Acute secondary adrenal insufficiency after traumatic brain injury: A prospective study*

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Objective: **To determine the prevalence, time course, clinical characteristics, and effect of adrenal insufficiency (AI) after traumatic brain injury (TBI).**

Design: **Prospective intensive care unit–based cohort study.**

Setting: **Three level 1 trauma centers.**

Patients: **A total of 80 patients with moderate or severe TBI (Glasgow Coma Scale score, 3–13) and 41 trauma patients without TBI (Injury Severity Score, >15) enrolled between June 2002 and November 2003.**

Measurements: **Serum cortisol and adrenocorticotropic hormone levels were drawn twice daily for up to 9 days postinjury; AI was defined as two consecutive cortisols of ≤15 μg/dL (25th percentile for extracranial trauma patients) or one cortisol of <5 μg/dL. Principal outcome measures included: injury characteristics, hemodynamic data, usage of vasopressors, metabolic suppressive agents (high-dose pentobarbital and propofol), etomidate, and AI status.**

Main Results: **AI occurred in 42 TBI patients (53%). Adrenocorticotropic hormone levels were lower at the time of AI (median, 18.9 vs. 36.1 pg/mL; $p = .0001$). Compared with patients without AI, those with AI were younger ($p = .01$), had higher injury severity ($p = .02$), had a higher frequency of early ischemic insults (hypotension, hypoxia, severe anemia) ($p = .02$), and were more likely to have received etomidate ($p = .049$). Over the acute postinjury period, patients with AI had lower trough mean arterial pressure ($p = .001$) and greater vasopressor use ($p = .047$). Mean arterial pressure was lower in the 8 hrs preceding a low (≤15 μg/dL) cortisol level ($p = .003$). There was an inverse relationship between cortisol levels and vasopressor use ($p = .0005$) and between cortisol levels within 24 hrs of injury and etomidate use ($p = .002$). Use of high-dose propofol and pentobarbital was strongly associated with lower cortisol levels ($p < .0001$).**

Conclusions: **Approximately 50% of patients with moderate or severe TBI have at least transient AI. Younger age, greater injury severity, early ischemic insults, and the use of etomidate and metabolic suppressive agents are associated with AI. Because lower cortisol levels were associated with lower blood pressure and higher vasopressor use, consideration should be given to monitoring cortisol levels in intubated TBI patients, particularly those receiving high-dose pentobarbital or propofol. A randomized trial of stress-dose hydrocortisone in TBI patients with AI is underway. (Crit Care Med 2005; 33:2358–2366)**

KEY WORDS: traumatic brain injury; adrenal insufficiency; pituitary; hypopituitarism; cortisol; stress response; vasopressor; etomidate; pentobarbital; propofol

Traumatic brain injury (TBI) is a disorder of major public health importance. In the United States, TBI results in approximately 50,000 deaths annually (1) and remains the leading cause of disability among children and young adults (2). The fact that treatment strategies utilized in multiple recent clinical trials have failed to improve outcome after TBI (3) mandates that novel pathophysiological mechanisms be explored and targeted for therapy. Although several lines of evidence indicate that TBI may predispose to pituitary injury, neuroendocrine dysfunction is rarely considered in current TBI management. Autopsy studies of fatal head-injury victims confirm that up to one third sustain anterior pituitary gland necrosis (4–8). Moreover, numerous case reports (9, 10), retrospective reviews (11, 12), and recent prospective cohort studies (13–16) have documented acute and chronic posttraumatic hypopituitarism.

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is an important protective response during critical illness. Untreated adrenal insufficiency (AI) may lead to hemodynamic instability and poor outcome. Recent trials have established that short-term treatment with physiologic doses of corticosteroids improve outcome in critically ill septic pa-

***See also p. 2440.**

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Supported, in part, by National Institutes of Health grants R01 NS 40777 (to D. F. Kelly); K23 RR 1729801 (to P. Cohan); and M01 RR 00425, M01 RR 00865, and M01 RR 19975 to the General Clinical Research Centers at Harbor–UCLA, UCLA, and University of California–Davis Medical Centers, respectively.

All authors report negative financial disclosures.

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DOI: 10.1097/01.CCM.0000181735.51183.A7

tients with relative AI (17–20). Assessment of the HPA axis is particularly relevant in the context of acute TBI because: 1) the signals that regulate cortisol synthesis and secretion originate from the hypothalamus, 2) many TBI patients require vasopressors to maintain systemic blood pressure and cerebral perfusion pressure, and 3) high-dose glucocorticoids are no longer routinely administered after acute TBI (21–25).

The biochemical diagnosis of AI is often difficult in the setting of critical illness such as acute TBI. Insulin tolerance testing is infeasible in acutely ill patients, and the standard 250-μg corticotropin stimulation test lacks sensitivity and specificity for secondary AI (26). In this prospective study, we define the prevalence and time course of AI in TBI patients by comparing their HPA stress response with a control cohort of extracranial trauma (ECT) patients without TBI. In addition, we evaluate clinical characteristics and factors associated with AI after head injury. It was hypothesized that specific injury characteristics including brain injury severity (low Glasgow Coma Scale [GCS] and computed tomographic [CT] findings) systemic hypoperfusion (e.g., hypotension, hypoxia, severe anemia), and use of metabolic suppressive agents (e.g., high-dose pentobarbital and propofol) may affect the HPA response after TBI.

