

An assessor-blinded, randomized, controlled, single center, parallel design trial to compare the incidence of postoperative pulmonary complications (PPCs) associated with rocuronium neuromuscular reversal with Sugammadex versus Neostigmine in patients 70 years of age or older undergoing surgery of at least 3 hours (SugPPC)

**Protocol
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INTRODUCTION

Postoperative pulmonary complications (PPCs) refer to unexpected problems involving the lungs or airway in the post-surgical period. There is precedent from multiple randomized controlled trials for grouping these events and treating them as a composite outcome. These events can be grouped together because they impact patient outcome and account for a great deal of surgery and anesthesia attributed morbidity and mortality. The National Surgical Quality Improvement Program, or NSQIP, found that postoperative complications involving the lungs result in a longer length of stay and increase hospital cost more than complications involving any other organ system (Dimick, Chen, Taheri, Henderson, Khuri, & Campbell, 2004). In addition, the Centers for Medicare and Medicaid recently updated the pneumonia readmission measure to include patients with “aspiration pneumonia...and sepsis patients coded with pneumonia present on admission” (Centers for Medicare & Medicaid Services, 2016). To this extent, hospitals will be very interested in ways to reduce respiratory complications that may result in readmissions, as the penalties for readmissions are increasing substantially.

The definition for PPCs varies by study. In general, they are diagnosed as any clinically meaningful dysfunction of the lungs or airway that negatively impact a patient’s hospital course. PPC are a nice endpoint as a primary outcome because they are a composite of multiple adverse events and as such have an incidence much greater than any single perioperative respiratory complication. This higher prevalence allows for clinical questions to be answered in a randomized controlled trial with a smaller number of patients enrolled. For this study, the definition of PPCs will include any of the following occurring at any time during the patient’s hospitalization:

1. Postoperative pneumonia: any patient given antibiotics for a respiratory indication with at least one of the following: WBC > 12,000, new or changed sputum, new lung opacities on chest x-ray, or temperature > 38.0 C
2. Aspiration pneumonitis: any patient diagnosed with acute lung injury by chest x-ray, MRI or CT after a clinical story consistent with inhalation of gastric contents
3. Atelectasis: any patient diagnosed with more than minimal atelectasis by a radiologist on chest x-ray
4. Pneumothorax: any patient diagnosed with a pneumothorax by radiologist on chest x-ray
5. Desaturation/hypoxemia: any patient requiring supplemental oxygen for a PaO₂ < 60 mm Hg, PaO₂/FiO₂ < 300, or Sat < 90%
6. Upper airway obstruction: any patient requiring a nasal airway or oral airway in the PACU
7. Acute respiratory insufficiency: any patient requiring mechanical ventilator support (non-invasive or invasive)

The overall incidence of postoperative pulmonary complications varies by article, but averages around 5% of all patients. Canet J et al. (Canet, et al., 2010) found nine independent predictors of PPCs: higher age, male sex, low preoperative sat, respiratory infection in the month preceding surgery, a preoperative hemoglobin less than 10 g/dL, positive cough test (a patient is asked to take a deep breath and cough once, in a positive cough test the patient continues to cough), upper abdominal or thoracic surgery, longer surgery, and emergent surgery. The risk for a PPC was greatly affected by increasing age (most notably above age 80), a greater than 40 pack-year smoking history, a preoperative saturation < 90%, and a surgery > 3-hours. Based upon this study, older patients having > 3-hour surgery are most likely to fall into the high risk category (they are already almost there with those 2 characteristics and they will most likely have at least one additional minor risk factor) which gives them a 42.1% risk of PPCs. Age and surgical length are

highlighted amongst the nine independent predictors of PPC because they are easy to glean from a surgical posting sheet.

Residual neuromuscular blockade is defined as a TOF ratio < 0.9 after reversal has been administered. The incidence of residual neuromuscular blockade after neuromuscular reversal with neostigmine has been well studied. In general, residual neuromuscular blockade in the PACU is common and ranges in incidence between 30% and 55% (Yip, Hannam, Cameron, & Campbell, 2010) (Kumar, Nair, Murthy, Jalaja, Ramachandra, & Parameshwara, 2012) (Murphy & Brull, 2010) (Fortier, et al., 2015). Residual neuromuscular blockade has been found to be even higher at the time of extubation (Fortier, et al., 2015). Murphy et al. found a mean TOF ratio immediately before tracheal Extubation of 0.67, with an astounding 88% of patients with a TOF ratio < 0.9, which would meet criteria for a diagnosis of residual neuromuscular blockade (Murphy, Szokol, Marymont, Franklin, Avram, & Vender, Residual paralysis at the time of tracheal extubation, 2005).

Incomplete recovery of neuromuscular blockade has been shown to be associated with PPCs. Glenn Murphy's group has done a great deal of research on this topic and he has found that patient's diagnosed with postoperative critical respiratory events had a mean TOF ratio of 0.62 versus matched control patients that did not have critical respiratory events with a mean TOF ratio of 0.98 (Murphy, Szokol, Marymont, Greenberg, Avram, & Vender, Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit, 2008). In this article, it was noted that none of the control subjects that did not have critical respiratory events had a TOF ratio < 0.7 (Murphy, Szokol, Marymont, Greenberg, Avram, & Vender, Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit, 2008). Residual neuromuscular blockade with a median TOF ratio of 0.7 has been linked to the development of desaturation in the PACU (Sauer, Stahn, Soltesz, Noeldge-Schomburg, & Mencke, 2011). In a study comparing residual neuromuscular with pancuronium, atracurium or vecuronium, PPCs were similarly found to be associated with residual blockade (Berg, et al., 1997).

