Adv Ther (2021) 38:4736–4755
https://doi.org/10.1007/s12325-021-01835-2

ORIGINAL RESEARCH

Neuromuscular Blockade and Reversal Agent Practice Variability in the US Inpatient Surgical Settings

Lori D. Bash · Vladimir Turzhitsky · Wynona Black · Richard D. Urman

Received: May 16, 2021 / Accepted: June 18, 2021 / Published online: July 28, 2021

ABSTRACT

Introduction: The management of neuromuscular blockade (NMB) has evolved over time and remains a critical component of general anesthesia. However, NMB use varies by patient and procedural characteristics, clinical practices, protocols, and drug access. National utilization patterns are unknown. We describe changes in NMB and NMB reversal agent administration in surgical inpatients since the US introduction of sugammadex in December 2015.

Methods: In a retrospective observational study of inpatients involving NMB with rocuronium or vecuronium in the Premier Healthcare Database, we estimate associations between factors related to choice of (1) active NMB reversal versus spontaneous recovery and (2) sugammadex versus neostigmine as the reversal agent.

Results: Among 4.3 million adult inpatient encounters involving rocuronium or vecuronium, the most widely administered NMB agent was rocuronium alone (86%). Over time, gradual declines in both neostigmine use and spontaneous reversal were observed (64% and 36% in 2014 to 38% and 28%, respectively in the first half of 2019). Several factors were independently associated with use of active versus spontaneous NMB recovery including years since 2016, patient (age, race, comorbidities), and procedure (admission and surgery type) characteristics. Among those actively reversed, these and other factors were independently associated with choice of reversal agent administered, including size and teaching affiliation of hospital. While both impacted choices in treatment, the direction and magnitude of effect of patient comorbidities and procedure type varied in their impact on choice of mode (pharmacologic vs. spontaneous) and agent (neostigmine vs. sugammadex) of NMB reversal independent of other factors and each other. Sites which adopted sugammadex earlier were more likely to choose sugammadex over neostigmine compared with later adopters independent of other factors.

Conclusions: Among US adult inpatients administered NMBs, we observed complex relationships between patient, site, procedural characteristics, and NMB management choices

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-021-01835-2.

L. D. Bash
Merck & Co., Inc., Kenilworth, NJ, USA

V. Turzhitsky · W. Black
Merck & Co., Inc., Boston, MA, USA

R. D. Urman (✉)
Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115, USA
e-mail: rurman@bwh.harvard.edu

as NMBA choice and active reversal options among inpatient cases changed over time.

PLAIN LANGUAGE SUMMARY

Neuromuscular blocking agents, medications that temporarily paralyze muscles, are used frequently during surgical procedures to facilitate intubation and patient immobility. Over time, muscle function can return spontaneously or through pharmacological reversal agents. This study looked at how the use of reversal agents in inpatients undergoing surgical procedures changed after a new reversal agent, sugammadex, became available for use in the USA in December 2015.

Medical records of 4.3 million adult patients treated with neuromuscular blocking agents (rocuronium or vecuronium) in the USA were studied. In 2014 (before sugammadex was available), one-third of patients (36%) recovered spontaneously from a neuromuscular blocking agent and two-thirds (64%) were treated with the reversal agent neostigmine. The use of both neostigmine and spontaneous recovery reduced gradually after sugammadex became available, so that by the first half of 2019, 38% of patients were treated with neostigmine and 28% of patients recovered spontaneously.

Whether or not a patient was treated with a reversal agent and what type of agent was chosen were affected by the length of time since 2016, patient characteristics, the type of surgical procedure that was performed as well as local hospital characteristics and practice differences.

Keywords: Anesthesia; Inpatients; Neostigmine; Neuromuscular blockade; Rocuronium; Sugammadex

Key Summary Points

The management of neuromuscular blockade (NMB) is a critical component of general anesthesia, though national utilization patterns are not well known.

A retrospective analysis of US adult inpatients who underwent surgical procedures using neuromuscular blockade (NMB) with rocuronium and/or vecuronium between January 2014 and June 2019 was conducted to better understand how the utilization of NMB agents has changed over time in the US inpatient setting.

Among US adult inpatients administered NMBs, we observed complex relationships between patient, site, procedural characteristics, and NMB management choices as NMBA choice and active reversal options among inpatient cases changed over time.

These findings help us to better understand the anesthesia trends in the inpatient setting which will continue to change over time, particularly with the ongoing shift in care to the outpatient setting.

DIGITAL FEATURES

This article is published with digital features, including a plain language summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14807928.

INTRODUCTION

Inpatient surgical procedures are performed less often than outpatient procedures (42.2% vs. 57.8% in the USA) [1], and this increasingly will be the case with growing trends towards more outpatient surgery over inpatient [1–4]. This trend will not be universal; patients undergoing inpatient surgeries often have acute illnesses or comorbidities [5]. As a result of the inherent higher-risk nature of many inpatient surgeries and the patient population, inpatient surgeries remain associated with worse outcomes and longer recovery times relative to outpatient procedures [1].

Neuromuscular blocking agents (NMBAs) are components of balanced general anesthesia [6], facilitating intubation and ensuring patient immobility to help optimize surgical conditions. In practice, the choice of NMB reversal agent is dependent on patient and procedure requirements such as the time to onset, depth, and duration of neuromuscular blockade (NMB) [6–8]. At the end of the procedure, patients may be allowed to spontaneously recover neuromuscular function, or may be administered a pharmacological NMB reversal agent for more rapid recovery of neuromuscular function. Complete reversal of NMB is important as residual NMB in the post-anesthesia care unit (PACU) may increase the risk of complications, including serious pulmonary complications [9–12].

Sugammadex, a modified gamma-cyclodextrin, reverses NMB induced by rocuronium or vecuronium by encapsulation [13]. Recent studies have demonstrated that sugammadex provides a more rapid, predictable, and safe reversal of NMB [14] with reduced incidence of residual NMB [15] and reduced risk of adverse events related to the acetylcholinesterase inhibitor neostigmine [14, 16–19]. There is a need to evaluate the use of NMBAs as part of balanced anesthesia and the use of NMB reversal methods for recovery, to gain a better understanding of healthcare resource utilization patterns in the inpatient setting. Since the US Food and Drug Administration (FDA) approval of sugammadex on December 15, 2015 [20], practice patterns within inpatient settings have changed. While sugammadex may be recognized as the preferred therapy because of its better safety and efficacy [14], it may not be universally adopted as the preferred agent in clinical practice because of its higher cost compared with generic neostigmine. Limited utilization data for NMB and reversal agents use since 2015 have indicated changes in practice patterns in the USA [21]. However, trends and variation in the choices made in NMB management, including the use of sugammadex in the broader US community inpatient surgical settings since the market availability of the drug [20], remain unclear. We sought to (1) describe the real-world temporal trends associated with the use of NMBAs and NMB reversal agents in adults undergoing procedures in the US hospital inpatient setting and (2) identify factors associated with the choice to pharmacologically reverse non-depolarizing NMB and, specifically, the choice of NMB reversal agent among those that are pharmacologically reversed.

METHODS

Study Design

This was a retrospective longitudinal analysis of a national electronic healthcare database (Premier Healthcare Database [PHD]) of US adult (at least 18 years of age) inpatient surgical data. The Premier Healthcare Database is considered exempt from institutional review board (IRB) oversight as dictated by Title 45 Code of Federal Regulations, Part 46 of the USA, specifically 45 CFR 46.101(b)(4). In accordance with the HIPAA Privacy Rule, disclosed data from the PHD are considered de-identified per 45 CFR 164.514(b)(1) through the "Expert Determination" method. This study was also reviewed and approved by the Mass General Brigham IRB (Protocol # 2021P001328), which determined that the study does not classify as human subjects research.

