Critical Review Form
Therapy

The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock, *Intensive Care Med* 2009; 35:1868–1876

Objective: **To test the hypothesis "that bolus doses of etomidate results in an increased proportion of non-responders to corticotropin and an increase in mortality, and that hydrocortisone treatment decreases mortality in patients receiving etomidate". (p. 1869)**

Methods: **Investigators conducted an *a priori* sub-study of CORTICUS, a 52-ICU, 9-country randomized double blind placebo-controlled trial of low-dose hydrocortisone in septic shock from March 2002 until November 2005. Inclusion criteria included clinical evidence of infection with evidence of systemic response, SBP <90 mmHg despite adequate fluid replacement OR need for vasopressors for at least one hour and evidence of hypoperfusion or organ dysfunction. Exclusion criteria included underlying disease with poor prognosis, immunosuppression, or prior administration of corticosteroids. The study protocol discouraged -- but did not prohibit -- the use of etomidate. Evidence based guidelines for patient management was encouraged. Intervention subjects received hydrocortisone hemisuccinate.**

Data collected included demographics, SAPS II, SOFA score, short corticotrophin test responsiveness (non-responder defined as ≤ 9 µg/dL cortisol increase at 60 minutes), and timing of etomidate administration at up to 72-hours before corticotrophin testing. Shock reversal was defined as maintenance of BP ≥ 90 mmHg for at least 24-hours after stopping vasopressor support. Patients were followed up to 28 days. Random quality assurance of data acquisition occurred with 10% of charts.

Although the denominators differed, the primary outcomes were corticotrophin response (etomidate subjects), all-cause 28-day mortality (etomidate or no-etomidate subjects), and impact of hydrocortisone on mortality (etomidate subjects). Two multivariate logistic regression models were assessed. Model-1 included treatment group (steroid/placebo) corticotrophin responsiveness, baseline cortisol level, and SAPS-II score. The second model included all of these confounding variables and added SOFA score.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, but not by etomidate administration.
2.	Was randomization concealed (blinded)?	Yes, double-blinded trial.
3.	Were patients analyzed in the groups to which they were randomized?	No clear intention-to-treat or CONSORT statement in this manuscript.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Etomidate subjects were older (68 vs. 64) with higher SAPS II score (49 vs. 47), lower SOFA score (10 vs. 11), and lower "baseline" cortisol level (20.3 vs. 25.9 µg/dL).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No, double-blinded.
2.	Were clinicians aware of group allocation?	No.
3.	Were outcome assessors aware of group allocation?	Uncertain.
4.	Was follow-up complete?	No loss to follow-up is reported.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 499 subjects were enrolled including 96 who received etomidate within a median 14.5-hours prior to study inclusion despite the study protocol. • Corticotropin non-responders were significantly more common in the etomidate group (61% vs. 44.6%, p = 0.004). • **Etomidate was associated with increased mortality on univariate analysis** (OR 1.70, 95% CI 1.07 – 2.68 p= 0.02). • Etomidate was almost independently significant in the first logistic regression model for increased 28-d mortality (OR 1.60, 95% CI 0.98 – 2.62, p = 0.06) and was **significant in the second model incorporating SOFA** (OR 1.75, 95% CI 1.06 – 2.09, p = 0.03). • Hydrocortisone administration did not reduce mortality (45% etomidate group vs. 40% in non-etomidate group) (Table 2, p. 1871). • Cumulative reversal of shock was not effected by etomidate in the hydrocortisone or placebo groups nor was mean time to shock reversal in the placebo (6.2 days etomidate vs. 5.7 days) or hydrocortisone (3.0 days etomidate, 3.8 days no etomidate p = 0.42) groups. • There was no effect on SOFA scores from etomidate at day 7. (p. 1870)
2.	How precise was the estimate of the treatment effect?	Sufficiently narrow CI as noted above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	

1.	Were the study patients similar to my patient?	No. These are not solely ED patients and the location, setting, provider skill sets, and situation these patients presented for intubation are not well described. Although this represents a portion of the evidence emergency provides can utilize in evaluating the safety of etomidate for septic patient intubation, ED-based studies would provided enhanced external validity.
2.	Were all clinically important outcomes considered?	Yes – patient mortality and time to shock reversal.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. This study's findings suggest that "a bolus dose of etomidate is associated with an increased incidence of IRC (inadequate response to corticotropin) and is also associated with increased mortality in at least one of our models". (p.1870) Furthermore, "Hydrocortisone treatment had no effect on outcome in patients who received etomidate". (p. 1870)

Limitations

1) **Non ED-based study with limited external validity to U.S. emergency airway management, although still compelling data from 52 ICU's.**
2) **Sub-study not randomized on etomidate intervention and not powered specifically to test this hypothesis.**
3) **Baseline measures for etomidate are not truly baseline since the etomidate exposure could have been up to 72-hours prior (median 14.5 hours).**
4) **No control for or reporting of interventions (EGDT) post-etomidate exposure.**

Bottom Line

Large 52-ICU study suggests that etomidate exposure within the previous 72-hours in septic patients is associated independently with increased 28-day mortality that does not improve when hydrocortisone is administered a median of 14.5-hours after etomidate exposure. Etomidate exposure does not delay overall septic shock reversal or time-to-reversal. Despite stringent study guidelines advising against etomidate use, 20% of clinicians within these institutions still choose to use it indicating significant equipoise remains about the risk vs. benefit of etomidate in septic shock patients.