EM Advances

Adrenal inhibition following a single dose of etomidate in intubated traumatic brain injury victims

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ABSTRACT

Background: Etomidate is frequently used to intubate traumatic brain injury (TBI) victims, even though it has been linked to adrenal insufficiency (AI) in some populations. Few studies have explored the risk of prolonged etomidate-induced AI among TBI victims.

Objective: To determine the risk and the length of AI induced by etomidate in patients intubated for moderate and severe TBI.

Methods: Participants in this observational study were moderate to severe intubated TBI victims aged ≥ 16 years. The anesthetic used (etomidate versus others) was determined solely by the treating emergency physician. Adrenocorticotropic hormone (ACTH) stimulation tests (250 μg) were performed 24, 48, and 168 hours after intubation. AI was defined as an increase in serum cortisol 1 hour post–ACTH test (delta cortisol) of less than 248.4 nmol/L.

Results: Forty subjects (participation 42.6%) underwent ACTH testing. Fifteen received etomidate, and 25 received another anesthetic. There were no statistically significant differences between groups as to the cumulative incidence of AI at any measurement time. However, at 24 hours, exploratory post hoc analyses showed a significant decrease in delta cortisol (adjusted means: etomidate group: 305.1 nmol/L, 95% CI 214.7–384.8 versus other anesthetics: 500.5 nmol/L, 95% CI 441.8–565.7). This decrease was not present at 48 and 168 hours.

Conclusion: In TBI victims, although a single dose of etomidate does not increase the cumulative incidence of AI as defined, it seems to decrease the adrenal response to an ACTH test for 24 hours. The clinical impacts of this finding remain to be determined.

RÉSUMÉ

Contexte: L'étomidate est souvent utilisé dans l'intubation des personnes ayant subi une lésion cérébrale traumatique (LCT), malgré le fait que le produit soit lié à une insuffisance surrénalienne (IS) dans certains groupes de patients. Peu d'études ont porté sur le risque d'IS prolongée, causée par l'étomidate, chez les patients ayant subi une LCT.

Objectif: L'étude visait à déterminer le risque d'IS causée par l'étomidate, et sa durée, chez des patients intubés après avoir subi une LCT modérée ou grave.

Méthodes: Les participants à cette étude d'observation étaient des personnes âgées de 16 ans et plus, intubées après avoir subi une LCT modérée ou grave. Le choix de l'anesthésique (étomidate ou autres produits) ne relevait que de l'urgentologue traitant. Des épreuves de stimulation par la corticotrophine (ACTH; 250 μg) ont été effectuées 24, 48, et 168 heures après l'intubation. L'IS a été définie comme une augmentation du cortisol sérique, inférieure à 248.4 nmol/L, 1 heure après l'administration d'ACTH (delta cortisol).

Résultats: Quarante sujets (participation 42.6%) ont été soumis à des épreuves à l'ACTH. Quinze avaient reçu de l'étomidate et 25 un autre anesthésique. Il n'y avait pas de différence statistiquement significative entre les groupes en ce qui concerne l'incidence cumulée de l'IS, à n'importe quel point de mesure dans le temps. Toutefois, les analyses exploratoires, au bout de 24 heures, ont révélé une diminution importante du delta cortisol (moyennes ajustées:

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étomidate: 305.1 nmol/L, IC à 95% 214.7–384.8; autres anesthésiques: 500.5 nmol/L, IC à 95% 441.8–565.7), mais cette diminution avait disparu au bout de 48 et 168 heures.
Conclusion: Bien que l'administration d'une seule dose d'étomidate chez les personnes ayant subi une LCT n'augmente pas l'incidence cumulée de l'IS, telle qu'elle a été définie ici, elle semble toutefois diminuer la réaction surrénalienne à l'épreuve de stimulation par l'ACTH pendant 24 heures. On ne connaît cependant pas la portée clinique de cette constatation.

Keywords: adrenal insufficiency, etomidate, traumatic brain injury

Etomidate is one of the most frequently used anesthetics for intubating head trauma patients.[1–3] The favourable cardiovascular and neuroprotective effects of etomidate make it an ideal agent for these patients.[4,5] Although etomidate is safe in elective surgical patients,[6–10] in critically ill patients, studies have shown adrenal insufficiency (AI) lasting 48 hours after a single bolus.[11–13] Authors have therefore suggested that etomidate be avoided for critically ill patients, especially those in septic shock.[14–17] In trauma patients, a randomized, controlled trial (RCT) comparing etomidate to fentanyl showed that etomidate increased the risk of AI measured 6 hours after administration. Etomidate was also related to more ventilator days and longer intensive care unit (ICU) lengths of stay.[18] An RCT that enrolled 469 patients showed that etomidate did not increase 28-day mortality compared to ketamine (81% versus 72%, $p = 0.2$); however, it increased the risk of AI (86% versus 56%, $p < 0.0001$) measured 7 hours after administration. In a subgroup of 104 trauma patients, including 78 traumatic brain injury (TBI) victims, this RCT found no differences in outcomes between the two agents.[19] A systematic review on the impact of etomidate on all patient populations could not conclude definitively about the possible harm or benefit of etomidate on mortality, ventilator duration, ICU length of stay, and adrenal suppression beyond 12 hours because of limited data.[20] Thus, more research is needed on this topic.

IMPORTANCE OF THE QUESTION

Every year, about 1.5 million patients die from TBI worldwide.[21,22] Given that TBI victims are known to be at risk for AI from injury to the pituitary gland[23–25] and from other causes,[26,27] the additional AI that could result from using etomidate might increase TBI mortality and morbidity. Given that high-dose corticosteroids have been shown to increase TBI mortality,[28,29] corticosteroids are avoided in this population. This decrease in the use of corticosteroids offers an opportunity to better determine the length of etomidate-induced AI and to assess the deleterious effects of etomidate-induced AI in TBI victims.

