Randomized Controlled Assessor Blinded Clinical Trial of Sugammadex versus Neostigmine/Glycopyrrolate for Reversal of Rocuronium Induced Neuromuscular Blockade: Time to Discharge From Post Anesthesia Care Unit and Assessment of NMB Recovery

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title: Randomized Controlled Assessor Blinded Clinical Trial of Sugammadex versus Neostigmine/Glycopyrrolate for Reversal of Rocuronium Induced Neuromuscular Blockade: Time to Discharge From Post Anesthesia Care Unit and Assessment of NMB Recovery

Objectives:

1) To compare the difference in duration from administration of NMB reversal agent to the time the patient is ready for discharge from PACU after NMB reversal with sugammadex versus neostigmine.

2) To measure the quality of recovery from anesthesia and NMB and subjective patient assessment after reversal with SUG or NEO.

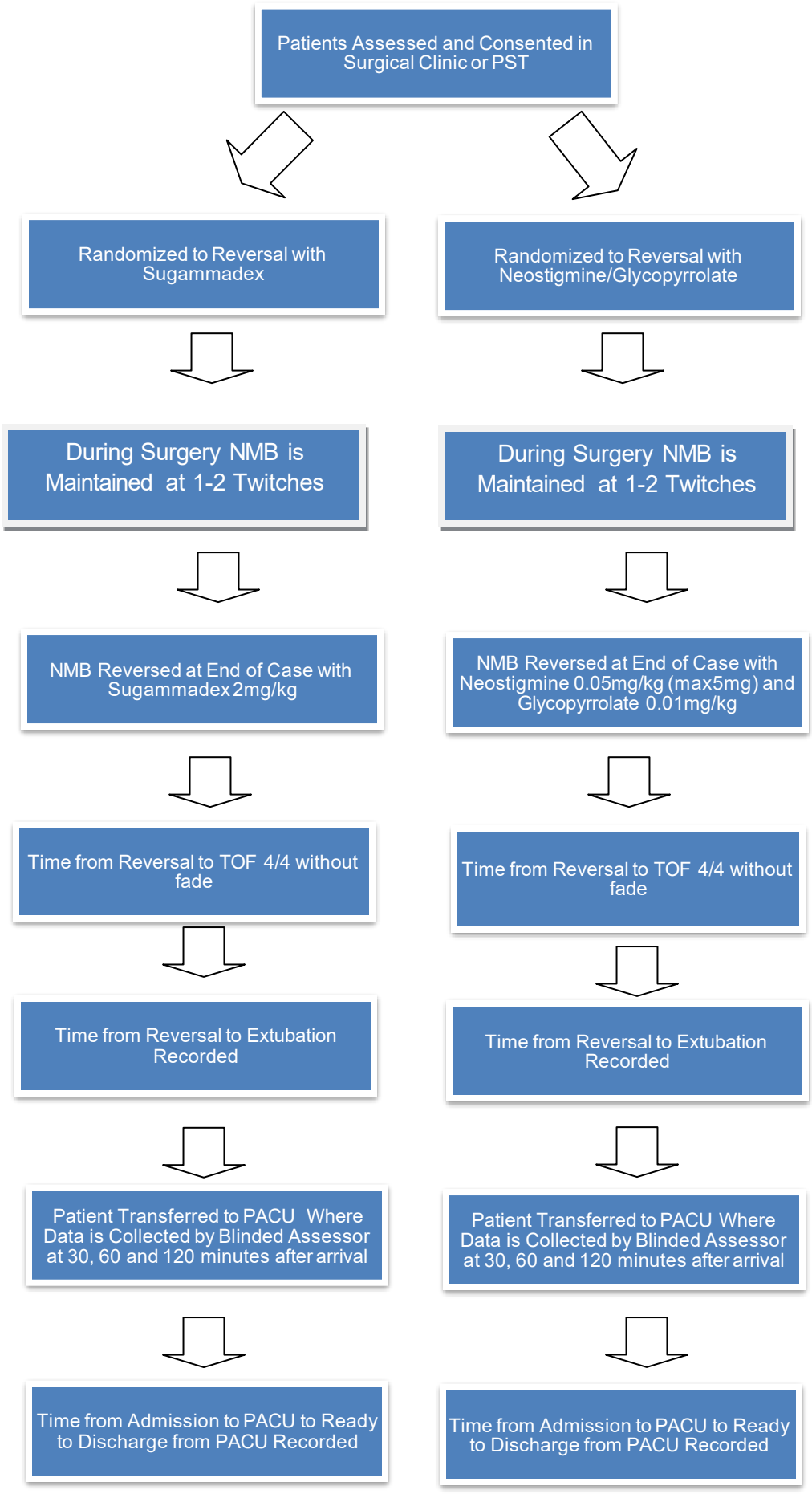
3) To compare the differences in costs in PACU stay associated with the use of each drug.

Patient Population: Patients greater than or equal to 18 years of age scheduled to undergo moderate length surgeries (scheduled for $\leq$ 6 hours) requiring neuromuscular blockade.

Design: Prospective randomized controlled assessor blinded trial.

Treatment Plan: Patients will be randomized to receive either SUG or NEO NMB reversal after rocuronium (ROC) induced muscle paralysis at the conclusion of their surgical procedure. They will be assessed for time to ready to discharge from PACU, difficulty with breathing, the presence of diplopia or other visual disturbances, difficulty speaking, difficulty swallowing, the presence of nausea or vomiting, the presence of pain, feeling worried or anxious (all indicators of post operative muscle weakness) and muscle strength at the biceps brachii muscle (Oxford Scale, Appendix 1)

Time to Completion: We will need to accrue 202 patients and expect the study to be completed and reported within 1- 2 years.


