Trends in the use of Sugammadex for the Reversal of Neuromuscular Blockade in a Tertiary Care Academic Center

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Abstract

Introduction: Neuromuscular blockade plays an integral role in anesthesia and surgery. However, residual paralysis has been associated with postoperative respiratory complications and increased airway collapsibility. Sugammadex, is a modified gamma-cyclodextrin used for the reversal of rocuronium and vecuronium. The aim of this retrospective descriptive study was to summarize the use of Sugammadex after non-cardiac surgery and identify factors that may be associated with any Sugammadex use.

Methods: 133,121 adult non cardiac surgeries were evaluated retrospectively, of these, 61,936 met inclusion criteria. Four descriptive aims were explored; dose of Sugammadex used, situational use of Sugammadex, Sugammadex use given type of steroidal muscle relaxant administered and class of muscle relaxant used before vs. after introduction of Sugammadex. 31 selected factors were used in a multivariable logistic regression model to find association with Sugammadex use.

Results: Of the 2,475 surgeries where Sugammadex was utilized, it was used as a primary reversal agent in 2,248 (90.8%) cases and as a secondary reversal after routine reversal with neostigmine in 225(9.1%) cases. The use of Sugammadex as a rescue reversal is limited to 3 cases (0.12%). Of 31 a priori selected factors believed to be potential influences in the decision to use Sugammadex, 12 were found to be associated.

Conclusions: Neostigmine still remains the most commonly used reversal agent. Sugammadex is mostly being used as a primary reversal agent and its use is rising dramatically. The use of Sugammadex as a rescue agent in a cannot intubate/cannot ventilate event is exceedingly rare. Keywords: term, term, term

Introduction

Neuromuscular blockade has played an integral role in anesthesia, helping to provide adequate skeletal muscle relaxation to facilitate intubation and surgical working conditions. However, along with neuromuscular blockade comes the necessary reversal and its presenting challenges. Residual paralysis has been associated with postoperative respiratory complications and increased airway collapsibility.1-3 Traditional reversal of blockade includes the use of an anticholinesterase inhibitor, commonly neostigmine, and a muscarinic anticholinergic agent, commonly glycopyrrolate. A new agent, Sugammadex, is a modified gamma-cyclodextrin used for the reversal of neuromuscular

blockade that works by forming a 1:1 complex with rocuronium and vecuronium. Compared to neostigmine, Sugammadex provides significantly faster recovery to a train of four (TOF) ratio of 0.9.4 A systematic review showed that Sugammadex also reduces residual postoperative paralysis as well as minor respiratory events when compared to neostigmine.5 It received FDA approval in December 2015, and was introduced into clinical practice at Cleveland Clinic Foundation (CCF) in May 2016. This retrospective descriptive study summarizes the use of Sugammadex after non-cardiac surgery and presents results from an exploratory analysis identifying factors that may be associated with any Sugammadex use vs. Neostigmine only as a reversal agent.

Methods

The goal of this study was to describe trends in the use of Sugammadex after non-cardiac surgery, and explore factors which may be associated with its use over Neostigmine at CCF. All adult patients who underwent non-cardiac surgery at CCF main campus between January 2014 and August 2017 were considered for analysis in this retrospective descriptive and exploratory study. Institutional review board approval was obtained from CCF. We evaluated data from 133,121 adult non cardiac surgeries; of these, 61,936 met our inclusion criteria. (40,378 before the introduction of Sugammadex at CCF, 21,558 after). We excluded surgeries performed under monitored anesthesia care, local anesthesia, or neuraxial (spinal/epidural) anesthesia; surgeries where neither steroidal nor benzylisoquinolinium non-depolarizing muscle relaxants (MRs) were administered; and all non-index surgeries.

Patient characteristics, surgical information, and dose and type of muscle relaxant (MR) are summarized by type of reversal agent – (1) Sugammadex only; (2) Neostigmine only; (3) both; and (4) none. Continuous variables are reported as mean±standard deviation (SD) or median [Q1,Q3], as appropriate; binary and categorical variables are reported as N(%).

Descriptive Aims

Four descriptive aims are explored:

(I.) Dose of Sugammadex used (mg/kg) was described via mean±SDs among patients who received it as a reversal agent.

(II.) N(%) are used to summarize Sugammadex use as a reversal agent for steroidal non-depolarizing MRs (rocuronium, vecuronium, pancuronium) under three scenarios: (1) elective use of Sugammadex only; (2) after routine reversal with Neostigmine; and (3) for rescuing reversal in three "cannot intubate" or "cannot ventilate" situations (i. within 5 minutes of the first dose of steroidal non-depolarizing MRs; ii. before the time stamp for intubation; and iii. in large doses above 16 mg/kg).

(III.) N(%) of patients who received Sugammadex given the type of steroidal MR administered by year are presented.

