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Hydrocortisone Therapy for Patients with Septic Shock

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ABSTRACT

BACKGROUND

Hydrocortisone is widely used in patients with septic shock even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin.

METHODS

In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.

RESULTS

Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, $P=0.69$) or between those who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, $P=1.00$). At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died ($P=0.51$). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock.

CONCLUSIONS

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)

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Severe sepsis is a major cause of mortality and morbidity worldwide.[1,2] Septic shock, the most severe manifestation, occurs in 2 to 20% of inpatients.[3] The incidence of the condition has been rising,[4] and a death rate of 33 to 61% has been reported in the placebo groups of multicenter trials.[5-8]

The use of corticosteroids as an adjunctive therapy has been controversial for decades.[9] After the study by Schumer,[10] a short course of high-dose corticosteroids became accepted therapy. Subsequent studies, however, did not confirm a survival benefit with this regimen and suggested an increase in superinfection-related mortality.[11-13] Studies that have used lower doses of hydrocortisone (200 to 300 mg per day) for longer durations have reported earlier reversal of shock[14-18] and improved survival.[14,16] The prognostic importance of the response to corticotropin had been recognized in critical illness previously,[19,20] and the results in the hydrocortisone studies were particularly apparent in patients who did not have a response to a corticotropin test. Meta-analyses,[21,22] reviews,[20] and guidelines[23] have advocated the use of low-dose hydrocortisone in patients with septic shock. These recommendations were based primarily on a study of patients with septic shock who remained hypotensive after at least 1 hour of resuscitation with fluids and vasopressors.[16] In this study, a survival benefit was seen in patients with no response to corticotropin who received hydrocortisone and fludrocortisone. Our trial, called the Corticosteroid Therapy of Septic Shock (CORTICUS) study, evaluated the efficacy and safety of low-dose hydrocortisone therapy in a broad population of patients with septic shock — in particular, patients who had had a response to a corticotropin test, in whom a benefit was unproven.[9]

METHODS

STUDY DESIGN

In this multicenter, randomized, double-blind, placebo-controlled study, the protocol was approved by the ethics committee at each of the 52 participating intensive care units (ICUs). Patients were enrolled from March 2002 to November 2005, after providing written informed consent. In cases in which a patient lacked mental competency, consent was obtained either from a surrogate, the next of kin, or a legal representative (with retrospective consent obtained from patients who regained competency), according to national regulations. An independent data and safety monitoring board met after each of three interim analyses. At the end of the study, a clinical evaluation committee whose members were unaware of study-group assignments assessed the appropriateness of antiinfective treatments.

The authors designed the study, gathered and analyzed the data, and vouch for the completeness and accuracy of the data and the analysis. The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

PATIENTS

Patients who were 18 years of age or older and had been hospitalized in participating ICUs were prospectively enrolled in the study if they met all eligibility criteria. (For details, see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Inclusion criteria were clinical evidence of infection, evidence of a systemic response to infection, and the onset of shock within the previous 72 hours (as defined by a systolic blood pressure of <90 mm Hg despite adequate fluid replacement or a need for vasopressors for at least 1 hour) and hypoperfusion or organ dysfunction attributable to sepsis. Notable exclusion criteria included underlying disease with a poor prognosis, a life expectancy of less than 24 hours, immunosuppression, and treatment with long-term corticosteroids within the past 6 months or short-term corticosteroids within the past 4 weeks.

RANDOMIZATION

Randomization (in a 1:1 ratio) was stratified according to study center in blocks of four with the use of a computerized random-number generator list provided by a statistician who was not involved in the determination of eligibility, administration of a study drug, or an assessment of outcomes. In each center, the study drug (hydrocortisone or placebo) was sealed in sequentially numbered, identical boxes that contained the entire treatment for each patient to be administered sequentially. The sequence was concealed from the investigators. All patients, medical and nursing staff members, pharmacists, investigators,

and members of the monitoring board remained unaware of study-group assignments throughout the study period.

STUDY DRUGS

Hydrocortisone (Rotexmedica) was prepared in vials containing 100 mg of hydrocortisone hemisuccinate powder with ampules containing 2 ml of sterile water diluent; the vials were then coded and masked centrally (Klocke Verpackungs Service). Vials containing placebo were identical to those containing hydrocortisone. The study drugs were administered as a 50-mg intravenous bolus every 6 hours for 5 days, then tapered to 50 mg intravenously every 12 hours for days 6 to 8, 50 mg every 24 hours for days 9 to 11, and then stopped. A total of 29 doses were given. Evidence-based guidelines for the treatment of patients were encouraged.[24]

DEFINITIONS

Organ-system failure was defined for each of the six major organ systems as a Sequential Organ Failure Assessment (SOFA) score of 3 or 4 points (on a scale ranging from 0 to 4 for each organ system, for an aggregate score of 0 to 24, with higher scores indicating more severe organ dysfunction).[25] Reversal of shock was defined as the maintenance of a systolic blood pressure of at least 90 mm Hg without vasopressor support for at least 24 hours. Superinfection was defined as a new infection occurring 48 hours or more after the initiation of a study drug.[26] New sepsis was defined as a new septic episode with or without microbiologic confirmation. New septic shock was defined as a new episode of septic shock after reversal of the initial episode. The absence of a response to a corticotropin test was defined as an increase in the cortisol level of no more than 9 μg per deciliter (248 nmol per liter).[16]

DATA COLLECTION

Clinical Evaluation

The following data were recorded: general characteristics of the patients, including demographic data, diagnoses, and recent surgery; the severity of illness, as assessed by vital signs, the Simplified Acute Physiology Score (SAPS) II (on a scale from 0 to 163, with higher scores indicating more severe organ dysfunction),[27] and the SOFA score[25]; and interventions, including the type and doses of vasopressors, antibiotics, and adjunctive treatments such as corticosteroids and etomidate.