Patients Assessed and Consented in Surgical Clinic or PST
Randomized to Reversal with Sugammadex
Randomized to Reversal with Neostigmine/Glycopyrrolate
During Surgery NMB is Maintained at 1-2 Twitches
During Surgery NMB is Maintained at 1-2 Twitches
NMB Reversed at End of Case with Sugammadex 2mg/kg
NMB Reversed at End of Case with Neostigmine 0.05mg/kg (max5mg) and Glycopyrrolate 0.01mg/kg
Time from Reversal to TOF 4/4 without fade
Time from Reversal to TOF 4/4 without fade
Time from Reversal to Extubation Recorded
Time from Reversal to Extubation Recorded
Patient Transferred to PACU Where Data is Collected by Blinded Assessor at 30, 60 and 120 minutes after arrival
Patient Transferred to PACU Where Data is Collected by Blinded Assessor at 30, 60 and 120 minutes after arrival
Time from Admission to PACU to Ready to Discharge from PACU Recorded
Time from Admission to PACU to Ready to Discharge from PACU Recorded

2.1 OBJECTIVES AND SCIENTIFIC AIMS

The protocol objectives are to compare the time for and quality of recovery, both subjective and objective (muscle strength), after reversal of NMB comparing 2 different reversal agents (SUG versus NEO) in patients undergoing moderate length surgical procedures requiring paralysis.

Primary Objective

To compare the difference in duration from administration of NMB reversal agent to the time the patient is ready for discharge from PACU after NMB reversal with sugammadex versus neostigmine.

Secondary Objectives

1) To compare the patient-reported quality of post operative recovery using standard symptoms of subclinical weakness or paralysis after NMB reversal with SUG vs NEO, specifically:
   a. difficulty with breathing
   b. presence of diplopia or other visual disturbances
   c. difficulty with speaking
   d. difficulty with swallowing
   e. the presence of nausea or vomiting
   f. the presence of pain
   g. feeling worried or anxious
   h. presence of muscle strength at the biceps brachii muscle (Oxford Scale, Appendix 1)

2) To compare the differences in PACU costs associated with use of each drug

3.0 BACKGROUND AND RATIONALE

Neuromuscular transmission is the transfer of a chemical impulse between a nerve and a muscle at the neuromuscular junction, causing muscle contraction. Transmission occurs when an action potential reaches the presynaptic terminal and opens calcium channels allowing calcium ions to enter the neuron. The release of the neurotransmitter acetylcholine (ACh) diffuses across the synaptic cleft and binds to the nicotinic receptors on the muscle fiber causing muscle contraction.

Non-depolarizing neuromuscular blocking agents (NMBA) work at the neuromuscular junction by binding to the acetylcholine (ACh) receptor and acting as competitive antagonists, preventing Ach from generating an action potential, causing reversible paralysis of skeletal muscle.

Neuromuscular blockade (NMB) is used by anesthesia providers in the operating room (OR) to facilitate endotracheal intubation and mechanical ventilation and to provide improved surgical conditions.[1] The level of blockade is routinely measured by stimulating a peripheral motor nerve and evaluating the muscle response to a supramaximal stimulus (20-25% above that required for a maximal response).

After administration of a neuromuscular blocking agent, the muscle response decreases in parallel with the number of fibers blocked, corresponding to the degree of blockade. There are several patterns used to evaluate neuromuscular function. We will be using the train-of-four (TOF) count where four supramaximal stimuli are given every 0.5 seconds.[2-4] The muscle contracts with each stimulus and the "fade" is assessed either visually or tactilely. Prior to administration of a NMB agent, all four twitches are the same (control) without fade.

Recovery from NMB begins with the return of the fourth twitch. Trials of NMB reversal have led to the general agreement that the quantitative assessment of a TOF ratio of 0.9 at the end of surgery should be the goal[5,6]. Clinically this correlates with no perceived fade, indicating sufficient neuromuscular recovery.[7-17]

Residual weakness from incomplete metabolism or inadequate reversal with a neuromuscular blockade antagonist occurs frequently in the postoperative period[18-22] adding increased morbidity to recovery[23] and delaying discharge from the PACU and increasing costs.[21,24]

Presently in our ORs we use the acetylcholinesterase inhibitor neostigmine (NEO) to reverse NMB. Cholinesterase inhibition increases availability of acetylcholine in the postsynaptic cleft. Neostigmine binds to cholinesterase and blocks enzymatic cleavage of Ach. This increase in Ach concentration leads not only to activation of nicotinic but also to stimulation of muscarinic receptors. Consequently, neostigmine is usually administered with an anticholinergic such as glycopyrrolate or atropine to counteract the muscarinic side effects. These include nausea and vomiting, bradycardia, bronchospasm and miosis. Of interest, high dose neostigmine or administration after the TOF ratio returns to 0.9 may increase the incidence of pulmonary complications and increase PACU length of stay.[19,25-29]

