Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday, October 20, 2016
1830 HOURS

LOCATION:
The River Mill Restaurant
2 Cataraqui Street

PRESENTING ARTICLES:
Dr. Melinda Fleming & Liban Ahmed

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SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
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Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

Nondepolarizing Neuromuscular Blocking Agents, Reversal, and Risk of Postoperative Pneumonia

Catherine M. Bulka, M.P.H., Maxim A. Terekhov, M.S., Barbara J. Martin, R.N., M.B.A., Roger R. Dmochowski, M.D., Rachel M. Hayes, B.S.N., Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H.

ABSTRACT

Background: Residual postoperative paralysis from nondepolarizing neuromuscular blocking agents (NMBAs) is a known problem. This paralysis has been associated with impaired respiratory function, but the clinical significance remains unclear. The aims of this analysis were two-fold: (1) to investigate if intermediate-acting NMBA use during surgery is associated with postoperative pneumonia and (2) to investigate if nonreversal of NMBAs is associated with postoperative pneumonia.

Methods: Surgical cases (n = 13,100) from the Vanderbilt University Medical Center National Surgical Quality Improvement Program database who received general anesthesia were included. The authors compared 1,455 surgical cases who received an intermediate-acting nondepolarizing NMBA to 1,455 propensity score–matched cases who did not and 1,320 surgical cases who received an NMBA and reversal with neostigmine to 1,320 propensity score–matched cases who did not receive reversal. Postoperative pneumonia incidence rate ratios (IRRs) and bootstrapped 95% CIs were calculated.

Results: Patients receiving an NMBA had a higher absolute incidence rate of postoperative pneumonia (9.00 *vs.* 5.22 per 10,000 person-days at risk), and the IRR was statistically significant (1.79; 95% bootstrapped CI, 1.08 to 3.07). Among surgical cases who received an NMBA, cases who were not reversed were 2.26 times as likely to develop pneumonia after surgery compared to cases who received reversal with neostigmine (IRR, 2.26; 95% bootstrapped CI, 1.65 to 3.03).

Conclusions: Intraoperative use of intermediate nondepolarizing NMBAs is associated with developing pneumonia after surgery. Among patients who receive these agents, nonreversal is associated with an increased risk of postoperative pneumonia.
(ANESTHESIOLOGY 2016; 125:647-55)

ANESTHESIOLOGISTS can monitor neuromuscular transmission in the operating room to assess the degree of neuromuscular block using train-of-four (TOF) stimulation. However, this monitoring is often subjective, inaccurate, and inconsistently applied.[1] Sometimes, acetylcholinesterase inhibitors, most commonly neostigmine, are administered to reverse the neuromuscular blockade. Using acetylcholinesterase inhibitors increases the amount of acetylcholine in the synaptic cleft and thus counteracts the effects of neuromuscular blocking agents (NMBAs).[2] Despite these strategies, the effects of nondepolarizing NMBAs can last beyond the time the patient leaves the operating room. Approximately 40% of patients who receive intermediate-acting NMBAs enter the postanesthesia care unit (PACU) with postoperative residual neuromuscular block (PORB), defined as a TOF ratio less than 0.9.[3] PORB is associated with impaired pharyngeal function,[4,5] increased aspiration risk,[5] upper airway muscle weakness,[6] and partial upper airway obstruction.[6] These symptoms have been observed even among patients with TOF ratios between 0.7 and 0.9, which were historically considered acceptable recovery.[7,8] Such symptoms may lead to impaired breathing or diminished protective airway reflexes, which are essential in order to avoid respiratory complications.[9]

What We Already Know about This Topic

- The effects of nondepolarizing neuromuscular blocking agents can last beyond the time the patient leaves the operating room despite monitoring neuromuscular transmission and reversing neuromuscular blockade with acetylcholinesterase inhibitors
- Postoperative residual neuromuscular block is associated with symptoms that may lead to impaired breathing or diminished protective airway reflexes

What This Article Tells Us That Is New

- The incidence of pneumonia in patients receiving a neuromuscular blocking agent was 1.79 times that of propensity-matched patients who did not receive a neuromuscular blocking agent
- The incidence of pneumonia in patients receiving a neuromuscular blocking agent without reversal of neuromuscular blockade with neostigmine was 2.26 times that of propensity-matched cases who received reversal with neostigmine

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 611. This article has an audio podcast.

Submitted for publication August 6, 2014. Accepted for publication June 14, 2016. From the Department of Anesthesiology (C.M.B., M.A.T., J.M.E.), Quality, Safety, and Risk Prevention (B.J.M.), Department of Urology (R.R.D.), Section of Surgical Sciences (R.M.H., J.M.E.), Department of Biomedical Informatics (J.M.E.), and Department of Health Policy (J.M.E.), Vanderbilt University Medical Center, Nashville, Tennessee.

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The availability of validated retrospective data from the National Surgical Quality Improvement Program (NSQIP), which include patient demographic information, preoperative conditions, intraoperative variables, and 30-day postoperative occurrences, enabled the examination of intraoperative NMBA use and NMBA reversal as risk factors for postoperative respiratory complications at our university-affiliated tertiary-care hospital.[10,11] Of these respiratory complications, we selected postoperative pneumonia, which is associated with increased mortality, morbidity, hospital stays, and healthcare costs.[12] We hypothesized that patients who receive NMBAs during surgery may be more likely to develop postoperative pneumonia. Additionally, among patients who receive NMBAs, we hypothesized that patients who do not receive reversal with an acetylcholinesterase inhibitor may also have an increased risk of postoperative pneumonia.

Materials and Methods

Eligibility

Surgical cases who received general anesthesia and who underwent surgery between July 2005 and September 2013 were extracted from Vanderbilt University Medical Center's (VUMC; Amsterdam, the Netherlands) NSQIP database. NSQIP data are entered by a trained surgical clinical reviewer. After a baseline sample of 15 general and vascular surgery cases, all colectomies, proctectomies, and ventral hernia repairs performed in a NSQIP-determined 8-day cycle are targeted for selection; additional cases are randomly sampled if necessary to achieve the requisite 40 cases per cycle.[13] Cases are followed up for 30 days postoperatively.[11] NSQIP excludes patients who are less than 18 yr old, those who are admitted for trauma or transplantation, and those whose operative procedure results from complications of another diagnostic or surgical procedure within the previous 30 days. Supplemental intraoperative data regarding medications were obtained from VUMC's perioperative data warehouse. For statistical analyses, we excluded surgical cases with no follow-up and surgical cases with incomplete intraoperative medication documentation. Additionally, we excluded cases who received pancuronium, a long-acting nondepolarizing NMBA, since it is uncommonly used and has been associated with a higher incidence of postoperative residual block and pulmonary complications compared to intermediate-acting agents.[14]

Postoperative Pneumonia Definition

Patients were defined as having postoperative pneumonia if they met the NSQIP definition of pneumonia after surgery. NSQIP defines pneumonia as the presence of at least one definitive chest radiologic examination and at least one sign of pneumonia (fever, leukopenia, leukocytosis, or altered mental status with no other cause), as well as at least one microbiologic laboratory finding (positive cultures from blood, bronchoalveolar lavage, or pleural fluid specimens) or at least two symptoms (new onset of purulent sputum, new onset of or worsening, cough, dyspnea or tachypnea, rales or rhonchi breath sounds, or worsening gas exchange).[15] Patients with an underlying pulmonary or cardiac disease are required to have at least two or more definitive serial chest radiologic exams. An element of the infection criterion could be present before the surgery, as long as all elements used to satisfy the definition were present together after the time of surgery. We excluded patients who met the definition criteria for pneumonia at the time of surgery.

Statistical Analysis

To control for potential confounding, we performed two propensity score–matched analyses. Logistic regression modeling was used to calculate the probability of receiving an intermediate-acting nondepolarizing NMBA (either cisatracurium, rocuronium, or vecuronium) during surgery. Patient age, sex, body mass index (BMI), American Society of Anesthesiologists physical status classification, emergency surgery status, scheduled duration of the surgical procedure, procedure type (classified using Clinical Classifications Software [CCS] groupers),[16] primary surgeon on the case, primary anesthesiologist on the case, if the surgery occurred during normal business hours, and the year of surgery were included as independent variables in the model. Sparsely represented CCS categories were combined in a separate "other" CCS category. BMI was modeled as a categorical variable with four levels: underweight (BMI less than or equal to 18.5 kg/m^2), normal ($18.5 < BMI \leq 25$), overweight ($25 < BMI \leq 30$), and obese (BMI greater than or equal to 30 kg/m^2).*[17] Scheduled surgical duration was modeled as a categorical variable with four levels: less than 24, 24 to 48, 48 to 96, and greater than 96 h. Anesthesiologists who performed less than 500 cases were combined into a separate provider group. The same logic was applied to surgeons. Age was modeled using restricted cubic splines to allow for nonlinear associations. To account for observations with missing data, we performed five rounds of multiple imputation (using the PROC MI, a multiple imputation procedure, in SAS, SAS Institute Inc., USA). We then calculated the average propensity score across the five imputed data sets. Surgical cases who received an NMBA were matched to those who did not in a 1:1 ratio using 8 to 1 greedy matching.[18] This algorithm first matches the exposed to the unexposed on eight digits of the propensity score. For those who do not match on eight digits, the exposed are then matched to the unexposed on seven digits of the propensity score. The algorithm proceeds sequentially to the lowest digit match on propensity score (one digit).

* Standard weight status categories associated with BMI ranges for adults.[17]

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For the second propensity score–matched analysis, we only included surgical cases who had received an NMBA during surgery. We then calculated the propensity score of receiving reversal of NMBA with an acetylcholinesterase inhibitor. In addition to the covariates included in the first propensity score model, we included the amount of time between the last dose of NMBA administered and the end of the surgical case (*i.e.*, the time the patient left the operating room). Along with age, the time between the last dose of NMBA and the end of surgery was modeled using restricted cubic splines. Again, we calculated the mean propensity score across the five imputed datasets for observations with missing data and then matched each surgical case who received NMBA reversal to a case who did not, using an 8 to 1 greedy matching algorithm. At least 98% of matches in scores occurred at two-digit levels in both analyses.

Balance between the matched cohorts was assessed using the standardized difference before and after propensity score matching,[12] with and without imputed values. Variables with skewed distributions were compared by calculating the standardized difference as the difference in mean rankings divided by a pooled estimate of the within-group SD of rankings.[13] Categorical variables with more than two levels were compared by calculating the standardized difference using a multivariate Mahalanobis distance method.[14,15]

The incidence rate of postoperative pneumonia was defined as the number of new cases over the total person-time at risk. Person-time at risk was counted as the number of days the patient was at risk of developing postoperative pneumonia. Follow-up began when the patient left the operating room and extended through a 30-day period, death, or occurrence of the primary study endpoint (postoperative pneumonia). Patients who were lost to follow-up contributed person-time for the duration of hospital stay after surgery. If the patient died during surgery, the patient was excluded.

Incidence rate ratios (IRRs) were calculated to compare the rate of postoperative pneumonia among surgical cases who received an NMBA to those who did not. Among surgical cases who received an NMBA, IRRs compare those who did not receive reversal to those who received an NMBA with an acetylcholinesterase inhibitor. We calculated percentile 95% CIs based on 1,000 bootstrap samples.[19] Statistical significance was set at $\alpha = 0.05$. All statistical analyses were performed using SAS version 9.4.

Results

There were 13,290 surgical cases included in VUMC's NSQIP database who received general anesthesia (fig. 1). A total of 190 cases were excluded from analysis; 35 cases had pneumonia present at the time of surgery, 109 had incomplete intraoperative medication documentation, 13 died in the operating room, 10 were lost to follow-up immediately after leaving the operating room, and 23 received pancuronium. Of the remaining 13,100 eligible surgical cases, we matched 1,455 cases who received an NMBA to 1,455 who did not. Among the 10,594 surgical cases who received an NMBA, we matched 1,320 who did not receive reversal to 1,320 who received neostigmine. No other acetylcholinesterase inhibitor was administered during this time period in our patient cohort. In the final propensity-matched patient cohorts, only two variables had more than 1% missing data: BMI and scheduled surgical duration (5% and 2% missing data, respectively).