Laboratory Measures

Hematologic and chemical data, blood gas analyses, and cultures of blood and other specimens that were obtained from potential sites of infection were recorded. A short corticotropin test was performed with the use of blood samples taken immediately before and 60 minutes after an intravenous bolus of 0.25 mg of cosyntropin (Novartis or Alliance). After centrifugation, serum samples were stored at a temperature no higher than –20°C until assayed. To reduce heterogeneity in the determination of cortisol levels, all samples were measured blindly and serially before interim and final analyses in a central laboratory with the use of the Elecsys cortisol assay (Roche Diagnostics).

FOLLOW-UP

During the 28-day period after randomization, data were collected regarding vital signs, results from laboratory tests and cultures of specimens drawn from any new site of infection, and any major interventions that were performed. Rates of death at 28 days, in the ICU, in the hospital, and at 1 year after randomization were recorded.

END POINTS

The primary end point was the rate of death at 28 days in patients who did not have a response to corticotropin. Secondary end points were the rates of death at 28 days in patients who had a response to corticotropin and in all patients, the rates of death in the ICU and in the hospital, the rates of death at 1 year after randomization, a reversal of organ system failure (including shock), and the duration of the stay in the ICU and the hospital.

Safety was assessed by recording adverse events, particularly superinfection, gastrointestinal bleeding, hyperglycemia, hypernatremia, clinical muscular weakness, stroke, acute myocardial infarction, and peripheral ischemia. Methods to enhance the quality of measurements included holding biannual meetings of investigators, sending newsletters, and conducting random quality-assurance evaluations.

STATISTICAL ANALYSIS

A sample size of 800 patients (400 per group) was needed to achieve a statistical power of 80%

to detect an absolute decrease in mortality of 10% from an existing death rate of 50% in patients who did not have a response to corticotropin (40% of the total group). All analyses were performed according to a prespecified plan. The population was analyzed according to an intention-to-treat principle. The rate of death from all causes at 28 days was analyzed with the use of Fisher's exact test for differences between study groups. A maximum overall two-sided probability of a type I error of 5% was accepted. The test result was corrected for two interim analyses for efficacy. Splitting the alpha error function was performed according to the O'Brien–Fleming method ($P=0.0006$, $P=0.005$, and $P=0.047$ for the first, second, and final analysis, respectively).

The difference in the rate of death at 28 days between the two study groups was considered to have statistical significance if the stopping criteria of the interim analysis were met or the two-sided P value of the final analysis was less than 0.047. The differences between all other secondary efficacy variables were assumed to have statistical significance for P values of less than 0.05. Kaplan–Meier curves for cumulative survival during the 28-day observation period were constructed and compared with the use of the log-rank test. The median time until the reversal of septic shock was calculated with the use of Kaplan–Meier analysis. Adverse events were reported for the per-protocol population.

RESULTS

PATIENTS

Five hundred patients were enrolled in the study (Fig. 1). One patient in the hydrocortisone group was excluded because consent was withdrawn. Of the remaining 499 patients, all met the entry criteria, although 15 also fulfilled the exclusion criteria (8 patients in the hydrocortisone group and 7 in the placebo group) since 14 had received previous corticosteroid therapy and 1 had undergone previous cardiopulmonary resuscitation. Eighty-seven percent of patients in both the hydrocortisone group and the placebo group received at least 90% of the doses of a study drug.

Of 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group); 254 patients (50.9%) did have a response to corticotropin (118 in the hydrocortisone group and 136 in the placebo group). Results were unknown for eight patients in the hydrocortisone group and four in the placebo group (2.4%). Etomidate was used in 51 of 251 patients in the hydrocortisone group (20.3%) and in 45 of 248 patients in the placebo group (18.1%) before study entry and in 22 patients (8.8%) and 20 patients (8.1%), respectively, after study enrollment. Among the 96 patients who had received etomidate, 58 did not have a response to corticotropin (60.4%), as compared with 175 of 403 who did

