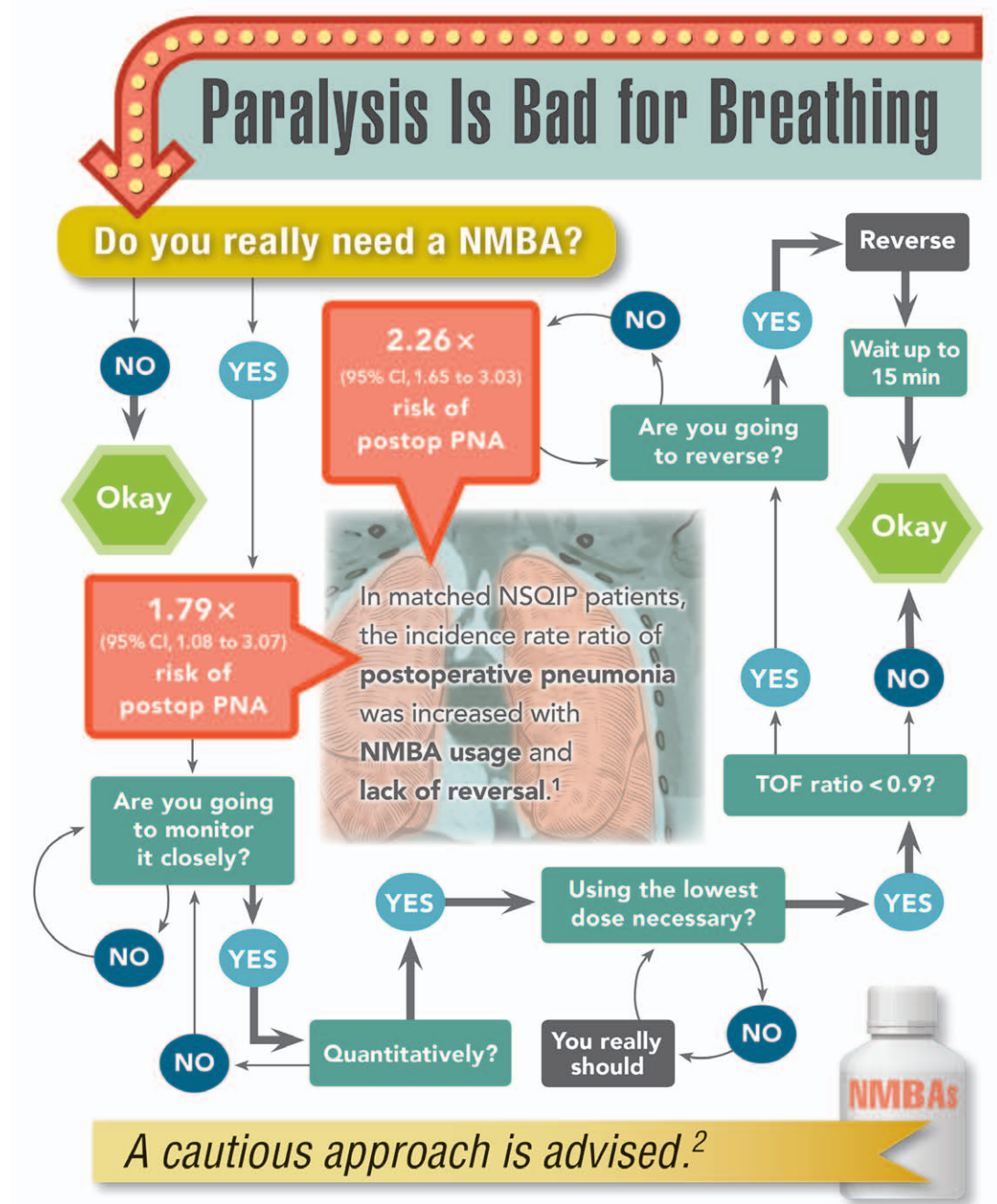


ANESTHESIOLOGY



NMBA = nondepolarizing neuromuscular blocking agent; NSQIP=National Surgical Quality Improvement Program; PNA = pneumonia; postop = postoperative; TOF = train of four.

