Hydrocortisone Therapy for Patients With Multiple Trauma

The Randomized Controlled HYPOLYTE Study

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Context The role of stress-dose hydrocortisone in the management of trauma patients is currently unknown.

Objective To test the efficacy of hydrocortisone therapy in trauma patients.

Design, Setting, and Patients Multicenter, randomized, double-blind, placebo-controlled HYPOLYTE (Hydrocortisone Polytraumatise) study. From November 2006 to August 2009, 150 patients with severe trauma were included in 7 intensive care units in France.

Intervention Patients were randomly assigned to a continuous intravenous infusion of either hydrocortisone (200 mg/d for 5 days, followed by 100 mg on day 6 and 50 mg on day 7) or placebo. The treatment was stopped if patients had an appropriate adrenal response.

Main Outcome Measure Hospital-acquired pneumonia within 28 days. Secondary outcomes included the duration of mechanical ventilation, hyponatremia, and death.

Results One patient withdrew consent. An intention-to-treat (ITT) analysis included the 149 patients, a modified ITT analysis included 113 patients with corticosteroid insufficiency. In the ITT analysis, 26 of 73 patients (35.6%) treated with hydrocortisone and 39 of 76 patients (51.3%) receiving placebo developed hospital-acquired pneumonia by day 28 (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.30-0.83; $P=.007$). In the modified ITT analysis, 20 of 56 patients (35.7%) in the hydrocortisone group and 31 of 57 patients (54.4%) in the placebo group developed hospital-acquired pneumonia by day 28 (HR, 0.47; 95% CI, 0.25-0.86; $P=.01$). Mechanical ventilation–free days increased with hydrocortisone by 4 days (95% CI, 2-7; $P=.001$) in the ITT analysis and 6 days (95% CI, 2-11; $P<.001$) in the modified ITT analysis. Hyponatremia was observed in 7 of 76 (9.2%) in the placebo group vs none in the hydrocortisone group (absolute difference, –9%; 95% CI, –16% to –3%; $P=.01$). Four of 76 patients (5.3%) in the placebo group and 6 of 73 (8.2%) in the hydrocortisone group died (absolute difference, 3%; 95% CI, –5% to 11%; $P=.44$).

Conclusion In intubated trauma patients, the use of an intravenous stress-dose of hydrocortisone, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia.

Trial Registration clinicaltrials.gov Identifier: NCT00563303

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SEVERE TRAUMA IS ONE OF THE leading causes of death and morbidity in the world.[1] The overall rate of posttraumatic pneumonia reaches an incidence of 40% to 60%, mainly in patients with traumatic brain injury (TBI).[2-4] Early posttraumatic pneumonia increases the duration of mechanical ventilation, hospitalization,[5] and risk of death. Thus, prevention of posttrauma pneumonia is a major clinical and economical issue.

Stress-dose hydrocortisone was suggested as a means of improving outcome in septic patients with critical illness–related corticosteroid insufficiency.[6] Recommendations advocate the use of long-term stress-dose hydrocortisone (200 mg/d) in patients with septic shock[7]

For editorial comment see p 1242.

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and with severe community-acquired pneumonia.[8] Both experimental[9,10] and clinical[11,12] data suggest that corticosteroid use may decrease the occurrence and severity of nosocomial pneumonia in patients treated in intensive care units (ICUs).

Persistent systemic inflammatory response syndrome was predictive of nosocomial infection in trauma patients.[13,14] Trauma-related corticosteroid insufficiency was also correlated with systemic inflammatory response syndrome.[15] It has been suggested that hydrocortisone attenuates the overwhelming inflammatory response without immunosuppression, restoring an adequate immune response to infection.[10] We postulated that treatment with stress-dose levels of hydrocortisone would diminish the prevalence of hospital-acquired pneumonia, the first cause of infection in trauma patients.

METHODS

Study Design

This multicenter, randomized, double-blind, parallel, placebo-controlled study was approved by the institutional review board of Angers, France. Patients were enrolled from November 15, 2006, to August 4, 2009, when recruitment was completed at the 7 participating French ICUs. Patients were enrolled after a next-of-kin provided written informed consent. Retrospective consent, when available, was obtained from patients. The authors designed the study, but data were gathered and analyzed by an independent monitoring board.

Patients with multiple trauma who were older than 15 years 3 months and expected to require mechanical ventilation for more than 48 hours were included in the study. Those with previous adrenal insufficiency, previous immunosuppression (for clinical definitions, see eAppendix available at http://www.jama.com), treatment with corticosteroids within the last 6 months, or were pregnant were excluded.

Multiple trauma was defined as having 2 or more traumatic injuries and an injury severity score higher than 15. *Severe TBI* was defined as a Glasgow Coma Scale score of less than or equal to 8 after initial care.[16] *Corticosteroid insufficiency* was defined as basal cortisolemia level lower than 15 µg/dL (to convert to nanomoles per liter multiply by 27.588)[17] or a maximal increase in the cortisol level lower than 9 µg/dL in the 60 minutes following a short corticotropin test.[6,7]

Pneumonia was considered when at least 2 signs (body temperature >38°C; leukocytosis >12 000/mL, or leukopenia <4000/mL; purulent pulmonary secretions) associated with the appearance of a new infiltrate were present or when change occurred in an existing infiltrate on chest x-ray.[18-20] The diagnosis needed to be confirmed by a lower respiratory tract sample using a quantitative culture with a predefined positive threshold of 10^4 colony-forming units per milliliter (CFU/mL) for a bronchoalveolar lavage or nonbronchoscopic sample and 10^3 CFU/mL for a protected specimen brush. Hospital-acquired pneumonia was defined as pneumonia that occurs 48 hours after admission that had not been incubating at the time of admission. The definitions of other infections as well as organ failure are provided as supplemental material (eAppendix). Patients were randomized in a 1:1 ratio in fixed blocks of 4 and stratified according to the treatment center, the presence of severe TBI, and injury severity score higher than 30 by a computerized number generator list provided by a statistician not involved in the determination of eligibility or in the assessment of outcomes. All assignments were made through a central randomization center. In each center, an unblinded pharmacist who was not involved in the determination of eligibility or in the assessment of outcomes prepared the study drug. Patients, investigators, and members of the monitoring board and medical and nursing staff were unaware of the patients' treatment assignment.

