The use of Sugammadex as rescue therapy following inadequate reversal with neostigmine
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PROTOCOL TITLE:

The use of sugammadex as rescue therapy following inadequate reversal with neostigmine

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IND EXEMPT

REVISION HISTORY

Revision #	Version Date	Summary of Changes
3	10/14/2024	Change in PI

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1. Study Summary

Project Title	The use of sugammadex as rescue therapy following inadequate reversal with neostigmine
Project Design	Double-blind randomized placebo-controlled dose-response trial
Primary Objective	To determine what is an appropriate dose of sugammadex as rescue therapy following inadequate reversal with neostigmine
Secondary Objective(s)	
Research Intervention(s)/Interactions	2 mg/kg, 1 mg/kg, 0.5 mg/kg, 0.25 mg/kg, 0.125 mg/kg of sugammadex and placebo
Study Population	- Aged 18 years and above - Scheduled to undergo an elective surgery in the main operating room or outpatient surgery center at Grady Memorial Hospital, - Receive general anesthesia (standardized to sevoflurane for maintenance), - Receive rocuronium for NMB, - Receive neostigmine for NMB reversal, and - Achieve a TOF count of at least 3 twitches but not a TOF ratio of 0.9 fifteen minutes after neostigmine has been given.
Sample Size	36
Study Duration for individual participants	1 day (from start of surgery until PACU discharge)
Study Specific Abbreviations/ Definitions	NMB: neuromuscular blockade PACU: post anesthesia care unit TOF: train of four
Funding Source (if any)	Georgia CTSA (Clinical & Translational Science Alliance) pilot grants program

2. Objectives

Objective: To determine what is an appropriate dose of sugammadex as rescue therapy following inadequate reversal with neostigmine.

Hypothesis: That a lower dose of sugammadex than currently recommended by the manufacturer is enough to achieve adequate reversal following neostigmine.

3. Background

Neuromuscular blocking agents (NMBAs) are commonly used in the practice of anesthesiology for skeletal muscle relaxation to facilitate tracheal intubation, mechanical ventilation, and to provide optimal surgical conditions. They fall into two categories, i.e. the non-depolarizing agents versus succinylcholine, which is the only depolarizing agent in clinical use. Non-depolarizing NMBAs in turn are classified as either an aminosteroid or benzylisoquinolinium compound; the former include pancuronium, vecuronium, and rocuronium, whereas the latter include atracurium, cisatracurium and mivacurium (1). In order to prevent residual NMB, it is vital to adequately reverse any use of a non-depolarizing NMBA. This was historically done using an anticholinesterase such as neostigmine, which would increase the concentration of acetylcholine at the neuromuscular junction leading to the return of neuromuscular transmission.

Unfortunately, there are disadvantages to the use of an anticholinesterase. Firstly, there is a "ceiling" effect, i.e. "once the acetylcholinesterase enzyme is maximally inhibited by an anticholinesterase agent and peak concentrations of acetylcholine are present, the administration of additional drug will not further increase acetylcholine levels or enhance recovery of neuromuscular blockade" (2, p. 842). Secondly, the use of an anticholinesterase with relatively mild residual blockade may lead to paradoxical muscle weakness. Thirdly, anticholinesterase agents have a multitude of adverse effects due to their muscarinic effects such as nausea, bradycardia, and bronchospasm. (2) Thus, an alternative method to antagonize the non-depolarizing NMBAs came to be a topic of research.

It was in this context that sugammadex was found to be a valuable addition to the anesthesiologist's armamentarium. It is a modified γ-cyclodextrin that encapsulates the aminosteroid NMBAs rocuronium and vecuronium. It was first discovered by the Organon Laboratories in Scotland and was then known as the agent Org 25969. The successful results of the first *in vivo* study was published in 2002 (3), where rocuronium was reversed in anesthetized monkeys, and the first phase I study was published in 2005 (4). It was approved by the United States Food and Drugs Administration (FDA) in 2015, with the following three dosing ranges, i.e. 2 mg/kg if the train-of-four (TOF) stimulation reaches the second twitch, 4 mg/kg if there is no twitch response to TOF stimulation but there are 1 to 2 post-tetanic counts (PTC), and 16 mg/kg after administration of 1.2 mg/kg of rocuronium (5).

In the clinical assessment of NMBA reversal, a TOF ratio[1] of 0.7 was historically seen as adequate, but this has been revised in the face of recent evidence that showed a TOF ratio of any less than 0.9 could result in "impaired pharyngeal function, airway obstruction, an increased risk of aspiration of gastric contents, an impaired hypoxic ventilatory control, and unpleasant symptoms of muscle weakness" (2, p. 836). Even if the TOF stimulation count is 4 but there is still detectable TOF fade, the TOF ratio will equate to 0.1-0.4 (6); this does not significantly change with a 5-second, 50-Hz tetanic stimulation (TOF ratio ~0.3) and is only slightly improved with double-burst stimulation (TOF ratio ~0.6-0.7) (2).

Carvalho *et al.* conducted a meta-analysis of 53 studies (12,664 adult patients), where the pooled residual NMB incidence ranged from 0.115 when quantitative neuromuscular monitoring was used to 0.331 where no neuromuscular monitoring was used (7). Raval *et al.* conducted a meta-analysis of 20 randomized controlled trials (1,923 adult patients), where residual NMB (TOF ratio < 0.9) was found in 2.8% of patients who received sugammadex compared to 39% of those who received neostigmine 15 minutes post administration for a moderate block (TOF count 1-4) compared to 1.1% for sugammadex versus 99.1% for neostigmine 15 minutes after administration for a deep block (PTC 1-5) (8). Concerningly, 60 minutes after administration, 2.1% of the sugammadex group versus 19% of the neostigmine group still had NMB in the moderate block group compared to 0.4% of the sugammadex group versus 39.3% of the neostigmine group in the deep block group. When expanded to observational studies (58 studies with 25,277 adult patients), the incidence of residual NMB (TOF ratio < 0.9 upon arrival to PACU) ranged from 0% to 90.5% (median 30%), which was significantly lower (0% to 16%) in the sugammadex group compared to 3.5% to 90.5% in the neostigmine group and 15% to 89% in the spontaneous recovery group (9).