This analysis was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22]. NMB and reversal patterns were examined for the pre-sugammadex period (prior to FDA approval of sugammadex [December 2015]), and the post-sugammadex period (after sugammadex was available at participating PHD hospital sites). Primary study outcomes included administration of NMBA and utilization of NMB reversal agent (sugammadex or neostigmine) in patients receiving non-depolarizing neuromuscular blockade agents (vecuronium or rocuronium, with or without succinylcholine). Further, among those administered rocuronium and/or vecuronium, we evaluated the association of patient, procedure, and provider characteristics with NMB reversal choices.

Patient Population

All adult cases undergoing general anesthesia and receiving NMBA by bolus or infusion, between January 1, 2014 and June 30, 2019 were eligible for the study. Patients with renal failure, myasthenia gravis, or those receiving pyridostigmine therapy were excluded. Patients administered NMB with rocuronium or vecuronium were included, and patients administered a neuromuscular block reversal agent (NMBRA) with both sugammadex and neostigmine were excluded from the main analyses evaluating reversal agent use.

Variables

Patient demographics and clinical characteristics were captured for each eligible patient (e.g., age, sex, comorbidities) and site characteristics (hospital size/number of beds, geographic and census region, urban/rural) were described for each encounter. Surgical procedures were categorized by body region, based on the ICD-PCS (International Classification of Disease Procedure Coding System), classified by the Clinical Classifications Software (CCS) developed by the Healthcare Cost and Utilization Project (HCUP) for ICD-PCS (ICD-10) after October 1, 2015 and ICD-9 prior to October 2015. Primary ICD codes were used for each encounter, and grouped on the basis on their CCS1 category: those missing any ICD procedure code, or falling within CCS1 of obstetrical procedure (used as the closest proxy as no variable for “pregnant” was available; there is neither clinical trial data on the use of sugammadex in pregnant women nor is there any relevant data on lactating women/ human milk [20]) or miscellaneous, were excluded. Remaining CCS1 categories were combined when the procedures were likely to be completed by the same clinical specialty (Supplementary Table 1 includes most frequently observed primary ICD-PCS codes within each surgical category). This resulted in each encounter being classified into one of ten procedure categories.

Data Source

The PHD is a large, US hospital-based, service-level, all-payer database of information on outpatient encounters and inpatient discharges, from non-profit, non-governmental, community and teaching hospitals. Data are derived from member hospital statistics provided through a combination of self-reporting and the American Hospital Association Annual Survey Database™ and comprise information on over 10 million inpatient admissions per year since 2012 [23]. This is estimated to cover approximately 25% of all US inpatient admissions. Patient data are de-identified and Health Insurance Portability and Accountability Act (HIPAA)-compliant.

Analysis

NMBA utilization patterns were reported over time descriptively by patient characteristics, site characteristics, and procedure type. Utilization patterns of NMB reversal options (i.e., active pharmacologic reversal [sugammadex or neostigmine] versus spontaneous recovery) were assessed among patients treated with rocuronium or vecuronium (with or without succinylcholine).

Multivariable logistic regression analyses assessed the independent association of patient, site, and procedure characteristics with NMB reversal choice. Adjusted odds ratios (OR), 95% confidence intervals (CI), and *P* values were reported for the likelihood of a patient being administered active pharmacologic (either sugammadex or neostigmine) versus spontaneous NMB reversal for the entire period 2014–2019. After preliminary results showed differential associations by region, further stratification was done to assess potential for interaction. In our

Table 1 Patient characteristics by neuromuscular blockade agent reversal method

	Overall		**Neostigmine**		**Sugammadex**		**Spontaneous reversal**	
	***N* = 4,263,658**	**%**	***N* = 2,333,762**	**%**	***N* = 528,736**	**%**	***N* = 1,401,160**	**%**
Patient characteristics								
Age								
Mean (SD)	58.2 (16.56)		57.6 (16.62)		59.0 (16.49)		58.8 (16.45)	
Age range								
18–30	313,904	7.4	177,437	7.6	35,484	6.71	100,983	7.21
31–40	395,318	9.3	230,396	9.87	47,538	8.99	117,384	8.38
41–50	575,850	13.5	333,542	14.29	68,052	12.87	174,256	12.44
51–60	887,726	20.8	483,335	20.71	107,014	20.24	297,377	21.22
61–70	1,044,013	24.5	557,963	23.91	132,193	25	353,857	25.25
71–80	722,225	16.9	381,183	16.33	94,477	17.87	246,565	17.6
80+	324,622	7.6	169,906	7.28	43,978	8.32	110,738	7.9
Sex								
Female	2,357,026	55.3	1,355,626	58.09	296,475	56.07	704,925	50.31
Male	1,904,508	44.7	976,841	41.86	232,246	43.92	695,421	49.63
Unknown	2124	0.0	1295	0.06	15	0	814	0.06
Race								
Black	429,017	10.1	249,730	10.7	49,128	9.29	130,159	9.29
Other/missing	490,011	11.5	271,645	11.64	49,350	9.34	168,996	12.06
White	3,344,650	78.4	1,812,387	77.66	430,258	81.37	1,102,005	78.65
Hispanic								
No/missing	3,965,095	93.0	2,175,836	93.23	482,687	91.29	1,306,572	93.25
Yes	298,563	7.0	157,926	6.77	46,049	8.71	94,588	6.75
Comorbidities								
Comorbidities $\geq$ 1	3,351,656	78.6	1,778,152	76.19	424,106	80.21	1,149,398	82.03
Blood loss anemia	47,309	1.1	26,302	1.13	5484	1.04	15,523	1.11
Cardiac arrhythmias	721,439	16.9	321,049	13.76	79,570	15.05	320,820	22.9
Chronic pulmonary disease	811,014	19.0	411,185	17.62	102,611	19.41	297,218	21.21
Coagulopathy	121,667	2.9	44,892	1.92	7826	1.48	68,949	4.92
Congestive heart failure	260,761	6.1	95,724	4.1	31,380	5.93	133,657	9.54
Diabetes (complicated)	247,869	5.8	104,993	4.5	39,644	7.5	103,232	7.37

Table 1 continued

	Overall		Neostigmine		Sugammadex		Spontaneous reversal	
	N = 4,263,658	%	*N* = 2,333,762	%	*N* = 528,736	%	*N* = 1,401,160	%
Diabetes (uncomplicated)	642,395	15.1	347,480	14.89	71,145	13.46	223,770	15.97
Drug abuse	170,018	4.0	68,709	2.94	17,878	3.38	83,431	5.95
Fluid/electrolyte disorders	847,306	19.9	366,604	15.71	90,698	17.15	390,004	27.83
Hypertension (complicated)	151,208	3.5	50,959	2.18	29,217	5.53	71,032	5.07
Obesity, overweight	935,581	21.9	526,920	22.58	130,645	24.71	278,016	19.84
Other neurological disorders	323,607	7.6	115,946	4.97	33,177	6.27	174,484	12.45
Paralysis	86,863	2.0	35,261	1.51	10,629	2.01	40,973	2.92
Peripheral vascular disorders	310,192	7.3	149,854	6.42	39,733	7.51	120,605	8.61
Pulmonary circulation disorders	99,480	2.3	36,869	1.58	9863	1.87	52,748	3.76
Solid tumor without metastasis	424,701	10.0	247,446	10.6	70,514	13.34	106,741	7.62
Sleep apnea	353,738	8.3	188,859	8.09	49,207	9.31	115,672	8.26
Valvular disease	255,501	6.0	98,767	4.23	24,490	4.63	132,244	9.44
Weight loss	214,827	5.0	95,734	4.1	27,496	5.2	91,597	6.54
Procedure characteristics								
ICD-10 PCS classification								
Cardiovascular	520,482	12.2	187,575	8.04	49,689	9.4	283,218	20.21
Digestive	1,213,034	28.5	815,072	34.93	173,702	32.85	224,260	16.01
Endocrine	21,251	0.5	10,896	0.47	2460	0.47	7895	0.56
ENT	27,517	0.6	11,273	0.48	3750	0.71	12,494	0.89
Eye	2838	0.1	1381	0.06	483	0.09	974	0.07
Female genital	230,611	5.4	161,418	6.92	25,996	4.92	43,197	3.08
Integumentary, hemic, and lymphatic	146,206	3.4	71,769	3.08	19,750	3.74	54,687	3.9
Respiratory	158,834	3.7	82,171	3.52	25,691	4.86	50,972	3.64
Musculoskeletal and nervous	1,530,397	35.9	837,597	35.89	189,484	35.84	503,316	35.92