(IV.) N(%) of type of MR (both steroidal and benzylisoquinolinium classes of MR) used before and after Sugammadex was approved and first used at CCF are provided. Chi-square tests were used to evaluate the hypotheses that the availability of Sugammadex would (1) increase the use of steroidal MRs and (2) reduce the use of benzylisoquinolinium MRs.

Exploratory Aim

Multivariable logistic regression was used to identify factors that may be associated with any Sugammadex use as a reversal agent (vs. Neostigmine only). Several variables including demographic, preoperative comorbid conditions, surgical information, and dose of steroidal MR by type, all selected a priori, were included in the logistic regression model as explanatory variables with "any Sugammadex" vs. "Neostigmine only" as the outcome. Variance inflation factors (VIF) were checked as a guard against multicollinearity. Post-hoc tests were performed and estimates obtained for all pairwise comparisons for type of surgery. As this is an exploratory analysis, adjustment for multiple testing was not implemented. Adjusted odds ratios (ORs) for odds of any Sugammadex use (vs. Neostigmine only), 95% confidence intervals (CIs), and p-values are presented. SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analysis.

Results

Patients

There were 133,121 adult non-cardiac procedures performed at CCF main campus between January 2014 and August 2017. 61,936 procedures met our inclusion/exclusion criteria, with additional aim-specific exclusions applied, as summarized in Figure 1. Sample characteristics summarizing potential factors associated with selection of reversal agent, by reversal agent group, are presented in Table 1.

Descriptive Aims

Sugammadex was first used as a reversal agent at CCF in May 2016. Between then and August 2017, Sugammadex was used in 2,475 surgeries: 2,249 surgeries used Sugammadex alone while 226 used a combination of Sugammadex and Neostigmine. On average, 2.8±1.2 mg/kg of Sugammadex was used per surgery. A slightly higher dose was used when Sugammadex was the only agent used versus when it was used in combination with Neostigmine (2.9±1.2 mg/kg vs. 2.4±1.2 kg/kg, respectively). Of the 2,475 surgeries in which any Sugammadex was used, it was employed electively in 2,248

(90.8%) surgeries, in combination with Neostigmine after routine reversal in 225 (9.1%) surgeries, and 3(0.12%) times for rescuing reversals. In the even of rescue reversal, the dose of Sugammadex was given before the time stamp for intubation and given in a less than 16mg/kg dose. Sugmammadex was given in 11.5% of the time when rocuronium was administered, 13.4% of the time vercuronium was administered and 3.3% of the time pancuronium was administered. Overall, non-depolarizing steroidal MRs were used in 61,072 (98.6%) surgeries and benzylisoquinolinium MRs were used in 1,122 (1.8%) surgeries within the eligible study period. The rate of use for both steroidal (P=0.20) and benzylisoquinolinium (P=0.06) MRs were consistent before and after Sugammadex was available for use at CCF.

All results for our descriptive aims are summarized in Table 2.

Exploratory Aim

We examined the odds of any Sugammadex use (vs. Neostigmine only) for 31 factors selected a priori which we believed could be associated with an anesthesiologists decision to use Sugammadex or not. Twelve of the thirty one factors were associated with any Sugammadex use including sex, higher BMI, pre-op neurological disorder, ASA status, type of surgery, year of surgery, increased crystalloid administration, increased colloid administration, increased urine output and increased rocuronium administration (Table 3). Excluding post-hoc OR estimates for pairwise comparisons for type of surgery classifications, increased blood loss and increased duration of surgery were the only two factors with P<0.05 associated with decreased odds of Sugammadex use.

Multivariable logistic regression was used to identify factors that may be associated with any Sugammadex use as a reversal agent (vs. Neostigmine only). Surgeries performed during the period Sugammadex was not used at CCF (i.e., before May 2016), surgeries that did not use any steroidal MRs, and surgeries where no reversal agent was recorded were excluded. Post-hoc tests were performed and estimates obtained for all pairwise comparisons for type of surgery. As this is an exploratory analysis, adjustment for multiple testing was not implemented.

OR interpretations:

Preoperative Comorbid Conditions

Neurological Disorder: Patients with neurological disorders were 1.65 (95% CI: (1.36,1.99), Padj=<.001) times more likely to receive Sugammadex as a reversal agent than those who had no baseline neurological disorders.

ASA Status: The odds for use of Sugammadex as a reversal agent increase 28% (OR (95% CI): 1.28 (1.17,1.40), Padj<.001) per 1 level increase in ASA status.

Surgery Information

Type of Surgery: Odds of Sugammadex use as a reversal agent differed significantly by type of surgery performed (Padj<.001). (There are a lot of significant results but the interpretation for all significant ORs will follow either of these formats:

If OR > 1: "Patients who had surgery performed on their (1st surgery listed) were (OR) (95% CI: (CI), Padj) times more likely to receive Sugammadex as a reversal agent than those who had surgery performed on their (2nd surgery listed)."

