include patients with at least moderate vasopressor doses (per published guidelines [10]). The upper threshold (0.7 μg/kg/min) was chosen to minimize selection bias since no patients with such high initial vasopressor needs were assigned to low-dose hydrocortisone (refractory shock is commonly defined as doses exceeding 0.3–0.5 μg/kg/min [12–15]). Exclusion criteria were major trauma; major bleeding; ST-elevation myocardial infarction; mechanical circulatory support (as this would confound assessment of vasopressor dosage); concurrent administration of corticosteroids other than hydrocortisone; and administration of vasopressors other than those for which conversion factors are defined (11).

Pharmacy records were used to identify all prescriptions of hydrocortisone. Charts were then manually reviewed for inclusion and exclusion criteria and collection of clinical data. Baseline data were collected at time of the first dose of hydrocortisone. In order to assess shock reversal, vasopressor dose and blood pressure were documented in 4-hour intervals until all vasopressors were discontinued or up to 96 hours. Hydrocortisone dose, blood glucose measurements, insulin doses, and serum sodium concentration were recorded for 96 hours or until death/hospital discharge. Patients were grouped into "low-dose hydrocortisone" and "standard-dose hydrocortisone" cohorts defined by the initial dose prescribed, regardless of how dosages were subsequently altered by clinicians. To obtain a clear separation between low-dose and standard-dose hydrocortisone, low-dose was defined as 75–150 mg/d and standard-dose defined as 200–400 mg/d; patients prescribed doses outside this range were excluded. Low-dose hydrocortisone was compared with standard-dose hydrocortisone rather than placebo because the superiority of standard-dose hydrocortisone over placebo in reversing shock (our primary outcome) has already been extensively demonstrated in placebo-controlled trials.

The primary outcome was shock reversal assessed by rate of change in vasopressor requirement and by rate of withdrawal of vasopressors. Secondary outcomes were in-hospital mortality, length of stay, mean blood glucose, daily insulin requirements, frequency of hypernatremia, frequency of gastrointestinal bleeding, and frequency of nosocomial infections (occurring after hydrocortisone initiation, using Center for Disease Control surveillance definitions). A small number of missing baseline values of lactate and bilirubin concentration were imputed using stochastic regression imputation. Continuous variables were compared using Student *t* test or Wilcoxon rank-sum test, and categorical variables were compared using chi-square test or Fisher exact test, as appropriate. Lactate and previous pressor hours (prior to starting hydrocortisone) were log-transformed for regression analysis, due to skewness. Average rate of change of vasopressor dosage was compared in bivariate analysis using *t* test and in multivariate analysis using linear regression. The outcome of complete vasopressor withdrawal was evaluated using both traditional Cox proportional hazards with noninformative death censoring (conditional hazard rate) and by nonparametric comparison of cumulative probability functions, treating death on vasopressors as a competing risk (16). To assess for the possibility of selection bias, propensity score analysis was performed for the primary outcome. Matched cohorts were created using nearest-neighbor propensity score matching in a 1:2 ratio for low-dose to standard-dose cohorts. Weighted regressions were also performed using inverse propensity score weighting. Instrumental variable regression (IVR) using two-stage least squares regression was also performed to assess for unobserved confounders, using the attending ICU physician as a proxy for hydrocortisone dose assignment. In this analysis, patients randomly assigned to a physician based at admission date and time are handled equally based on that physician's prescribing habits, regardless of the actual dose prescribed. This results in removal of unobserved selection bias not captured by recorded baseline characteristics. All *p* values reported are two-tailed. All statistical analysis was done using Stata/IC, release 14 (StataCorp, College Station, TX).

RESULTS

Three-hundred eighty-nine patients prescribed IV hydrocortisone for septic shock were identified. Of these, 213 satisfied all inclusion and exclusion criteria and form the basis for this study. Reasons for exclusion were use of excluded pressor (16%), major trauma (3%), major hemorrhage (10%), ST-elevation myocardial infarction (3%), mechanical circulatory support (0.6%), hydrocortisone not administered or treatment course less than 24 hours (6%), hydrocortisone dose out of specified range (0.5%), and initial vasopressor dose out of specified range (11%).