Recently available on formulary at MSK is the gamma-cyclodextrin NMB reversal agent sugammadex, which inactivates non depolarizing aminosteroid based NMB agents by forming tight complexes in the vascular system and releasing the Ach receptors, reversing relaxation.[30] Due to its direct mechanism on the NMB agent, there is no effect on the nicotinic or muscarinic receptors and therefore no cholinergic side effects, allowing reversal of deeper levels of neuromuscular blockade. [31] Several studies have shown that sugammadex more rapidly reverses rocuronium block than neostigmine.[31-33] In addition, sugammadex has been shown not to impair upper airway muscle activity.[34]

We propose to evaluate the patient's objective and subjective post operative recovery from neuromuscular blockade in the PACU following reversal from rocuronium paralysis with either sugammadex or neostigmine in a randomized assessor and patient blinded fashion and to assess the impact on PACU length of stay and medication costs. Our goal is to

determine whether SUG results in improved patient safety and comfort with NMB reversal post operatively, and decreases the time it takes for the patient to be ready to discharge from the PACU. The trial will be performed in a single center major cancer center. The effects of SUG vs NEO have not been studied in this patient population before in the current literature.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This will be a prospective, randomized, assessor and patient blinded study. Patients eligible for the trial will be those scheduled for surgical procedures expected to last ≤ 6 hours which require muscular paralysis. There will be a total of 101 cases needed in each arm. We expect to be able to complete the trial within 1-2 years. Eligible patients will be consented and registered for the trial during a pre-operative clinic appointment. Patients will be randomized to either the SUG group or the NEO group. Randomization will occur through the Clinical Research Database (CRDB) per institutional protocol. The process will be accessible only for un-blinded team members, ie those members taking care of the patient in the OR. The patients will also be blinded to which group they are in.

In the operating room general anesthesia will be induced and maintained in a standard fashion. The NMB agent used for this trial will be rocuronium, an aminosteroid type of non depolarizing NMB. At the conclusion of surgery, the patient will be reversed with either SUG or NEO/GLYCO, and the time from reversal to extubation criteria are met will be documented along with time to extubation.

The patient will then be transferred to the PACU where s/he will be evaluated by a trained clinician assessor blinded to the reversal agent at 30, 60 and 120 minutes (+/- 5 minutes and until the patient is ready for PACU discharge) after admission for quality of post operative recovery including:

a. difficulty with breathing
b. presence of diplopia or other visual disturbances
c. difficulty with speaking
d. difficulty with swallowing
e. the presence of nausea or vomiting
f. the presence of pain
g. feeling worried or anxious
h. presence of muscle strength at the biceps brachii muscle (Oxford Scale, Appendix 1)
i. readiness for discharge from PACU (time patient meets PACU discharge criteria (Appendix 1)

At discharge from PACU, the cost of the study drugs will be compared along with the time of the PACU stay from admission to ready to discharge (RTD).

4.3 Intervention

The goal of this study is to compare objective and subjective post operative recovery from rocuronium neuromuscular blockade with sugammadex (SUG) to that with neostigmine (NEO/GLYCO).

Patients will be consented in either the pre anesthesia or surgical clinics and randomized by the CRDB prior to surgery to receive reversal of NMB with either SUG or NEO/GLYCO at the conclusion of the surgical procedure. The patient and assessors will be blinded as to the randomization assignment.

On the day of surgery, the patient will be brought to the OR and secured onto the operative table after appropriate identification. Routine monitors will be placed (EKG, NIBP, SpO2, NMT [SunStim™ Peripheral Nerve Stimulator by SunMed]). The TOF count pattern of stimulation will be used, where four supramaximal stimuli are generated at 0.5 second intervals, to quantify the muscle response. The TOF count (number of detected muscle responses) will be used to guide subsequent ROC administration for maintenance of neuromuscular blockade.

The NMT electrodes will be placed on the wrist along the ulnar nerve 5 cm apart. Since different muscle groups have different sensitivities to NMB[35] we will use this location only for assessment of depth of blockade prior to reversal agent administration. As the ulnar nerve is more sensitive than the diaphragm to NMB, this will provide a margin of safety at reversal since there will be less residual neuroblockade at the diaphragm. The distal electrode will be placed 1 cm proximal to the flexion crease on the volar side of the wrist. The proximal electrode will be placed 5 cm proximal.[36] For robotic and laparoscopic cases, facial nerve TOF will be used for intraoperative monitoring of depth of blockade as the arms will be tucked for these procedures. This will be done exclusively for purposes of intraoperative re-dosing of neuromuscular blocker. Ulnar nerve TOF will be assessed and documented prior to reversal administration in all cases.

An intravenous catheter will be placed if not already present and a crystalloid solution will be started. Antibiotics, heparin and other medications will be administered as ordered by the surgical service. If an epidural is present, it will be used at the standard post operative analgesic rate.

Anesthesia will be induced in a standard fashion. Prior to paralysis, a baseline twitch response will be elicited (TOF count 4/4 with no perceived fade). Then neuromuscular blockade will be achieved with rocuronium 0.6mg/kg. A Time Out will be performed and the patient will be positioned, prepared and draped for surgery.

Anesthesia will be maintained in accordance with the current standard management technique. Patients on an ERAS protocol will continue on pathway. Anti-emetic medication will be given per institutional protocol unless contraindicated. The TOFcount will be measured at 15 minute intervals and will be recorded in the anesthetic record. After recovery

from the induction dose, additional doses of ROC (0.1-0.2 mg/kg) will be administered when the TOF count reaches 3 to maintain the TOF count at 1-2 twitches throughout the surgical procedure. In the event that deeper paralysis is required for surgical exposure, we will delay reversal until at least one twitch has returned. It should be possible to bring the patient back to one twitch during surgical closure and before reversal. Acetaminophen and ketorolac will be used at the discretion of the attending surgeon.