Infographic created by Jonathan P. Wanderer, Vanderbilt University School of Medicine, and James P. Rathmell, Brigham and Women's Health Care/Harvard Medical School. Illustration by Annemarie Johnson, Vivo Visuals. Address correspondence to Dr. Wanderer: jon.wanderer@vanderbilt.edu.

1. Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM: Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. *ANESTHESIOLOGY* 2016; 125:647-55

2. Murphy GS, Kopman AF: "To reverse or not to reverse?" The answer is clear! *ANESTHESIOLOGY* 2016; 125:611-4

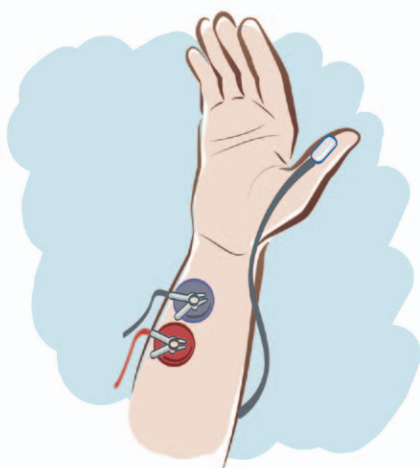
“To Reverse or Not To Reverse?”

The Answer Is Clear!

Glenn S. Murphy, M.D., Aaron F. Kopman, M.D.

BY the late 1980s, it was well recognized that undetected postoperative residual neuromuscular block (PRNB) was a common occurrence in most postanesthesia care units (PACUs).^{1–4} However, an editorial in 1989 noted that there was little, if any, objective evidence to validate the hypothesis that PRNB was associated with long-term or even transient adverse respiratory outcomes.⁵ In the two and a half decades since the editorial by Miller⁵ was published, outcome data regarding this important patient safety issue have slowly accumulated, but the relevant database remains quite sparse. In this issue of *ANESTHESIOLOGY*, Bulka *et al.*⁶ provide an important addition to the small list of studies that attempt to examine the long-term consequences of PRNB. They report two main findings: (1) the use of neuromuscular blocking agents (NMBAs) was associated with a higher absolute rate of postoperative pneumonia (POP) when compared to matched cases where patients did not receive relaxants and (2) failure to reverse NMBAs at the end of surgery was associated with a 2.25-fold increase in the incidence of POP. Why should these findings be less than surprising?

Bulka *et al.*⁶ noted that the incidence rate ratio (1.79) for POP was significantly higher in patients who received NMBAs. This observation is consistent with the findings from several large database investigations, which have described an association between intraoperative NMBA use and major morbidity and mortality. More than 60 yr ago, Beecher and Todd⁷ reported that the risk of death related to anesthesia was six times higher in patients receiving NMBAs



“The hazards of postoperative residual neuromuscular block are well-documented; reversal of neuromuscular blocking agents should be routine.”

compared to those administered no muscle relaxants. An analysis of data collected over a 10-yr period (1967 to 1976) involving 240,483 anesthetics revealed that “respiratory inadequacy after myoneural blockade” was the second most common cause of death after surgery.⁸ Similarly, a study from Great Britain reported that postoperative respiratory failure secondary to dosing of NMBAs was a primary cause of mortality.⁹ In a large prospective study, the use of the long-acting NMBA pancuronium entailed a higher risk of postoperative pulmonary complications.¹⁰ More recent studies reported that patients administered NMBAs had a higher risk of postoperative desaturations and need for reintubation¹¹ and that those given high doses of NMBAs had an increased risk of postoperative respiratory complications.¹² The increased incidence of morbidity and mortality reported in patients administered NMBAs is likely secondary to PRNB. Incomplete neuromuscular recovery during a vulnerable postoperative period (between tracheal extubation and achieving a train-of-four [TOF] ratio of less than 0.9 in the PACU) may impair upper airway patency, protective airway reflexes, breathing, swallowing, and coughing, resulting in an increased risk of significant respiratory events (like POP) and death.

