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Postoperative Pulmonary Complications' Association with Sugammadex *versus* Neostigmine: A Retrospective Registry Analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Compared with neostigmine, sugammadex demonstrates improved rates of residual neuromuscular blockade
- There are limited data using validated surgical registry outcome data to evaluate the association between use of sugammadex and reduced pulmonary complications

What This Article Tells Us That Is New

- At a medical center that implemented a complete switch from neostigmine to sugammadex, a statistically significant difference in pulmonary complication rates was not observed between 7,800 general surgery patients receiving neostigmine *versus* 2,691 general surgery patients receiving sugammadex
- Although rates of pulmonary complication after general surgery are decreasing, some of this change may be attributable to temporal trends in practice unrelated to the use of neostigmine *versus* sugammadex

ABSTRACT

Background: Postoperative residual neuromuscular blockade related to nondepolarizing neuromuscular blocking agents may be associated with pulmonary complications. In this study, the authors sought to determine whether sugammadex was associated with a lower risk of postoperative pulmonary complications in comparison with neostigmine.

Methods: Adult patients from the Vanderbilt University Medical Center National Surgical Quality Improvement Program database who underwent general anesthesia procedures between January 2010 and July 2019 were included in an observational cohort study. In early 2017, a wholesale switch from neostigmine to sugammadex occurred at Vanderbilt University Medical Center. The authors therefore identified all patients receiving nondepolarizing neuromuscular blockades and reversal with neostigmine or sugammadex. An inverse probability of treatment weighting propensity score analysis approach was applied to control for measured confounding. The primary outcome was postoperative pulmonary complications, determined by retrospective chart review and defined as the composite of the three postoperative respiratory occurrences: pneumonia, prolonged mechanical ventilation, and unplanned intubation.

Results: Of 10,491 eligible cases, 7,800 patients received neostigmine, and 2,691 received sugammadex. A total of 575 (5.5%) patients experienced postoperative pulmonary complications (5.9% neostigmine *vs.* 4.2% sugammadex). Specifically, 306 (2.9%) patients had pneumonia (3.2% *vs.* 2.1%), 113 (1.1%) prolonged mechanical ventilation (1.1% *vs.* 1.1%), and 156 (1.5%) unplanned intubation (1.6% *vs.* 1.0%). After propensity score adjustment, the authors found a lower absolute incidence rate of postoperative pulmonary complications over time (adjusted odds ratio, 0.91 [per year]; 95% CI, 0.87 to 0.96; $P < .001$). No difference was observed on the odds of postoperative pulmonary complications in patients receiving sugammadex in comparison with neostigmine (adjusted odds ratio, 0.89; 95% CI, 0.65 to 1.22; $P = 0.468$).

Conclusions: Among 10,491 patients at a single academic tertiary care center, the authors found that switching neuromuscular blockade reversal agents was not associated with the occurrence of postoperative pulmonary complications.

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Neuromuscular blocking agents are commonly administered during general anesthesia to facilitate endotracheal intubation and to optimize surgical conditions.[1] However, residual neuromuscular blockade remains a complication of nondepolarizing neuromuscular blocking agents. Clinically, residual neuromuscular blockade is associated with adverse physiologic effects, including impaired pharyngeal function, decreased functional residual capacity, and impaired hypoxic ventilatory response,[2,3] which contribute to multiple postoperative complications, including weakness, aspiration, reintubation, and pneumonia.[4–8] Thus, appropriate reversal guided by neuromuscular transmission

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monitoring is critical to decreasing the risk of postoperative pulmonary complications.[9]

Neostigmine, an acetylcholinesterase inhibitor reversal agent, may decrease the likelihood of postoperative pneumonia.[10] However, it is ineffective in reversing deep neuromuscular blockade.[11] Additionally, neostigmine may be associated with paradoxical muscle weakness if administered when full recovery of neuromuscular function has occurred.[12] Moreover, muscarinic side effects, including bradycardia, double vision, and postoperative nausea and vomiting, are an important consideration in routine use.[13] Sugammadex, a novel reversal agent, has been approved by the Food and Drug Administration (Silver Spring, Maryland) in 2015 as an alternative to neostigmine and entered broad usage. Reversal using sugammadex has been reported to lower the incidence of residual paralysis,[14] with more rapid reversal, less bradycardia,[15] and a lower hospital readmission rate.[16] The association between postoperative pulmonary complications and sugammadex reversal, however, remains unclear.

The primary aim of this analysis is to determine whether reversal with sugammadex is associated with a lower risk of pulmonary complications within the 30-day postoperative period compared with reversal with neostigmine. We hypothesized that use of sugammadex was protective for the development of postoperative pulmonary complications.

Materials and Methods

This retrospective observational cohort study received approval from the Institutional Review Board at Vanderbilt University Medical Center (Nashville, Tennessee). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used to report this study, and the article adheres to the applicable guidelines.[17]