OBJECTIVE OF INVESTIGATION

We sought to determine the risk and length of AI after a single bolus dose of etomidate to intubate TBI victims in an emergency department (ED).

METHODS

Study design and setting

Subjects of this observational study were recruited at a level 1 trauma centre with the approval of the Institutional Review Board. Two groups were constituted: one group of patients who had received etomidate and another group composed of patients who had received any other anesthetic. Exposure to etomidate was not randomized but was determined by the treating emergency physician. We performed three high-dose (250 μg) adrenocorticotropic hormone (ACTH) stimulation tests on each subject 24, 48, and 168 hours after administration of etomidate and compared the cumulative incidence and length of AI of the two groups.

Selection of participants

All trauma victims seen in the ED during the recruitment period (August 2003 to October 2004) aged ≥ 16 years were considered for inclusion. Patients transferred from other hospitals within 24 hours after intubation were also eligible. Inclusion criteria consisted of intubated moderate and severe TBI victims with or without other organ injuries, a Glasgow Coma Scale (GCS) score ≤ 12, and evidence of brain injury on a computed tomographic (CT) scan as determined by a radiologist. Patients were excluded if they were allergic to cosyntropin (ACTH), were known to have pre-existing AI, had received systemic corticosteroids in the previous 6 months, had received corticosteroids during the first 24 hours of the study, had

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undergone pituitary surgery, developed cerebral death in the first 24 hours of the study, were septic at the moment of intubation, were taking ketoconazole, were pregnant, or were seropositive for human immunodeficiency virus (HIV). Screening for eligible patients was performed daily in the ED and ICU. We contacted family members to assess exclusion criteria and seek consent in the first 24 hours after intubation. Patients were excluded if consent could not be obtained in the first 24 hours.

Interventions

As this was an observational study, etomidate and other anesthetics were administered according to drug availability and physicians' preferences. Thus, physicians were not blinded to the anesthetic used.

Patients underwent ACTH stimulation tests 24, 48, and 168 hours after intubation. Serum cortisol levels were determined at baseline and 30 and 60 minutes after administering ACTH in any available intravenous line. Blood samples were sent immediately to the laboratory, where they were centrifuged and frozen.

Methods of measurement

Samples were analyzed in batches using the same AxSym immunoassay system from Abbott (Abbott Park) so as to decrease interassay variability. The coefficient of variability was 10 to 15% for 75 nmol/L, 5% for 450 nmol/L, and 6% for 850 nmol/L.[30] When levels of cortisol were over 1,656 nmol/L, a dilution process was performed, introducing negligible imprecision.

The treating physician was not given the assay results. When she or he requested immediate results, additional assays were performed with the Beckman Coulter Access Immunoassay System (Beckman Coulter, Inc., Brea, CA), the only system in our hospital that can produce immediate results 24 hours per day.

Data collection and processing

The results for cortisol assays were collected by a biochemist who was blinded to the anesthetic used. For all patients screened, we collected baseline data about age, gender, GCS score, anesthetic used, and reason for exclusion (if applicable). Other baseline characteristics were collected retrospectively from the Quebec Trauma Registry or extracted from the medical charts using a structured data collection form. Follow-up ended at hospital discharge and was completed for every subject enrolled.

Outcome measures

The primary outcome measure was the cumulative incidence of AI at 24, 48, and 168 hours. As per Annane and colleagues' criterion,[31] we defined AI as a delta cortisol of less than 248.4 nmol/L. Although controversial,[32] this definition has been associated with increased mortality in septic shock patients.[33] Delta cortisol was defined as the difference between the maximum increase in cortisol at 30 or 60 minutes after the ACTH stimulation test and the baseline cortisol level. Secondary outcomes were mortality and cumulative incidence of patients treated for adrenal insufficiency at 7 days.

Given that this study was observational, potential confounding variables had to be measured to adjust estimates of the strength of the associations. A priori, we selected three variables in this regard: age, gender, and the Injury Severity Score (ISS). In light of research published after our study began, we also considered other potentially confounding variables (Appendix 1).

Statistical analysis

The distribution of variables was first verified, and missing or outlying data were checked to control quality. We compared baseline demographic variables using the chi-square test, Fisher exact test, Student *t*-test, or Mann-Whitney test. Then we analyzed the crude association between exposure to etomidate and the cumulative incidence of AI at 24, 48, and 168 hours in bivariate analyses using the Fisher exact test. Mortality and cumulative incidence of patients treated for AI were also analyzed using the Fisher exact test. In an exploratory post hoc analysis, we compared delta cortisol in bivariate analyses using the Mann-Whitney test to assess the effect of etomidate on adrenal reserve at 24, 48, and 168 hours. We also performed multiple logistic regression analyses (planned a priori for cumulative incidence of AI) and analysis of covariance (performed post hoc for delta cortisol) to produce results adjusted for actual confounders. Potential confounding variables that changed the regression coefficient of exposure to etomidate by $> 10\%$ were kept in the final models. To test the robustness of the final models, we analyzed the outlying residuals. The level of significance retained for all analyses was 0.05.

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Sensitivity analyses were performed to estimate the impact of a potential selection bias on outcomes (Appendix 2). Data were analyzed using the *SAS* version 9.1 statistical program (SAS Institute, Cary, NC).

