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Utilization Patterns of Perioperative Neuromuscular Blockade Reversal in the United States: A Retrospective Observational Study from the Multicenter Perioperative Outcomes Group

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Abstract

BACKGROUND—Following the introduction of sugammadex to the United States clinical practice, scarce data are available to understand its utilization patterns. This study aimed to characterize patient, procedure, and provider factors associated with sugammadex administration in the US patients.

METHODS—This retrospective observational study was conducted across 24 Multicenter Perioperative Outcomes Group institutions in the United States with sugammadex on formulary at the time of the study. All American Society of Anesthesiologists (ASA) physical status 1-4 adults undergoing noncardiac surgery from 2014 to 2018 receiving neuromuscular blockade were eligible. The study established three periods based on the date of first documented sugammadex use at each institution: the pre-sugammadex period, 0-6 month transitional period, and 6+ months post-sugammadex period. The primary outcome was reversal using sugammadex during the post-sugammadex period - defined as 6 months after sugammadex was first utilized at each institution. A multivariable mixed-effects logistic regression model controlling for institution was developed to assess patient, procedure, and provider factors associated with sugammadex administration.

RESULTS—A total of 934,798 cases met inclusion criteria. Following the 6-month transition period, sugammadex was used on average in 40.0% (95% CI 39.8%-40.2%) of cases receiving neuromuscular blockade. Multivariable analysis demonstrated sugammadex use to be associated with train-of-four count of 0-1 (adjusted odds ratio 4.06, 95% CI 3.83-4.31) or 2 (2.45, 2.29-2.62) versus 3-4 twitches before reversal; the amount of neuromuscular blockade (NMB) administered (3.01, 2.88-3.16) for the highest Effective Dose 95 quartile compared to the lowest quartile; advanced age (1.83, 1.71-1.95) compared to age less than 41; male sex (1.36, 1.32-1.39) compared to female sex; major thoracic surgery (1.26, 1.13-1.39); congestive heart failure (1.17, 1.07-1.28); and ASA 3 or 4 (1.13, 1.10-1.16) versus ASA 1 or 2.

CONCLUSIONS—Our data demonstrates broad early clinical adoption of sugammadex following Food and Drug Administration approval. Sugammadex is used preferentially in cases with higher degrees of neuromuscular blockade prior to reversal and in patients with greater burden of comorbidities and known risk factors for residual blockade or pulmonary complications.

INTRODUCTION

Residual neuromuscular blockade following surgery is a persistent problem¹⁻³ associated with poor outcomes such as postoperative pulmonary complications⁴⁻⁷ and increased healthcare costs.⁸⁻¹⁰ Sugammadex, a novel neuromuscular blockade (NMB) reversal agent, has been demonstrated to improve short-term postoperative recovery room outcomes,¹¹ and enables providers to effectively reverse deeper levels of NMB, including emergent reversal of large doses of rocuronium.^{12,13} To date, the international data on sugammadex use has been largely limited to published survey results.¹⁴⁻¹⁶ Sugammadex was recently introduced to the United States (US) market following its Food and Drug Administration (FDA) approval in December 2015, and its utilization in clinical settings and the extent to which it is used preferentially compared with other recovery strategies remains unknown.

The introduction of any new drug into clinical practice and a hospital's formulary demands rigorous analysis of published evidence to evaluate its potential benefits, assess risks, and

estimate financial impact based on anticipated changes in drug utilization patterns. In the case of sugammadex, several factors (e.g. hospital restrictions, variable availability in the operating rooms, cost effectiveness, volume of use, unknown wastage, etc.) create challenges for anesthesiologists, pharmacists, and hospital administrators to accurately predict the effects of introducing sugammadex into their clinical practice. Because postoperative complications may be delayed and often occur outside of the immediate intraoperative period, anesthesia providers may not be aware of their true incidence. The clinical evidence for sugammadex reducing inpatient postoperative complications beyond the recovery room compared to neostigmine remains limited.¹⁷ The adoption of sugammadex may be limited by cost concerns^{8,18} and hospital restrictions on the use of sugammadex.¹⁹

This study aimed to identify practice changes in the management of NMB reversal following FDA approval of sugammadex in the US on December 15, 2015. The goal was to provide data enabling individual anesthesia providers and groups to benchmark their use of sugammadex to 24 institutions and thousands of providers included in this study. We hypothesized that individual hospitals would demonstrate wide variation in sugammadex use and that sugammadex would be used in a minority of eligible patients.