Table 1 continued

	Overall		Neostigmine		Sugammadex		Spontaneous reversal	
	N = 4,263,658	%	*N* = 2,333,762	%	*N* = 528,736	%	*N* = 1,401,160	%
Urinary and male genital	172,583	4.0	107,229	4.59	24,563	4.65	40,791	2.91
Others/unknown/ missing	239,905	5.6	47,381	2.03	13,168	2.49	179,356	12.8
Site characteristics								
Teaching								
No	2,138,450	50.2	1,173,622	50.29	253,138	47.88	711,690	50.79
Yes	2,125,208	49.8	1,160,140	49.71	275,598	52.12	689,470	49.21
Urban, rural								
Rural	425,823	10.0	218,987	9.38	54,250	10.26	152,586	10.89
Urban	3,837,835	90.0	2,114,775	90.62	474,486	89.74	1,248,574	89.11
Bed size								
0–99	167,959	3.9	94,217	4.04	17,581	3.33	56,161	4.01
100–199	482,414	11.3	279,131	11.96	55,991	10.59	147,292	10.51
200–299	650,669	15.3	380,053	16.28	53,510	10.12	217,106	15.49
300–399	687,451	16.1	369,556	15.84	93,105	17.61	224,790	16.04
400–499	620,399	14.6	351,214	15.05	67,742	12.81	201,443	14.38
500+	1,654,766	38.8	859,591	36.83	240,807	45.54	554,368	39.56
Census region								
Midwest	950,357	22.3	510,908	21.89	154,854	29.29	284,595	20.31
Northeast	526,340	12.3	318,398	13.64	51,340	9.71	156,602	11.18
South	2,034,434	47.7	1,132,230	48.52	239,772	45.35	662,432	47.28
West	752,527	17.6	372,226	15.95	82,770	15.65	297,531	21.23

ICD PCS International Classification of Disease Procedure Classification, *ENT* ear, nose, throat procedures

first model (model 1), we assessed characteristics related to active (i.e., pharmacological) reversal via administration of any reversal agent (sugammadex or neostigmine) versus spontaneous NMB recovery overall (model 1a), and by geographic region (model 1b). Our second model (model 2) examined the association of these factors with the choice of pharmacological reversal agent (sugammadex versus neostigmine) among the subset of patients receiving active reversal, overall (model 2a) and by geographic region (model 2b) for the period after which sugammadex was available (December 2015 to June 2019), and for sites in which sugammadex was available. An additional analysis investigating the effect of earlier institutional utilization of sugammadex on the reversal choice was conducted on encounters where pharmacologic reversal was used in order to understand the impact of early clinical adoption on the choice of NMB reversal agent. In this model (model 2c), the year of first institutional use of sugammadex was included among the independent variables (i.e., early [2016] versus late [2018] adoption of sugammadex), removing calendar year (due to collinearity). This model only included encounters taking place at sites (in which sugammadex was available and) with continuous presence in the PHD dataset (in the period 2016–2019).

All statistical analyses were performed using SAS® software, version 9.4 (Cary, NC, USA).

RESULTS

Study Population

A total of 930 clinical sites and 4,825,660 total inpatient encounters included the use of any NMB, and 92.3% of those encounters included administration of rocuronium and/or vecuronium. Among those, 4,263,658 inpatient encounters across 927 sites met all inclusion criteria and were the focus of these analyses. Most sites were smaller (79% with fewer than 400 beds), urban (71%), and nonacademic (70%) (Supplementary Table 2). More than half (60%) of the sites adopted clinical use of sugammadex within its first 2 years of availability, while 22% in the PHD database remained non-adopters as of the data cut in June 2019.

Patient characteristics for encounters involving rocuronium or vecuronium are summarized in Table 1. On average, patients were 58.2 years old (median IQR, 60 [47, 70]), more often women (55.3%), White (78.4%), non-Hispanic (93.0%), and most (78.6%) had at least one comorbidity. Obesity/overweight status (21.9%), diabetes (15.1%), electrolyte disorders (19.9%), chronic pulmonary disease (19.0%), and cardiac arrhythmias (16.9%) were among those most commonly reported. Most inpatient cases were from urban areas (90%) and treated in large (400+ beds) hospitals (53.4%), and about half (49.8%) were from academic sites (Supplementary Fig. 1, Table 1). The most frequently reported procedures performed were musculoskeletal (35.9%), digestive (28.5%), or cardiovascular (12.2%) in nature (Table 1, Supplementary Table 1).

Utilization Patterns of NMBAs and NMB Reversal Agents

Throughout 2014 to 2019, rocuronium alone was used in the vast majority (83.6–90.3%) of inpatient cases. Vecuronium alone or rocuronium/vecuronium with succinylcholine was each used in less than 10% of cases (Fig. 1a). The trends in NMB reversal approach included gradual declines in neostigmine use (64% in 2014 to 38% by June 2019) and spontaneous recovery (36.5% in 2014 to 27.6% by June 2019). Sugammadex use was reported in 4.6% of cases in 2016, which increased to 34.2% of all inpatient cases 3 years later, by June 2019 (Fig. 1b).

Both the age of the population and the proportion of elderly patients increased modestly over time (2014 to June 2019), and across all modes of reversal (Fig. 2a). Though the distributions of age groups by reversal type and reversal choice by age group were similar, in concurrent years, those reversed with sugammadex tended to more often be older than the neostigmine population and younger than those spontaneously reversed. Most were at least 50 years old; 72% of patients who spontaneously recovered were over 50 years old compared to 71.4% reversed with sugammadex and 68.2% reversed with neostigmine (Table 1). The neostigmine population tended to have the greatest proportion of young patients, with 17.5% of the population age 18–40, compared to 15.6% among the spontaneously reversed (Table 1). Over time, the proportion of patients with one or more comorbidities increased (75.7% in 2014 increasing to 82.5% by June 2019). The proportion of patients with comorbidities increased modestly across all NMB reversal modes, with increases standing out among complicated diabetes (with relatively steady rates of total diabetes), solid tumor, and obesity (Fig. 2b). The difference in distributions of comorbidities by NMB reversal mode varied