Data demonstrating an association between failure to reverse neuromuscular blockade and adverse postoperative outcomes are less certain. A large case-control database investigation revealed that the primary anesthetic management characteristic associated with a reduction in mortality and coma was reversal of the effects of NMBAs.¹³ In a

Image: ImagePower Productions, John Ursino.

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retrospective data analysis, pulmonary complication outcome scores were significantly improved in older patients with comorbidities reversed with sugammadex, compared to those reversed with neostigmine or not given reversal agents.¹⁴ In contrast to these investigations, large-scale studies from the Massachusetts General Hospital suggested an association between neostigmine use and an increased risk of hypoxemia, atelectasis, and postoperative reintubation.^{11,15} An important limitation of all of these investigations (as well as the study by Bulka *et al.*⁶) is that the presence or absence of PRNB was not measured in the PACU with quantitative monitoring; therefore, it is uncertain whether postoperative muscle weakness was the cause of the reported adverse events.

There is ample evidence that failure to antagonize nondepolarizing block may result in a very high incidence of PRNB. Baillard *et al.*¹⁶ reported that 42% of patients who received vecuronium but no anticholinesterase had TOF ratios less than 0.7 on arrival to the PACU. A multicenter trial revealed that 95 of 175 patients (57%) administered cisatracuriums with no reversal agent had TOF ratios less than 0.9 in the PACU.¹⁷ A recent observational study examined the incidence of PRNB when muscle relaxation was not antagonized and intraoperative monitoring of neuromuscular function was not performed.¹⁸ On admission to the PACU, only 11% of elderly patients and 23% of younger patients had achieved an acceptable level of neuromuscular recovery ratio (TOF ratio less than 0.9)!

The authors of this editorial believe that appropriate doses of reversal agents (either neostigmine or sugammadex) should always be administered when NMBAs are used, unless full neuromuscular recovery has been documented with quantitative monitoring. In clinical practice, however, less than one third of anesthesiologists routinely administer anticholinesterase agents.¹⁹ The reasons why many anesthesiologists fail to routinely reverse the residual effects of NMBAs are uncertain but, no doubt, multifactorial. Many clinicians still appear to harbor concerns regarding the administration of anticholinesterase/antimuscarinic drugs and associated adverse cardiovascular and respiratory effects, as well as the potential for an increased incidence of postoperative nausea and vomiting.¹⁹ In addition, 80 to 90% of respondents to an international survey assert that they had never observed patients in the PACU with residual neuromuscular weakness.¹⁹ There also appears to be a lack of appreciation of the duration of effect of an "intubating dose" of an NMBA. Two hours after a single 2 times the ED₉₅ dose of a relaxant of intermediate duration, 37% of individuals will still not have recovered to a TOF ratio of 0.9 and 10% will still have TOF values less than 0.7.²⁰ Furthermore, the use of qualitative neuromuscular monitors (conventional peripheral nerve stimulators) may provide reassuring but misleading information to the clinician. Once the TOF ratio exceeds 0.4, most individuals can no longer detect the presence of fade by tactile or visual observation.^{21,22}

Another reason for reluctance to administer neostigmine to reverse NMBAs may be related to concerns about the

potential of this drug to produce paradoxical muscle weakness when administered at full neuromuscular recovery. In an attempt to understand why the use of NMBAs appears to be associated with an increase in the incidence of POP, Bulka *et al.*⁶ suggest that neostigmine may contribute to severe postoperative respiratory complications when used in an unwarranted fashion (anticholinesterase administration when neuromuscular recovery is already almost complete). They cite several recent articles as the basis for this hypothesis.^{15,23,24} Their thesis is also compatible with the assertions of Gross-Sundrup *et al.*¹¹ and Sasaki *et al.*¹⁵ that neostigmine reversal increases the risk of postoperative desaturations and atelectasis. We are not convinced that neostigmine-induced block is the most likely explanation for the association between NMBA administration and POP.