METHODS

Study Design

This study was approved by the Institutional Review Board (IRB) (HUM00121356, University of Michigan Medical School, Ann Arbor, Michigan), and the requirement for patient consent was waived by the IRB due to minimal risk and the secondary use of existing data collected for clinical and operational purposes. This was a retrospective observational study using Multicenter Perioperative Outcomes Group (MPOG) data to examine patterns of neuromuscular reversal. The study covered three distinct periods - the pre-sugammadex period, the first six months after sugammadex was utilized at each institution (the transitional period), and the post-sugammadex period defined as 6 months after first sugammadex use at each institution. The transitional period was excluded from the primary analysis. The analysis conducted and reported was consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²⁰

Setting

This multi-center study was conducted across all participating MPOG institutions in the United States that had sugammadex on formulary at the time of the study. Only institutions providing continuous data throughout the study period were included. Each institution contributing data has local institutional board approval to transmit a limited dataset compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) that contains no direct patient identifiers. The protocol was registered with the MPOG publications committee on November 12, 2018.²¹

Patient Population

All adult anesthesia cases (≥ 18 years of age) receiving an NMB agent by bolus or infusion occurring between January 1, 2014 and August 31, 2018 were eligible for inclusion. For patients undergoing multiple procedures during a 30-day period, only the index procedure was included. Exclusion criteria were American Society of Anesthesiologists (ASA) physical status 5 or 6, mechanical ventilation prior to operating room arrival, postoperative transportation directly to the intensive care unit, cardiac surgery, lung, or liver transplantation, cases receiving neostigmine or sugammadex to facilitate intraoperative neurologic monitoring, cases receiving a median positive end-expiratory pressure > 10 cm H₂O, cases with a diagnosis of myasthenia gravis or receiving pyridostigmine therapy, and cases with evidence of renal comorbidity (defined by Elixhauser comorbidity or preoperative estimated glomerular filtration rate of < 30 ml/min).^{22,23} Cases receiving both sugammadex and neostigmine for reversal were excluded from this analysis. Additionally, cases with implausible or inaccurately documented timestamps or where the location could not be accurately identified, were excluded.

Variables

Type of NMB agent was captured as a binary concept for each of the following - vecuronium, rocuronium, atracurium and cisatracurium. Total dose of non-depolarizing NMB agents was converted to effective dose to produce 95% depression of twitch height (ED₉₅) equivalents using the following ratios: 0.05 mg/kg for vecuronium, 0.3 mg/kg for rocuronium, 0.26 mg/kg for atracurium, and 0.05 mg/kg for cisatracurium per ideal body weight.²⁴ In cases of multiple NMB agent use, each drug was converted to an ED₉₅ equivalent and summed. To adjust for variation in procedure duration, the total ED₉₅ was divided by anesthesia duration hours.

The primary outcome was the administration of a NMB reversal agent. During the pre-sugammadex period, this included reversal with neostigmine. During the post-sugammadex period, reversal choices included sugammadex or neostigmine. Clinicians could also choose not to use a reversal agent (spontaneous recovery). Both the type of reversal and the count of reversal agent doses were captured. Sugammadex doses were categorized into the following dose ranges < 2, >2 to < 4, >4 to < 12, > 12 to < 16, > 16 mg/kg of actual body weight. Neostigmine doses were grouped into 1-20, 21-44, 45-55, 56-64, 65-75 and > 76 mcg/kg of actual body weight.

Covariates of interest included patient-level factors, such as age, height, weight, sex, ASA physical status, emergent status, World Health Organization (WHO) body mass index (BMI) category, and Elixhauser comorbidities defined by International Classification of Diseases, 9th and 10th edition discharge codes. Case-level covariates were surgical procedure defined by anesthesia Current Procedural Terminology (CPT) codes grouped by body region, admission type, number of documented train-of-four counts (TOF_c) last documented TOF_c prior to extubation, anesthesia type, primary in-room provider (faculty, Certified Registered Nurse Anesthetist (CRNA) or resident) and intraoperative timed events: time from last NMB dose to first reversal, time from first reversal to extubation, and time from last NMB to extubation. Peripheral nerve stimulators were used to provide qualitative measurement of

neuromuscular blockade. Institution-specific characteristics included university affiliation and number of days since the first sugammadex case. Additionally, participating institutions were asked whether any institution-specific protocols or restrictions regarding local use of sugammadex existed; responses were recorded as a Boolean yes or no.