RESULTS

Characteristics of the study subjects

Figure 1 shows the flow of patients in the study. Among the 185 patients considered, 94 were eligible to participate. Nineteen were excluded because of corticosteroid use (see Figure 1). The 54 missed patients were less severely injured than participants (Appendix 3). Overall, 40 patients underwent ACTH stimulation tests (participation 42.6%), with 15 having received etomidate and 25 having received another induction agent. Table 1 presents the characteristics of these subjects. The only statistically significant differences between both groups were that patients who received etomidate were more likely to have been intubated at the level I trauma centre (without transfer) ($p < 0.0001$) and had shorter transfer times ($p = 0.002$) than those who had received another agent. Without reaching statistical significance, there was a trend for patients who received etomidate to be younger ($p = 0.11$), to have higher ISSs ($p = 0.23$), and to have a lower mean arterial pressure ($p = 0.48$).

Main results

Table 2 presents the results of bivariate analyses conducted for the primary and secondary outcomes. The results do not show that etomidate significantly increases the cumulative incidence of AI defined as a delta cortisol less than 248.4 nmol/L at any measurement time. Over the 7 days, the cumulative incidence was 7 of 15 (26.7%) in the etomidate group and 4 of 25 (16%) in the other anesthetic group.

At 24 hours, the crude odds ratio of AI was 1.8 (95% CI 0.3–10.5); it was 4.6 (95% CI 0.3–67.5) after adjustments. In both cases, the confidence intervals were very large and indicated no effect of etomidate on the risk of AI at 24 hours defined as a delta cortisol less than 248.4 nmol/L. However, our exploratory post hoc analyses found that etomidate negatively impacts delta cortisol at 24 hours. As shown in Figure 2 and Table 3, the etomidate group had significantly lower crude delta cortisol results at 24 hours than the other group. This difference remained significant after adjustment for confounders (see Table 3) and when extreme values were excluded from the regression model. At 48 and 168 hours, this effect was not present.

Table 4 (etomidate group) and Table 5 (other anesthetic group) present crude results for baseline cortisol and delta cortisol for each patient included in this study. The reasons for censoring are described as well. Three deaths occurred in the etomidate group during the first 7 days (3 of 15; 20%) compared to one death in the other group (1 of 25; 4%). This difference in mortality was not statistically significant (see Table 2). One of the deceased patients exposed to etomidate had proven AI (see Table 4, patient 8). The only death in the other group was not related to AI. None of the deceased patients had received hydrocortisone. Hydrocortisone was given to three patients (20%) exposed to etomidate and to two patients (8%) in the other group (see Table 2). Of the three etomidate recipients treated with hydrocortisone, one had proven AI as per ACTH testing (see Table 4, patient 14). This patient also had possible hypopituitarism with diabetes insipidus. Another etomidate recipient treated with hydrocortisone had a normal delta cortisol assay measurement (250.4 nmol/L) as per the AxSym immunoassay system but received hydrocortisone because clinicians suspected AI and performed a simultaneous assay with the Access immunoassay system, which found an abnormal delta cortisol (213 nmol/L) (see Table 4, patient 10). No subjects in the other group with biochemically proven AI received hydrocortisone. Both hydrocortisone recipients in the other anesthetic group were considered to have hypopituitarism as per pituitary hormonal assays (Table 5, patients 10 and 13).

DISCUSSION

Comparison with previous literature

Our study did not find a statistically significant difference in the cumulative incidence of AI at 24, 48, or 168 hours. In comparison with Vinclair and colleagues, who showed that etomidate-induced AI lasted up to 48 hours in a group of critically ill patients (n = 40, including 18 trauma victims),[13] we found a lower risk of AI at 24 hours (20%) and 48 hours (9%) than they did (49% and 22%, respectively). This difference might be due to the inclusion of patients with spontaneous subarachnoid hemorrhage who might

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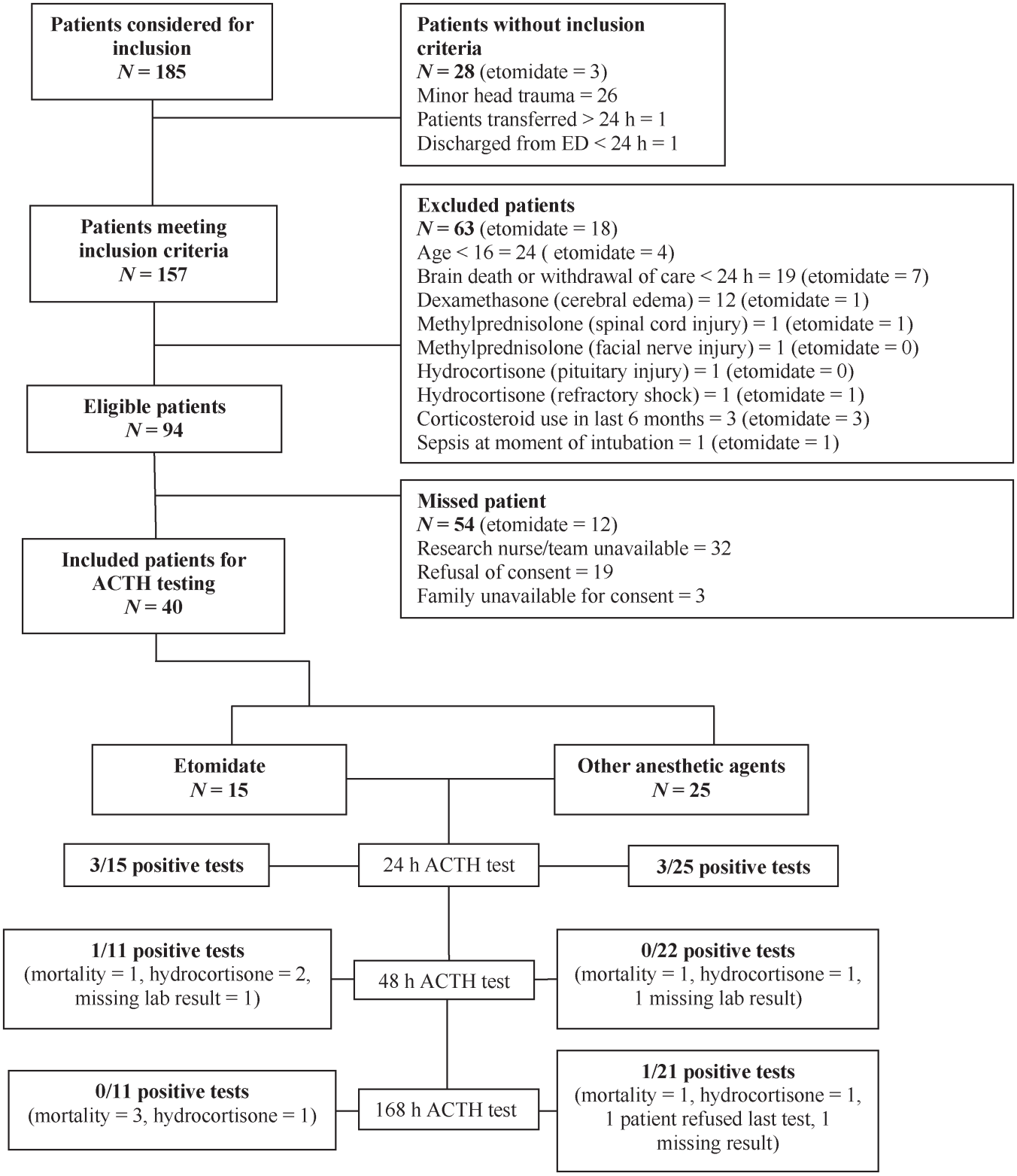