Data Collection

Data were derived from a local, single-center copy of the National Surgical Quality Improvement Program database, merged with data from the electronic health record and anesthetic record.[18,19] Our primary outcome, postoperative pulmonary complication, was defined as the composite of the three National Surgical Quality Improvement Program–tracked postoperative respiratory occurrences: pneumonia, requiring mechanical ventilation for more than 48 h, and unplanned intubation. A global rank composite methodology was applied to develop the composite pulmonary complications with severity ranking.[20] Outcome data were obtained by combining our local, National Surgical Quality Improvement Program outcomes data with our local, identified electronic health record data. Vanderbilt University Medical Center National Surgical Quality Improvement Program data were abstracted from the medical record by a trained surgical clinical reviewer. After the transmission of deidentified data to National Surgical Quality Improvement Program, our National Surgical Quality Improvement Program chart abstractor team downloaded the data from the National Surgical Quality Improvement Program site to create a local, identified copy. These data were loaded into our Perioperative Data Warehouse on a quarterly basis. An electronic data query was designed to collect baseline, perioperative, and postoperative data from the copy of Vanderbilt University Medical Center National Surgical Quality Improvement Program database, and the supplemental demographic, clinical, and intraoperative data regarding medications were obtained from the Vanderbilt University Medical Center Perioperative Data Warehouse. The National Surgical Quality Improvement Program and Vanderbilt University Medical Center Perioperative Data Warehouse are the source of the data used; the National Surgical Quality Improvement Program has not verified and is not responsible for the validity of the statistical analysis or the conclusions derived by this study. The sample size was based on our available National Surgical Quality Improvement Program data, and a statistical power analysis of cohorts of cases and controls was performed before the study.

Practice Changes

Sugammadex was introduced at Vanderbilt University Medical Center in May 2016 and was initially restricted to emergency reversal of a rapid sequence intubation dosage of rocuronium, resulting in infrequent usage in the operating room. In March 2017, its locally approved indication was broadened to include routine reversal, and it replaced neostigmine in the standard pharmacy tray distributed to operating rooms. This resulted in an immediate, wholesale switch from utilization of neostigmine to sugammadex at that time.

We have previously described that our institution, like our peer institutions, has gradually adopted utilization of lung protective ventilation strategies in the operating room.[21] In addition to practice changes that appear to have occurred without active quality improvement intent, we have also developed and implemented clinical decision support to identify patients at risk of acute lung injury and recommend usage of lung protective ventilation strategies. Two separate clinical decision support interventions were made, in June 2014 and again in March 2017. Analysis of these changes has demonstrated that they were not effective (*i.e.*, did not impact adoption of lung protective ventilation strategies when the background rate of practice change was considered). Additionally, we modified our default ventilator settings in April 2017 to a tidal volume of 450 ml (from 600 ml) and positive end-expiratory pressure of 5 cm H_2O (from none).

Our institution has also focused on the development and implementation of enhanced recovery after surgery protocols that seek to minimize exposure to opioids in the preoperative, intraoperative, and postoperative phases. These

protocols also emphasize the importance of goal-directed fluid therapy, appropriate postoperative nausea and vomiting prophylaxis, glycemic control, and usage of lung-protective ventilation. We have described this work previously in colorectal patient populations[22] and surgical weight loss patients,[23] and the scope of these implementations includes 14 service lines. Within our colorectal patient population, we have also shown that implementation of these protocols has been broadly associated with the reduction of postoperative complications.[24]

In addition to these practice changes, we have performed focused work on improving our documentation of neuromuscular blockade depth. This work began in September 2015 and continued through November 2016 and has been previously described.[25] The effect of these changes to our documentation practices was modest.

Eligibility

Eligible patients received general anesthesia with the use of nondepolarizing neuromuscular blocking agents, and procedures were performed between January 2010 and July 2019. These cases had previously been selected for National Surgical Quality Improvement Program review using the National Surgical Quality Improvement Program sampling methodology and followed by trained surgical clinical reviewers using consistent data definitions. Of note, during the study period, several sampling methodology changes were introduced by the National Surgical Quality Improvement Program. Although all cases were included based on a randomization schedule prescribed by the American College of Surgeons (Chicago, Illinois) before January 2011, hospitals were allowed to selectively include higher volumes of chosen procedures under the Procedure Targeted Program since then. Meanwhile, a change to targeted sampling was made in January 2015 by eliminating ventral hernia repair and replacing it with appendectomy, a high-volume, low-risk operation that is monitored as a bellwether for procedural variation that may lead to increasing complications.

For each eligible case, we identified patients with the intraoperative administration of neuromuscular blockade, followed by use of a reversal agent (neostigmine or sugammadex). The patients who received intermediate-acting nondepolarizing neuromuscular blocking agents (cisatracurium, vecuronium, or rocuronium) were included in the cohort.[26] The National Surgical Quality Improvement Program sampling methodology automatically filters out pediatric patients (birth to 18 yr of age), transplantation cases, and those cases that resulted from complications of another diagnostic or surgical procedure within the previous 30 days.[10] Furthermore, patients who received cisatracurium were excluded from further analysis.[27] Moreover, patients receiving both sugammadex and neostigmine were excluded from the study. Additionally, we excluded surgical cases with incomplete intraoperative medication documentation in terms of neuromuscular blocking agents and reversal agents.

Primary Outcomes

Postoperative Pneumonia Definition. Patients were defined as having postoperative pneumonia if they met the National Surgical Quality Improvement Program definition of pneumonia after surgery. Pneumonia is defined by National Surgical Quality Improvement Program 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).[10,28] Patients with an underlying pulmonary or cardiac disease are required to have at least two or more definitive serial chest radiological exams. Patients who were known or suspected to have pneumonia before surgery were excluded. Of note, the pneumonia definition was updated in 2012, which strengthened requirements for radiographic and laboratory data. In 2015, an additional clarification was added, allowing physician documentation of the absence of pneumonia to contravene the surveillance-based assignment of the occurrence.

On Ventilator Greater Than 48 h Definition. Patients with a cumulative duration of ventilator-assisted respirations greater than 48 h during the postoperative hospitalization and any subsequent hospitalizations within 30 days after a principal operative procedure are assigned a postoperative occurrence of "on ventilator greater than 48 h."[28] Patients who are intubated before surgery are excluded.