Data sources/management

MPOG Registry—The MPOG infrastructure, described elsewhere,²⁵ consists of more than 40 hospitals across the United States and Europe routinely extracting enterprise-wide and departmental electronic health record and administrative data to the MPOG database. The MPOG centralized research database contains more than 11,000,000 detailed anesthesia records combined with long term outcome data – both from the enterprise and national data sources. These data also include preoperative assessment, laboratory values, surgeon and anesthesiology provider elements, and surgical procedure details. Clinical concepts are mapped from local electronic health record lexicons into standardized, interoperable MPOG variables, allowing comparison across centers. Additionally, the MPOG database incorporates administrative charge capture data - professional fee charge capture and hospital discharge diagnoses and procedures - from many participating institutions.

Bias Mitigation—To increase generalizability, this study utilized a robust, national, multi-center dataset, containing data from both academic medical centers and community health systems. To minimize information bias and measurement error, local data at each institution undergo rigorous diagnostic and validation processes prior to upload into the MPOG central database. More than 100 data quality and consistency checks are performed on the data at each center and attested to by a trained clinician or informatician. A random subset of cases is manually reviewed each month and compared to the source electronic health record and administrative data systems to ensure data quality and consistency.

Statistical Methods

All statistical analyses were performed using SAS® software, version 9.4 (Cary, NC). Missingness across covariates was tabulated. For continuous variables, normality and outliers were analyzed. Categorical variables were summarized with counts and frequencies; continuous variables were summarized by medians and interquartile ranges. Ninety-five percent confidence intervals were calculated.

To evaluate how practice patterns change over time with the introduction of a new medication, the distribution of cases by reversal category were plotted per month since the FDA approval of sugammadex on December 15, 2015. Despite the single time point of sugammadex FDA approval, each hospital goes through its own process to add a medication to inpatient formulary and make it available for use. The date of first documented sugammadex administration at each institution was recorded. Cases were divided into whether they occurred before sugammadex was available at each institution (pre-sugammadex period), 0-6 months after introduction of sugammadex (transitional period), and 6+ months after sugammadex was available (post-sugammadex period). Cases during the transitional period were excluded from analysis. Demographics, anthropometrics, comorbidities, and intraoperative management variables were reported by reversal agent.

Variation in NMB management prior to sugammadex availability and after 6 months of availability were compared using Pearson chi-square tests or Mann-Whitney U tests, as appropriate.

To explore factors associated with use of sugammadex for reversal of a nondepolarizing steroidal neuromuscular blockade (vecuronium or rocuronium), a multivariable mixed-effects logistic regression model was developed with the outcome of reversal with sugammadex versus neostigmine after sugammadex was available for at least 6 months. Only cases with complete data were included. Upon inspection of data and prior to analysis, Elixhauser comorbidities were missing in approximately twenty-one percent of cases, and thus a sensitivity analysis excluding them from the multivariable mixed-effects logistic regression model was performed. Collinearity diagnostics assessed independence across candidate variables; condition indices more than 30 and Pearson correlations more than 0.7 identified highly correlated covariates. All remaining covariates were entered into a non-parsimonious regression model as fixed effects to identify patient, procedural, and center covariates associated with reversal agent choice. Anesthesia duration was transformed using a log base 2 transformation prior to entering it in the model. A random effect for institution was included, as well as fixed effects for days since first case with sugammadex at the institution and whether the institution had restrictions on sugammadex use. Adjusted odds ratios with 95% confidence intervals and p-values were reported; a p-value of <0.05 denoted statistical significance.

Study Size

No a priori power analysis was conducted since all available patients meeting the inclusion and exclusion criteria were considered for analysis.

RESULTS

Among 1,247,739 adult index cases receiving a modern NMB agent available for study, a total of 934,798 met inclusion criteria (Figure 1) across 24 institutions. First documented administration of sugammadex occurred five months following its approval date, with gradual increase in clinical use over time (Figure 2). Table 1 illustrates the characteristics of the 337,596 cases reversed with neostigmine before sugammadex was available, the 174,695 cases reversed with neostigmine, and the 154,351 cases reversed with sugammadex starting 6 months after sugammadex was first used.