Patient demographics and clinical characteristics before and after propensity score matching are presented in table 1. Standardized differences are presented in figures 2

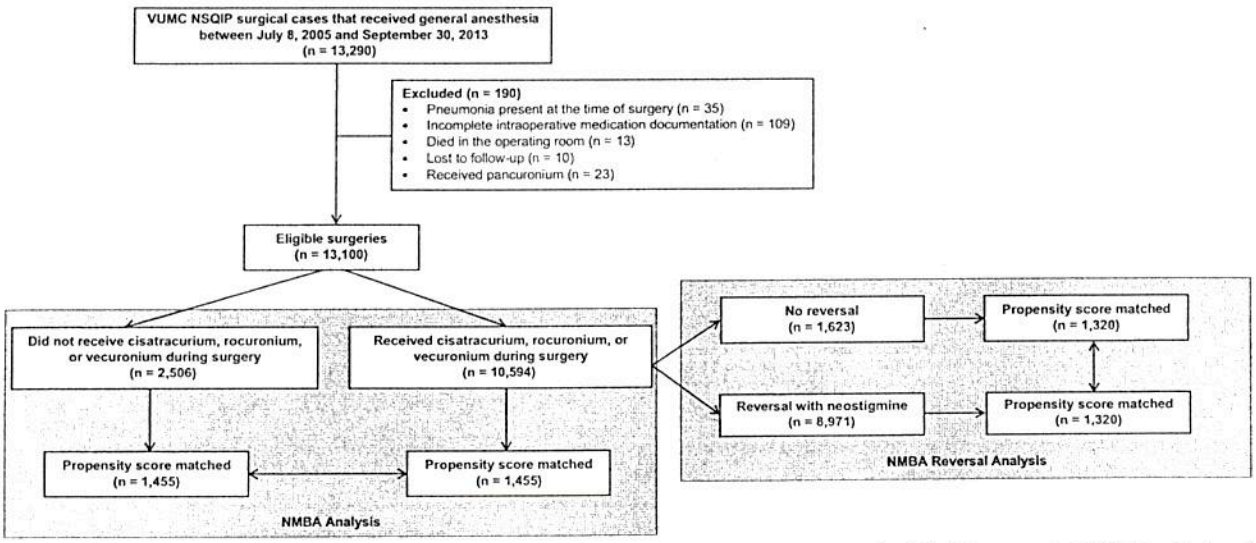

Fig. 1. Flowchart of inclusion/exclusion criteria. NMBA = nondepolarizing neuromuscular blocking agent; NSQIP = National Surgical Quality Improvement Program; VUMC = Vanderbilt University Medical Center.

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Table 1. Patient Demographics and Clinical Characteristics before and after Matching

	Before Matching		After Matching	
NMBA Analysis	Received NMBA (n = 10,594)	Did Not Receive NMBA (n = 2,506)	Received NMBA (n = 1,455)	Did Not Receive NMBA (n = 1,455)
Age (yr), mean (SD)	53 (16)	53 (15)	54 (15)	53 (15)
ASA class, median (IQR)	3 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)
Body mass index, median (IQR)	28.7 (24.4–35.3)	27.6 (24.0–32.4)	27.8 (23.9–32.5)	27.9 (24.1–32.4)
Emergency case, n (%)	852 (8.0)	63 (2.5)	53 (3.6)	57 (3.9)
Men, n (%)	4,681 (44.2)	752 (30.0)	542 (37.0)	538 (37.3)
Scheduled surgical duration (min), median (IQR)	180 (120–240)	120 (90–180)	150 (90–180)	120 (90–180)
	Before Matching		After Matching	
NMBA Reversal Analysis	No Reversal (n = 1,623)	Reversal with Neostigmine (n = 8,971)	No Reversal (n = 1,320)	Reversal with Neostigmine (n = 1,320)
Age (yr), mean (SD)	55 (16)	53 (16)	54 (16)	54 (16)
ASA class, median (IQR)	3 (2–4)	3 (2–3)	3 (2–3)	3 (2–3)
Body mass index (kg/m^2), median (IQR)	28.7 (24.2–34.5)	28.7 (24.5–35.4)	28.7 (24.3–34.8)	28.7 (24.2–34.5)
Emergency case, n (%)	352 (21.7)	500 (5.6)	167 (12.7)	196 (14.9)
Men, n (%)	761 (46.9)	3,920 (43.7)	588 (45.7)	610 (47.4)
Minutes between last NMBA dose and surgery end, median (IQR)	63 (39–101)	68 (51–91)	67 (44–104)	69 (52–97)
Scheduled surgical duration (min), median (IQR)	150 (120–240)	180 (120–240)	180 (120–240)	179 (120–240)

ASA = American Society of Anesthesiologists; IQR = interquartile range; NMBA = nondepolarizing neuromuscular blocking agent.

and 3. Patient age, sex, BMI, American Society of Anesthesiologists physical status, emergency surgery status, scheduled duration, procedure type, primary surgeon, primary anesthesiologist, the year of surgery, and the amount of time between the last dose of NMBA administered and the end of the surgical case (for reversal analysis) were not significantly different ($P > 0.05$) across groups after propensity score matching, and all standardized differences were less than 0.15, representing sufficient balance in the matched groups. The top 10 surgical procedures (classified using the Agency for Healthcare Research and Quality CCS categories) included in the matched cohort are shown in the appendix table.

The surgical cases who received an NMBA during surgery contributed 42,202 person-days at risk (table 2). Of the 1,455 surgical cases in this cohort, 38 developed pneumonia within 30 days after surgery. The surgical cases who did not receive an NMBA contributed 42,161 person-days at risk. Of these cases, 22 developed postoperative pneumonia. The IRR was statistically significant (IRR, 1.79; 95% bootstrapped CI, 1.08 to 3.07). The 1,320 surgical cases who received an NMBA during surgery without reversal contributed 35,300 person-days at risk. A total of 149 of these surgical cases went on to develop postoperative pneumonia. The surgical cases who received reversal of neuromuscular blockade with neostigmine contributed 37,138 person-days at risk. Of these surgical cases, 70 developed pneumonia within 30 days after surgery. The IRR comparing surgical cases who were not reversed to those who received neostigmine was 2.26 (95% bootstrapped CI, 1.65 to 3.03).

A *post hoc* sample size and power analysis of matched sets of cases and controls was performed after the conclusion of the study. In this analysis, one matched control per case indicated that the probability of exposure (nondepolarizing NMBAs) among controls was 0.05 and the correlation coefficient for exposure between matched cases and controls was 0.6. If the true odds ratio for postoperative pneumonia in exposed subjects relative to unexposed subjects was 1.75, we would have needed to study 1,549 patients—with one matched control per case—to be able to reject the null hypothesis that this odds ratio equals 1 with power of 0.9. The type I error probability associated with this test of this null hypothesis is 0.05. Given the sample size, the current study was therefore sufficiently powered to detect the hypothesized treatment effect. A 75% higher odds for postoperative pneumonia in exposed subjects relative to unexposed was recognized to be clinically meaningful and concordant with previous literature.[20]

Discussion

We found evidence of an association between the use of intermediate-acting NMBAs during surgery and the risk

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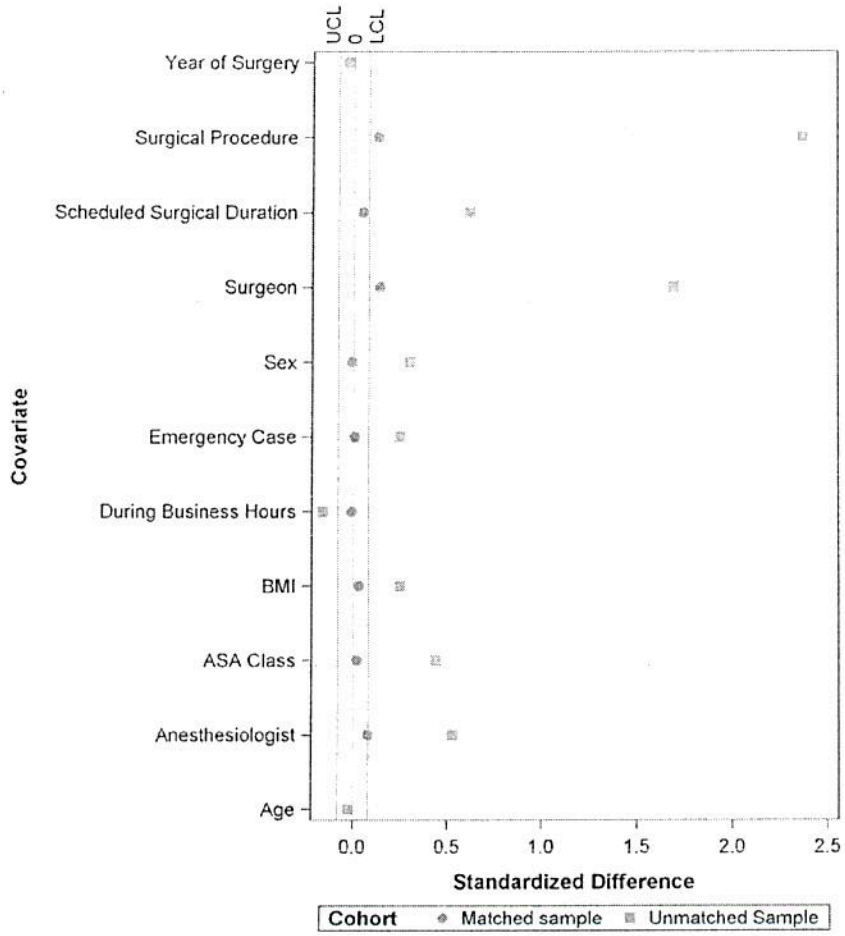

Fig. 2. Standardized differences between surgical cases who received nondepolarizing neuromuscular blocking agents and those who did not. The standardized differences compare the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured across different units. ASA = American Society of Anesthesiologists; BMI = body mass index; LCL = lower control limit; UCL = upper control limit.

of postoperative pneumonia. Among patients who received such agents, those who were not reversed with an acetylcholinesterase inhibitor were more than twice as likely to develop pneumonia after surgery (IRR, 2.26; 95% bootstrapped CI, 1.65 to 3.03). The association between receiving a nondepolarizing muscle relaxant during surgery and developing postoperative pneumonia is consistent with previous studies, which have identified associations between intermediate-acting nondepolarizing agents and postoperative respiratory complications.[20] The association between nonreversal and increased risk of postoperative pneumonia is a novel finding that extends our understanding of the risk of developing postoperative pneumonia.

Prospective studies in the 1990s highlighted the association between NMBA use during surgery and postoperative respiratory complications.[14,21] These studies found that the long-acting NMBA pancuronium was associated with a greater risk of postoperative pulmonary complications than the intermediate-acting NMBAs. Since that time, there has been a focus on PORB resulting from NMBA use in the literature,[3,8,22–25] but few studies have assessed downstream health outcomes.[26,27] Of those that have, the findings suggest that PORB is associated with respiratory complications and increased PACU lengths of stays, but the causal pathway between NMBAs, reversal, PORB, and postoperative outcomes remains unclear. Correspondingly, there is a dearth of work that quantifies the clinical significance of not administering an antagonist after administration of an NMBA. Two randomized controlled trials have found nonreversal to be associated with residual neuromuscular blockade (TOF ratio less than 0.80)[28] and hypoxemia (arterial oxygen saturation less than 93%) in the PACU[29] when compared to reversal with neostigmine, which appears to support our finding that not receiving neostigmine is associated with an increased risk of developing postoperative pneumonia.