Ketamine, if used, will be discontinued at the beginning of surgical closure to prevent interference with emergence. At the conclusion of the operation, NMB will be reversed after fascial closure and when the patient has at least TOF count 1-2/4 at the ulnar nerve. The anesthesia provider will reverse the patient with either sugammadex (2 mg/kg) or neostigmine (0.05mg/kg up to 5mg) and glycopyrrolate (0.2mg [1ml] for each ml of neostigmine used), after which the patient will be emerged from anesthesia. The reversal agent will be listed as IRB Protocol 17-207 Study Drug A (NEO/GLYCO) or B (SUG), in the anesthesia record to maintain blinding to those other than the intraoperative anesthesia care team. At the time of reversal agent administration, the TOF count and fade assessment will be performed every minute until TOF count 4/4 with no perceived fade is achieved. When the patient has recovered to a TOF count 4/4 (with no perceived fade), the patient will be extubated. The time from administration of reversal agent (fascial closure) to TOF count 4/4 with no perceived fade, as well as extubation will be recorded. The patient will then be transferred to the postoperative bed and taken to the PACU. If the TOF count does not reach 4/4 with no perceived fade after a reasonable time (approximately 30 minutes after reversal), the patient may be extubated and transferred to the PACU at the discretion of the anesthesia provider after traditional extubation criteria have been met (Appendix 1).

Upon arrival to the PACU, the patient will be admitted and vital signs recorded. The patient will be evaluated by a clinician, trained by the PI, who will act as a blinded assessor at 30, 60, and 120 minutes following arrival (+/- 5 minutes until the patient meets discharge criteria) for the following. S/he may be assisted by a trained PACU RN or APP if necessary. The parameters being assessed are:

a. difficulty with breathing (yes/no)
b. presence of diplopia or other visual disturbances (yes/no)
c. difficulty with speaking (yes/no)
d. difficulty with swallowing (yes/no)
e. the presence of nausea or vomiting (yes/no)
f. the presence of pain (yes/no)
g. feeling worried or anxious (yes/no)
h. presence of muscle strength at the biceps brachii muscle (Oxford Scale, Appendix 1)

At discharge from PACU, the cost of the study drugs will be compared along with the time of the PACU stay from admission to ready to discharge from PACU (RTD).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

There will be no new therapeutic or diagnostic agents used as part of this study. All drugs and materials will be obtained through the standard source of supply at MSKCC. The reversal agents used for this study, sugammadex and neostigmine/glycopyrrolate, are routinely stocked in the Omnicell machines in the operating rooms and are directly available to the anesthesia provider to dispense per the randomization. The medication will be listed on the anesthesia record as IRB protocol 17-207 Study Drug A (NEO/GLYCO) or B (SUG), and therefore will be blinded to everyone but the intraoperative anesthesia care team.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1) Adult patients age 18 years of age or greater who are capable of giving consent
2) Undergoing surgical procedures of expected length ≤ 8 hours requiring NMB

6.3 Subject Exclusion Criteria

1) Pregnancy
2) History of documented anaphylaxis or contraindication to any of the study medications
3) Active coronary disease with a positive cardiac stress test
4) History of severe chronic obstructive pulmonary disease (COPD) defined as an FEV1 < 50% of predicted
5) Serum Creatinine ≥ 2.0 mg/dL
6) Severe hepatic dysfunction accompanied by coagulopathy
   Definiton:

   - Known liver diease AND
   - INR >1.5 (except for patients on anticoagulants) AND
   - Platelet count <100,000/μL without other obvious cause
7) Chronic sustained-release opioid use for > 2 weeks duration pre op (in the 30 days prior to surgery)
8) Use of toremifene
9) Significant cognitive impairment or documented psychologic impairment
10) Myasthenia gravis or other neuromuscular disease
11) Patients who are not eligible for standard anesthetic induction, eg, those needing rapid sequence induction or awake fiberoptic bronchial intubation.
12) American Society of Anesthesiologists (ASA) Status > 3

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at MSKCC. If the investigator is a member of the

treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study.

The principal investigator may screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

All patients scheduled to undergo surgical procedures booked for ≤ 6 hours who meet eligibility criteria will be approached for participation in the study during the surgical or anesthesia preoperative visit by a member of the research team. Patients using hormonal contraceptive therapy will be cautioned to use another method of birth control for 7 days postoperatively.

The eligibility and exclusion criteria do not discriminate either explicitly or implicitly against gender, race or ethnicity. Consent will be obtained by the attending surgeon. Details pertinent to the trial, expected outcomes and potential risks and adverse outcomes will be discussed in detail before enrollment. Informed consent will be obtained and documented in the patient's chart. The patients will then be registered and assigned a unique identification number. Study subjects will not receive any compensation for participation in the study. There will not be any additional costs for the patients derived from participation.

During the initial conversation between the investigator/research staff and the patients, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If that patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

All patients will be evaluated by an attending surgeon from the appropriate service. Once eligibility is assessed, the patient will be approached regarding participation in the trial. Prior to the operation, the following will be performed (all standard before any operation).