METHODS

Approval

The institutional review boards of each participating center approved this research study. Informed written proxy consent was obtained within 48 hrs of admission at Harbor–UCLA and UCLA Medical Centers and within 24 hrs of injury at UC–Davis Medical Center.

Patient Selection

TBI Cohort. Between June 2002 and November 2003, patients aged 14–80 yrs old admitted to the intensive care units (ICUs) of one of three level 1 trauma centers, UCLA, Harbor–UCLA and UC Davis Medical Centers, within 24 hrs of moderate or severe TBI (postresuscitation GCS score of 3–8 for severe and 9–13 for moderate, with intracranial hemorrhage on head CT, or deterioration to a GCS score of ≤13 within 24 hrs of admission) were prospectively enrolled into the study. Patients were excluded if they were pregnant, had cancer, AIDS, severe neurologic or psychiatric illness, preexisting adrenal or pituitary insufficiency, or received glucocorticoids within 3 months of injury. Subjects with fewer than three consecutive cortisol levels were excluded. In total, 91 TBI subjects were enrolled, of whom 11 were excluded, leaving 80 evaluable TBI subjects. Reasons for exclusions were previous medical conditions (three subjects), glucocorticoid use (four subjects), and less than three consecutive cortisol levels (four subjects).

ECT Cohort. Between June 2002 and February 2004, patients 14–80 yrs old admitted to the participating ICUs within 24 hrs of trauma with an Injury Severity Score (ISS) of ≥15 were prospectively enrolled into the study. Injury types included chest, abdominal/pelvic, limb, and neck. Patients were excluded if they sustained significant TBI (postresuscitation GCS score of ≤13, loss of consciousness related to TBI, or acute intracranial injury or skull fracture on head CT) or a spinal cord injury. Other exclusion criteria were the same as for TBI subjects. During the study period, 45 ECT subjects were enrolled, and of these, four were excluded, leaving 41 evaluable subjects. Reasons for exclusion were low ISS (two subjects), glucocorticoid use (one subject), and withdrawal of consent (one subject).

TBI Patient Management

All patients were admitted to the ICU after initial stabilization or after craniotomy for evacuation of an intracranial hematoma. Patient management was in accordance with the "Guidelines for the Management of Severe Head Injury" (25) and included an algorithm for maintaining intracranial pressure (ICP) of <20 mm Hg and cerebral perfusion pressure (CPP) above 60–70 mm Hg.

Serial ACTH and Cortisol Blood Draws

During the acute postinjury period, TBI and ECT subjects had paired serial measurements of plasma adrenocorticotropic hormone (ACTH) and serum cortisol. The first ACTH and cortisol levels were drawn within 24 hrs of injury, with subsequent draws occurring at 6 am and 4 pm up to postinjury day 9, as long as the subjects remained in the ICU. These times were chosen both to avoid nursing shift change times and to ensure timely turnaround of results from clinical laboratories. In those subjects who needed surgery, no precaution was taken to draw the level before or after surgery. Serum cortisol levels were measured by polyclonal antibody assay on the Elecsys 2010 Analyzer (Roche Diagnostic, Indianapolis, IN), enzyme immunoassay (Diagnostic System Laboratories, Webster, TX), and Quest Diagnostics (Sacramento, CA) utilizing chemiluminescence assay with the Bayer-Centaur instrument (Bayer Diagnostics, Tarrytown, NY) at UCLA, Harbor–UCLA, and UC–Davis, respectively. The reference range for morning cortisol level for all three centers ranged from 4 to 27 μg/dL. The between-run coefficients of variation were 2–3%, 8.5–10%, and 5–8% at UCLA, Harbor–UCLA, and UC–Davis, respectively. To compare cortisol levels determined by the different laboratories, 75 samples assayed at UC–Davis and 113 samples assayed at UCLA were reanalyzed at the Harbor–UCLA Laboratory. Compared with Harbor–UCLA, mean cortisol levels were 10% higher at UC Davis (95% confidence interval, 4.6% to 15.4 %) and 0.2% higher at UCLA (95% confidence interval, −4.1% to + 4.6%). Based on these differences for single cortisol measurements, not more than one subject at either UC–Davis or UCLA would have had AI status reclassified (based on two consecutive cortisol values) if, instead, a central laboratory at Harbor–UCLA had been used. All serum ACTH levels were determined at Harbor–UCLA General Clinical Research Center Laboratory using an enzyme immunoassay kit (Diagnostic System Laboratories) with a reference range of 7–51 pg/mL.

Definition of AI. TBI subjects were defined as having AI if two consecutive cortisol levels fell below the 25th percentile value of the ECT cohort cortisol values, which was ≤15 μg/dL, or one cortisol level of <5 μg/dL. Patients with a cortisol level of <5 μg/dL were classified as having severe AI, and treating physicians were notified within 6 hrs of the blood draw to assess the clinical need for glucocorticoid replacement.

Low-dose Cortrosyn (ACTH) Stimulation Testing

A low-dose (1 μg) Cortrosyn (ACTH) stimulation test was performed at 3 and 6 months after injury in 30 of the 80 TBI subjects. The remaining 50 subjects were not assessed because they were in a vegetative state (four subjects), deceased (19 subjects), lost to follow-up (12 subjects), refused consent (12 subjects), or dropped from the study (three subjects). The Cortrosyn stimulation test protocol was adapted from previous studies (27, 28). Briefly, 1 μg of Cortrosyn in 1 mL of saline was injected as an intravenous bolus, and blood samples for cortisol were drawn at baseline and 20 and 30 mins postinjection. All cortisol levels were measured by enzyme immunoassay (Diagnostic System Laboratories).

