Reversal of Neuromuscular Blockade in Patients with Severe Renal Impairment

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PROJECT SUMMARY

Introduction and Purpose:
Inadequate reversal of neuromuscular blockade is a common problem and contributes to postoperative respiratory complications including hypoventilation, hypoxia, reintubation, and a prolonged hospital stay [1-5]. Neostigmine has been the mainstay for reversal of neuromuscular blockade, but has a multitude of side effects such as bronchospasm, nausea/vomiting, hypotension, and bradycardia [6]. Sugammadex is a novel agent for reversal of neuromuscular paralysis induced by steroidal neuromuscular blocking drugs and belongs to a new category of drugs known as 'selective relaxant binding agents.' Sugammadex selectively binds rocuronium in a 1:1 fashion and can reverse any depth of neuromuscular blockade and has been used in patients with severe renal impairment [7][8-11].

Use of sugammadex has been proven to be safe in patients with a history of severe renal impairment [8-11]. The current standard of care for these patients is to use cisatracurium, which undergoes Hofmann elimination, which is independent of renal function. Antagonism of neuromuscular blockade is then subsequently achieved with neostigmine. Currently, there are no specific studies in patients with severe renal impairment evaluating the return of neuromuscular function after reversal of cisatracurium with neostigmine versus reversal of rocuronium with sugammadex. Patients with severe renal impairment often have other comorbidities and are at high risk for postoperative cardiac and pulmonary complications. Additionally, the simultaneous evaluation of clinical outcomes and quality of postoperative recovery has not been undertaken.

The duration of rocuronium in patients with severe renal impairment is prolonged and can be unpredictable. Therefore, cisatracurium is the preferred agent for neuromuscular blockade in patients with severe renal impairment since it undergoes Hofmann elimination, which is independent of renal function. Neuromuscular blockade has also been achieved with rocuronium and successful reversed with sugammadex, even in patients with severe renal impairment. Dialysis through a high-flux filter effectively removes sugammadex and the sugammadex-rocuronium compound from the circulation [26].

There has been anecdotal evidence that patients treated with sugammadex have better subjective measures of recovery compared to patients treated with neostigmine. However, very few studies have systematically evaluated this. Some authors have shown that patients treated with sugammadex have less postoperative nausea and vomiting or pain compared to patients treated with cholinesterase inhibitors [27, 28]. Amorim et al. showed that in an observational study of 101 patients, those treated with sugammadex had improved psychological and nociceptive postoperative recovery and higher overall satisfaction compared to those treated with neostigmine [29]. As patient-reported outcomes have become increasingly important for hospitals, treatments that have the potential to increase patient satisfaction are being studied closely [30]. The postoperative quality recovery scale (PQRS) is a tool that assesses recovery in terms of different domains over time and compares them to baseline values [31]. Some of the advantages of the PQRS are that it is validated, takes less than 5 minutes to administer, has a low patient refusal rate, and is acceptable to patients across a wide range of ages [34].

This will be a prospective, randomized, double-blinded study of surgical patients with severe renal impairment that seeks to address the following:

Specific Aim 1:
To determine whether rocuronium-induced moderate neuromuscular blockade and reversal with sugammadex achieves recovery of neuromuscular function (TOF ≥ 0.9) faster than reversal of

cisatracurium-induced moderate neuromuscular blockade and reversal with neostigmine in patients with severe renal impairment.

Primary Hypothesis:
Patients with severe renal impairment who are reversed with sugammadex after rocuronium will achieve a TOF ≥0.9 within a time frame that is one-third of the time it takes for reversal with neostigmine after cisatracurium.

Specific Aim 2:
To determine if reversal with sugammadex versus neostigmine results in improved postoperative recovery, as measured by the postoperative quality recovery scale (PQRS) and QoR score.

Secondary Hypothesis:
Patients reversed with sugammadex (versus neostigmine) will have a higher quality of recovery in the postoperative period.

Background:
The incidence of residual postoperative neuromuscular blockade has been reported to be 30-60%, as defined by a train of four ratio (TOFR) <0.9 [1, 22-25]. Critical respiratory events (e.g., severe hypoxemia, upper airway obstruction, reintubation, aspiration) are significantly increased with TOFR <0.9 on admission to the PACU [1, 25]. Patients with severe renal impairment often have major comorbidities with little tolerance for postoperative residual neuromuscular blockade. Neostigmine takes much longer to achieve full reversal from neuromuscular paralysis than sugammadex [7, 12-15].