Study drug infusion began within 36 hours of the trauma onset, immediately after the completion of a short corticotropin test. Hydrocortisone hemisuccinate (Upjohn, Serb laboratory, Paris, France) and placebo were prepared immediately before use in a syringe containing 48 mL of saline isotonic solution. In addition to standard of care, the study drugs were continuously administered intravenously as follows: 200 mg/d for 5 days, 100 mg on day 6, and 50 mg on day 7 for patients with corticosteroid insufficiency. After receiving the results of the short corticotropin test (in the first 48 hours following inclusion), the treatment was stopped if patients had an adapted corticosteroid function.

Each patient's general characteristics including demographics, injury severity score and abbreviated injury score, fluid infusions, vasopressors, antibiotic prophylaxis, etomidate use, surgery, infections, organ failures, length of ventilatory support, and ICU hospitalization and death at day 28 were recorded.

Immediately before beginning the treatment, but at least 8 hours after a bolus injection of etomidate,[6] a short corticotropin test was performed: cortisolemia before and 30 and 60 minutes after an intravenous bolus of 0.25 mg of corticotropin (Novartis, Rueil-Malmaison, France). In patients with corticosteroid insufficiency, a second short corticotropin test was performed 24 hours after the end of treatment.

During the 28-day period after randomization, clinical assessments were performed twice a day in the ICU. Methods to enhance the quality of measurements included holding triannual telephone contact with investigators, sending e-mails, and conducting random quality assurance evaluations.

The study's primary outcome was occurrence of hospital-acquired pneumonia within 28 days of randomization. The secondary outcomes were duration of mechanical ventilation and length of ICU stay, rates of death, other infections, and organ failures, and duration of vasopressor support on day 28. Safety was assessed by recording adverse events.

Modifiable risk factors of hospital-acquired pneumonia[18] were prospectively recorded (eTable 1). Clinical

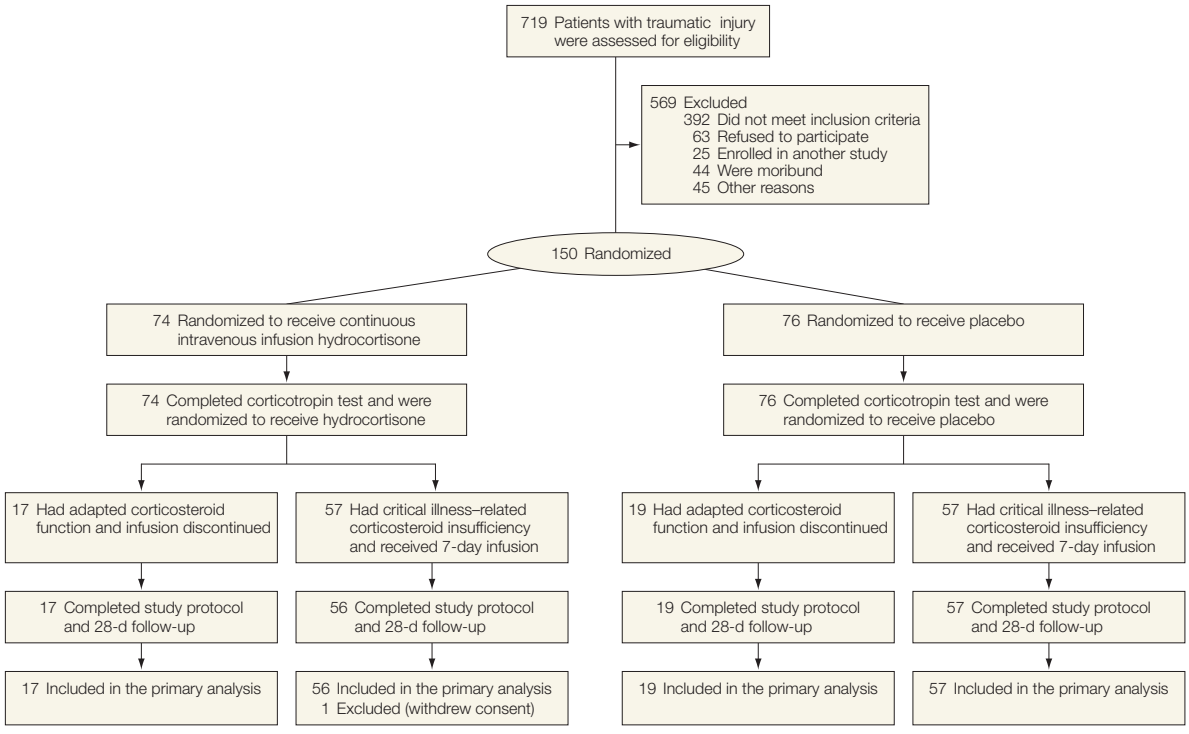
evaluation for diagnosis of pneumonia was performed twice a day in the ICU. A chest x-ray was taken as soon as pneumonia was suspected after clinical examination. A culture sample was collected immediately when radiographic infiltrates and antibiotic therapy was not modified.