Ex (1): Patients who had surgery performed on their cardiovascular system were 1.78 (95% CI: (1.43,2.21), Padj<.001) times more likely to receive Sugammadex as a reversal agent than those who had surgery performed on their digestive system.

Ex (2): Patients who had surgery performed on their cardiovascular system were 3.07 (95% CI: (2.22,4.26), Padj<.001) times more likely to receive Sugammadex as a reversal agent than those who had surgery performed on their Endocrine, Hemic, and Lymphatic Systems.

If OR < 1: "Patients who had surgery performed on their (1st surgery listed) were (1 – OR)×100% (OR (95% CI): OR(CI), Padj) less likely to receive Sugammadex as a reversal agent than those who had surgery performed on their (2nd surgery listed)."

Ex (1): Patients who had surgery performed on their Endocrine, Hemic, and Lymphatic Systems were 52% (95% CI: 0.48 (0.35,0.64), Padj<.001) less likely to receive Sugammadex as a reversal agent than those who had surgery performed on their Respiratory System.

Ex (2): Patients who had surgery performed on their Integumentary and Musculoskeletal Systems were 45% (OR (95% CI): 0.55 (0.44,0.69), Padj<.001) less likely to receive Sugammadex as a reversal agent than those who had surgery performed on their Nervous System.

Duration of Surgery: The odds for use of Sugammadex as a reversal agent decrease 18% (OR (95% CI): 0.82 (0.79,0.84), Padj<.001) per 30 min increase in duration of surgery.

Year of Surgery: Patients who had surgery performed in 2017 were 3.02 (95% CI: (2.72,3.35), Padj=<.001) times more likely to receive Sugammadex as a reversal agent than those who had their surgery performed in 2016.

Intraoperative Factors

Colloids Fluid: The odds for use of Sugammadex as a reversal agent increase 21% (OR (95% CI): 1.21 (1.15,1.28), Padj<.001) per 250 cc increase in colloids fluids used intraoperatively.

Type and Dose of Steroidal Muscle Relaxant

Rocuronium: The odds for use of Sugammadex as a reversal agent increase 6% (OR (95% CI): 1.06 (1.05,1.07), Padj<.001) per 10 mg increase in rocuronium used intraoperatively.

Discussion

Since the introduction of Sugammadex at CCF in May 2016, there has been a significant increase in its use. We aimed to identify trends and have found that when Sugammadex was used; it is primarily used electively, occasionally used with routine reversal combined with neostigmine and glycopyrrolate and very rarely as a rescue agent in a cannot intubate/cannot ventilate scenario. We expect that when Sugammadex was utilized with routine reversal, it was likely used after routine reversal was given as an adjunct to reversal potential muscle and respiratory weakness. The rate of steroidal and benzylisoquinolinium muscle relaxants did not change significantly after the introduction of Sugammadex likely due to the pre-existing low utilization rate of benzylisoquinolinium muscle relaxants.

Twelve of the thirty one variables were associated with any Sugammadex use including sex (females more than males), higher BMI, pre-op neurological disorder, ASA status, type of surgery, year of surgery (2017 vs 2016), increased crystalloid administration, increased colloid administration, increased urine output and increased rocuronium administration. Increased blood loss and increased duration of surgery were the only two factors with $P<0.05$ associated with decreased odds of Sugammadex use. A plausible explanation is the reluctance of anesthesia providers to use Sugammadex in large blood loss cases especially with knowledge of its potential to increase PTT/PT/INR. In addition, longer duration surgeries allow for more careful titration of muscle relaxants, thereby reducing the need for Sugammadex reversal.

This is a descriptive study meant to summarize Sugammadex use and identify factors which may influence an anesthesiologist's decision to use it as a reversal agent. We thus caution against drawing statistical inferences based on the p-values presented. We only examined 31 factors we believed that could be associated with the decision to use Sugammadex. There may be additional factors which may be associated with this decision that we either were unable to access or were not considered. Inclusion of other potential factors could alter the estimates and associations we observed in our exploratory analysis. Therefore, this list should not be considered exhaustive list of variables associated with Sugammadex use.