Unplanned Intubation Definition. Patients were defined as having unplanned intubation if they met the National Surgical Quality Improvement Program definition of unplanned intubation. Unplanned intubation is defined by National Surgical Quality Improvement Program as requiring placement of an endotracheal tube secondary to the onset of respiratory or cardiac failure as evidenced by severe respiratory distress, hypoxia, hypercarbia, or respiratory acidosis within 30 days of the operation.[28] Intubation for a return to the operating room is not included. In 2012, the unplanned intubation definition was broadened to include emergent airway management for any reason, including reintubation before leaving the operating room.

The primary outcome was the development of postoperative pneumonia, prolonged mechanical ventilation, or unplanned intubation using a global rank composite methodology.[20] Postoperative occurrence of pneumonia, prolonged mechanical ventilation, and unexpected intubation were determined as clinical endpoints of interest and then were combined to form a composite outcome using the global rank method. The global rank is a composite of two

or more outcomes that are assessed independently and that can be naturally ordered. In our study, unplanned intubation was considered most severe, followed by prolonged ventilation and pneumonia. The global rank was the hierarchical order of the most severe outcome that occurred within the postoperative follow-up period, with 0 indicating no complication, 1 indicating pneumonia, 2 indicating prolonged mechanical ventilation, and 3 indicating unplanned intubation. Meanwhile, we summed up the global rank for patients who had more than one postoperative respiratory complication. Thus, the global rank composite ranging from 0 to 6 captured the incidence and severity of postoperative pulmonary complications.

Statistical Analysis

Demographic, clinical, and procedural variables were used to characterize the study population with mean ± SD for parametric variables, with medians and interquartile range for nonparametric variables and with percentages for categorical variables. The incident rates of the postoperative pulmonary complications after neostigmine and sugammadex use were reported.

To control for potential confounding variables, we performed a propensity score analysis with inverse probability of treatment weighting.[29] This is a propensity score weighting method that mimics a matched analysis. This method allows for the use of all available data and does not require specification of a matching algorithm, which is a source of uncertainty in matched analyses.[30] We identified patients who had received intermediate-acting nondepolarizing neuromuscular blockers (vecuronium or rocuronium) and reversal (neostigmine or sugammadex). The propensity score model was constructed by regressing the odds of receiving sugammadex *versus* neostigmine onto patient age, sex, weight, body mass index, American Society of Anesthesiologists (Schaumburg, Illinois) physical status classification, emergency surgery status, duration of the surgical procedure, procedure type (classified using Clinical Classifications Software Groupers),[31] selected Elixhauser comorbidities associated with the risk of postoperative pulmonary complications (chronic pulmonary disease, congestive heart failure, paralysis, liver disease, and cardiac arrhythmia),[32] primary surgeon volume, primary attending anesthesiologist volume, and whether or not the surgery occurred during normal business hours. Following the automated Harrell's knot placement suggestions, a restricted cubic splines approach was applied on patient age for modeling nonlinear associations. Body mass index was recategorized into four levels: underweight (body mass index less than or equal to 18.5 kg/m^2), normal (body mass index greater than 18.5 and less than or equal to 25 kg/m^2), overweight (body mass index greater than 25 and less than or equal to 30 kg/m^2), and obesity (body mass index greater than or equal to 30 kg/m^2).[33] Primary surgeon volume (the number of surgeries performed by the primary surgeon) was modeled as a categorical variable with two levels: low-volume (less than or equal to 100 cases) and high-volume (more than 100 cases), and primary attending anesthesiologist volume was modeled using the same logic.[10] Of note, primary surgeon volume and primary attending anesthesiologist volume were restricted to the analyzed cohort, which therefore underestimated the actual procedure volume due to registry sampling. Meanwhile, for a case with multiple attendings, the first attending anesthesiologist was defined as the primary attending. In addition, last train-of-four before the administration of reversal agents was not included in primary analysis owing to incompleteness of the data. The propensity score weights were computed for each case,[30] and the balance between the propensity score–weighted cohorts was assessed using the standardized difference before and after propensity score weighting.

The cohorts with computed propensity score weights were analyzed, and the primary exposure variable, the association between reversal with sugammadex *versus* neostigmine, and the distribution of the global rank composite for pulmonary complications were assessed using multivariable weighted ordinal logistic regression. Many other intraoperative covariates, including surgery date, intraoperative tidal volume (median volume per ideal body weight[34]), and intraoperative opioid administration (morphine equivalents in $mg \cdot kg^{-1} \cdot h^{-1}$) were controlled as covariates in the regression model to adjust for any possible residual confounding and secular trends that might confound the assessment of two reversal agents. Associations were summarized using the ordinal odds ratios and 95% CI and tested using a Wald-type test with 5% type-I error rate. The ordinal odds ratio is interpreted as follows: Let the ordinal global rank composite for pulmonary complications be denoted by Y and one of its levels by y (*e.g.*, 0, 1, 2, 3, 4, 5, or 6). The ordinal odds are the odds that $Y \geq y$, which is the probability that $Y \geq y$ divided by one minus itself $\left(\frac{P}{1-P}\right)$.[35] Thus, in this study, the odds ratio is interpreted as the fold-change in the odds of more severe postoperative pulmonary complications, associated with sugammadex *versus* neostigmine. A diagnostic goodness-of-link test was examined to discriminate the model fit.[36]

Sensitivity Analyses

Several sensitivity analyses were prespecified. First, the associations between reversal with sugammadex *versus* neostigmine and the odds of each individual outcome (*i.e.*, pneumonia, prolonged mechanical ventilation, and unplanned intubation) were assessed and summarized using weighted multivariable logistic regression as sensitivity analyses. Surgery date, intraoperative tidal volume, and intraoperative opioid administration were controlled as covariates in all three logistic regression models.