Statistical Analysis

After verifying that the cumulative probability of hospital-acquired pneumonia on day 28 was significantly decreased in the hydrocortisone group compared with the placebo group using a stratified log-rank test (test initially planned for the primary end point), we decided a posteriori to perform complementary sensitivity analyses with an adjustment for etomidate use. The final a posteriori primary analysis consisted of evaluating the effect of hydrocortisone on the primary outcome (ie, pneumonia within 28 days), with adjustment by means of a Cox multivariate proportional hazards model that included 3 predefined covariates: the center, TBI (presence or absence), and the injury severity score (≤30 or >30). Corresponding hazard ratios (HRs) along with their 95% confidence intervals (CIs) were reported. If a significant difference was confirmed for the primary end point, then subgroup analysis for TBI (presence or absence) was performed. The hierarchical testing procedure allowed us to control the family-wise type I error rate. A second complementary analysis was a priori planned considering mortality as part of the outcome (composite outcome). We also reported the crude Kaplan-Meier estimator at day 28. Because the randomization process came before the corticotropin test, an intention-to-treat analysis (ITT) that includes the whole population was first performed followed by a modified ITT for patients with corticosteroid insufficiency.

For the power calculation, we a priori defined that patients with corticosteroid insufficiency would be treated, whereas treatment would be stopped for patients with appropriate corticosteroid function. The power calculation was performed for comparison between the hydrocortisone and placebo groups in patients with corticosteroid insufficiency. The sample size needed to detect an absolute decrease in pneumonia incidence of 20% was 45 patients in each group, assuming a basal rate of 50%[2-4] in a 2-sided test performed with a statistical power of 80% and an α risk of .05. Assuming a rate of 50% of corticosteroid insufficiency,[15,17,21,22] 180 patients (45 patients in each group, and 90 patients with normal corticosteroid function who were untreated) were needed. After inclusion of the first 75 patients, an a priori intermediate analysis using the O'Brien and Fleming method for α risk spending was used ($P = .005$ and $P = .048$ for the first and final analysis, respectively) and data showed that the incidence of corticosteroid insufficiency reached 70%. The sample size needed to ensure that the initial power was therefore achieved, and the study was stopped after enrolling 150 patients.

Figure 1. Flow of Participants



Mantel-Haenszel tests, linear regressions, or the Wilcoxon rank-sum test were used as appropriate. All statistical tests were 2-sided. A *P* value less than .05 was considered statistically significant. Adverse events were reported according to an ITT model. The normality of the variables was tested with a Kolmogorov-Smirnoff test. Continuous parametric data were expressed as the mean (SD), and nonparametric data were expressed as the

Table 1. General Characteristics

Characteristics	All Patients		Patients With Critical Illness–Related Corticosteroid Insufficiency		Patients With Adapted Corticosteroid Function (n = 36)
	Hydrocortisone (n = 73)	Placebo (n = 76)	Hydrocortisone (n = 56)	Placebo (n = 57)	
Age, mean (SD), y	36 (18)	36 (18)	35 (17)	35 (18)	41 (19)
Men, No. (%)	56 (76.7)	61 (80.3)	42 (75.0)	47 (82.5)	28 (77.8)
Medical history, No. (%)					
Diabetes mellitus	3 (4.1)	2 (2.6)	2 (3.6)	2 (3.5)	1 (2.8)
Cardiac insufficiency	2 (2.7)	3 (4.0)	1 (1.8)	3 (5.3)	1 (2.8)
Obesity	15 (20.6)	6 (7.9)	10 (17.9)	3 (5.3)	8 (22.2)
Chronic pulmonary disease	3 (4.1)	2 (2.6)	2 (3.6)	2 (3.5)	1 (2.8)
Smoking	3 (4.1)	2 (2.6)	1 (1.8)	2 (3.5)	2 (5.6)
Traumatic brain injury, No. (%)	42 (57.5)	42 (55.3)	32 (57.1)	35 (61.4)	17 (47.2)
Injury severity score, median (IQR)	29 (22-35)	27 (22-38)	30 (22-36)	30 (22-38)	27 (22-34)
AIS scoring, median (IQR)					
Encephal/neck	3 (1-4)	3 (0-4)	3 (1-5)	3 (0-5)	3 (0-4)
Face	0 (0-2)	0 (0-2)	0 (0-2)	1 (0-2)	0 (0-2)
Thorax	3 (2-3)	3 (2-3)	3 (2-3)	3 (1-3)	3 (2-3)
Abdomen/perineum	0.5 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	0 (0-2)
Extremities/pelvis	2 (0-3)	3 (0-3)	3 (0-3)	2 (0-3)	2 (0-3)
Skin	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Aspiration pneumonia, No. (%)	2 (2.7)	2 (2.6)	1 (1.8)	1 (1.8)	2 (5.6)
Hypotension prior to inclusion, No. (%)[a]	46 (63.9)	42 (56.0)	35 (63.6)	31 (55.4)	22 (61.1)
Fluid infusion prior to inclusion, median (IQR)					
Red cell units, No.	4 (2-9)	4 (0-10)	5 (2-9)	4 (0-9)	4 (0-11)
Colloid fluid infusion, L	1.5 (1.0-2.8)	1.5 (1.0-2.5)	1.5 (1.0-2.5)	1.5 (1.0-3.0)	1.5 (1.0-2.5)
Crystalloïd fluid infusion, L	3.0 (2.0-4.0)	3.0 (1.9-3.8)	2.5 (2.0-3.5)	3.0 (1.9-4.0)	3.0 (2.2-4.2)
Norepinephrine prior to inclusion, median (IQR), µg/kg per min	0.3 (0.1-0.5)	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.2 (0.1-0.4)
Surgical procedure prior to study inclusion					
Duration of initial surgical procedure, median (IQR), h	2 (1-5)	2.5 (1-5)	2 (2-5)	2 (1-4)	3 (1-8)
Type, No. (%)					
Orthopedic	37 (50.7)	38 (50.0)	27 (48.2)	25 (43.9)	23 (63.9)
Digestive	13 (18.1)	11 (14.7)	10 (17.9)	7 (12.3)	7 (20.6)
Thoracic	16 (22.2)	22 (29.3)	15 (26.8)	13 (22.8)	10 (29.4)
Neurologic	16 (22.2)	20 (26.7)	13 (23.2)	18 (31.6)	5 (14.7)
Otorhinolaryngologic	7 (9.7)	5 (6.7)	5 (8.9)	4 (7.0)	3 (8.8)
Other	10 (14.7)	17 (26.2)	7 (13.2)	12 (25.0)	8 (25.0)
Duration between events, median (IQR), min					
Trauma and tracheal intubation	45 (20-120)	70 (40-180)	57 (20-120)	60 (35-150)	60 (30-360)
Tracheal intubation and corticotropin test	1290 (960-1660)	1379 (1165-1710)	1275 (950-1525)	1410 (1165-1710)	1370 (1140-1750)
Etomidate injection, No. (%)					
Prior to inclusion	44 (62.0)	50 (65.8)	36 (65.5)	43 (75.4)	15 (42.9)
After inclusion	0	0	0	0	0
Short corticotrophin test, median (IQR), µg/dL					
Basal cortisolemia	20 (14-27)	17 (12-28)	20 (12-28)	16 (11-27)	21 (18-26)
Change at 30 min	5 (2-11)	7 (2-13)	4 (2-9)	5 (1-12)	11 (8-13)
Change at 60 min	8 (4-15)	9 (4-17)	6 (3-13)	7 (2-16)	15 (11-17)