Of the 213 included patients, 41 (19%) were treated with low-dose hydrocortisone and 172 (81%) with standard-dose hydrocortisone. Most baseline characteristics, including SOFA score, serum lactate, and initial vasopressor dose, were similar in the low-dose and standard-dose cohorts. Blood pressure was similar

in both cohorts over the 96-hour follow-up. All patients were treated with intermittent bolus dosing of hydrocortisone. Actual daily dose of hydrocortisone administered was tapered over time in both groups but remained significantly lower in the low-dose cohort throughout the follow-up period (**Table 1**).

Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/CCX/A154; legend: mean vasopressor dose over time) suggests that vasopressor dose decreases nonlinearly with time, in a decelerating fashion. The observed average rate of change in vasopressor requirement was virtually identical for low-dose and standard-dose cohorts (**Table 2**). In multivariate analysis higher age, SOFA score, and lactate levels predicted slower decrease in vasopressor dose. Hydrocortisone dose, previous vasopressor hours, and starting vasopressor dose (at time of hydrocortisone initiation) were not predictive of rate of change (Table 2). A test for interaction between initial vasopressor dose and hydrocortisone dose was negative, indicating similar rate of change in vasopressor requirement for low-dose and standard-dose hydrocortisone, regardless of initial pressor dose.

In the survival analysis using a Cox proportional hazards model with noninformative censoring at death, low-dose and standard-dose hydrocortisone had very similar rates of vasopressor withdrawal, contingent upon survival (cause-specific hazard ratio for low-dose = 1.09 ± 0.24 [SE]; $p = 0.7$) (**Table 3**). In multivariate analysis, higher age, SOFA score, and initial vasopressor dose predicted lower rate of vasopressor withdrawal, whereas hydrocortisone dose, lactate level, and hours prior to initiating hydrocortisone did not (Table 3). A test for interaction between initial vasopressor dose and hydrocortisone dose was negative, indicating that the similar effect of low-dose and standard-dose hydrocortisone dose on vasopressor withdrawal does not depend on initial vasopressor requirement. Cumulative probability functions for complete vasopressor withdrawal were estimated for low-dose and standard-dose cohorts, treating death as a competing risk. The cumulative probability of vasopressor withdrawal in the two cohorts was similar ($p = 0.9$). **Figure 1** shows that the curves for the two cohorts are essentially superimposed, demonstrating that the cumulative probability over time of complete vasopressor withdrawal for low-dose and standard-dose hydrocortisone was similar after accounting for death as a competing event.

In the propensity score matched analysis, ninety-one patients were included (32 low-dose, 59 standard-dose). Baseline characteristics were nearly identical in the matched cohorts (**Supplementary Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCX/A155), as were the distributions of propensity scores. The average rate of change of vasopressor dose and the rate of complete vasopressor withdrawal were no different in the low-dose and standard-dose hydrocortisone cohorts, with point estimates similar to those from the primary analysis (Table 2). Propensity score weighted regressions were performed on the 175 patients in the region of common propensity score support (36 low-dose, 139 standard-dose). Baseline characteristics were well-matched after weighting, as in the matched-cohort analysis. Weighted regressions yielded results quantitatively similar to those from the propensity score-matched cohorts. There were no differences observed between low-dose and standard-dose hydrocortisone in the rate of vasopressor dose decrease or the rate of complete vasopressor withdrawal.

The first stage of IVR showed that the instrument was a strong predictor of hydrocortisone dose (F-statistic, 26.85; $p < 0.0001$). In the second stage, the effect of hydrocortisone dose on rate of vasopressor decrease was estimated using predicted hydrocortisone dose rather than actual dose. The estimated effect of hydrocortisone dose was nearly zero (mean difference –0.000058 μg/kg/min per hour for low-dose hydrocortisone, with negative value indicating faster decrease in dose; $p = 0.99$). When the outcome (shock reversal) was assessed only in the subset of patients who received standard-dose hydrocortisone, outcomes were very similar for the attending physicians who had prescribed low-dose hydrocortisone compared with the remainder of physicians who always prescribed standard-dose hydrocortisone. This verifies that the instrumental variable does not introduce additional confounding due to differences in care provided by attending physicians beyond different propensities to use low-dose hydrocortisone.

The daily insulin requirement in the low-dose cohort appeared to be lower than for standard-dose hydrocortisone (12.3 vs 17.9 U/d; $p = 0.10$). In the subgroup of patients with diabetes mellitus, low-dose hydrocortisone was associated with a markedly lower insulin requirement (26 vs 48 U/d; $p = 0.007$), and slightly lower average blood glucose (185 vs 205 mg/dL; $p = 0.04$). The rate of nosocomial infection was numerically lower in the low-dose cohort (10% vs 17% for standard-dose) but did not reach statistical significance ($p = 0.2$). Other secondary outcomes were similar in low-dose and standard-dose cohorts (**Table 4**).