As an observational study, we cannot establish causality or rule out the possibility of bias from unmeasured confounders. Assignment of pneumonia is based on a retrospective review of the medical record, not on clinical

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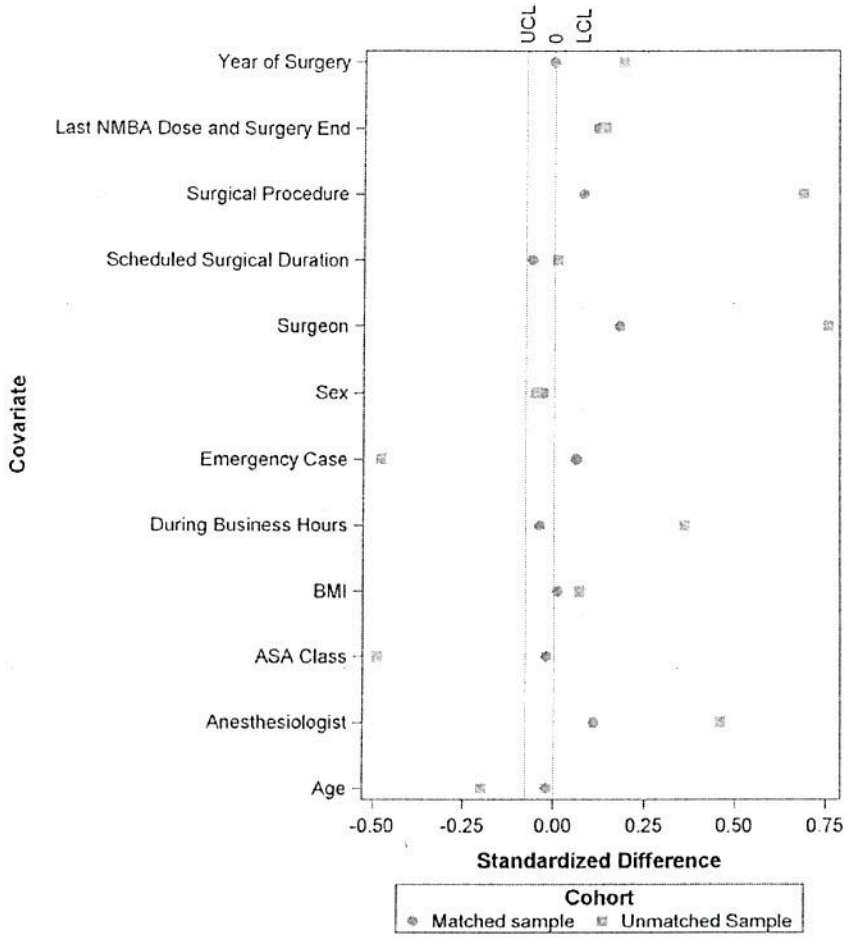

Fig. 3. Standardized differences between surgical cases who received nondepolarizing neuromuscular blocking agents (NMBA) reversal and those who did not. The standardized differences compare the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured across different units. ASA = American Society of Anesthesiologists; BMI = body mass index; LCL = lower control limit; UCL = upper control limit.

Table 2. Postoperative Pneumonia Incidence Rate Ratios

NMBA Analysis	Received an NMBA (n = 1,455)	Did Not Receive an NMBA (n = 1,455)
Developed postoperative pneumonia	38 surgical cases	22 surgical cases
Person-time at risk (d)	42,202	42,161
Incidence per 10,000 person-days at risk	9.00	5.22
Incidence rate ratio (95% bootstrapped CI)	—	1.79 (1.08–3.07)
NMBA Reversal Analysis	**No Reversal (n = 1,320)**	**Reversal with Neostigmine (n = 1,320)**
Developed postoperative pneumonia	149 surgical cases	70 surgical cases
Person-time at risk (d)	35,300	37,138
Incidence per 10,000 person-days at risk	4.22	1.88
Incidence rate ratio (95% bootstrapped CI)	—	2.26 (1.65–3.03)

NMBA = nondepolarizing neuromuscular blocking agent.

assessment of patients. As with any surveillance system, interpretation of clinical data with reference to definition criteria may lead to misclassification. Bias in availability of clinical documentation may occur with provider variation in clinical practice, as patients who are older or sicker may be more likely to receive radiographic and laboratory testing required for assignment of postoperative occurrences.[30] However, we relied on the NSQIP data surveillance system, which uses trained nurse reviewers for case adjudication and has been well validated.[31,32] Our results were

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observed at a large academic medical center where procedures tend to have longer operative times and patients tend to undergo certain types of surgeries; therefore, generalizability is another potential limitation of this study. Finally, this study did not evaluate TOF data. Quantitative acceleromyographic monitoring is not routinely performed at our hospital. While our anesthesiologists do perform qualitative neuromuscular monitoring, these data are not reliably captured and have questionable efficacy in the detection of residual paralysis.[33] Furthermore, as an intermediate variable in the causal pathway from nonreversal to postoperative pneumonia, controlling for TOF values as a metric for PORB could have potentially introduced overadjustment bias to our analysis.[34]

Neostigmine remains the most common acetylcholinesterase inhibitor in the United States, as sugammadex has only been recently approved by the Food and Drug Administration.[35] While neostigmine accelerates recovery from neuromuscular blockade,[36] the exact timing of neostigmine administration is crucial as giving this drug to patients who have already spontaneously recovered from neuromuscular block can lead to significant upper airway collapsibility (comparable to a TOF ratio of 0.5).[37] In fact, several recent reports have indicated that neostigmine may contribute to severe postoperative respiratory complications (including increased atelectasis, pulmonary edema, and reintubation) when used in an unwarranted fashion.[38–40] We therefore conclude that the judicious use and proper management of neuromuscular blockade are important components in the care of surgical patients and preventing downstream respiratory complications. Our study's findings suggest that there may be a benefit to modifying current approaches to the use of neuromuscular blockade reversal agents since failing to reverse residual neuromuscular block may result in adverse clinical consequences. Such strategies, such as routine use of quantitative neuromuscular monitoring, would likely be best evaluated in a prospective clinical trial.

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Competing Interests

The authors declare no competing interests.

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Appendix. Summary of Case Matching

Top 10 CCS Procedure Descriptions	NMBA		
	Did Not Receive NMBA, n (%)	Received NMBA, n (%)	Total
Thyroidectomy, partial or complete	101 (46.12)	118 (53.88)	219
Mastectomy	113 (52.07)	104 (47.93)	217
Other therapeutic endocrine procedures	106 (51.21)	101 (48.79)	207
Other hernia repair	58 (51.79)	54 (48.21)	112
Other OR lower gastrointestinal therapeutic procedures	46 (48.94)	48 (51.06)	94
Other therapeutic procedures, hemic and lymphatic system	36 (52.94)	32 (47.06)	68
Other OR procedures on vessels other than head and neck	26 (48.15)	28 (51.85)	54
Inguinal and femoral hernia repair	29 (59.18)	20 (40.82)	49
Lumpectomy, quadrantectomy of breast	22 (48.89)	23 (51.11)	45
Amputation of lower extremity	18 (47.37)	20 (52.63)	38

CCS = Clinical Classification Software; NMBA = nondepolarizing neuromuscular blocking agent; OR = operating room.

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Review Article

A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade

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Summary

We reviewed systematically sugammadex vs neostigmine for reversing neuromuscular blockade. We included 17 randomised controlled trials with 1553 participants. Sugammadex reduced all signs of residual postoperative paralysis, relative risk (95% CI) 0.46 (0.29–0.71), p = 0.0004 and minor respiratory events, relative risk (95% CI) 0.51 (0.32–0.80), p = 0.0034. There was no difference in critical respiratory events, relative risk (95% CI) 0.13 (0.02–1.06), p = 0.06. Sugammadex reduced drug-related side-effects, relative risk (95% CI) 0.72 (0.54–0.95), p = 0.02. There was no difference in the rate of postoperative nausea or the rate of postoperative vomiting, relative risk (95% CI) 0.94 (0.79–1.13), p = 0.53, and 0.87 (0.65–1.17), p = 0.36 respectively.

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Introduction

Sugammadex is a gamma-cyclodextrin drug that reverses non-depolarising neuromuscular blockade, induced by aminosteroids such as rocuronium and vecuronium [1, 2]. It has been compared with acetylcholinesterase inhibitors, mainly neostigmine [3].

Residual neuromuscular blockade is one of the main causes of postoperative pulmonary and respiratory complications, hypoxia, upper airway obstruction and decreased oxygen saturation, which can increase the incidence of tracheal re-intubation in critical care units [4–9]. Sugammadex reverses neuromuscular blockade more rapidly and reliably than acetylcholinesterase inhibitors [3]. Anticholinergics are often administered with neostigmine to counteract its muscarinic side-effects, but in turn these may cause nausea and vomiting, increased secretions, heart rhythm abnormalities and bronchospasm.

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We performed this systematic review to update the relative harm and benefit that results from the reversal of neuromuscular blockade with sugammadex vs neostigmine.

Methods

We conducted this registered systematic review using recommended methods [10–13]. We included randomised controlled trials of sugammadex vs neostigmine for reversing neuromuscular blockade (train-of-four at least 0.9) generated by rocuronium or vecuronium in adults. We excluded studies that compared sugammadex with placebo, or combined sugammadex with neostigmine, or compared different doses of sugammadex. The primary outcome was the rate of postoperative residual paralysis. Secondary outcomes were the rates of drug-related adverse events, including postoperative nausea or vomiting. We subgrouped signs of residual paralysis as severe or not severe. We defined severe signs as: hypoxaemia ($S_pO_2 < 90\%$) after intervention with an oxygen flow of at least 3 $l.min^{-1}$ via nasal cannulae; difficulty breathing, swallowing or speaking; a respiratory rate $> 20\ min^{-1}$, accessory muscle use or tracheal tug; tracheal intubation; invasive or non-invasive ventilation. We defined signs that were not as severe as muscular weakness that improved following intervention or SpO_2 90–93%.

We searched Embase, MEDLINE and CENTRAL to September 2014 for studies published in any language. We also contacted industry representatives and searched retrieved trials for additional studies. We excluded trials published in abstract. Two authors (AAG and JRM) independently assessed each title and abstract for inclusion. Two different authors (AE and EMH) extracted data, discrepancies in which were resolved by a third author (JMCV).

Two authors (EMH and JRM), adjudicated by a third (JMCV), assessed risks of bias in seven methodological domains with the Cochrane Collaboration risk of bias tool [14]. We classified trial bias risk as high if any domain bias was judged as unclear or high. We anticipated that some trials would compare multiple

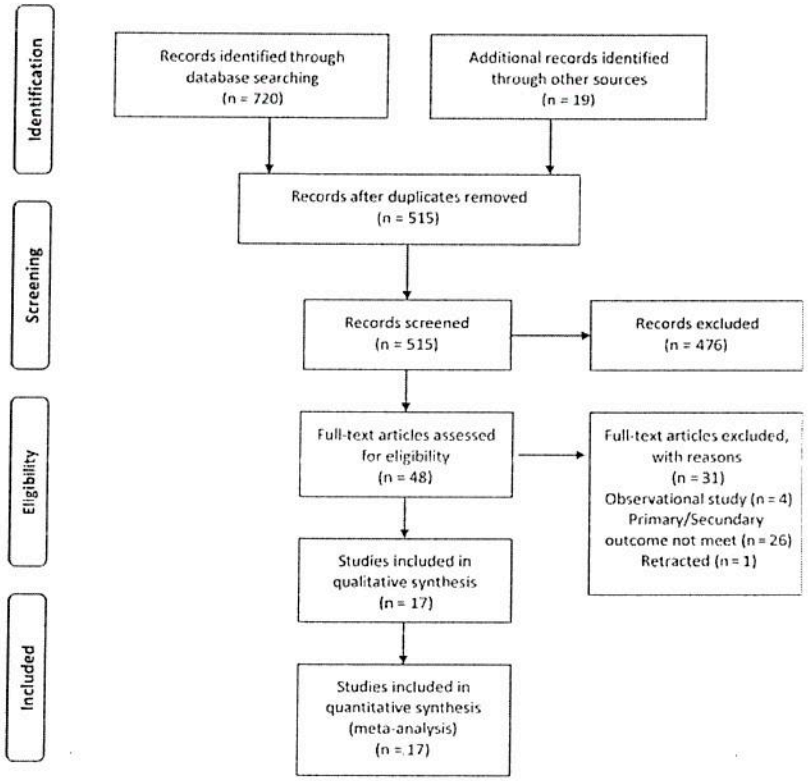

Figure 1 PRISMA flow diagram of trial selection.

