TAKE-HOME MESSAGE

Single-use etomidate in intubation for critically ill patients may result in transient adrenal and other organ dysfunction, but with no effect on mortality.

Is Single-Dose Etomidate Induction Safe in Emergency Intubation of Critically Ill Patients?

EBEM Commentators
Suneel Upadhye, MD, MSc
McMaster University
Hamilton, Ontario, Canada
Olga Cyganik, MD
Department of Family Medicine
University of Toronto
Toronto, Ontario, Canada

METHODS

DATA SOURCES

Unrestricted electronic searches included MEDLINE, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing & Allied Health Literature, EMBASE, Literatura Latino Americano em Ciencias da Saude, Web of Science, Database of Abstracts of Reviews of Effects, ISI Biosis, and International Pharmaceutical Abstracts up to August 2014. The Scopus dissertation database, conference proceedings, and US Food and Drug Administration databases were also searched. A manual search of major emergency medicine, critical care, and anesthesiology journals and conference proceedings from 1990 was conducted. Gray-literature searches were conducted of Cochrane Controlled Trials Register, National Health Systems registry, clinicaltrials.gov, and National Emergency Airway Registry Web sites.

STUDY SELECTION

Three authors independently reviewed abstracts and included studies. Studies included randomized controlled trials of patients undergoing emergency intubation for critical illness (including trauma, stroke, acute myocardial infarction, and septic/hemorrhagic/undifferentiated shock), comparing single-dose etomidate versus other rapid single-dose induction agents. A PRISMA statement was provided for inclusion and exclusion details.

Results

Outcome	Studies, Number of Patients	Relative Effect (95% CI)	Heterogeneity (I^2), %
Mortality	6 studies, 772 patients	OR 1.17 (0.86 to 1.6)	0
Duration of mechanical ventilation, days	3 studies, 621 patients	Avg duration: 1.5–13 days; etomidate effect 2.14 days (−1.67 to 5.95 days)	86
Organ dysfunction (SOFA scores)	1 study, 469 patients	Mean SOFA score: 9.6; etomidate effect 0.7 (0.01 to 1.39)	

OR, Odds ratio; *SOFA*, Sequential Organ Failure Assessment score.

Of 1,395 potential titles screened, 8 studies were included in the review; however, only 7 were combined in a metaanalysis. Two of these 7 studies were determined to be at low risk of bias, whereas 5 were considered to be at moderate risk.

Commentary

Etomidate has been a controversial induction agent in emergency intubation for a number of years because of concerns about adrenal suppression and subsequent adverse outcomes.[1,2] The concern about etomidate safety in septic patients was first raised in an observational substudy of the Corticosteroid Therapy of Septic Shock trial.[3] The specific flaws of this study are elaborated elsewhere,[4] revealing multiple confounding factors and reporting omissions that preclude the erroneous conclusion that etomidate increases mortality in septic patients. This mistake was perpetuated in a meta-analysis with the same conclusion,[5] although examination of the forest plots show a clear outlier result driving the increased mortality conclusion. A recent summary of that meta-analysis discussed this outlier observational trial in the context of other randomized controlled trials that show no mortality increase.[6] The Cochrane review by Hohl et al[7] rightly excluded this observational study in the overall mortality analysis and corrected the erroneous conclusion of etomidate harm from the meta-analysis by Chan et al.[5]

Assessment of publication bias was not completed.

DATA EXTRACTION AND SYNTHESIS

Data were independently abstracted (3 authors) with standardized forms. Risk of bias was assessed with Cochrane Handbook tools. Meta-analysis with random-effects analysis was used (7 studies).

A thorough systematic review by Hohl et al[7] showed that etomidate does transiently (<24 hours) reduce adrenal function. That review was underpowered to note a difference in hospital or ICU length of stay, ventilation duration, or mortality. In this updated Cochrane review, moderate evidence (6 trials, 772 patients) confirms no increase in mortality or any other clinically important endpoint (eg, ventilation duration). A "worst-case scenario" analysis using imputation for missing patients also failed to show increased mortality (odds ratio 1.15; 95% confidence interval 0.86 to 1.53). A clinically inconsequential reduction in adrenal function was observed. No subgroup analysis focusing on specific diagnostic groups (eg, septic shock) was undertaken.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Bruder EA, Ball IM, Ridi S, et al. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. *Cochrane Database Syst Rev*. 2015;(1): CD010225.**

1. Walls RM, Murphy MF. Continue to use etomidate for intubation of patients with septic shock. *Ann Emerg Med*. 2008;52:13-14.
2. Sacchetti A. Etomidate: not worth the risk in septic patients. *Ann Emerg Med*. 2008;52: 14-15.
3. Cuthbertson BH, Sprung CL, Annane D, et al. The effects of etomidate on adrenal suppression and mortality in patients with septic shock. *Int Care Med*. 2009;35: 1868-1876.
4. Green R, Gorman SK. Safety of etomidate bolus administration in patients with septic shock. *CJEM*. 2011;13:105-108.
5. Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis. *Crit Care Med*. 2012;40:2945-2953.
6. Hunter BR, Kirschner J. In patients with severe sepsis, does a single dose of etomidate to facilitate intubation increase mortality? *Ann Emerg Med*. 2013;61: 571-572.
7. Hohl CM, Kelly-Smith CH, Yeung TC, et al. The effect of a bolus dose of etomidate on cortisol levels, mortality and health services utilization: a systematic review. *Ann Emerg Med*. 2010;56:105-113.

Michael Brown, MD, MSc, Alan Jones, MD, and David Newman, MD, serve as editors of the SRS series.