Abbreviations: AIS, abbreviated injury scale; a global severity scoring system that classifies each injury according to its relative severity on a 6-point ordinal scale: 1 minor, 2 moderate, 3 serious, 4 severe, 5 critical, 6 maximal (or untreatable); IQR, interquartile range.
[a]Systolic blood pressure less than 90 mm Hg.

median and interquartile range (IQR). Categorical data were expressed as numbers and percentage, as well as the absolute difference (95% CI). Analyses were performed with SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients

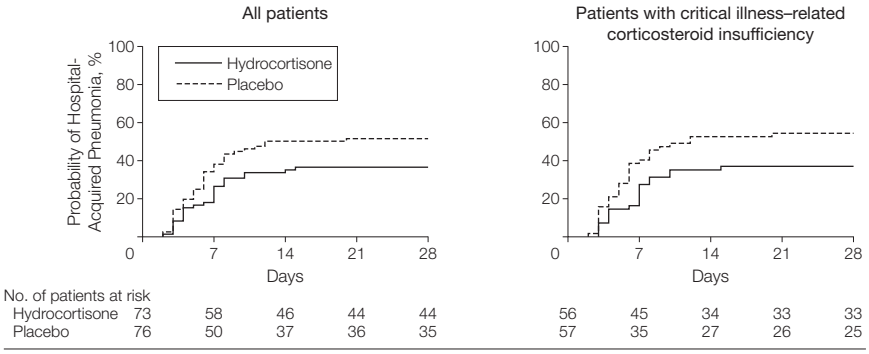
Patients were treated in level I trauma centers according to the Advanced Trauma Life Support principles. Of the 150 patients included, 1 patient was excluded because consent was withdrawn; the 149 remaining patients were analyzed (FIGURE 1). All patients were intubated prior to randomization. One hundred thirteen patients (76%) had corticosteroid insufficiency (56 in the hydrocortisone group and 57 in the placebo group), and 36 patients (24%) had reached normal corticosteroid function (Figure 1). The median injury severity score was 29 (interquartile range [IQR], 22-35) in the hydrocortisone group and 27 (IQR, 22-38) in the placebo group (TABLE 1). Of 94 patients who had received etomidate, 79 (84%) had criteria for corticosteroid insufficiency compared with 34 of 55 (62%) who had not received etomidate ($P=.01$). Forty-four patients (62%) in the hydrocortisone and 50 patients (65.8%) in the placebo groups received a single bolus injection of etomidate prior to inclusion. A surgical procedure was performed prior to randomization in 128 patients (85.9%). The median time between trauma and study drug administration was 25 hours (IQR, 20-33 hours).

Primary Outcome

Twenty-six of 73 patients (35.6%) treated with hydrocortisone and 39 of 76 patients (51.3%) treated with placebo developed hospital-acquired pneumonia at day 28 (HR, 0.51; 95% CI, 0.30-0.83; $P=.007$; FIGURE 2). The Kaplan-Meier estimator at day 28 was 36.6% in the hydrocortisone group and 51.6% in the placebo group, with an absolute diminution in the hydrocortisone group of –15% (95% CI, –30.9% to 0.9%; $P=.08$). There was no difference between groups in terms of modifiable risk factors of hospital-acquired pneumonia or in terms of pathogens involved (eTable 1 and eTable 2 available at http://www.jama.com). Considering mortality as part of the outcome (composite outcome), the difference between the 2 groups remained significant (HR, 0.56; 95% CI, 0.34-0.92; $P=.02$). The second analysis was adjusted for etomidate, and the HR for hospital-acquired pneumonia in the hydrocortisone group was 0.55 (95% CI, 0.32-0.93; $P=.03$).