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Author	Year	Random sequence generation (Selection bias)	Allocation Concealment (Selection bias)	Bilinding of participants & personnel (Performance bias)	Bilinding of outcome Assesment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias
Jones	2008	+	+	?	?	+	+	?
Flockton	2008	+	+	−	?	−	+	+
Blobner	2010	+	+	?	?	+	+	?
Lemmens	2010	+	+	?	?	+	+	?
Khueni-Brady	2010	+	+	−	?	+	+	?
Schaller	2010	+	+	+	?	?	+	?
Adamus	2011	+	?	−	−	+	?	?
Illman	2011	?	+	+	+	−	+	+
Sabo	2011	+	?	+	+	?	+	?
Gaszynski	2012	?	?	−	?	+	+	?
Geldner	2012	+	?	−	?	+	+	?
Mekawy	2012	+	?	?	−	?	?	?
Carron	2013	+	+	−	?	+	?	?
Woo	2013	?	−	−	?	?	?	?
Castro	2014	+	−	−	−	+	+	?
Wu	2014	+	+	−	?	?	?	?
Koyuncu	2015	?	−	+	−	+	?	?

Figure 2 Risks of bias for individual trials: green, low risk; yellow, unclear risk; red, high risk.

doses of sugammadex with neostigmine, for which we only analysed outcomes after the 2 $mg.kg^{-1}$ sugammadex dose. We analysed outcomes following lower doses of sugammadex for trials that did not investigate 2 $mg.kg^{-1}$.

We used the Metafor package in R (versions 1.9-6 and 3.1.3 respectively) for statistical analyses [15–17]. We presented the most conservative result from random-effects and fixed-effect models and presented dichotomous outcomes as risk ratio (RR) with a 95% confidence interval (CI) [18]. We considered a p value < 0.05 to be statistically significant. We quantified statistical heterogeneity as the I^2 statistic. We categorised heterogeneity as: low, < 25%; moderate, 25–50%; substantial, > 50% [19]. We analysed heterogeneity with a chi-squared test; we considered a p value < 0.10 statistically significant.

We used trial sequential analysis (TSA) to determine the statistical significance of differences in outcome between sugammadex and neostigmine, which adjusts the size of difference required to reach statistical significance with the addition of each trial, thereby controlling the false discovery rate [20]. We sequenced the addition of trials by year of publication and then alphabetical order. We plotted the cumulative difference in effects between sugammadex and neostigmine on graphs illustrating the cumulative thresholds (monitoring boundaries) for statistical significance [21, 22]. We used the Bonferroni–Jakobsen procedure to adjust for multiple comparisons (see also Supporting Information Fig. S1) [23, 24]. We used trial sequential analysis program version 0.9 beta (http://www.ctu.dk/tsa) [22, 25, 26]. We set trial

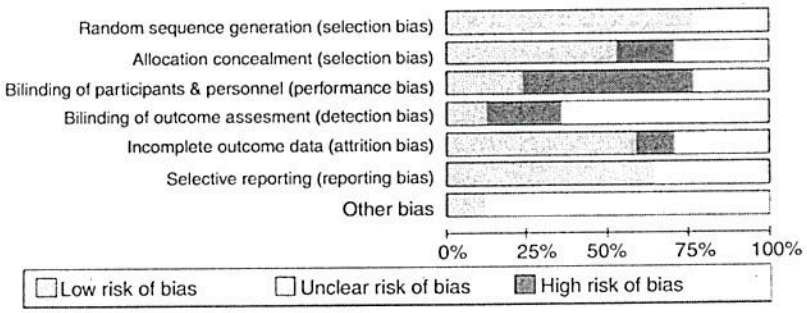

Figure 3 Summary of risks of bias: green, low risk; yellow, unclear risk; red, high risk.

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Table 1 Characteristics of included studies.

Author	Surgery (n)	Drug	Blockade intensity	Sugammadex	Comparison	Primary outcome	Funding
Flockton et al. 2008 [28]	Various (34/39)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + glycopyrrolate 10 μg.kg^{-1}	Time to TOF 0.9	Schering-Plough
Jones et al. 2008 [29]	Various (37/38)	Rocuronium	Posttetanic counts 1–2; train-of-four 0	4 mg.kg^{-1}	Neostigmine 70 μg.kg^{-1} + glycopyrrolate 14 μg.kg^{-1}	Time to TOF 0.9	Schering-Plough
Blobner et al. 2010 [33]	Various (48/48)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + glycopyrrolate 10 μg.kg^{-1}	Time to TOF 0.9	MSD
Khuenl-Brady et al. 2010 [30]	Various (48/45)	Vecuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + glycopyrrolate 10 μg.kg^{-1}	Time to TOF 0.9	Schering-Plough
Lemmens et al. 2010 [31]	Various (41/34)	Vecuronium	Posttetanic counts 1–2; train-of-four 0	4 mg.kg^{-1}	Neostigmine 70 μg.kg^{-1} + glycopyrrolate 14 μg.kg^{-1}	Time to TOF 0.9	MSD
Schaller et al. 2010 [32]	Various (43/51)	Rocuronium	Train-of-four < 2	0.0625, 0.125, 0.25, 0.5 or 1 mg.kg^{-1}	Neostigmine 5, 8, 15, 25 or 40 μg.kg^{-1}	Time to TOF 0.9	Not stated
Adamus et al. 2011 [36]	Intervertebral fusion (11/10)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	Time to TOF 0.9 and to lumbar stimulation	State funding
Gaszinski et al. 2011 [37]	Bariatric (35/35)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	Time to TOF 0.9	State funding
Illman et al. 2011 [34]	Various (24/23)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + glycopyrrolate 10 μg.kg^{-1}	Time to TOF 0.9	Finnish MSD
Sabo et al. 2011 [35]	Major abdominal (51/49)	Rocuronium	Train-of-four < 2	4 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + glycopyrrolate 10 μg.kg^{-1}	Time to TOF 0.9 and residual paralysis	Merck
Geldner et al. 2012 [38]	Cholecystectomy or appendicectomy (66/67)	Rocuronium	Posttetanic counts 1–2/train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	Time to TOF 0.9	MSD
Mekawy et al. 2012 [39]	Sinonasal (20/20)	Rocuronium	Posttetanic counts 1–2; train-of-four 0	4 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	Respiratory complications	Not stated
Carron et al. 2013 [41]	Bariatric (20/20)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	Duration of anaesthesia	Not stated
Woo et al. 2013 [40]	Various (59/59)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + glycopyrrolate 10 μg.kg^{-1}	Time to TOF 0.9	Merck
Castro et al. 2014 [42]	Bariatric (44/44)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	PONV	Not stated
Wu et al. 2014 [43]	Various (149/141)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 50 μg.kg^{-1} + atropine 0.02 mg.kg^{-1}	Time to TOF 0.9	MSD
Koyuncu et al. 2015 [44]	Extremities (50/50)	Rocuronium	Train-of-four < 2	2 mg.kg^{-1}	Neostigmine 40 μg.kg^{-1} + atropine 0.07 mg.kg^{-1}	PONV	MSD

MSD, Merck Sharp and Dohme; PONV, postoperative nausea or vomiting; TOF, train of four.

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sequential monitoring boundaries of 90%, 75% and 50% for relative risk reductions of complications and 50%, 25% and 10% for other outcomes, with a p value of 0.05 and powers of 80%, corrected for heterogeneity with the diversity (D^2) value (we used a minimum value of 15). Publication bias was assessed by funnel plots and Egger's regression test for more than ten studies. We evaluated the evidence with GRADE methodology [27].

Results

We included 14 randomised controlled trials of 1553 participants (Fig. 1) for which we detailed and summarised risks of bias (Figs. 2 and 3, respectively) [28–45]. Table 1 details characteristics of the included trials. The Bonferroni–Jakobsen adjusted p value for significance was < 0.029.

Sugammadex reduced all signs of residual postoperative paralysis compared with neostigmine (Fig. 4),

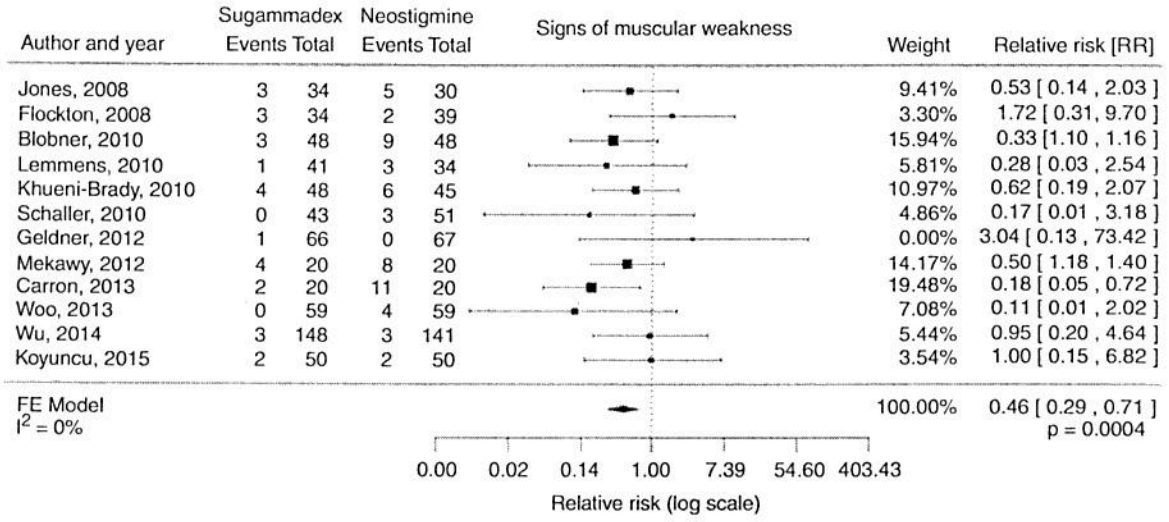

Figure 4 Forest plot of the relative risks of overall signs of postoperative residual paralysis after reversal of neuromuscular blockade by sugammadex vs neostigmine.

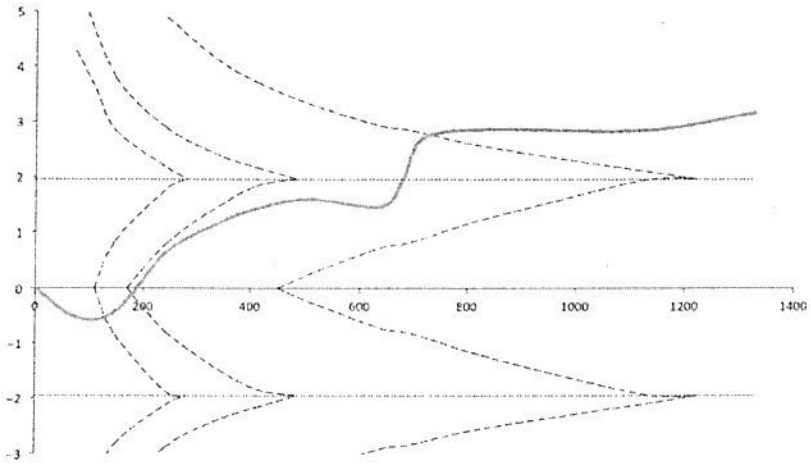

Figure 5 Trial sequential analysis (red line) for overall signs of postoperative residual paralysis after reversal of neuromuscular blockade by sugammadex vs neostigmine. The boundaries for relative risk reductions are indicated by the dashed lines: left, 90% relative risk reduction; middle, 75% relative risk reduction; and right, 50% relative risk reduction. The horizontal axis is the number of participants and the vertical axis is the cumulative Z value. Values more than 0 favour sugammadex.

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with trial sequential analysis confirming a reliable relative risk reduction of at least 50%, but less than 75% (Fig. 5). The pooled rate of residual paralysis after neostigmine was 8.4 per 100 participants, which sugammadex reduced by 4.5 per 100 to 3.9 per 100 i.e. 1 in 22 patients given sugammadex rather than neostigmine avoided residual paralysis.

Sugammadex reduced minor signs of postoperative residual paralysis compared with neostigmine (Fig. 6), with trial sequential analysis confirming a reliable relative risk reduction of at least 75%, but less than 90% (Fig. 7). The pooled rate of minor weakness after neostigmine was 9.4 per 100, which sugammadex reduced by 4.7 per 100 to 4.7 per 100, that is 1 in 21 patients given sugammadex rather than neostigmine avoided minor weakness.