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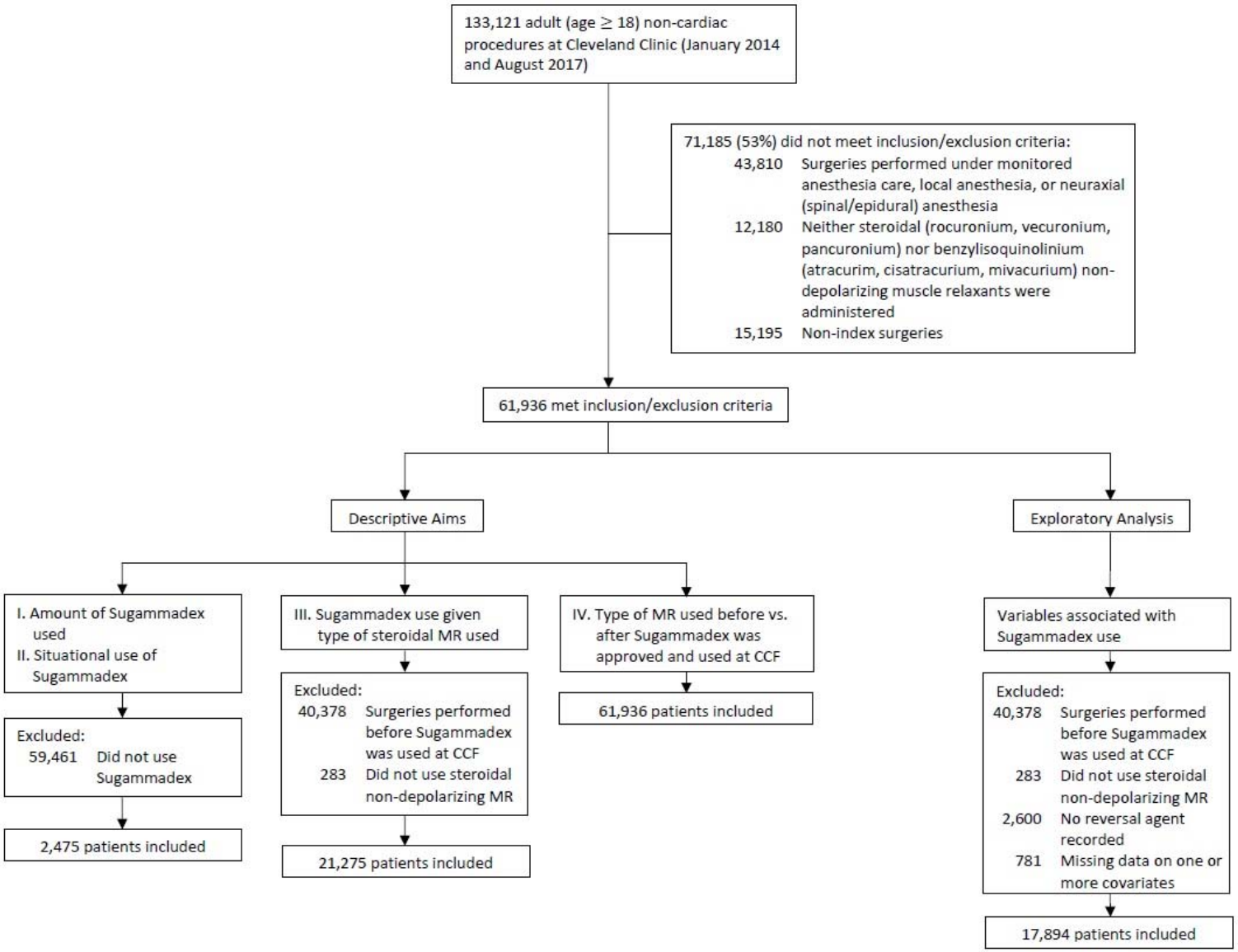
Figure 1: Types and numbers of exclusions of available adult non-cardiac surgeries performed at CCF main campus between January 2014 and August 2017.