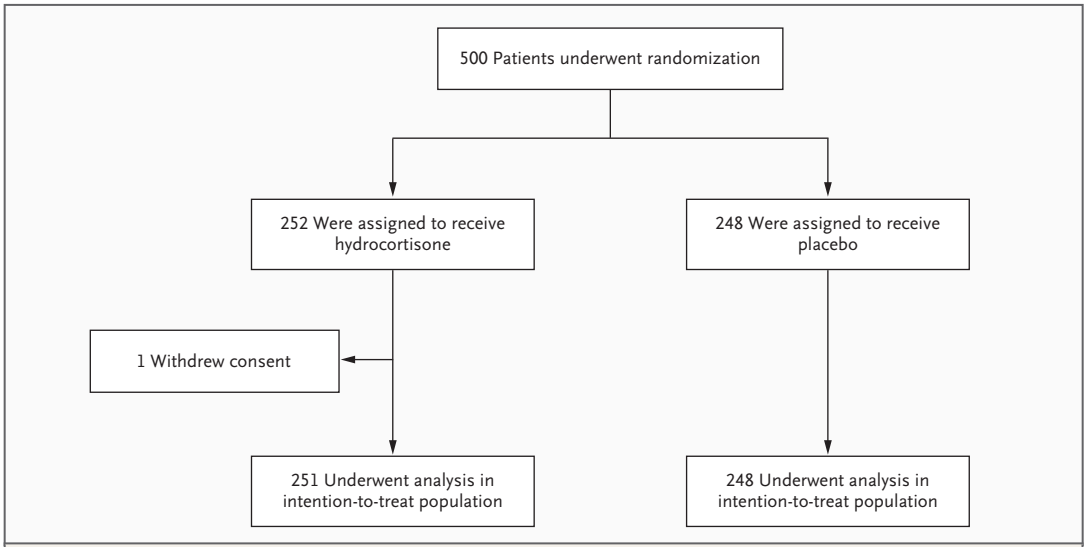

Figure 1. Enrollment and Outcomes.

not receive etomidate (43.4%, P=0.004). The median time between the last dose of etomidate and enrollment was 14 hours (range, 1 to 67).

At baseline, the two study groups were well balanced with regard to demographic characteristics (Table 1), clinical characteristics (Table 2), and the type and site of infection and infecting organisms (Table 2 of the Supplementary Appendix).

PRIMARY END POINTS

Mortality

There was no significant difference between the two study groups in the primary outcome, the rate of death at 28 days among patients who did not have a response to corticotropin. There were 49 deaths in 125 patients in the hydrocortisone group (39.2%; 95% confidence interval [CI], 30.5 to 47.9) and 39 deaths in 108 patients in the placebo group (36.1%; 95% CI, 26.9 to 45.3; P=0.69). Likewise, there was no significant difference in the rate of death at 28 days in patients who had a response to corticotropin. There were 34 deaths in 118 patients in the hydrocortisone group (28.8%; 95% CI, 20.6 to 37.0) and 39 deaths among 136 patients in the placebo group (28.7%; 95% CI, 21.1 to 36.3; P=1.00). Overall, there were 86 deaths in the hydrocortisone group (34.3%; 95% CI, 28.3 to 40.2) and 78 deaths in the placebo group (31.5%; 95% CI, 25.6 to 37.3; P=0.51).

No differences in mortality were seen between the study groups or between the corticotropin subgroups at any other time point (Fig. 2 and Table 3). Twenty-one post hoc analyses were performed to elucidate the reasons for the rates of death at 28 days in subgroups of patients. These analyses showed that among patients with a systolic blood pressure persisting at less than 90 mm Hg within 30 hours after study entry, 31 of 69 patients in the hydrocortisone group (44.9%)

Table 1. Demographic Characteristics of the Patients, According to Subgroup.*

Characteristic	No Response to Corticotropin		Response to Corticotropin		All Patients	
	Hydrocortisone (N=125)	Placebo (N=108)	Hydrocortisone (N=118)	Placebo (N=136)	Hydrocortisone (N=251)	Placebo (N=248)
Age — yr	63±13	63±15	62±14	64±16	63±14	63±15
Sex — no. (%)						
Male	85 (68)	69 (64)	76 (64)	95 (70)	166 (66)	166 (67)
Female	40 (32)	39 (36)	42 (36)	41 (30)	85 (34)	82 (33)
White race — %†	119 (95)	101 (94)	110 (93)	125 (92)	236 (94)	228 (92)
Previous disease — no./total no. (%)						
Hypertension	48 (38)	37 (34)	39 (33)	60/133 (45)	89 (35)	98/245 (40)
Coronary artery disease	20 (16)	26 (24)	17 (14)	21/133 (16)	37 (15)	47/245 (19)
Congestive heart failure	5 (4)	8 (7)	4 (3)	12/133 (9)	10 (4)	20/245 (8)
Neurologic	19 (15)	10 (9)	14 (12)	14/133 (11)	33 (13)	25/245 (10)
Chronic obstructive pulmonary disease	14 (11)	12 (11)	11 (9)	17/133 (13)	27 (11)	29/245 (12)
Other pulmonary disorder	6 (5)	12 (11)	17 (14)	12/133 (9)	23 (9)	24/245 (10)
Cancer	27 (22)	21 (19)	18 (15)	16/133 (12)	47 (19)	37/245 (15)
Diabetes	22 (18)	19 (18)	28 (24)	37/133 (28)	51 (20)	56/245 (23)
Liver	14 (11)	10 (9)	9 (8)	7/133 (5)	23 (9)	17/245 (7)
Chronic renal failure	12 (10)	11 (10)	10 (9)	10/133 (8)	22 (9)	21/245 (9)
Admission category — no./total no. (%)						
Medical	39 (31)	35/107 (33)	37/116 (32)	57/135 (42)	80/249 (32)	93/246 (38)
Emergency surgery	69 (55)	63/107 (59)	66/116 (57)	67/135 (50)	138/249 (55)	132/246 (54)
Elective surgery	17 (14)	9/107 (8)	13/116 (11)	11/135 (8)	31/249 (12)	21/246 (9)

* Plus–minus values are means ±SD.
† Race was reported by the investigators.