The incidence of residual NMB in the pediatric population has been variably reported. Ledowski *et al.* published in 2015 a series of 64 children (average age 8.2 years) who received NMBA for tracheal intubation, only 33 of whom received NMB reversal (32 with neostigmine 0.08 mg/kg and 1 with sugammadex); 19.4% of those who received no reversal and 37.5% of those who received neostigmine was found to have residual NMB (TOF ratio < 0.9) prior to extubation using acceleromyometry, giving an overall incidence of 28.1% (10). Similarly, Klucka *et al.* published in 2019 a series of 291 children (range: 29 weeks to 19 years of age) who received NMBA for surgery, 68 of whom received NMB reversal; the TOF ratio was found to be < 0.9 in 48.2% of patients prior to extubation in the OR versus 26.9% upon arrival to the PACU using accelerometry (11).

A Cochrane systematic review published in 2017 (12) analyzed 41 randomized controlled trials of 4,206 adults who received non-depolarizing NMBAs for elective surgery, and found that a 2 mg/kg dose of sugammadex was 6.6 times faster (10.22 minutes) than a 0.05 mg/kg dose of neostigmine in reversing moderate NMB from the second twitch (T2) to a TOF ratio > 0.9, while

[1] The ratio of the fourth (T4) to the first (T1) twitch after a TOF stimulation

a 4 mg/kg dose of sugammadex was 16.8 times faster (45.78 minutes) than a 0.07 mg/kg dose of neostigmine in reversing deep NMB from a PTC 1-5 to TOF ratio > 0.9.

However, less is known when there is shallow NMB, i.e. when the TOF count is 4 but there is still detectable TOF fade. Concerningly, Kirkegaard *et al.* found in 2002 that the maximal 0.07 mg/kg dose of neostigmine was unable to reverse all patients to a TOF ratio of 0.9 within 30 minutes, even at a pre-intervention TOF count of 4 (13). Whether a lower dose of sugammadex would be sufficient to achieve a TOF ratio of 0.9 after shallow NMB has been examined by Schaller *et al*. in 2010 and Pongrácz *et al.* in 2013. The former group found that in a group of 94 adults undergoing elective surgery, a dose of 0.22 mg/kg of sugammadex was equivalent to a dose of 0.034 mg/kg of neostigmine in reversing NMB from a TOF ratio of 0.5 to 0.9 within 5 minutes in 95% of their patients (14). Conversely, Pongrácz's group found that a 0.5 mg/kg dose of sugammadex reversed NMB from a TOF count of 4 to a TOF ratio of 1.0 in 4.1 minutes on average compared to 2.1 minutes for a 1.0 mg/kg dose of sugammadex, 1.8 minutes for a 2.0 mg/kg of sugammadex, and 8.5 minutes for a 0.05 mg/kg dose of neostigmine (15).

Due to the high cost of sugammadex, some researchers have hypothesized that a lower dose is required when combined with neostigmine. A 2015 study from Beirut in adults undergoing elective surgery demonstrated that a dose of 2 mg/kg of sugammadex combined with neostigmine 0.05 mg/kg was non-inferior to the standard dose of 4 mg/kg of sugammadex in reversing deep NMB, defined as returning from a TOF count of 0 to a TOF ratio of 0.9 within 5 minutes, with similar times to extubation as well as no cases of recurarization in the post anesthetic care unit (PACU) (16). Lobaz, Sammut and Damodaran reported in 2013 the use of sugammadex as rescue therapy for a 71-year-old patient with end stage renal disease who was unable to be weaned off the ventilator almost five hours after receiving a single 1.2 mg/kg dose of rocuronium. He had initially achieved a TOF of 4, was reversed with 2.5 mg of neostigmine 45 minutes after induction, but failed to maintain adequate spontaneous ventilation despite his TOF remaining at 4, and was transferred to the intensive care unit 3 hours post induction. There, his TOF steadily declined to 2, as a result of which he received a 6 mg/kg dose of sugammadex, causing him to be successfully extubated ten minutes later (17). It is similarly important to dose sugammadex appropriately; Carollo *et al.* published a case report in 2019 of an 8-month-old patient who had recurarization after a 4 mg/kg dose of sugammadex was given with a TOF count of 2/4, which fortunately resolved after a second 4 mg/kg dose of sugammadex (18).

Lastly, known common adverse effects of neostigmine include bradycardia, nausea and vomiting (19), while the use of sugammadex has been found to lead to nausea, vomiting, hypotension and headache in ≥ 10% of patients (5). There have also been case reports of marked bradycardia possibly leading to cardiac arrest with the use of both agents.

4. Study Endpoints

Primary study outcome:

> The time taken to achieve a TOF ratio of 0.9 after the use of the intervention drug versus placebo in a patient population that has already received neostigmine for NMB reversal.

Secondary study outcome:

> The percentage of patients who achieve a TOF ratio of 0.9 within 1 minute, 2 minutes, 5 minutes, and 10 minutes.

Safety outcomes:

> The incidence in PACU (measured in %) of:

i. Nausea,
ii. Vomiting,
iii. Bradycardia[2],
iv. Tachycardia[3], and
v. Hypotension[4].