CCF = Cleveland Clinic Foundation

MR = muscle relaxant

Table 1: Summary Statistics of Sample Characteristics

Variable	Total (N=61,936)	Sugammadex Only (N=2,249)	Neostigmine Only (N=52,308)	Both (N=226)	Neither (N=7,153)	P-value[&]
Demographic Information						
Age	56.5±15.9	58.3±15.8	56.3±15.9	58.7±16.0	57.9±15.7	<0.001[a]
Sex, female*	33,502(54.1)	1,220(54.2)	28,510(54.5)	124(54.9)	3,648(51.0)	<0.001[c]
BMI, kg/m^2*	30.0±8.1	30.4±8.9	29.9±8.0	32.1±9.7	29.9±8.6	<0.001[a]
Preoperative Comorbid Conditions						
Current smoker*	8,537(14.4)	322(14.9)	7,185(14.3)	38(17.5)	992(15.3)	0.065[c]
Hypertension*	30,431(49.4)	1,188(52.9)	25,168(48.3)	140(62.2)	3,935(55.4)	<0.001[c]
Coronary artery disease*	7,061(11.5)	276(12.3)	5,710(11.0)	35(15.6)	1,040(14.6)	<0.001[c]
COPD*	4,679(7.6)	259(11.5)	3,663(7.0)	22(9.8)	735(10.3)	<0.001[c]
Asthma*	5,505(8.9)	249(11.1)	4,492(8.6)	22(9.8)	742(10.4)	<0.001[c]
Obstructive sleep apnea*	7,561(12.3)	317(14.1)	6,373(12.2)	39(17.3)	832(11.7)	0.002[c]
Congestive heart failure/cardiomyopathy*	3,329(5.4)	121(5.4)	2,477(4.8)	24(10.7)	707(10.0)	<0.001[c]
Chronic kidney disease*	2,501(4.1)	64(2.9)	1,763(3.4)	12(5.3)	662(9.3)	<0.001[c]
DM*	11,507(18.7)	457(20.4)	9,442(18.1)	53(23.6)	1,555(21.9)	<0.001[c]
Dementia*	450(0.73)	23(1.0)	305(0.59)	7(3.1)	115(1.6)	<0.001[c]
Neurological disorder*	4562(7.4)	196(8.7)	3407(6.5)	14(6.2)	945(13.3)	<0.001[c]
Obesity (BMI >35)*	12,939(20.9)	485(21.6)	10,878(20.8)	64(28.3)	1,512(21.1)	0.033[c]
Malnutrition (BMI < 18)*	1,083(1.7)	41(1.8)	871(1.7)	1(0.44)	170(2.4)	<0.001[c]
Current steroid Use (Within 1 month)	5,325(8.6)	209(9.3)	4,310(8.2)	22(9.7)	784(11.0)	<0.001[c]
Alcohol abuse*	1,069(1.7)	35(1.6)	755(1.5)	7(3.1)	272(3.8)	<0.001[c]
Preoperative ascites*	1,064(1.7)	24(1.1)	619(1.2)	4(1.8)	417(5.9)	<0.001[c]
Hypoalbuminemia*	630(1.0)	12(0.53)	467(0.90)	3(1.3)	148(2.1)	<0.001[c]
ASA status						<0.001[b]
1	1,661(2.7)	33(1.5)	1,444(2.8)	5(2.2)	179(2.5)	
2	14,697(23.7)	394(17.5)	13,069(25.0)	30(13.3)	1,204(16.8)	
3	36,746(59.3)	1,443(64.2)	31,674(60.6)	147(65.0)	3,482(48.7)	
4	8,643(14.0)	374(16.6)	6,082(11.6)	44(19.5)	2,143(30.0)	
5	189(0.31)	5(0.22)	39(0.07)	0(0.0)	145(2.0)	
Surgery Information						
Type Of Surgery*						<0.001[c]

Cardiovascular System	3,766(6.3)	180(8.2)	2,886(5.7)	13(5.9)	687(10.5)	
Digestive System	15,446(25.8)	630(28.6)	13,285(26.1)	73(32.9)	1,458(22.3)	
Nervous System	6,407(10.7)	219(9.9)	5,346(10.5)	11(5.0)	831(12.7)	
Respiratory System	4,427(7.4)	383(17.4)	3,495(6.9)	32(14.4)	517(7.9)	
Eye, Ear, Nose, Mouth, and Pharynx	2,769(4.6)	85(3.9)	2,145(4.2)	3(1.4)	536(8.2)	
Obstetrical, Female or Male Genital Organs	13,048(21.8)	465(21.1)	11,899(23.4)	57(25.7)	627(9.6)	
Endocrine, Hemic, and Lymphatic System	3,801(6.3)	65(2.9)	3,341(6.6)	9(4.1)	386(5.9)	
Integumentary and Musculoskeletal	10,204(17.0)	177(8.0)	8,519(16.7)	24(10.8)	1,484(22.7)	
Miscellaneous Diagnostic and Therapeutic Procedures	1,935(3.1)	35(1.6)	1,306(2.5)	4(1.8)	590(8.3)	
Duration of surgery, min	191.0[125.0,277.0]	147.0[90.0,235.0]	189.0[126.0,268.0]	167.5[104.0,267.0]	243.0[134.0,442.0]	<0.001[b]
Year of Surgery						<0.001[b]
2014	18,200(29.4)	0(0.0)	16,137(30.8)	0(0.0)	2,063(28.8)	
2015	16,691(26.9)	0(0.0)	14,860(28.4)	0(0.0)	1,831(25.6)	
2016	16,139(26.1)	605(26.9)	13,436(25.7)	71(31.4)	2,027(28.3)	
2017	10,906(17.6)	1,644(73.1)	7,875(15.1)	155(68.6)	1,232(17.2)	
Time between Last MR Dose and Extubation, min	77[55,111]	56[40,78]	77[55,109]	64[46,84]	104[61,237]	<0.001[b]
Intraoperative Factors						
Fluid balance, cc*	1600[1000,2700]	1200[700,2200]	1600[1000,2600]	1400[800,2300]	2000[1000,4200]	<0.001[b]
Total crystalloid use, cc	1600[1000,2500]	1200[700,2000]	1600[1000,2500]	1300[800,2100]	1900[1000,3500]	<0.001[b]
Total colloid use (albumin/hetastarch), cc	0(0,16000)	0(0,3500)	0(0,4250)	0(0,2250)	0(0,16000)	<0.001[b]
Total blood product use (red cells/FFP/platelets/cell salvage), cc	0(0,72407)	0(0,4187)	0(0,6569)	0(0,1371)	0(0,72407)	<0.001[b]
Estimated blood loss, cc	30.0[5,150]	10[2,75]	25[10,100]	20[5,80]	50[10,350]	<0.001[b]
Urine output, cc*	110[0,415]	0[0,285]	100[0,400]	0[0,250]	265[0,800]	<0.001[b]
Muscle Relaxant[#]						
Class of Muscle Relaxant						<0.001[c]
Steroidal Only	60,814(98.2)	2,243(99.7)	51,353(98.2)	225(99.6)	6,993(97.8)	
Benzylisoquinolinium Only	864(1.4)	1(0.04)	758(1.4)	1(0.44)	104(1.5)	
Both	258(0.42)	5(0.22)	197(0.38)	0(0.0)	56(0.78)	
Type of Muscle Relaxant						
Rocuronium	59,902(96.7)	2,136(95.0)	50,627(96.8)	215(95.1)	6,924(96.8)	<0.001[c]
Vecuronium	1,393(2.2)	126(5.6)	1,113(2.1)	10(4.4)	144(2.0)	<0.001[c]
Pancuronium	172(0.28)	1(0.04)	108(0.21)	0(0.0)	63(0.88)	<0.001[c]
Atracurium	251(0.41)	0(0.0)	200(0.38)	0(0.0)	51(0.71)	<0.001[c]