Additionally, we implemented a sensitivity analysis using interrupted time series segmented regression to evaluate

the possibility of secular trends that were not explained by the propensity score–weighted ordinal logistic regression. The cohort was split into three groups by date of surgery: before January 1, 2013 (neostigmine period I [before the implementation of new Ventilator-Associated Events definitions]), from January 1, 2013 to March 31, 2017 (neostigmine period II [after the implementation of new Ventilator-Associated Events definitions]), and after April 1, 2017 (sugammadex period). The data in three groups were divided into quarterly subsets to adjust for variation in case volume.

A protocol with an *a priori* analytic plan was written and filed with the institutional review board at Vanderbilt University Medical Center before data were accessed. A two-sided hypothesis testing with a P value less than 0.05 was deemed to indicate statistical significance. All statistical programming was implemented in SAS 9.4 (SAS Institute Inc., USA).

Results

There were 10,817 surgical cases included in the Vanderbilt University Medical Center National Surgical Quality Improvement Program database who received general anesthesia with the intraoperative administration of neuromuscular blockade, followed by use of a reversal agent. A total of 326 cases were excluded from analysis; 1 patient was under the age of 18 yr at the time of surgery, 9 received both sugammadex and neostigmine, 52 had incomplete intraoperative medication documentation, and 264 received cisatracurium. *A priori* power analysis showed that we would need to study at least 3,919 cases (2,506 receiving neostigmine and 1,413 receiving sugammadex) to detect a clinically relevant ordinal odds ratio of 0.7 with a power of 0.8 in comparing patients who received neostigmine *versus* sugammadex. Our study included a total of 10,491 cases that met the inclusion criteria. Of all eligible cases, 7,800 patients received neostigmine, and 2,691 received sugammadex; the overall incident rate of postoperative pulmonary complications was 5.9% for the neostigmine subgroup and 4.2% for the sugammadex subgroup. Specifically, a total of 306 (2.9%) patients experienced postoperative pneumonia (3.2% neostigmine *vs.* 2.1% sugammadex), 113 (1.1%) prolonged mechanical ventilation (1.1% *vs.* 1.1%), and 156 (1.5%) unplanned intubation (1.6% *vs.* 1.0%; table 1).

The standardized mean differences of the patient demographics and clinical characteristics before and after propensity score weighting are presented in table 2. The standardized differences compared the difference in means in units of the pooled SD, enabling comparison of the relative balance of variables measured across different units. Figure 1 shows the standardized differences of two groups. After propensity score weighting, the differences of patient age, sex, body mass index, selected Elixhauser comorbidities, American Society of Anesthesiologists physical status, emergency surgery status, surgery duration, procedure type, primary surgeon, primary anesthesiologist, and the total logit propensity score were balanced across groups, with all standardized differences less than 0.05.

From the result of primary analysis, a later surgery date was found to be associated with a reduced probability of getting postoperative pulmonary complications (adjusted odds ratio, 0.91 [per year]; 95% CI, 0.87 to 0.96; $P < .001$). The intraoperative tidal volume (adjusted odds ratio, 0.98 [per ml/kg]; 95% CI, 0.95 to 1.00; $P = 0.078$) and opioid administration (adjusted odds ratio, 1.07 [per mg · kg^{-1} · h^{-1}]; 95% CI, 0.52 to 2.17; $P = 0.856$) were not associated with the risk of postoperative pulmonary complications. Compared with the patients receiving neostigmine, no difference was found regarding the occurrence of postoperative pulmonary complications for the patients receiving neuromuscular blockade followed by reversal with sugammadex (adjusted odds ratio, 0.89; 95% CI, 0.65 to 1.22; $P = 0.468$). Logit link function was found among the best in terms of the goodness-of-link test ($P = 0.020$; Supplemental Digital Content 1, http://links.lww.com/ALN/C565, contains full model results and diagnostics).

Three sensitivity analyses revealed more specific associations with each individual outcome. In comparing patients who received neostigmine, the adjusted odds ratio of having postoperative pneumonia in sugammadex group was 0.94 (95% CI, 0.66 to 1.34; $P = 0.750$), having prolonged mechanical ventilation was 0.83 (95% CI, 0.48 to 1.44; $P = 0.508$), and having unplanned intubation was 1.17 (95% CI, 0.73 to 1.86; $P = 0.509$).

The interrupted time series segmented analysis was conducted to evaluate the incident rate of postoperative pulmonary complications over time. One hundred four cases were excluded from segmented analysis because of the overlaps: 89 patients in the neostigmine period (3.3%) cohort received sugammadex, and 15 patients in the sugammadex period (0.2%) received neostigmine. No significant trend change was found in the incidence of any composite postoperative pulmonary complication during the neostigmine period I (4.7 to 5.2%, $P = 0.719$), the neostigmine period II (3.8 to 2.6%, $P = 0.156$), and the sugammadex period (3.0 to 2.2%, $P = 0.335$). However, a significant downtrend was observed after combining the neostigmine periods I and II (slope, –0.03; $P = 0.004$), which was consistent with the primary analysis. No immediate change was observed with the transition from the neostigmine period I to neostigmine period II (5.2% [offset] to 3.8%; $P = 0.167$) and from the neostigmine period II to sugammadex period (2.6% [offset] to 3.0%; $P = 0.660$; fig. 2).