A bit of history may be instructive. A study from 1980 demonstrated that in patients who were not given NMBAs, one or two injections of 2.5 mg neostigmine caused a substantial reduction in the peak tetanic contraction and severe tetanic fade, which persisted for about 20 min (although single twitch height was slightly potentiated).²⁵ These results were subsequently confirmed by Goldhill *et al.*²⁶ However, the decrement in tetanic tension observed was very brief, lasting not more than 10 min. The authors concluded that "even when considerable spontaneous recovery of muscle power has occurred, a single modest dose of reversal agent is unlikely to cause clinically important muscle weakness, and any effects are probably short lived."²⁶

The duration of effect (residual paralysis) appears to be of critical importance. This concept was demonstrated in the only large-scale, randomized trial designed to examine the relationship between PRNB in the PACU and longer term outcomes (POP within 6 days of surgery).²⁷ In patients who received atracurium or vecuronium, the incidence of POP was approximately 5% and was unrelated to the TOF ratio upon arrival in the PACU. In patients who received the long-acting NMBA pancuronium with TOF ratios of less than 0.7, the incidence of POP was almost 17%. The conclusion is that prolonged as opposed to a transient postoperative weakness is a risk factor for pneumonia.

Muscle relaxants are often essential components of a balanced anesthetic technique; yet, they may produce life-threatening complications if not dosed and monitored appropriately. The findings of Bulka *et al.*⁶ provide further support to the concept raised more than 60 yr ago that NMBA use is associated with increased morbidity. In order to optimize patient outcomes, clinicians should only administer NMBAs when clinically necessary. If NMBAs are needed intraoperatively, the lowest dose required for surgical relaxation should be used, the depth of neuromuscular blockade should be monitored, and NMBA administration should be minimized during the last hour of the procedure.

Ideally, neostigmine should not be administered until at least the fourth response to TOF stimulation appears; however, the time to achieve acceptable neuromuscular

recovery may be as much as 15 min in this setting, even after a large dose (0.06 to 0.07 mg/kg) of neostigmine.^{28,29} Unless there is quantitative evidence that the TOF ratio at the adductor pollicis has returned to a value of more than or equal to 0.9, an appropriate dose of an anticholinesterase agent or sugammadex should be administered at the end of surgery. When no tactile or visual fade is detectable with TOF stimulation, reversal agents should still be administered since the TOF ratio may be as low as 0.4.^{21,22} We are unaware of any clinical evidence that suggests that doses of neostigmine of 0.03 mg/kg or less may produce adverse respiratory effects, even when neuromuscular recovery is essentially complete.^{30–33}

The investigation by Bulka *et al.*⁶ adds important additional insights into our growing body of knowledge about the long-term risks of failure to reverse neuromuscular blocking agents. On the basis of existing data, we believe that the well-documented hazards of postoperative residual neuromuscular blockade outweigh any theoretical risks of paradoxical muscle weakness and that reversal of neuromuscular blocking agents should be routine.

Competing Interests

Dr. Murphy has served as a consultant for Merck. The other author declares no competing interests.