Sugammadex did not reduce life-threatening complications associated with residual paralysis at the

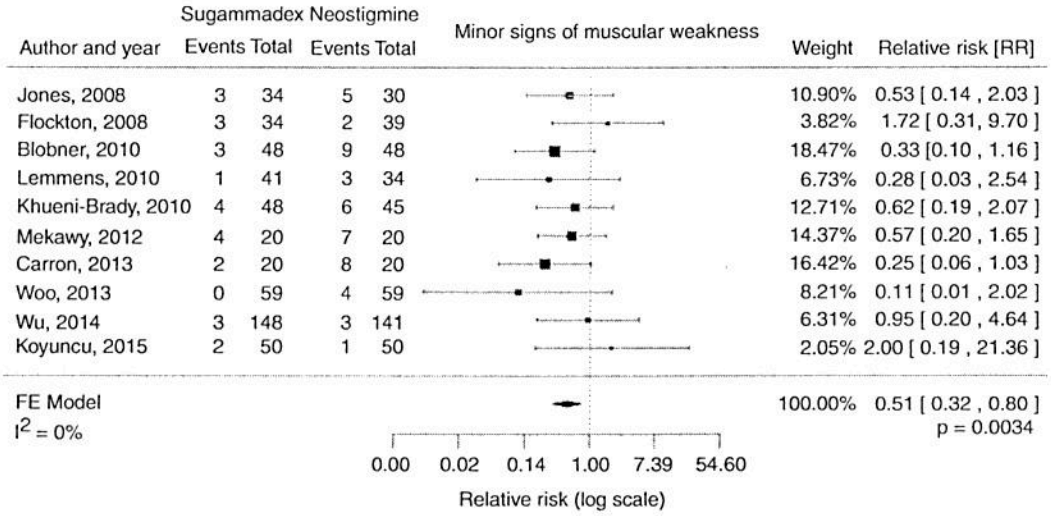

Figure 6 Forest plot of the relative risks of minor signs of postoperative residual paralysis after reversal of neuromuscular blockade by sugammadex vs neostigmine.

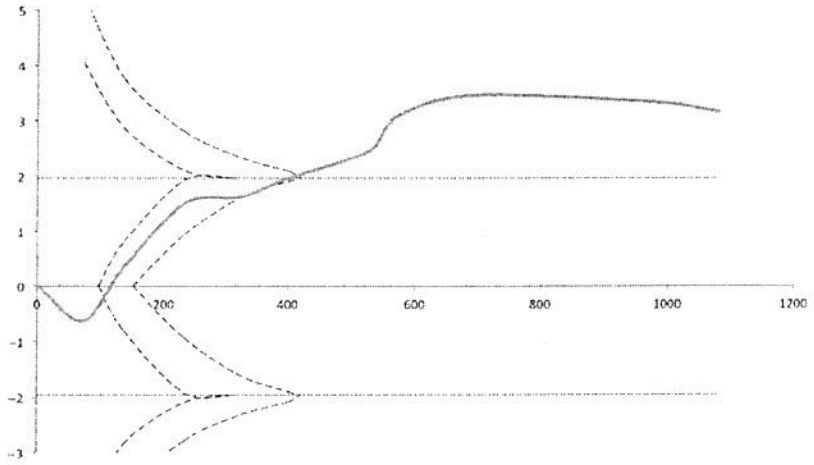

Figure 7 Trial sequential analysis (red line) for minor signs of postoperative residual paralysis after reversal of neuromuscular blockade by sugammadex vs neostigmine. The boundaries for relative risk reductions are indicated by the dashed lines: left, 90% relative risk reduction; and right, 75% relative risk reduction. The horizontal axis is the number of participants and the vertical axis is the cumulative Z value. Values more than 0 favour sugammadex.

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adjusted p value of 0.029 (Fig. 8). The trial sequential analysis confirmed that the pooled data from 407 participants had insufficient power, given 1/199 events after sugammadex and 8/208 events after neostigmine, with a total of 2815 participants being required to accept or refute a 50% relative risk reduction (Fig. 9).

Sugammadex reduced drug-related side-effects compared with neostigmine (Fig. 10), but trial sequential analysis confirmed that the pooled data of 1482 patients had insufficient power, given 92/746 events after sugammadex and 129/736 after neostigmine, with a total of 2503 participants being required to accept or refute a 75% relative risk reduction (Fig. 11). The rates of postoperative nausea and vomiting were similar for sugammadex and neostigmine (Figs. 12 and 13).

We excluded the following trials in post-hoc sensitivity analyses: the smallest trial; the largest trial; trials financed by industry and trials with high risk of bias. The relative rate (95% CI) of residual paralysis remained reduced by sugammadex compared with neostigmine when we excluded the smallest trial, 0.22 (0.08–0.66), p = 0.0007, or the largest trial, 0.15 (0.05–

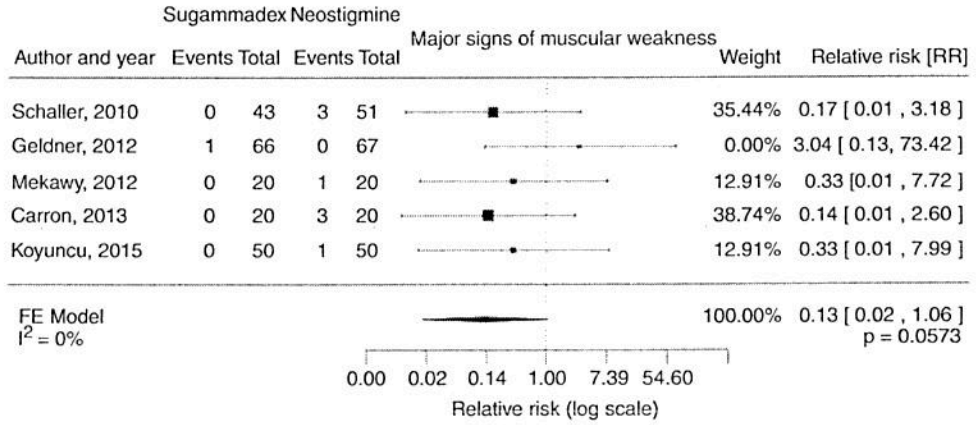

Figure 8 Forest plot of the relative risks of re-intubation after reversal of neuromuscular blockade by sugammadex vs neostigmine.

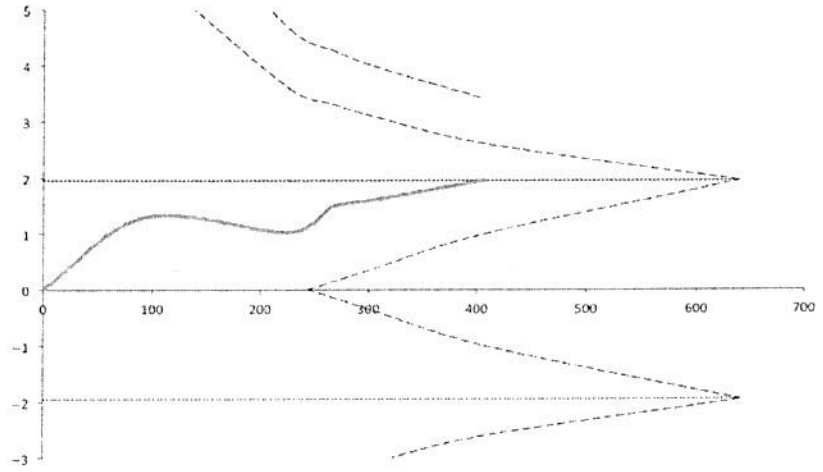

Figure 9 Trial sequential analysis (red line) for signs of postoperative residual paralysis requiring life support after reversal of neuromuscular blockade by sugammadex vs neostigmine. The boundaries for relative risk reductions are indicated by the dashed lines: left, 90% relative risk reduction; right, 75% relative risk reduction. The horizontal axis is the number of participants and the vertical axis is the cumulative Z value. Values more than 0 favour sugammadex.

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0.42), p = 0.0003. The exclusion of 9/12 trials financed by industry did not alter the relative risk, 0.05 (0.01–0.34), p = 0.002. Sugammadex still reduced the rate of residual paralysis when we excluded trials with selection bias with poor sequence generation, relative risk (95% CI) 0.15 (0.06–0.46), p = 0.0007 or when we excluded trials with selection bias due to poor masking of the allocation sequence, relative risk (95%) 0.15 (0.05–0.50), p = 0.0018. There was no funnel plot asymmetry for any outcome. We have summarised the GRADE evidence (see also Supporting Information Fig. S1).

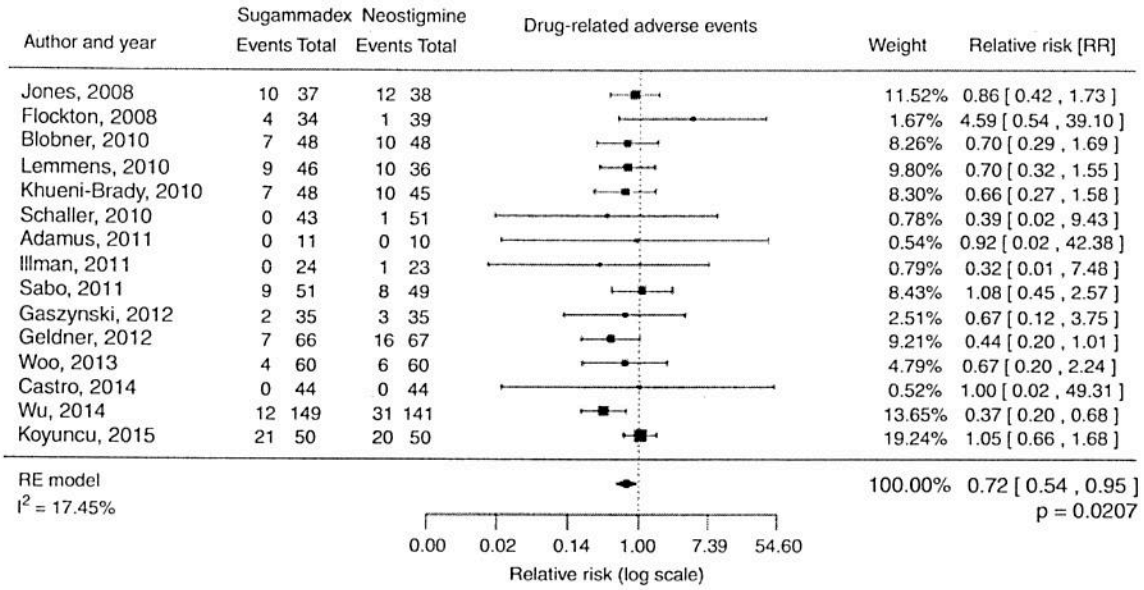

Figure 10 Forest plot of the relative risks of any drug-related side effect after reversal of neuromuscular blockade by sugammadex vs neostigmine.

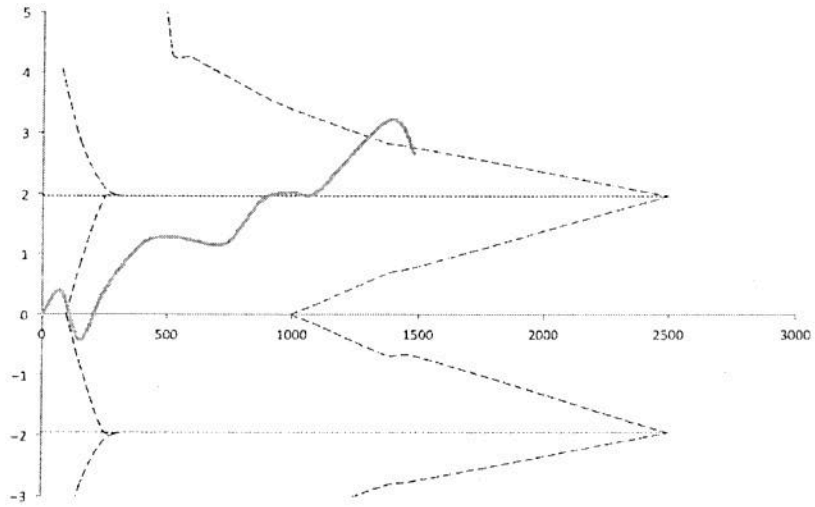

Figure 11 Trial sequential analysis (red line) for drug-related side-effects after reversal of neuromuscular blockade by sugammadex vs neostigmine. The boundaries for relative risk reductions are indicated by the dashed lines: left, 75% relative risk reduction; right, 50% relative risk reduction. The horizontal axis is the number of participants and the vertical axis is the cumulative Z value. Values more than 0 favour sugammadex.