Several *post hoc* sensitivity analyses were performed. To minimize the potential impact of the definition and sampling strategy changes in 2013 and 2015, we restricted the propensity score analyses to the cases after 2013 and 2015, respectively. For cases after 2013, no significant difference

Table 1. Patient Demographics and Clinical Characteristics of the Study Sample

Variables	Reversal with Neostigmine (n = 7,800)	Reversal with Sugammadex (n = 2,691)
Age, yr, mean ± SD	52 ± 16	51 ± 17
Body mass index, kg/m^2, mean ± SD	29.8 ± 8.1	29.9 ± 8.1
Weight, kg, mean ± SD	89.0 ± 27.4	89.4 ± 27.1
Sex (%)		
Female	4,163 (53.4%)	1,414 (52.6%)
ASA classifications (%)		
I	289 (3.7%)	145 (5.4%)
II	2,765 (35.5%)	843 (31.3%)
III	4,462 (57.2%)	1,601 (59.5%)
IV and V	284 (3.6%)	102 (3.8%)
ASA emergency (%)	627 (8.0%)	294 (10.9%)
Primary surgeon volume (%)		
High-volume	6,318 (81.0%)	1,890 (70.2%)
Primary attending anesthesiologist volume (%)		
High-volume	4,832 (62.0%)	1,085 (40.3%)
Surgery duration, min, median (interquartile range)	176 (127–247)	190 (130–268)
Hospital length of stay, days, median (interquartile range)	3 (1–6)	3 (1–5)
Intraoperative tidal volume (median volume per ideal body weight), ml/kg, median (interquartile range)	8.3 (7.4–9.4)	7.5 (6.8–8.3)
Intraoperative opioid administration (morphine equivalents), mg · kg^{-1} · h^{-1}, median (interquartile range)	0.1 (0.1–0.2)	0.1 (0.0–0.1)
Surgical service (%)		
General surgery	4,515 (57.9%)	1,361 (50.6%)
Oncology surgery	1,202 (15.4%)	376 (14.0%)
Trauma surgery	912 (11.7%)	364 (13.5%)
Emergency general surgery	320 (4.1%)	306 (11.4%)
Vascular surgery	500 (6.4%)	171 (6.4%)
Hepatobiliary surgery	312 (4.0%)	107 (4.0%)
Other	39 (0.5%)	6 (0.2%)
Normal business hours surgery (%)		
Yes	6,823 (87.5%)	2,495 (92.7%)
Selected Elixhauser comorbidities (%)		
Chronic pulmonary disease	399 (5.1%)	436 (16.2%)
Congestive heart failure	243 (3.1%)	162 (6.0%)
Paralysis	28 (0.4%)	20 (0.7%)
Liver disease	308 (4.0%)	381 (14.2%)
Cardiac arrhythmia	432 (5.6%)	448 (16.7%)
Year of surgery		
2010	974 (12.5%)	—
2011	1,080 (13.9%)	—
2012	1,074 (13.8%)	—
2013	1,153 (14.8%)	—
2014	1,085 (13.9%)	—
2015	1,121 (14.3%)	—
2016	1,064 (13.6%)	3 (0.1%)
2017	241 (3.1%)	921 (34.2%)
2018	8 (0.1%)	1,121 (41.7%)
2019	—	646 (24.0%)
Pulmonary complications rate (%)		
Pneumonia	249 (3.2%)	57 (2.1%)
Prolonged mechanical ventilation	84 (1.1%)	29 (1.1%)
Unplanned intubation	128 (1.6%)	28 (1.0%)

ASA, American Society of Anesthesiologists.

was observed in the incidence of postoperative pulmonary complications for the patients receiving sugammadex (adjusted odds ratio, 0.88; 95% CI, 0.58 to 1.33; $P = 0.540$), as was also the case with cases after 2015 (adjusted odds ratio, 0.80; 95% CI, 0.45 to 1.27; $P = 0.296$). Moreover, to evaluate the temporal change before sugammadex was widely used in our institution (neostigmine periods I and II), we restricted the analysis to patients receiving neostigmine and found that the later date of the surgery was associated with a reduced probability of having postoperative pulmonary complications (adjusted odds ratio, 0.89 [per year]; 95% CI, 0.84 to 0.95; $P < .001$).

Table 2. Standardized Differences between Neostigmine-reversed and Sugammadex-reversed Groups before and after Inverse Probability of Treatment Propensity Score Weighting

Variable	Observations	Mean Difference	SD	Standardized Difference	Percent Reduction	Variance Ratio
Logit prop score	All	0.64	0.8	0.80		1.6
	Weighted	−0.01		−0.01	98.3%	0.9
ASA class	All	0.02	0.6	0.03		1.1
	Weighted	−0.01		−0.01	69.0%	1.1
Age	All	−0.88	16	−0.05		1.1
	Weighted	0.05		0.00	93.9%	1.1
Weight	All	0.87	27.3	0.03		1.0
	Weighted	−1.02		−0.04	0.0%	0.9
Body mass index	All	0.00	0.8	0.01		1.0
	Weighted	0.00		0.00	31.9%	1.0
Hospital length of stay	All	−0.19	5	−0.04		0.9
	Weighted	0.13		0.03	28.4%	1.4
Surgical procedure	All	−0.93	51.6	−0.02		1.0
	Weighted	−1.95		−0.04	0.0%	0.9
Surgery duration	All	18.61	112	0.17		1.4
	Weighted	−1.71		−0.02	90.8%	1.1
Chronic pulmonary disease (Elixhauser)	All	0.11	0.3	0.36		2.8
	Weighted	0.00		−0.01	98.5%	1.0
Congestive heart failure (Elixhauser)	All	0.03	0.2	0.14		1.9
	Weighted	0.01		0.04	74.2%	1.2
Paralysis (Elixhauser)	All	0.00	0.1	0.05		2.1
	Weighted	0.00		0.01	73.9%	1.2
Liver disease (Elixhauser)	All	0.10	0.3	0.36		3.2
	Weighted	0.00		−0.01	97.3%	1.0
Cardiac arrhythmia (Elixhauser)	All	0.11	0.3	0.36		2.6
	Weighted	0.00		0.00	99.1%	1.0
Sex	All	−0.01	0.5	−0.01		1.0
	Weighted	0.00		0.00	86.0%	1.0
Emergency case	All	−0.02	0.3	−0.07		1.2
	Weighted	−0.01		−0.03	55.8%	1.1
During business hours	All	0.01	0.2	0.05		1.2
	Weighted	0.01		0.02	53.4%	1.1
Primary attending anesthesiologist volume	All	0.22	0.5	0.44		1.0
	Weighted	0.00		0.00	99.4%	1.0
Primary surgeon volume	All	0.10	0.4	0.23		1.3
	Weighted	0.01		0.01	93.9%	1.0