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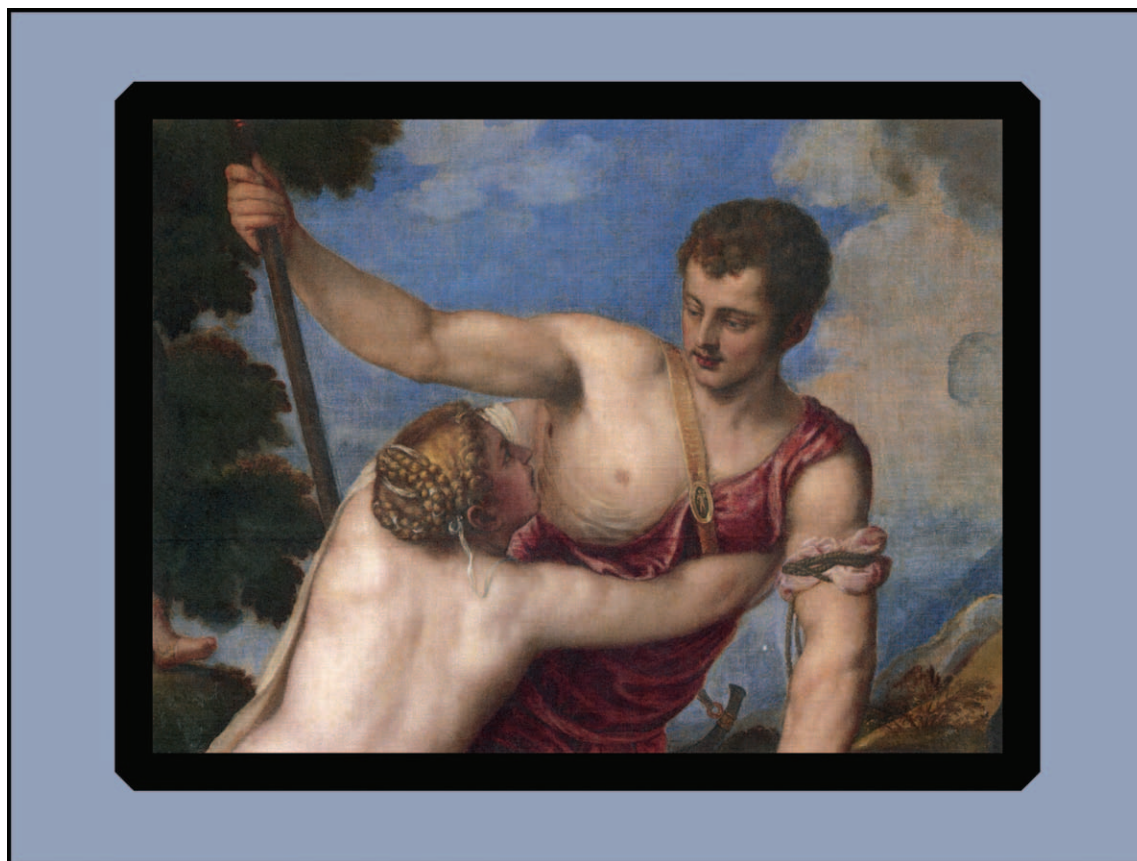
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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From *Venus and Adonis*: Shakespearean Inebriation and Colton Gas



As painted in 1554 by Titian, lovesick Venus (*left*) throws herself shamelessly at disdainful Adonis (*right*), her handsome foster son. In Shakespeare's narrative poem, *Venus and Adonis*, the goddess "treads the path that she untreads again" as she frets about the safety of Adonis. The Bard compares her behavior to "the proceedings of a drunken brain." The author of *Shakspeare* [sic] and *the Bible*, nitrous oxide pioneer G. Q. Colton (1814 to 1898) parlayed the American public's awareness of "drunken" behavior at recreational demonstrations of his "Colton gas" into public confidence in trying an apparently familiar agent, laughing gas, as an anesthetic for dental extraction. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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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

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

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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

