

Etomidate and General Anesthesia: The Butterfly Effect?

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Induction of general anesthesia with control of ventilation remains a routine procedure both in critically ill patients and in those undergoing elective surgery. Etomidate is considered the drug of choice for emergency intubation procedure because of a good perceived benefit/risk ratio, including hemodynamic stability, and minor side effects such as, myoclonus.

Administered in conjunction with a rapid-onset neuromuscular-blocking drug, etomidate remains the preferred drug by most emergency physicians, anesthesiologists, and intensivists for rapid sequence induction of anesthesia. Publication of observational cohort studies suggesting increased mortality with the use of etomidate in septic patients has, however, raised safety concerns. In a systematic review and meta-analysis in septic patients, including randomized controlled trials and observational studies, Chan et al.¹ reported that a single dose of etomidate for induction of anesthesia was associated with increased 28-day mortality (relative risk 1.20, 95% confidence interval, 1.02–1.4). Similar findings were observed in a post hoc analysis of the Corticosteroid Therapy of Septic Shock (CORTICUS) trial. An increased 28-day mortality rate (43% vs 31%, $P = 0.03$) was noted in patients who received etomidate compared with patients who did not.² However, other authors did not observe such an increased risk of mortality when using etomidate in septic patients³ and even observed a decreased mortality rate after adjustment for severity of illness.⁴ Similarly, randomized controlled trials have not provided evidence for an increased risk of death following a single dose of etomidate in critically ill patients (Fig. 1).^{5–8} In the largest multicenter study in the prehospital setting, Jabre et al.⁶ observed no statistical difference in

the Sequential Organ Failure Assessment (SOFA) score and mortality between patients randomized to receive ketamine or etomidate for emergency tracheal intubation. However, the trials were not properly powered to address the difference in mortality.

Etomidate-induced adrenal insufficiency has long been the suspected culprit for the negative impact on mortality. However, such a causal relationship remains speculative. Etomidate has consistently been found to induce biological adrenal insufficiency (i.e., nonresponse to the corticotropin stimulation test) up to 48 hours after a single dose by inhibiting the 11- β -hydroxylase and the conversion of 11-deoxycortisol into cortisol. However, the results of studies using hydrocortisone substitution remain conflicting. In a single center study, hydrocortisone supplementation after etomidate injection improved systemic hemodynamics and shortened the duration of vasopressor support.⁹ The authors found no difference in mortality, but the study was underpowered for this outcome. Likewise, Cuthbertson et al.² found no effect of glucocorticoid substitution on outcome. All the above-mentioned studies focused on critically ill patients.

In this issue of the journal, Komatsu et al.¹⁰ explored the influence of etomidate on outcome in patients undergoing mostly elective noncardiac surgery. The study explored, for the first time, the impact of the use of etomidate as an induction drug in the operating room. The authors used the electronic records of 31,148 ASA physical status III to IV patients who had noncardiac surgery at the Cleveland Clinic to evaluate the impact of etomidate administration on 30-day postoperative mortality. Among them, 2144 patients who received etomidate for induction of anesthesia were propensity matched with 5233 patients who received propofol. Anesthesia was maintained with a volatile inhaled anesthetic agent. The results are striking and troubling: they show a 2.49 (98.3% confidence interval, 1.85–3.35) estimated odds ratio of dying and 1.51 (1.14–1.94) odds of having major cardiovascular morbidity when etomidate was used. Etomidate was also associated with prolonged hospital stay. Interestingly, the relationship between etomidate and the outcome did not depend on comorbidities or on the emergency characteristic of the procedure.

The strengths of the study are the large sample size and the appropriate use of propensity score to overcome several biases associated with retrospective observational studies. The weaknesses are the nonrandomized design, the pitfalls associated with collection of data from electronic charts, and the potential for inadvertently excluding important

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Accepted for publication September 15, 2013.

Funding: This work was supported only by institutional funding.

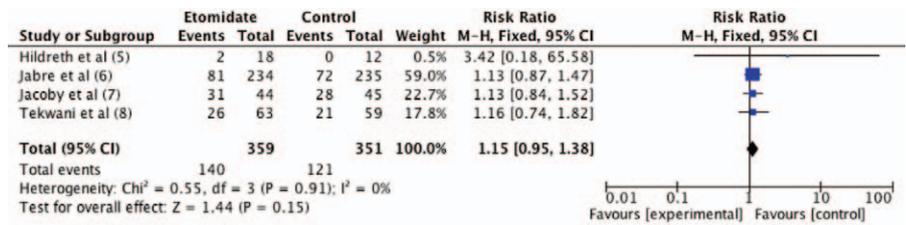
The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000000003

Figure 1. Pooled relative risks for all-cause mortality of randomized controlled trials with etomidate versus other anesthetic drug. CI = confidence interval; RR = relative risk. Analysis performed with Review Manager (RevMan™), Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.



causative factors in the propensity matching. It is likely that several factors that may have influenced the physicians' choice of etomidate may not have been recorded and included in the propensity analysis. It would have been worth mentioning the causes of death and the time elapsed from the surgical procedure. Furthermore, the authors chose 30-day mortality as the main end point, while the standard is mortality at 28 days. This study could not explore the potential mechanism of the negative impact on outcome, including adrenal insufficiency. Finally, as always, single center data are to be interpreted cautiously, since the same group of anesthesiologists was involved. There is likely a high propensity score group of patients in which etomidate was preferred over propofol. Several reasons may have guided the clinicians' decision to use etomidate in such patients, including the influence of institutional practice or training, which may not be generalizable to other centers.