Characteristics Associated with AI Clinical Variables

Age, postresuscitative GCS score, postresuscitative pupillary status (both normal, one abnormal, both abnormal), ISS, presence or absence of sepsis, length of ICU stay, and

6-month Glasgow Outcome Scale score was recorded for each subject (29).

Ischemia Factors. Factors associated with possible ischemic insult to the HPA axis included hypotension (systolic blood pressure of <90 mm Hg) or severe anemia (hematocrit of <25%) within 72 hrs of injury or hypoxia (Pao_2 < 60 mm Hg, Sao_2 < 90%) within 24 hrs of injury or agonal respirations or apnea in the field (30–34). An ischemia score ranging from 0 to 3 was also calculated for each subject with 1 point each for hypotension, hypoxia, or severe anemia.

ICP, CPP, and Blood Pressure. For patients in whom an ICP monitor was placed, mean ICP and CPP, total hours ICP was >20 mm Hg, and total hours CPP was <60 mm Hg were recorded (32, 33, 35–37). Hourly mean arterial pressure (MAP) was also recorded.

CT Findings. The following were recorded from patients' first and second CT scans (obtained within 24 hrs of injury): basilar cistern compression (compressed or absent), diffuse bilateral brain swelling, midline shift of >4 mm, evacuated acute subdural hematoma, and subarachnoid hemorrhage (36, 38). Diagnoses of hypothalamic hemorrhagic and swelling and sphenoid and sellar skull base fractures were also noted. A CT composite score from 0 to 8 was calculated for each subject, with 1 point for the findings of: bilateral swelling, abnormal cisterns, midline shift of >4 mm, suprasellar subarachnoid hemorrhage, evacuated subdural hematoma, hypothalamic hemorrhage/swelling, and fracture of sphenoid or sella.

Medication Effects. Subjects treated with etomidate or metabolic suppressive agents (e.g., pentobarbital and propofol) were identified. Etomidate, when given, was administered as a single dose immediately before intubation. Given that pentobarbital has a half-life of 15 to 48 hrs, a blood draw for ACTH and cortisol was considered to be influenced by this drug if the patient was receiving pentobarbital or blood was drawn in ≤48 hrs of stopping the infusion (39, 40). Because propofol has a half-life of only 24 to 64 mins, a blood draw for ACTH and cortisol was considered influenced by this drug only if the patient was receiving an infusion of ≥100 $\mu g/\cdot kg^{-1}\cdot min^{-1}$, generally considered the threshold rate to achieve electroencephalographic burst suppression (41–45).

Vasopressor Requirements. To determine whether AI was associated with increased vasopressor requirements, hourly vasopressor usage (dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin) was recorded. An hourly rating of low (1 point), moderate (2 points), or high (3 points) was determined for each of five vasopressors then summed for an overall vasopressor score (range, 0–15). Assigned dose ratings (low, moderate, high) were: dopamine (1–5, 5–10, 10–20 $\mu g/\cdot kg^{-1}\cdot min^{-1}$), norepinephrine (0.01–0.05, 0.05–0.10, 0.10–0.20 $\mu g/\cdot kg^{-1}\cdot min^{-1}$), phenylephrine (0.02–0.20, 0.20–1.0, 1.0–5.0 $\mu g/\cdot kg^{-1}\cdot min^{-1}$), epinephrine (0.03–0.05, 0.05–0.10, 0.10–0.20 $\mu g/\cdot kg^{-1}\cdot min^{-1}$), and vasopressin (none, 0.01–0.02, 0.02–0.40 units/min) (46, 47). The vasopressor score was calculated for the 8-hr time period within ±4 hrs of a given cortisol blood draw.

Global Outcome Measurement

Neurologic outcome was assessed at 6 months postinjury by staff blinded to AI status and other clinical data using the Glasgow Outcome Scale, with favorable outcome defined as good recovery (Glasgow Outcome Scale score of 5) or moderate disability (Glasgow Outcome Scale score of 4) (29, 48). Known predictors of neurologic outcome (age, GCS score, pupillary status, early hypotension or hypoxia, CT findings, ICP, and CPP time course) were also assessed (30–38, 49).

Data Analysis

Data with approximately normal distributions (MAP, cortisol) are summarized with mean values and 95% confidence intervals. Data with skewed distributions (age, GCS, ISS, CT score, length of ICU stay, vasopressor score) are summarized with percentiles. Comparisons between groups (TBI vs. ECT or AI vs. non-AI) at the subject level were performed with Student's *t*-tests for normally distributed data, Mann-Whitney tests for skewed data, and Fisher's exact tests for percentages. Differences between morning and afternoon cortisol values were performed with Wilcoxon's signed-rank test. Comparisons between groups at the blood draw level were performed with mixed models to account for the varying number of blood draws per subject and their intercorrelations. Multiple regression and logistic regression were used to adjust for the effect of potential confounding factors on continuous and on occurrence outcomes, respectively. Rates of AI were compared over global outcome categorizations using the Jonckheere-Terpstra test for trend. Because other factors related to outcome (age, GCS, ISS, pupillary status, early hypotension, hypoxia, CT findings, ICP, and CCP) are strongly correlated, a propensity score for AI derived as a function of these factors was used as a stratifying factor in logistic regression analyses predicting outcome from AI (50). A .05 level of significance was used, with no formal correction for multiple comparisons. Results of 50 statistical tests are reported here; approximately 100 additional tests were performed in exploring this voluminous multivariable data set.