Sugammadex is a modified gamma cyclodextrin that forms a complex with the steroidal neuromuscular blocking agents rocuronium and vecuronium. This complex is then renally excreted, which reduces the amount of neuromuscular blocking agent available to bind to nicotinic cholinergic receptors in the neuromuscular junction. Therefore, the administration of sugammadex results in the rapid reversal of neuromuscular blockade induced by rocuronium and vecuronium. Neostigmine has been the mainstay for reversal of neuromuscular blockade but is associated with adverse side effects such as nausea/vomiting, abdominal pain, and increased secretions. Neostigmine also takes much longer to achieve full reversal from neuromuscular paralysis than sugammadex [7-11]. Furthermore, unwarranted administration of neostigmine can actually result in worsening of neuromuscular paralysis [24-29].

Concise Summary of Project:
This study is intended to be a single-site, prospective, randomized, double-blinded study that intends to enroll a total of 60 patients with severe renal impairment undergoing surgery with general endotracheal anesthesia at Parkland Hospital. Patients will be randomized to receive either neostigmine (for reversal of cisatracurium) or sugammadex (for reversal of rocuronium). A standardized anesthetic protocol that is usual and customary for the type of operation the patient is having will be provided to the anesthesia teams of enrolled subjects. The remainder of the anesthetic care of the subject will not deviate from the standard of care. All patients will be monitored with continuous pulse oximetry postoperatively for 24 hours.

Study Procedures:
Screening and Informed Consent
A member of the research team will use a screening form to look for surgical patients that meet all of the inclusion and exclusion criteria. Patients will be informed that they will receive no compensation for participating in the study and there will be no adverse consequences if they choose not to participate. If the subjects agree to participate, informed written consent will be obtained prior to any study procedures and this document will be sent to pmhresearchparticipants@phhs.org, for inclusion in the patient's medical record, per Parkland regulations. The study duration is approximately 30 days, from the start of anesthesia until POD 30.

Baseline Subjective Measures
In the preoperative area, patients will be asked to complete the baseline assessment for the postoperative quality recovery scale (Appendix 1) and demographic information will be gathered.

Anesthesia Protocol (Appendix 2)
The anesthesia team that will be caring for the patient during surgery will be given the protocol for the study, which standardizes the general anesthetic technique. Patients in the rocuronium/sugammadex group will receive 0.6 mg/kg of rocuronium for neuromuscular paralysis during induction. Additional rocuronium will be given in 0.15 mg/kg increments to keep the patient at a neuromuscular depth of 1 twitch throughout the surgery until the last 30 minutes, during which the patient will be kept at 2 twitches. Patients in the cisatracurium/neostigmine group will receive 0.2 mg/kg of cisatracurium for neuromuscular paralysis during induction. Additional cisatracurium will be given in 0.03 mg/kg increments to keep the patient at a neuromuscular depth of 1 twitch throughout the surgery until the last 30 minutes, during which the patient will be kept at 2 twitches. All patients will have the depth of neuromuscular block monitored at the adductor pollicis with a TwitchView electromyography-based device (Blink, Seattle, WA) that provides real time feedback of the strength of contraction and graphically displays the relevant ratios. All assessments of depth of neuromuscular blockade will be recorded into the patient's electronic medical record.

Maintenance of anesthesia will be with sevoflurane in 50% oxygen, titrated to keep the bispectral index (BIS) between 40-60. All patients will have a forced air warming device (e.g., Bair Hugger, 3M, Maplewood, MN) used to maintain normothermia throughout the surgery. Subjects will be randomized to receive all blinded study drugs: <u>either</u> neostigmine for reversal of cisatracurium or sugammadex for reversal of rocuronium. The reversal agent will be administered intravenously at the beginning of skin closure when the patient has moderate neuromuscular blockade (i.e., TOF = 2 twitches). The anesthesia team will be completely blinded and the postoperative assessments will also be completed by a separate blinded member of the research team. The induction neuromuscular blocking agent syringe will be drawn up by pharmacy and contain either cisatracurium 0.2 mg/kg or rocuronium 0.6 mg/kg and filled with normal saline to make identical 10mL syringes. If the patient is ≥ 100 kg, a 20mL syringe will be used (instead of 10mL). The maintenance neuromuscular blocking agent syringe will be drawn up by pharmacy and contain 5 or 10mL of either rocuronium (10 mg/mL) or cisatracurium (2 mg/mL) [both in their original, undiluted concentrations]. The reversal agent will also be drawn up by pharmacy and will contain neostigmine 50 mcg/kg mixed (maximum 5mg) with glycopyrrolate 10 mcg/kg (maximum 1mg) or sugammadex 2 mg/kg. The blinded study drug ("reversal agent") will be prepared into a 10 mL syringe by a pharmacist in Investigational Drug Service (IDS) Pharmacy and labeled as "sugammadex <u>or</u> neostigmine/glycopyrrolate." Any volume of blinded study drug that is less than 10 mL will be supplemented with 0.9% normal saline solution so that all syringes contain a volume of 10 mL and appear *identical* in order to preserve blinding. The remaining aspects of the anesthetic will be standardized and not differ from the standard of care for all patients.

