Critical Review Form
Therapy

A Prospective Observational Study of the Effect of Etomidate on Septic Patient Mortality and Length of Stay, *Acad Emerg Med* 2009; 16: 11-14

Objective: **"To determine the differences in in-hospital mortality and hospital length of stay (LOS) between septic patients given etomidate and patients given alternative induction agents for rapid-sequence intubation in our ED. '' (p. 12)**

Methods: **Prospective, non-randomized, observational cohort study at Advocate Christ Medical Center (Oak Lawn, IL) from February – October 2007. Eligible subjects at this suburban tertiary care medical center were > 18 years old with ≥ 2 SIRS criteria* with suspected or documented infection who underwent intubation. To identify subjects, physicians had to notify study coordinators although investigators also attempted to cross reference etomidate used with eligible subjects.**

A standardized data abstraction form was used for data collection (patient demographics, induction agent, time of intubation, supplementary steroid used, hospital LOS, discharge status, MEDS score). The primary outcome was in-hospital mortality and the secondary outcome was overall hospital LOS.

Investigators compared the etomidate rapid sequence intubation (RSI) to other or no induction agent RSI groups via univariate analysis. They also conducted multiple logistic regression analysis for mortality to obtain adjusted OR's controlling for age, vital signs at time of RSI, gender, vasopressor or steroid use, and MEDS score. They conducted a multiple linear regression analysis for LOS adjusting variables for the same confounding variables. To assess for interactions between confounding they examined plots of residuals against independent variables.

*** SIRS criteria include: temp < 36° C or > 38° C, heart rate > 90, respiratory rate > 20, p CO_2 <32 mm Hg, WBC > 12 or < 4, or >10% bands**

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?	No, this was an observational cohort.
2.	Was randomization concealed (blinded)?	No, there was no randomization.
3.	Were patients analyzed in the groups to which they were randomized?	Subjects were not randomized, so there was no cross-over and all groups were analyzed within their respective treatment arm.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	"Although a slightly higher proportion of patients not receiving etomidate received supplemental steroids, no statistically significant differences in age, MEDS score, mean arterial pressure, heart rate, gender, use of supplemental steroids, or vasopressor use was seen between cohorts''. (p. 12)
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?	Yes, not randomized or blinded.
2.	Were clinicians aware of group allocation?	Yes, not randomized or blinded.
3.	Were outcome assessors aware of group allocation?	Yes, not randomized or blinded.
4.	Was follow-up complete?	No loss to follow-up is reported, but a more pertinent question would be were all eligible subjects identified? "For five days each week, we instituted daily monitoring of our electronic tracking board by a research assistant to identify patients potentially meeting our study criteria. To confirm that all potentially eligible patients were included in our study, we obtained weekly records from our Omnicell medication dispensing cabinet to identify all instances in which intubation medications were used.'' (p. 12)

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• A total of 106 subjects met eligibility criteria (74 etomidate, 32 other agent). Of the 32 "other agent" subjects there were 22 benzodiazepines, 3 ketamine, 1propofol, 1 ketamine and benzodiazepine, 5 did not receive any induction agent during intubation. • **Mortality did not differ significantly between etomidate (38%, 95% CI, 28% - 49%) and "other agent" cohort (44% 95% CI, 28% - 61%).** The mortality for the five who received no induction medication was 20%. • Although the interquartile ranges overlap, there was a **trend towards longer median hospital LOS in the etomidate group (8 days, IQR 3 – 13 days) compared with the other agent group (6.5 days, IQR 3 – 9.75 days).** • This LOS trend continued for those surviving to hospital discharge. For etomidate 10 days (IQR 7 – 16.25) or other 7.5 days (IQR 4.75 – 10, p=0.08) • Multiple linear regression modeling showed that only the use of vasopressors remained a significant predictor of outcome (p = 0.008) for LOS. • Logistic regression analysis demonstrated that only mean arterial blood pressure at the time of intubation remained a significant predictor of patient mortality (OR = 1.02, 95% CI 1.001 to 1.05, p = 0.04). • No suggestion of interactions between confounding variables were identified. • Although the investigators do not report a post-hoc power calculation for their sample size, one can generate a power using this website Died Lived Etomidate 28 46 Other 14 18

2.	How precise was the estimate of the treatment effect?	95% CI and IQR widely overlap but study under-powered so Type II error very possible.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. Critically ill septic patients presenting to tertiary medical center and requiring intubation.
2.	Were all clinically important outcomes considered?	Mortality is the most important patient oriented outcome. Other confounding variables might include appropriate or sufficiently broad spectrum initial antibiotic selection, uniform application of EGDT or accurate EM identification of infectious etiology. Additionally, the MEDS score does not incorporate lactate or co-morbid illness burden so initial prognosis may have been unequal although the MEDS score is currently the single sepsis prognostic tool validated for use in the ED (Carpenter 2009).
3.	Are the likely treatment benefits worth the potential harm and costs?	"The lack of statistical significance of our finding does not, at this point, provide convincing evidence that the use of a single-bolus dose of etomidate for intubation in the ED should be abandoned. An ongoing randomized trial at our institution comparing etomidate to midazolam (ClinicalTrials.gov Identifier NCT00441792) will attempt to further quantify this link". (p. 13)

Limitations

1) **Non-randomized observational trial. The medical literature is replete with examples of therapies that appeared equivalent or superior in observational trials only to be disproven with subsequent RCT. Therefore, the pending RCT will be invaluable to definitively address this question controlling for the confounding variables we cannot understand or statistically manipulate.**

2) **Limited external validity with small, single-center sampling and an unstable statistical model that changes when as few as two patients change outcome category.**

3) **No *a priori* or post-hoc power or sample-size calculation. When the informed reader conducts a post-hoc power calculation one finds the study is under-powered to confidently conclude equivalence since there is a strong possibility of a Type II error.**

4) **Non-consecutive sampling dependent upon physician reporting to research assistants or retrospective identification by correlating etomidate use to septic patients (even though etomidate can be used for other intubation or procedural sedation) and no chart review methods were provided so there is a potential selection bias.**

5) **No inclusion of EGDT received, antimicrobial coverage, or co-morbid illness burden on statistical modeling.**

Bottom Line

Although limited by the small sample size and incomplete confounding variable inclusion in statistical modeling, as well as all the biases of a convenience-sampling of non-randomized patients, this data suggests that the use of etomidate for RSI of septic patients in the ED may increase median hospital LOS (8 days vs. 6.5 days) without impacting mortality.