For the safety outcomes, patients who were recruited but did not receive the intervention drug will be compared to patients who did receive the intervention drug to determine if their rates of adverse effects are similar. However, the sample size in this study is too low to perform formal non-inferiority tests on this data.

5. Study Intervention/Investigational Agent

Study intervention:

> Patients will be randomized to six groups: 2 mg/kg (the lowest dose approved by the FDA), 1 mg/kg, 0.5 mg/kg, 0.25 mg/kg, 0.125 mg/kg of sugammadex and placebo (normal saline).

The Grady Memorial Hospital operating room pharmacy will store and dispense the study drug, while the anesthesia provider in the operating room will administer it.

As elaborated before, sugammadex is a FDA-approved drug that is in routine clinical use for NMB reversal.

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[2] Heart rate < 60 beats per minute over two or more recordings if not present pre-operatively
[3] Heart rate > 100 beats per minute over two or more recordings if not present pre-operatively
[4] Systolic blood pressure < 90 mmHg and/or mean arterial pressure < 65 mmHg over two or more recordings

The study protocol was submitted to the U.S. FDA, and found to be exempt from IND regulations (PIND 162798 dated 2022-Jul-13).

6. Procedures Involved

This project is a double-blind randomized placebo-controlled dose-response trial that aims to determine the time taken to achieve adequate reversal comparing five doses of sugammadex as rescue therapy following inadequate reversal with neostigmine.

We will identify patients in the Grady Memorial Hospital OR who are scheduled to undergo an elective surgery under general anesthesia, received rocuronium for NMB and neostigmine for NMB reversal, and achieved a TOF count of at least 3 twitches but not a TOF ratio of 0.9 fifteen minutes after neostigmine has been given.

These patients will be randomized using the Emory University REDCap (Research Electronic Data Capture) software to six groups: 2 mg/kg (the lowest dose approved by the FDA), 1 mg/kg, 0.5 mg/kg, 0.25 mg/kg, 0.125 mg/kg of sugammadex and placebo. Doses would be based on actual body weight. The time taken to reach a TOF ratio of 0.9 thereafter would be measured. If the patient fails to achieve this goal by 10 minutes, sugammadex would be given in 2 mg/kg increments until the patient reaches this threshold and can be safely extubated. The TOF ratio would be measured again at 30 minutes after arrival at the PACU to exclude delayed residual NMB with the plan to give further 2 mg/kg doses of sugammadex if detected.

The inclusion of a placebo group would allow us to examine if patients may recover spontaneously over that time without needing any sugammadex at all, and what parameters may predict that subset of patients. It will also improve the dose response modelling, in that randomization has been weighted so that patients who are least likely to need sugammadex (i.e. if they achieved a TOF count of 4 twitches without fade) are more likely to be in the placebo group or at the lowest dose of sugammadex that is being tested.

The time taken to a TOF ratio of 0.9 after the intervention drug has been given would be compared for statistically significant differences, controlling for the:

- TOF count (3 twitches, 4 twitches with fade, 4 twitches without fade), and
- TOF ratio (0 to < 0.9)

15 minutes after neostigmine has been given and prior to giving the intervention drug.

Quantitative neuromuscular monitoring will be carried out using electromyography, which measures the TOF ratio every 20 seconds. The TOF count (between 0 to 4) and the TOF ratio (0 to 1) would be measured and recorded at baseline and after administration of the study drug. If the TOF ratio remains < 0.9 after this, or if the patient exhibits any symptoms or signs of residual NMB blockade, a further 2 mg/kg dose of sugammadex would be given until the patient achieves a TOF ratio of 0.9.

7. Statistical Analysis Plan

Power Analysis

An *a priori* power analysis was conducted using G*Power 3.1.9.4 (20). We used an ANOVA F-Test for one-way omnibus difference between groups, alpha threshold of 0.05 for rejecting the null hypothesis, statistical power of 0.80 and a "very large" effect size of 0.765 was calculated based on results from a 2013 randomized controlled trial that examined time from TOF count = 4 to TOF ratio 1.0 comparing neostigmine to three different doses of sugammadex: 0.5, 1.0, and 2.0 mg/kg (15). This gave a required sample size of N=24. This number was increased to N=36 to account for patients with poor modeling from a high starting TOFR (resulting in few data points for that patient) or incomplete recovery within the maximum ten minutes allotted. An anticipated 70% of those enrolled will become ineligible because of an initial TOFR of 90% or greater, thus not requiring any medications, so up to 120 patients may need to be recruited and screened, but only 36 will receive any treatment.

Methodology

Randomization will occur with permuted block randomization, divided into 18 groups, to ensure proportional allocation of participants in each group over time. Dose randomization will be assigned after stratifying by initial TOFC, with a set number of patients recruited for each group, as seen the table below. This ensures that patients who likely need a lower dose are more likely to receive it. Randomization will not occur until participation is assured, i.e., their TOFR is <0.90.