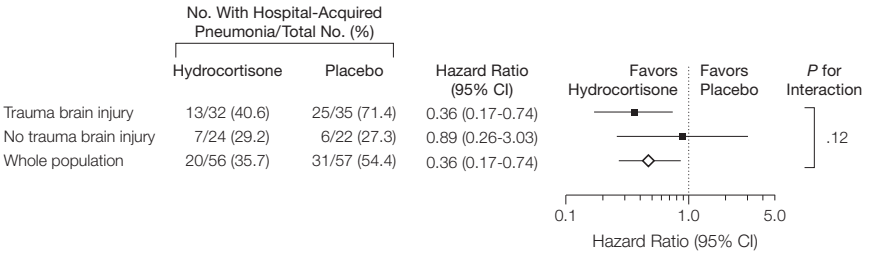
The ITT analysis showed a significant difference between placebo and hydrocortisone group. The planned modified ITT analysis was performed using data of patients with corticosteroid insufficiency.

Figure 2. Kaplan-Meier Curves for Hospital-Acquired Pneumonia



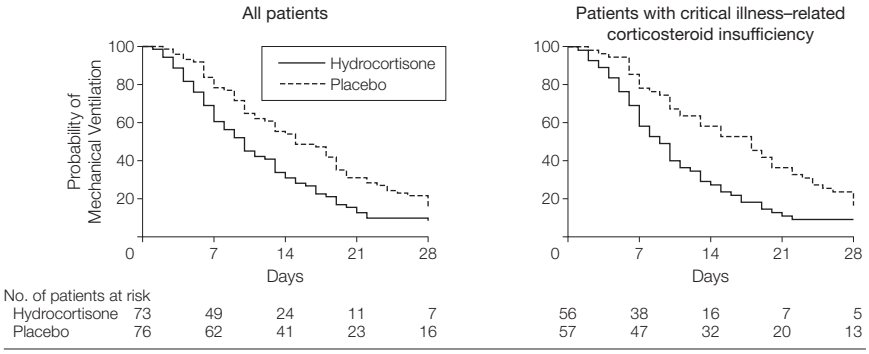
Comparison of hydrocortisone group vs placebo using a stratified Cox model.

Figure 3. Patients With Critical Illness–Related Corticosteroid Insufficiency Presenting With Traumatic Brain Injury



Sixty-seven patients had a traumatic brain injury (32 in the hydrocortisone group and 35 in the placebo group); 46 did not have traumatic brain injury (24 in the hydrocortisone group and 22 in the placebo group).

Figure 4. Kaplan-Meier Curves for Duration of Mechanical Ventilation



Comparison of hydrocortisone group vs placebo using a stratified Cox model.

Twenty of 56 patients with corticosteroid insufficiency (35.7%) who were treated with hydrocortisone and 31 of 57 patients (54.4%) receiving placebo developed hospital-acquired pneumonia at day 28 (HR, 0.47; 95% CI; 0.25-0.86; $P = .01$; Figure 2). The Kaplan-Meier estimator at day 28 was 37.1% in the hydrocortisone group and 54.4% in the pla-

Table 2. Secondary Outcomes[a]

