Correlation Between Cardiac Output and Recovery Time After Reversal of Rocuronium-Induced Blockade With Sugammadex

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Correlation between cardiac output and recovery time after reversal of rocuronium-induced blockade with sugammadex

Regulatory Sponsor
Principal Investigator: J. Ross Renew, MD

Funding Sponsor: Departmental Resources

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Study Product: TetraGraph

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1 Protocol Approval Form

Protocol Number: 20-001771

Study Name: Correlation between cardiac output and recovery time after reversal of rocuronium-induced blockade with sugammadex

This protocol has been reviewed and approved by the following:

17/Aug/2022___

J. Ross Renew, MD
Principal Investigator

Date

2 List of Abbreviations

AE	Adverse Event/Adverse Experience
AMG	Acceleromyography
CE	Conformite Europeene
CFR	Code of Federal Regulations
cMAPs	Compound Muscle Action Potentials
CO	Cardiac Output
CRF	Case Report Form
CTSA	Center for Translational Science Activities
DSMB	Data and Safety Monitoring Board
EHR	Electronic Health Record
EMG	Electromyography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICU	Intensive Care Unit
IRB	Institutional Review Board
KMG	Kinemyography
MMG	Mechanomyography
NMBA	Neuromuscular Blocking Agent
Non-UPIRTSO	Non-Unanticipated Problems Involving Risk to Subjects or Others
PACU	Post Anesthesia Care Unit
PHI	Protected Health Information
PI	Principal Investigator
PTC	Post-tetanic Potentiation
SAE	Serious Adverse Event/Serious Adverse Experience
SGX	Sugammadex
SOP	Standard Operating Procedure
TOF	Train-of-four
TOFC	Train-of-four count
TOFR	Train-of-four ratio
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others
VNRS	Verbal Numeric Rating Scale

3 Study Summary

Title	Correlation between cardiac output and recovery time after reversal of rocuronium-induced blockade with sugammadex
Running Title	CO and Sugammadex
Phase	N/A
Methodology	Open-Label
Overall Study Duration	6 months
Subject Participation Duration	2 – 5 hours
Single or Multi-Site	Single site
Objectives	The primary aim of this study is to correlate the temporal relationship between cardiac output and clinical recovery of neuromuscular block affected by sugammadex.
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Patients undergoing elective surgery and requiring administration of rocuronium, and the use of a pulmonary artery catheter intraoperatively.
Study Device	TetraGraph
Duration of Administration	Single stimulation of ulnar nerve repeated at specific intervals as outlined in the Study Procedures (Section 9.2)

4 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

4.1 Abstract

Sugammadex has been introduced into the market as a fast-acting selective relaxant binding agent to reverse rocuronium-induced neuromuscular block. Several studies have shown that longer times are required in older patients to recover from rocuronium-induced neuromuscular block, which is likely related to age-related decreases in cardiac output. The aim of this study is to evaluate the correlation between cardiac output and speed of reversal of rocuronium-induced neuromuscular block with sugammadex in patients.

4.2 Background

Neuromuscular blocking agents (NMBAs) are a class of medications routinely used during anesthesia to facilitate endotracheal intubation (1), and improve conditions for optimal surgery (2). Routine reversal of neuromuscular blockade is very common in order to return patients' spontaneous breathing and prevent residual blockade and all the associated complications (3, 4). Sugammadex, a novel γ-cyclodextrin, is a unique neuromuscular reversal drug discovered by Anton Bom. It is the first in a new class of selective relaxant binding agents, and it was designed to rapidly reverse rocuronium-induced neuromuscular block (5, 6). Sugammadex-rocuronium interaction reduces the amount of free muscle relaxant in the plasma, reducing the level of free NMBA at the neuromuscular junction (7). Some studies have shown that longer times are required in older patients to recover from rocuronium-induced neuromuscular block (8). Suzuki et al, showed that achieving a TOFR of 0.9 was slower in older than younger patients. In addition, Yoshida et al (9), reported that in elderly patients (65 years or older), the time to reach a TOFR of 0.9 following 2 mg/kg sugammadex was dependent on the cardiac output. These studies suggested that the slower duration to reach a TOFR of 0.9 in older patients is probably attributable to their lower cardiac output. However, they had a limitation and it was the technique they used to measure the cardiac output because compared with other invasive techniques, FloTrac/Vigileo tends to underestimate the cardiac output (10).

