

vessels to act at the neuromuscular junction, and did not demonstrate so far biologic effects when given in the absence of a neuromuscular blocking agent. We did not administer maximum tolerated doses. Of note, we did not conduct pharmacokinetic/pharmacodynamic analyses required to determine E_{max} , as we did not intend to study if a further increase in blood concentration would have further increased speed of reversal.

In our study, we rather assessed “effectiveness,” the power to produce a desired effect⁸ between two reversal drugs (sugammadex and calabadiol) given at the same molar concentrations in three models, *in vitro*, *ex vivo*, and *in vivo*. We found that calabadiol 2 reversed rocuronium- and vecuronium-induced neuromuscular blockade with a 1:1 binding ratio, like sugammadex, but it had a higher *in vitro* binding affinity and a higher molar potency *in vivo*. Therefore, we argue that the *effectiveness* to reverse rocuronium- and vecuronium-induced neuromuscular blockade of calabadiol is higher compared with Bridion. To our knowledge, the *efficacy* of these compounds has not been tested by us or by others in any previously published study, probably because E_{max} of encapsulating agents cannot be studied rigorously. In addition, knowledge on maximum speed of reversal of neuromuscular blockade by maximum tolerated doses of calabadiol and sugammadex adds marginal value to the available literature on preclinical effectiveness of these encapsulating agents.

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Competing Interests

Dr. Eikermann holds equity shares of Calabash Bioscience, Inc. (College Park, Maryland), which is developing calabadiol 2 for biomedical applications. The other author declares no competing interests.

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Should Deidentified Case Data Be Treated as Independent Data Points?

To the Editor:

We read with interest Whitlock *et al.*'s¹ review of perioperative mortality derived from the National Anesthesia Clinical Outcomes Registry database. One shortcoming of the National Anesthesia Clinical Outcomes Registry database they briefly allude to is “the inability to eliminate patients who had multiple anesthetics” from the analysis. We suggest that this can be a major confounder in the retrospective analysis of such databases. For example, analysis of case data for the past 3 yr from our tertiary pediatric center showed a 48-h mortality of 85 per 70,194 cases (0.12%) or 64 per 42,808 patients (0.15%). Fifty patients had one procedure during this 48-h period, nine patients had two procedures, four patients had three procedures, and one patient underwent five procedures. The share of patients who had multiple procedures was even higher for 30-day mortality. This is not unexpected, as the sickest, most-likely-to-die patients are likely to have multiple procedures before their death.

Large databases allow collection of a sufficient number of relatively rare events (*e.g.*, perioperative death) to identify statistically meaningful associations between outcomes of interest (*e.g.*, perioperative mortality) and risk factors. Despite the large numbers of cases included in such analyses, *e.g.*, nearly 3,000,000 in the study by Whitlock *et al.*,¹ or approximately 244,400 in the study by Mathis *et al.*,² the actual numbers of index cases are still rather small, *e.g.*, 944 and 232, respectively. Therefore, counting multiple procedures in the same patient as independent data points may introduce significant bias toward attributes found in those patients. This problem is not limited to mortality alone, but may apply to any infrequent serious outcome.

A potential remedy would be for national and institutional databases to assign a unique number to each patient with the key held by the institutional administrator. Patient data would have to be linked to this unique number before being submitted in a deidentified manner to the national database. Alternatively, the incidence of “double counting” should be determined first with identifiable data at the institutional level, and the potential effects of such bias should be discussed in each publication that relies on large deidentified databases.

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Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Stucke and colleagues for bringing attention to this important issue and for providing an illuminating example from their own institution. Failure to correct for multiple procedures in the same patient may bias estimates unpredictably. Unfortunately, no single-patient identifier is available through the National Anesthesia Clinical Outcomes Registry (NACOR).

After we concluded our analysis,¹ NACOR began releasing more granular date-of-procedure information; the data set now includes year, month, and day of individual procedures. We merged procedure dates from the newer files with cases from the older file used in our manuscript. Of 944 cases reporting perioperative death, 50 cases were identified as occurring in

the same facility on the same year, month, and day in patients with identical age and sex, implying 24 unique patients with more than 1 procedure on the same date (23 patients with 2 procedures; 1 patient with 4), who ultimately died. Reassuringly, eliminating those patients' “second procedure” does not impact our findings in an informal *post hoc* sensitivity analysis we performed to answer this letter. We have not attempted to identify procedures beyond same-day cases, however, because this methodology is already quite crude.

Simple tricks like the above may be helpful in sensitivity analyses, but we emphatically agree that a unique patient number would be vastly preferable. A “hashed” identifier (anonymous, unable to be decrypted, and based on static unique patient identifiers) was proposed in detail by the Multicenter Perioperative Outcomes Group not only to identify duplicate cases, but also to link patient-level data from multiple sources.² This could include multiple institutional databases, insurance payor files, surgical databases (e.g., American College of Surgeons' National Surgical Quality Improvement Program), and national files (e.g., Social Security Death Index).

The Anesthesia Quality Institute is currently reorganizing its data collection structure and will reopen this question in the near future. Commentary on limitations stemming from the inability to identify multiple procedures in the same patient, like the letter from Dr. Stucke and his colleagues, serves to raise awareness of this important issue. We echo their call for careful consideration about the inclusion of an anonymized patient identifier, which we believe would further NACOR's mission of improving the quality of anesthesia care.

Competing Interests

The authors declare no competing interests.

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