Table 2. Clinical Characteristics of the Patients at Baseline, According to Subgroup.*

Variable	No Response to Corticotropin				Response to Corticotropin				All Patients			
	No. of Patients	Hydrocortisone (N=125)	No. of Patients	Placebo (N=108)	No. of Patients	Hydrocortisone (N=118)	No. of Patients	Placebo (N=136)	No. of Patients	Hydrocortisone (N=251)	No. of Patients	Placebo (N=248)
Temperature — °C	124	37.7±1.6	108	37.9±1.6	116	38.0±1.4	135	38.1±1.3	248	37.9±1.5	247	38.0±1.4
Heart rate — bpm	124	121±24	108	119±23	115	116±29	136	117±26	247	119±26	248	118±25
Systolic blood pressure — mm Hg	124	92±22	108	97±25	116	94±24	136	95±29	248	94±23	248	95±27
SAPS II score†	125	50.7±17.8	108	49.0±16.3	117	47.9±18.0	136	48.4±16.9	250	49.5±17.8	248	48.6±16.7
SOFA score‡	125	11.0±3.4	108	10.7±3.4	118	10.3±3.4	136	10.5±2.9	251	10.6±3.4	248	10.6±3.2
Leukocytes — thousands/mm^3	121	15.8±11.2	106	13.8±9.8	114	14.3±8.1	133	15.4±9.8	243	14.9±9.8	243	14.7±9.8
Platelets — thousands/mm^3	121	205±131	106	200±150	114	218±140	132	203±119	243	212±135	242	202±133
Glucose — mg/dl	117	140±65	102	126±52	111	139±59	133	146±45	235	140±65	239	137±50
Arterial lactate — mmol/liter	102	4.6±4.0	94	4.0±3.9	94	3.1±3.0	114	4.1±4.0	202	3.9±3.6	212	4.1±4.1
Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen	107	159±89	94	161±72	99	162±82	119	149±73	214	162±89	216	154±73
Cortisol — μg/dl	125		108		118		136		243		244	
Before corticotropin		30±20		29±19		27±19		29±21		28±20		29±20
60 min after corticotropin		33±19		32±18		46±22		46±23		39±22		39±22
Response to corticotropin test		3±4		3±4		18±11		16±6		11±11		10±8
Receiving vasopressor or inotrope at baseline — no. (%)		125 (100)		108 (100)		117 (99)		131 (96)		249 (99)		243 (98)
Type of vasopressor§												
Norepinephrine — no. (%)		116 (93)		104 (96)		103 (87)		124 (91)		224 (89)		231 (93)
Maximum dose — μg/kg/min		0.5±0.5		0.5±0.5		0.4±0.7		0.4±0.5		0.5±0.6		0.4±0.5
Epinephrine — no. (%)		19 (15)		9 (8)		14 (12)		13 (10)		35 (14)		22 (9)
Maximum dose — μg/kg/min		0.8±1.6		0.2±0.1		0.3±0.4		1.4±3.3		0.6±1.2		0.9±2.6
Dopamine — no. (%)		10 (8)		9 (8)		16 (14)		19 (14)		27 (11)		29 (12)
Maximum dose — μg/kg/min		12.9±9.6		7.1±6.3		9.8±6.1		8.3±7.1		10.4±7.5		7.9±6.6

Ventilatory support at baseline												
Mechanical ventilation — no. (%)	125	113 (90)	108	99 (92)	118	108 (92)	134	110 (82)	251	228 (91)	246	212 (86)
Tidal volume — ml/kg	99	7.6±2.1	80	7.5±2.1	95	7.6±2.2	97	7.7±2.2	201	7.7±2.1	180	7.6±2.1
Fraction of inspired oxygen — %	117	67±25	104	64±25	106	60±24	125	63±24	231	64±25	232	63±24
Positive end-expiratory pressure — cm of water	108	8±4	92	8±3	99	9±4	114	9±4	215	9±4	209	9±4
Activated protein C — no. (%)¶	125	11 (9)	108	13 (12)	118	6 (5)	136	7 (5)	251	17 (7)	248	20 (8)
Antithrombin — no. (%)¶	125	24 (19)	108	17 (16)	118	15 (13)	136	19 (14)	251	40 (16)	248	36 (15)

* Plus–minus values are means ±SD. To convert the values for cortisol to nanomoles per liter, multiply by 27.59. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† The Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, with higher scores indicating more severe organ dysfunction.
‡ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating more severe organ dysfunction.
§ Five patients received vasopressin, four in the hydrocortisone group and one in the placebo group.
¶ Patients may have received these drugs after baseline.

and 32 of 57 patients in the placebo group (56.1%) had died, with an absolute difference in the hydrocortisone group of –11.2% (95% CI, –18.6 to 6.2; P=0.28); among those whose systolic blood pressure was measured at 90 mm Hg or more within 30 hours after study entry, 55 of 181 in the hydrocortisone group (30.4%) and 46 of 189 in the placebo group (24.3%) died, with an absolute difference in the hydrocortisone group of 6.1% (95% CI, –3.0 to 15.1; P=0.20). In post hoc analyses, the rates of death among the 384 patients who received a study drug within 12 hours after baseline were similar in the two groups: 73 of 198 patients in the hydrocortisone group (36.9%) and 58 of 186 patients in the placebo group (31.2%, P=0.28) (Table 3 of the Supplementary Appendix).