Cisatracurium	876(1.4)	6(0.27)	760(1.5)	1(0.44)	109(1.5)	<0.001[c]
Dose of Muscle Relaxants						
Total Dose of Muscle Relaxants before Extubation, mg*	65[50,90]	60[50,90]	65[50,90]	70[50,100]	60[45,110]	0.003[b]
Rocuronium, mg	65[50,100]	65[50,100]	67.8[50,95]	70[50,110]	60[40,120]	0.15[b]
Vecuronium, mg*	0(0,640)	0(0,640)	0(0,140)	0(0,15)	0(0,600)	<0.001[b]
Pancuronium, mg	0(0,1800)	0(0,800)	0(0,1800)	0(0,0)	0(0,1000)	<0.001[b]
Atracurium, mg*	0(0,1120)	0(0,0)	0(0,640)	0(0,0)	0(0,1120)	<0.001[b]
Cisatracurium, mg	0(0,344)	0(0,64)	0(0,218)	0(0,14)	0(0,344)	<0.001[b]

Statistics presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).

[&] p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's Chi-Square, d=Fisher's Exact test.

[#] Mivaracurium was not used in any surgeries considered for analysis

*Data not available for all subjects. Missing values:

Demographic Information: Sex, female = 1, BMI = 349

Preoperative Comorbid Conditions: Current smoker = 2670, Hypertension = 299, Coronary artery disease = 299, COPD = 299, Asthma = 299, Obstructive sleep apnea = 299, Congestive heart failure/cardiomyopathy = 299, Chronic kidney disease = 290, DM = 299, Dementia = 299, Neurological disorder = 299, Obesity (BMI >35) = 6, Malnutrition (BMI < 18) = 6, Alcohol abuse = 299, Preoperative ascites = 299, Hypoalbuminemia = 299

Surgery Information: Type of Surgery = 131

Intraoperative Factors: Fluid balance, cc = 1, Urine output, cc = 1

Muscle Relaxant: Total Dose of Muscle Relaxants before Extubation, mg = 4, Vecuronium, mg = 1, Atracurium, mg = 1

Table 2: Descriptive summaries of Sugammadex use as a reversal agent and its impact on the utilization of non-depolarizing steroidal and benzylisoquinolinum MRs, overall and over time. Sugammadex was not administered as a reversal agent at CCF main campus until May 2016. Also, this study only includes surgeries through August 2017. Thus "2016" summarizes data from May 2016 – December 2016 and "2017" includes surgeries from January 2017 – August 2017. To investigate temporal trends in MR use as a function of Sugammadex availability, we dichotomized the data into before/after Sugammadex was both approved and used at CCF.