SD of all observations used to compute standardized differences. ASA, American Society of Anesthesiologists.

Discussion

In this retrospective observational study, we found that the choice of neuromuscular blockade reversal agents in general anesthesia was not associated with the occurrence of postoperative pulmonary complications.

Our results contribute to delineating the associations of neostigmine and sugammadex with respiratory outcomes that were observed in the literature. Although sugammadex was demonstrated to decrease residual postoperative paralysis and minor respiratory events, a systematic review of 1,553 patients by Abad-Gurumeta *et al.* found no difference in critical respiratory events such as intubation and invasive or noninvasive ventilation.[37] Similarly, a 2017 Cochrane review indicated no difference in risks of serious adverse events between the two drugs at any dose, which included cases of pneumonia and respiratory failure.[15] A multicenter observational cohort study (Postanaesthesia Pulmonary Complications after Use of Muscle Relaxants; POPULAR) of 22,803 European patients showed that the choice of sugammadex instead of neostigmine was not associated with improved pulmonary outcomes, including suspected pulmonary infection.[38] Chae *et al.* also reported no differences in 30-day postoperative outcomes after sugammadex and acetylcholinesterase inhibitor use.[39] Thus, our results are in line with previous published studies.

Although a recent observational study found a 31% reduction in reintubation and initiation of noninvasive ventilation during a system-wide transition from neostigmine to sugammadex, its authors attributed the significant reduction to less demand for noninvasive ventilation, and the study was not sufficiently powered to detect difference in reintubation owing to low incidence.[40] Whereas a meta-analysis by Carron *et al.* found a lower likelihood of respiratory adverse events in the sugammadex group than neostigmine, their analysis did not stratify events based on severity.[41] In addition, a recent