In sensitivity analyses, shock reversal rates were estimated with inclusion of patients requiring greater than 0.7 μg/kg/min norepinephrine equivalents. An additional 16 patients were included (all received standard-dose hydrocortisone). In multivariate analysis, the average rate of vasopressor decrease and rate of complete vasopressor withdrawal were nearly identical between the hydrocortisone dose cohorts when these 16 patients were included. The point estimates obtained are essentially unchanged from the primary analysis results shown in Table 2 and Table 3. When shock reversal was assessed only in the 113 patients (53%) with microbiologically proven infection, results were again similar to the primary analysis, and did not differ by hydrocortisone dose.

DISCUSSION

This study demonstrates that in septic shock, "low-dose" hydrocortisone doses of 75–150 mg/d result in quantitatively similar rates of shock reversal as compared with standard doses of 200–400 mg/d, and may result in lower blood glucose and insulin requirement during treatment. To our knowledge, this is the first study to date evaluating the effect of hydrocortisone at doses less than 200 mg/d in septic shock.

Shock reversal was chosen as the primary outcome because this is the most consistently demonstrated benefit of hydrocortisone in placebo-controlled trials. In this study, within the range of doses studied, hydrocortisone dosage did not influence rates of shock reversal as measured by rate of change of vasopressor dose and rate of vasopressor withdrawal (Tables 2–3 and Fig. 1). This

TABLE 1. Patient Characteristics at Time of First Dose of Hydrocortisone[a]

Variable	Low-Dose Hydrocortisone ($n = 41$)	Standard-Dose Hydrocortisone ($n = 172$)	p
Age (yr)	66 ± 14	60 ± 15	0.01
Weight (kg)	78.2 (66.5–100.2)	89 (71–107.9)	0.08
Prior hours on pressors	27 (11–58)	16.5 (6–29.7)	0.009
Total days of hydrocortisone treatment	4 (3–5)	5 (3–7)	0.01
IV fluids in previous 24 hr (mL)	3,183 (1,504–4,295)	3,592 (2,026–5,164)	0.057
Left ventricular ejection fraction	63 ± 11	58 ± 14	0.03
WBC (1,000/mm^3)	13.3 ± 3.1	13.4 ± 3.1	0.9
Sequential Organ Failure Assessment score	16 ± 13	17 ± 13	0.6
Creatinine (mg/dL)	2.2 ± 1.6	2.1 ± 1.3	0.7
Sodium (mmol/L)	138 ± 7.4	138 ± 6.7	0.9
Platelets (1,000/mm^3)	171 ± 142	174 ± 124	0.9
Lactate (mmol/L)	2.5 (1.6–4.4)	2.5 (1.4–4.3)	0.6
Bilirubin (mg/dL)	1.5 (0.6–3.9)	1.2 (0.6–3.7)	0.7
Glasgow Coma Scale	9 (6–12)	8 (6–11)	0.7
Temperature (°C)	37 ± 1.2	37.1 ± 1.2	0.5
Pao_2/Fio_2	225 (169–321)	195 (145–296)	0.21
Initial pressor dose (μg/kg/min)	0.26 ± 0.15	0.30 ± 0.16	0.12
Hydrocortisone dose administered days 1–4			
Day 1	115 ± 28	215 ± 37	< 0.001
Day 2	109 ± 41	190 ± 46	< 0.001
Day 3	88 ± 54	145 ± 76	< 0.001
Day 4	51 ± 45	108 ± 83	< 0.001
Mean arterial pressure days 1–4 (mm Hg)	75 ± 11	74 ± 10	0.16
Male sex	24 (59%)	86 (50%)	0.33
Corticosteroids in last 30 d	7 (17%)	31 (18%)	1.00
Mechanical ventilation	27 (66%)	136 (79%)	0.073
Cirrhosis	13 (32%)	32 (19%)	0.065
End-stage renal disease	2 (5%)	12 (7%)	1.00
Diabetes mellitus	15 (37%)	37 (22%)	0.04
Source of infection			
Lung	21 (51%)	102 (59%)	0.35
Urine	11 (27%)	24 (14%)	0.046
Abdominal	10 (24%)	39 (23%)	0.8
Other	21 (51%)	85 (49%)	0.8
Inappropriate antibiotics	4 (10%)	14 (8%)	0.8
Neutropenia	1 (2%)	9 (5%)	0.7
Immunosuppression	8 (20%)	34 (20%)	1.00

[a]At time of hydrocortisone administration.