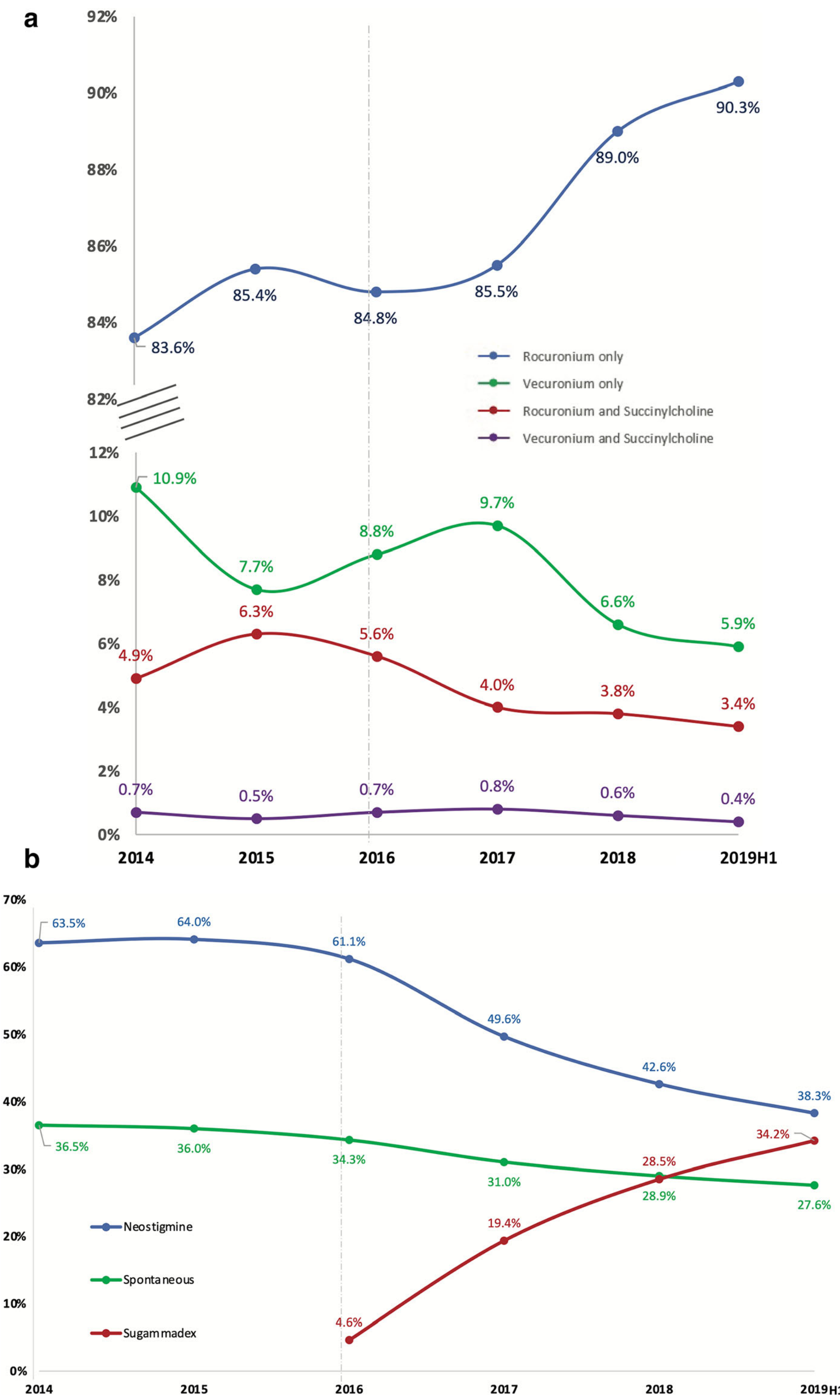

Fig. 1 Anesthesia practice trends over time in US adult inpatient surgical procedures (2014–2019): **a** NMB and **b** NMB reversal agents. Food and Drug Administration approval of sugammadex on December 15, 2015 is represented by the vertical dashed line. NMB neuromuscular blockade

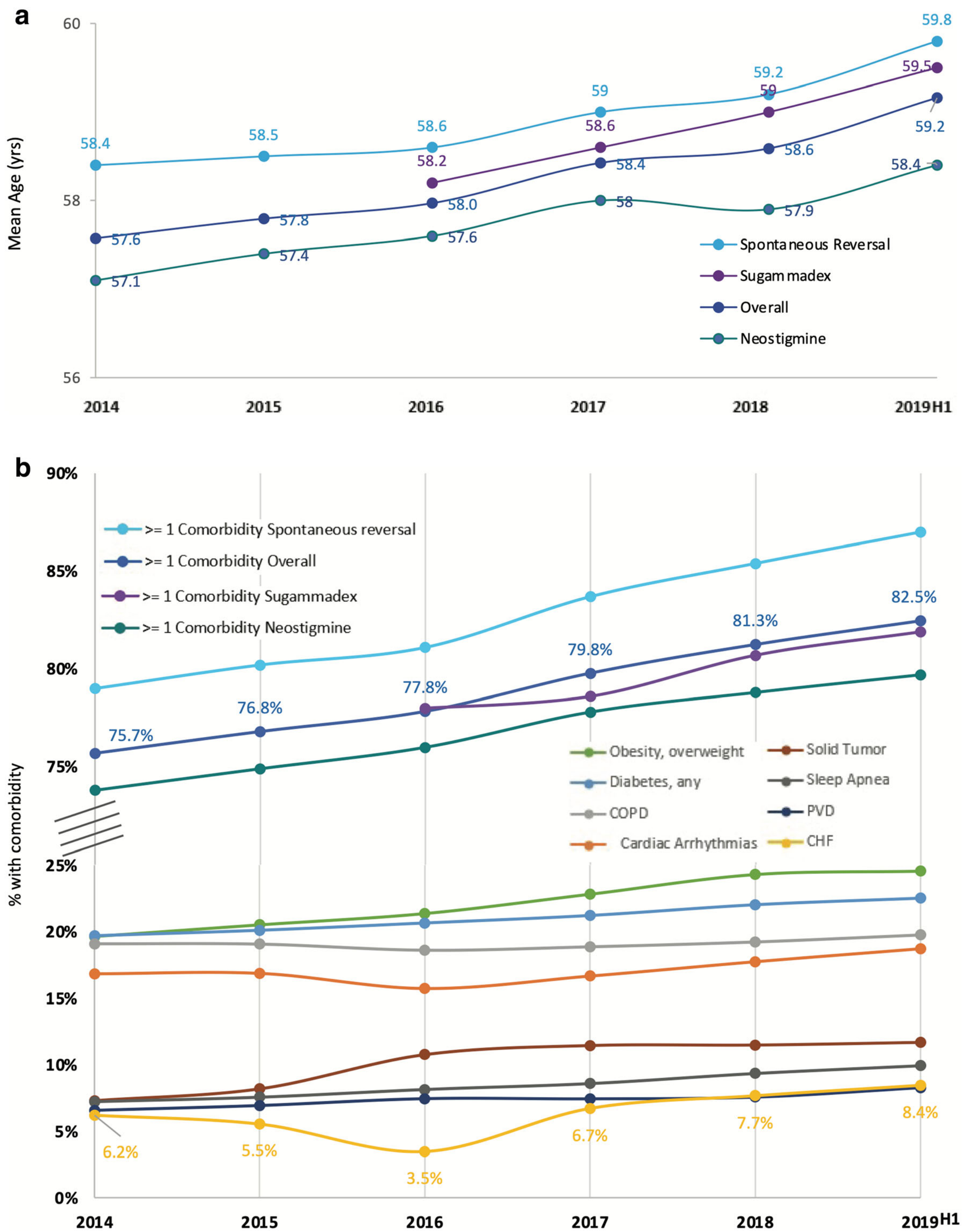

Fig. 2 US adult surgical inpatient characteristics over time (2014–2019) and by NMBRA: **a** age and **b** comorbidities

Fig. 3 NMB reversal trends over time and by **a** age, **b** comorbidity, and **c** procedure type. NMB neuromuscular blockade

