Retrospective Analysis of the Safety and Efficacy of Sugammadex Versus Neostigmine for the Reversal of Neuromuscular Blockade in Children

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BACKGROUND: Sugammadex, with its novel mechanism of action of encapsulation and noncompetitive binding of aminosteroid neuromuscular-blocking agents (rocuronium and vecuronium), may offer distinct advantage to pediatric patients where residual neuromuscular blockade may be poorly tolerated. Data describing its use in the pediatric population are limited, and no large-scale studies are available evaluating the occurrence of adverse event across the full spectrum of ages. We sought to measure the occurrence of adverse events, assess the severity and clinical significance of the events, and quantify a surrogate measure of efficacy of sugammadex compared to neostigmine in a large population and in the full age range of children.

METHODS: Beginning in September 2016 through initiation of data collection, we identified from our data warehouse that all patients were treated with sugammadex for reversal of neuromuscular blockade, from birth through adolescence, and retrospectively matched, by case type and age group, to historical neostigmine-treated controls. From subsequent chart review, we quantified occurrence of adverse events and administration of medications to treat adverse events. All cases in the originally identified cohort treated with epinephrine after administration of sugammadex underwent chart review to elicit the cause, in the event that an infrequently occurring event was not captured after the case-matching process. "End-Interval Time," the time from administration of reversal agent to time out of the procedure room, was measured as an indirect assessment of efficacy.

RESULTS: Fewer cases of bradycardia were observed in the sugammadex group compared to the neostigmine group in the overall cohort ($P < .001$) and in the subgroups of older children ($P < .001$) and adolescents ($P < .001$). End-interval time, the time measured from administration of neuromuscular blockade (NMB) reversal agent to time out of the operating room, was significantly shorter in sugammadex-treated groups in the overall cohort (mean difference, 2.8; 95% CI, 1.85–3.77; $P < .001$) and all age groups except for first year (31 days through 12 months). This observation was most pronounced in the neonatal subgroup (mean difference, 11.94 minutes; 95% CI, 4.79–19.1; $P < .001$). No other adverse events measured were found to be different between treatment groups.

CONCLUSIONS: This study provides data supporting the safe and effective use of sugammadex for reversal of neuromuscular blockade throughout the entire range of ages in the pediatric population. Within age groups, sugammadex demonstrates faster completion of operation compared with neostigmine, with the greatest difference observed in the neonatal population. (Anesth Analg 2019;129:1124–9)

KEY POINTS

- **Question:** Is sugammadex safe and effective as compared with neostigmine for reversal of neuromuscular blockade in the full age range of pediatric patients in a large population study?
- **Findings:** Reversal of neuromuscular blockade by sugammadex, as compared with neostigmine, was associated with less bradycardia in older children and adolescents and with a shorter end-interval time, most notable in the neonatal group.
- **Meaning:** In a large pediatric population, use of sugammadex for reversal of neuromuscular blockade, as compared to neostigmine, appears to be as safe as neostigmine and may be of particular benefit for the neonate.

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Sugammadex, the newest agent for reversal of neuromuscular blockade, uniquely encapsulates and binds aminosteroid nondepolarizing molecules, rendering them ineffective at the neuromuscular junction.[1] By its noncompetitive action, it provides complete and rapid reversal of neuromuscular blockade (NMB), in a dose-dependent fashion, even when very dense blockade is present.[2–5] By lacking receptor interaction, its use potentially avoids side effects of muscarinic stimulation problematic with administration of cholinesterase inhibitors.

Adverse events after administration of sugammadex measured in adult patients include bradycardia (1%–5%), hypotension (4%–13%), anaphylaxis (0.3%–0.4%), and nausea (23%–26%)/vomiting (11%–13%).[1,6] While the occurrence of these events in adults is infrequent, no large-scale study has analyzed the incidence and significance of these events in the pediatric population. Although Food and Drug Administration (FDA) approved for use in adults, its use remains restricted to off-label indications in children, such as the "Can't intubate, Can't ventilate" scenario. Pediatric studies to date include case reports, small case series, and meta-analyses of small prospective and retrospective studies.[2,7–12] These represent a small number of patients and contain much heterogeneity, limiting analysis, and extrapolation to the total population.

Children often present with conditions that may particularly benefit from complete restoration of optimal respiratory mechanics after reversal of NMB (ie, neonates, myopathic syndromes, muscular dystrophies, pulmonary hypertension, etc). Reversal of NMB with anticholinesterase inhibitors, even in appropriate doses and with evidence of reversibility, may result in postoperative weakness from residual neuromuscular blockade and may be present in a significant number of patients.[2,13,14] Suboptimal respiratory mechanics may increase the risk of postoperative morbidity in this population. In addition, children may present with syndromes associated with difficult airway or may have unrecognized difficult airway after administration of NMB. Rapid reversal of NMB and return to spontaneous ventilation may be life-saving.