Outcomes	All Patients				Patients With Corticosteroid Insufficiency			
	Hydrocortisone (n = 73)	Placebo (n = 76)	Absolute Difference (95% CI)[c]	*P* Value	Hydrocortisone (n = 56)	Placebo (n = 57)	Absolute Difference (95% CI)[c]	*P* Value
Hospital-acquired pneumonia, No. (%)								
0 Episodes	47 (64.4)	37 (48.7)			36 (64.3)	26 (45.6)		
1 Episode	24 (32.9)	31 (40.8)		.02	18 (32.1)	24 (42.1)		.03
2 Episodes	2 (2.7)	8 (10.5)			2 (3.6)	7 (12.3)		
Mechanical ventilation–free days, mean (SD)	16 (8)	12 (8.5)	4 (2 to 7)	.001[b]	16 (10)	10 (12)	6 (2 to 11)	<.001[b]
Length of ICU stay, mean (SD), d	18 (15)	24 (16)	−6 (−11 to −1)	.03[b]	17 (13)	25 (17)	−8 (−13 to −3)	.002[b]
Vasoactive drugs								
Duration, median (IQR), d	2.0 (1.0 to 4.0)	3.0 (0.0 to 5.0)	−1 (−2 to 0)	.64	2.5 (1.0 to 4.0)	3.0 (1.0 to 5.0)	−2.0 (−4.1 to 0.00)	.04
Norepinephrine, No. (%)	55 (77.5)	55 (72.4)	5 (−9 to 19)	.48	45 (81.8)	44 (77.2)	5 (−0 to 20)	.37
Dosage Δ in the first 24 h, mean (SD), µg/kg per min	−0.19 (0.35)	−0.10 (0.21)	−0.09 (−0.18 to 0.01)	.08	−0.23 (0.38)	−0.11 (0.20)	−0.13 (−0.24 to −0.01)	.03
Epinephrine, No. (%)	2 (2.82)	1 (1.35)	0.01 (−0.03 to 0.06)	.61	2 (3.6)	1 (1.8)		
Dobutamine, No. (%)	1 (1.41)	2 (2.70)	−0.01 (−0.06 to 0.03)	>.99	1 (1.8)	2 (3.6)		
Other infections, No. (%)								
Tracheobronchitis	6 (8.2)	2 (2.6)	6 (−2 to 13)	.16	4 (7.4)	2 (3.5)	4 (−5 to 12)	.40
Urinary tract infection	6 (8.2)	4 (5.3)	3 (−5 to 11)	.53	5 (8.9)	4 (7.0)	1 (−8 to 12)	.65
Bacteriemia	5 (6.9)	2 (2.6)	4 (−3 to 11)	.27	5 (8.9)	2 (3.5)	5 (−3 to 14)	.20
Surgical wound infection	4 (5.5)	9 (11.8)	−6 (−15 to 3)	.17	4 (7.1)	7 (12.3)	−5 (−16 to 6)	.36
Organ failures, No. (%)								
ARDS or ALI	3 (4.3)	11 (14.5)	−10 (−19 to −1)	.04	3 (5.7)	8 (14.0)	−8 (−19 to 3)	.17
Acute kidney Injury	8 (11.3)	8 (10.5)	1 (−9 to 11)	.89	7 (12.7)	6 (10.5)	2 (−10 to 14)	.62
Myocardial insufficiency	0 (0)	1 (1.3)	−1 (−4 to 1)	>.99	0	1 (1.8)	−1.8 (−5 to 2)	.34
Hepatic insufficiency	2 (2.8)	1 (1.3)	2 (−3 to 6)	.61	2 (3.6)	1 (1.8)	2 (−4 to 8)	.67
Hematologic insufficiency	2 (2.8)	2 (2.6)	0 (−5 to 5)	>.99	2 (3.6)	2 (3.5)	0.1 (−7 to 7)	.90
Glucocorticoid function at day 8[d,e]								
Glucocorticoid insufficiency, No. (%)					25 (62.5)	17 (33.3)	29 (9 to 49)	<.001
Basal cortisolemia, median (IQR), µg/dL					20 (16 to 26)	22 (15 to 29)	−2 (−6 to 2)	.39
Change at 30 min, median (IQR), µg/dL					8 (4 to 11)	13 (9 to 19)	−5 (−8 to −3)	<.001
Change at 60 min, median (IQR), µg/dL					10 (5 to 15)	17 (13 to 23)	−6 (−11 to −2)	.01
Death, No. (%)	6 (8.2)	4 (5.3)	3 (−5 to 11)	.44	6 (10.7)	3 (5.3)	5 (−5 to 15)	.23
Metabolic tolerance, No. (%)								
Hyperglycemia ≥180 mg/dL	6 (8.3)	4 (5.3)	3 (−5 to 11)	.44	5 (8.9)	3 (5.3)	4 (−4 to 11)	.44
Hyperkalemia ≥5.0 mEq/L	2 (2.8)	4 (5.3)	−2 (−9 to 4)	.68	2 (3.6)	3 (5.3)	−2 (−9 to 4)	.71
Hypernatremia ≥150 mmol/L	8 (11.1)	9 (11.8)	−1 (−11 to 10)	.88	7 (12.5)	6 (10.5)	1 (−10 to 11)	.69
Hypokalemia ≤3.0 mmol/L	6 (8.3)	3 (4.0)	4 (−3 to 12)	.32	5 (8.9)	3 (5.3)	4 (−3 to 12)	.43
Hyponatremia ≤130 mmol/L	0	7 (9.2)	−9 (−16 to −3)	.01	0	7 (12.3)	−12 (−18 to −4)	.008
Gastrointestinal bleeding or digestive perforation, No. (%)	1 (1.4)	0	1 (−1 to 4)	.49	1 (1.8)	0	2 (−1 to 4)	.31

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval ; ICU, intensive care unit; IQR, interquartile range. Blank cells for *P* values and 95% CIs indicate that there were too few patients for calculations. For the glucocorticoid function, statistical analysis was not performed due to a lack of power.

[a] Secondary outcomes were evaluated on day 28 (unless otherwise stated).

[b] Calculated from Cox regression analysis.

[c] The absolute difference was calculated as (hydrocortisone – placebo) and expressed as absolute value (95% CI).

[d] Glucocorticoid function was not assessed on day 8 for patients with adapted corticosteroid function.

[e] Glucocorticoid function was assessed for 40 patients in the hydrocortisone group and 51 patients in the placebo group.

cebo group, with an absolute diminution in the hydrocortisone group of –17.3% (95% CI, –35.6% to 0.9%; $P = .07$). There was no difference between groups in terms of modifiable risk factors of hospital-acquired pneumonia or in terms of pathogens involved (eTable 1 and eTable 2). Considering mortality as part of the outcome (composite outcome), the HR in the hydrocortisone group compared with the placebo was 0.56 (95% CI, 0.31-1.00; $P = .049$). The second analysis was adjusted for etomidate, and the HR for hospital-acquired pneumonia with hydrocortisone was 0.48 (95% CI, 0.26-0.90; $P = .02$).

Among patients with corticosteroid insufficiency presenting with TBI, 13 of 32 (40.6%) in the hydrocortisone group and 25 of 35 (71.4%) in the placebo group developed hospital-acquired pneumonia at 28 days (HR, 0.36; 95% CI, 0.17-0.74). The test for interaction between treatment group and TBI subgroup was not significant (P for interaction = .12; FIGURE 3).

Of the 17 patients with appropriate corticosteroid function treated with hydrocortisone, 6 (35.3%) and 8 of 19 (42.1%) in the placebo group developed hospital-acquired pneumonia at 28 days (HR, 0.82; 95% CI, 0.23-2.93; $P = .76$; eFigure 1). The short exposure to treatment did not alter the outcomes for patients with an adapted corticosteroid function (eFigure 2 and eTable 4).