Post hoc analyses also revealed an increased rate of death at 28 days among patients who received etomidate before randomization in both groups (23 of 51 in the hydrocortisone group [45.1%] and 18 of 45 in the placebo group [40.0%]), as compared with patients who did not receive etomidate (63 of 200 in the hydrocortisone group [31.5%] and 60 of 203 in the placebo group [29.6%, P=0.03]).

REVERSAL OF SHOCK

The proportions of patients who underwent a reversal of shock were similar among patients who did not have a response to corticotropin: 95 of 125 in the hydrocortisone group (76.0%; 95% CI, 68.5 to 83.5) and 76 of 108 in the placebo group (70.4%; 95% CI, 61.8 to 79.0; P=0.41); among patients who had a response to corticotropin: 100 of 118 patients in the hydrocortisone group (84.7%; 95% CI, 78.3 to 91.2) and 104 of 136 in the placebo group (76.5%; 95% CI, 69.3 to 83.6; P=0.13); and among all patients: 200 of 251 in the hydrocortisone group (79.7%; 95% CI, 74.7 to 84.7) and 184 of 248 in the placebo group (74.2%; 95% CI, 68.7 to 79.6; P=0.18).

The duration of time until the reversal of shock was significantly shorter among patients receiving hydrocortisone for all patients (P<0.001), for those who had a response to corticotropin (P<0.001), and for those who did not have a response to corticotropin (P=0.06) (Fig. 3). The median time until reversal of shock was also shorter in the hydrocortisone group than in the placebo group: for all patients, 3.3 days (95% CI, 2.9 to 3.9) versus 5.8 days (95% CI, 5.2 to 6.9);

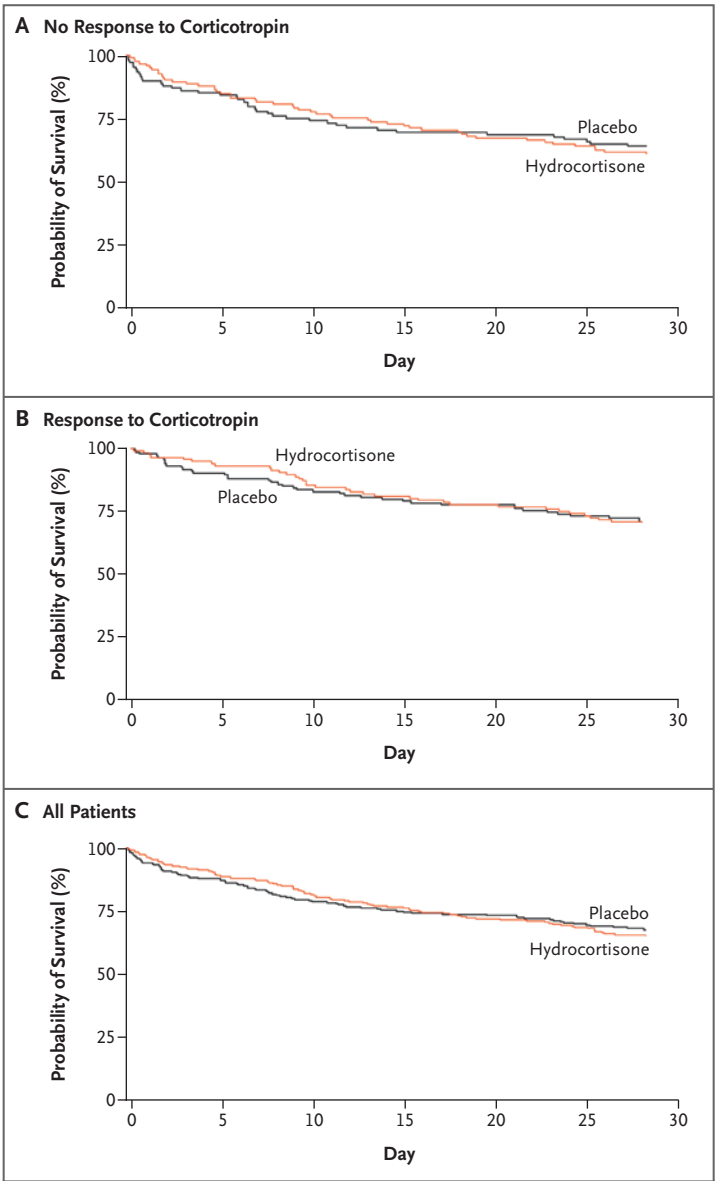

Figure 2. Kaplan–Meier Curves for Survival at 28 Days.

For the comparison between patients with septic shock who received hydrocortisone and those who received placebo, there was no significant difference among those who did not have a response to a corticotropin test (Panel A), those who had a response to corticotropin (Panel B), and all patients who underwent evaluation (Panel C).

for those who had a response to corticotropin, 2.8 days (95% CI, 2.1 to 3.3) versus 5.8 days (95% CI, 5.2 to 6.9); and for those who did not have a response, 3.9 days (95% CI, 3.0 to 5.2) versus 6.0 days (95% CI, 4.9 to 9.0).

The number of extubated patients on day 28 was similar in the two study groups: 119 of 228 patients who underwent ventilation at baseline in the hydrocortisone group (52%) and 113 of 212 patients in the placebo group (53%). For the 357 patients with cultured pathogens for their primary infection, the clinical evaluation committee determined that appropriate antimicrobial therapy was given to 126 of 173 in the hydrocortisone group (72.8%) and 145 of 184 in the placebo group (78.8%). There was no significant difference in outcome between study groups among patients receiving appropriate antibiotic therapy and those receiving inappropriate therapy.