- The patient will sign informed consent for the surgery
- The patient will have a complete history and physical examination within 4 weeks of surgery
- Patient demographics will be recorded
- Preoperative testing, which may include a basic metabolic panel, complete blood count, and coagulation profile per surgical service guidelines will be performed within 4 weeks of surgery
- Electrocardiogram and chest xray will be obtained if required per institutional guidelines
- Formal medical evaluation for preoperative clearance will be obtained for any patient whose history warrants
- For women between the ages of 11 and 50, a negative serum pregnancy test within 30 days prior to surgery or a negative urine pregnancy test on the morning of surgery will be required, as per MSKCC guidelines

9.1 TREATMENT/INTERVENTION PLAN

Patients participating in this trial will undergo routine anesthetic and perioperative care. None of the interventions are outside the scope of standard perioperative care.

- An intravenous catheter will be placed.
- An arterial line will be placed if deemed necessary.
- Continuous monitoring of heart rate, blood pressure, ECG (leads II, V5), end tidal CO2 (etCO2), oxygen saturation (SpO2), depth of neuromuscular blockade, temperature, urine output and blood loss will be recorded.
- The anesthetic will proceed according to current standard management using rocuronium as the paralytic agent.
- NMB will be maintained at a TOF count of 1-2 twitches after recovery from the induction dose.
- Intraoperative labs will be drawn as deemed necessary by the anesthesia provider.
- If the intraoperative trigger for blood products is reached (7mg/dl), or the attending surgeon or anesthesia provider deems it necessary, appropriate blood products will be transfused.
- At the conclusion of fascial closure, NMB will be reversed with the trial drug, sugammadex (2 mg/kg) or neostigmine (0.05mg/kg up to 5mg) and glycopyrrolate (0.2mg [1ml] for each ml of neostigmine used) both of which are approved reversal agents on the MSKCC formulary. The drugs will be labeled in the anesthetic record at IRB Protocol 17-207 Study Drug A (NEO/GLYCO) or B (SUG).
- The patient will be emerged and extubated when TOF count reaches 4/4 with no perceived fade and traditional extubation criteria are met.

- If the patient has not reached extubation criteria by 30 minutes after administration of study drug, s/he may be transported to the PACU with the ETT in place and timing of extubation will be documented in PACU.
- Additional dosing of reversal agents will not be allowed.
- At 30 minutes (+/-5) after arrival to the PACU, after routine vital signs are assessed, the patient will be questioned and examined by a trained clinician who is blinded to the study drug for the quality of post operative recovery as described above. A PACU RN or APP, blinded to randomization and also trained by the PI, may assist in the assessments.
- The same parameters will be assessed at 60 and 120 minutes (+/- 5) after admission to the PACU then RTD will be assessed every 30 minutes until the patient meets eligibility criteria.
- Time to RTD from PACU will be documented (Primary Outcome) and PACU costs will be calculated.
- The subjective parameters will be scored out of 7 and muscle strength will be recorded.

The trial period is concluded in the PACU when the patient meets PACU discharge criteria.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

Preoperative data

- Name
- Medical record number
- Case number
- Date of birth
- Weight
- Height
- Laboratory values (basic metabolic panel, CBC, coags if requested by surgeon)
- Medications

Intraoperative data

- Standard intraoperative monitoring will be carried out for all patients
- Volume and types of fluids given intraoperatively
- Estimated blood loss and urine output
- Total dose of rocuronium used and time of last dose
- Time of surgical fascial closure
- Intraoperative complications, if any
- Depth of NMB (TOF count) at the time of reversal agent administration
- Time and quality of NMB reversal (TOF count, presence of fade)
- Time extubation criteria are met (See appendix 1)

- Time of extubation whether or not TOF count 4/4 with no perceived fade is metTime patient leaves OR (or is deemed ready to leave OR by intraoperative anesthesia care team in the event of PACU hold)
- Time of arrival to PACU

At 30, 60 and 120 minutes (+/-5) after arrival to the PACU, the patient will be assessed for symptoms and complications relevant to this patient population. In addition to the below, patients will be assessed for the presence of any adverse events per MSKCC standard PACU care. In the PACU, the patient is covered by nursing at a ratio of 1:1 or 1:2 with continuous bedside evaluation of vital signs, hemodynamics and telemetry in a critical care setting. Patients are assessed as per nursing protocol and any adverse events that come up are addressed and documented by the nurse and the APP, possibly the attending and a CIS event note is written. This is the standard of MSK post operative care and documentation in the PACU. We will review these records for inclusion in our adverse events reporting.

Patients will be asked to report:

a. difficulty with breathing (yes/no)
b. presence of diplopia or other visual disturbances (yes/no)
c. difficulty with speaking (yes/no)
d. difficulty with swallowing (yes/no)
e. the presence of nausea or vomiting (yes/no)
f. the presence of pain (yes/no)
g. feeling worried or anxious (yes/no)
h. presence of muscle strength at the biceps brachii muscle (Oxford Scale, Appendix 1)

Except for the evaluation of muscle strength, the assessments will be made in a binary fashion.

- Time PACU discharge criteria (Appendix 1) are met

<u>At discharge from PACU</u>

- Cost of PACU stay from admission to Ready to Discharge

11.0 TOXICITIES/SIDE EFFECTS

The potential toxicities/side effects of this study pertain to those potentially and specifically associated with each operative procedure. Side effects from each of the study drugs are infrequent and may include bradycardia, nausea, anaphylaxis and hypersensitivity. Patients will be assessed in PACU for any adverse events and documented as described above.