Supplemental Table 1 provides additional information on patient and case characteristics for the 421,754 cases included in the pre-sugammadex period, 127,075 cases included in the 0-6 month transitional period, and 385,969 cases included in 6+ month post-sugammadex group. Following the 6-month transition period, sugammadex became the reversal drug of choice in 40.0% (95% CI 39.8%-40.2%) of cases receiving NMB agents. During the same time period, neostigmine use fell from 80.1% (79.9%-80.2%) prior to sugammadex availability to 45.3% (45.1%-45.4%) of cases 6 months after availability (p-value<0.001), while spontaneous recovery decreased from 20.0% (19.8%-20.1%) to 14.8% (14.6%-14.9%) of cases (p<0.001). Figure 3 illustrates the inter-institutional variability in use of reversal agents during the post-sugammadex period. The majority of patients administered sugammadex

received a dose between 2-4 mg/kg (52.6%), with 6.1% of patients receiving doses >4 mg/kg (Table 1) and 36.0% (55,421) of sugammadex cases received a dose of exactly 200 mg.

Changes in the management of NMB included lower percentage of cases with no documented TOF monitoring, 28.9% (95% CI 28.8%-29.1%) of cases before vs 21.1% for sugammadex (20.9%-21.3%; $p<0.001$) and 24.2% (24.0%-24.5%; $p<0.001$) for neostigmine after. The overall amount of NMB administered (in ED95 equivalents) was 1.1 (IQR 0.8 - 1.5) for all patients before sugammadex introduction, and 1.2 (IQR 0.8 - 1.5) for neostigmine patients versus 1.3 (0.9 - 1.7) for sugammadex patients (Table 1 and Supplemental Table 2). The median doses of neostigmine were 41.2 mcg/kg (95% CI 31.9-50.4 mcg/kg) before vs 38.8 mcg/kg after (29.9-48.3 mcg/kg; $p<0.001$), however its use increased in cases with higher degree of neuromuscular recovery prior to reversal, 60.4% (60.2%-60.6%) of TOF 3-4 before vs 66.2% (66.0%-66.5%) after ($p<0.001$; Table 1).

In multivariable analysis (Table 2, Table 3 and Supplemental Table 3), compared to neostigmine, use of sugammadex was associated with patient age over 80 years (OR 1.83, 95% CI 1.71-1.95, $p<0.001$) compared to patients less than 41 years old; male sex (1.36, 1.32-1.39, $p<0.001$) compared to female sex; ASA 3/4 (1.13, 1.10-1.16, $p<0.001$) compared to ASA 1/2; Class III obesity (1.08, 1.03-1.13, $p=0.001$) compared to Normal weight; chronic pulmonary disease (1.06, 1.02-1.09, $p<0.001$); congestive heart failure (1.17, 1.07-1.28, $p<0.001$); major thoracic surgery (1.26, 1.13-1.39, $p<0.001$); TOF_c of 0-1 before reversal (4.06, 3.83-4.31, $p<0.001$) compared to TOF_c 3-4; TOF_c of 2 (2.45, 2.29-2.62, $p<0.001$) compared to TOF_c 3-4; and the amount of NMB administered (3.01, 2.88-3.16, $p<0.001$) for the highest ED95 quartile compared to the lowest quartile.

Cases performed outside of academic medical centers were associated with reduced use of sugammadex compared to those within (OR 0.06, 95% CI 0.02-0.23, $p<0.001$).

Sensitivity Analysis

Sensitivity analysis of mixed-effects logistic regression excluding Elixhauser comorbidities revealed similar results (Supplemental Table 4).

DISCUSSION

Our results confirm the initial hypothesis that individual hospitals would demonstrate wide variation in sugammadex use. Compared to non-university medical centers, university academic centers had significantly higher use of sugammadex. Our results also refuted our second hypothesis that sugammadex would be used only in a minority of eligible cases -- within a few months following FDA approval sugammadex was administered in 40% of cases, indicating broad early clinical adoption and utilization in NMB reversal.