Randomization & Dosing:
Patients will be randomized to one of two groups for neuromuscular blockade and reversal of neuromuscular paralysis:

1. **Group 1**- cisatracurium + neostigmine (NEO group)
    a. Induction neuromuscular blockade with 0.2 mg/kg cisatracurium
    b. Maintenance neuromuscular blockade with boluses of 0.03 mg/kg cisatracurium to keep TOF 1-2 twitches
    c. Reversal: neostigmine 50 mcg/kg, maximum 5 mg mixed with glycopyrrolate, 10 mcg/kg, maximum 1 mg

2. **Group 2**- rocuronium + sugammadex (SUG group)
    a. Induction neuromuscular blockade with 0.6 mg/kg rocuronium
    b. Maintenance neuromuscular blockade with boluses of 0.15 mg/kg rocuronium to keep

TOF 1-2 twitches

c. Reversal: Sugammadex 2 mg/kg

The statistician will make randomization envelopes by using a random number generator. These envelopes will be provided to Investigational Drug Services (IDS) Pharmacy before any subjects are screened and later only as needed to replenish supply. The words 'cisatracurium + neostigmine/glycopyrrolate' or 'rocuronium + sugammadex' will be printed on a piece of paper and placed in an opaque manila envelope that bears a unique subject number. Upon receiving the physician order for the subject, the IDS Pharmacist will randomize the subject to a treatment group by opening the randomization envelope bearing the subject number corresponding to the subject number written on the physician order.

The Investigator or Co-Investigator will write the patient's weight on the order form so that the pharmacist can perform necessary dose calculations and draw up the appropriate intravenous dose of the blinded study drugs. After the blinded study drug syringes are prepared, a pharmacist or pharmacy technician will deliver the syringe to the operating room to the anesthesia provider, who will sign for receipt of study drug syringe.

Blinding/Un-blinding:

The patient, all medical providers (surgeons, anesthesia faculty, anesthesia residents, certified registered nurse anesthetists, nurses), and the postoperative evaluator will be blinded as to what neuromuscular blocking drug and reversal agent the patient receives. A member of the research team that is not involved in the direct care or assessment of the patient will provide the randomization envelopes to IDS Pharmacy. IDS Pharmacy staff will be the only un-blinded personnel.

In emergency scenarios when un-blinding becomes necessary (e.g., anaphylaxis), the principal investigator or co-investigators may call the IDS Pharmacy to ascertain which specific medication(s) was dispensed. A detailed log of patient enrollments, randomization assignments and drug accountability will be kept in Investigational Drug Service (IDS) Pharmacy, which has controlled security access.

Calculation of Key Times

The time that the reversal agent (sugammadex versus neostigmine) is given will be marked as 'Reversal Time', and times to last stitch, extubation, and out of OR will be ascertained from the electronic medical record (EMR) (i.e., Epic Systems, Verona, WI). Once the patient arrives in the PACU, a trained research assistant will assess the degree of neuromuscular function the patient has using the TwitchView set to 30mA. Adequate reversal will be defined as a train of four ratio (TOFR) $\geq$ 0.9. Anything less than 0.9 will be defined as residual paralysis or inadequate reversal.

PACU Assessment

A blinded, trained research assistant will observe and record all parameters from the time the patient arrives in the PACU until they are discharged from the PACU. All episodes of hypoxia and any use of supplemental oxygen will be recorded. All vital signs will be extracted from the EMR. Any drugs given in the PACU will be recorded. At 15 minutes (T_{15}), 40 minutes (T_{40}), and 80 minutes (T_{80}) after arrival to the PACU, the patient will be assessed using the postoperative quality recovery scale (PQRS) in 3 domains (Appendix 1).

Postoperative Day (POD) 1 Assessments

All patients will be admitted to the hospital for continuous SpO_2 monitoring for 24 hours. Patients who are on dialysis will resume their normal dialysis schedule, which will be recorded. On POD 1 the patient will be assessed using the postoperative quality of recovery scale (PQRS) in 5 domains (Appendix 3). Patients who are still in the hospital on POD 2 will be assessed using the PQRS as well. Patients who are discharged home will be called on the telephone and the PQRS will be assessed in 4 domains (no physiological assessments). All patients will be followed for their total hospital length of stay and assessed for any major adverse events (reintubation, pneumonia,

myocardial infarction, stroke, unplanned hospital admission, or readmission within 30 days of hospital discharge).

Data Sources
Protected health information including name, medical record number, and date of birth will be recorded and stored securely in an IRB approved, secured REDCap database.