All complications will be prospectively recorded and any complication felt to be due to the reversal medication will be reported to the IRB within 5 days. An anesthesia research study assistant will query the Memorial Sloan-Kettering Surgical Secondary Events Program Database at 30 days post-operatively for any potential morbidity data for patients enrolled in

the study. We do not expect any adverse events or side effects from the study medications that are not evident immediately after administration.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary objective of this study is to determine whether SUG, as compared to NEO decreases time for patients to be ready for discharge from the PACU and associated cost savings as well as quality of patient recovery from NMB.

Secondary patient-reported parameters being evaluated are:

a. difficulty with breathing
b. presence of diplopia or other visual disturbances
c. difficulty with speaking
d. difficulty with swallowing
e. the presence of nausea or vomiting
f. the presence of pain
g. feeling worried or anxious
h. presence of muscle strength at the biceps brachii muscle (Oxford Scale, Appendix 1)

- Time patient meets PACU discharge criteria (Appendix 1)

All questions except the Oxford Scale muscle strength assessment will be answered in a binary yes/no fashion.

These parameters will be evaluated in the PACU at 30, 60 and 120 minutes (+/- 5) after arrival. RTD from PACU will be assessed at 30 minute intervals until criteria are reached.

At discharge from PACU, the cost of the PACU stay from admission to ready to discharge will be calculated including the cost of the study medication when unblinding occurs.

We do not anticipate any obstacles to assessing patient response or inclusion in the study results.

13.0 CRITERIA FOR REMOVAL FROM STUDY

A subject may be removed from the study at any time if the attending surgeon or anesthesia provider deems it necessary for patient safety, or if the patient expresses desire to be removed. We do not expect any toxicity associated with the study intervention.

14.0 BIOSTATISTICS

This is a randomized assessor blinded study comparing two reversal agents: neostigmine (NEO, control arm) and sugammadex (SUG, intervention arm) in terms of time for and quality of recovery after reversal of NMB. We plan to enroll 202 patients (101 in each treatment arm) with planned moderate length surgical procedures requiring paralysis. The primary outcome is the duration between administration of NMB reversal agent and the time the patient is ready for discharge from PACU (PACU discharge criteria, Appendix 1).

The sample size calculation is first based on a hypothesized ratio of 0.80 in SUG to NEO mean duration (i.e., the mean duration between NMB reversal agent and ready for PACU discharge under SUG is 20% shorter than the mean duration under NEO). This hypothesis based on the ratio of means can then be translated into a hypothesis about the difference in mean duration on the log scale for the purpose of sample size calculation and interim and final analyses. This approach was used because there is no published literature with the necessary statistics in this particular population of interest.

Stating the hypothesis as a ratio requires specification of (1) the hypothesized ratio and (2) the coefficient of variation (CV = standard deviation divided by mean) to describe the amount of variability relative to the mean. The hypothesized ratio of 0.80 in SUG to NEO mean duration is within the range of estimated reduction in other populations[37,38]. Literature also report CV between 0.2 and 0.4 in the outcome measures among other populations, so we proceed with a more conservative choice of CV of 0.5 for this study. Hence, the hypothesis based on the ratio of 0.8 and CV of 0.5 is equivalent to a two-sample t-test assuming logged-mean of 0 under NEO versus -0.223 under SUG, with the standard deviation of 0.472.

Based on the two-sample t-test of two means on log scale and two-sided alpha of 0.05, a total sample size of 192 patients who undergo surgery yields 90% power to detect the desired differences in logged-means, or equivalently, a ratio of 0.8 in SUG to NEO mean duration. This sample size also allows for an interim analysis halfway through enrollment, using O'Brien-Fleming boundaries with Lan de Mets spending function for both efficacy and futility. If $p \leq 0.002$ at the interim analysis, enrollment will stop with the conclusion that PACU stay is significantly different between the treatments. If $0.002 < p < 0.846$, the trial will continue to full enrollment, and we will conclude that the treatments are significantly different if $p < 0.049$. We increase the sample size by 5% (total 202 patients) to address drop outs or missing primary outcomes due to any reason (e.g., surgery did not occur). Evaluable patients are those randomized, completed surgery, and are able to provide the primary outcome of duration between administration of NMB reversal agent and ready to discharge from PACU.

Analysis of the primary outcome will utilize the two-sample t-test to compare the two randomized treatment arms in terms of the mean duration between reversal of NMB to ready for PACU discharge on the log scale. The conclusion will also be presented in terms of the ratio. The primary analysis will be performed under the intent-to-treat (ITT) principle, including all randomized patients in the evaluable set. The analysis of the primary outcome will be repeated with modified ITT to exclude patients with intraoperative/PACU complications (e.g., unable to extubate).

In reviewing institutional data, the average number of patients who die in the PACU is 1 every 5+ years, and return to OR from PACU is approximately 1 every year. In the rare case that patients

could only contribute only partial information on the primary endpoint, we may pursue survival analysis approach instead, comparing the duration until ready to PACU discharge, and censored at time of PACU exit other than meeting discharge criteria, taking into account potential informative censoring. Accrual rate is 8-16 per month, and the study is expected to be completed in approximately one to two years.