USE OF CORTICOSTEROIDS AND OTHER DRUGS

Eleven patients in the hydrocortisone group (4.4%) and 10 patients in the placebo group (4.0%) received corticosteroids after study enrollment for allergic reactions, laryngeal edema, bronchospasm, brain edema, replacement of long-term corticosteroid therapy whose history was unknown at enrollment, acute respiratory distress syndrome, and septic shock. Five patients received corticosteroids for septic shock after completion of the course of a study drug. The numbers of patients in both groups who received activated protein C, antithrombin, or both were similar (Table 2).

ADVERSE EVENTS

In the hydrocortisone group, there was an increased incidence of superinfections, including new episodes of sepsis or septic shock, with a combined odds ratio of 1.37 (95% CI, 1.05 to 1.79); there was also an increased incidence of hyperglycemia and hypernatremia (Table 4). Neuromuscular weakness was rarely reported.

DISCUSSION

In our study, the use of low-dose hydrocortisone had no significant effect on the rate of death in patients with septic shock at 28 days, regardless of the patients' adrenal responsiveness to corticotropin. The proportion of patients in whom reversal of shock was achieved was similar in the two groups, though this goal was achieved earlier in patients who received hydrocortisone.

These results are in marked contrast to those of the study by Annane et al.,[16] in which both improved survival and reversal of shock were reported in patients with no response to corticotropin who received hydrocortisone plus fludro-

Table 3. Outcomes According to Subgroup.*

Variable	No Response to Corticotropin		P Value	Response to Corticotropin		P Value	All Patients		P Value
	Hydrocortisone (N=125)	Placebo (N=108)		Hydrocortisone (N=118)	Placebo (N=136)		Hydrocortisone (N=251)	Placebo (N=248)	
Death within 28 days — no. (%)	49 (39.2)	39 (36.1)	0.69	34 (28.8)	39 (28.7)	1.00	86 (34.3)	78 (31.5)	0.51
Relative risk (95% CI)	1.09 (0.77 to 1.52)			1.00 (0.68 to 1.49)			1.09 (0.84 to 1.41)		
Absolute difference — % (95% CI)	3.1 (–9.5 to 15.7)			0.1 (–11.2 to 11.4)			2.8 (–5.5 to 11.2)		
Death in ICU — no./total no. (%)	58/125 (46.4)	44/108 (40.7)	0.43	41/118 (34.7)	45/135 (33.3)	0.89	102/251 (40.6)	89/247 (36.0)	0.31
Relative risk (95% CI)	1.14 (0.85 to 1.53)			1.04 (0.74 to 1.47)			1.13 (0.90 to 1.41)		
Absolute difference — % (95% CI)	5.7 (–7.1 to 18.4)			1.4 (–10.3 to 13.1)			4.6 (–3.9 to 13.1)		
Death during hospitalization — no./total no. (%)	60/125 (48.0)	50/108 (46.3)	0.90	48/118 (40.7)	50/133 (37.6)	0.70	111/251 (44.2)	100/245 (40.8)	0.47
Relative risk (95% CI)	1.04 (0.79 to 1.36)			1.08 (0.79 to 1.47)			1.08 (0.88 to 1.33)		
Absolute difference — % (95% CI)	1.7 (–11.1 to 14.6)			3.1 (–9.0 to 15.2)			3.4 (–5.3 to 12.1)		
Death at 1 yr — no./total no. (%)	73/124 (58.9)	60/105 (57.1)	0. 89	61/111 (55.0)	67/126 (53.2)	0.80	137/242 (56.6)	127/235 (54.0)	0.58
Relative risk (95% CI)	1.03 (0.83 to 1.29)			1.03 (0.82 to 1.31)			1.05 (0.89 to 1.23)		
Length of stay — days									
In ICU	17±19	17±17	0.47	18±22	19±16†	0.26	19±31	18±17†	0.51
In hospital	29±26	31±27	0.82	36±40	35±43‡	0.68	34±41	34±37‡	0.47

* Relative risks and percent differences are for the comparison between the hydrocortisone group and the placebo group. P values for categorical variables were calculated with the use of Fisher's exact test. P values for continuous variables were calculated with the use of the Wilcoxon rank-sum test. ICU denotes intensive care unit.
† Data were missing for one patient.
‡ Data were missing for three patients.

