code definitions that had been previously validated against chart review when possible (see Supplementary Digital Content 5). Although heterogeneous, these outcomes were selected because they were of interest in other studies of patients with OSA. Furthermore, the significant 28-day mortality rates after both respiratory and cardiovascular complications (26 and 18%) testify to their clinical significance, even if their exact clinical meaning is uncertain.

The sensitivity and specificity of administrative data to clinical events vary by diagnosis.[3] We can only hypothesize that a diagnosis of cardiac arrest and shock was the most frequently documented cardiovascular complication in both patients with OSA and their controls because it was more consistently detected and/or documented in the discharge abstract than acute coronary syndrome or atrial fibrillation, particularly, at the time the data were collected (1987–2008). Differences in the availability of cardiac troponin assays, the use of postoperative telemetry, and the range of included surgeries may explain the different rates of these complications between our study and another administrative database.[2] Finally, the biologic plausibility of increased risk of cardiac arrest in patients with untreated OSA that Dr. Kaw is seeking can be found in the third last paragraph of the article.

In summary, by linking polysomnography and administrative data, we created a large, unique database of postoperative outcomes in patients with OSA, from a time before routine preoperative screening and intensive postoperative monitoring. We carefully planned our study to address the limitations of administrative data and maximize its clinical applicability. It addressed important research questions that have eluded previous clinical studies for lack of statistical power[4] and previous large administrative database studies for lack of polysomnography data.[2] The results were cautiously interpreted within the limitations of the data and can help strengthen and refine current guidelines,[5] with the goal of improving postoperative outcomes for patients with OSA.

Competing Interests

Dr. Kryger is a volunteer board member with the National Sleep Foundation (Arlington, Virginia). He has received research grants from Respironics, Inc. (Murrysville, Pennsylvania), ResMed Corp. (San Diego, California), and Dymedix Diagnostics Inc. (Shoreview, Minnesota) that were not used to fund this research. Since this research has been completed, he has received consultancy fees from Inspire Medical Systems Inc. (Maple Grove, Minnesota), Ventus Medical Inc. (Belmont, California), Dymedix, Medtronic (Minneapolis, Minnesota), and Merck & Co., Inc. (Whitehouse Station, New Jersey). The other authors declare no competing interests.

Thomas C. Mutter, M.D., F.R.C.P.C., M.Sc., Dan Chateau, Ph.D., Michael Moffatt, M.D., F.R.C.P.C., M.Sc., Clare Ramsey, M.D., F.R.C.P.C., M.S., Leslie L. Roos, Ph.D., Meir Kryger, M.D., F.R.C.P.C. University of Manitoba, Winnipeg, Manitoba, Canada (T.C.M.). tmutter@exchange.hsc.mb.ca

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Neostigmine: You Can't Have It Both Ways

To the Editor:

We read the recent study by Sasaki *et al.*[1] with interest but were confused by its clinical take-home message (or lack thereof). This article represents the logical extension of previous work by Eikermann and coworkers, which states that "… neostigmine and qualitative neuromuscular transmission monitoring did not mitigate the increased risk of postoperative respiratory complications linked to the use of non-depolarizing neuromuscular blocking agents. Furthermore, neostigmine may [adversely] affect postoperative respiratory function…"[2,3] In their current study, the authors conclude "Neostigmine reversal … was associated with increased atelectasis. High-dose neostigmine or unwarranted use of neostigmine may translate to increased postoperative respiratory morbidity." We find the authors' discussion highly unbalanced. They spend considerable time reviewing the well-known limitations of neostigmine as an antagonist of moderate to deep neuromuscular block but essentially ignored the clinical reality that for those clinicians who do not have access to sugammadex, neostigmine represents a valuable and necessary addition to our armamentarium.

In a prominent place under the heading What This Article Tells Us That Is New is the statement "Neostigmine reversal did not reduce signs and symptoms of postoperative respiratory failure, and was associated with an increased incidence of atelectasis." We think this message may be easily misinterpreted by the naïve reader. At the end of surgery when the train-of-four (TOF) count has returned to three palpable responses or four with fade, do the authors imply that the risks of neostigmine administration outweigh its benefits? We would hope not.

In addition, we find several aspects of the protocol of authors problematic. For example, the authors define unwarranted use of neostigmine as "neostigmine administration in the absence of neuromuscular transmission monitoring or if the last documented TOF [train-of-four] before neostigmine administration was 0 of 4 twitches." These are hardly comparable situations. It is certainly no surprise that attempted reversal of residual nondepolarizing block with neostigmine at a TOF count of 0 will result in slow and inadequate return of neuromuscular function. However, is neostigmine antagonism 45 to 60 min after rocuronium 0.60 mg/kg (in the absence of neuromuscular monitoring) unwarranted? Although we would agree that qualitative monitoring (at a minimum) should be universally used, we also know that this standard is far from generally practiced. Thus, we question *automatically* labeling neostigmine administration unwarranted in these circumstances. Certainly, at this point in time, the majority of patients will have TOF ratios less than 0.90, and perhaps 30% will have TOF ratios less than 0.70.[4]

Similarly, the authors lump all individuals who required reintubation within 7 days of surgery into one group. We do not think this is sensible. Furthermore, the incidence of postoperative pulmonary complications was taken from hospital billing records. Did the authors ever review the actual patient charts to examine these outcomes more closely?