Parameters:
1. Protected health information (PHI): name, medical record number, date of birth, phone number
2. Demographic information (age, weight, height, BMI), medical and surgical history, ASA status
3. Preoperative PQRS assessment
4. Intraoperative parameters
    - Frequency and dose of all neuromuscular blocking and reversal agents
    - Intraoperative vitals (systolic, diastolic, and mean blood pressures, temperature, heart rate) at least every 3 minutes
    - ECG rhythm
    - Fluids administered
    - End-tidal concentration of anesthetic (e.g., sevoflurane)
    - Total intraoperative opioids
    - Length of surgery
    - The time from last neuromuscular blocking agent given to reversal agent (min)
    - The time from neuromuscular reversal to last stitch (min)
    - The time from neuromuscular reversal to extubation (min)
    - The time from neuromuscular reversal to discharge from the OR (min)
    - The time from surgery completed (bandage on) to discharge from the OR (min)
    - Depth of neuromuscular blockade throughout the surgery at 15-minute intervals
    - Presence of hemodynamic changes, rash, erythema, or flushing after reversal agent given
5. PACU parameters
    - Evaluation of residual paralysis with train of four (TOF) stimulation using the TwitchView within 5 minutes of PACU arrival and every 5 minutes until a TOF $\geq$ 0.9 is reached
    - Time it takes to achieve TOFR $\geq$ 0.9
    - Vitals during PACU stay (BP, temperature, HR, SpO_2) every 10 minutes
    - Number of hypoxic episodes (SpO_2<95%)
    - Lowest observed SpO_2 during any episode of airway obstruction
    - Need for supplemental oxygen
    - Any episodes of airway obstruction and treatment (e.g., jaw thrust, insertion of nasopharyngeal, oropharyngeal or laryngeal mask airway or reintubation).
    - The time when PACU discharge criteria are met
    - Total PACU time (PACU arrival to actual discharge from PACU)
    - PQRS in 3 domains (Appendix 1) at 15 minutes, 40 minutes and 80 minutes
6. Postoperative day 1-2 evaluation
    - PQRS in 4-5 domains (Appendix 3)
8. Adverse event monitoring (until POD 30)
    - Reintubation
    - Recurarization
    - Critical respiratory adverse event including bronchospasm, atelectasis, pulmonary edema
    - Cardiovascular adverse events such as tachycardia, bradycardia, cardiac arrhythmias, hypotension, and hypertension
    - Major adverse postoperative events (pneumonia, reintubation, myocardial infarction, stroke)
    - Unplanned hospital admission

Criteria for Inclusion of Subjects:

- 18-80 years old
- Severe renal impairment (CrCl < 30 mL/min)
- Undergoing non-emergent surgery that requires neuromuscular blockade
- Planned extubation in the operating room immediately after surgery
- ASA physical status classification 3 to 4
- Willing and able to consent in English or Spanish
- No personal history of neuromuscular disease

Criteria for Exclusion of Subjects:

- Age less than 18 or older than 80
- Patient does not speak English or Spanish
- Morbidly obese (BMI≥ 40-49.9 kg/m^2)
- Planned postoperative intubation/ventilation
- Allergy to sugammadex, neostigmine, glycopyrrolate, cisatracurium, or rocuronium
- Family or personal history of malignant hyperthermia
- Patient refusal
- "Stat" (emergent) cases
- Patients undergoing thoracic operations (e.g., video assisted thoracoscopic surgery, thoracotomy)
- Pre-existing muscle weakness of any etiology
- Patients with moderate to severe COPD
- Patients with sleep apnea
- Patients on toremifene (a selective estrogen receptor modulator)
- Women of childbearing age who:
  a. Have a positive pregnancy test
  b. Are on oral contraceptives and not willing to use a non-hormonal method of contraception for 7 days after surgery
  c. Nursing women

Sources of Research Material:

- Identifying patient information including name, medical record number, and birth date
- Medical history
- Surgical history
- Weight and height
- Medication list
- Laboratory studies
- Vital signs
- ECGs and radiologic studies
- Intraoperative anesthetic record
- Postoperative notes and discharge summary

Recruitment Methods and Consenting Process:

Subjects who meet all inclusion and exclusion criteria will be approached by a member of the research team either in the pre-anesthesia evaluation clinic or in the preoperative area of day surgery in a private room or in their private room on the floor if they are an inpatient. All study procedures will be explained to the patient in layman's terms. If the subject agrees to participate, he or she (or their legal representative) will sign the consent form and HIPAA Authorization Form prior to any study procedures.

Potential Risks:

The additional risks posed by participation in this study are not different than the usual risks associated with surgery and general anesthesia. There is a potential for a direct benefit to the patient

if they receive sugammadex, based on available literature, which reports that sugammadex is superior to neostigmine for reversal of neuromuscular blockade [7-17]. The anesthetic management of subjects will not differ from the standard care. Patients will be randomized to receive either neostigmine or sugammadex for reversal of neuromuscular paralysis.