RESULTS

Demographics

As seen in Table 1, the TBI and ECT cohorts were similar in terms of age and sex. However, median ISS was higher (26 vs. 24, $p = .005$) and length of ICU stay was longer (median, 6.0 vs. 4.0; $p = .004$) in the TBI cohort.

Incidence and Time Course of AI

The mean cortisol levels throughout the entire ICU admission were significantly greater for the TBI cohort than for the ECT cohort (median, 21.7 vs. 17.9 μg/dL; $p = .006$) (Table 1). In both cohorts, serum cortisol and ACTH levels were highest within 24 hrs of injury and declined thereafter (Figs. 1 and 2). Diurnal variation of cortisol release was lost in both the TBI and ECT cohorts ($p = .45$) (Table 1).

In total, 42 of 80 TBI subjects (53%; 95% confidence interval, 42–64%) met criteria for AI, with similar rates of AI at the three trauma centers ($p = .50$). Plasma ACTH levels were significantly lower ($p < .0001$) at time points when criteria for AI was met (median, 18.9 pg/mL) than for other times (median, 36.1 pg/mL). TBI subjects who developed AI first did so at a median of 2.4 days postinjury (range, 0.5–5.8 days), with 75% of them developing AI within 4 days. Throughout hospitalization, mean daily cortisol levels were significantly lower for AI than non-AI subjects ($p < .0001$), but ACTH levels were generally similar (Fig. 2).

Based on evaluation of 44 healthy volunteers (22 men and 22 women; median age, 36 yrs), the normal cortisol response to low-dose Cortrosyn was determined to be 11.1 to 27.9 μg/dL (mean − 2 SD, mean + 2 SD). A total of 30 of the 80 TBI subjects had Cortrosyn stimulation tests performed; most (27 of 30, 90%) had favorable global outcomes (good recovery or moderate disability). Among this group, AI subjects (n = 13) had lower mean peak cortisol response than non-AI subjects (n = 16) at 3 months postinjury (16.1 vs. 18.3 μg/dL, $p = .04$), although all results were within the normal range. At 6 months postinjury, repeat testing showed that AI subjects' mean peak cortisol response increased so that AI (n = 11) and non-AI (n = 14) groups had similar mean peak cortisol response (19.8 vs. 19.8 μg/dL, $p = .98$).

Clinical Characteristics Associated with AI

Table 2 displays characteristics of the TBI cohort at time of injury and across the entire ICU admission categorized by

Table 1. Characteristics of subjects with extracranial trauma (ECT) and traumatic brain injury (TBI)

	ECT		TBI		*p* Value
No. of subjects	41		80		
Age, yrs	25	(21, 45)	29	(21, 49)	.72
Male sex, n (%)	35	(85)	65	(81)	.62
ISS	24	(16, 25)	26	(24, 34)	.005
GCS, mean (%)					
14–15	41	(100)	0		
9–13	0		23	(29)	
3–8	0		57	(71)	
Days in ICU	4.0	(3, 7)	6.0	(4, 9)	.004
Cortisol, μg/dL					
Daily mean	17.9	(15.3, 22.6)	21.7	(18.6, 26.2)	.006
Morning mean	17.1	(15.1, 22.3)	21.8	(17.4, 26.4)	.008
Afternoon mean	17.7	(14.2, 24.4)	20.5	(17.0, 26.0)	.03
Afternoon–morning[a]	0.77	(−3.0, 5.5)	0.19	(−3.7, 4.0)	.42

ISS, Injury Severity Score; GCS, Glasgow Coma Scale; ICU, intensive care unit.

[a]Difference between afternoon (4 pm) and morning (6 am) cortisol values were, not significantly different from 0 for both ECT ($p = .46$) and TBI ($p = .95$) groups. All characteristics except sex and Glasgow Coma Scale (GCS) score are summarized with median (25th percentile, 75th percentile).

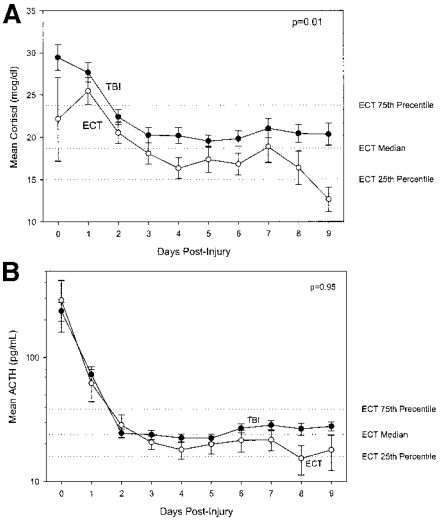

Figure 1. Mean daily serum cortisol (*top*) and plasma adrenocorticotropic hormone (*ACTH*; *bottom*) levels plotted as a function of days postinjury in extracranial trauma (*ECT*; *open circles*) and traumatic brain injury (*TBI*; *closed circles*) subjects. The *dotted horizontal lines* denote the 75th percentile, median, and 25th percentile values of the ECT cohort.