We conducted a retrospective analysis of 968 pediatric patients treated with sugammadex for reversal of NMB, across a wide range of ages, matched with historical neostigmine controls, and report the observed rates of bradycardia, hypotension, bronchospasm, anaphylaxis, nausea, and vomiting. To enhance capture of adverse events and to assess severity, medications administered to treat adverse events were documented. We measured efficacy of sugammadex by comparing the difference in time from administration of reversal agent to time the patient exited the operating room (end-interval time). We hypothesized that the use of sugammadex for reversal of NMB was as safe and at least as effective as neostigmine for reversal of NMB in the full age range of children.

METHODS

After Institutional Review Board (IRB) approval and waiving of informed consent, this retrospective cohort study evaluated pediatric patients presenting to the Monroe Carrell Jr Children's Hospital at Vanderbilt University Medical Center receiving general anesthesia for a variety of procedures. We identified all patients receiving sugammadex from September 2016 (start of sugammadex availability) to June 2018 and retrospectively matched each patient with another receiving neostigmine for reversal of NMB during this time interval. All patients receiving neostigmine also received an anticholinergic agent, glycopyrrolate, or atropine for bradycardia prevention.

The Vanderbilt Perioperative Informatics Research (VAPIR) group maintains a data warehouse of prospectively collected data suitable for retrospective review. Patient data were provided by querying our perioperative data warehouse and included primary procedure, primary procedure category, defined as the first 3 digits of the clinical procedure code (CPT), date of surgery, birthdate, height, weight, sex, body mass index (BMI), ASA status, dosing time, out of room time, and operating room duration. For purposes of matching, we defined age groups as follows: neonate (<31 days), first year (31–365 days), young child (365 days to 6 years), older child (6–13 years), adolescent (13–19 years), and adult (≥19 years).

We conducted a chart review of intraoperative and postoperative outcome measures. Intraoperative outcomes, measured as a change from time immediately before administration of reversal agent to the first 15 minutes after administration of reversal agent, were recorded as yes/no data and included evidence of bradycardia (defined as a 20% reduction in heart rate), hypotension (defined as systolic blood pressure drop of 20%), bronchospasm (defined as documentation of event and/or treatment with albuterol and/or epinephrine), and anaphylaxis (defined as documented rash/hives associated with hypotension or bronchospasm). This time frame was chosen as a conservative window for capture of adverse events after review of previously reported cases of adverse events and their occurrence within 4 minutes after treatment with sugammadex.[12] To enhance capture of potential events and assess severity, intraoperative treatment given for bradycardia, anaphylaxis, and bronchospasm (epinephrine, albuterol, diphenhydramine, dexamethasone) was recorded as yes/no nominal data. The postoperative flowsheet was reviewed for documentation and/or treatment of nausea/vomiting, recorded as yes/no administration of ondansetron, metoclopramide, scopolamine, or diphenhydramine.

During the time frame of the study, patient data were maintained in 2 electronic medical record (EMR) systems. Due to a platform change occurring in November 2017, patient data were initially collected in Star Panel (Vanderbilt University Medical Center, Nashville, TN) and after November, collected in Epic (Epic Systems, Inc, Verona, WI). Due to limitations of Star Panel, "End-Interval Time," defined as the time from administration of reversal agent to "time out of the room," was used as an indirect measure of efficacy, as "time of extubation" was not routinely documented in the Star Panel database.

Study size was based on the number of pediatric patients receiving general anesthesia undergoing procedures receiving sugammadex for reversal of NMB during the time frame listed above. No a priori power analysis was performed because all available patients were considered for entry into the study.