Table 1: Randomization plan for patients (n=36)

Sugammadex Dose (mg/kg) →			**0.00**	**0.125**	**0.25**	**0.50**	**1.00**	**2.00**	
Initial TOFR	**Initial TOFC**	**Fade**	**placebo**						**Total**
≥ 0.9	NA	NA	No treatment; track for adverse events						0
< 0.9	4	No	3 pt	3 pt	2 pt	2 pt	1 pt	1 pt	12
		Yes	2 pt	2 pt	2 pt	2 pt	2 pt	2 pt	12
	3	NA	1 pt	1 pt	2 pt	2 pt	3 pt	3 pt	12
< 0.9	0-2	NA	No treatment; track for adverse events						0
Total # of Patients (pt)			6	6	6	6	6	6	36

Statistical Methodology

Assuming assumptions are valid, an increasing exponential regression model with random intercept will be fitted with Time of Four Ratio versus Time, stratified by the natural log of the five dose levels (modeled below). This translates to a slow response initially followed by a more rapid response later. The random intercept will allow for different initial TOFR values.

$$TOFR = \frac{1}{B}e^{(A+time)/B} + TOFR_{initial} + C * \ln(dose)$$

"Success" will be defined as TOFR of ≥0.9 within 5 minutes for 95% of patients, following the model estimate, adjusting for the 95% confidence intervals of the estimates, based on initial TOF ratios, which may be grouped as needed. A secondary analysis will be conducted by TOFC to determine optimal dose at each TOFC level, and if TOFC correlates strongly with TOFR.

8. Data and/or Specimen Banking

N/A

9. Sharing of Results with Participants

N/A

10. Study Timelines

All subjects are anticipated to participate in the study from the start of their surgery to the time of their discharge from the PACU, which should be on the same day. It is expected that 1 year would be required to enroll all study subjects, and for the study to be completed by July 2023.

11. Inclusion and Exclusion Criteria

Individuals will be screened for eligibility at the anesthesia pre-admission clinic.

Inclusion criteria:

- Patients aged 18 years and above who will
- Undergo an elective surgery in the main operating room or outpatient surgery center at Grady Memorial Hospital,
- Receive general anesthesia (standardized to sevoflurane for maintenance),
- Receive rocuronium for NMB,
- Receive neostigmine for NMB reversal,
- Achieve a TOF count of at least 3 twitches but not a TOF ratio of 0.9 fifteen minutes after neostigmine has been given, and
- Able and willing to provide informed consent.

Exclusion criteria:

- Pregnancy and/or lactating,
- BMI ≥ 40,
- Severe renal impairment, i.e. chronic kidney disease stages IV and V as defined by GFR < 30 ml/min/1.73 m^2 (21),
- Severe hepatic impairment, i.e. Child-Pugh score C[5] (22, 23),
- Pre-existing neuromuscular disease,
- Anticipated need for postoperative intubation, and/or
- Known hypersensitivity reactions to rocuronium, neostigmine and/or sugammadex.

12. Population

We will not be including the following special populations:

- Adults unable to consent
- Individuals under the age of 18 years
- Pregnant women
- Prisoners
- Cognitively impaired or Individuals with Impaired Decision-Making Capacity
- Individuals who are not able to clearly understand English

Racial and ethnic classification of subjects would be collected from their electronic medical record (which is based on self-identification) for descriptive statistics. Race would comprise the following six categories: white, black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and two or more races. Ethnicity would be either Hispanic/Latino or not Hispanic/Latino. This information will not be used as a variable to explain differences between participants, but will be presented in Table 1 as part of the study's demographic data, which may help in assessing if the study could be generalized to other patient populations in turn.

The number of individuals who are not able to clearly understand English constitute a minority of the patient population at Grady Memorial Hospital.

13. Vulnerable Populations

N/A

14. Local Number of Participants

Up to 120 patients may need to be enrolled and screened, but only 36 will receive any treatment. We anticipate a similar percentage of participants according to sex, but the majority

[5] Child-Pugh classification includes bilirubin, INR, albumin, ascites and encephalopathy. A total score of 5-6 is class A, 7-9 is class B and 10-15 is class C.

would likely be either white or black due to general patient demographics in Grady Memorial Hospital.

15. Recruitment Methods

All patients presenting to the anesthesia pre-admission clinic as well as inpatients scheduled for the operating room the next day would be screened via electronic medical record on a day-to-day basis to determine if they are eligible to participate in the study. Eligibility screening would be determined based on their most recent surgical notes (i.e. whether the patient would likely undergo general anesthesia as well as NMB).

Patients who are eligible would then be contacted and introduced to the study by a study team member for potential recruitment, at a minimum the day before the date of surgery in order to allow enough time for the patient to consider the risks and benefits of participation.

16. Withdrawal of Participants

Patients may be withdrawn from the research study without their consent if they are found to not meet the study's inclusion criteria, e.g.

- Did not require general anesthesia for surgery,
- Did not require NMB,
- Did not receive neostigmine for NMB reversal,
- Had a TOF count < 3 or a TOF ratio ≥ 0.9 fifteen minutes after neostigmine, or
- Remained intubated in the immediate postoperative period.

As the study intervention is a one-time dose of the study drug in the OR, no further action should be required if the patient decides to later withdraw from the study. The study will be terminated when the number of participants has reached the required threshold.

17. Risk to Participants

The most common risks of sugammadex as listed by the FDA (5) include:

- Nausea (23-26%)
- Vomiting (11-15%)
- Pain (36-52%)

Uncommon but serious risks of sugammadex include:

- Hypotension (4-13%)
- Tachycardia (2-5%)

- Bradycardia (1-5%)
- Anaphylaxis (0.3%)

Notably, all of these are known to be risks of general anesthesia as well as surgery and are routinely monitored for and treated in the PACU.

18. Potential Benefits to Participants

All study subjects will have any residual NMB reversed, which will prevent any postoperative complications such as respiratory compromise or weakness.