Risk of Sugammadex:
The most common adverse reactions after administration of sugammadex are nausea/vomiting, pain, hypotension, dizziness, itching, and headache. There is a 0.3% chance of an allergic reaction to sugammadex.

Neuromuscular blockade recurrence could theoretically occur after the administration of sugammadex due to displacement of rocuronium from sugammadex by other drugs.This has not been reported in the literature. The association rate of rocuronium with sugammadex is very high and the dissociation rate is very low, due to the intermolecular (van Der Waals') forces and hydrophobic interactions. It is estimated that for every 25 million sugammadex-rocuronium compounds, only 1 dissociates (Nag 2013).

The sugmmadex label has a warning for the use of the drug in patients with severe renal impairment. Sugammadex is "not recommended" for use in patients with severe renal impairment, including those requiring dialysis. The label states that sugammadex is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function and the elderly because elderly patients are more likely to have decreased renal function. The half-life of sugammadex in patients with mild, moderate and severe renal impairment is 4, 6, and 19 hours, respectively.

Marked bradycardia can be seen, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of sugammadex. This is not different for patients with vs without renal impairment.

The sugammadex label states that it may bind to progesterone thereby decreasing exposure. Therefore, the administration of a bolus dose of sugammadex is considered to be equivalent to missing dose(s) of oral contraceptives containing an estrogen or progesterone. If an oral contraceptive is taken on the same day that sugammadex is administered, the patient must use an additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days. Female subjects who are using oral contraceptives will be informed during the consenting process that they will need to use a non-hormonal method of contraception for 7 days if they participate in the study. Women who do not wish to do this will not be enrolled in the study. Women who do choose to participate will be provided a letter (in English or Spanish) with this information and phone number of the PI if they have any additional questions.

Risks of Rocuronium
The most common adverse reactions after administration of rocuronium are nausea, vomiting, light headedness, and minor changes in blood pressure.

Risks of Cisatracurium
The most common adverse reactions after administration of cisatracurium are nausea, vomiting, light headedness, and minor changes in blood pressure.

Risks of Neostigmine
The most common adverse reactions after administration of neostigmine are nausea, vomiting, and low heart rate, but another drug called glycopyrrolate is always given along with neostigmine to counteract the potential drop in heart rate.

Risks of Glycopyrrolate

The most common adverse reactions after administration of glycopyrrolate are tachycardia, dry mouth, nausea/vomiting, and headache. A rare but serious complication of glycopyrrolate is a severe rise in body temperature and abnormal heart rhythm.

Psychological Stress
There is minimal risk for psychological stress to the patient as a result of participation in this study. Subjects may refuse to answer any of the questions or take a break or stop participation in the study at any time.

Subject Safety and Data Monitoring:
Study oversight will include a Data Safety and Monitoring Board (DSMB). The DSMB will be chaired by a faculty member that is not the PI and will include specialists from different specialties including anesthesiology, critical care medicine, and nephrology. The DSMB will meet quarterly as needed to review all patient enrollments. If necessary, the DSMB will meet more often to review specific study subjects, unanticipated events, protocol violations, and adverse events. All study subjects will be reviewed by the DSMB for any study-related adverse outcomes. A written record of all meetings will be kept. The IRB will be notified in writing of any adverse study-related outcomes. The PI will provide to the Parkland Office of Research Administration (ORA) safety progress reports after the first 3 patients, then again at 10 patients and then with the annual continuing review.

Procedures to Maintain Confidentiality:
A non-identifiable code will be assigned to the data collection sheet so that there is not a direct link to specific names. Patient IDs will be standardized in chronological order as subject 1, subject 2, etc. A key to the coding system will be maintained in a locked storage cabinet with limited access until all the data is collected and analyzed. Access to study data will be restricted to authorized study personnel only. Following the completion of the analysis and the project, the key to the coding system or subject identifiers themselves will be destroyed by shredding the documents so that there is no direct or indirect link to subject identifiers and information.

All data from the study will be kept on encrypted computers belonging to the University, which are stored in secured areas. All electronic study data will be password protected and passwords will be changed on a regular basis.

All data will be de-identified when exported from the REDCap database. Patient data will be analyzed without patient identifiers by assigning study ID subject numbers that are de-linked from patient identifiers. Signed consent forms, HIPAA forms, and study questionnaires will remain in a locked cabinet in the PI's office.

Potential Benefits:
This study is not designed to directly benefit the study subjects who participate in this study, but there may be potential for a direct benefit to the patient if they receive sugammadex, based on available literature, which reports that sugammadex is superior to neostigmine for reversal of neuromuscular blockade [7-17]. This study is intended to evaluate if sugammadex provides superior reversal of neuromuscular blockade compared to neostigmine with regard to decreased hypoxia, increased operating room efficiency, and improved postoperative recovery quality.

Statistics:
The principal investigator will be responsible for analyzing the study data with a biostatistician. For the final analysis, the database will not be unblinded until enrollment, medical review, protocol violations, and data have been collected.