Secondary Outcomes

In the entire population, the HR for weaning from mechanical ventilation in the hydrocortisone group compared with the placebo was 1.71 (95% CI, 1.20-2.44; $P = .003$; FIGURE 4). The mean (SD) of mechanical ventilation–free days was 16 (8) days in the hydrocortisone group and 12 (9) days in the placebo group, with a mean absolute increase in the hydrocortisone group of 4 days (95% CI, 2-7; $P = .001$; TABLE 2). Three of 73 patients (4.1%) in the hydrocortisone group and 11 of 76 patients (14.5%) in the placebo group developed an acute lung injury or an acute respiratory distress syndrome (ARDS), with an absolute reduction of –10% (95% CI, –19% to –1%; $P = .04$; Table 2). The mean (SD) length of ICU stay was 18 (15) days in the hydrocortisone group and 24 (16) days in the placebo group, with a mean absolute reduction in the hydrocortisone group of –6 days (95% CI, –11 to –1; $P = .03$; Table 2). No difference was observed between the study groups regarding other outcomes (Table 2).

In patients with corticosteroid insufficiency, the HR for weaning from mechanical ventilation in the hydrocortisone group compared with the placebo group was 1.90 (95% CI, 1.25-2.89; $P < .001$; Figure 4). The mean (SD) mechanical ventilation–free days was 16 (10) days in the hydrocortisone group and 10 (12) days in the placebo group, with a mean absolute increase in the hydrocortisone group of 6 days (95% CI, 2-11; $P < .001$; Table 2). Three of 56 patients (5.7%) in the hydrocortisone group and 8 of 57 patients (14%) in the placebo group developed an acute lung injury or acute respiratory distress syndome, with a mean absolute reduction in the hydrocortisone group of –8% (95% CI, –19% to 3%; $P = .17$; Table 2). The mean (SD) length of ICU stay was 17 (13) days in the hydrocortisone group and 25 (17) days in the placebo group, with a mean absolute reduction in the hydrocortisone group of –8 days (95% CI, –13 to –3; $P = .002$; Table 2). No difference was observed regarding other infections, organ failure, or death rate (Table 2). On day 8, 25 of 40 patients (62.5%) in the hydrocortisone group vs 17 of 51 (33.3%) in the placebo group continued to have corticosteroid insufficiency, with a mean absolute difference in the hydrocortisone group of 29% (95% CI, 9% to 49%; $P < .001$; Table 2).

For the entire study population, 6 of 73 patients (8.2%) died in the hydrocortisone group and 4 of 76 (5.3%) died in the placebo group, with a mean absolute difference of 3% (95% CI, –5% to 11%; $P = .44$; see eTable 3 for cause of deaths, available at http://www.jama.com). Six of 56 patients (10.7%) with corticosteroid insufficiency in the hydrocortisone group and 3 of 57 (5.3%) in placebo group died, with a mean absolute difference of 5% (95% CI, –5% to 15%; $P = .23$, see eTable 3). Seven of 76 patients (9.2%) in the placebo group and none of the 73 in the hydrocortisone group developed hyponatremia, with a mean absolute difference of –9% (95% CI, –16% to –3%; $P = .01$; Table 2). One patient (1.4%) in the hydrocortisone group who had abdominal trauma, and none in the placebo group developed an ileum perforation with gastrointestinal bleeding.

COMMENT

This study shows that hydrocortisone treatment reduced the occurrence of hospital-acquired pneumonia within 28 days in trauma patients.

Hydrocortisone may prevent hospital-acquired pneumonia at the cellular level. At stress doses, corticosteroids have been shown to increase neutrophil activity,[9] increase the homing of dendritic cells with preservation of monocyte function,[23] preserve interleukin 12 function, and attenuate the overwhelming inflammatory response[10] that leads to sepsis in trauma patients.[14,24,25]

The diagnosis of hospital-acquired pneumonia is difficult in the ICU, and we used previously described[3,19,20] and recommended[18] criteria. Trauma is a major risk factor for hospital-acquired pneumonia[26]; the high rates of hospital-acquired pneumonia currently reported have already been described in patients experiencing severe trauma, notably patients with TBI.[2-4] Moreover, the reductions of mechanical ventilation duration as well as acute respiratory distress syndome incidence in the hydrocortisone group emphasize the clinical relevance of the current treatment.[27] Finally, it has already been reported that corticosteroid treatment leads to a reduction of nosocomial pneumonia in patients with acute respiratory distress syndome.[12] Subgroup analysis suggests that hydrocortisone was particularly effective for patients with TBI. These results contrast with those of the Corticosteroid

Randomization After Significant Head Injury (CRASH) study[28] in which corticosteroid therapy increased the risk of death in patients with TBI without modifying the incidence of pneumonia. In the CRASH study, a high dose of methylprednisolone for a short duration (2 days) was used in patients without corticosteroid function assessment.

As previously described,[5,29,30] we report a low mortality rate with no statistical difference between groups. However, there was a 2-fold higher mortality rate in the steroid-treated group. Two patients treated with hydrocortisone but no patient treated with placebo died during the first 48 hours from intracranial hypertension or refractory hemorrhage, the main causes of early death after trauma.[5,29,30] Regarding the mortality rate after 48 hours, 4 of 56 patients (7.1%) in the hydrocortisone group and 3 of 57 patients (5.3%) in the placebo group died (eTable 3 available at http://www.jama.com). Finally, considering mortality in the composite outcome did not modify the primary outcome results.