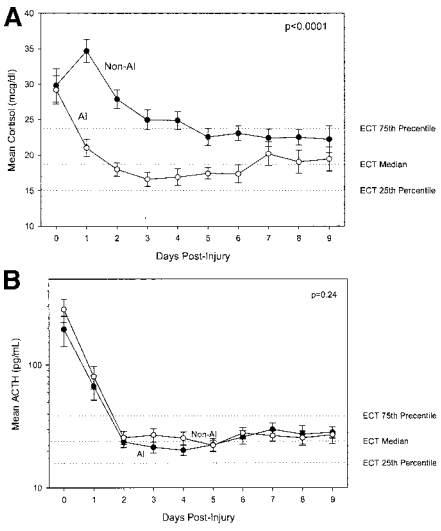

Figure 2. Mean daily serum cortisol (*top*) and plasma adrenocorticotropic hormone (*ACTH*; *bottom*) levels plotted as a function of days postinjury in adrenal insufficiency (*AI*; *open circles*) and non-AI (*closed circles*) subjects with traumatic brain injury. The *dotted horizontal lines* denote the 75 percentile, median, and 25th percentile values of the extracranial trauma (*ECT*) cohort.

AI status. The AI subjects were younger (median, 26 vs. 40 yrs of age; $p = .01$) and had more severe injuries by ISS (median, 28 vs. 25; $p = .02$). The postresuscitation GCS score was ≤8 in 79% of subjects with AI and in 63% of those without AI. The AI group had a greater frequency of ischemic insults than the non-AI group (ischemia score, $p = .02$). No TBI subject in either the AI or non-AI cohorts had sepsis.

Medication Effects: Etomidate. In total, 33 of 41 subjects (81%) with AI received etomidate, and 22 of 38 subjects (58%) without AI received etomidate ($p = .049$) (Table 2). In those who received etomidate, there was a significant positive correlation ($r = .35$; $p = .01$) between the time from etomidate administration to the first subsequent blood draw (at a mean of 10 hrs after etomidate administration) and cortisol level at that blood draw, with cortisol increasing a mean of 0.81 μg/dL per hour after etomidate administration. Among all blood samples taken within 24 hrs of injury, mean cortisol levels in subjects who had been given etomidate were significantly lower than those without etomidate (27.2 vs. 35.5 μg/dL, $p = .002$), but this difference was minimal in the second day postinjury (22.1 vs. 24.6 μg/dL, $p = .32$) (Table 3).

Medication Effects: Metabolic Suppressive Agents. Metabolic suppressive agents were used at some time during the ICU hospitalization in twice as many AI subjects as non-AI subjects (26.2% vs. 13.1%), but this difference did not reach statistical significance ($p = .17$). However, mean cortisol measurements taken under metabolic suppression agents (87 out of a total of 860 blood draws—10.1% of total), irrespective of AI status, were lower than those without metabolic suppression influence (14.7 vs. 23.4 μg/dL, $p < .0001$).

Hemodynamic Status and Vasopressor Usage. Over the ICU course, MAP was <60 mm Hg at some time in 26.2% of AI subjects compared with 13.1% of non-AI subjects ($p = .002$), with the lowest MAP lower for the AI cohort (median, 56.2 vs. 63.4; $p = .001$). Vasopressors were used in 57.1% of AI subjects compared with 34.2% of non-AI subjects ($p = .047$) (Table 2), and vasopressors scores were higher ($p = .01$) in the AI cohort compared with the non-AI cohort. Irrespective of AI status, mean MAP (in the 8 hrs preceding each blood draw) was slightly but significantly lower before a cortisol level of ≤15 μg/dL compared with blood draws when cortisol was at >15 μg/dL (87.0 vs. 89.6 mm Hg, $p = .003$), as was the minimal MAP in the 8-hr period (77.6 vs. 79.69 mm Hg, $p = .008$). As shown in Table 3, during the ±4 hrs around a cortisol blood draw, mean cortisol levels in the absence of vasopressor use were higher than when any vasopressor was used (23.4 vs. 19.7 μg/dL, $p = .0005$). Similar results are observed for a ±2-hr window (data not shown).

Multivariate Analysis. Most of the associations in Table 2 remain after adjusting for other factors in the Table. The exceptions are as follows. The etomidate association ($p = .049$) is reduced to nonsignificant levels ($.05 < p < .15$) after adjustment for age, GCS, and MAP measures. The difference in the prevalence of any vasopressor use (57.1% vs. 34.2%, $p = .047$) is reduced to nonsignificant levels ($.05 < p < .15$) after adjustment for GCS, ISS, hypotension, hypoxia, ischemia score, metabolic suppressive agents,

Table 2. Traumatic brain injury (TBI) subject characteristics according to adrenal insufficiency status

	Non-Adrenal Insufficiency		Adrenal Insufficiency		*p* Value
No. of subjects	38		42		
At Time of Injury					
Age	40	(25, 56)	26	(19, 35)	.010
Male sex (%)	33/38	(86.8)	32/42	(76.2)	.26
GCS (postresuscitation)	7.0	(6, 10)	6.5	(3, 8)	.10
ISS	25	(17, 29)	28	(25, 36)	.022
Early ischemia factors (%)					
Hypotension[a]	16/38	(42.1)	27/42	(64.3)	.072
Hypoxia[b]	7/38	(18.4)	14/41	(34.2)	.13
Hematocrit <25%[c]	7/38	(18.4)	12/42	(28.6)	.31
Ischemia score (%)[d]					.021
0	19/38	(50.0)	11/41	(26.8)	
1	8/38	(21.1)	12/41	(29.3)	
2	11/38	(29.0)	13/41	(31.7)	
3	0/38	(0.0)	5/41	(12.2)	
CT Findings					
Abnormal cisterns on CT (%)	23/38	(60.5)	22/42	(52.4)	.50
CT composite score[e]	2.0	(0, 4)	2.0	(0, 3)	.37
Medications					
Received etomidate (%)	22/38	(57.9)	33/41	(80.5)	.049
Received metabolic suppressive agents (%)[f]	5/38	(13.1)	11/42	(26.2)	.17
Vasopressor score[g]					
Mean	0.21 (0.03–0.39)		1.04 (0.62–1.47)		.001
50th/75th/90th percentiles	0.0/0.13/0.91		0.10/1.83/2.83		.007
>0 (%)	13/38	(34.2)	24/42	(57.1)	.047
Blood Pressure, ICP, CPP					
Mean arterial pressure					
Lowest	63.4	(60.5–66.3)	56.2	(52.8–59.5)	.001
Ever <60 (%)	10/38	(26.3)	26/42	(61.9)	.002
Mean	90.1	(87.0–93.1)	86.8	(84.2–89.5)	.11
Mean ICP[h]	16.1	(11.3–20.9)	17.3	(15.0–19.5)	.66
Mean CPP[h]	74.4	(68.3–80.4)	70.9	(67.2–74.7)	.32