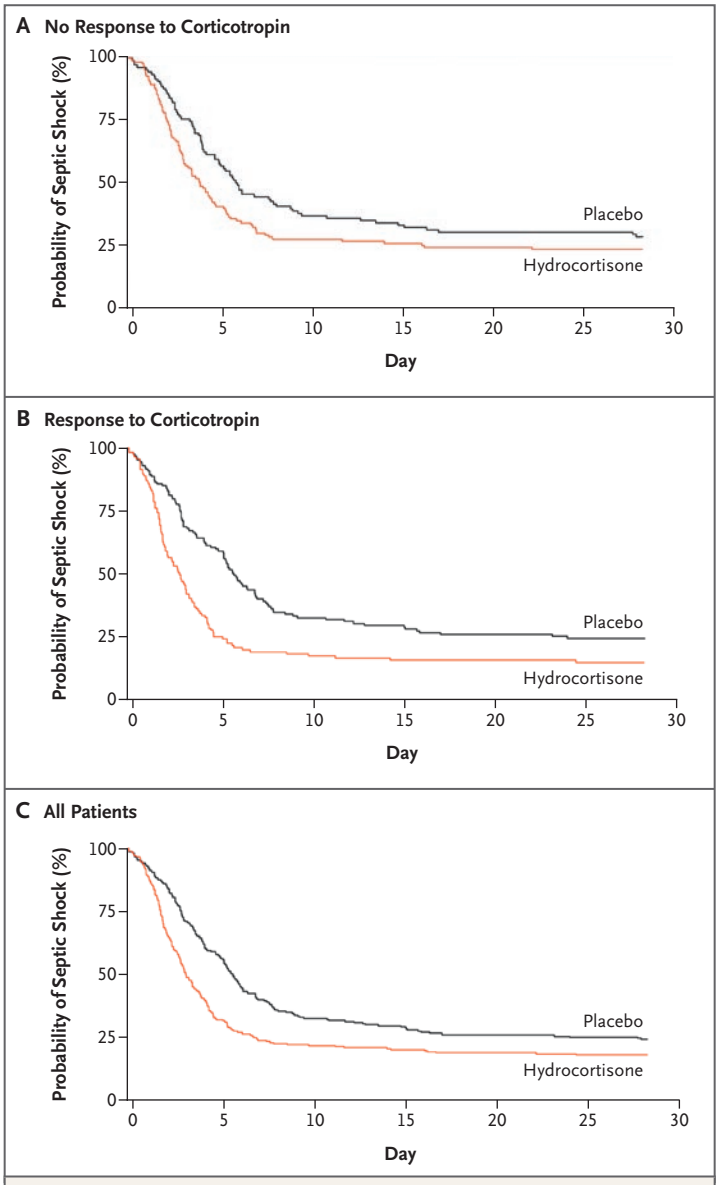

Figure 3. Kaplan–Meier Curves for the Time to Reversal of Shock.

For the comparison between patients with septic shock who received hydrocortisone and those who received placebo, P=0.06 for patients who did not have a response to a corticotropin test (Panel A) and P<0.001 both for patients who had a response to corticotropin (Panel B) and for all patients (Panel C).

cortisone. Differences between the two studies may stem from several factors. First, the studies involved dissimilar populations of patients. In the Annane study, the patients had higher SAPS II scores at baseline, and the entry requirement for systolic blood pressure was less than 90 mm Hg for more than 1 hour despite fluid and vasopressor therapy; there also was a much higher rate of death at 28 days in the placebo group (61%, as compared with 32% in our study). Second, enrollment in the Annane study was allowed only within 8 hours after fulfilling entry criteria, as compared with a 72-hour window in our study. Third, fludrocortisone was not given to patients in our study, since 200 mg of hydrocortisone should provide adequate mineralocorticoid activity.[28] Furthermore, absorption of oral fludrocortisone is variable in the shock state. Although an analysis of patients in our study who had a systolic blood pressure that persisted below 90 mm Hg at 1 day after fluid and vasopressor resuscitation showed a rate of death of 56.1% in the placebo group and an absolute reduction in mortality of 11.2% in the hydrocortisone group (results that are similar to those reported by Annane et al.), the subgroups of patients who received a study drug within 12 hours after baseline did not show any significant differences in outcome.

As reported previously,[14,15,18] our study showed a decrease in the time to reversal of shock in the hydrocortisone group. However, the total number of patients who underwent reversal of shock was unaffected. It remains unclear why vascular tone improves in some patients but not in others. In an unexpected finding, the earlier rate of reversal of shock was greater in patients who had had a response to corticotropin but was not associated either with survival benefit or a reduction in duration of stay in either the ICU or the hospital. These findings may be unrelated to adrenal insufficiency but could instead result from a direct interaction with mechanisms producing vascular hyporeactivity.[29,30] Alternatively, the effect may be due to a more widespread antiinflammatory action of corticosteroids, which inhibit the expression of proinflammatory cytokines, mediators, and receptors.[31]

The duration of the administration of corticosteroids may be pertinent, with the possibility that any gain that was achieved by an earlier reversal of shock was counterbalanced by later complications.[9] In the Annane study, corticosteroid treatment was stopped abruptly after 7 days, whereas in our study, therapy was tapered from day 5 to day 11. Tapering was used because of the increase in proinflammatory mediators and hemodynamic deterioration after abrupt cessation