Among patients with corticosteroid insufficiency, norepinephrine was withdrawn earlier in the hydrocortisone group than in the placebo group. Indeed, hydrocortisone raises blood volume, increases vascular tone, enhances endothelial reactivity to vasopressors,[21] and reduces time-to-shock reversal.[6,31] Etomidate may inhibit the metabolism of corticosteroids for 24 hours,[32] but the clinical consequences of etomidate-induced corticosteroid insufficiency remain controversial.[33] In our study, a single bolus of etomidate increased the risk of corticosteroid insufficiency, and the differences between groups remained significant when the analysis was adjusted for etomidate.

Some considerations should be emphasized. First, the higher rate of corticosteroid insufficiency on day 8 in the treatment group advocates for a slower tapering of hydrocortisone infusion. Moreover, the persistence of corticosteroid insufficiency in both groups suggests that hydrocortisone should be administered for a longer period. Second, the selection of patients likely to benefit from treatment with hydrocortisone is of particular interest. It has been argued that the measurement of free cortisol is more accurate than total cortisol,[34] but no clear cutoff are currently available in clinical practice.[7] Finally, 15% of patients would not have a corticosteroid insufficiency if the current definition of the consensus statement[7] was used; further studies are warranted to confirm the accuracy of the corticosteroid insufficiency definition in trauma patients.

In conclusion, a stress dose of hydrocortisone for 7 days is associated with a reduction in the rate of hospital-acquired pneumonia at day 28 together with a decreased requirement for mechanical ventilation and length of ICU stay in trauma patients. The effects and safety of corticosteroid therapy with stress-dose levels of hydrocortisone should be confirmed in trauma patients and investigated in other ICU populations, particularly in TBI patients.

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Online-Only Material: Four eTables, 2 eFigures, and supplementary information are available at http://www.jama.com.
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REFERENCES

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-1504.
2. Bronchard R, Albaladejo P, Brezac G, et al. Early

onset pneumonia: risk factors and consequences in head trauma patients. *Anesthesiology*. 2004;100 (2):234-239.
3. Leone M, Delliaux S, Bourgoin A, et al. Risk factors for late-onset ventilator-associated pneumonia in trauma patients receiving selective digestive decontamination. *Intensive Care Med*. 2005;31 (1):64-70.
4. Lepelletier D, Roquilly A, Demeure dit latte D, et al. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. *J Neurosurg Anesthesiol*. 2010;22(1):32-37.
5. Osborn TM, Tracy JK, Dunne JR, Pasquale M, Napolitano LM. Epidemiology of sepsis in patients with traumatic injury. *Crit Care Med*. 2004;32(11):2234-2240.
6. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock [published correction appears in *JAMA*. 2008;300(14):1652]. *JAMA*. 2002;288(7):862-871.
7. Marik PE, Pastores SM, Annane D, et al; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-1949.
8. Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2): S27-S72.
9. Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. *Intensive Care Med*. 2008;34(2):344-349.
10. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med*. 2003;167(4):512-520.
11. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med*. 2005;171(3):242-248.
12. Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354(16):1671-1684.
13. Bochicchio GV, Napolitano LM, Joshi M, McCarter RJ Jr, Scalea TM. Systemic inflammatory response syndrome score at admission independently predicts infection in blunt trauma patients. *J Trauma*. 2001; 50(5):817-820.
14. Hoover L, Bochicchio GV, Napolitano LM, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. *J Trauma*. 2006;61 (2):310-316.
15. Hoen S, Asehnoune K, Brailly-Tabard S, et al. Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock. *Anesthesiology*. 2002;97(4):807-813.
16. Bratton SL, Chestnut RM, Ghajar J, et al; Brain Trauma FoundationAmerican Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury [published correction appears in J Neurotrauma. 2008;25(3): 276-278]. *J Neurotrauma*. 2007;24(suppl 1):S1-S106.
17. Cohan P, Wang C, McArthur DL, et al. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. *Crit Care Med*. 2005; 33(10):2358-2366.
18. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.
19. Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. *N Engl J Med*. 2004;350(5):451-458.
20. Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med*. 2006;355 (25):2619-2630.
21. Hoen S, Mazoit JX, Asehnoune K, et al. Hydrocortisone increases the sensitivity to alpha1-adrenoceptor stimulation in humans following hemorrhagic shock. *Crit Care Med*. 2005;33(12): 2737-2743.
22. Offner PJ, Moore EE, Ciesla D. The adrenal response after severe trauma. *Am J Surg*. 2002;184 (6):649-653.
23. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annu Rev Immunol*. 2002;20:125-163.
24. Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. A time-dependent analysis of intensive care unit pneumonia in trauma patients. *J Trauma*. 2004; 56(2):296-301, discussion 301-303.
25. Muehlstedt SG, Richardson CJ, Lyte M, Rodriguez JL. Systemic and pulmonary effector cell function after injury. *Crit Care Med*. 2002;30(6):1322-1326.
26. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med*. 1998;129 (6):433-440.
27. Klompas M. The paradox of ventilator-associated pneumonia prevention measures. *Crit Care*. 2009;13(5):315.
28. Edwards P, Arango M, Balica L, et al; CRASH trial collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet*. 2005;365(9475):1957-1959.
29. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? an analysis of trauma mortality patterns, 1997-2008. *J Trauma*. 2010;69 (3):620-626.
30. Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010; 376(9734):23-32.
31. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2): 111-124.
32. Malerba G, Romano-Girard F, Cravoisy A, et al. Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. *Intensive Care Med*. 2005;31(3):388-392.
33. Jabre P, Combes X, Lapostolle F, et al; KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet*. 2009;374(9686):293-300.
34. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med*. 2004;350(16):1629-1638.