GCS, Glasgow Coma Scale; ISS, Injury Severity Score; CT, computed tomography; ICP, intracranial pressure; CCP, cerebral perfusion pressure.

[a]Systolic blood pressure < 90 within 72 hrs of injury.

[b]Pa_{O_2} < 60 within 24 hrs of injury, or apnea or agonal respirations in the field; [c]lowest hematocrit within 72 hrs of injury; [d]the ischemia score ranges from 0 to 3, with 1 point for each of hypotension, hypoxia, and hematocrit of <25%, and the *p* value is from the Cochran-Armitage test for trend; [e]CT composite score ranges from 0 to 8, with 1 point for each of bilateral swelling, abnormal cisterns (compressed or absent), midline shift of >4 mm, suprasellar subarachnoid hemorrhage, evacuated subdural hematoma, hypothalamic hemorrhage, hypothalamic swelling, and sphenoid/sellar fracture; [f]propofol = 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or any pentobarbital; [g]larger scores indicate greater use of dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin (see text for definition); [h]restricted to n = 22 non-adrenal insufficiency and n = 33 adrenal insufficiency subjects with ICP monitors. Age, GCS, ISS, and CT score are summarized with median (25th percentile, 75th percentile). Mean ICP, CPP, vasopressor score, and mean and lowest mean arterial pressures are summarized with mean (95% confidence interval).

minimum MAP, and etomidate use. The ISS association, with $p = .02$, is reduced to nonsignificant levels ($.05 < p < .15$) after adjustment for age, hypotension, and ischemia score and to $p = .22$ after adjustment for GCS. The AI association with ischemia score ($p = .02$) is reduced to nonsignificant levels ($.05 < p < .15$) after adjustment for ISS, GCS, MAP < 60, and vasopressor use and to $p = .31$ and .20 after adjustment for minimum MAP and mean vasopressor score, respectively.

The factors in Table 2 were also reassessed by restricting the analysis to the subgroup of 64 subjects who received no metabolic suppressive agents. Associations observed in the full set of subjects are maintained, with the exception of ischemia score, vasopressor score, and etomidate use, which all have similar trends in this smaller group. Although the mean score is still higher in the AI group than the non-AI group ($p = .008$); statistical significance is lost for vasopressor score distribution (50th/75th/90th percentiles = 0/0/0.38 and 0/1.6/2.0, $p = .10$) and for prevalence with any vasopressor use (42% vs. 27%, $p = .29$). Etomidate use is almost identical in this subgroup as in the full set of subjects (58% vs. 80%), but significance is lost with only 64 subjects ($p = .11$). The *p* value for ischemia score is increased from .02 to .07.

Subjects with Cortisol Levels of <5 μg/dL: Severe AI. Of the 42 subjects with AI, 13 (31%) met criteria by having a serum cortisol level of <5 μg/dL. All of these subjects also had at least one additional cortisol level of ≤15 μg/dL. The associations noted in Table 2 remained when this subgroup was compared with those without AI, except that injury severity lost significance (26 vs. 25, $p = .27$) and the use of metabolic suppressive agents gained significance (46.2% vs. 13.1%, $p = .02$).

Outcome Analysis by Glasgow Outcome Scale. As shown in Figure 3, rates of favorable outcome (good recovery or moderate disability) at 6 months postinjury were lower in both subsets of subjects with AI compared with the non-AI group. This trend for poorer outcome with increasing severity of AI was also seen when the cohort was categorized into three groups of non-AI vs. moderate AI (two cortisol levels of ≤15 μg/dL) vs. severe AI (one cortisol level of <5 μg/dL) but was not statistically significant ($p = .09$, Jonckheere-Terpstra test). However, poor outcome was strongly associated with other factors that have been identified previously: lower initial GCS score ($p < .001$), abnormal pupillary status ($p = .001$), hypotension or hypoxia ($p < .0001$), poorer CT findings ($p < .0001$), increased ICP ($p = .0004$), and decreased CPP ($p = .001$). Multivariate adjustment for these factors did not change the weak association between AI and outcome ($p = .12$).

DISCUSSION

This is the largest prospective study performed to date that systematically defines the incidence of AI and its associated clinical characteristics during the first 9 days after TBI. We found that transient relative AI occurred in approximately 50% of patients with moderate or severe TBI, that AI seemed to be central in origin, and that AI was associated with younger age, greater injury severity, early ischemic insults, etomidate administration, lower MAP, and higher vasopressor requirements.