Table 4. Adverse Events (Per-Protocol Population).*

Event	Hydrocortisone (N=234)	Placebo (N=232)	Relative Risk (95% CI)
	no. of patients (%)		
Superinfection	78 (33)	61 (26)	1.27 (0.96–1.68)
Catheter-related	3 (1)	3 (1)	0.99 (0.20–4.86)
Lung	34 (15)	30 (13)	1.12 (0.71–1.77)
Gastrointestinal	22 (9)	19 (8)	1.15 (0.64–2.06)
Urinary tract	11 (5)	10 (4)	1.09 (0.47–2.52)
Wound	9 (4)	7 (3)	1.27 (0.48–3.37)
Other	16 (7)	8 (3)	1.98 (0.87–4.54)
New sepsis	6 (3)	2 (1)	2.97 (0.61–14.59)
New septic shock	14 (6)	5 (2)	2.78 (1.02–7.58)
Other adverse event			
Anastomotic leak	4 (2)	4 (2)	0.99 (0.25–3.92)
Wound dehiscence	2 (1)	2 (1)	0.99 (0.14–6.98)
Repeat shock	72 (31)	57 (25)	1.25 (0.93–1.68)
Bleeding			
Any	21 (9)	16 (7)	1.30 (0.70–2.43)
Gastrointestinal	15 (6)	13 (6)	1.14 (0.56–2.35)
Polyneuropathy	2 (1)	4 (2)	0.50 (0.09–2.68)
Multiple organ system failure	34 (15)	33 (14)	1.02 (0.66–1.59)
Refractory shock	20 (9)	25 (11)	0.79 (0.45–1.39)
Pulmonary	8 (3)	13 (6)	0.61 (0.26–1.44)
Renal	7 (3)	6 (3)	1.16 (0.39–3.39)
Neurologic	1 (<1)	1 (<1)	0.99 (0.06–15.76)
Hyperglycemia (glucose ≥150 mg/dl on any day from day 1 to day 7)†	186 (85)	161 (72)	1.18 (1.07–1.31)
Hypernatremia (sodium ≥150 mmol/liter on any day from day 1 to day 7)‡	67 (29)	42 (18)	1.58 (1.13–2.22)
Possibly related to shock			
Stroke	3 (1)	1 (<1)	2.97 (0.31–28.39)
Acute myocardial infarction	14 (6)	13 (6)	1.24 (0.34–4.56)
Peripheral limb ischemia	0	1 (<1)	

* Some patients had more than one adverse event. Relative risks are for the comparison between the hydrocortisone group and the placebo group. To convert values for glucose to millimoles per liter, multiply by 0.05551.
† For the diagnosis of hyperglycemia, 220 patients were evaluated in the hydrocortisone group and 225 patients in the placebo group.
‡ For the diagnosis of hypernatremia, 231 patients were evaluated in the hydrocortisone group and 229 patients in the placebo group.

of corticosteroids.[17] Our study showed an increased incidence of superinfection, including new episodes of sepsis or septic shock, in the hydrocortisone group. Previous studies with high-dose corticosteroids have shown similar findings,[11] whereas the study conducted by the Acute Respiratory Distress Syndrome (ARDS) Network[32] using higher doses of corticosteroids and meta-analyses of studies that used low doses[21,22] did not report higher rates of infectious complications.

Studies involving critically ill patients have reported an association between corticosteroid therapy and the incidence of neuromuscular weakness.[32,33] We did not see this in our study, although electrophysiological testing was not performed. However, the duration of mechanical ventilation was similar in the two study groups. Finally, the increased glucose levels in the hydrocortisone group may have contributed to increased mortality.[34]

The use of etomidate for induction of anesthesia in our study (in 26% of patients) was similar to that in the Annane study (24%). Etomidate has a low profile of cardiovascular complications,[35] but a single dose can inhibit the metabolism of corticosteroids for at least 24 hours in patients who are critically ill.[36] An association between etomidate and the likelihood of adrenal hyporesponsiveness was also found in our study.

The prognostic importance of adrenal insufficiency in septic shock is well described.[19] Routine testing of adrenal function has been advocated to guide corticosteroid therapy.[16,18-21] In our study, a modest increase in the rate of death at 28 days was seen in patients who did not have a response to corticotropin (38%), as compared with those who had a response (29%). However, there was no difference in outcome in either subgroup of the hydrocortisone group. The short corticotropin test does not appear to be useful for determining the advisability of corticosteroid treatment in patients with septic shock, and our results call into question the definition of relative adrenal insufficiency. Indeed, significant variability in cortisol levels has been described, depending on the measurement methods used.[37] Studies have described the poor relationship between total and free cortisol levels[38] and other issues concerning the dose, timing, and type of corticotropin.[39]

The strengths of our study include the fact that it was initiated by the investigators and involved 52 ICUs in nine countries. Limitations include the lack of adequate power, since only 500 patients were enrolled rather than the projected 800. This was due to a combination of slow recruitment (which was probably related to a loss of equipoise in view of the various guidelines recommending corticosteroid use[23]), termination of funding, and time expiry of the trial drug. On the basis of the current data, however, the likelihood of seeing any difference in outcomes between the two study groups was unlikely. Finally, 21 patients received open-label corticosteroids (4.2%), although this finding was unlikely to have had a material effect on the outcome.

In summary, the use of hydrocortisone did not decrease mortality in a general population of patients with septic shock, even though the drug hastened reversal of shock. This lack of improvement may be related to an increased incidence of superinfection and new septic episodes. No benefit was seen in a subgroup of patients who had had no response to corticotropin, as was shown previously for patients with severe septic shock. This finding may be related to methodologic issues surrounding the accurate diagnosis of adrenal insufficiency in critically ill patients or to a decreased prognostic importance of this phenomenon in less severe shock. On the basis of these findings, hydrocortisone cannot be recommended as general adjuvant therapy for septic shock (vasopressor responsive), nor can corticotropin testing be recommended to determine which patients should receive hydrocortisone therapy. Hydrocortisone may have a role among patients who are treated early after the onset of septic shock who remain hypotensive despite the administration of high-dose vasopressors (vasopressor unresponsive).[16]

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APPENDIX

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