Secondary outcomes related to the quality of post-operative recovery during PACU stay will be measured at 30, 60 and 120 minutes (+/-5) after arrival to the PACU. Secondary patient-reported outcomes will be analyzed using the mixed-effects models with random effects (patient-level) and fixed effects (time point of measurement and arm assignment). Outcomes measured on a continuous scale will be analyzed with the identity link in the longitudinal models, while binary outcomes will be analyzed with logit link: Oxford scale of muscle strength at the biceps brachii muscle (0-5 likert scale, Appendix 1); quality of life measures relevant to the current study will be summarized analyzed separately, such as difficulty with breathing, presence of pain, and feeling worried or anxious (yes/no for occurrence of each item, Appendix 1). These analyses are exploratory because they are of secondary interest and we do not estimate statistical power. The age of patients in the oncological surgical category may be higher than general anesthesia cases as a whole. Age affects pharmacokinetics and pharmacodynamics and hence may bias the treatment effect (Br J Anaesth 2011 PMID 21531745). As an exploratory objective, we will perform subgroup analyses of the primary and secondary objectives only among the elderly patients ($\geq$70 years old).[39] As such, randomization of patients will be stratified by age (<70 years vs ≥ 70 years).

Costs associated with the use of each drug and relationship to the duration of PACU stay will be compared between the two treatment arms. Costs of drugs and PACU stay (from arrival to ready for discharge) will be obtained from pharmacy and administration. As of June 19, 2016, the cost of each reversal medication is $80 for NEO ($50 NEO and $30 Glyco prefilled syringes) and $90 for SUG 200mg. Cost of PACU stay from admission to ready for discharged will be estimated based on the 15-minute PACU costs quoted by administration (includes surgeon and anesthesia provider's reimbursement, facility fees etc.). The net cost of SUG (and NEO) is calculated as the drug's acquisition cost minus the value of any reduction in PACU recovery with the drug. Cost analyses will be conducted based on pairwise threshold analyses, which addresses the question "how much reduction in recovery time would SUG need to achieve, and with what value per minute of staff time, to justify its additional acquisition price?" [40]

The rate of removal will be reported with the study results. Patients who are removed from the study intraoperatively will be continued to be followed unless consent is withdrawn. Pulmonary and airway complications in the PACU will be summarized by arms. Any complications which occur will be documented and submitted as potential SAEs as outlined in Section 17.2.

The evaluable criterion also includes the type of recording device used intraoperatively: randomized patients who are on any recording device other than the SunStim monitors will be considered inevaluable (and excluded from anlyses) due to non-reproducible/unreliable recordings. These patients will be replaced in the study.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

This is an assessor and patient only blinded randomized trial comparing sugammadex versus neostigmine. There will be a total of 202 patients recruited for this study, 101 in each arm, consented during a preoperative clinic appointment. Randomization will be stratified by age (<70 years vs ≥ 70 years). After eligibility is established and consent is obtained, patients will be registered by the CRCs in the Clinical Trials Management System (CTMS) and randomized using the Clinical Research Database (CRDB). Only the anesthesia research team (CRMs and CRCs) and the anesthesia care team in the OR will have access to the unblinded treatment assignments.

16.1 DATA MANAGEMENT ISSUES

A clinical research coordinator (CRC) will be assigned to the study. The responsibilities of the CRCinclude project compliance, patient registration, assistance with data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization and coordination of the activities of the protocol study team. The CRC will be integrated into current weekly and monthly meetings where complications are recorded, procedures reviewed and outcomes documented. The PI's will personally meet with the CRC on a weekly basis to assist with and review the collection and entry of data.

All data to be collected are listed within Section 10.0, and will only be used for the purposes of the study. It will be maintained in a confidential clinical research database by research study personnel only under the direct supervision of the principal investigator. The database will be kept in a password protected computer and will not be transferred outside the hospital network. A minimum dataset will be kept in CRDB. The data will be linked to the patients by means of unique tracking subject numbers, the key to which will also be password protected and only to be accessed by research personnel. Data will be reported to the IRB as required.

We estimate accrual to be approximately 2-4 patients per week allowing completion and reporting of the study within 1-2 years.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, more frequently if indicated.

The principal investigator will maintain final responsibility for the maintenance, quality and integrity of all data collection during the study and during the final analysis of data. Breaches of protocol, problems with eligibility, informed consent or discrepancies in data accuracy will be reported to the IRB at MSKCC as required.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the Document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at: http://cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http:/mskweb5.mskcc.org/intranet/assets/tables/content/359709/DSMPlans07.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

- The responsible principal investigator (PI) will ensure that this study is conducted in agreement with the declaration of Helsinki (Tokyo, Venice, Hong King, Somerset

West and Edinburgh amendments). The study will seek to protect the rights of human subjects in every way.

- The potential risks, including adverse drug reactions and potential benefits in terms of post operative recovery will be discussed in detail with the patients.
- Potential side effects will also be discussed with the patients.
- No patient will be required to participate in the study and participation, or refusal to do so, will not affect the patient's care or treatment.
- The patient will not incur any financial cost as a result of participation in the study.
- Participation will be purely voluntary, and subjects will not be reimbursed for participation in the study.
- Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study.
- All adverse events will be fully disclosed to the IRB in a timely fashion as required.

17.2 Privacy

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to have access to this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 "Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event.