Previous Studies. The acute effects of head injury on the HPA axis have been investigated for over three decades (51–56). However, shortcomings of previous

Table 3. Medications and cortisol levels

	No. of Blood Draws	Cortisol, μg/dL Mean (95% Confidence Interval)
Etomidate[a]		
Blood draws within 24 hrs of injury		
Previous etomidate	99	27.2 (24.3–30.2)
No previous etomidate	44	35.5 (31.2–39.9)
p value		.002
Blood draws 24–48 hrs after injury		
Previous etomidate	108	22.1 (19.4–24.8)
No previous etomidate	44	24.6 (20.4–28.8)
p value		.32
Metabolic suppressive agents[b]		
Under influence	87	14.7 (11.4–18.0)
Not under influence	773	23.4 (21.7–25.0)
p value		<.0001
Vasopressor score[c]		
0	743	23.4 (22.0–24.9)
>0	218	19.7 (17.6–21.8)
>0 to ≤3	145	20.1 (18.0–22.2)
>3	73	19.6 (16.8–22.5)
p value: 0 vs. >0		.0005

[a]Etomidate, when given, was administered as a single dose immediately before intubation; [b]under the influence of metabolic suppressive agents = at least 100 μg/kg/min of propofol administered at the time of blood draw, or any pentobarbital in the 48 hrs before the blood draw; [c]larger scores indicate greater use of dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin (see text for definition).

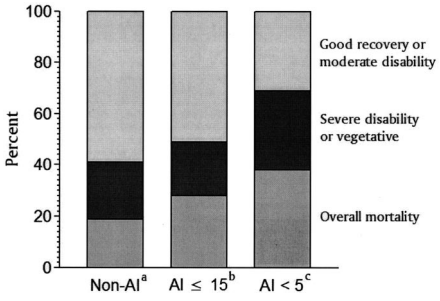

Figure 3. Long-term outcome by Glasgow Outcome Scale. [a]*Non-AI,* subjects without adrenal insufficiency. One subject in this group (n = 38) was lost to follow-up. [b]AI ≤ 15, (moderate) adrenal insufficiency subjects with two consecutive serum cortisols of ≤15 μg/dL. [c]AI < 5, (severe) adrenal insufficiency subjects with a serum cortisol of <5 μg/dL (and at least one other cortisol of ≤15 μg/dL). $p = .09$ (Jonckheere-Terpstra test for trend).

studies include single time point hormone sampling in some (53), the failure to measure both ACTH and cortisol in others (51, 52, 54, 55), and relatively small sample size in all previous studies. Moreover, these studies evaluated neither the effect of medications on cortisol levels nor the hemodynamic consequences of low serum cortisol levels. In the recent prospective study of Dimopoulou et al. (57), with study aims and design closely resembling ours, the HPA axis of 34 TBI subjects was assessed by means of a corticotropin-releasing hormone stimulation test done at a single time point the day after weaning from mechanical ventilation. Defining AI as post–corticotropin-releasing hormone peak cortisol levels of <20 μg/dL, one quarter of patients were classified as having AI. In a subsequent analysis (58), the same group reported that approximately 15% of TBI subjects responded inappropriately to low-dose (1 μg) corticotropin and that these "corticotropin nonresponders" more frequently required vasopressors. Compared with our findings, the lower rate of AI observed in the studies of Dimopoulou et al. may be explained by two factors: 1) a selection bias was introduced by assessing only those patients who survived to be successfully weaned from mechanical ventilation, and 2) the corticotropin-releasing hormone test assesses pituitary and adrenal responsiveness but fails to detect AI in individuals with hypothalamic injury.

Definition of AI. Due to the multitude of factors (e.g., variability in injury severity and alterations in cortisol-binding globulin) that complicate the assessment of the adrenal axis during critical illness, we recognized that determining an absolute biochemical definition of AI in the context of acute TBI might be untenable. Instead, we sought to derive a working definition of AI by assessing the HPA response of a group of 41 age- and sex-matched ECT patients who had not sustained significant head injury. Because the signals that regulate cortisol release (i.e., corticotropin-releasing hormone and ACTH) ultimately emanate from the brain, we thought that such a group would control for those factors common to the critical illness that accompanies acute trauma in general yet permit the influences unique to TBI to persist. The 25th percentile cortisol value of the ECT group corresponded to a value of 15 μg/dL. Because of the high variability noted in successive cortisol determinations, and to minimize overdiagnosis of AI, we defined AI as two consecutive cortisol values falling below this threshold of 15 μg/dL. Based on three lines of evidence, we think that this was a suitable biochemical definition of AI that minimized overclassification: 1) overall, the mean cortisol level of the ECT cohort was lower than the TBI cohort, a difference likely explicable by greater injury severity in the latter group and which served to lower the absolute cortisol level for the diagnostic threshold of AI; 2) throughout the ICU hospitalization, the mean daily cortisol curves of those who met the criteria of AI were significantly separated from those who did not (Fig. 2, *top*); and 3) several other studies suggest that a cortisol level of <15 μg/dL in the context of critical illness significantly increases suspicion for hypoadrenalism (59–62).

We also recognize that cortisol-binding globulin levels may change during critical illness. Therefore, measuring serum total cortisol may not reflect the free or bioavailable cortisol (63). Although cortisol-binding globulin measurements are being done in stored serum from our subjects and in our ongoing hydrocortisone-replacement trial after TBI, cortisol-binding globulin measurement is not practical in an acute setting, and a surrogate measure of free cortisol such as salivary cortisol monitoring may be preferable.