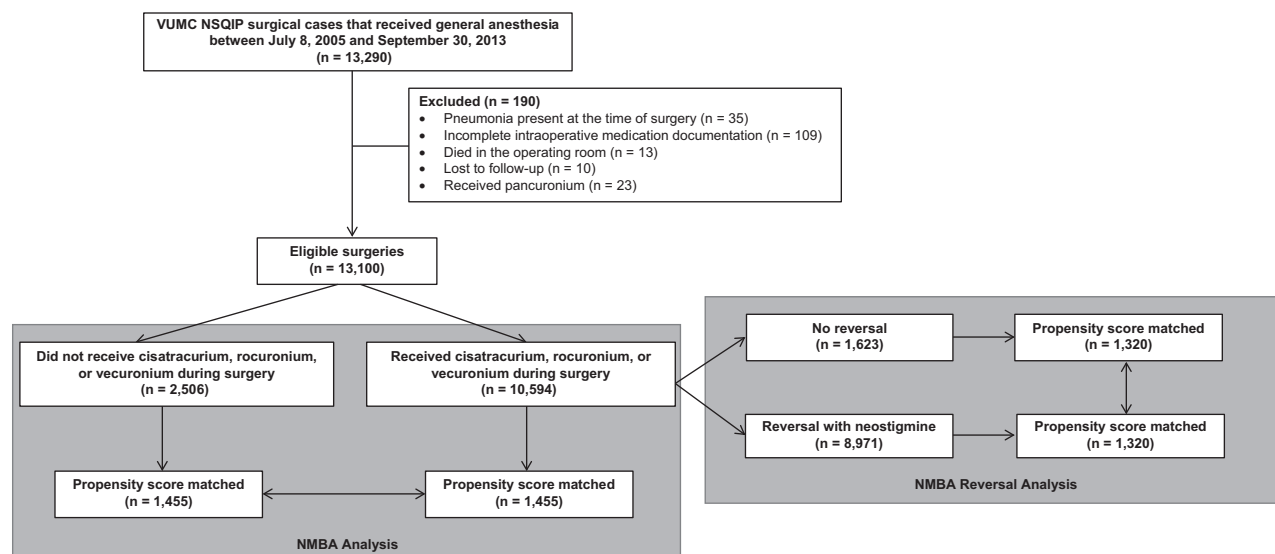


Fig. 1. Flowchart of inclusion/exclusion criteria. NMBA = nondepolarizing neuromuscular blocking agent; NSQIP = National Surgical Quality Improvement Program; VUMC = Vanderbilt University Medical Center.

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

NMBA Analysis	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)
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)

NMBA Reversal Analysis	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)
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