19. Compensation to Participants

N/A

20. Data Management and Confidentiality

Data to be collected include:

i. Baseline demographics: MRN, date of birth, sex (male/female), race (white, black, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, two or more races), ethnicity (Hispanic or Latino, not Hispanic or Latino), weight (kg)
ii. Preoperative details: ASA status (I-IV)
iii. Surgery details: date of surgery, diagnosis, surgery, start case time (hr: min), end case time (hr: min)
iv. Anesthesia details: if succinylcholine was used (Y/N), total amount of rocuronium given (mg), the last dose of rocuronium that was given (mg), the time that the last dose of rocuronium was given (hr:min), neostigmine dose (mg), the time that neostigmine was given (hr: min), the time that the study drug was given (hr: min).
v. TOF ratio (0-1)
    - Before any paralytic is given at the start of the case
    - Before neostigmine is given at the end of the case
    - Before the study drug is given
    - 30 minutes after PACU arrival
vi. TOF count (0-4 ± fade)
    - Before neostigmine is given at the end of the case
    - Before the study drug is given
vii. The time taken to achieve a TOF ratio of 0.9 (seconds).
viii. Postoperative details: if there was any of the following adverse effects: nausea, vomiting, bradycardia, tachycardia, hypotension (Y/N).

Baseline demographics and postoperative complications will be collected for patients who were enrolled but did not meet the study inclusion criteria to receive the intervention drug and their data will be used as a control group for the safety outcomes.

The data collection form is in the Emory University REDCap database but a similar form has been attached to this protocol as an Excel spreadsheet. Data would be collected by the study team in the OR and PACU. Data will be stored on the Emory University REDCap and OneDrive databases and may also be sent confidentially between study team members through the Emory University Outlook email network. The REDCap and OneDrive databases as well as the Outlook email network are all secure, encrypted and password protected. Paper consent forms will be stored in a locked box in the principal investigator's office at Grady Memorial Hospital. All data and records will be retained for at least 6 years following study completion.

Results will be reported in an aggregate form and in a de-identified manner. The form with protected health information (date of birth, date of surgery and MRN) will be recorded on a form separate to the form with data to be analyzed. Only study team members will have access to the form that links the study IDs with protected health information. Mr. David Boorman, the biostatistician for the Emory University Department of Anesthesiology, will conduct the data analysis in collaboration with the principal investigator.

If a participant declines to participate in all portions of the study, the participant will not be assigned a study ID number and the study team members will refrain from collecting any data on the participant. If the participant agrees to participate in some portions of the study but not others, the participant will be assigned a study ID number and the study team members will be instructed to collect data only on those aspects of the study to which the participant has agreed to participate. These procedures will help prevent unauthorized inclusion of the patient's data in the database.

21. Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

X More than minimal risk

Review our Data and Safety Monitoring Questionnaire and insert the relevant monitoring table at the end of this section. Also upload the completed questionnaire in the "Basic Study Information" smartform section in eIRB, question #8, as a separate document.

Select one of the following:	
☐ Medium Complexity	
☐ High Complexity Category A	

☒ High Complexity Category B

The study team will review the safety endpoints (nausea, vomiting, bradycardia, hypotension) on a monthly basis for the duration of the study. These safety endpoints are collected at each study visit and recorded in the study database. Patients are routinely assessed for these side effects in the PACU by their bedside nurse as well as the anesthesia resident who is responsible for discharging them from the PACU.

		Subgroup n=6		**Total N=36**	
Event	**Assumed Probability Risk (upper end)**	**p<0.01**	**Safety cut short if...**	**p<0.01**	**Safety cut short if...**
Nausea (high)	0.25	p=0.0046	n≥5	p=0.0086	n≥16
Vomiting (high)	0.15	p=0.0059	n≥4	p=0.0048	n≥12
Bradycardia (high)	0.05	p=0.0022	n≥3	p=0.0083	n≥6
Hypotension (high)	0.15	p=0.0059	n≥4	p=0.0048	n≥12

Using the binomial equation (see below), we calculated the probability of seeing a set number of patients in each group, if the actual probability in the normal surgical population is at the level specified in the 'assumed probability' column.

For example, if the 'normal' probability of nausea is up to 25% (that is, the risk with treatment is the same as the risk under standard surgical conditions), then the chance of having 5 or more patients with nausea in any one treatment group is 0.0046, and the chance of having 16 or more patients with nausea in total is p=0.0048. Since this is unlikely, we will reject the null hypothesis, and conclude that the actual risk in our trial is actually higher than that. So if 5 or more patients report nausea in any one group or if 16 or more patients report nausea in total, this would trigger a suspension of the trial for further review.

$$P(X \geq x) = \sum_{x}^{N} \binom{N}{x} p^{x}(1-p)^{(N-x)}$$

Data on serious adverse events such as death, perioperative cardiac arrest, and unplanned hospitalization as well as any other adverse events will also be collected up to the time of PACU discharge for both study participants as well as screen failures (participants who were recruited but not enrolled in the trial due to not fulfilling the study inclusion criteria).

Monitoring Table 3

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Real-time review of participant data during initial data collection.	PI will review the data as it is being collected.	Every data collection timepoint *Expectation is that this happens every time you obtain information.*	PI
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	*There should be a standard operating procedure to review data (whether a sample or 100%) at pre-determined intervals to ensure that there is adequate documentation of critical elements such as eligibility criteria. Monitoring is required at the following timepoints (but may be done more frequently):* • *study initiation* • *at least every six months while participants are receiving intervention and* • *annually while participants are in follow-up*	Every 6 months *At a minimum, a review is required annually when no one has been enrolled or the study is in long term follow up. Additional risk-based interim monitoring may be required at least once every 12-24 weeks based on the site activity, to include the possibility of remote monitoring.*	PI (self-assessment tool) *Delegate a responsible party for each requirement below.* Self-assessment is acceptable*. *Self-assessment*: a process for self-assessment of protocol compliance and data integrity which can be part of an overall DSMP. See CTAC's self-assessment tool on their webpage.