Patient demographic data for the full cohort and the matched cases were analyzed with t tests for continuous data and χ^2 for nominal data as appropriate. Case–control matching was performed (IBM SPSS version 25.0; IBM Inc, Armonk, NY) using exact match tolerances for age group and procedure category. Once the final dataset was achieved, chart review was performed to record intraoperative and postoperative outcome variables. Outcome data were analyzed between the test groups, and subgroup analysis was analyzed by age group. χ^2 tests were used to compare nominal data between the groups, and the Bonferroni

Table 1. Demographic Data for Overall Group and Matched Group After Case–Control Matching

	Overall Group			Matched Group		
	Neostigmine n = 4136	Sugammadex n = 1946	*P* Value	Neostigmine n = 968	Sugammadex n = 968	*P* Value
Age, mean (SD)						
Years	8.5 (5.9)	9.9 (8.4)	<.001	8.5 (5.9)	8.6 (5.9)	.803
Months	107.2 (71.6)	124.2 (100.8)	<.001	107.9 (71.6)	108.7 (71.3)	.796
Days	3277 (2179)	3795 (3067)	<.001	3297 (2181)	3323 (2170)	.794
Age group, n (%)			<.001			1.000
Neonate	111 (2.7)	43 (2.2)		18 (1.9)	18 (1.9)	
First year	541 (13.1)	214 (11.0)		137 (14.2)	137 (14.2)	
Young child	830 (20.1)	408 (21.0)		186 (19.2)	186 (19.2)	
Older child	1269 (30.7)	547 (28.1)		296 (30.6)	296 (30.6)	
Adolescent	1385 (33.5)	604 (31.0)		331 (334.2)	331 (334.2)	
Adult	0 (0.0)	130 (2.1)		0 (0.0)	0 (0.0)	
Height, mean (SD)	124 (41)	123 (42)	.313	124 (42)	119 (42)	.019
Weight, mean (SD)	37.0 (28.5)	37.3 (36.4)	.864	37.1 (28.6)	33.5 (28.9)	.022
BMI, mean (SD)	20.3 (9.5)	21 (20.8)	.254	20.2 (8.8)	20.3 (8.9)	.890
Sex, n (%)			.008			.552
Female	1877 (45)	812 (42)		403 (42)	394 (41)	
Male	2259 (55)	1133 (58)		564 (58)	574 (59)	
ASA class, n (%)			<.001			.560
I	370 (9.0)	105 (5.4)		73 (7.5)	75 (7.7)	
II	2229 (53.9)	810 (41.6)		512 (52.9)	458 (47.3)	
III	1299 (31.4)	780 (40.1)		291 (30.1)	344 (35.5)	
IV	235 (5.7)	251 (129)		91 (9.4)	91 (9.4)	
V	1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

correction was applied to adjust the significance level for the number of tests, with a *P* value of <.01 considered statistically significant. In the subgroups that had an expected count <5, the Fisher exact test was reported. Continuous data were analyzed with paired *t* tests, and a *P* value of <.05 was considered statistically significant.

This manuscript adheres to applicable Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) guidelines.[15]

RESULTS

We identified 1946 patients who received sugammadex and 4136 patients who received neostigmine from our cohort of pediatric patients having general anesthesia for procedures. After age and case matching, 968 patients in each group were available for chart review. The 2 groups were not statistically different with regards to age, age group, sex, BMI, or ASA classification. (Demographic data are available in Table 1.)

The adverse events by age group and the overall cohort are presented in Table 2. Bradycardia was observed more commonly in neostigmine patients than in sugammadex patients in the total cohort 150 vs 71 ($P < .001$). In the subgroup analysis, differences in the incidence of bradycardia were observed in the young children, older children, and the adolescent groups but were only significant in the latter 2 groups ($P < .001$ and $P < .001$, respectively). The incidence of other adverse events, hypotension, bronchospasm, anaphylaxis, or vomiting, was not found to be different between the 2 groups overall or when analyzed by subgroup.

The treatment of anaphylaxis events as measured by the administration of certain indicator medications is given in Table 3. The administrations of epinephrine, albuterol diphenhydramine, and dexamethasone did not differ between the groups.

Anaphylaxis was documented in only 1 patient, occurring in the neostigmine-treated group. Two highly suspected cases of anaphylaxis were observed from chart review of all patients initially available for case matching that received epinephrine after treatment with sugammadex. These cases were not captured in our case-matching process because a suitably matched neostigmine-treated control was not available but are represented in our description of anaphylaxis in the discussion. Inclusion of these patients gives a maximum observed incidence of anaphylaxis with sugammadex of 0.1% and is not different from the observed incidence seen with neostigmine (0.1%).

All matched patients receiving epinephrine underwent chart review to ascertain the underlying adverse event requiring treatment. One patient in the sugammadex group received epinephrine to treat primary bradycardia with secondary hypotension, 1 patient in the neostigmine group required epinephrine for anaphylaxis, and all others experienced bronchospasm or some other airway-related event necessitating treatment.