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Discussion

We found that one would need to give sugammadex rather than neostigmine to between 21 and 22 patients to avoid one showing signs of residual paralysis. There was no difference in the rate of respiratory events that required tracheal re-intubation.

The faster reversal of neuromuscular blockade by sugammadex has been reviewed previously, but clinical signs of residual paralysis have not [3, 45, 46]. The slightly higher rate of signs of residual blockade after neostigmine in this review was from closely monitored trials that only extubated patients' tracheas in whom

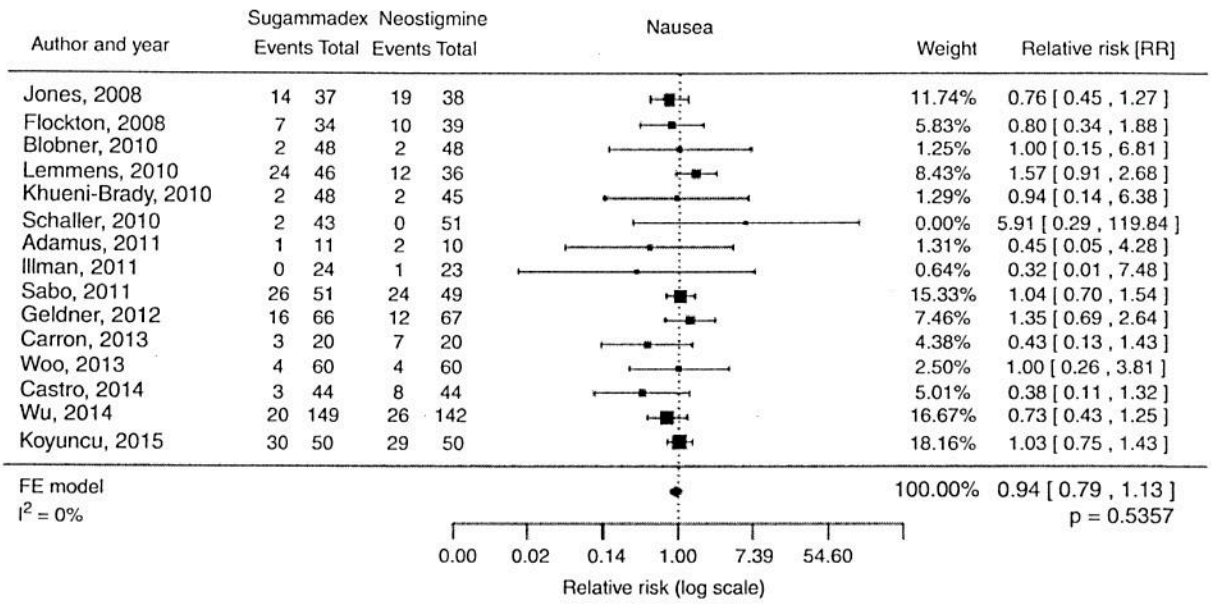

Figure 12 Forest plot of the relative risks of nausea after reversal of neuromuscular blockade by sugammadex vs neostigmine.

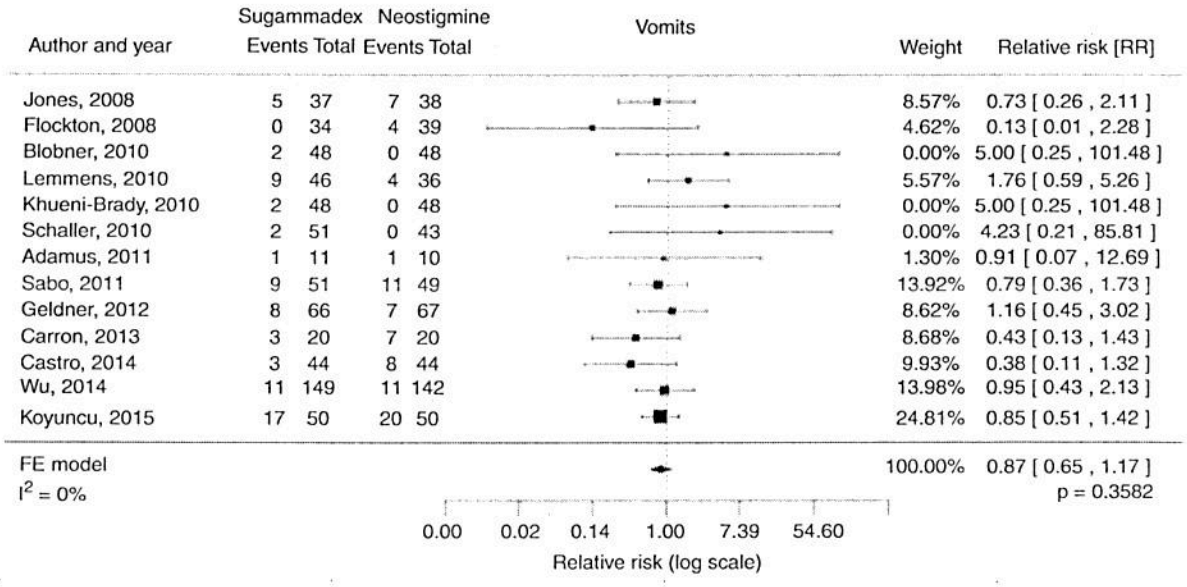

Figure 13 Forest plot of the relative risks of vomiting after reversal of neuromuscular blockade by sugammadex vs neostigmine.

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the train-of-four ratio was > 0.9 [7–9]. Train-of-four ratios > 0.9 may be associated with atelectasis, pulmonary oedema, tracheal re-intubation and prolonged hospital stay when high doses of neostigmine (> 0.6 $\mu g.kg^{-1}$) are used [6, 47]. Tracheal extubation with train-of-four ratios < 0.9 is associated with more hypoxia, upper airway obstruction, oxygen desaturation, microaspiration and re-intubation [5–7, 9]. The rates of these complications might be higher without accelerometric monitoring of neuromuscular blockade and reversal [4, 8]. Neuromuscular blockade is monitored in less than a third of paralysed patients [8], due to unavailable or broken monitors and ignorance of the adverse effects of residual neuromuscular blockade [4, 5]. Neuromuscular blockade can persist after giving sugammadex, particularly if inadequate doses are given and its effects are not monitored [48–54].

A previous meta-analysis did not find evidence for differences in side-effects between sugammadex and neostigmine [3]. The trial sequential analysis of drug-related side-effects in our review did not reach the required sample size to confirm their apparent excess with neostigmine. In addition, differences in such a composite outcome would be difficult to interpret due to the varied events pooled.

Many trials were conducted in single centres – only one investigated more than 100 participants per group [43, 44]. Smaller studies tend to be conducted and analysed with less methodological rigour than larger studies. Trials of lower quality also tend to show larger intervention effects. The trials gave drugs in different doses in different populations, although there was little or no heterogeneity in the pooled results.

In conclusion, sugammadex reduced the number of patients with clinical signs of postoperative residual paralysis caused by rocuronium, when compared with neostigmine. Further studies are needed to determine whether sugammadex might reduce the rate of critical respiratory events.

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Competing interests

No other conflict of interests declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. GRADE of evidences.

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The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade

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Jean-François Pouliot, PhD,‡‡ and André Galarneau, MSc, PhD‡‡

BACKGROUND: Postoperative residual neuromuscular blockade (NMB), defined as a train-of-four (TOF) ratio of <0.9, is an established risk factor for critical postoperative respiratory events and increased morbidity. At present, little is known about the occurrence of residual NMB in Canada. The RECITE (Residual Curarization and its Incidence at Tracheal Extubation) study was a prospective observational study at 8 hospitals in Canada investigating the incidence and severity of residual NMB.

METHODS: Adult patients undergoing open or laparoscopic abdominal surgery expected to last <4 hours, ASA physical status I–III, and scheduled for general anesthesia with at least 1 dose of a nondepolarizing neuromuscular blocking agent for endotracheal intubation or maintenance of neuromuscular relaxation were enrolled in the study. Neuromuscular function was assessed using acceleromyography with the TOF-Watch® SX. All reported TOF ratios were normalized to the baseline values. The attending anesthesiologist and all other observers were blinded to the TOF ratio (T4/T1) results. The primary and secondary objectives were to determine the incidence and severity of residual NMB (TOF ratio <0.9) just before tracheal extubation and at arrival at the postanesthesia care unit (PACU).

RESULTS: Three hundred and two participants were enrolled. Data were available for 241 patients at tracheal extubation and for 207 patients at PACU arrival. Rocuronium was the NMB agent used in 99% of cases. Neostigmine was used for reversal of NMB in 73.9% and 72.0% of patients with TE and PACU data, respectively. The incidence of residual NMB was 63.5% (95% confidence interval, 57.4%–69.6%) at tracheal extubation and 56.5% (95% confidence interval, 49.8%–63.3%) at arrival at the PACU. In an exploratory analysis, no statistically significant differences were observed in the incidence of residual NMB according to gender, age, body mass index, ASA physical status, type of surgery, or comorbidities (all $P > 0.13$).

CONCLUSIONS: Residual paralysis is common at tracheal extubation and PACU arrival, despite qualitative neuromuscular monitoring and the use of neostigmine. More effective detection and management of NMB is needed to reduce the risks associated with residual NMB. (Anesth Analg 2015;121:366–72)

Postoperative residual neuromuscular blockade (NMB) is a common finding in anesthesia practice, with the incidence ranging from 26% to 88%, depending on the definitions used, the setting, the neuromuscular blocking agent used, and the patient population studied.[1–9] After the introduction of train-of-four (TOF) monitoring in 1970,[10] residual NMB was defined as a TOF ratio <0.7.[11,12] However, subsequent studies have demonstrated that a TOF ratio of 0.7 to 0.9 is associated with an increased risk of aspiration, airway obstruction, hypoxia, and pharyngeal/esophageal complications.[13,14] An increased risk of critical respiratory events and a significant prolongation of the length of stay in the postanesthesia care unit (PACU) are associated with residual NMB.[15,16] As a result, a TOF ratio ≥0.9 has been suggested as the minimally acceptable level of recovery of neuromuscular function.[17]

To date, there have been no prospective studies of the incidence of residual NMB in Canada using acceleromyography to assess neuromuscular function. The primary objective of the prospective RECITE (Residual Curarization and its Incidence at Tracheal Extubation) study was to investigate the incidence of residual NMB, defined as a TOF ratio <0.9, at the time of tracheal extubation at 8 Canadian centers. The secondary objectives were to determine the incidence of residual NMB at arrival to the PACU and the severity of residual NMB at both time points, and to form hypotheses regarding the association between the severity of residual

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NMB and the incidence of perioperative complications. This trial is registered at clinicaltrials.gov (NCT01318382).

METHODS

Before patient enrolment, all documentation regarding the design, objectives, and conduct of the study was approved by the institutional review board or independent ethics committee at each study site. Written, informed consent was obtained from all participants before entry into the study. Participants were enrolled between June 2011 and May 2012.

Participants were enrolled if they were adults undergoing open or laparoscopic abdominal surgery expected to last <4 hours, ASA physical status I–III, and scheduled for general anesthesia with at least 1 dose of a nondepolarizing neuromuscular blocking agent for endotracheal intubation or maintenance of NMB.

Acceleromyography with TOF stimulation was performed using the TOF-Watch® SX (Organon, Inc., West Orange, NJ). Readings during surgery were obtained at 10 specific time points: baseline before the administration of neuromuscular blocking agent; the first and last fascial stitch at the end of surgery; the last skin stitch or staple; at the administration of the NMB reversal agent; at 3, 5, and 10 minutes after administration of the reversal agent; and immediately before tracheal extubation. The final TOF readings were performed at arrival in the PACU. Similarly to other studies,[16,18] data were acquired at all time points by capturing 2 TOF ratio readings. If the difference between the 2 readings was ≤0.1, the results were averaged for the analysis. If the difference was >0.1, a third reading was obtained and the 2 closest results were averaged. Indeterminate results underwent blinded evaluation by a panel of investigators to adjudicate inclusion or exclusion in the data set.