Figure 1. Flow of subjects through the study. ACTH = adrenocorticotropic hormone; ED = emergency department.

have a higher risk of AI.[34] Our results are consistent with the findings of Hildreth and colleagues, where the etomidate group presented a blunted response to ACTH 6 hours postintubation (delta cortisol = 116 ± 135 nmol/L) compared to the fentanyl-midazolam group (delta cortisol = 309 ± 168 nmol/L).[18]

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Table 1. Baseline characteristics of participants who underwent ACTH tests

	Etomidate (n = 15)	Other anesthetics (n = 25)
Mean age, yr (SD)	35 (12)	45 (19)
Male sex, *n* (%)	11 (73)	18 (72)
Mean arterial pressure, mm Hg (SD)	84 (20)	90 (26){1}*
Mean GCS score (SD)	7 (3)	7 (3)
GCS score ranges, *n* (%)		
14–15	1 (7)	1 (4)
9–13	4 (27)	5 (20)
3–8	10 (66)	19 (76)
Subjects transferred, (*n* (%)	4 (27)	22 (88)
Subjects who underwent surgery in first 24 h, *n* (%)	6 (40)	8 (32)
Mechanism of injury, *n* (%)		
Motor vehicle	11 (73)	16 (64)
Fall	4 (27)	7 (28)
Isolated blunt head injury	0	2 (8)
Alcohol detected in blood test, *n* (%)	4 (27)	5 (21)
Illicit drug detected in urine test, *n* (%)	1 (7)	2 (8)
Mean ISS score (SD)	35 (12)	31 (9)
ISS score ranges, *n* (%)		
0–24	2 (13)	5 (20)
25–49	10 (67)	20 (80)
50–75	3 (20)	0
APACHE II score (SD)	20 (7)	19 (5)
Median units of packed red blood cells administered (IQR 25–75%)	0 (0–2)	0 (0–0)
Vasopressors used, *n* (%)	1 (7)	3 (13)
Median transfer time, h (IQR 25–75%)	0.9 (0.6–7.4)	5.3 (3.2–7.3) {1}*
Median total fluid volume in the emergency department, mL (IQR 25–75%)	1,640 (820–3,350)	2000 (900–3,000)

ACTH = adrenocorticotropic hormone; APACHE = Acute Physiology and Chronic Health Evaluation; GCS = Glasgow Coma Scale; IQR = interquartile range; ISS = Injury Severity Score; SD = standard deviation. * Number of missing values for this variable.

Other studies have reported varying estimates of the risk of AI following TBI ranging between 15%[24] and 53%,[26] depending on the definition of AI used,[26] the population studied,[35] the exposure to etomidate,[35] and the time at which the ACTH test was performed,[35] making comparisons difficult. For example, using the same definition, Bernard and colleagues found a higher risk of AI (25%) in TBI victims not exposed to etomidate compared to our study (12%).[36] However, all patients in this study were hemodynamically unstable, increasing their risk of AI. Thus, we agree with Bernard and colleagues, who called for more standardization in the definition of AI after TBI.[36] We would add that the time elapsed after TBI is also important in reporting the risk of AI.

In contrast to our results, etomidate seemed to cause less AI in TBI victims than in patients with severe hemorrhagic shock (47%),[37] those with septic shock (94%),[31] and critically ill surgical patients (88%).[11]

Strengths of the study

This is the first study to perform serial ACTH stimulation tests at predetermined time points beyond the first 12 hours and in the first 7 days after TBI to formally measure the cumulative incidence of AI in moderate and severe TBI patients exposed to etomidate and in those not exposed to etomidate. Our results also add to the limited data available on the use of etomidate in TBI and trauma victims (Hildreth and colleagues, n = 30[18]; Jabre and colleagues, n = 78 [subgroup of TBI victims][19]; Vinclair and colleagues, n = 18 [subgroup of trauma patients][13]; Price and colleagues, n = 22[35]; Cohan and colleagues, n = 80[26]; and Hoen and colleagues, n = 34[37]).