Specific Aim 1:

To determine whether rocuronium-induced moderate neuromuscular blockade and reversal with sugammadex achieves recovery of neuromuscular function (TOF ≥ 0.9) faster than reversal of cisatracurium-induced moderate neuromuscular blockade and reversal with neostigmine in patients with severe renal impairment.

Primary Hypothesis:
Patients with severe renal impairment who are reversed with sugammadex after rocuronium will achieve a TOF ≥0.9 within a time frame that is one-third of the time it takes for reversal with neostigmine after cisatracurium.

Sample Size Justification:
The sample size calculation is based on the assumption that the treatment group (SUG) will have a 10 min faster time to mean recovery to TOF ≥0.9 compared to the control group (NEO) (assuming 5 minutes reversal time for SUG group and 15 minutes for NEO group). With 24 subjects in each group, this gives the study a power > 99% to detect a difference of at least 10 min in the mean time to recovery, assuming a SD of 1.5 min in the SUG group and a SD of 5.5 min in the NEO group. Accounting for dropouts, protocol deviations, or unexpected postoperative ventilation, etc. a maximum of 60 patients will be enrolled.

Analysis Plan:
In the primary analysis, we will compare the mean time to recovery to TOF≥0.9 by the two-sample t test, using a Satterthwaite correction to the degrees of freedom to account for an anticipated difference in the variances between the treatment arms. Two key secondary outcomes are the numbers of hypoxic episodes in the recovery room and in the first 24 hours postoperatively. We will also analyze these data using two-sample t tests with the Satterthwaite correction. For each type of adverse event, we will create a two-way table cross-classifying subjects by treatment arm and whether they experienced the adverse event. We will conduct a Fisher exact test on each such table to determine whether there is a significant association between treatment arm and the event. As these are safety analyses, we will not adjust for multiplicity.

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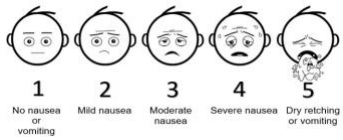
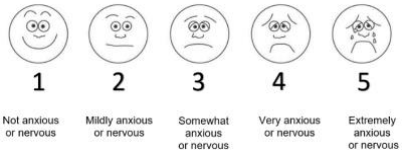
Appendix 1: Postoperative Quality Recovery Scale evaluation at baseline, T_{15}, T_{40}, T_{80}

Demographic and Preoperative Data[a]	
Age	yrs
Gender	Male or Female
ASA Status	1 2 3 4
Weight	kg
Height	in
BMI	kg/m^2
Education	Highest level finished:
Alcohol consumption	units/wk
Smoking status	Never, used to but quit, current smoker
Employment	Unemployed Employed and plan to return Employed but plan not to return Occupation: Approximate hrs/wk:
Inpatient	Yes or No
Surgical procedure	
Physiological Factors[a,d]	
P1 Blood Pressure Please record the patient's blood pressure	/ 3= SBP 90-140; 2= SBP 70-89 or 141-180; 1= SBP <70 or >180
P2 Heart Rate Please record the patient's heart rate	 3= 45-100; 2= 35-44 or 101-139; 1= <35 or >140
P3 Temperature Please record the patient's temperature	*Method 1. Sublingual 2. Tympanic 3. Esophageal* 3= 36-37.6; 2= 35-35.9 or 37.7-38.9; 1= <35 or >39
P4 Respiration Please record the patient's respiratory rate	/breaths per minute
P5 Oxygen use to maintain SpO_2 Please record oxygen requirement	3= Oxygen administered by protocol or not required 2= Any SpO_2 <95% requiring oxygen as an intervention 1= Any SpO_2 <90% requiring oxygen as an intervention
P6 Airway Please record the number corresponding to the assessment	3= Self-maintenance of airway 2= Maintenance of airway with support (describe) 1= Device *in situ*
P7 Agitation Please record the number corresponding to the assessment	3= Shows no signs of agitation 2= Patient shows occasional agitation 1= Patient shows severe agitation
P8 Alertness Please record the number corresponding to the actual	5= Awake, following commands 4= Responds to name spoken in normal tone 3= Responds only after name is spoken

assessment	loudly and repeatedly or both 2= Responds only after mild prodding or shaking 1= Does not respond to mild prodding or shaking
P9 What is the level of your strength now? Please record the number corresponding to the actual assessment	3= No weakness 2= A little weak 1= Very weak
Nociceptive Factors[a,b,c]	
N1 I am going to show you a series of faces and I would like you to indicate which face, number or description most accurately describes your level of pain at the moment.	
N2 I am going to show you a series of faces and I would like you to indicate which face, number, or description most accurately describes your level of feeling nauseous or vomiting at the moment.	
Emotional Factors[a,b]	
E1 I am going to show you a series of faces and I would like you to indicate which face, number, or description accurately describes to what extent you feel sad, low, or depressed at the moment.	
E2 I am going to show you a series of faces and I would like you to indicate which face, number, or description accurately describes to what extent you feel anxious or nervous at the moment.	