End-interval time was found to be significantly shorter in the sugammadex group overall (mean difference, 2.81 minutes; 95% CI, 1.85–3.77; $P < .001$) than in the neostigmine group (Table 4). In the subgroup analysis, all groups except the first-year group had significantly shorter end-interval times in the sugammadex group as compared to the neostigmine patients. The greatest difference between treatment groups was observed in the neonatal cohort, with sugammadex-treated neonates observing an 11.94-minute faster end-interval time ($P = .012$). Despite the small sample size in this subgroup, post hoc power analysis indicated that this study has a power of 0.915 to detect a difference of this magnitude.

Table 2. Adverse Events by Age Group

	Neonates (n = 18)	First Year (n = 137)	Young Children (n = 186)	Older Children (n = 296)	Adolescent (n = 331)	Total (n = 968)
Bradycardia						
Cases observed						
Neostigmine cases	1	1	17	63	68	150
Observed sugammadex	1	5	11	19	35	71
P value	1.000[a]	.214[a]	.238	<.001	.001	<.001
Hypotension						
Cases observed						
Neostigmine cases	0	7	6	19	19	51
Observed sugammadex	0	10	7	19	20	56
P value	…	.452	.778	.606	.567	.357
Bronchospasm						
Cases observed						
Neostigmine cases	0	1	3	4	1	9
Observed sugammadex	0	4	5	3	1	13
P value	…	.370[a]	.724[a]	1.000[a]	.606[a]	.421
Anaphylaxis						
Cases observed						
Neostigmine cases	0	0	0	0	1	1
Observed sugammadex	0	0	0	0	0	0
P value	…	…	…	…	.317[a]	.317
Nausea/vomiting						
Cases observed						
Neostigmine cases	0	4	5	27	43	79
Observed sugammadex	0	0	5	34	47	86
P value	…	.122[a]	1.000	.344	.551	.518

[a]Fisher exact test.

Table 3. Treatment of Anaphylaxis Events

	Neonates (n = 18)	First Year (n = 137)	Young Children (n = 186)	Older Children (n = 296)	Adolescent (n = 331)	Total (n = 968)
Epinephrine						
Cases observed						
Neostigmine cases	0	1	2	1	0	4
Observed sugammadex	1	3	2	0	1	7
P value	1.000[a]	.622[a]	1.000[a]	1.000[a]	.368[a]	.402
Albuterol						
Cases observed						
Neostigmine cases	0	3	2	4	3	12
Observed sugammadex	0	1	6	4	1	12
P value	…	.622[a]	.284[a]	1.000[a]	.365[a]	.606
Diphenhydramine						
Cases observed						
Neostigmine cases	0	0	0	2	3	5
Observed sugammadex	0	0	0	0	0	0
P value	…	…	…	.499[a]	.134[a]	.049[a]
Dexamethasone						
Cases observed						
Neostigmine cases	0	2	6	3	6	17
Observed sugammadex	0	1	2	1	3	7
P value	…	1.000[a]	.284[a]	.624[a]	.363[a]	.073

[a]Fisher exact test.

Table 4. End Interval Time

End Interval	Neonates (N = 18)	First Year (N = 137)	Young Children (N = 186)	Older Children (N = 296)	Adolescent (N = 331)	Total (N = 968)
Mean difference (neostigmine–sugammadex)	11.94	1.83	2.33	3.38	2.52	2.81
95% CI	4.77–19.1	−1.2 to 4.9	0.28–4.4	1.7–5.0	0.92–4.1	1.85–3.77
P value	.012	.175	.010	<.001	.002	<.001

Paired sample *t* test.
Abbreviation: CI, confidence interval.

DISCUSSION

Liu et al,[11] in a meta-analysis comprised of 10 studies and 575 pediatric patients, demonstrated reduction in the risk of bradycardia after treatment with sugammadex, as compared to neostigmine, with no difference in the incidence of other adverse events such as nausea and vomiting or bronchospasm. Criticism by the authors of this meta-analysis included the lack of a consistent definition of bradycardia between the studies and the presence of considerable amount heterogeneity within the studies despite sensitivity and subgroup analysis.[11] Our study minimizes heterogeneity by the study design and case-matching process, defines bradycardia as an outcome variable, and strives to assess clinical severity of adverse events based on treatment.

