

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

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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

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

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

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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/m²), normal (18.5 < BMI ≤ 25), overweight (25 < BMI ≤ 30), and obese (BMI greater than or equal to 30 kg/m²).^{*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

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

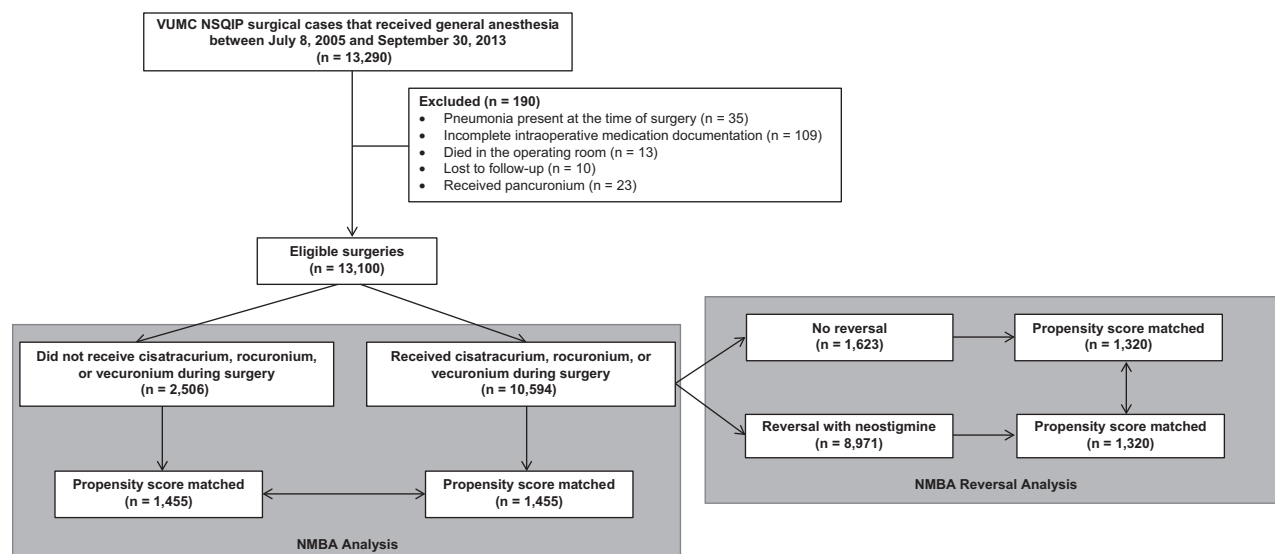


Fig. 1. Flowchart of inclusion/exclusion criteria. NMBA = nondepolarizing neuromuscular blocking agent; NSQIP = National Surgical Quality Improvement Program; VUMC = Vanderbilt University Medical Center.

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

	Before Matching		After Matching	
	Received NMBA (n = 10,594)	Did Not Receive NMBA (n = 2,506)	Received NMBA (n = 1,455)	Did Not Receive NMBA (n = 1,455)
NMBA Analysis				
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	
	No Reversal (n = 1,623)	Reversal with Neostigmine (n = 8,971)	No Reversal (n = 1,320)	Reversal with Neostigmine (n = 1,320)
NMBA Reversal Analysis				
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