Study limitations

Our study was exposed to a potential selection bias because of the low participation rate. Thus, we

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Table 2. Crude comparison of exposure groups for the primary and secondary outcomes

	Etomidate (n = 15)	Other induction agents (n = 25)	p value*
Cumulative incidence of AI at 24 h (%)	3 (20.0)	3 (12.0)	0.65
Cumulative incidence of AI at 48 h (%)	4 (26.7)[†]	3 (12.0)[‡]	0.39
Cumulative incidence of AI at 168 h (%)	4 (26.7)[§]	4 (16.0)[‖]	0.44
Positive ACTH test at 24 h (%)	3 (20.0)	3 (12.0)	0.65
Positive ACTH test at 48 h (%)	1 (9.1)[†]	0[‡]	0.33
Positive ACTH test at 168 h (%)	0[§]	1 (4.8)[‖]	0.54
Patients treated for suspected AI during the first 7 days (%)	3 (20.0)	2 (8.0)	0.34
Mortality at 168 days	3 (20.0)	1 (4.0)	0.14

ACTH = adrenocorticotropic hormone; AI = adrenal insufficiency.
*Fisher exact test
[†]Three subjects did not undergo the ACTH test (mortality = 1, administration of hydrocortisone = 2), and one laboratory result went missing.
[‡]Two subjects did not undergo the ACTH test (mortality = 1, administration of hydrocortisone = 1), and one laboratory result went missing.
[§]Four subjects did not undergo an ACTH test (mortality = 3, administration of hydrocortisone = 1).
[‖]Four subjects did not undergo an ACTH test (mortality = 1, administration of hydrocortisone = 1, withdrawal of consent = 1), and one laboratory result went missing.

conducted sensitivity analyses (Appendix 2) to estimate the impact of eligible patients who did not participate (n = 54) on our results. Although these analyses showed that imputing normal results to these patients favoured the null hypothesis, the direction of the negative effect of etomidate on adrenal responsiveness to ACTH stimulation did not change. Hence, we think it is safer to place greater weight on the results from the worst-case scenario so as to expose all possible harm of continued use of etomidate.

Our results can be generalized to all adult patients with moderate and severe TBI; however, this study should be reproduced in the pediatric population because our study only included four patients aged between 16 and 18 years.

Clinicians were not blinded to the anesthetic used, and it is possible that they perceived subjects exposed to etomidate as being at a higher risk for AI and thus administered more hydrocortisone to members of this group, exposing the study to a possible Hawthorne effect.[38] Among the 40 subjects tested, 5 were clinically diagnosed with AI requiring hydrocortisone and 3 of them had received etomidate. This potential effect prohibits any conclusion about the association between etomidate exposure and the need for hydrocortisone, but it does not influence our results for the laboratory diagnosis of AI.

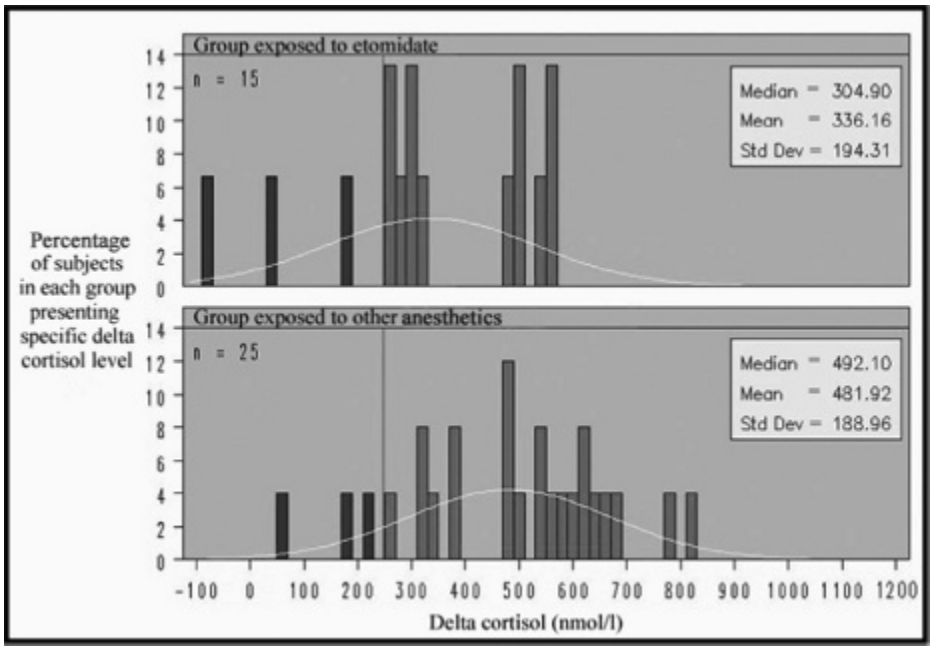

Figure 2. Distribution plots for crude delta cortisol measured at 24 hours by exposure group. The *white line* represents the normal distribution curve. The *thin black vertical line* represents the delta cortisol cutoff criteria for adrenal insufficiency (< 248.4 nmol/L).