Overall, across all centers sugammadex was used preferentially in cases with higher degrees of NMB prior to reversal and in patients with known risk factors for residual NMB or postoperative pulmonary complications.^{1,2,26} This suggests that despite the absence of definitive evidence linking sugammadex to improvement in clinical outcomes, providers are selecting it for patients who are at higher risk for postoperative complications due to limited

physiologic reserves and medical comorbidities (older patients, congestive heart failure, chronic obstructive pulmonary disease, obesity, ASA physical status classification 3 or 4), patients with higher degree of NMB prior for reversal, and patients undergoing surgical procedures that have been identified as high risk for postoperative respiratory complications.²⁶ This information provides useful context for creating clinical guidelines and protocols for selection of sugammadex as an appropriate reversal agent. For example, centers that had placed arbitrary restrictions on sugammadex use, may refine their protocols by benchmarking their recommendations with the patterns of sugammadex use across the 24 MPOG institutions included in this study. Following addition of sugammadex to the formulary in this cohort of hospitals, its actual use varied widely. For the majority of cases using sugammadex, the reversal doses have stayed between 2 mg/kg and 4 mg/kg, and the overall use of NMB agents has not changed, providing reassurance against earlier claims of major impacts on NMB management.²⁷ Some of the secondary changes observed in our study, such as a decrease in the number of cases without administration of any reversal agent and an increase in the use of NMB monitoring, are likely attributable to secular trends and increased awareness for risk factors for residual NMB. In a separate analysis of 12 MPOG centers, we recently observed an association between sugammadex use and improved postoperative pulmonary outcomes.¹⁷ These data need to be reproduced using other datasets, populations, and potentially, prospective randomized trials.

Although our study provides a broad perspective on the use of sugammadex in the US, it does have some limitations. In addition to the common limitations of a retrospective observational study, our design did not allow us to focus on the effects of policy or practice restrictions that may exist at the individual MPOG institutions participating in this study or the rates of compliance with such restrictions. Also we were unable to assess the patterns of sugammadex use outside standard guidelines or in special clinical scenarios.²⁸ However, we used a well-established methodology that included a very large sample size to describe patterns of sugammadex use following its introduction to the US market. In addition, the sampling bias associated with a focus on MPOG hospitals limits the ability to extend these data to all hospitals. However, the integration of non-university and university academic hospital data in MPOG does provide some generalizability.

In summary, the data and analysis presented in this study represent a broad view on how sugammadex is used in current clinical anesthesia practice in the US. This information is useful for individual anesthesia providers and groups looking to benchmark their use of sugammadex nationally. It supplies information that allows for realistic estimation of economic impact for hospitals that are looking to introduce sugammadex to their drug formularies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY OF TERMS

AIDS	acquired immune deficiency syndrome
ASA	American Society of Anesthesiologists

BMI	body mass index
CPT	Current Procedural Terminology
CRNA	Certified Registered Nurse Anesthetist
ED95	effective dose to produce 95% depression of twitch height
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IRB	Institutional Review Board
MPOG	Multicenter Perioperative Outcomes Group
NMB	neuromuscular blockade
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TOFc	Train of four count
US	United States
WHO	World Health Organization

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KEY POINTS

QUESTION: What patient, procedure, and provider factors are associated with the use of sugammadex as a neuromuscular reversal agent?

FINDINGS: Compared to neostigmine, sugammadex use is associated with patient age, ASA 3 or 4, Class III obesity, chronic pulmonary disease, congestive heart failure, major thoracic surgery, higher degree of neuromuscular blockade prior to reversal and the amount of NMB agent administered.

MEANING: Following its introduction to the US market, sugammadex is preferentially selected for patients with greater burden of comorbidities and known risk factors for residual blockade or pulmonary complications.

Figure 1.
Study population.

Figure 2.

Patterns of neuromuscular blockade reversal across 24 hospitals by month; Food and Drug Administration approval of sugammadex on December 15, 2015 indicated by dashed line.

Figure 3. Patterns of neuromuscular blockade reversal across 24 anonymized hospitals, during the post-sugammadex period per institution (pattern denotes non-university affiliated institution and solid denotes university affiliated institution).

Table 1.

Patient characteristics stratified by reversal agent, N=666,642 cases.

