Etomidate and Treatment Propensity

To the Editor:

Wagner *et al.*[1] must be congratulated for their robust and interesting work into the effects of a single dose of etomidate on long-term outcomes. Nonetheless, we consider that several elements would benefit from greater information and discussion. First, the doses of etomidate administered were not reported and therefore any dose–response effect remains unclear; it may be that higher doses may induce decrements in long-term outcomes. Ideally, information on drug doses should be included. Perhaps the most important criticism relates to the case mix included in the analysis. When understanding whether etomidate is safe, it is necessary to compare the drug with other induction drugs. Inclusion of patients who did not receive an induction drug, such as those presenting in cardiogenic shock and already intubated, therefore appears inappropriate. The authors have recognized this to some degree: "We also performed a sensitivity analysis in which patients who did not receive any induction drugs were excluded from the analysis. The results from the sensitivity analysis were qualitatively similar to those reported in table 3." However, these are *the* critical data to report, as it excludes patients who did not receive the induction of anesthesia for surgery. Hence, these data should not be considered supplementary information rather we ask the authors to publish them in full. Other sensitivity analyses that are worth conducting include subgroup analyses for elective and emergency surgery as these factors may affect treatment propensity. Furthermore, although we consider that the authors' use of propensity scoring is appropriate,[2] we suggest that a propensity score-matching approach for "etomidate only" with other induction agents such as "propofol only" or "midazolam only" would also be of interest to provide a more direct comparison of the induction agents. This is also important, as midazolam appears to be associated with a shorter duration of mechanical ventilation and length of stay in hospital. Given the deleriogenic effects of midazolam,[3,4] this observation appears surprising, but may relate to superior cardiovascular stability with this approach. Nonetheless, this requires further discussion especially because patients with cardiogenic shock were more likely to receive "midazolam only." Of course the data are slightly more complex given the use of coinduction with midazolam and etomidate or propofol. Given that there is a clear clinical preference for coinduction, these two combinations should also be compared with each other by propensity score matching. Finally, the association of angiotensin-converting enzyme inhibitors with prolonged hospital length of stay, but not with mortality (although the point estimate is shifted toward increased mortality), is of interest given a recent meta-analysis suggesting increased mortality and acute kidney injury in cardiac surgical patients administered these drugs.[5] Here the authors may wish to consider adjusting for hypertension as a potential confounder by indication. In summary most of these criticisms could be approached by the publication of the sensitivity analysis removing patients with cardiogenic shock, as well as conducting some additional analyses. Despite our critique we applaud the authors for their hard work and robust statistical approach, they have identified an important topic for research and made substantial contributions to clarifying the role of etomidate for induction of anesthesia for cardiac surgery.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Sanders *et al.* for their interest in our work.[1] We address their comments with additional summaries and responses to specific comments.

Sanders *et al.* requested that drug doses be used in our analyses. We recognize the lack of drug dose as a potential weakness to our analysis; however, all induction drugs, including etomidate (median dose of 0.15 mg/kg), were administered to achieve hypnosis. We did not model the induction dose of etomidate because etomidate suppresses

adrenal function at concentrations less than 10 ng/ml, which are one-twentieth of the concentration associated with hypnosis (200 ng/ml; 1 μM).[2–4] We therefore believe it is reasonable to assume that the overwhelming majority of patients who received a hypnotic dose of etomidate achieved concentrations well above the adrenal suppression threshold.

Sanders *et al.* requested that we compare among all induction drugs and that we exclude those patients who did not receive an induction drug due to already having been intubated. Table 1 shows that it does not necessarily appear that attendings so much as choose among single induction agents (etomidate, midazolam, or propofol); approximately 20% (n = 619) of all patients received only one agent. In fact, 93% received midazolam (n = 2,906). Among those receiving midazolam, 648 also received propofol only, 1,572 received etomidate only, and 220 received both propofol and etomidate. We therefore did not necessarily see the decision to use etomidate as a choice between it and another agent because it was most often given with another agent (midazolam with or without propofol). Our analysis sought to examine whether *adding* etomidate to an induction regimen was associated with harm. In fact if one sought to compare the different agents, one could have used the results provided in the figures in the article. For example, from figure 1 in our original article, if one sought to contrast the addition of etomidate to that of propofol, the odds ratio for vasoplegia is estimated to be 0.80/0.73 = 1.09 (standard errors are more difficult to calculate).

Table 1. Induction Agent Combinations Observed among 3,127 Surgeries

	N	%
No agent	38	1.2
Etomidate only	106	3.4
Propofol only	47	1.5
Midazolam only	466	14.9
Etomidate and propofol	30	1.0
Etomidate and midazolam	1,572	50.3
Propofol and midazolam	648	20.7
All three (E + P + M)	220	7.0

E = etomidate; M = midazolam; P = propofol.

The number of patients who did not receive an induction agent was 1.2% (38 of 3,127). As an additional analysis, we removed those patients and reran our regression model as suggested by Sanders *et al.* Our results shown in table 2 suggest that etomidate may be associated with longer lengths of hospital stay when compared with midazolam and propofol at the unadjusted significance level of 0.05. Statistical significance is not preserved with Bonferroni adjustments to control family-wise error rates. That said, we again question whether interdrug comparisons are most appropriate. As can also be seen from table 2, adding etomidate to an existing regimen is associated with nonsignificant decreases in length of stay (hazard ratio, 1.05; 95% CI, 0.96 to 1.16).