The purpose of this study is to determine the recovery time from rocuronium-induced blockade after reversal with sugammadex as a function of cardiac output in elderly and young patients. Cardiac output measurements will be performed pulmonary artery catheterization, which is passing a catheter into the right side of the heart and the arteries leading to the lungs to monitor heart function and blood flow pressures. It is important to highlight that pulmonary artery catheter would be part of the normal care and intraoperatively proceedings. Neuromuscular monitoring will be performed using TetraGraph (Senzime AB, Uppsala, Sweden) which is a standalone EMG-based quantitative monitor that is FDA approved. EMG measures electrical activity within the muscle following peripheral nerve stimulation and is unaffected by involuntary patient motion or restricted muscle movements from surgical positioning.

4.3 Risks and Benefits

- The benefits of using neuromuscular blockade monitoring devices:
  Early detection of optimal time for tracheal intubation; optimal management of intraoperative depth of neuromuscular block to facilitate surgical procedures; determination of appropriate time and dose of sugammadex reversal; and detection of residual neuromuscular blockade
- The risks of using neuromuscular blockade monitoring devices:
  Slight discomfort when electrical stimulation is administered in awake volunteers; however, our patients will be anesthetized, rendering this risk as extremely minor.

5 Study Objectives

Primary Objective
To determine the recovery time from rocuronium-induced blockade after reversal with sugammadex as a function of cardiac output.

Secondary Objective
To determine the correlation between the speed of recovery from NMBA with sugammadex and age.

6 Study Design

6.1 General Description

This single center, prospective, observational study will involve 50 patients undergoing surgical procedure that involved administration of neuromuscular blockade agents intraoperatively.

6.2 Number of Subjects

Fifty

6.3 Duration of Participation

2-5 hours, depending on duration of surgery

6.4 Primary Study Endpoints

The primary endpoint of the study will be to examine the correlation between cardiac output and the time of recovery after reversal with sugammadex as measured by TOFR ≥0.9.

6.5 Secondary Study Endpoints

The secondary endpoint is the incidence of postoperative residual weakness at the time of extubation.

6.6 Identification of Source Data

The study data points will be recorded on the developed Case Report Forms (CRFs) by the study team members. In addition to the data collected intraoperatively, several intraoperative characteristics will also be extracted from the medical record (Table 18.2). These will include type and total dose of NMBA used, time and dose of last NMBA administration, time and dose of specific reversal agent administration, time of tracheal extubation, and TOF ratio at the time of extubation (if available).

7 Subject Selection Enrollment and Withdrawal

7.1 Inclusion Criteria

- Age > or = 18 years old
- Patients willing to participate and provide an informed consent
- Patients undergoing an elective surgical procedure requiring administration of rocuronium, and the use of a pulmonary artery catheter intraoperatively.

7.2 Exclusion Criteria

- Patients with unilateral disorders, such as stroke, carpal tunnel syndrome, broken wrist with nerve damage, Dupuytren contracture
- Patients with systemic neuromuscular diseases such as myasthenia gravis
- Patients with significant organ dysfunction that can significantly affect pharmacokinetics of neuromuscular blocking and reversal agents, i.e., severe renal impairment or end-stage liver disease.
- Patients having surgery that would involve prepping the arm or leg into the sterile field

7.3 Subject Recruitment, Enrollment and Screening

On a daily basis, there are over 20 elective surgical cases performed at Mayo Clinic in Florida and thus no difficulties in accrual are anticipated based on historical volumes. We will target at least 3 participants per week to complete this study. The initial accrual period will last at least 3 months followed by interim analysis and additional time for accrual will be determined to meet the target. Patients will be provided with a Research Participant Consent and Privacy Authorization Form describing the study devices, protocol, inclusion and exclusion criteria, as well as risks and benefits of participation.

7.4 Early Withdrawal of Subjects

7.4.1 When and How to Withdraw Subjects

Patients are free to withdraw at any time and for whatever reason. If patient withdraws consent prior to arrival to operating room, the study data will not be collected. If patient withdraws consent after study data was already completed, the participant will need to provide instructions to the study team to remove his/her data from the data set. Pre-specified reasons for discontinuing include, but are not limited to, the following:

- Patient Request: Patient decided that he/she did not want to continue (for any reason)
- Adverse Event: Patient experienced a related or unrelated event that would interfere with the study objectives/evaluation
- Inclusion/Exclusion Discrepancy/Violation: Patient should not have been enrolled
- Other: Any other reason

7.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a Participant withdraws from the study, no additional attempts will be made to contact the Participant.

8 Study Device

8.1 Description

TetraGraph device is a FDA approved neuromuscular transmission monitor capable of measuring the depth of neuromuscular block in anesthetized patients who received neuromuscular blocking agents. TetraGraph uses EMG to measure the muscle action potentials that are generated in response to electrical neurostimulation via skin (ECG) electrodes. TetraGraph data is recorded on the monitor's built-in SD card, and all intraoperative data will be recorded and later downloaded for purposes of analysis. The recorded data do not contain PHI, only the date/time of recording, and any additional intraoperative interventions, such as the time of NMBA dose administration, time of antidote administration, time of extubation, etc. These events are flagged in the monitor's integrated SD card recordings.