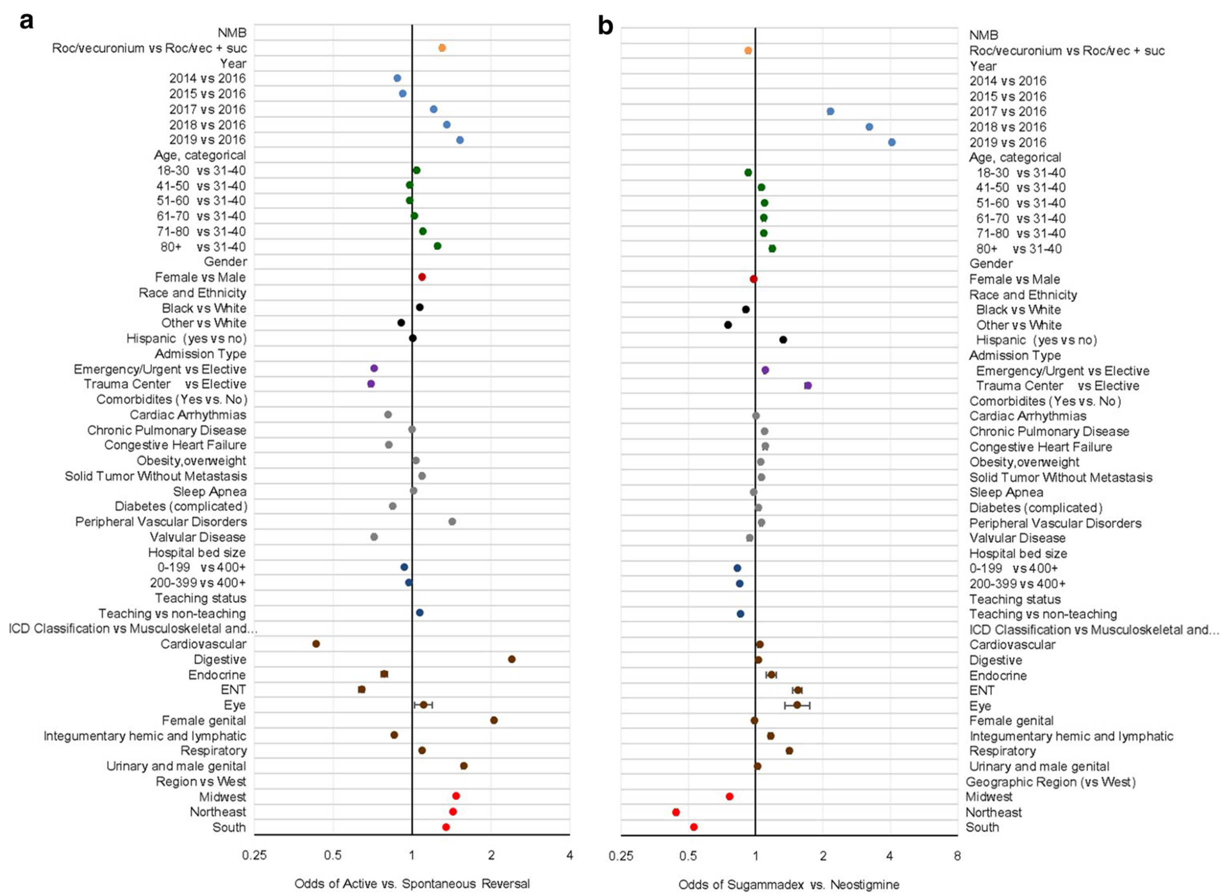

Fig. 4 Forest plot of odds ratio estimates: **a** model 1a—active pharmacologic reversal versus spontaneous recovery, **b** model 2a—sugammadex use versus neostigmine use

to some extent, with spontaneous reversal and neostigmine typically having the greatest and least proportion of comorbidities present, respectively.

While in general, active pharmacologic reversal increased in this time period (Fig. 1b), we observed this to be true across various patient characteristics including age, comorbidities, and procedure (Fig. 3). In looking across patient age groups, we observed an increase in active pharmacologic reversal after 2016 coinciding with the introduction of sugammadex, while trends were similar across age groups (Fig. 3a) and varied to a greater extent by comorbidity (Fig. 3b) and procedure (Fig. 3c).

Active pharmacologic reversal was administered in 69% and 75% of encounters of patients with no comorbidities present, in the pre- and post-sugammadex periods, respectively, compared to 62% and 68% of encounters where at least one comorbidity was present. Among the comorbidities identified as most relevant to NMB reversal choices, patients with congestive heart failure were least often (45% and 50% of the time) actively reversed, and patients with solid tumor, most similar to those without any reported comorbidities, most often pharmacologically reversed (70% and 77% of the time) (Fig. 3b). Even greater differences in NMB reversal choices were observed between surgical procedure types (Fig. 3c), with cardiovascular and digestive procedures being least (42% and 48%) and most frequently (79% and 83%) pharmacologically reversed, respectively.

There were 21,487 unique primary ICD-PCS codes cited across all encounters which were then grouped into ten broad procedure classes. While the types of procedures performed within each of these ten categories varied to some extent, they provided relatively homogenous groupings for analysis as relatively few primary ICD-PCS codes represented a relatively large proportion of the procedures within each category. The 15 most frequently cited primary ICD-PCS codes covered from a low of about one-third (musculoskeletal/nervous system procedures) to a high of 79% (endocrine) of the primary procedure codes within each category (Supplementary Table 1).

Multivariable Logistic Regression Analyses

Many of the observed univariate trends were also observed in multivariable analyses. Odds ratios and 95% CIs of factors assessed for association with the use of active NMB reversal versus spontaneous recovery are shown in Fig. 4a and Supplementary Table 3 (model 1a). A total of 1,851,377 (69.1%) inpatient encounters (between 2016 and June 2019) were pharmacologically reversed with sugammadex or neostigmine. Odds ratios and 95% CIs of factors evaluated for association with choice of reversal agent among those actively reversed are shown in Fig. 4b and Supplementary Table 3 (model 2a).

Time Trends

Encounters observed in the year 2014, prior to the introduction of sugammadex, had a lower likelihood of active reversal as compared to encounters in 2016 (2014 to 2016: OR 0.87; 95% CI 0.87–0.88 and 2015 to 2016: OR 0.92; 95% CI 0.91–0.92). Relative to 2016, later calendar years had a monotonically increasing likelihood for active reversal (OR [95% CI], 2017: 1.21 [1.20–1.22] to 2019: 1.52 [1.51–1.53]).

Multivariable analyses demonstrate that choice of NMB reversal agent was also independently associated with several factors. Compared with the first year of market availability of sugammadex (2016), among inpatient surgeries that were administered pharmacologic NMB reversal, later years were positively associated with sugammadex use (OR 2.15–4.05 between 2017 and 2019; Fig. 4b, Supplementary Table 3).

A total of 590 sites provided continuous yearly data to the PHD over the 2016–2019 study period. Among these sites, those with later years of sugammadex adoption (year of first sugammadex use) compared to earlier adoption (first site use in 2017 and 2018 or after, compared to 2016) were negatively associated with sugammadex use vs. neostigmine (OR 0.42; 95% CI 0.41–0.42 and OR 0.12; 95% CI 0.11–0.12, respectively; $P < 0.0001$) (model 2c, Supplementary Table 4).

Patient Characteristics

Patient age 61 years and older was independently associated with active reversal (Fig. 4a, Supplementary Table 3). Among patients who were pharmacologically reversed, a similar association with age and likelihood to be reversed with sugammadex was observed, though it was apparent for patients age 51 and above, while patients ages 30 and below were slightly less likely to be given sugammadex compared to neostigmine (Fig. 4b, Supplementary Table 3).