I. Total dose of Sugammadex used (mg/kg)[#]	**Total**	**2016**	**2017**	**p-value**
1. Any Sugammadex Use	2.8±1.2	2.9±1.2	2.8±1.2	0.15[a]
2. Sugammadex Only	2.9±1.2	2.9±1.2	2.8±1.2	0.10[a]
3. Sugammadex+Neostigmine Only	2.4±1.2	2.4±1.1	2.4±1.3	0.85[a]
II. Situational use of Sugammadex	**Total (N=2,475)**	**2016 (N=676)**	**2017(N=1,799)**	**p-value**
1. Elective Use (Any Steroidal MRs and Sugammadex Only)	2,248(90.8)	605(89.5)	1,643(91.3)	0.16[c]
2. After Routine Reversal (Any Steroidal MRs and Sugammadex + Neostigmine Combination)	225(9.1)	71(10.5)	154(8.6)	0.13[c]
3. For rescuing reversal in "Cannot intubate"/"Cannot ventilate" scenarios	3(0.12)	1(0.15)	2(0.11)	0.99[d]
i. within 5 minutes of the first dose of steroidal MR	0(0.0)	0(0.0)	0(0.0)	--
ii. Before the time stamp for intubation	3(0.12)	1(0.15)	2(0.11)	0.99[d]
iii. In a large dose about 16 mg/kg	0(0.0)	0(0.0)	0(0.0)	--
III. Frequency of sugammadex use in patients receiving steroidal non depolarizing muscle relaxants (rocuronium/vecuronium/pancuronium) by year after sugammadex became available	**Total**	**2016**	**2017**	**p-value**
1. Rocuronium	2,351(11.5)	675(6.5)	1,676(16.8)	<0.001[c]
2. Vecuronium	136(13.4)	2(2.8)	134(14.2)	0.006[c]
3. Pancuronium	1(3.3)	1(5.0)	0(0.0)	1.0[d]
4. Any steroidal MR[&]	2,473(11.6)	676(6.4)	1,797(16.7)	<0.001[c]
IV. Class of MR used before vs. after Sugammadex was approved and used at CCF	**Total (N=61,936)**	**Before May 2016 (N=40,378)**	**After May 2016 (N=21,558)**	**p-value**
1. Any steroidal[&]	61,072 (98.6)	39,797(98.6)	21,275 (98.7)	0.20[c]
2. Any Benzylisoquinolinium[+]	1,122(1.8)	761(1.9)	361(1.7)	0.062[c]

Statistics presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).
p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.
[#] Ns for Descriptive Aim I: (1) Total N=2,475; 2016 N=676; 2017 N=1,799; (2) Total N=2,249; 2016 N=605; 2017 N=1644; (3) Total N=226; 2016 N=71; 2017 N=155
[+] Any benzylisoquinolinium = Atracurium and/or Cistracurium; Mivaracurium was not used in any surgeries considered for analysis
MR = muscle relaxant
CCF = Cleveland Clinic Foundation

Table 3: Relationship between factors potentially associated with the decision to use any Sugammadex (Sugammadex only or Sugammadex+Neostigmine combination vs. Neostigmine only)

Variable	OR (95% CI)	p-value
Demographic Variables		
Age, per 10 years	1.03 (1.00,1.07)	0.081
Sex: Female vs. Male	1.17 (1.06,1.28)	0.002
BMI, per 5 kg/m^2	1.07 (1.02,1.12)	0.005
Preoperative Comorbid Conditions		
Current Smoker	1.02 (0.89,1.16)	0.780
Hypertension	1.09 (0.98,1.21)	0.119
Coronary Artery Disease	0.93 (0.80,1.09)	0.375
COPD	1.16 (0.91,1.49)	0.238
Asthma	0.95 (0.75,1.21)	0.703
Obstructive Sleep Apnea	0.99 (0.86,1.14)	0.878
Congestive Heart Failure/Cardiomyopathy	1.00 (0.80,1.23)	0.964
Chronic Kidney Disease	0.85 (0.64,1.13)	0.271
DM	1.04 (0.92,1.18)	0.509
Dementia	0.95 (0.60,1.51)	0.835
Neurological Disorder	1.60 (1.33,1.92)	<.001
Obesity (BMI > 35)	0.85 (0.71,1.01)	0.066
Malnutrition (BMI < 18)	1.09 (0.74,1.59)	0.667
Current Steroid Use (within 1 Month of Surgery)	1.13 (0.96,1.33)	0.151
Alcohol Abuse	1.48 (1.00,2.21)	0.052
Ascites	0.66 (0.42,1.03)	0.070
Hypoalbuminemia	0.96 (0.54,1.73)	0.903
ASA Status		<.001
2 vs. 1	1.05 (0.72,1.53)	0.790
3 vs. 1	1.42 (0.97,2.06)	0.070
4 vs. 1	1.76 (1.18,2.63)	0.006
5 vs. 1	2.45 (0.77,7.76)	0.128
Surgery Information		
Type of Surgery		<.001
Cardiovascular System vs. Digestive System	1.67 (1.36,2.06)	<.001
Cardiovascular System vs. Endocrine, Hemic, and Lymphatic Systems	2.86 (2.09,3.90)	<.001
Cardiovascular System vs. Eye, Ear, Nose, Mouth, and Pharynx	2.01 (1.48,2.72)	<.001
Cardiovascular System vs. Integumentary and Musculoskeletal Systems	3.60 (2.83,4.58)	<.001
Cardiovascular System vs. Miscellaneous diagnostic and therapeutic procedures	3.99 (2.65,6.03)	<.001
Cardiovascular System vs. Nervous System	2.13 (1.68,2.70)	<.001
Cardiovascular System vs. Obstetrical, Female or Male Genital Organs, and Urinary System	1.94 (1.57,2.40)	<.001
Cardiovascular System vs. Respiratory System	1.38 (1.09,1.74)	0.007
Digestive System vs. Endocrine, Hemic, and Lymphatic Systems	1.71 (1.31,2.22)	<.001