Cardiac Output will be measured continuously (as per standard of care) through pulmonary artery catheter, which is the passing of a thin tube into the right side of the heart and arteries leading to the lungs. This catheter will be used as part of the standardized management during the surgical procedure.

8.2 Method for Assigning Subjects to Treatment Groups

This is a single-blinded investigation and all study participants are assigned to both standard of care and investigational device use in the operating room.

8.3 Masking/Blinding of Study

This is an open-label pilot investigation. Masking and blinding procedures are not applicable.

9 Study Procedures

9.1 Visit 1 (Screening and Enrollment up to the day of surgery)

- Review of medical record
- Informed Consent - Patients will be identified during their preoperative appointment and introduced to a study; they will be provided with a copy of the consent document and information about the study. The consenting will take place after additional discussion on the day of surgery.

9.2 Visit 2 (Treatment – day of surgery)

- Elective surgical procedure as per standard of care
- Anesthetic management will be at the discretion of the attending anesthesiologist as per standard of care practice.
- Prior to induction of anesthesia, Tetragraph electrodes will be placed over the ulnar nerve and the thumb and/or pinky finger to measure the response of adductor digit minimi nerve (location of Tetragraph will be at a discretion of the anesthesiologist).
- Following induction of anesthesia but prior to NMBA administration, baseline values will be recorded after calibration.
- Cardiac output will be measured continuously through the pulmonary artery catheter and the values will be obtained from EHR.
- Near the conclusion of the operation but prior to the reversal of NMBA, a set of measurements will be taken
- After sugammadex administration, measurements will be taken every 20 seconds until consecutive measurements demonstrate a TOFR >0.9 (adequate recovery)
- Each neurostimulation with the TetraGraph will be conducted simultaneously with one observer.
- Time to recovery following SGX (TOFR ≥0.9) will be documented as well as time toextubation.
- Following measurements obtained the device will be removed and the patient will proceed along the standard recovery pathway.

9.3 Schedule of Events

	Schedule of Events

Study Activity	Visit 1	Visit 2
Tetragraph		X
Informed consent	X	
Review of Medical Record	X	
Adverse event evaluation		X

10 Statistical Plan

10.1 Sample Size Determination

Based on Pearson correlation test, 50 patients will allow us to detect the correlation of 0,6 or greater between cardiac output and the time of recovery after reversal with sugammadex with a power greater than 90% and a significance level of 0.05.

10.2 Statistical Methods

Continuous variables will be summarized as mean (standard deviation) or median (range) while categorical variables will be reported as frequency (percentage). Pearson correlation or Spearman correlation will be used to test 1) the correlation between cardiac output and the time of recovery after reversal with sugammadex and 2) the correlation between age and the time of recovery. Linear regression model will be used to estimate the change of recovery time per unit change in cardiac output or age. If time to recovery does not follow a normal distribution, log transformation will be performed before analysis. All test are two-sided with alpha level set of 0.05 for statistical significance.

10.3 Handling of Missing Data

This is a prospective pilot study and therefore we do not anticipate any missing data. In the event of any unexpected missing data, no attempt to impute this missing data will be made; missing data will simply be treated as missing in the statistical analysis, and replacement participants will be enrolled to achieve the target accrual of n=50 participants.

10.4 Subject Population(s) for Analysis

Each participant who goes through the surgery and completes monitoring of residual neuromuscular blockade will be included in the primary analysis regardless of study withdrawal

for any reason. In the event of any study withdrawals, in secondary analysis we will examine the sensitivity of our results to the exclusion of patients who withdrew.

11 Safety and Adverse Events

11.1 Definitions

11.1.1 Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

11.1.2 Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

11.1.3 Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

11.1.4 Adverse Event Reporting Period

For this study, the follow-up period is defined as up to 10 minutes after arrival to PACU or TOF ratio is > 0.9 (whichever occurs first).

11.1.5 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

11.1.6 Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

11.1.7 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

11.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the electronic case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting

Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

11.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

11.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures. Each participating site will report SAEs to their respective IRB or Ethics Committee with copy of submission and review provided to the leading site. Should there be any SAEs at any of the participating sites; the study team at that site will notify the primary site (Mayo Clinic in Florida) within 24 hours of learning of the event.