Covariate	Cases before sugammadex		Cases 6+ months after sugammadex was available			
	Neostigmine		Neostigmine		Sugammadex	
	N=337,596		N=174,695		N=154,351	
	N	%	N	%	N	%
Female sex	195,661	58.0%	103,415	59.2%	83,511	53.1%
ASA 1 or 2	185,508	55.0%	92,608	53.1%	75,783	49.3%
ASA 3 or 4	151,627	45.0%	81,749	46.9%	77,985	50.7%
Pulmonary disease	3,616	1.4%	1,715	1.2%	2,341	1.9%
Cardiac arrhythmias	22,695	8.8%	14,541	10.2%	14,573	11.6%
Thoracic surgery	36,271	10.7%	19,037	10.9%	17,276	11.2%
Abdominal surgery	129,902	38.5%	64,234	36.8%	53,835	34.9%
University Institution	229,925	68.1%	112,955	64.7%	147,156	95.3%
Last TOFc before extubation						
Not documented	97,569	28.9%	42,353	24.2%	32,619	21.1%
0 or 1 twitches	11,320	3.4%	3,701	2.1%	11,626	7.5%
2 twitches	8,685	2.6%	3,359	1.9%	6,725	4.4%
3 or 4 twitches	203,891	60.4%	115,703	66.2%	76,385	49.5%
Sustained tetany	16,131	4.8%	9,579	5.5%	26,996	17.5%
Neostigmine Dose						
1-20 mcg/kg	19,470	5.8%	12,158	7.0%	-	-
21-44 mcg/kg	178,508	52.9%	102,628	58.8%	-	-
45-55 mcg/kg	79,717	23.6%	35,886	20.5%	-	-
56-64 mcg/kg	27,236	8.1%	11,533	6.6%	-	-
65-75 mcg/kg	14,615	4.3%	5,870	3.4%	-	-
76+ mcg/kg	6,798	2.0%	2,696	1.5%	-	-
Missing or Invalid Data	11,252	3.3%	3,924	2.3%	-	-
Sugammadex Dose						
2 mg/kg	-	-	-	-	53,664	34.8%
>2 to 4 mg/kg	-	-	-	-	81,233	52.6%
>4 to <12 mg/kg	-	-	-	-	9,398	6.1%
12 to <16 mg/kg	-	-	-	-	52	0%
16 mg/kg	-	-	-	-	61	0%
Missing or Invalid Data		-	-	-	9,943	6.4%
	Median	IQR	Median	IQR	Median	IQR
Age	54	[40, 66]	54	[40, 66]	56	[42, 67]
BMI	28.1	[24.2, 33.3]	28.3	[24.4, 33.5]	28.2	[24.3, 33.4]
ED 95 of NMB ^a	1.1	[0.8, 1.5]	1.2	[0.8, 1.5]	1.3	[0.9, 1.7]

	Cases before sugammadex		Cases 6+ months after sugammadex was available			
Covariate	Neostigmine		Neostigmine		Sugammadex	
	N=337,596		N=174,695		N=154,351	
	N	%	N	%	N	%
Neostigmine Dose ^b	41.2	[31.9, 50.4]	38.8	[29.9, 48.3]	-	-
Sugammadex Dose ^b	-	-	-	-	2.0	[2.0, 2.5]

^a Per hour of case duration

^b Mcg per kg of actual body weight

ASA = American Society of Anesthesiologists; ED95 = effective dose to produce 95% depression of twitch height; NMB = neuromuscular blockade; TOFc = train-of-four count.

Table 2.

Statistically significant patient and procedural covariates from the mixed-effects logistic regression model predicting odds of reversal with sugammadex versus neostigmine, controlling for institution, N=246,790 cases (n=133,777 neostigmine, n=113,013 sugammadex), 6 months after sugammadex was introduced at each institution.