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Table 3. Comparison of exposure groups for baseline cortisol, crude delta cortisol, and adjusted delta cortisol at 24, 48, and 168 hours

	Etomidate, nmol/L (95% CI)	Other agents, nmol/L (95% CI)	*p* value[†]
Cortisol level* before ACTH test at 24 h	525.8 (326.8–724.8)	574.8 (423.7–725.9)	0.72
Delta cortisol* after the ACTH test at 24 h	336.2 (228.6–443.8)	481.9 (403.9–559.9)	0.03
Adjusted[‡] delta cortisol* at 24 h	305.1 (197.8–412.4)	500.5 (421.9–579.2)	0.02
	n = 15	*n* = 25	
Cortisol level* before ACTH test at 48 h	396.3 (202.5–590.1)	397.5 (411.8–728.8)	0.98
	n = 11	*n* = 22	
Delta cortisol* at 48 h	569.9 (447.1–692.7)	634.8 (548.0–721.6)	0.43
	n = 11	*n* = 22	
Adjusted[‡] delta cortisol* at 48 h	570.3 (411.8–728.8)	634.8 (532.2–737.4)	0.57
	n = 11	*n* = 22	
Cortisol level* before ACTH test at 168 h	397.5 (312.5–482.6)	436.4 (339.4–533.3)	0.41
	n = 11	*n* = 22[§]	
Delta cortisol* at 168 h	627.9 (496.2–759.6)	582.4 (487.1–677.7)	0.74
	n = 11	*n* = 21[§]	
Adjusted[‡] delta cortisol* at 168 h	662.8 (484.6–841.1)	561.0 (444.4–677.6)	0.48
	n = 11	*n* = 21[§]	

ACTH = adrenocorticotropic hormone.
*Cortisol and delta cortisol levels are presented as means.
[†]Mann-Whitney test with normal approximation.
[‡]Adjusted for age, gender, Injury Severity Score, and transfer time.
[§]Baseline cortisol levels were available for 22 patients, but delta cortisol levels were available for 21 patients.

Based on published data at the time of planning this study, we determined the sample size from the hypothesis that the baseline AI rate would be 50%[37] and that etomidate would increase the rate of AI by 40%.[11] Fixing the alpha level (type I error) at 0.05, our study had an 80% statistical power to detect a 40% difference in the cumulative incidence of AI with 40 participants. To detect a difference of 8% in the risk of AI in the same conditions, however, a sample size of 329 (in each group) would have been required, which would be extremely difficult to reach given the severity of the condition of these patients and the major ethical issues. This lack of power is reflected in the wide confidence intervals of the odds ratio for AI. Conscious of our limited statistical power, we also analyzed delta cortisol, the variable used to define AI. Analysis of this continuous variable permitted us to better document the effects of etomidate on adrenal reserve as measured by the ACTH stimulation test.

Clinical significance of results and suggestions for future research

The clinical significance of etomidate-induced AI remains uncertain in TBI victims. Although our results showed a trend for increased hydrocortisone use and mortality in the etomidate group, no conclusions can be made from our small observational study. Jabre and colleagues found that etomidate-induced AI did not impact mortality or morbidity compared to ketamine.[19] Although these authors suggested that ketamine is a safe alternative to etomidate, their study was underpowered to examine mortality in TBI victims specifically (TBI victims were only a subgroup [*n* = 78] of the total study [*N* = 469]; Frédéric Adnet, MD, personal communication, July 2009).

If etomidate's short-lived advantages in terms of hemodynamic stability and neuroprotective properties are accompanied by longer-acting negative side effects,[18] alternative options, such as ketamine, could be considered.[19] However, even though a systematic review suggested that ketamine is safe for TBI victims,[39] a formal trial is needed to address this question.[40] Thus, the ideal anesthetic agent for TBI victims remains to be identified. Hohl and colleagues suggested that "the burden of proof is to show that etomidate is as safe as other anesthetics and a noninferiority study would be needed to accomplish this."[20] A large RCT would be ideal, but this is a daunting task in the unstable TBI victim in the ED.

A recent RCT exploring the effects of stress-dose hydrocortisone supplementation (200 mg/d) after etomidate use on the hemodynamic status of critically

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Table 4. Baseline and delta cortisol results for all patients who received etomidate ($n = 15$)

Patient	Medication used at intubation (other than etomidate)	Etomidate dose (mg/kg)	Baseline cortisol level at 24 h (nmol/L)	Delta cortisol at 24 h (nmol/L)	Baseline cortisol level at 48 h (nmol/L)	Delta cortisol at 48 h (nmol/L)	Baseline cortisol level at 168 h (nmol/L)	Delta cortisol at 168 h (nmol/L)
1	S	0.03	354.5	479.4	558.2	664.8	631.9	932.2
2	L, R, S	0.025	143.7	509.9	483.9	240.8	273.9	521.7
3	F, N, L, S	22 mg*	361.7	507.8	Missing data	Missing data	581.2	990
4	L, S	0.024	358.1	254.9	403.7	494	331.1	429.4
5	Lo, F, R	0.027	442.6	569.2	310.4	762.2	216.9	665.1
6	F, R, S	0.026	710.1	294.2	835.9	399.3	341	391.8
7	F, R, S	18 mg*	496.9	563.1	361.7	860.1	Subject deceased	Subject deceased
8	L,S	0.03	740.2	187.3	196.5	361.8	Subject deceased	Subject deceased
9	L, F, S	20 mg*	465.8	329.3	429.1	400.6	198.1	672.9
10	L, R, S	0.03	344.6	250.4	Subject treated for AI[†]	Subject treated for AI	418	379.8
11	L, R, S	20 mg*	343.4	304.9	Subject deceased	Subject deceased		
12	S	0.03	1591.5	−70.5	373	944.3	427.2	562.5
13	S, F	0.028	459.2	286.2	312.9	459.8	545.4	527.2
14	L, F	0.04	912	32	Subject treated for AI[‡]	Subject treated for AI	Subject treated for AI	Subject treated for AI
15	L, F, R, S	0.027	163.3	544.8	94.1	681	408	834