Treatment with active vs. spontaneous reversal of NMB was modestly associated with patient race (Black patients were more likely to be reversed compared to White patients) independent of other patient, procedure, and site characteristics (Supplementary Table 3). Among those who were pharmacologically reversed, these associations were less consistent and more pronounced, with non-Whites being about 10–25% less likely, and Hispanics, about 33% more likely to be reversed with sugammadex compared to neostigmine ($P < 0.0001$) independent of other factors and each other (Supplementary Table 3), with some variability by region (Supplementary Table 6). This interaction was most apparent by ethnicity: while Hispanics were more likely to be pharmacologically reversed in the Northeast and the West (Supplementary Table 5), when pharmacologically reversed in the Northeast, they were nearly 17% less likely to be reversed with sugammadex ($P < 0.0001$; Supplementary Table 6).

Patient comorbidities also impacted provider choices in NMB management: those with peripheral vascular disorders (PVD) were associated with increased likelihood for active reversal of NMB relative to those without PVD (OR 1.42; 95% CI 1.41–1.43; $P < 0.0001$), while among those reversed, it was minimally associated with reversal with sugammadex (OR 1.06, $P < 0.0001$). In contrast, patients that had cardiac arrhythmias (OR 0.81), congestive heart failure (OR 0.81), diabetes (OR 0.84), and valvular disease (OR 0.71) were negatively associated with pharmacological reversal, compared to patients without these conditions (all $P < 0.0001$) and more likely to spontaneously recover. Among patients who were actively reversed, the presence of comorbidities (COPD, CHF, obesity, solid tumor, PVD) was modestly, but independently associated with reversal with sugammadex over neostigmine ($P < 0.0001$).

Procedure Characteristics

Relative to elective inpatient admissions, urgent/emergency admissions were independently negatively associated with active reversal (OR 0.72; 95% CI 0.71–0.72; $P < 0.0001$). However, when looking at patients who were pharmacologically reversed, patients whose procedures resulted from these admissions (emergency and urgent) were independently more likely to be reversed with sugammadex relative to elective admissions (OR 1.10; 95% CI 1.09–1.11); the same was observed among admissions made through a trauma center (OR 1.70 [1.66, 1.75]; Supplementary Table 3). NMB choices by admission type were consistent between regions, with the exception of the Northeast, where, among those actively reversed, providers less often reversed non-elective cases with sugammadex (Supplementary Table 6).

Both choice of NMB agent and type of surgical procedure were associated with choice of NMB reversal independent of each other and other patient and site characteristics. Administration of rocuronium or vecuronium alone versus with succinylcholine was positively associated (OR 1.30; 95% CI 1.29–1.31; $P < 0.0001$) with pharmacologic reversal as were surgical procedures involving the digestive system, female genital organs, urinary system and male genital organs compared with musculoskeletal and nervous system procedures (OR 2.40; 95% CI 2.38–2.45; OR 1.97; 95% CI 1.94–1.99; OR 1.50; 95% CI 1.48–1.51, respectively, all $P < 0.0001$). In contrast, surgeries involving the cardiovascular system were negatively associated with active reversal (OR 0.43; 95% CI 0.43–0.43 all $P < 0.0001$). Similarly, ear, nose, and throat (ENT) procedures and endocrine system procedures were negatively associated with active reversal (OR 0.64; 95% CI 0.62–0.66 and OR 0.78; 95% CI 0.76–0.80, respectively, both $P < 0.0001$).

Among surgeries where NMB was pharmacologically reversed, trends in the choice of neostigmine compared to sugammadex varied. Surgeries involving the respiratory system, the eye, endocrine, integumentary/hemic/lymphatic, or ENT surgeries were independently and positively associated with sugammadex use (ORs 1.16–1.54, $P < 0.0001$).

Site Characteristics

We observed geographic differences in NMB management choices; anesthesia providers in the Midwest, Northeast, and South were more likely to actively reverse patients, independent of other patient and procedure characteristics compared with sites in the West (Supplementary Table 3, Fig. 4a). When stratified by region (model 1b), the association of patient and procedure characteristics was generally similar in magnitude and direction to those observed in the overall sample, and each other. However, there were some differences observed. Notably, the association of NMB reversal choice and NMB agent varied: in the Midwest patients administered rocuronium/vecuronium alone compared to in combination with succinylcholine were less likely to actively reverse compared to other regions where the converse was true. Likewise, associations varied by site characteristics (size and academic affiliation): the Northeast and the South seemed to vary, respectively, from others (Supplementary Table 5).

In model 2c (Supplementary Table 4) we observed sites which adopted sugammadex early (e.g., 2016) to be more likely to choose sugammadex over neostigmine compared to later adopters (2017 and after) independent of other factors. These early adoption sites were more often academic, large (400+ beds), urban, and in the Midwest (37% of Midwest sites compared to only 13% of Northeast sites adopted sugammadex in 2016; Supplementary Table 2).

Among procedures that were pharmacologically reversed, providers in the Northeast, Midwest, and South, relative to the West, were less likely to reverse with sugammadex (compared to neostigmine) independent of other factors (ORs ranging 0.43–0.71; all $P < 0.0001$; Fig. 4b). Upon stratification by region, differences in practice preferences were also observed in the reversal choices made relative to hospital size (and choice to reverse in the Northeast, Supplementary Table 6) and type (teaching or nonacademic), specifically among those actively reversing in the Midwest and South (Supplementary Table 6). However, in general, teaching hospitals were more likely to reverse patients compared to nonacademic facilities. When pharmacologically reversing, smaller hospitals (compared to larger [400+ beds]) and academic hospitals (compared to nonacademic) were less likely to do so with sugammadex independent of other factors.

DISCUSSION

We assessed the temporal trends in clinical practice associated with the use of NMBAs and NMB reversal approaches in adult inpatients undergoing surgery.

From 2014 to 2019, the use of active reversal continuously increased and spontaneous reversal decreased (Fig. 2). By June 2019, 3.5 years after its regulatory approval in the USA, sugammadex was available in 78% of the 927 sites in this analysis. Not surprisingly, of those surgeries using active reversal, sugammadex use increased and neostigmine decreased over time, suggesting clinical equipoise among the two active reversal agents in anesthesia practice in the inpatient setting. Indeed, the year in which the surgical procedure was performed was the most impactful factor that independently influenced the odds of selecting sugammadex vs. neostigmine (Fig. 4b). A similar trend in time was observed in the active vs. spontaneous reversal model (model 1a, Fig. 4a), although it was not as pronounced. The choice of active vs. spontaneous reversal was more strongly dependent on patient comorbidities and even more so by procedure type. While both impacted the choices made in NMB management, the direction and magnitude of effect of patient comorbidities and procedure type varied in their degree of impact on choice of mode (pharmacologic vs. spontaneous) and agent (neostigmine vs. sugammadex) of NMB reversal, independent other factors and each other (Fig. 4a vs. b).

Over the study period, the use of NMB with rocuronium alone increased to a high of 90.3% in June 2019, with an accompanying decline in the use of short-acting agents such as succinylcholine, perhaps owing to the introduction of a faster reversal option. The use of active NMB reversal increased overall over the study period, with spontaneous recovery dropping to 27.6% in 2019. Choice of reversal with sugammadex seemed to displace, to some extent, both spontaneous recovery and active reversal with neostigmine over time. Certain patient characteristics influenced the choice of NMB reversal approach more than others. This finding was consistent with trends observed in a recent similar outpatient study [24] as well as a recent retrospective observational study of sugammadex utilization conducted in adult general anesthesia inpatient cases from the Multicenter Perioperative Outcomes Group (MPOG), across 24 US centers between 2014 and 2018 [21], though the association between sugammadex use and age was far more pronounced in the latter population.