Our findings that subjects with AI had lower blood pressure and higher vasopressor requirements provide physiologic credence for the cut-point of 15 μg/dL. To that end, we have begun a randomized, placebo-controlled, 4-day trial of physiologic stress dose hydrocortisone (50 mg intravenously every 8 hrs) in TBI patients who meet these criteria for AI. Our rationale and study design is quite different from the recently published CRASH trial (corticosteroid randomiza-

Because lower cortisol levels were associated with lower blood pressure and higher vasopressor use, consideration should be given to monitoring cortisol levels in intubated patients with traumatic head injury, particularly those receiving high-dose pentobarbital or propofol.

tion after significant head injury), which noted increased mortality in TBI patients treated with methylprednisolone (64). In that study, subjects were treated regardless of their adrenal status with supraphar macologic doses of glucocorticoids (approximately 200 times higher than the physiologic dose we are using). Our intent is to randomize only TBI patients with AI and use a hydrocortisone dose roughly equivalent to physiologic stress levels of cortisol and similar to the study of Annane et al. (19), in which a short course of low-dose hydrocortisone reduced mortality in patients with septic shock and relative AI.

Pathophysiology of AI after TBI. We hypothesized that hypothalamic-pituitary hypoperfusion might play a role analogous to Sheehan's postpartum pituitary necrosis (65), particularly in light of the pituitary gland's delicate infundibular-hypothalamic structures and vulnerable vascular supply, and results of autopsy studies that document acute pituitary necrosis in up to one third of fatal head injury victims (4–8). Indeed, the ischemia score used in this study to assess the cumulative effect of hypotension, hypoxia, or severe anemia suggests that such insults in the acute postinjury period may predispose TBI subjects to acute AI.

Our data also indicate that metabolic suppressive agents such as high-dose pentobarbital or propofol are strongly associated with lower cortisol levels. Although reduction in serum cortisol levels has been reported in critically ill patients sedated with propofol, these effects on adrenal steroidogenesis have generally been regarded as clinically insignificant (66, 67). Data on the effects of pentobarbital on adrenal axis in humans are lacking, although another barbiturate, phenobarbital, is known to induce hepatic microsomal enzymes and thereby increase corticosteroid metabolism (68). A potential shortcoming in our study is that we did not assess the effect of other pharmacologic agents such as the sedative midazolam, narcotic analgesics like morphine and fentanyl, and anticonvulsants, which may also blunt the HPA axis or interfere with corticosteroid metabolism (69–71). These agents were not studied given that their use in this patient population is typically at low doses in contrast to high-dose pentobarbital and propofol. Even if these agents blunt the HPA axis, a central question remains: are these reductions in serum cortisol pathologic (and therefore warranting treatment) or merely the physiologic result of lowering the stress of illness? At this time, a definitive answer is only available for etomidate, which has been unequivocally shown to inhibit adrenal steroidogenesis (72–74), a property that has even been exploited to treat Cushing's syndrome (75).

Regarding etomidate, although 70% of our subjects received etomidate, its use was limited to a single dose before intubation soon after admission. When used in this fashion, the effect of etomidate on adrenocortical function is controversial: some studies show little (76) or no (77) effect, whereas others document lingering effects on the HPA axis for ≥24 hrs (78, 79). In keeping with the latter, we noted that AI subjects were more likely to have received etomidate, but etomidate did not affect cortisol levels after the first postinjury day. Therefore, it is likely that its effect on the development of subsequent AI was likely minimal in many patients given that the median onset of AI was 2.4 days postinjury.

Time Course of AI. The fact that all subjects with acute AI assessed at 3 or 6 months, or both, postinjury responded normally to low-dose (1 μg) Cortrosyn suggests it is a transient phenomenon, at least in the subset of survivors with largely favorable long-term outcomes who were able to be tested. However, the lower peak cortisol response in the AI group compared with the non-AI group at 3 months suggests that the influence of TBI on the HPA axis may persist for up to 3 months, with full recovery likely occurring by 6 months postinjury. Previous studies on chronic pituitary insufficiency after TBI also indicate that the HPA axis is relatively resilient to head injury and that chronic AI is uncommon (12–14).

CONCLUSIONS

Our data indicate that a transient state of relative AI, associated with lower MAP and increased vasopressor requirements, occurs commonly after moderate or severe TBI. In light of these findings and because 1) hypotension is a strong predictor of poor outcome after TBI (80) and 2) excessive vasopressor use has been associated with a higher rate of systemic complications after TBI (81), strong consideration should be given to routine monitoring of serum cortisol levels acutely in this patient population. The ultimate clinical benefit of providing stress-dose glucocorticoids to intubated head-injured patients with AI as defined in this study will be determined by a randomized, prospective study that is currently underway.

ACKNOWLEDGMENTS

We thank Diana Nikas, RN, NP, Charlene Chaloner, RN, Nancy Rudisill, RN, Janice Wang-Polagruto, PhD, Lori Madden, RN, NP, Sylvia Lopez, RN, and Dioni Rovello-Freking, RN, NP, for their invaluable assistance as coordinators of this study; the General Clinical Research Center nurses of the three clinical sites; Pauruchisty Buxey for dedicated support as manager of the database; and Noreen Mirza, James Wiseman, Stephanie Griffiths, the Core Laboratory of the Harbor–UCLA Medical Center General Clinical Research Center, and Anthony Butch, PhD, of the UCLA Clinical Laboratory for their assistance.

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