		A longer frequency could be acceptable with justification about risk to participants.	
100% review of regulatory files	DCTR will review all regulatory files at study initiation as well as on an annual basis, either in electronic or paper form.	At study initiation & annually *Reviewed at a minimum of first and close-out visits*	DCTR
100% review of consent forms	DCTR will review all consent forms on a monthly basis.	Every month	DCTR
Review of credentials, training records, the delegation of responsibility logs (if applicable)	DCTR will review the credentials of all study personnel at study initiation and on an annual basis.	At study initiation & annually	DCTR
Comparison of case report forms (CRF) to source documentation for accuracy and completion	PI will compare CRF to the source documentation in the patient's Epic charts on a monthly basis.	Every month	PI
Review of documentation of all adverse events	PI will review all adverse events as reported on a monthly basis.	Every month	PI
Monitoring of critical data points (eligibility, study endpoints, etc.)	PI will monitor all critical data points on a monthly basis.	Every month	PI
Laboratory review of processing and storage of specimens	N/A	N/A *Reviewed at first and close-out visits and at least biannually*	N/A
Assessment of laboratory specimens stored locally	N/A	N/A	N/A
Test article accountability review	Grady Pharmacy IDS will review the study drug accountability records at least every 6 months.	Every 6 months *Reviewed at first and close-out visits and at least biannually*	Grady Pharmacy IDS

Accountability logs, dispensing records, and other participant records	Grady Pharmacy IDS will review the study drug records at least every 6 months.	Every 6 months *At least biannually*	Grady Pharmacy IDS
For FDA regulated studies, the following requirements apply:		Timing, frequency, and intensity of monitoring	
Monitoring methods (may include centralized, on-site, and self-assessment)	On-site & Self-assessment	Every 6 months	PI
*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.			

DCTR: Emory University Department of Anesthesiology Division of Clinical and Translational Research staff member
IDS: Investigational Drug Services
PI: Principal Investigator

22. Provisions to Protect the Privacy Interest of Participants

The research procedures are not beyond what is routinely used in a patient's intraoperative and postoperative anesthetic management. The patient will be given the option to not interact with study team members whenever he/she is not comfortable. The research team will contact the subject up to the time of discharge from the PACU, and only beyond that if necessary (e.g. if there is a significant adverse event that may or may not be related to the study).

23. Economic Burden to Participants

N/A

24. Informed Consent

We will be informing and consenting patients in the anesthesia pre-admission clinic. This consent will be checked on the day of surgery itself to ensure ongoing consent. The principal investigator will be the one consenting study participants. Study subjects will be informed that participation in the study has no bearing on their clinical care, and will be given the opportunity to withdraw from the study at any time point.

The consent form has been attached to this protocol.

25. Setting

This is a single-site study at the Grady Memorial Hospital. Potential participants will be identified and recruited at the anesthesia pre-admission clinic on site. Research procedures will be performed in the main operating room and ambulatory surgery center on site.

26. Resources Available

The study drug and equipment required for the study are all in routine clinical use at the Grady Memorial Hospital. As the inclusion criteria are broad and there is an average of 20-30 cases per weekday of elective surgeries requiring tracheal intubation and NMB, we anticipate that there would be minimal problems in recruiting the required number of suitable subjects within the aforementioned recruitment period. We will be briefing the anesthesiology department staff prior to the study commencement on the details of this research study.

27. Multi-Site Research When Emory is the Lead Site

N/A

28. References

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6. Kopman AF. Neostigmine versus sugammadex: which, when, and how much? Anesthesiology. 2010;113(5):1010-1.
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29. Protocol Checklist

Please note that protocol sections with an asterisk (*) should always be included in the protocol; if the section does not have an asterisk, and you have not included the section in the protocol, the IRB will consider it your attestation that the section does not apply to your study.

Protocol Section	Added to the protocol?
External Collaborators- if applicable, add each external collaborator information and indicate whether that institution's IRB will review (or has already reviewed) that individual's engagement in human participants research activities)	☐ **Yes**
Funding Source*: Include the information for the funding entity for this study. Please explain if this study is covered by a sub-award or other pertinent information. Say "department" if you do not have any other funding.	☒ **Yes**
Objectives*: Describe the purpose, specific aims, or objectives and state the hypotheses to be tested	☒ **Yes**
Background*: Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data. Provide the scientific or scholarly background for, the rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge	☒ **Yes**
Study Endpoints*: Describe the primary and secondary study endpoints. Describe any primary or secondary safety endpoints.	☒ **Yes**
Study Intervention/Investigational Agent*: Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.	☒ **Yes**
Drug/Device Handling: If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on participants and be used only by authorized investigators. If using a drug, explain if the control of the drug is managed by IDS (or VA/Grady/CHOA research pharmacies). If not, provide IDS exemption document. If a device, explain how the device is being stored and managed.	☒ **Yes**
If the drug is under an FDA REMS, plan to complete the REMS checklist found here, on the IRB website.	☐ **Yes**
If the drug is considered a controlled substance, make sure you have filled out this form.	☐ **Yes**
If applicable, identify the holder of the IND/IDE/Abbreviated IDE. An Emory investigator who holds an IND or IDE is considered to be a Sponsor-Investigator (S-I). If the study is under an S-I, review this section of our website for additional requirements.	☐ **Yes**