Patients identifying as Black or "other" races as well as Hispanics were negatively associated with sugammadex use relative to White and non-Hispanic patients. Differences observed according to race or ethnicity were of modest magnitude, and while they were independent of other patient and site characteristics, they may reflect differences in access to care and be associated with site or regional differences in practice. Notably, we observed that in the Northeast, Hispanics were about 26% more likely to be pharmacologically reversed compared to non-Hispanics, though when reversed, they were about 16% less likely to receive sugammadex. Interestingly, in the South and West, Hispanics receiving active NMB reversal were 38–44% more likely to be reversed with sugammadex compared to non-Hispanics independent of other factors. Black and Hispanic patients made up only 10% and 7% of the population, respectively. While these are interesting observations lending insight to potential health disparities in clinical practice and access to care at a site or regional level, a follow-on sensitivity analysis (not shown) found that ethnicity was not a statistically significant contributor to NMB reversal choice (neither mode nor type of agent) when the correlation of observations within institutions was taken into account via a generalized estimating equations (GEE) model. However, race was a statistically significant contributor to choice of active vs. spontaneous reversal (but not type of agent) even after accounting for the correlation within institutions. These observations may point to some disparities in NMB treatment choices. Further research in understanding the source of these treatment disparities is both necessary and beyond the scope of this paper.

Emergency/urgent and trauma cases were all negatively associated with pharmacological reversal compared with elective cases. This is not surprising as most elective cases have planned extubation prior to operating room discharge compared to emergency cases which may be more likely to have prolonged intubation, obviating a need for NMBA reversal. However, when pharmacologically reversed, use of sugammadex was modestly, but positively associated with emergency/urgent (OR 1.10; $P < 0.0001$) and trauma (OR 1.65; $P < 0.0001$) cases compared to elective cases. These findings are similar to that reported in the MPOG study [21], which reported greater use of sugammadex for emergent surgeries (OR 1.09; 95% CI 1.04–1.14; $P < 0.001$). Sugammadex is indicated for urgent NMB reversal [20] and most emergency rooms carry sugammadex, which may also influence the choice of reversal agent in emergency/trauma patients. Associations observed with trauma centers should be interpreted with caution, as the majority of trauma cases in this study came from five or fewer sites. This may, in part, account for the difference in association between choice of reversal agent and type of admission within the Northeast.

Specifically, cardiovascular procedures were also independently negatively associated with active pharmacologic reversal and were more than twice as likely to be spontaneously reversed compared to musculoskeletal procedures. This observation is consistent with the conventional practice not to extubate patients undergoing cardiovascular surgeries who remain sedated and are under prolonged ventilation following surgery (specifically this may be seen in the open approach coronary artery bypass graft and valve replacement procedures frequently observed here [Supplementary Table 1]). It is unclear whether this observed association may be despite the introduction of enhanced recovery pathways (which have endorsed early extubation as part of “Fast-Track” cardiac surgery for improved patient outcomes over the last several years, with mixed results with regard to reduction of complications [25, 26]), or if associations would be even more pronounced in the absence of these efforts. Perhaps as a result of differences in adoption and practice of enhanced recovery pathways by site and region, interestingly, among the Midwest sites, when they chose to pharmacologically reverse in cardiovascular procedures, anesthesia providers’ preference to reverse with sugammadex was more pronounced than in other regions (Fig. 4; OR 1.27; $P < 0.0001$, Supplementary Table 4, compared to musculoskeletal procedures).

Independent negative associations with active pharmacologic reversal were also observed among ENT and endocrine procedures (which may not require as long or as deep NMB), while digestive system procedures, female genital, and urinary/male genital procedures were considerably more likely to be pharmacologically reversed compared to musculoskeletal procedures.

The pattern of active reversal versus spontaneous recovery varied with patient comorbidity profiles. While these associations were observed, independent of other patient and procedure characteristics and each other, there may be collinearity, or some degree of residual confounding between certain comorbidities, and types of procedures. Among patients receiving pharmacologic NMB reversal, there was some variability in choice of sugammadex vs. neostigmine across presence of comorbidities, though these were less pronounced than differences observed between pharmacologic and spontaneous reversal choices. Trends and magnitude of effect were similar to those observed in a previous multicenter inpatient study [21] and slightly less pronounced compared to those observed in a similar outpatient study conducted within PHD [24]. While it is not surprising that a number of comorbidities putting patients at increased surgical risk [5, 24] showed trends for the preferential use of sugammadex, it is surprising that the presence of sleep apnea (a risk factor for pulmonary complications) was not [27].

While larger academic hospitals were more likely to pharmacologically reverse patients compared to smaller non-teaching hospital, in general, these characteristics had relatively less impact than they did on choice of reversal agent once a patient was pharmacologically reversed. We observed, perhaps paradoxically, that both smaller and teaching hospitals were less likely to use sugammadex when they do reverse, though these differences were not statistically significant when correlation within sites was taken into account with GEE. This varied somewhat by region (model 2b, Supplementary Table 6), where for instance in the Midwest providers were more likely to use sugammadex when pharmacologically reversing patients in smaller hospitals. One may speculate that the relationship between NMB reversal choices and site characteristics may be related to the volume of cases seen at a hospital as well as local pharmacy budget restrictions.

When investigating the influence of hospital adoption timing and NMB choices, we found that more academic sites adopted clinical use of sugammadex within the first year of its availability (40.31% in 2016) than in later years (2.5% in 2019) (Supplementary Table 2). Observed regional imbalances in sugammadex uptake may also be related to some of the observed regional differences in practice. This may be due to restrictions at the site level as each facility undergoes its own process to add medications to inpatient formulary and make them available for use [21]. Regional and center characteristics may also relate to care access, practice preference, or systemic trends of clinical inertia.

Among US adult inpatients administered NMBs, we observed complex relationships between patient, site, regional, procedural characteristics, and NMB management choices. Observations (Fig. 4, Supplementary Table 3–6) suggest that patient and procedural characteristics are important factors in NMB reversal choices in both whether and how a patient is pharmacologically reversed, while external factors may be more influential in impacting choice of pharmacological reversal agent once a patient is actively reversed. While observed differences in anesthesia practice by site, race, and ethnicity are not consistent across all geographic regions, sites, or clear in their root cause, they raise awareness of potential health disparities in perioperative care, access to care, and trends of clinical practice preference variability independent of those accounted for by clinical characteristics and drug availability. Our findings help us to better understand the choices made in NMB management and anesthesia trends in the inpatient setting which will likely continue to change over time. Although our study did not include data from 2020, analyzing trends is particularly pertinent, with the COVID-19 pandemic causing major changes in hospital protocols and restrictions on elective surgeries in response to the unprecedented burden on the healthcare system.

Study Strengths and Limitations

The PHD represents approximately 25% of inpatient surgical settings, covering academic and nonacademic sites [23], and our study sample included over 4.8 million inpatient encounters. However, as already indicated, there was an overrepresentation of the South (47.7% of patient encounters) and underrepresentation of the Northeast (12.3% of patient encounters) regions of the USA, which limit the interpretation and generalizability of the results for any specific region or type of center. While most encounters originate from large, urban, academic centers, most sites originate from small nonacademic centers (Supplementary Table 2).

Inpatient status is determined by the hospital site itself, and there will likely be minor site variation in transitions from day case to inpatient surgeries. In addition, information on local policies or access restrictions for sugammadex by site, which will have impacted the choice of reversal agent, was not available. Data on drug dosing and availability of quantitative neuromuscular monitoring and on select, but important patient characteristics including ASA class, body mass index, and smoking status were also not available and may have an impact on anesthetic treatment and NMB management choices.

This analysis utilized multivariable logistic regression to help understand associations in NMB reversal. However, it is clear that clinical practice is a dynamic landscape where the reversal choices and clinical preferences are constantly shifting. We captured this broadly with a few time-dependent variables, which can reveal the overall trends but may fail to capture changes in more specific areas of clinical practice.