The attending anesthesiologist administering the anesthesia and all nurses were blinded to the TOF-Watch quantitative (recorded) results during the trial. No other quantitative monitoring of neuromuscular transmission (e.g., mechanomyography, electromyography) was permitted. All other qualitative (visual and tactile) monitoring measures were allowed. Participants were excluded if their medical condition, surgical procedure, or positioning would interfere with the operation, calibration, or accuracy of the TOF-Watch. Anesthesiologists were permitted to use qualitative measures (e.g., peripheral nerve stimulator and/or clinical criteria) to assess the degree of NMB as per their pattern of practice. As this study was observational, anesthesia practice was not standardized—dosing of NMB drugs, administration of reversal agents, and the decision to extubate were at the discretion of the attending anesthesiologist and consistent with routine anesthesia practice at their trial site.

Statistical Analysis

Based on an estimated incidence of residual NMB of 30%, a sample size of 300 participants would provide a precision level of 5.2%, which is within acceptable levels of precision.

All analyses were performed on the per-protocol sets, defined as all eligible participants who were monitored with the TOF-Watch and had evaluable TOF ratio results at baseline and at tracheal extubation or at PACU arrival. Normalized TOF (nTOF) ratios were calculated by dividing each TOF ratio by the participant's baseline value as described previously,[19,20] and their correlation with the nonnormalized values was assessed with the Pearson correlation coefficient (r). Descriptive statistics were produced for all variables in the study. Measures of central tendency (mean) and dispersion (standard deviation) were produced for all continuous scale variables. Frequency distributions were produced for all categorical scale variables. Calculation of the 95% confidence intervals (95% CIs) around the point estimate of the incidence of residual NMB was done with the normal approximation method.

The association between patient characteristics and residual NMB, as well as between the severity of residual NMB and perioperative complications at tracheal extubation and at PACU arrival, was assessed for exploratory purposes. The P values in these analyses were calculated as a measure of the strength of the association and not as a measure of causal inference. Between-group comparisons for continuous variables were assessed for statistical significance with the Student t test or the Wilcoxon rank sum test, depending on the normality of the data (as assessed with the Shapiro-Wilk test (i.e., when the Shapiro-Wilk test was significant, the Wilcoxon rank sum test was used); for categorical variables, the χ^2 test or Fisher exact test was used, as appropriate. Univariable logistic regression was used for the assessment of the association between nTOF ratio and perioperative complications and the association between rocuronium dose and neostigmine usage. Negative binomial regression was used to evaluate the impact of nTOF ratio on the number of PACU nurse visits. All univariable associations to be tested were prespecified. All statistical tests were 2-sided with an α level of 0.05. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

This prospective observational study was conducted at 8 Canadian hospitals. A total of 326 patients were screened for eligibility, and 302 participants were entered in the study (Fig. 1). Data were available for 241 patients at tracheal extubation (TE data set) and for 207 patients at arrival in the PACU (PACU data set). As per protocol, patient data were excluded if there were TOF-Watch or computer technical issues, excessive variability in TOF ratio measures (as adjudicated by the blinded investigators), or early discontinuation.

The mean age of patients in the TE and PACU data sets was 48.0 and 47.3 years, respectively (Table 1), and the majority were female (70.1% and 74.4%) and ASA class II (52.7% and 54.1%). A similar proportion of patients underwent open abdominal versus laparoscopic surgery. Rocuronium was the NMB agent used in >99% of cases, with remaining participants receiving cisatracurium (0.8% and 0.5%). Those patients who were tracheally intubated with succinylcholine (6.2% and 2.9%) received at least 1 dose of nondepolarizing agent for maintenance of NMB. Neostigmine was used to reverse NMB in 73.9% and 72.0% of TE and PACU patients, respectively.

The incidence of residual NMB (nTOF ratio <0.9) was 63.5% (95% CI, 57.4%–69.6%) at tracheal extubation and 56.5% (95% CI, 49.8%–63.3%) at arrival at the PACU (Fig. 2A). When using the nonnormalized TOF data, the incidence of

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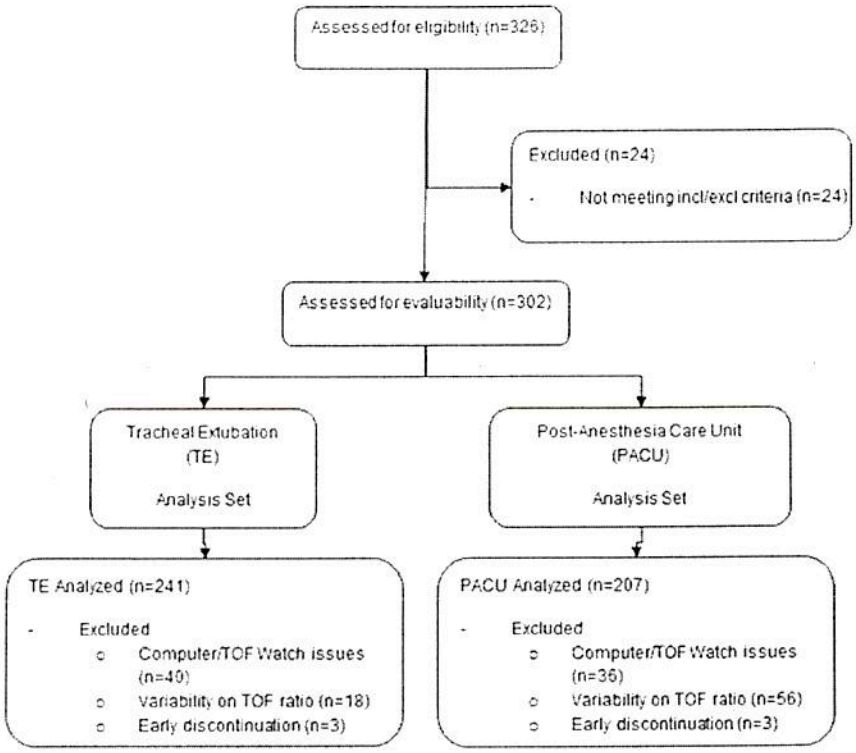

Figure 1. Consort diagram for study participants.

Table 1. Demographics and Clinical Characteristics of Patients at Tracheal Extubation and at Arrival at the Postanesthesia Care Unit (PACU)

	Tracheal extubation (*n* = 241)	PACU arrival (*n* = 207)
Sex, *n* (%)		
Male	72 (29.9%)	53 (25.6%)
Female	169 (70.1%)	154 (74.4%)
Mean age, y (±SD)	48.0 ± 13.7	47.3 ± 13.3
Mean body mass index (±SD)	28.7 ± 6.4	28.6 ± 6.3
ASA physical status, *n* (%)		
I	63 (26.1%)	55 (26.6%)
II	127 (52.7%)	112 (54.1%)
III	51 (21.2%)	40 (19.3%)
Type of surgery, *n* (%)		
Open abdominal	109 (45.2%)	96 (46.4%)
Laparoscopic	128 (53.1%)	108 (52.2%)
Laparoscopic to open abdominal	4 (1.7%)	3 (1.4%)
Neuromuscular blocking agent, *n* (%)		
Rocuronium	240 (99.6%)	207 (100%)
Cisatracurium	2 (0.8%)	1 (0.5%)
Succinylcholine	15 (6.2%)	6 (2.9%)
Reversal agent use, *n* (%)		
Neostigmine	178 (73.9%)	149 (72.0%)
Peripheral nerve stimulator use, *n* (%)	162 (67.2%)	137 (66.2%)
Comorbidities, *n* (%)		
Cardiovascular	56 (23.2%)	51 (24.6%)
Pulmonary	72 (29.9%)	63 (30.4%)
Renal insufficiency	4 (1.7%)	5 (2.4%)
Diabetes	17 (7.1%)	13 (6.3%)
History of cancer	44 (18.3%)	37 (17.9%)

residual NMB at tracheal extubation and at PACU arrival was 56.0% (95% CI, 49.7%–62.3%) and 44.0% (95% CI, 37.7%–50.2%), respectively. Overall, a strong positive linear correlation was observed between normalized and nonnormalized TOF data both at tracheal extubation ($r = 0.943$, $P < 0.001$) and at PACU arrival ($r = 0.895$, $P < 0.001$).

Between-group comparisons showed no statistically significant differences in the incidence of residual NMB (nTOF ratio <0.9) according to gender, age (<50 vs >50 years), body mass index (<30 vs >30), ASA class, type of surgery, or comorbidities (Table 2). The incidence of residual NMB both at tracheal extubation and at arrival to the PACU was positively associated with a significantly higher dose of rocuronium per minute of surgery (Table 3). Similar results were observed at PACU arrival. Furthermore, the use of qualitative peripheral neuromuscular monitoring was associated with a lower incidence of residual NMB at PACU arrival (51.1% vs 67.1%; $P = 0.028$). The findings of this exploratory analysis may merit future investigation.

Figure 3 describes the results of an exploratory analysis describing the association between the severity of residual NMB and perioperative complications at tracheal extubation (Fig. 3A) and at PACU arrival (Fig. 3B). Each increase of the nTOF ratio at tracheal extubation by 0.1 was associated with significantly lower odds of requiring oxygen administration in the PACU (OR [95% CI] = 0.894 [0.802–0.997]). Regarding the number of PACU nurse bed visits using negative binomial regression, a significant association was observed where each increase in TOF ratio by 0.1 was associated with 4% fewer bed visits ($P = 0.013$). The results of these exploratory analyses may merit further investigation. A similar exploratory analysis for the relationship between nTOF ratio and perioperative complications at PACU arrival is presented in Figure 3B. The impact of nTOF ratio on postoperative pulmonary complications could not be assessed due to their low incidence. Notably, only 3 patients

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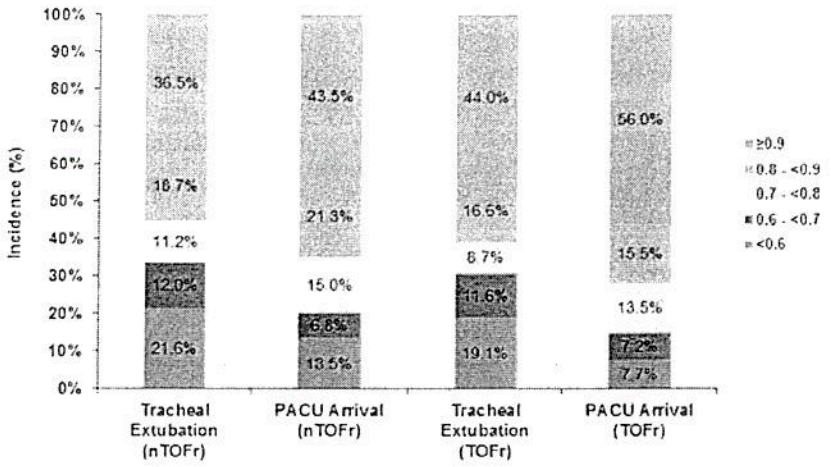

Figure 2. Incidence of residual neuromuscular blockade. nTOFr = normalized train-of-four ratio; TOFr = nonnormalized train-of-four ratio.

Table 2. Incidence of Residual Neuromuscular Blockade (rNMB) at Tracheal Extubation and at Arrival at the Postanesthesia Care Unit (PACU) by Patient Characteristics

	Tracheal extubation (n = 241)		PACU arrival (n = 207)	
	Incidence rNMB (%)	P[a]	Incidence rNMB (%)	P[a]
Sex				
Male vs female	62.5 vs 63.9	0.836	58.5 vs 55.8	0.737
Age				
<50 vs ≥50 yr	63.3 vs 63.7	0.947	55.6 vs 57.8	0.756
Body mass index				
<30 vs ≥30	60.9 vs 67.8	0.285	52.6 vs 63.5	0.130
ASA class				
I vs II vs III	61.9 vs 63.8 vs 64.7	0.949	58.2 vs 55.4 vs 57.5	0.933
Type of surgery				
Open abdominal vs laparoscopic vs laparoscopic to open	61.5 vs 64.8 vs 75.0	0.882	55.2 vs 58.3 vs 33.3	0.643
Reversal agent use[b]				
No vs yes	60.3 vs 64.6	0.543	48.3 vs 59.7	0.135
Qualitative peripheral nerve stimulator				
No vs yes	68.4 vs 61.1	0.273	67.1 vs 51.1	0.028
Comorbidities, no vs yes				
Cardiovascular	62.7 vs 66.1	0.646	55.8 vs 58.8	0.702
Pulmonary	62.7 vs 65.3	0.706	53.5 vs 63.5	0.181
Renal	75.0 vs 63.3	>0.999	55.9 vs 80.0	0.390
Endocrine	63.4 vs 64.7	0.914	55.7 vs 69.2	0.340
Oncologic	61.4 vs 72.7	0.159	57.1 vs 54.1	0.738

[a]Between-group comparisons were assessed for statistical significance with the χ^2 test or Fisher exact test, as appropriate.
[b]Neostigmine.

had a diagnosis of pneumonia or atelectasis. One patient required mechanical or noninvasive ventilation, and 1 was reintubated.