Procedures involved*: Describe and explain the study design and include a study schema. Describe all research procedures being performed and when they are performed, including procedures being performed to monitor participants for safety or minimize risks	☒ **Yes**
Procedures-Minimizing risk*: describe the procedures performed to lessen the probability or magnitude of risks.	☒ **Yes**
Procedures- Drug/Device Use: describe all drugs and devices used in the research and the purpose of their use and their regulatory approval status	☒ **Yes**
Procedures-Source Records*: describe source records that will be used to collect data about participants. Attach all surveys, scripts, and data collection forms to the submission.	☒ **Yes**
Procedures-Data collection*: describe what data will be collected during the study and how that data will be obtained	☒ **Yes**
Procedures- Long Term Follow Up*: once all research-related procedures are complete, what data will be collected during this period. If no data is collected after procedures are completed, please state in the submission.	☒ **Yes**
Data and Specimen Banking: describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens. Depending on the volume and nature of the collection, this may require a separate repository-specific IRB submission. The VA Data Repository SOP is required if the study is creating a data repository at the Atlanta VA. List the data to be stored or associated with each specimen. Describe the procedures to release data or specimens, including the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.	☒ **Yes**
Sharing of Results with Participants*: Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with participants or others (e.g., the participant's primary care physicians) and if so, describe how the results will be shared If applicable (e.g. for studies involving scans and/or panels of exploratory testing on specimens) Plan for managing the types of findings that might arise. This should include any secondary findings that are being sought actively, findings that might be anticipatable, and findings that might be un-anticipatable. Plan for recognizing, analyzing, and handling incidental findings and how incidental findings will be communicated to participants during the consent process. If the plan is not to	☒ **Yes**

disclose any findings, then this should be included. This plan might include the option for participants to opt-out of receiving incidental findings. Description of the research team's responsibilities following disclosure of a finding. This should detail educational information about the nature of the finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required. Reminder to include language in the consent form to let the participants know your plans for this – see Modular Language for Informed Consent Forms on IRB website)	
Study timelines*: describe the duration of an individual participant's participation in the study; anticipated time to enroll all study participants and the estimated date for the investigators to complete this study (complete primary analyses)	☒ **Yes**
Inclusion and Exclusion Criteria*: describe how individuals will be screened for eligibility and the criteria that define who will be included or excluded in your final study sample	☒ **Yes**
Population*: describe the study popualation and indicate specifically whether you will include or exclude each of the following special populations: • Adults unable to consent • Individuals who are not yet adults (infants, children, teenagers) • Pregnant women • Prisoners Note: you cannot exclude people with limited English proficiency unless you can demonstrate the scientific need for such exclusion. Community Participation: For studies aimed at addressing issues that affect a certain community or group: How, if at all, will this study involve people from the target community in the design of the study? Conduct of the study? How will the results of the research be shared with the participants and/or the target community/ies? **If studying Race or Ethnicity, have you defined these terms, and explained their proposed mechanism of action if these characteristics will be used in an explanatory model?**	☒ **Yes**
Research with pregnant women, fetuses, or neonates: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☐ **Yes**
Research with neonates of uncertain viability: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☐ **Yes**

Research involving prisoners: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☐ **Yes**
Research involving children: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☐ **Yes**
Research involving cognitively impaired adults: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☐ **Yes**
Research involving economically or educationally disadvantaged persons: describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects	☐ **Yes**
Local Number of Participants*: Indicate the total number of participants to be accrued locally. If applicable, distinguish between the number of participants who are expected to be enrolled and screened, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.) Provide your projected enrolling goals, including the percentage of participants according to sex and race.	☒ **Yes**
Recruitment Methods*: Describe when, where, and how potential participants will be recruited. Describe the source of participants. Describe the methods that will be used to identify potential participants. Describe materials that will be used to recruit participants. Attach copies of these documents with the application. If including advertisements, attach the final copy of them. When advertisements are taped for broadcast*, attach the final* audio/videotape. You may submit the wording of the advertisement before taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/videotape. Describe the amount and timing of any payments to participants. Reimbursement for expenses/travel? If using contests or raffles as incentive, you must offer entry to all potential participants, not just those who enroll in the study/complete study-related procedures, per Georgia State Law. All research recruitment through social media needs to follow this guidance, which does not allow the use of personal social media accounts for some recruitment activities.	☒ **Yes**
Withdrawal of Participants*: Describe anticipated circumstances under which participants will be withdrawn from the research without their consent. Describe any procedures for orderly termination. Describe procedures that will be followed when participants withdraw from the research, including partial withdrawal from procedures with continued data collection.	☒ **Yes**

Risk to Participants*: List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related to the participant's participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks. If applicable, indicate which procedures may have risks to the participants that are currently unforeseeable. If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. If applicable, describe risks to others who are not participants.	☒ **Yes**
Potential Benefits to Participants*: Describe the potential benefits that individual participants may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit. Do not include benefits to society or others.	☒ **Yes**
Compensation to Participants*: Describe if/how subjects will be compensated for participation in this study. Indicate what method compensation will be delivered (e.g. cash, gift card, school credit). Describe the amount and timing of any payments to participants. How much? What kind? Is tax information required? (if so, must be reflected in the informed consent form). Will payments be pro-rated if a participant withdraws early?	☒ **Yes**
Data Management and Confidentiality*: Describe the data analysis plan, including any statistical procedures or power analysis. Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission. Describe any procedures that will be used for the quality control of collected data.	☒ **Yes**
Describe how data or specimens will be handled study-wide*: What information will be included in that data or associated with the specimens? • Where and how data or specimens will be stored? • How long the data or specimens will be stored? • Who will have access to the data or specimens? • Who is responsible for receipt or transmission of the data or specimens? • How data or specimens will be transported?	☒ **Yes**
Data Monitoring and Participants Safety (if this study is more than minimal risk, this section is required):	☒ **Yes**

Ensure that you review our Data and Safety Monitoring plan guidance for specific details about this section, and examples of what the IRB will be requiring according to the level of risk.