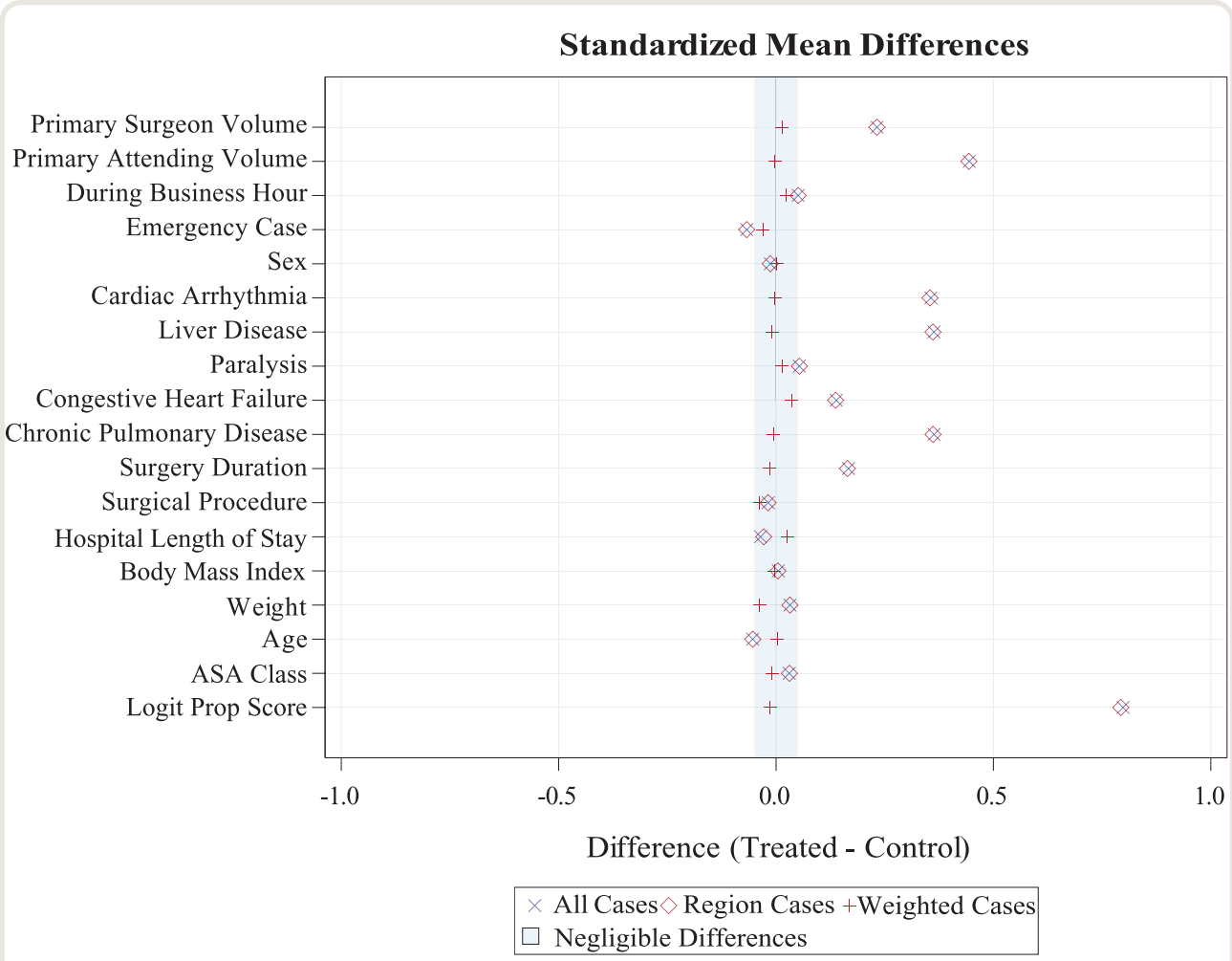

Fig. 1. Visualization of the standardized differences between neostigmine-reversed and sugammadex-reversed groups before and after inverse probability of treatment propensity score weighting (negligible difference is 0.05.)

multicenter observational cohort study (Sugammadex *versus* Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications; STRONGER) by Kheterpal *et al.* reported the sugammadex administration was associated with a 30% reduced risk of pulmonary complications compared to neostigmine; however, temporal bias may account for some of the reduction in complications given its 5-yr study period.[32]

In comparison with previous studies, our analysis captured a more comprehensive picture of pulmonary complications by examining a global rank composite of pneumonia, prolonged mechanical ventilation, and unplanned intubation up to 30 days after surgery, using rigorously defined outcomes and consistent data definitions. Specifically, compared with the patients receiving neostigmine, patients who received sugammadex were not observed to be associated with a reduced risk of any individual pulmonary complication within 30 postoperative days. Although sugammadex is well known for its use in reducing the risk of postoperative residual neuromuscular blockade in well-controlled studies, this has not always improved clinical measures of postoperative strength and has not always reduced postoperative pulmonary complications.[42,43] In daily clinical practice, the data regarding its impact on postoperative pulmonary complications have been mixed.[44] We observed a lower absolute incidence rate of postoperative pulmonary complications over time; however, we were simply unable to distinguish that from background improvements that we observed in our cohort. Although we did not observe a relationship between intraoperative tidal volumes and reduced pulmonary complication rates in this study, we made improvements that resulted in more consistent usage of lung-protective ventilation and decreases in postoperative pulmonary complications.[21,24] As compared with other hospitals,[45] it is possible that our institution was already performing well with respect to postoperative pulmonary complications, well enough that

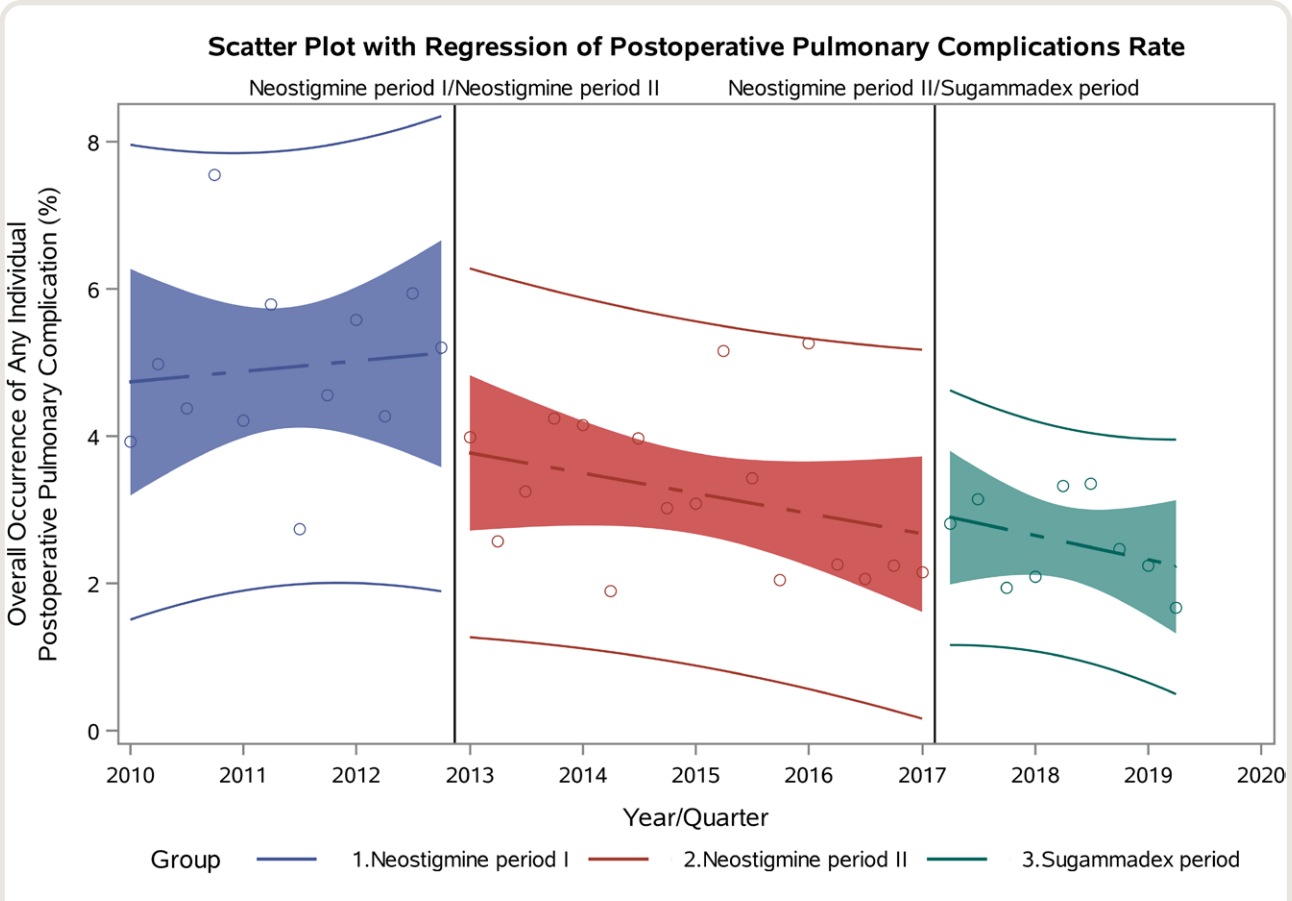

Fig. 2. Visualization of the overall occurrence of the postoperative pulmonary complications over time.