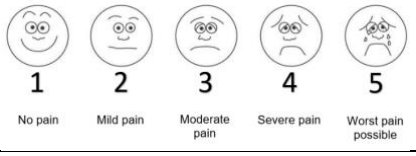
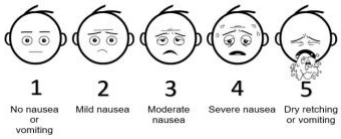
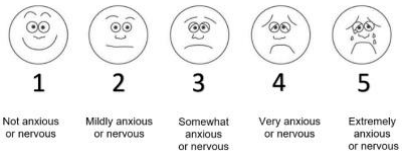
a. Patient questionnaire adapted from Royse et al. 2010 and Amorim et al. 2014
b. Pain, depression, and anxiety scales are modified from Wong and Baker 1988
c. Nausea scale is modified from Baxter et al. 2011
d. Alertness scale adapted from Doufas et al. 2001

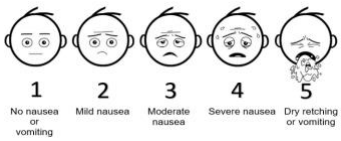
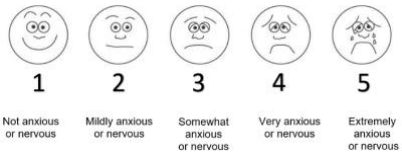
Appendix 2: Anesthesia Protocol for Reversal of Neuromuscular Blockade in Patients with Severe Renal Impairment

1. **Monitoring**
    a. Standard ASA monitors + BIS monitor
    b. All patients will be monitored with a TwitchView accelerometer device at 15-minute intervals. This device records real time feedback of the strength of contraction and graphically displays the relevant ratios.
2. **Induction**
    a. Propofol 1.5 – 2.0 mg/kg
    b. Fentanyl 1 – 1.5 mcg/kg
    c. Lidocaine 0.5 – 1.0 mg/kg
    d. NMBD Syringe (will contain either cisatracurium 0.2 mg/kg OR rocuronium 0.6 mg/kg)-
3. **Maintenance Anesthesia**:
    a. FiO2 50% (No Nitrous Oxide)
    b. Fentanyl ~ 0.5-1 mcg/kg/hr in divided doses as appropriate
    c. Sevoflurane inhalational anesthesia to maintain BIS 40-60
    d. Maintenance NMBD at 0.015 mL/kg (equal to rocuronium in 0.15 mg/kg increments or Cisatracurium in 0.03 mg/kg increments)
    e. Keep TOF at 1 until 30 minutes prior to anticipated conclusion of surgery (allow TOF to reach 2 twitches before reversal!)
    f. Bair Hugger to maintain normothermia
    g. Ventilatory parameters to maintain normocapnia
4. **Prophylaxis**
    a. Ondansetron 4 mg
    b. Dexamethasone 4 mg
5. **Reversal**
    a. The patient will be randomized to receive sugammadex vs. neostigmine/glycopyrrolate. A research assistant will bring a 10mL syringe labeled 'reversal agent' to the OR. You will not be told what reversal agent the patient has been randomized to receive, as this is a double-blinded study. The syringe will contain either sugammadex 2mg/kg or neostigmine 50 mcg/kg mixed with glycopyrrolate 10 mcg/kg.
    b. Please administer the reversal agent at the START of skin closure and mark this time in EPIC with a Quick Note.
6. **Extubation**
    a. Patients will be extubated when all extubation criteria are met
    b. Patients will be transported to the PACU with 8L/min O_2 by face mask
7. **Post-anesthesia Care Unit (PACU)**
    a. T_0 will be the time the patient arrives to the PACU.
    b. All vital signs will be recorded every 10 minutes while the patient is in the PACU.
    c. The first postoperative PQRS assessment will occur 15 minutes after arrival to the PACU (T_{15}), the second PQRS assessment will occur 40 minutes after arrival to the PACU (T_{40}), and the third PQRS assessment will occur 80 minutes after arrival to the PACU (T_{80}).
    d. Patients will be weaned from supplemental oxygen to keep SpO2 $\geq$ 94%.
    e. The time at which the patient meets all criteria for discharge from the PACU will be recorded, as well as the actual PACU duration.