If a DSMB is needed, please describe the composition of the board (if not already detailed in the protocol). Review this guidance for more information. If the sponsor protocol does not contain all required information, please in this section.

Describe the plan to periodically monitor the data at the site level according to risk level. Include the appropriate completed monitoring table, if applicable.

Description of the plan for notifying the IRB of reportable events, whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them.

Please address the specific details below. If deemed not applicable, please provide rationale:

Subject safety:

- Specific subject safety parameters
- Frequency of subject safety observations
- Individual responsible for safety monitoring
- Subject stopping rules – under what conditions will a subject be removed from study participation and who will make the decision?
- Study stopping rules - under what conditions will the study be modified or stopped and who will make the decision?
- Reporting mechanisms (i.e. Deviations, adverse events, UPs)

Data Integrity:

- Specific data elements to be reviewed
- Frequency of monitoring data, points in time, or after a specific number of participants
- Individual responsible for data monitoring

Additional considerations for FDA regulated trials

Depending on the procedures affecting risks to participants, the site monitoring plan should specify:

- Categorization of activities done centrally and those on-site if applicable
- Monitoring methods (may include centralized/remote, on-site, and self-monitoring)
- Reference to any tools used (i.e. checklists)

• Identification of events that may trigger changes • Identification of deviations or failures that would be critical to study integrity	
Provisions to Protect the Privacy Interests of Participants*: • Describe the steps that will be taken to protect participants' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or whom they provide personal information. • Describe what steps you will take to make the participants feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a participant might experience in response to questions, examinations, and procedures. • Indicate how the research team is permitted to access any sources of information about the participants.	☒ **Yes**
Economic Burden to Participants*: Describe any costs that participants may be responsible for because of participation in the research.	☒ **Yes**
Consent Process*: Describe where the consent process will take place, any waiting period available between informing the prospective subject and obtaining the consent; and the process to ensure ongoing consent. Describe the role of the individuals listed in the application as being involved in the consent process; the time that will be devoted to the consent discussion; steps that will be taken to minimize the possibility of coercion or undue influence; and steps that will be taken to ensure the participants' understanding. **Note**: If you are planning to obtain consent via electronic signature, please review this document. Additional guidance on consent documentation and process can be found on our website, under the consent toolkit.	☒ **Yes**
Consent Process-Non-English-Speaking Participants*: Indicate what language(s) other than English are understood by prospective participants or representatives. If participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those participants will be in that language. Indicate the language that will be used by those obtaining consent. If you checked N/A, please provide reasoning of why subjects with limited English proficiency are excluded. **Note**: if you stated that subjects with LEP will be enrolled, you are approved for the use of the Emory IRB short forms. Please read the guidance about the use of short forms here.	☐ **Yes**

Consent Process-Children: After determining if the subject is a child per GA law (or if enrolled outside GA, per state/country law), please describe whether parental permission will be obtained from:	☐ **Yes**
• Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. • One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.	
Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.	
When assent of children is obtained describe whether and how it will be documented per Emory Policies and Procedures	
Consent Process-Cognitively Impaired Adults: describe the process to determine whether an individual is capable of consent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require children to sign assent documents.	☐ **Yes**
Consent Process-Adults Unable to Consent: List the individuals from whom permission will be obtained in the order of priority. (E.g., durable power of attorney for health care, a court-appointed guardian for health care decisions, spouse, and adult child.) For research conducted in the state, review "46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT" to be aware of which individuals in the state meet the definition of "legally authorized representative." For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. Describe the process for the assent of the participants. Indicate whether:	☐ **Yes**
• Assent will be required of all, some, or none of the participants. If some, indicated, which participants will be required to assent and which will not. • If assent will not be obtained from some or all participants, an explanation of why not.	
Describe whether the assent of the participants will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the	

consent document and does not routinely require assent documents and does not routinely require participants to sign assent documents	
Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception) Review the Emory IRB waiver document to ensure you have provided sufficient information for the IRB to make these determinations. If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations.	☐ **Yes**
Setting*: Describe the sites or locations where your research team will conduct the research including where the subject will be identified and recruited, where the research procedures will be performed, and if you will involve a community advisory board. For research conducted outside the organization and its affiliates describe the site-specific regulations or customs affecting the research outside the organization and the local scientific and ethical review structure outside the organization.	☒ **Yes**
Resources Available*: Describe the resources available to conduct the research such us the feasibility of recruiting the required number of suitable participants within the agreed recruitment period; describe the time that you will devote to conducting and completing the research; describe the availability of medical or psychological resources that participants might need as a result of an anticipated consequences of the human research; describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.	☒ **Yes**
Multi-Site Research when Emory is the Lead Site: Study -Wide Number of Participants: indicate the total number of participants to be accrued across all sites. Study-Wide Recruitment Methods: If this is a multicenter study and participants will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Describe when, where, and how potential participants will be recruited. Describe the methods that will be used to identify potential participants. Describe materials that will be used to recruit participants. Describe the processes to ensure communication among sites. See "WORKSHEET: Communication and Responsibilities (HRP-830)." All sites have the most current version of the protocol, consent document, and HIPAA authorization. All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record). All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.	☒ **Yes**

All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies. All local site investigators conduct the study in accordance with applicable federal regulations and local laws. All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"):	
• Problems (inclusive of reportable events). • Interim results. • The closure of a study	
If this is a multicenter study where you are a participating site/investigator, describe the local procedures for maintenance of confidentiality. (See "WORKSHEET: Communication and Responsibilities (HRP-830).")	
• Where and how data or specimens will be stored locally? • How long the data or specimens will be stored locally? • Who will have access to the data or specimens locally? • Who is responsible for receipt or transmission of the data or specimens locally? • How data and specimens will be transported locally?	