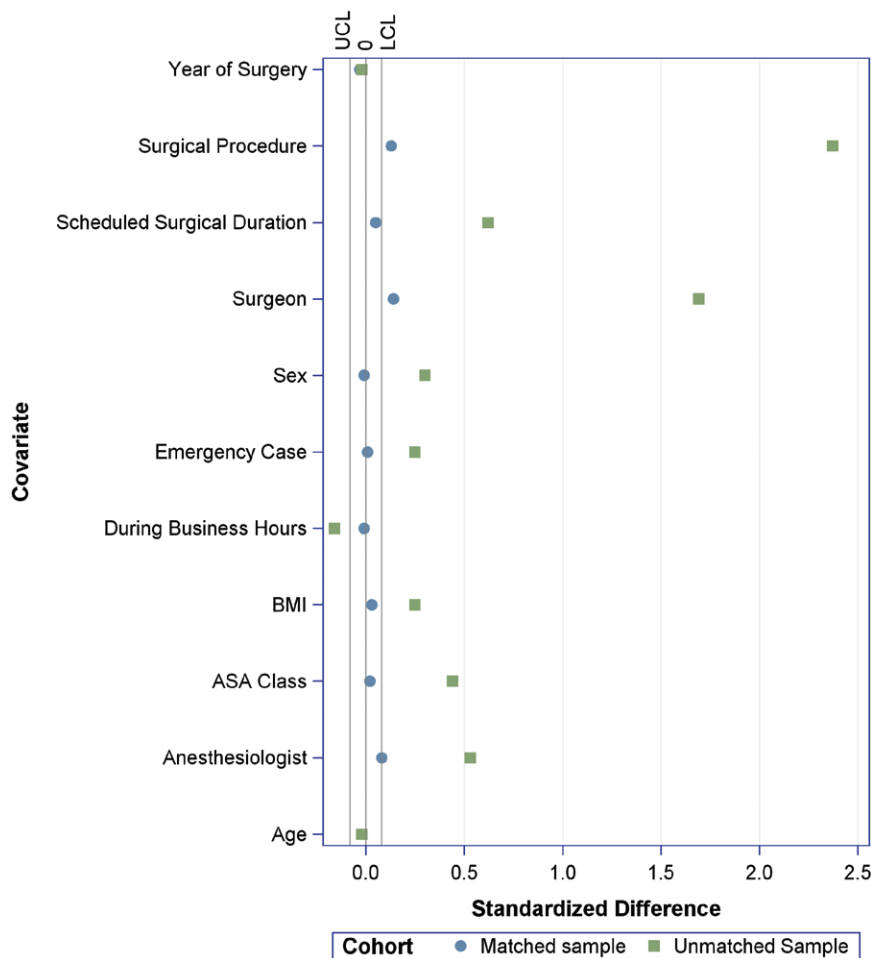


Fig. 2. Standardized differences between surgical cases who received nondepolarizing neuromuscular blocking agents and those who did not. The standardized differences compare the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured across different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

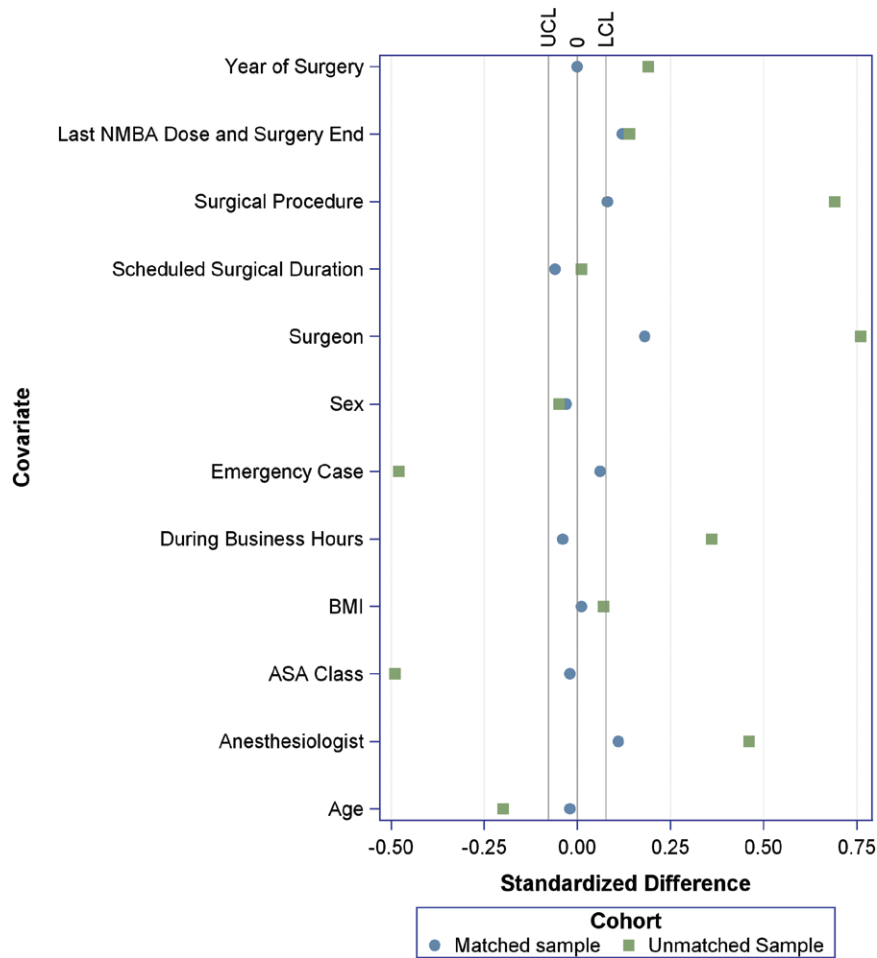


Fig. 3. Standardized differences between surgical cases who received nondepolarizing neuromuscular blocking agents (NMBA) reversal and those who did not. The standardized differences compare the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured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