F = fentanyl; L = lidocaine; Lo = lorazepam; M = midazolam; N = norcuronium; R = rocuronium; S = succinylcholine.
*Etomidate dose given in mg because the weight of the subject is missing.
[†]At 24 hours, this patient was treated with hydrocortisone for clinically significant adrenal insufficiency (AI). Clinicians suspected AI and requested a simultaneous dosing of cortisol at 24 hours done with the Beckman Coulter Immunoassay System, which revealed a delta cortisol of 213 nmol/L. No ACTH testing was done at 48 hours, but given that hydrocortisone treatment had ended at 168 hours, the adrenocorticotropic hormone (ACTH) test was performed.
[‡]This patient was treated for suspected AI and diabetes insipidus after the 24-hour testing was performed. This female patient was suspected of having panhypopituitarism. The following assays were performed (follicle-stimulating hormone < 1 U/L, luteinizing hormone < 1 U/L, estradiol = 123 pmol/L, prolactin = 22 µg/L, thyroid-stimulating hormone = 0.06 mU/L, free thyroxine = 11.6 pmol/L, triiodothyronine < 0.4 nmol/L). This diagnosis could not be verified at follow-up because the subject had died at day 28. In addition, this patient was receiving methylprednisolone after the 24-hour ACTH test for a suspected ophthalmic nerve injury. At 48 and 168 hours, the patient was still receiving methylprednisolone.

Table 5. Baseline and delta cortisol results for all patients who did not receive etomidate (n = 25)

Patient	Medication used at intubation	Baseline cortisol level at 24 h (nmol/L)	Delta cortisol at 24 h (nmol/L)	Baseline cortisol level at 48 h (nmol/L)	Delta cortisol at 48 h (nmol/L)	Baseline cortisol level at 168 h (nmol/L)	Delta cortisol at 168 h (nmol/L)
1	F, P	336.7	586.3	365.9	575.9	590.7	597.1
2	M	1134.1	323	586.6	832.5	343.4	881.7
3	F, S	512.6	679.6	480.9	620.4	52.7	603
4	M, F, P	274.7	567.3	475.4	355.7	548.6	199.4
5	F, S	485	492.1	259	414.7	802.1	382.2
6	L, N, S	628.1	264.7	332.1	558.4	472.6	529.6
7	S, P	288.6	592.7	457.3	559.9	Subject refused last assay	Subject refused last assay
8	M, F	406	648.7	344.3	610.3	486.4	714.3
9	N, L, T	393.5	773.3	345.2	697.3	Missing data	Missing data
10	L, F, R, M	223.8	543.5	Subject treated for AI*	Subject treated for AI	410.1	277.4
11	P, R	507.1	226.1	Missing data	Missing data	448	267
12	NIL	303	627	130.1	834.9	483.8	620
13	P, R	458	829	195.2	823.8	280 (subject treated for AI†)	Subject treated for AI
14	L, S, F	298.4	388.3	546.7	599.9	511.8	343.1
15	R, F, L, T, S	1712.5	334.5	Subject deceased	Subject deceased		
16	L, S, P	984.3	325	591.6	865.1	842.1	572.9
17	P, R, F, S	935.3	472.1	452.5	949.5	26.2	750.3
18	L, R, T, S	764.8	382.4	251.5	605.3	649	489.6
19	A	289.5	620	178.5	831.1	352.7	822.5
20	R, F, P	490.7	479.1	312	664.2	327	583
21	F, T, R, S	454.2	653	436.2	745.9	138.1	984.8
22	F, L, P, S	198.3	477	117.5	575.7	46.5	767.8
23	Mo, S	425.3	531.5	332.6	686	596.1	440.2
24	L, T, R, S	1210.3	54.8	1061.9	295.8	574.2	828.6
25	NIL	655.1	176.9	492.5	263.5	617.9	575.2

A = atropine; F = fentanyl; L = lidocaine; M = midazolam; Mo = morphine; N = norcuronium; NIL = no anesthetic given; P = propofol; R = rocuronium; S = succinylcholine; T = thiopental.
*Subject was suspected of having a pituitary injury and was treated empirically with hydrocortisone after the adrenocorticotropic hormone (ACTH) stimulation test done at 24 hours. This male patient had the following hormonal assay results: ACTH = 3 pmol/L (on day 7 before the ACTH stimulation test, with baseline cortisol of 410 nmol/L); follicle-stimulating hormone (FSH) < 1 U/L; luteinizing hormone < 1 U/L; prolactin = 34 μg/L; thyroid-stimulating hormone (TSH) = 1.68 mU/L; free thyroxine (T_4) = 10.3 pmol/L.
†This patient was treated for suspected hypopituitarism and diabetes insipidus diagnosed after the 48-hour ACTH test. A baseline cortisol was measured for this patient (280 nmol/L), but clinicians did not wait for the ACTH stimulation test to be performed and started hydrocortisone. Other hormonal assays for this female patient revealed the following results: FSH = 2 U/l; TSH = 1.07 mU/l; free T_4 = 17.7 pmol/L.

ill patients (n = 99) without septic shock, including isolated TBI (n = 18) and multiple trauma victims (n = 42), found a reduction in the need for vasopressor support in patients receiving hydrocortisone.[41] In this study, hydrocortisone was started only 6 hours after exposure to etomidate and continued for 48 hours. There was no benefit from hydrocortisone use with regard to ICU length of stay, duration of mechanical ventilation, or 28-day mortality. Another recent study with intubated trauma patients (N = 149), including patients exposed to etomidate (n = 94) and TBI victims (n = 84), found a decreased risk of hospital-acquired pneumonia for patients treated with stress doses of hydrocortisone compared to placebo.[42] Thus, in light of these two recent studies and the results of our study, the next step would be to conduct a larger RCT with an adequate sample size to determine whether hydrocortisone supplementation given for 24 hours and started immediately after etomidate use in TBI victims has any potential clinical benefit.