All values are reported as mean ± SD, median (interquartile range), or n (%).

TABLE 2. Average Rate of Change of Pressor Requirement[a]

Analysis	Low-Dose Hydrocortisone	Standard-Dose Hydrocortisone	Mean Difference	*p*
Bivariate analysis				
Rate of change[b] (μg/kg/min per hour)	−0.0058 ± 0.0089	−0.0059 ± 0.0077	−0.0001	0.9
Bivariate propensity score matched analysis				
Rate of change[b] (μg/kg/min per hour)	−0.0063 ± 0.0094	−0.0063 ± 0.0072	< 0.0001	1.00
Predictor	Coefficient	SE	*p*	95% CI
Multivariate analysis				
Low-dose hydrocortisone	−0.0011	0.0013	0.4	−0.0038 to 0.0015
Age (per 10 yr)	0.00097	0.00035	0.006	0.0003–0.0017
Sequential Organ Failure Assessment score	0.00063	0.00018	< 0.001	0.00028–0.00097
Lactate[c]	0.0015	0.0007	0.04	0.0001–0.003
Initial pressor dose (per 0.1 μg/kg/min)	−0.00059	0.00036	0.10	−0.0013 to 0.0001
Prior hours on pressors[c]	0.00058	0.00045	0.2	−0.0003 to 0.0015
(Constant)	−0.021	0.004	< 0.001	−0.028 to −0.014

[a]Negative sign indicates decreasing pressor dose.
[b]Values from bivariate and propensity score matched analyses reported as mean ± SD.
[c]Lactate and prior hours on pressors were log-transformed.

TABLE 3. Hazard for Complete Vasopressor Withdrawal

Predictor	Hazard Ratio[a]	SE	*p*	95% CI
Bivariate analysis				
Low-dose hydrocortisone	1.09	0.24	0.70	0.70–1.68
Bivariate propensity score matched analysis				
Low-dose hydrocortisone	0.85	0.24	0.56	0.50–1.47
Multivariate analysis				
Low-dose hydrocortisone	1.02	0.23	0.92	0.66–1.60
Age (per 10 yr)	0.85	0.050	0.007	0.76–0.96
Sequential Organ Failure Assessment score	0.89	0.029	0.001	0.84–0.95
Lactate[b]	0.89	0.11	0.35	0.71–1.13
Initial pressor dose (per 0.1 μg/kg/min)	0.76	0.050	< 0.001	0.67–0.87
Prior hours on pressors[b]	0.95	0.065	0.5	0.83–1.09

[a]Cause-specific hazard ratio for weaning, conditional on survival.
[b]Lactate and prior hours on pressors were log-transformed.

result was consistent across a wide range of initial vasopressor dose (no demonstrable interaction between initial vasopressor dose and hydrocortisone dose). Sixteen patients requiring greater than 0.7 μg/kg/min norepinephrine equivalents were excluded in order to prevent inclusion of a group known from previous studies to have very high mortality (17) and to minimize selection bias. These 16 patients were all prescribed standard-dose hydrocortisone (likely reflecting unwillingness of physicians to prescribe hydrocortisone at a dose not tested in randomized trials for patients with this extreme degree of hypotension), and their inclusion would have increased the severity of illness in the standard dose cohort relative to the low-dose cohort. Nonetheless, due to the high cutoff chosen for exclusion, several patients were included in both cohorts who meet published definitions for refractory shock, and the results for the primary outcome are robust to inclusion of these 16 patients.

In contrast to hydrocortisone dose, our results showed that conventional predictors of severity of illness do influence rates of shock reversal. Age and SOFA score, which are known to predict mortality (18, 19), consistently predicted lower rates of