This study evaluated nearly 1000 pediatric patients, across the full spectrum of ages, treated with sugammadex for reversal of neuromuscular blockade and compared the observed occurrence of various adverse events to historical, case-matched neostigmine controls. In the total study population, the incidence of bradycardia in sugammadex-treated patients was less than half of that observed in those treated with neostigmine (7.3% vs 15.5%), but this difference was seen primarily in the older pediatric population. The clinical severity of bradycardia was assessed indirectly by analyzing epinephrine administration. Epinephrine, used to treat a number of different clinical conditions such as bradycardia, bronchospasm, anaphylaxis, and hypotension, is the first-line medication indicated by pediatric advanced life support (PALS) to treat pediatric bradycardia not specifically known to be directly caused by vagal response.[16] The incidence of epinephrine administration in the total study population was low and not different between treatment groups (0.4% neostigmine treated versus 0.7% sugammadex treated; $P = .40$). Given that cardiac output is heart rate dependent in young children, it is reassuring that bradycardia in the pediatric population studied, when it did occur, did not appear to be severe enough to require such treatment.

Alonso et al[9] presented data supporting rapid reversal of NMB with sugammadex (4 mg/kg) in neonates (23 patients), ranging in age from birth to 1 month, showing no observed adverse events. Our study also observed no difference in the occurrence of adverse events between treatment groups in the neonatal population and offered a comparison to neostigmine. Of the neonates studied, 1 patient treated with sugammadex did receive epinephrine for treatment of bradycardia after extubation. Chart review of this event described bradycardia to be secondary to hypoxia from apnea, rather than drug reaction. Residual weakness or airway obstruction from inadequate pharyngeal muscle strength was not reported as contributory to the hypoxic/bradycardic event.

While all age groups demonstrated shorter end-interval time after treatment with sugammadex, this difference was greatest in the neonatal cohort where a nearly 12-minute shorter time from reversal agent administration to out of the operating room was observed. This finding may reflect more optimized respiratory mechanics in this population at risk for reduced efficiency of respiratory muscles, increased risk of functional residual capacity (FRC) loss, and increased airway resistance that may be associated with residual neuromuscular weakness.[17]

Anaphylaxis associated with sugammadex, reported to be 0.3%–0.4% in the adult population,[3] was observed less frequently in the pediatric population studied and was not statistically different between treatment groups. One adolescent patient treated with neostigmine experienced anaphylaxis compared with none in the sugammadex group in our matched cohort. Two patients in the initial unmatched cohort were identified from review of the medical record as receiving epinephrine to treat signs and symptoms of anaphylaxis after administration of sugammadex. These patients were not captured for study in the final matched population because a suitably matched neostigmine-treated control was lacking. Inclusion of these patients gives an observed incidence of anaphylaxis with sugammadex of 0.1% (2/1946) and is significantly lower than the 0.3%–0.4% previously reported in the adult literature.[3]

Limitations of this study include inadequate power within each age group–matched cohort to make strong statements of safety. As this is a retrospective observational study, aspects of the individual anesthetic management were not controlled and may be a source of heterogeneity and possible bias. The dose of sugammadex and neostigmine was not controlled as part of the matching process nor are there specific pediatric dosing guidelines for sugammadex. Dosing of sugammadex for pediatric patients is extrapolated from adult literature. Due to a paucity of data, our institution's pharmacy has no specific dosing guidelines in neonates and recommends 2–4 mg/kg for children based on train-of-four (TOF) measurements. The choice of end-interval time as an indirect assessment of efficacy (necessary, as "Extubation Time" was not consistently recorded in our previous EMR system), while seeming a crude measurement, may reflect more clinically relevant information. How fast a patient is reversed from neuromuscular blockade achieves readiness for extubation and demonstrates adequate respiratory mechanics dictates how soon they are able to leave the operating room. While practice variations not measured by the study may contribute to some confounding of the data, in a large population, this variability should be evenly distributed between treatment groups, decreasing potential bias between differing anesthesia providers.

These data support the use of sugammadex in the full range of ages in the pediatric population. The incidence of clinically significant bradycardia or the occurrence of anaphylaxis appears to have a low frequency, and the possible risk may be offset by the benefit of rapid return to optimal respiratory mechanics and neuromuscular strength. Large-scale prospective studies would offer greater power to detect further advantage over neostigmine within various age groups.

DISCLOSURES

Name: Renee S. Gaver, MD.
Contribution: This author helped design the study, develop the protocol, get Institutional Review Board (IRB) approval, analyze the results, and develop the manuscript.
Name: Bruce R. Brenn, MD.
Contribution: This author helped with case matching, statistical analysis, supervision of data collection, writing methods, and editing manuscript.

Name: Alison Gartley, BS.
Contribution: As a summer intern in the Vanderbilt Perioperative Informatics Research (VAPIR) program, this author helped collect the data, analyze the statistical data, and provide study support (literature searches, interim study progress presentations).
Name: Brian S. Donahue, MD, PhD.
Contribution: This author helped provide senior mentoring for study design, develop the protocol, and edit the manuscript.
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