CONCLUSION

The results of this study do not support the hypothesis that etomidate significantly increases the cumulative incidence of AI defined as a delta cortisol less than 248.4 nmol/L at 24, 48, or 168 hours. Exploratory post hoc analyses, however, show that etomidate negatively impacts the response to an ACTH test up to 24 hours among moderate to severe TBI victims. The clinical impacts of this finding remain to be determined.

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APPENDIX 1: LIST OF ADDITIONAL CONFOUNDING VARIABLES CONSIDERED

We considered respiratory rate, initial Glasgow Coma Scale (GCS) score, mean arterial pressure, presence of hemorrhagic shock, hypotensive episodes, fluid administration, blood transfusions, vasopressor use, transfer status, transfer time, underlying chronic illness (chronic hypertension, coronary heart disease, chronic respiratory illness, chronic liver disease), surgery in the first 24 hours of admission, mechanism of injury, presence of ethanol in the blood, illicit drug intoxication, New Injury Severity Score (NISS), baseline cortisol level, and albumin level. We hypothesized that these variables could increase the patient's risk of developing AI without receiving etomidate.

Confounding variables that changed the regression coefficient of exposure to etomidate by 10% or more were retained in the final models. Variables considered but not retained because of this criterion were initial GCS score, intoxication with an illicit drug, surgery in the first 24 hours of hospitalization, and the presence of hemorrhagic shock.

APPENDIX 2: SENSITIVITY ANALYSES

To estimate the impact of referral or selection bias on test outcomes, we performed two sensitivity analyses. Given that our study did not include all eligible subjects for the adrenocorticotropic hormone (ACTH) stimulation test (n = 94), we first estimated the effect of including all subjects on the risk of developing adrenal insufficiency and on delta cortisol levels at 24 hours. Our second sensitivity analysis concerned referrals. In our jurisdiction, all intubated traumatic brain injury (TBI) patients are supposed to be automatically transferred to a level 1 trauma centre. It is possible, however, that some centres in our jurisdiction with neurosurgeons on staff transfer only the most severe TBI victims. Our second analysis therefore excluded all subjects referred from centres with a neurosurgeon on staff.

The sensitivity analyses conducted to estimate the impact of participation of eligible patients who did not actually participate (n = 54) did not change our conclusions. Imputation of the abnormal adrenal insufficiency (AI) rate (20%) to etomidate-receiving nonparticipants and the normal AI rate (12%) to non–etomidate-receiving nonparticipants produced an odds ratio of 2.11 (95% CI 0.65–6.79) (p = 0.21). This calculation assumed that 3 of 12 nonincluded etomidate recipients (25%) would present with AI and that 5 of 42 nonincluded, nonetomidate recipients (12%) would present with AI. Imputation of the normal AI rate (12%) to both groups produced an odds ratio of 1.28 (CI 0.35–4.68) (p = 0.71). The assumption here was that AI would be experienced by 1 of 12 etomidate recipients (8%) and 5 of 42 recipients of another agent (12%). Finally, imputation of the abnormal mean delta cortisol (336.2 nmol/L) to the 12 etomidate recipients and the normal mean delta cortisol (481.9 nmol/L) to the 42 nonetomidate recipients did not change our conclusions. Imputing the normal mean delta cortisol to all missed subjects, however, nullified the statistical significance of our findings (etomidate group = 408.7 mmol/L versus nonetomidate group = 478.8 mmol/L; p = 0.2).

As regards the potential bias induced by the referral of patients (n = 3) from peripheral hospitals staffed by a neurosurgeon, sensitivity analyses for AI at 24 hours produced an adjusted odds ratio of 4.6 (CI 0.3–67.5) for all patients versus an odds ratio of 3.5 (CI 0.1–128.5) when the referred patients were excluded. Excluding these patients produced an adjusted delta cortisol at 24 hours of 331.6 (range 200.9–462.4) mmol/L for the etomidate group versus 498.4 (range 413.6–583.3) mmol/L for the nonetomidate group.

Appendix 3. Comparison of participants and eligible subjects who did not participate

	Study participants (n = 40)	Eligible subjects who did not participate in ACTH testing (n = 54)
Use of etomidate, *n* (%}	15 (38)	12 (22)
Mean age, yr (SD)	41 (17)	43 (19)
Male sex, *n* (%)	29 (73)	37 (69)
Mean respiratory rate (SD)	24 (9){12}*	23 (9){9}*
Mean arterial pressure, mm Hg (SD)	88 (24) {1}*	100 (20) {4}*
Mean Glasgow Coma Scale score (SD)	7 (3)	8 (4)
Subjects transferred, *n* (%)	26 (65)	45 (83)
Surgery in first 24 h, *n* (%)	14 (35)	17 (31)
Mechanism of injury, *n* (%)		
Motor vehicle	27 (68)	37 (69)
Fall	11 (28)	15 (28)
Isolated blunt head injury	2 (5)	1 (2)
Other	0	1 (2)
Alcohol detected in blood test, *n* (%)	9 (23)	11 (20)
Illicit drug detected in urine test, *n* (%)	2 (5)	4 (7)
Mean ISS (SD)	33 (10)	32 (10)
ISS ranges, *n* (%)		
0–24	7 (18)	10 (19)
25–49	30 (75)	43 (80)
50–75	3 (8)	1 (2)
Mean New ISS (SD)	53 (17)	47 (18)

ACTH = adrenocorticotropic hormone; ISS = Injury Severity Score; SD = standard deviation. * = Number of missing values for this variable.

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