CONCLUSION

Between 2014 and June 2019, there were broad changes in trends of NMBA use and NMB reversal agents in US adult patients admitted for inpatient surgeries. Our findings, deriving encounters from more than 900 US sites, represent country-level changes in a wide variety of patient and procedure types as well as treatment sites. Complex relationships exist between patient characteristics, procedure type, and provider-level characteristics that factor into NMB management decisions. Observations suggest that patient and procedural characteristics are important factors in NMB reversal choices of spontaneous vs. pharmacological reversal, while external factors such as hospital size, site, and regional practice characteristics may be more influential in impacting choice of pharmacological reversal agent when a patient is actively reversed. Current efforts to shift patient care towards the outpatient setting in light of the recent increased burden on health systems [4] will likely impact NMBA utilization and choice of reversal method in the future. Additional research to understand how these associations may continue to shift with increasing economic pressures on the US healthcare system is warranted.

ACKNOWLEDGEMENTS

Funding. This study, the Rapid Service and Open Access Fee was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The sponsors collaborated with the investigators in the design and conduct of the study, analysis of the data, and preparation of the manuscript.

Editorial Assistance. Editorial Assistance was provided by Laila Guzadhur, PhD and Valerie Moss PhD, CMPP^{TM}, of Scion, London, UK, and funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors had access to relevant data and participated in the drafting, review, and approval of this publication.

Author contributions. LDB and RDU helped design the study, VT and WB helped extract and analyze the data, LDB drafted the manuscript, RDU prepared the manuscript, and all authors helped to interpret the results and critically review the manuscript for important intellectual content.

Disclosures. Lori D. Bash, Wynona Black, and Vladimir Turzhitsky are full time employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, which manufactures and distributes sugammadex, and may own stock and/or hold stock options in the Company. Richard D. Urman reports grant support and consultant fees from Merck & Co., Inc., Kenilworth, NJ, USA, and unrelated funding or fees from AcelRx, Medtronic/Covidien, Pfizer and Heron.

Compliance with Ethics Guidelines. This study involved analysis of pre-existing, de-identified data, and did not require institutional review board (IRB) review per Federal Regulations for the protection of Human Research Subjects (45 CRF 46) and patient consent was not required. Taking a conservative approach, this study was approved by the Mass General Brigham IRB which also rendered it exempt from review for human subjects research.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to patient privacy. The authors would like to thank Ting Shi of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA for her contribution to the study analyses.

REFERENCES

1. Steiner CA, Karaca Z, Moore BJ, Imshaug MC, Pickens G. Surgeries in hospital-based ambulatory surgery and hospital inpatient settings, 2014. HCUP Statistical Brief #223 May 2017. Rockville: Agency for Healthcare Research and Quality; 2017.

2. Richter JP, Muhlestein DB. Patient experience and hospital profitability: is there a link? Health Care Manage Rev. 2017;42:247–57.

3. Deloitte Insights. Deloitte analyses based on data from AHA annual survey, Medicare Cost Reports (via Truven Health Analytics). 2018. https://www2.deloitte.com/us/en/insights/industry/health-care/outpatient-hospital-services-medicare-incentives-value-quality.html?icid=dcom_promo_featured%7Cus;en#endnote-sup-1. Accessed 9 Nov.

4. Centers for Medicare & Medicaid Services. CMS announces comprehensive strategy to enhance hospital capacity amid COVID-19 surge. 2020. https://www.cms.gov/newsroom/press-releases/cms-announces-comprehensive-strategy-enhance-hospital-capacity-amid-covid-19-surge. Accessed 15 Dec 2020.

5. Ho VP, Schiltz NK, Reimer AP, Madigan EA, Koroukian SM. High-risk comorbidity combinations in older patients undergoing emergency general surgery. J Am Geriatr Soc. 2019;67:503–10.

6. Robertson TR, A. Proposal for update of the anaesthesia and muscle relaxant sections of the WHO; 18th Expert Committee on the Selection and Use of Essential Medicines. 2010. http://www.who.int/selection_medicines/committees/expert/18/applications/anaesthetic_proposal.pdf. Accessed 10 July 2019.

7. Naguib M, Brull SJ, Kopman AF, et al. Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg. 2018;127:71–80.

8. Naguib M, Kopman AF, Lien CA, et al. A survey of current management of neuromuscular block in the United States and Europe. Anesth Analg. 2010;111:110–9.

9. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg. 2010;111:120–8.

10. Butterly A, Bittner EA, George E, et al. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br J Anaesth. 2010;105:304–9.

11. Thevathasan T, Shih SL, Safavi KC, et al. Association between intraoperative non-depolarising neuromuscular blocking agent dose and 30-day readmission after abdominal surgery. Br J Anaesth. 2017;119:595–605.

12. Cammu G. Residual neuromuscular blockade and postoperative pulmonary complications: what does the recent evidence demonstrate? Curr Anesthesiol Rep. 2020. https://doi.org/10.1007/s40140-020-00388-4:1-6.

13. Herring WJ, Woo T, Assaid CA, et al. Sugammadex efficacy for reversal of rocuronium- and vecuronium-induced neuromuscular blockade: a pooled analysis of 26 studies. J Clin Anesth. 2017;41:84–91.

14. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev. 2017;8:Cd012763.

15. Domenech G, Kampel MA, García Guzzo ME, et al. Usefulness of intra-operative neuromuscular blockade monitoring and reversal agents for postoperative residual neuromuscular blockade: a retrospective observational study. BMC Anesthesiol. 2019;19:143.

16. Kheterpal S, Vaughn MT, Dubovoy TZ, et al. Sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER): a multicenter matched cohort analysis. Anesthesiology. 2020;132:1371–81.

17. Evron S, Abelansky Y, Ezri T, Izakson A. Respiratory events with sugammadex vs. neostigmine following laparoscopic sleeve gastrectomy: a prospective pilot study assessing neuromuscular reversal strategies. Rom J Anaesth Intensive Care. 2017;24:111–4.

18. Krause M, McWilliams SK, Bullard KJ, et al. Neostigmine versus sugammadex for reversal of neuromuscular blockade and effects on reintubation for respiratory failure or newly initiated noninvasive ventilation: an interrupted time series design. Anesth Analg. 2020;131:141–51.

19. Martinez-Ubieto J, Ortega-Lucea S, Pascual-Bellosta A, et al. Prospective study of residual neuromuscular block and postoperative respiratory complications in patients reversed with neostigmine versus sugammadex. Minerva Anestesiol. 2016;82:735–42.

20. US Food and Drug Administration. Sugammadex injection—prescribing information. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022225lbl.pdf. Accessed 7 Aug 2020.

21. Dubovoy TZ, Saager L, Shah NJ, et al. Utilization patterns of perioperative neuromuscular blockade reversal in the United States: a retrospective observational study from the Multicenter Perioperative Outcomes Group. Anesth Analg. 2020;131:1510–9.

22. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.

23. Premier Applied Sciences® Premier Inc. Premier Healthcare Database white paper: data that informs and performs. 2020. Accessed 21 Aug 2020.

24. Bash LD, Black W, Turzhitsky V, Urman RD. Neuromuscular blockade and reversal practice variability in the outpatient setting: insights from US utilization patterns. Anesth Analg. 2021 (In press).

25. Wong WT, Lai VK, Chee YE, Lee A. Fast-track cardiac care for adult cardiac surgical patients. Cochrane Database Syst Rev. 2016;9:CD003587.

26. McCarthy KJ, Locke AH, Coletti M, et al. Outcomes following implantable cardioverter-defibrillator generator replacement in adults: a systematic review. Heart Rhythm. 2020;17:1036–42.

27. Memtsoudis SG, Cozowicz C, Nagappa M, et al. Society of Anesthesia and Sleep Medicine guideline on intraoperative management of adult patients with obstructive sleep apnea. Anesth Analg. 2018;127:967–87.