Digestive System vs. Eye, Ear, Nose, Mouth, and Pharynx	1.20 (0.93,1.55)	0.154
Digestive System vs. Integumentary and Musculoskeletal Systems	2.15 (1.80,2.56)	<.001
Digestive System vs. Miscellaneous diagnostic and therapeutic procedures	2.39 (1.61,3.53)	<.001
Digestive System vs. Nervous System	1.27 (1.06,1.52)	0.008
Digestive System vs. Obstetrical, Female or Male Genital Organs, and Urinary System	1.16 (1.02,1.32)	0.028
Digestive System vs. Respiratory System	0.82 (0.69,0.97)	0.023
Endocrine, Hemic, and Lymphatic Systems vs. Eye, Ear, Nose, Mouth, and Pharynx	0.70 (0.50,0.99)	0.043
Endocrine, Hemic, and Lymphatic Systems vs. Integumentary and Musculoskeletal Systems	1.26 (0.94,1.68)	0.122
Endocrine, Hemic, and Lymphatic Systems vs. Miscellaneous diagnostic and therapeutic procedures	1.40 (0.89,2.20)	0.147
Endocrine, Hemic, and Lymphatic Systems vs. Nervous System	0.75 (0.56,1.00)	0.050
Endocrine, Hemic, and Lymphatic Systems vs. Obstetrical, Female or Male Genital Organs, and Urinary System	0.68 (0.52,0.89)	0.005
Endocrine, Hemic, and Lymphatic Systems vs. Respiratory System	0.48 (0.36,0.64)	<.001
Eye, Ear, Nose, Mouth, and Pharynx vs. Integumentary and Musculoskeletal Systems	1.79 (1.35,2.37)	<.001
Eye, Ear, Nose, Mouth, and Pharynx vs. Miscellaneous diagnostic and therapeutic procedures	1.99 (1.27,3.10)	0.003
Eye, Ear, Nose, Mouth, and Pharynx vs. Nervous System	1.06 (0.80,1.41)	0.685
Eye, Ear, Nose, Mouth, and Pharynx vs. Obstetrical, Female or Male Genital Organs, and Urinary System	0.97 (0.75,1.25)	0.787
Eye, Ear, Nose, Mouth, and Pharynx vs. Respiratory System	0.68 (0.52,0.90)	0.006
Integumentary and Musculoskeletal Systems vs. Miscellaneous diagnostic and therapeutic procedures	1.11 (0.74,1.67)	0.613
Integumentary and Musculoskeletal Systems vs. Nervous System	0.59 (0.48,0.73)	<.001
Integumentary and Musculoskeletal Systems vs. Obstetrical, Female or Male Genital Organs, and Urinary System	0.54 (0.45,0.65)	<.001
Integumentary and Musculoskeletal Systems vs. Respiratory System	0.38 (0.31,0.47)	<.001
Miscellaneous diagnostic and therapeutic procedures vs. Nervous System	0.53 (0.36,0.80)	0.002
Miscellaneous diagnostic and therapeutic procedures vs. Obstetrical, Female or Male Genital Organs, and Urinary System	0.49 (0.33,0.72)	<.001
Miscellaneous diagnostic and therapeutic procedures vs. Respiratory System	0.34 (0.23,0.52)	<.001
Nervous System vs. Obstetrical, Female or Male Genital Organs, and Urinary System	0.91 (0.76,1.09)	0.315
Nervous System vs. Respiratory System	0.65 (0.52,0.80)	<.001
Obstetrical, Female or Male Genital Organs, and Urinary System vs. Respiratory System	0.71 (0.60,0.84)	<.001
Duration of Surgery, per 30 min	0.83 (0.81,0.85)	<.001
Year of Surgery: 2017 vs. 2016	2.98 (2.70,3.29)	<.001
Intraoperative Factors		
Crystalloids Fluid, per 250 cc	1.03 (1.01,1.05)	0.007

Colloids Fluid, per 250 cc	1.22 (1.16,1.28)	<.001
Total Blood Use, per 50 cc	1.01 (0.99,1.03)	0.387
Blood Loss, per 50 cc	0.98 (0.96,0.99)	0.002
Urine Output, per 100 cc	1.02 (1.00,1.03)	0.042
Type and Dose of Steroidal Muscle Relaxant		
Rocuronium, per 10 mg	1.06 (1.05,1.07)	<.001
Vecuronium, per 10 mg	1.06 (0.98,1.16)	0.167