More importantly, *patients who received neostigmine were three times more likely to have had abdominal or thoracic surgery than were those who did not receive this drug*. Thus, is it really a surprise that the incidence of atelectasis was higher in the neostigmine group? If the TOF ratios on admission to the postanesthesia care unit were identical and the incidence of postoperative residual neuromuscular block in both groups was also the same, to attribute an increase in pulmonary complications to neostigmine is unjustified when the case mixes were not identical. The authors present the association between the dose of neostigmine (0 to 60 *vs.* >60 μg/kg) and increased incidence of atelectasis and hospital length of stay in figs. 1 and 2, respectively. We wonder whether a similar association could be found by looking at the abdominal and thoracic surgery in relation to atelectasis and hospital length of stay.

Trying to extract a take-home message from this article is particularly difficult when it is read in the context of other investigations from Dr. Eikermann's department. Sample conclusions: "upper airway obstruction frequently occurs during minimal neuromuscular blockade (TOF ratio 0.8), and extubation may put the patient at risk."[5]; "The clinician should consider that post-operative recovery of the TOF ratio to 0.9 does not exclude an impairment of neuromuscular transmission."[6]; "impaired neuromuscular transmission, even to a degree insufficient to evoke respiratory symptoms, markedly impairs upper airway dimensions and function."[7]; "Minimal neuromuscular blockade markedly increases upper airway closing pressure... Increased airway collapsibility despite unaffected values for resting ventilation may predispose patients to postoperative respiratory complications."[8] These opinions suggest that this research group is quite concerned with the potentially adverse effects of even very modest levels of residual neuromuscular block on respiratory function and airway patency. The current authors need to explain how the preceding conclusions should be interpreted in relation to their current caveats regarding neostigmine. If one is apprehensive about the sequelae of even very shallow residual paralysis, then, for those clinicians without access to sugammadex, reversal with an appropriate dose of neostigmine[9] should be routine. However, if concern about potential adverse respiratory effects of neostigmine is primary, we are at a loss as to how the authors would have the clinician proceed. A clearer clinical directive is called for. You can't have it both ways.

Competing Interests

The authors declare no competing interests.

Aaron F. Kopman, M.D., Mohamed Naguib, M.B., B.Ch., M.Sc., F.C.A.R.C.S.I., M.D. New York, New York (A.F.K.). akopman@nyc.rr.com

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Drs. Kopman and Naguib contributed to the work equally and have approved the manuscript.

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In Reply:

We are very grateful for the impassioned reading of our article[1] by Drs. Kopman and Naguib as their contributions to the field of neuromuscular blockade research are outstanding. We understand their concern that our nuanced conclusion may be misinterpreted in the clinical world, especially one without better neuromuscular blockade reversal alternatives. We specifically performed our study to provide current and meaningful data to identify and/or reinforce best practices for the application of neostigmine in clinical settings where neuromuscular blockade reversal alternatives are unavailable. Our article is a hypothesis-driven study, and we draw our conclusions based on our data. We appreciate their perspective on our article and the opportunity to elaborate on our conclusion and address their question on our control for surgical complexity.

We agree with Drs. Kopman and Naguib that our study did not control for anatomical site of surgery, but we did control for "high-risk surgery" by using a method based on the previously published data.[2] In addition, we addressed the concern of surgical procedure–related confounding with a follow-up study. In the June 2015 edition of Anesthesiology, our laboratory published a retrospective analysis of nearly 50,000 patients who received intermediate-acting nondepolarizing neuromuscular-blocking agents.[3] This large sample size study controlled for both surgical body region and procedure relative value units. We identified a neostigmine dose-dependent increase in the risk of respiratory complications that is eliminated when neostigmine administration is guided by neuromuscular transmission monitoring.

The observed efficacy of neostigmine as a neuromuscular blockade reversal agent in clinical effectiveness studies, where clinicians independently administer and monitor its application, is different than in efficacy studies where clinicians follow strict protocols. Our article reinforces the phenomenon we have previously identified: Clinicians in everyday practice who routinely administer neostigmine reversal without neuromuscular transmission monitoring may be more likely to harm their patients than help.[4,5] Drs. Kopman and Naguib noted this paradox in an earlier publication, "Routine reversal of residual neuromuscular block is less common in parts of Europe than in the US, yet Europeans are less likely to have witnessed postoperative residual paralysis."[6] This observation supports the argument that the clinical use of neostigmine as a reversal agent varies and that this variation in practice may explain the variance in the incidence of residual neuromuscular blockade and postoperative respiratory complications.

The sixteenth-century physician Paracelsus concluded, "All substances are poisons. The right dose differentiates a poison and a remedy." Our data support the intraoperative monitoring of neuromuscular transmission, particularly before tracheal extubation. Intraoperative neuromuscular function should be evaluated by observing the mechanical response to peripheral nerve stimulation whenever a nondepolarizing relaxant is administered; clinical signs (*e.g.*, head lift, hand grip, respiratory effort) are not adequate indicators of depth of neuromuscular blockade. Our data also support the dosing of neostigmine based on train-of-four monitoring.[7]

The clinical take-home message is that the titration of neostigmine must be done carefully and under monitored conditions. We do not seek to have anything in both ways; we seek to have neostigmine administered in the safest way possible.

Competing Interests

Dr. Eikermann, M.D., Ph.D., has filed a patent application for a new drug to reverse the effects of neuromuscular-blocking agents. In addition, he receives funding for investigator-initiated research from Merck, Whitehouse Station, New Jersey, and Massimo, Irvine, California. The other authors declare no competing interests.

Matthew J. Meyer, M.D., Nobuo Sasaki, M.D., Matthias Eikermann, M.D., Ph.D. Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (M.J.M.). matthewjmeyer@gmail.com

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