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The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.2.1

There is no additional SAE reporting information required by the drug supplier.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Zhang B, Hepner DL, Tran MH, Friedman M, Korn JR, Menzin J. Neuromuscular blockade, reversal agent use, and operating room time: retrospective analysis of US inpatient surgeries. *Curr Med Res Opin.* 2009;25(4):943-950.
2. Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans. *Br J Anaesth.* 1970;42(11):967-978.
3. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block. II. *Br J Anaesth.* 1971;43(5):478-485.
4. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block. I. *Br J Anaesth.* 1971;43(5):473-477.
5. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology.* 1997;86(4):765-771.
6. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology.* 2003;98(5):1042-1048.
7. Eikermann M, Groeben H, Husing J, Peters J. Predictive value of mechanomyography and accelerometry for pulmonary function in partially paralyzed volunteers. *Acta anaesthesiologica Scandinavica.* 2004;48(3):365-370.
8. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth.* 2007;98(3):302-316.
9. Lien CA, Kopman AF. Current recommendations for monitoring depth of neuromuscular blockade. *Current opinion in anaesthesiology.* 2014;27(6):616-622.
10. Berg H, Roed J, Viby-Mogensen J, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta anaesthesiologica Scandinavica.* 1997;41(9):1095-1103.
11. Eikermann M, Groeben H, Husing J, Peters J. Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. *Anesthesiology.* 2003;98(6):1333-1337.

12. Engbaek J, Ostergaard D, Viby-Mogensen J, Skovgaard LT. Clinical recovery and train-of-four ratio measured mechanically and electromyographically following atracurium. *Anesthesiology.* 1989;71(3):391-395.
13. Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. *Anesthesiology.* 2003;98(5):1037-1039.
14. Eriksson LI, Lennmarken C, Wyon N, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. *Acta anaesthesiologica Scandinavica.* 1992;36(7):710-715.
15. Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. *Anesthesiology.* 1993;78(4):693-699.
16. Eriksson LI, Sundman E, Olsson R, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology.* 1997;87(5):1035-1043.
17. Viby-Mogensen J. Postoperative residual curarization and evidence-based anaesthesia. *Br J Anaesth.* 2000;84(3):301-303.
18. Murphy GS. Residual neuromuscular blockade: incidence, assessment, and relevance in the postoperative period. *Minerva anestesiologica.* 2006;72(3):97-109.
19. McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. *Anesthesiology.* 2015;122(6):1201-1213.
20. Maybauer DM, Geldner G, Blobner M, et al. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. *Anaesthesia.* 2007;62(1):12-17.
21. Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. *Br J Anaesth.* 2010;105(3):304-309.
22. Fortier LP, McKeen D, Turner K, et al. The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade. *Anesthesia and analgesia.* 2015;121(2):366-372.
23. Eikermann M, Vogt FM, Herbstreit F, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Respir Crit Care Med.* 2007;175(1):9-15.
24. Brueckmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. *Br J Anaesth.* 2015;115(5):743-751.
25. Grosse-Sundrup M, Henneman JP, Sandberg WS, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. *BMJ.* 2012;345:e6329.
26. Sasaki N, Meyer MJ, Malviya SA, et al. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. *Anesthesiology.* 2014;121(5):959-968.
27. Herbstreit F, Zigrahn D, Ochterbeck C, Peters J, Eikermann M. Neostigmine/glycopyrrolate administered after recovery from neuromuscular block increases upper airway collapsibility by decreasing genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology.* 2010;113(6):1280-1288.
28. Eikermann M, Fassbender P, Malhotra A, et al. Unwarranted administration of acetylcholinesterase inhibitors can impair genioglossus and diaphragm muscle function. *Anesthesiology.* 2007;107(4):621-629.
29. Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. *Anaesthesia.* 2009;64 Suppl 1:22-30.

30. Caldwell JE, Miller RD. Clinical implications of sugammadex. *Anaesthesia.* 2009;64 Suppl 1:66-72.
31. Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology.* 2008;109(5):816-824.
32. Sorgenfrei IF, Norrild K, Larsen PB, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. *Anesthesiology.* 2006;104(4):667-674.
33. Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine-glycopyrrolate and edrophonium-atropine. *Anesthesia and analgesia.* 2007;104(3):569-574.
34. Eikermann M, Zaremba S, Malhotra A, Jordan AS, Rosow C, Chamberlin NL. Neostigmine but not sugammadex impairs upper airway dilator muscle activity and breathing. *Br J Anaesth.* 2008;101(3):344-349.
35. Donati F, Antzaka C, Bevan DR. Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. *Anesthesiology.* 1986;65(1):1-5.
36. Brull SJ, Silverman DG. Pulse width, stimulus intensity, electrode placement, and polarity during assessment of neuromuscular block. *Anesthesiology.* 1995;83(4):702-709.
37. Carron M, Baratto F, Zarantonello F, Ori C. Sugammadex for reversal of neuromuscular blockade: a retrospective analysis of clinical outcomes and cost-effectiveness in a single center. *ClinicoEconomics and outcomes research : CEOR.* 2016;8:43-52.
38. Unal DY, Baran, I., Mutlu, M., et al. Comparison of Sugammadex versus Neostigmine Costs and Respiratory Complications in Patients with Obstructive Sleep Apnoea. *Turk J Anaesth Reanim.* 2015;43:387-395.
39. Suzuki T, Kitajima O, Ueda K, Kondo Y, Kato J, Ogawa S. Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients. *Br J Anaesth.* 2011;106(6):823-826.
40. Paton F, Paulden M, Chambers D, et al. Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. *Br J Anaesth.* 2010;105(5):558-567.

20.0 APPENDICES

- Appendix 1: Postoperative Assessment Form