Appendix 3: Postoperative Quality Recovery Scale evaluation at POD_1 and POD_2[**]

Physiological Factors[a,d]	
P1 Blood Pressure Please record the patient's blood pressure	/ 3= SBP 90-140; 2= SBP 70-89 or 141-180; 1= SBP <70 or >180
P2 Heart Rate Please record the patient's heart rate	 3= 45-100; 2= 35-44 or 101-139; 1= <35 or >140
P3 Temperature Please record the patient's temperature	*Method 1. Sublingual 2. Tympanic 3. Esophageal* 3= 36-37.6; 2= 35-35.9 or 37.7-38.9; 1= <35 or >39
P4 Respiration Please record the patient's respiratory rate	/breaths per minute
P5 Oxygen use to maintain SpO_2 Please record oxygen requirement	3= Oxygen administered by protocol or not required 2= Any SpO_2 <95% requiring oxygen as an intervention 1= Any SpO_2 <90% requiring oxygen as an intervention
P6 Airway Please record the number corresponding to the assessment	3= Self-maintenance of airway 2= Maintenance of airway with support (describe) 1= Device *in situ*
P7 Agitation Please record the number corresponding to the assessment	3= Shows no signs of agitation 2= Patient shows occasional agitation 1= Patient shows severe agitation
P8 Alertness Please record the number corresponding to the actual assessment	5= Awake, following commands 4= Responds to name spoken in normal tone 3= Responds only after name is spoken loudly and repeatedly or both 2= Responds only after mild prodding or shaking 1= Does not respond to mild prodding or shaking
P9 What is the level of your strength now? Please record the number corresponding to the actual assessment	 3= No weakness 2= A little weak 1= Very weak

Nociceptive Factors[a,b,c]	
N1 I am going to show you a series of faces and I would like you to indicate which face, number or description most accurately describes your level of pain at the moment.	
N2 I am going to show you a series of faces and I would like you to indicate which face, number, or description most accurately describes your level of feeling nauseous or vomiting at the moment.	
Emotional Factors[a,b]	
E1 I am going to show you a series of faces and I would like you to indicate which face, number, or description accurately describes to what extent you feel sad, low, or depressed at the moment.	
E2 I am going to show you a series of faces and I would like you to indicate which face, number, or description accurately describes to what extent you feel anxious or nervous at the moment.	
Activities of Daily Living[a]	
A1 Able to breathe easily Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A2 Been able to enjoy food Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A3 Feeling rested Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A4 *Have had a good sleep* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A5 *Able to look after personal toilet and hygiene unaided* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A6 *Able to communicate with family or friends* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A7 *Getting support from hospital doctors and nurses* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A8 *Able to return to work or usual home activities* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A9 *Feeling comfortable and in control* Please record the number corresponding to the	0 to 10, where 0=none of the time [poor] and 10=all

actual assessment	of the time [excellent]
A10 *Having a feeling of general well-being* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
Overall Patient Satisfaction[a]	
O1 Patient Satisfaction Please record the number corresponding to the actual assessment	5= Very satisfied 4= Satisfied 3= Moderately satisfied 2= Unsatisfied 1= Very Unsatisfied
Nociceptive Factors[a,b,c]	
N1 I am going to show you a series of faces and I would like you to indicate which face, number or description most accurately describes your level of pain at the moment.	
N2 I am going to show you a series of faces and I would like you to indicate which face, number, or description most accurately describes your level of feeling nauseous or vomiting at the moment.	
Emotional Factors[a,b]	
E1 I am going to show you a series of faces and I would like you to indicate which face, number, or description accurately describes to what extent you feel sad, low, or depressed at the moment.	
E2 I am going to show you a series of faces and I would like you to indicate which face, number, or description accurately describes to what extent you feel anxious or nervous at the moment.	
Activities of Daily Living[a]	
A1 Able to breathe easily Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A2 Been able to enjoy food Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A3 Feeling rested Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A4 *Have had a good sleep* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A5 *Able to look after personal toilet and hygiene unaided* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A6 *Able to communicate with family or friends* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A7 *Getting support from hospital doctors and nurses*	0 to 10, where 0=none of the time [poor] and 10=all

Please record the number corresponding to the actual assessment	of the time [excellent]
A8 *Able to return to work or usual home activities* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A9 *Feeling comfortable and in control* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
A10 *Having a feeling of general well-being* Please record the number corresponding to the actual assessment	0 to 10, where 0=none of the time [poor] and 10=all of the time [excellent]
Overall Patient Satisfaction[a]	
O1 Patient Satisfaction Please record the number corresponding to the actual assessment	5= Very satisfied 4= Satisfied 3= Moderately satisfied 2= Unsatisfied 1= Very Unsatisfied

** Patients who are discharged home by POD 2 will not be assessed in the physiological domain

a. Patient questionnaire adapted from Royse et al. 2010 and Amorim et al. 2014
b. Pain, depression, and anxiety scales are modified from Wong and Baker 1988
c. Nausea scale is modified from Baxter et al. 2011
d. Alertness scale adapted from Doufas et al. 2001

Appendix 4: Study Flowchart