Covariate	Adjusted Odds Ratio	Adjusted 95% Lower Confidence Interval	Adjusted 95% Upper Confidence Interval	Adjusted p-value
Age 41-50 (reference Age <41)	1.22	1.17	1.26	<0.001
51-60	1.42	1.37	1.47	<0.001
61-70	1.54	1.48	1.59	<0.001
71-80	1.64	1.57	1.72	<0.001
81-90+	1.83	1.71	1.95	<0.001
Male Sex	1.36	1.32	1.39	<0.001
ASA Status 3 or 4 ^a (reference ASA Status 1 or 2)	1.13	1.10	1.16	<0.001
Emergent Surgery	1.09	1.04	1.14	<0.001
Underweight WHO ^b BMI ^c (reference Normal)	1.20	1.11	1.30	<0.001
Overweight	0.90	0.88	0.93	<0.001
Class I	0.90	0.87	0.93	<0.001
Class II	0.95	0.91	0.99	0.009
Class III	1.08	1.03	1.13	0.001
AIDS/HIV Elixhauser Comorbidity	1.34	1.05	1.73	0.020
Cardiac Arrhythmias	1.05	1.01	1.09	0.021
Chronic Pulmonary Disease	1.06	1.02	1.09	<0.001
Congestive Heart Failure	1.17	1.07	1.28	<0.001
Drug Abuse	1.15	1.06	1.24	<0.001
Fluid/Electrolyte Disorders	1.10	1.05	1.15	<0.001
Hypertension (uncomplicated)	1.12	1.09	1.15	<0.001
Hypothyroidism	1.04	1.00	1.08	0.034
Liver Disease	1.16	1.09	1.23	<0.001
Metastatic Cancer	1.09	1.04	1.14	<0.001
Paralysis	1.32	1.18	1.47	<0.001
Pulmonary Circulation Disorders	1.20	1.10	1.32	<0.001
Rheumatoid / Collagen Vascular Diseases	1.13	1.06	1.22	0.001
Solid Tumor	1.09	1.06	1.13	<0.001
Weight Loss	1.20	1.12	1.27	<0.001
Non-outpatient Admission Type	1.06	1.03	1.09	<0.001
Head/Neck Major Procedure Type	1.12	1.01	1.24	0.028
Thorax Major	1.26	1.13	1.39	<0.001
Thorax Minor	0.70	0.62	0.77	<0.001

Covariate	Adjusted Odds Ratio	Adjusted 95% Lower Confidence Interval	Adjusted 95% Upper Confidence Interval	Adjusted p-value
Spine/Spinal Cord Major	0.64	0.58	0.71	<0.001
Upper & Lower Abdomen Major	0.68	0.62	0.75	<0.001
Urologic/Gynecologic Major	0.74	0.67	0.82	<0.001
Hip/Leg/Foot/Shoulder/Arm/Hand Major	0.56	0.50	0.62	<0.001
Hip/Leg/Foot/Shoulder/Arm/Hand Minor	0.68	0.61	0.75	<0.001
Radiologic Major	1.29	1.14	1.47	<0.001

^a ASA = American Society of Anesthesiologists

^b WHO = World Health Organization

^c BMI = body mass index

Intraoperative covariates from this integrated model are reported in Table 3.

Table 3.

Statistically significant intraoperative covariates from the mixed-effects logistic regression model predicting odds of reversal with sugammadex versus neostigmine, controlling for institution, N=246,790 cases (n=133,777 neostigmine, n=113,013 sugammadex), 6 months after sugammadex was introduced at each institution.

Covariate	Adjusted Odds Ratio	Adjusted 95% Lower Confidence Interval	Adjusted 95% Upper Confidence Interval	Adjusted p-value
Last TOFc ^a before extubation (reference 3 or 4 twitches)				
Not documented	0.94	0.91	0.97	<0.001
0 or 1 twitches	4.06	3.83	4.31	<0.001
2 twitches	2.45	2.29	2.62	<0.001
Sustained tetany	1.87	1.79	1.95	<0.001
GA, no volatile or nitrous oxide	1.51	1.43	1.59	<0.001
GA, with nitrous oxide	0.48	0.44	0.54	<0.001
Resident/Fellow In-Room Provider (reference Faculty Only)	1.29	1.23	1.35	<0.001
CRNA ^b	0.79	0.76	0.83	<0.001
NMB ^c Agent (reference Rocuronium only)				
Vecuronium	1.43	1.38	1.49	<0.001
Vecuronium and Rocuronium	0.98	0.92	1.04	0.459
ED 95 ^d of NMB ^c per hour of case duration (reference Quartile 1)				
Quartile 2	1.23	1.18	1.28	<0.001
Quartile 3	1.65	1.58	1.72	<0.001
Quartile 4 (high)	3.01	2.88	3.16	<0.001
Non-university medical center	0.06	0.02	0.23	<0.001
Institutional Restrictions on Sugammadex	1.10	0.29	4.22	0.891
Days since first sugammadex case (quarterly interval)	1.20	1.19	1.20	<0.001
Log base 2 transformed anesthesia duration (minutes)	1.28	1.25	1.30	<0.001
Time from last NMB ^c to first reversal (15 minute interval)	0.95	0.95	0.96	<0.001

^a.TOFc = train-of-four count

^b.CRNA = Certified Registered Nurse Anesthetist

^c NMB = neuromuscular blockade

^d ED₉₅ = effective dose to produce 95% depression of twitch height

Patient and procedural covariates from this integrated model are reported in Table 2.

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