Using a physics metaphor, the results of this study may be interpreted as a butterfly effect, that is, the very small differences in the initial state of a physical system can make a significant difference to the state at some later time. This study indeed strongly suggests, with sufficient confidence, that a single bolus dose of etomidate, with apparent short-lasting effects, may compromise homeostasis and affect the 30-day mortality rate in noncritically ill surgical patients. These findings are of major importance in light of the high number of patients who potentially receive etomidate each year worldwide. One might also wonder about the potential beneficial effects of propofol and how they may have affected outcome. Indeed, propofol has been suggested to possess anti-inflammatory and antioxidant effects and a protective mechanism against ischemia-reperfusion injury¹¹ or sepsis.¹²

What should we do now? There is accumulating evidence for an association between mortality and etomidate use, both in critically ill patients and now in ASA physical status III to IV patients undergoing noncardiac surgery. Since safe and efficient alternatives exist, a wise choice might certainly be the use of other anesthetic agents for induction of anesthesia pending additional studies. Ketamine in patients at greatest risk of hemodynamic instability appears safe, although psychiatric side effects may occur. Propofol is a drug of choice but exposes patients to potentially severe hypotension, especially in those with compromised cardiovascular function and in the elderly in whom low doses and slow titration are recommended.¹³

In summary, this study comparing etomidate and propofol is a good example of how we should evaluate our current practice. This study highlights once again the need for large observational studies to assess our therapeutic strategies. While hemodynamic effects of anesthetic drugs can easily be recognized and treated in routine practice, it

is hardly feasible to determine the potential effects of each of our actions on in-hospital mortality. Both the rather low number of events (mortality rate of 2.5% in the propofol group vs 6.5% in the etomidate group in the current study) and the delay between the action (i.e., anesthesia induction) and outcome (i.e., likely related death occurring several days after the procedure) make assessment of our practice difficult. Large sample-size studies like this one allow such explorations and put emphasis on a potential downstream, devastating effect on outcome of a single intervention during anesthesia (i.e., a single dose of anesthetic agent). However, only properly powered multicenter studies (ClinicalTrials.gov NCT01823328) will provide definitive answers and give us a sharper vision of the outcome associated with anesthetic drugs under the microscope of clinical research. Pending such trials, accumulation of data from observational studies should guide us in weighing the risk/benefit ratio of the anesthetic drugs we use and finding out whether the butterfly effect applies to anesthesiology. ■

DISCLOSURES

Name: Matthieu Legrand, MD, PhD.

Contribution: This author helped write the manuscript.

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Attestation: The author approved the final manuscript.

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REFERENCES

- Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis*. Crit Care Med 2012;40:2945-53
- Cuthbertson BH, Sprung CL, Annane D, Chevret S, Garfield M, Goodman S, Laterre PF, Vincent JL, Freivogel K, Reinhart K, Singer M, Payen D, Weiss YG. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. Intensive Care Med 2009;35:1868-76
- McPhee LC, Badawi O, Fraser GL, Lerwick PA, Riker RR, Zuckerman IH, Franey C, Seder DB. Single-dose etomidate is not associated with increased mortality in ICU patients with sepsis: analysis of a large electronic ICU database. Crit Care Med 2013;41:774-83
- Jung B, Clavieras N, Nougaret S, Molinari N, Roquilly A, Cisse M, Carr J, Chanques G, Asehounne K, Jaber S. Effects of etomidate on complications related to intubation and on mortality in septic shock patients treated with hydrocortisone: a propensity score analysis. Crit Care 2012;16:R224
- Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. J Trauma 2008;65:573-9
- Jabre P, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltrami A, Gamand P, Albizzati S, Perdrizet D, Lebaill G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant JY, Bollaert PE, Megarbane B, Ricard JD,

- Anguel N, Vicaut E, Adnet F; KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009;374:293–300
7. Jacoby J, Heller M, Nicholas J, Patel N, Cesta M, Smith G, Jacob S, Reed J. Etomidate versus midazolam for out-of-hospital intubation: a prospective, randomized trial. *Ann Emerg Med* 2006;47:525–30
 8. Tekwani KL, Watts HF, Sweis RT, Rzechula KH, Kulstad EB. A comparison of the effects of etomidate and midazolam on hospital length of stay in patients with suspected sepsis: a prospective, randomized study. *Ann Emerg Med* 2010;56:481–9
 9. Payen JF, Dupuis C, Trouve-Buisson T, Vinclair M, Broux C, Bouzat P, Genty C, Monneret D, Faure P, Chabre O, Bosson JL. Corticosteroid after etomidate in critically ill patients: a randomized controlled trial. *Crit Care Med* 2012;40:29–35
 10. Komatsu R, You J, Mascha EJ, Sessler DI, Kasuya Y, Turan A. Anesthetic induction with etomidate, rather than propofol, is associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery. *Anesth Analg* 2013;117:1329–37
 11. Yang SC, Chung PJ, Ho CM, Kuo CY, Hung MF, Huang YT, Chang WY, Chang YW, Chan KH, Hwang TL. Propofol inhibits superoxide production, elastase release, and chemotaxis in formyl peptide-activated human neutrophils by blocking formyl peptide receptor 1. *J Immunol* 2013;190:6511–9
 12. Inada T, Taniuchi S, Shingu K, Kobayashi Y, Fujisawa J, Nakao S. Propofol depressed neutrophil hydrogen peroxide production more than midazolam, whereas adhesion molecule expression was minimally affected by both anesthetics in rats with abdominal sepsis. *Anesth Analg* 2001;92:437–41
 13. Möller Petrun A, Kamenik M. Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. *Br J Anaesth* 2013;110:388–96