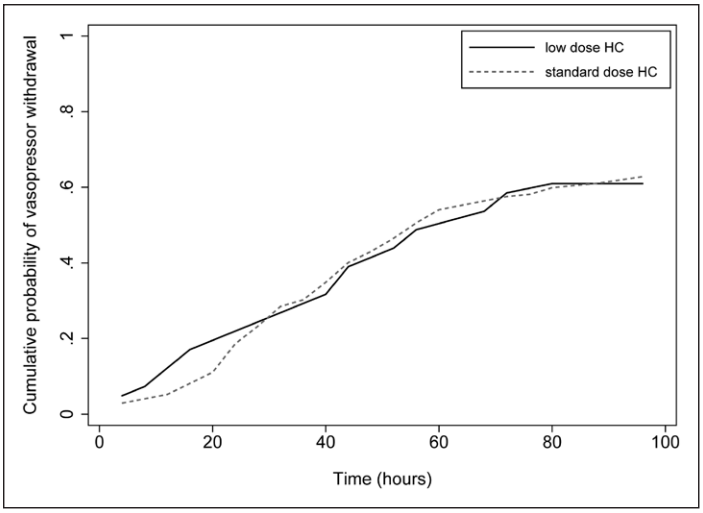

Figure 1. Cumulative probability of vasopressor withdrawal over time. HC = hydrocortisone.

shock reversal. For quantifying severity of illness, SOFA was chosen over other metrics due to its validation beyond the first 24 hours of ICU admission. Elevated serum lactate, also known to predict mortality, predicted slower decrease in vasopressor dose but not time-to-withdrawal. This discrepancy is likely the result of limited sample size and follow-up time. Since rate of change of vasopressor dose was independent of initial requirement, the observed effect of initial dose on rate of complete withdrawal is as expected.

In defining septic shock for inclusion criteria, we approximated the terms that were used in 1991 and subsequently widely implemented (20). In the most recent proposed definition, serum lactate is included (21). Lactate was omitted from inclusion criteria because existing clinical trials of hydrocortisone all used the older definitions of septic shock, and lactate level was unknown for some patients treated in our hospital. Nonetheless, it has been shown that patients who meet only the "old" definition of septic shock have a high risk of mortality despite a normal serum lactate level (1), and regressions models controlled for serum lactate.

In this study, the most notable difference in secondary outcomes was in insulin requirement. The point-estimate for insulin requirement was almost 50% higher with standard-dose hydrocortisone (p = 0.1), and nearly two-fold higher with standard-dose hydrocortisone in the subset of diabetic patients (p = 0.007). Blood glucose was also higher with standard-dose hydrocortisone in the subset with diabetes. Consistent with our results, metabolic derangements caused by hydrocortisone have been seen in several randomized studies of hydrocortisone versus placebo (3). There was also a signal suggesting lower rates of secondary nosocomial infection, which did not reach statistical significance, which may be in part to limited sample size. This observation is consistent with the results of some previous studies suggesting higher rates of secondary infection with standard-dose hydrocortisone versus placebo (5, 22). Other adverse events in our sample were not different.

The most important limitation of this study is its retrospective design. The possibility of unobserved selection bias cannot be ruled out. However, the low-dose and standard-dose cohorts were well-matched for baseline characteristics known to predict outcome in septic shock. Initial vasopressor dose at time of enrollment was also similarly distributed in the two groups. Furthermore, the (nil) effect of hydrocortisone dose was maintained in multivariate analysis, in propensity score analysis, and in IVR. Another limitation is that the study was conducted at a single center and had a modest sample size. Last, this study cannot assess the effect of hydrocortisone dose when administered in a continuous fashion, as was done in some randomized studies.

In conclusion, this is the first study to evaluate the effect of hydrocortisone doses less than 200 mg/d in septic shock. The results show that rates of shock reversal are similar to those

TABLE 4. Occurrence of Secondary Outcomes Was Assessed After the First Dose of Hydrocortisone

Outcome	Low-Dose Hydrocortisone	High-Dose Hydrocortisone	*p*
In-hospital mortality	18 (44%)	93 (54%)	0.24
Days to discharge (survivors)	10 (5–22)	11 (6–20)	0.6
New hypernatremia	9 (22%)	39 (23%)	1.00
Average blood glucose, day 1–4 (mg/dL)			
All patients	169 ± 57	168 ± 55	0.86
Patients with diabetes	185 ± 64	205 ± 61	0.04
Average insulin dose, days 1–4 (U/d)			
All patients	12 ± 26	18 ± 39	0.10
Patients with diabetes	26 ± 35	48 ± 54	0.007
Nosocomial infection	4 (10%)	30 (17%)	0.23
Gastrointestinal bleeding	1 (2%)	12 (7%)	0.5

All values are reported as mean ± SD, median (interquartile range), or *n* (%).

achieved with conventional doses, and may result in less metabolic derangement. Prospective randomized studies are needed to confirm these findings.

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