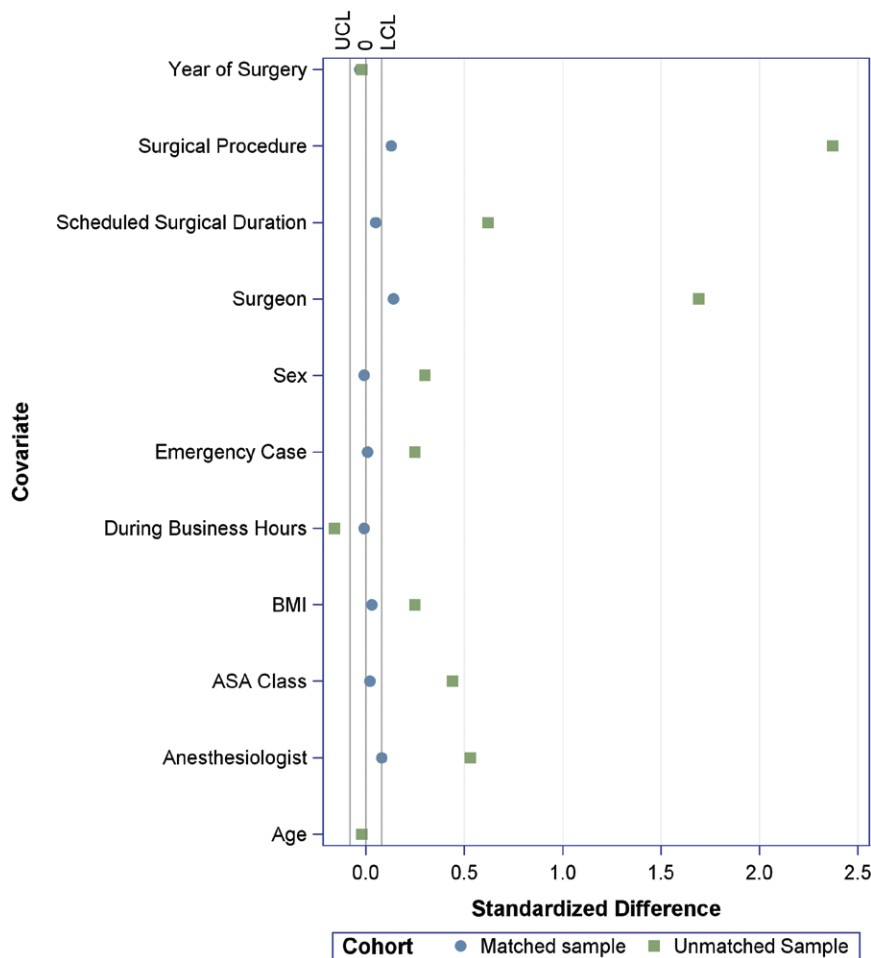


Fig. 2. Standardized differences between surgical cases who received nondepolarizing neuromuscular blocking agents and those who did not. The standardized differences compare the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured across different 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 PACU²⁹ 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

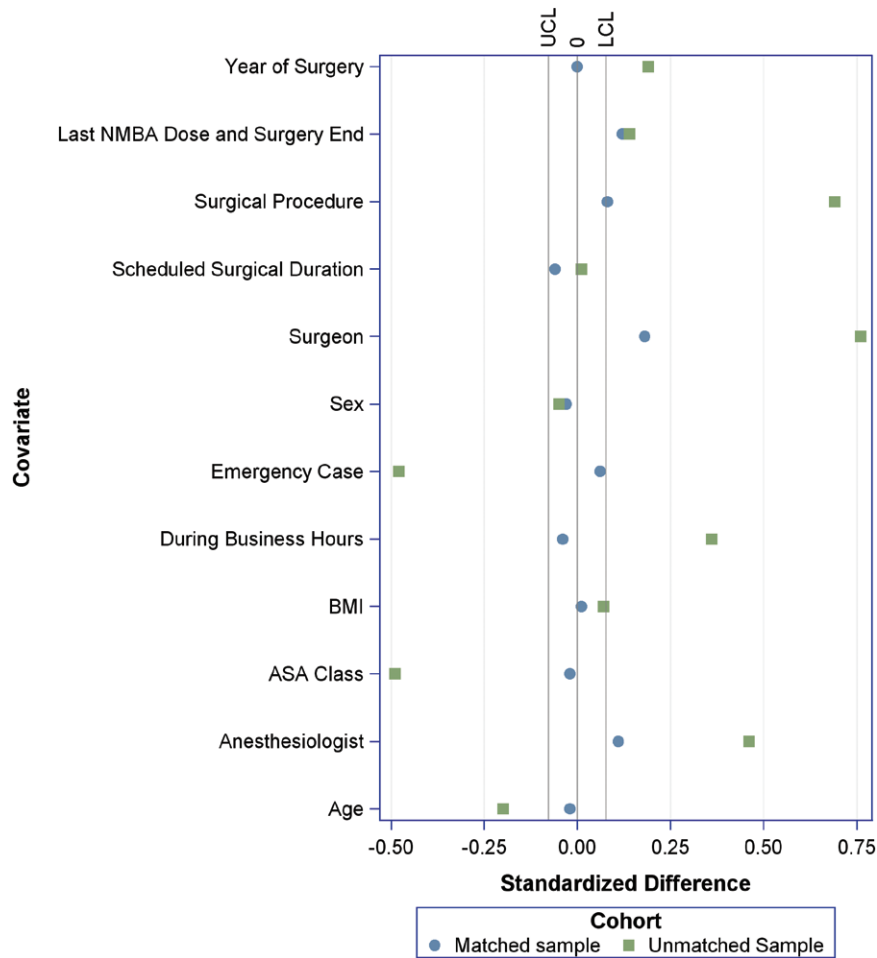


Fig. 3. Standardized differences between surgical cases who received nondepolarizing neuromuscular blocking agents (NMBA) reversal and those who did not. The standardized differences compare the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured 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

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		Total
	Did Not Receive NMBA, n (%)	Received NMBA, n (%)	
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.