switching from neostigmine to sugammadex did not generate a detectable signal in terms of improvement in our overall postoperative complication rate. In addition, given the statistical power of our study, clinically meaningful associations could be missed, and an adequately powered study may yield the opposite conclusion.

It is also noteworthy that an overall downtrend of postoperative pulmonary complications was observed over time at our medical center (adjusted odds ratio, 0.91 [per year]), with a downward trend even during the neostigmine period after 2013. Several initiatives have been reported to reduce the likelihood of postoperative pulmonary complications in general surgery patients over time.[45,46] Specific to our institute, one possible contributor is the implementation of new Ventilator-Associated Events definitions by the National Healthcare Safety Network in 2013, which included more objective criteria for Ventilator-Associated Pneumonia.[47] Additionally, our National Surgical Quality Improvement Program data were subjected to changes in oversampling of certain procedures over time. For instance, we began to oversample appendectomies in 2015. Despite their emergent nature, appendectomies are not at high risk for pulmonary complications. Also of note, during this period, our institution implemented enhanced recovery after surgery protocols that have been shown to shorten length of hospital stay and lower rates of complications.[48] Finally, our department had multiple quality improvement initiatives over the time period studied to encourage use of train-of-four ratio monitoring.[25] Thus, the reduction of the occurrence of postoperative pulmonary completions over time is multifactorial and should not be attributed to change in reversal agent, because it occurred before the adoption of sugammadex. The conclusion has been further confirmed by the *post hoc* sensitivity analyses.

Although we did not observe a lower occurrence of postoperative pulmonary complications with sugammadex, it has been shown to reduce postoperative residual neuromuscular blockade and its associated complications.[38] A 2017 Cochrane review showed that sugammadex can reverse neuromuscular block up to 17 times faster than neostigmine, depending on dosage.[15] Furthermore, sugammadex had an estimated 40% fewer overall adverse events, especially in risks of postoperative nausea and vomiting, bradycardia, and postoperative residual paralysis.[15]

There are important limitations to our study. First, our retrospective study design is prone to bias as a result

of residual confounding. However, we adjusted for measured known confounders through an inverse probability of treatment weighting propensity score analysis approach. Furthermore, because a sampled cohort was analyzed in this study, it enormously underestimated the surgical volumes of surgeons and attending anesthesiologists, and it may also have introduced sampling bias to certain anesthesia subspecialties. Moreover, although the measured administrative diagnoses were statistically indiscernible between two study groups after propensity score weighting, other unmeasured perioperative data elements may or may not be balanced. For instance, potential confounders such as the type of anesthesia providers, fluid administration, and last train-of-four were not controlled in the primary analysis. We were unable to control for the last train-of-four owing to missing data for approximately 40% of patients, which might cause the unmatched depth of neuromuscular block at the time of reversal between the two study groups. Therefore, further study is needed to determine whether the last train-of-four value is a meaningful contributor to our findings. Second, because there is no standardized definition of postoperative pulmonary complication, studies evaluating postoperative pulmonary complication use different combinations of individual adverse outcomes.[44] A systematic review for the American College of Physicians (Philadelphia, Pennsylvania) showed that about 60% of 16 studies used a combination of pneumonia and respiratory failure to define postoperative pulmonary complications.[49] Although the composite pulmonary outcome has yet to be validated as a reliable marker for postoperative pulmonary complications, the global rank methodology has been widely used in clinical trials.[20,50] Moreover, the impact of the changes in Ventilator-Associated Events definitions on our findings was not addressed in this study. Third, another limitation of our study is the adoption and eventually wide use of sugammadex at our institution over the study period. Because the temporal nature of this change was a potential confounder that could not be controlled by propensity score matching approach, we conducted several *post hoc* sensitivity analyses and an interrupted time series segmented analysis and did not observe a difference in pulmonary complications after adjustment between the periods of neostigmine and sugammadex use. In addition, despite the advantages of the National Surgical Quality Improvement Program, this study is subject to the less generalizable population because of the nature of single-center data, focusing on general surgery cases, and changes in data sampling methodology.

In conclusion, our single-center retrospective observational study of 10,491 general surgery patients showed no significant difference in the risk of composite outcome of pulmonary complications as defined by pneumonia, prolonged mechanical ventilation, and unplanned intubation in patients whose neuromuscular blockade was reversed with sugammadex in comparison with neostigmine within the 30-day postoperative period. Future investigations are therefore needed to validate our findings in a large-scale, multicenter, randomized, controlled trial. Additional examinations across different risk subgroups for pulmonary complications, and on the cost-effectiveness of sugammadex usage, would also necessary.

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Competing Interests

Dr. Li owns stock in Johnson and Johnson (New Brunswick, New Jersey). Dr. Freundlich reports grant funding and consulting fees from Medtronic (Minneapolis, Minnesota) and owns stock in Johnson and Johnson and 3M (Saint Paul, Minnesota). The other authors declare no competing interests.

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