DISCUSSION

Residual NMB is common in the early postoperative period. Moreover, residual blockade may persist after arrival at the PACU, which has been shown to be associated with significant morbidity and delays in recovery room discharge.[15,16] It has been proposed that the minimally acceptable level of recovery is a TOF ratio ≥0.9,[17] because even mild residual paralysis (TOF ratio 0.7–0.9) is associated with pharyngeal and esophageal dysfunction,[13,14] obstruction of the upper airway,[21] impaired hypoxic ventilatory response,[22] and patient discomfort.[23]

In the present study, residual NMB, defined as a nTOF ratio <0.9, was present in 63.5% of patients at tracheal extubation and in 56.5% on arrival at the PACU. These results are consistent with previous studies.[4,6] In a large series by Debaene et al.,[6] residual NMB (TOF ratio <0.9) was present in 45% of patients on arrival at the PACU; in 37% of patients, residual NMB was present 2 hours after administration of a muscle relaxant. Murphy et al.[4] obtained TOF ratios using acceleromyography following the clinician's determination of neuromuscular recovery using clinical criteria and peripheral nerve stimulation. The mean TOF ratio was 0.67 at tracheal extubation, and 88% had a TOF ratio <0.9. Upon arrival in the PACU, 32% had a TOF ratio <0.9. Thus, a high proportion of patients are incorrectly diagnosed using conventional methods and have residual NMB both at tracheal extubation and at PACU arrival.

A further concern is that, although the use of conventional neuromuscular reversal agents such as neostigmine is recommended, their use does not appear to markedly reduce the incidence of residual NMB, as defined by a TOF ratio of <0.9, during routine practice. In our study, among

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Table 3. Neuromuscular Blockade Agent Reversal Characteristics

Variable	Tracheal extubation TOF ≥ 0.9 (*N* = 106)	Tracheal extubation TOF < 0.9 (*N* = 135)	*P*[a]	PACU arrival TOF ≥ 0.9 (*N* = 116)	PACU arrival TOF < 0.9 (*N* = 91)	*P*[a]
Total dose of rocuronium per minute of surgery (μg/kg/min), mean ± SD	6.1 ± 2.6	7.0 ± 3.2	0.021	6.0 ± 2.4	7.0 ± 3.0	0.007
Total dose of neostigmine (mg/kg), mean ± SD	0.034 ± 0.012	0.035 ± 0.012	0.380	0.035 ± 0.011	0.036 ± 0.012	0.792
Time between last dose of neostigmine and tracheal extubation (min), mean ± SD[b]	15.4 ± 7.0	12.5 ± 5.8	0.002	16.2 ± 9.2	13.1 ± 6.3	0.011
Time between last dose of neostigmine and PACU arrival (min), mean ± SD[c]	21.1 ± 8.2	17.4 ± 6.2	0.007	21.6 ± 9.3	17.9 ± 6.90	0.007

PACU = postanesthesia care unit.

[a]Between-group comparisons were assessed for statistical significance with the Wilcoxon rank sum test upon assessing the normality of the data with the Shapiro-Wilk test (i.e., the Shapiro-Wilk test was significant and, thus, the Wilcoxon rank sum test was used instead of the Student *t* test).

[b]Four patients were removed from this analysis because the time of the last neostigmine dose given was later than the tracheal extubation time.

[c]Three patients for tracheal extubation and 2 patients for PACU arrival were removed from this analysis because the time of the last neostigmine dose given was later than the PACU arrival time.

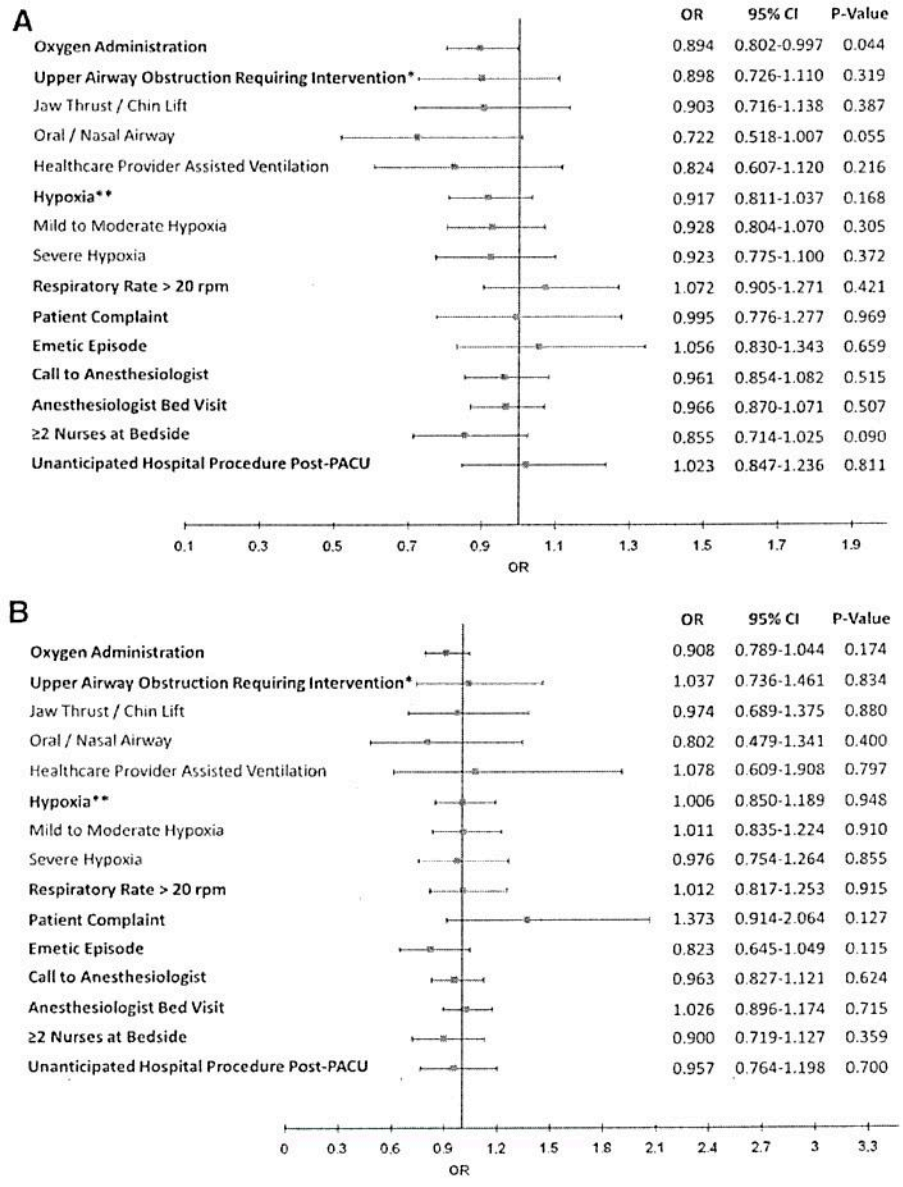

Figure 3. Association between normalized train-of-four ratio (nTOFr) and perioperative complications. A, Tracheal extubation (TE)[†]; (B) postanesthesia unit (PACU) arrival[†]. [†]Odds ratios represent increase in odds per 0.1 unit increase in nTOFr. *Includes jaw thrust/chin lift, oral/nasal airway, and healthcare provider assisted ventilation. **Includes mild to moderate hypoxia (Spo_2 90%–93% on ≥ 3 L O_2) and severe hypoxia (Spo_2 <90% on ≥3 L O_2). ***Use of squared root, square cubic, exponential, log, and log (x + 1) transformation did not have a considerable impact on the associations in terms of *P* values (no change in the significance for any association) and goodness of fit.

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patients receiving NMB reversal with neostigmine, residual paralysis was present in 64.6% at tracheal extubation and 59.7% at PACU arrival. This suggests that one cannot rely on neostigmine alone to avoid residual NMB. Instead, other factors such as precise titration of nondepolarizing neuromuscular blocking drugs, clinician attitude regarding the importance of avoiding residual NMB, and situational awareness of surgical timing are likely important.

Exploratory analysis showed that patients with residual NMB were, on average, tracheally extubated sooner after neostigmine administration than those without residual NMB (Table 3), and we believe this finding deserves further study.

As Capron et al.[24] have previously noted, qualitative measures of neuromuscular recovery such as clinical signs of muscle weakness and qualitative monitoring devices are not reliable, compared to acceleromyography, in detecting small degrees of residual paralysis. Our exploratory analysis shows that the use of qualitative peripheral neuromuscular monitoring was associated with significantly lower residual NMB at PACU arrival (but not at tracheal extubation). Despite the presence of qualitative monitoring and/or the use of neostigmine, a substantial proportion of patients had residual NMB at tracheal extubation and at PACU arrival. Furthermore, our data illustrate that, despite recent publications, continuing professional development, and editorials[17,25–31] with suggestions to change current NMB management, residual NMB is still a prevalent condition.

This was an observational investigation and has to be considered in the context of its limitations. The acceleromyography monitoring method in this study was designed to not interfere with the current practice, so no preload was applied to the thumb and no period of baseline signal stabilization was achieved before neuromuscular block was administered. Furthermore, the study was not powered to detect the association between severity of NMB and perioperative complications, given that these were exploratory study objectives. Thus, these results should be interpreted in light of their exploratory (hypothesis-generating not hypothesis-testing) and descriptive nature without attempting to make causal inferences or reaching clinical conclusions based on the associations identified. Overall, despite the considerable proportion of patients with residual NMB, there were not many critical respiratory events; 3 patients had a diagnosis of pneumonia or atelectasis, 1 patient required mechanical or noninvasive ventilation, and 1 patient was tracheally reintubated.

This is the first multicenter Canadian study to examine the incidence of residual NMB at tracheal extubation and at PACU arrival. The use of normalized acceleromyographic TOF ratio data is a significant strength of the study. The importance of TOF ratio normalization to account for within-patient variation and to reliably detect residual paralysis has been previously emphasized.[19,20]

Consistent with previous studies, the current work reinforces the continued high prevalence of residual NMB in regular clinical practice, despite education, qualitative TOF monitoring, and the use of neostigmine. These findings should provoke a re-examination of currently used techniques for the monitoring and reversal of NMB.

DISCLOSURES

Name: Louis-Philippe Fortier, MSc, MD, FRCPC.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Louis-Philippe Fortier has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Louis-Philippe Fortier consulted for Merck Canada.
Name: Dolores McKeen, MD, MSc, FRCPC.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Dolores McKeen reviewed the analysis of the data and approved the final manuscript.
Conflicts of Interest: Dolores McKeen received honoraria from Merck Canada and consulted for Merck Canada.
Name: Kim Turner, BScPhm, MSc, MD, FRCPC.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Kim Turner reviewed the analysis of the data and approved the final manuscript.
Conflicts of Interest: Kim Turner consulted for Merck Canada.
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Attestation: Étienne de Médicis reviewed the analysis of the data and approved the final manuscript.
Conflicts of Interest: Etienne deMedicis consulted for Merck Canada.
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Attestation: Brian Warriner reviewed the analysis of the data and approved the final manuscript.
Conflicts of Interest: Brian Warriner received honoraria from Merck Canada and consulted for Merck Canada.
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Attestation: Philip M. Jones reviewed the analysis of the data and approved the final manuscript.
Conflicts of Interest: The author declares no conflicts of interest.
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Attestation: Alan Chaput reviewed the analysis of the data and approved the final manuscript.
Conflicts of Interest: Alan Chaput consulted for Merck Canada.
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Attestation: Jean-François Pouliot has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Jean-François Pouliot worked for Merck Canada.
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Attestation: André Galarneau has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Conflicts of Interest: André Galarneau worked for Merck Canada.
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