Sanders *et al.* suggest conducting subgroup analyses "for elective and emergency surgery as these factors may affect treatment propensity." We dealt with differential treatment propensity by controlling for "emergent surgery" in our regression analyses. Whether there exists an interaction between treatment and many other possible subgroups, as implied by the suggestion of subgroup analyses, was not a goal of our study.

Sanders *et al.* suggest a propensity score-matching analysis approach for "etomidate only" *versus* "propofol only" or "midazolam only": As stated above, only 20% of all surgeries used only one induction agent. The analysis does not represent how attendings at our institution conduct their practices. For the vast majority of surgeries, attendings coinduce patients.

Sanders *et al.* suggest a propensity score-matching analysis for midazolam plus etomidate *versus* midazolam plus

Table 2. Regression Analysis Results Based on the 3,089 Patients Who Received at Least One of the Induction Agents

	Vasoplegia	Time to Removal from Mechanical Ventilator	Length of Hospital Stay	Mortality
Etomidate *vs.* propofol	1.11 (0.77–1.60)	1.00 (0.89–1.11)	0.89 (0.79–0.99)	0.86 (0.46–1.61)
Etomidate *vs.* midazolam	1.06 (0.61–1.85)	0.91 (0.77–1.08)	0.82 (0.69–0.97)	1.19 (0.51–2.79)
Propofol *vs.* midazolam	0.96 (0.56–1.66)	0.91 (0.77–1.09)	0.92 (0.77–1.10)	1.38 (0.60–3.19)
Etomidate *vs.* no etomidate	0.77 (0.56–1.06)	1.08 (0.98–1.19)	1.05 (0.96–1.16)	0.80 (0.47–1.35)

We summarize the regression models with between induction agent comparisons and a comparison of etomidate treatment with no etomidate treatment. Whereas for the vasoplegia and mortality analyses, we report odds ratios and 95% CIs, for the time to mechanical ventilator removal and length of hospital stay, we report hazard ratios and 95% CIs.

Table 3. Comparison of Etomidate to Propofol Induction Agents among the 2,210 Patients Who Received Either Midazolam Plus Etomidate or Midazolam Plus Propofol

	Vasoplegia	Time to Removal from Mechanical Ventilator	Length of Hospital Stay	Mortality
Regression-based analysis	1.09 (0.70–1.67)	1.00 (0.88–1.14)	0.89 (0.78–1.01)	0.86 (0.41–1.81)
Propensity score matching	1.22 (0.75–1.99)	1.08 (0.93–1.25)	0.96 (0.83–1.11)	0.73 (0.29–1.83)

propofol. We have subset the original dataset to the 2,210 patients who received one of those regimens and report a regression-based analysis as well as a propensity-matching analysis. Table 3 shows the comparison between regimens midazolam plus etomidate and midazolam plus propofol among the subset of patients who received one of the regimens using the suggested propensity-matching approach and a regression modeling approach. In neither case would we conclude any difference between the treatments.

Finally, Sanders *et al.* suggested that we adjust for hypertension as a potential confounder for the observed angiotensin-converting enzyme inhibitor effect seen in figure 3 of the original article. We agree that if interest was in angiotensin-converting enzyme inhibitor effects, controlling for hypertension would certainly be warranted. That said, even though we were explicit about showing all modeling results, our interest in including covariates was to control for confounding of etomidate effects. We are aware that one could always improve modeling approaches; however, ours was a prespecified model that we thought would be adequate (not perfect) in its capacity to control for confounding of etomidate associations with outcomes.

Competing Interests

The authors declare no competing interests.

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Total Local Anesthetic Administered Is Integral to the Syndrome of Local Anesthetic Systemic Toxicity

To the Editor:

We read with interest the report of local anesthetic systemic toxicity in the recent issue of Anesthesiology.[1] The authors deserve credit for their review of the subject and detailed analysis of factors culminating in the death of their patient. The transparency required to present such a case is of benefit to all anesthesiologists, who can apply the principles described to improve safety for patients undergoing regional anesthesia techniques.

However, we were concerned that one integral factor contributing to the poor outcome in this case was not discussed, and that is the total dose of local anesthetic (LA) administered. We believe that a relative overdose of LA was administered and subsequent systemic absorption was likely a factor in the toxicity observed.

Total doses of LA used include 30 ml of mepivacaine 1.5% without epinephrine (450 mg) plus 10 ml of bupivacaine 0.25% with epinephrine 1:200,000 (25 mg). The dose of mepivacaine exceeds the manufacturer's recommended maximum dose of 400 mg for an adult.[2] Of note, the manufacturer's product information inserts for mepivacaine and bupivacaine additionally caution that the dose should be reduced for elderly or debilitated patients.*†

Further to this point, maximum adult doses for LAs cited in textbooks often assume a adult patient of 70 kg.[2] When treating a patient less than the assumed weight, 45 kg in this case, the dose must be reduced. Lastly, an elderly, American Society of Anesthesiologists physical status 4 patient is presumed to have impaired hepatic and renal function, as well as increased susceptibility to toxicity because of cardiovascular disease and reduced serum protein binding capacity.[3] All these factors conspire to put such a patient at risk of local anesthetic systemic toxicity from seemingly "normal" doses of LA.

When a regional technique is chosen, LA dosing must take into account patient factors predisposing to local anesthetic systemic toxicity, and doses of LA must be reduced accordingly.

Competing Interests

The authors declare no competing interests.

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