Any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO will be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

The following information will be collected on the adverse event worksheet (and entered in the research database):

- Study ID
- Disease
- The date the adverse event occurred
- Description of the adverse event
- Relationship of the adverse event to the research device*
- Determination if the adverse event was expected
- The severity of the adverse event (severity scale described below**)
- If any intervention was necessary
- Resolution (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

*** Relationship Index**

The relationship of an AE to the Investigational Device is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the eCRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the use and proper application of study device.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to use of the study device which makes a causal relationship improbable and in which use of other devices, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to use of the study device but which could also be explained by concurrent disease or use of other devices or chemicals.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to use of the study device, unlikely to be attributed to concurrent disease or use of other devices or chemicals.

5. Definite: a reaction that follows a reasonable temporal sequence from the use of the study device.

**** Severity Scale**

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

11.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

12 Data Handling and Record Keeping

12.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

12.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records and any forms completed specifically for this study.

12.3 Case Report Forms

All data necessary for this study will be obtained from EHR or at the time devices are being used and recorded on the electronic Case Report Forms (CRFs) created in REDCap. All missing data will be explained.

12.4 Data Management

Study data to be collected and managed using EHR and study-generated source documents and transcribed into electronic CRFs in REDCap, electronic data capture software, hosted by CTSA at Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

12.5 Data Processing

All study date will be stored and analyzed at Mayo Clinic in Florida using the REDCap electronic data capture tool.

12.6 Data Security and Confidentiality

All source documents including clinical findings, observations or other activities will be stored in a REDCap database that will be designed by an Investigator. Access to the REDCap database will be limited to the Principal Investigator, Investigators, Study Team members, and Statistician.

12.7 Data Quality Assurance

Once the study is completed the Principal Investigator will randomly select 3 participants and compare the data documented in the EHR with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 50 patients to ensure accuracy.

12.8 Data Clarification Process

For any data query the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus.

12.9 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. Principal Investigator will maintain regulatory and essential study documents to ensure compliance with local and federal policies/guidelines.

The sponsor-investigator will retain the specified records and reports:

- As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

13 Study Monitoring, Auditing, and Inspecting

13.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the compliance or quality assurance reviewer is given access to all the study-related documents.

13.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

14 Ethical Considerations

This study is to be conducted according to United States and International government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the individual obtaining the informed consent.

15 Study Finances

15.1 Funding Source

This investigator initiated study is not funded. Study coordinator's time is supported by the Department of Anesthesiology and funding for statistical analysis will be provided from the Principal Investigator's research fund.

15.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

No financial conflicts of interested are anticipated or have been identified for this study.

15.3 Subject Stipends or Payments

No payment is given to study participants.

16 Publication Plan

The primary responsibility for publication of the study results is with the Primary Investigator. After the complication of study and prior to publication, the study results will be shared with all Investigators. The study will be registered at ClinicalTrials.gov prior to subject recruitment along with the posting of the results within 12 months of final data collection for the primary outcome measure.

17 References

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18 List of In-Text Tables

18.1 Schedule of Events

	Schedule of Events	
Study Activity	Visit 1	Visit 2

Tetragraph		X
Informed consent	X	
Review of Medical Record	X	
Adverse event evaluation		X

18.2 Intraoperative Data

Study ID:	Date of Surgery (dd / mm / yyyy):	Examiner's Initials:	
Wrist circumference (right):	Wrist circumference (left):		
Age (yrs):	Weight (kg):	Height (cm):	BMI:
Muscle relaxant name:			
Muscle relaxant total dose (mg):			
Time of first muscle relaxant dose (mm : hh):	:	am / pm	
Time of last muscle relaxant dose (mm : hh):	:	am / pm	
Sugammadex dose (mg):			
Time of Sugammadex administration (mm : hh):	:	am / pm	

Time of extubation:	: am / pm

TetraGraph (TG) Arm tested: dominant / non-dominant

	Time	TOFC # 1	TOFC # 2	TOFC # 3	CO
		TOFR # 1	TOFR # 2	TOFR # 3	
Calibrated baseline and supramax current					
TOFC=0 (after initial NMBA dose)					
pre-SGX					
+20 sec			N/A	N/A	
+40 sec			N/A	N/A	
+60 sec			N/A	N/A	
+80 sec			N/A	N/A	
+100 sec			N/A	N/A	
+120 sec			N/A	N/A	
+140 sec			N/A	N/A	
+160 sec			N/A	N/A	

+180 sec			N/A	N/A	
+200 sec			N/A	N/A	
+220 sec			N/A	N/A	
+240 sec			N/A	N/A	
+260 sec			N/A	N/A	
+280 sec			N/A	N/A	
+300 sec			N/A	N/A	
Extubation			N/A	N/A	
Time to recovery following SGX (TOFR ≥0.9) (two consecutive measurements)					

19 List of In-Text Figures

19.1 TetraGraph