Several adverse physiologic changes have been found to be associated with residual neuromuscular blockade. Residual neuromuscular blockade has been found to be associated with reductions in forced vital capacity and peak expiratory flow in the PACU (Kumar, Nair, Murthy, Jalaja, Ramachandra, & Parameshwara, 2012). It has also been linked to pharyngeal dysfunction and an increased rate of aspiration, decreased upper esophageal resting tone, and depressed carotid body chemoreceptor hypoxic ventilatory response (Murphy & Brull, 2010).

Sugammadex is a novel new drug for specific reversal of rocuronium neuromuscular blockade. It is unique from neostigmine in that it can reverse any degree of blockade. It has been shown to eliminate residual neuromuscular paralysis when administered in appropriate doses. In a study of 154 subjects having abdominal surgery with rocuronium blockade randomized to either sugammadex or neostigmine, zero patients given sugammadex had residual neuromuscular paralysis while 43.4% of patients administered neostigmine had residual paralysis in the PACU (Brueckmann, et al., 2015).

The efficacy of sugammadex in preventing PPCs has not been previously established. We propose a randomized controlled trial to evaluate the efficacy of sugammadex versus neostigmine on the incidence of PPCs in patients ≥ 70 years of age that are scheduled for surgery ≥ 3 hours in length. It is estimated, based upon previously published data, that this cohort of patients will have a 42% incidence of PPCs with neostigmine reversal. We hypothesize that higher quality neuromuscular

blocking agent reversal with sugammadex will be effective in preventing PPCs, compared to neostigmine.

STUDY OBJECTIVES

Primary Hypothesis

Substantial respiratory morbidity has been associated with postoperative residual paralysis. We hypothesize that compared to neostigmine, reversal of rocuronium neuromuscular blockade with sugammadex will reduce the proportion of patients with any postoperative pulmonary complication.

Primary Objective

To determine if a strategy of rocuronium neuromuscular reversal with sugammadex will reduce the proportion of patients with any postoperative pulmonary complication, compared to neostigmine.

Secondary Hypotheses

We hypothesize that compared to neostigmine, reversal of rocuronium neuromuscular blockade with sugammadex will reduce the following:

- The proportion of patients with residual neuromuscular blockade in the post-anesthesia care unit (PACU) (defined a TOF < 0.7 taken on the adductor pollicis within 5 minutes of arrival to the PACU)
- PACU phase 1 recovery time

Secondary Objectives

To determine if a strategy of rocuronium neuromuscular reversal with sugammadex will reduce the following:

- The proportion of patients with residual neuromuscular blockade in the PACU
- PACU phase 1 recovery time

Exploratory Objectives

To compare the effect of sugammadex, relative to neostigmine, on changes in the following parameters, in patients ≥ 70 years of age and having surgery ≥ 3 hours in duration:

- Hospital length of stay
- The proportion of patients that require hospital readmission for any cause within 4 weeks of hospital discharge
- The proportion of eligible patients diagnosed with a respiratory complication as defined in the National Surgical Quality Improvement Program (NSQIP) (pneumonia, unplanned re-intubation for any reason other than a return trip to the operating room, and ventilator times greater than 48 hours - excluding operating room time)

Safety Objective

To evaluate the safety of sugammadex, relative to neostigmine, with regards to the occurrence of the following adverse events in patients ≥ 70 years of age and having surgery ≥ 3 hours in duration:

- Bronchospasm defined by requirement for albuterol treatment;
- Laryngospasm defined by need for positive pressure hand ventilation and/or administration of propofol or succinylcholine for airway obstruction;
- Drug hypersensitivity reaction defined by flushing, urticaria, new edema, sudden hypotension or tachycardia, or wheezing within 5 minutes of Sugammadex administration;
- Recurarization defined by TOF ratio assessments <0.7 in PACU.

STUDY OVERVIEW

Study Design

Design: Assessor-blinded, randomized controlled, single center, parallel design trial

Intervention Arm: Sugammadex for reversal of Rocuronium neuromuscular blockade will be administered at a dose of 2 mg/kg once T2 has reappeared on a TOF and before T3 has reappeared

Control/Standard Arm: Neostigmine and Glycopyrrolate will be administered in a manner consistent with product labeling and standard practice at OHSU once at T2 has reappeared on a TOF and before T3 has reappeared (i.e. 0.07 mg/kg neostigmine to a maximum of 5 mg and 0.10-0.2 mg of glycopyrrolate per 1.0 mg of neostigmine administered).

Randomization and Assignment: Subjects will be randomly assigned to either the intervention (sugammadex) or control (neostigmine) arm. Before initiation of the clinical portion of the study, 200 opaque sealed envelopes will be prepared by a researcher not involved in subject recruitment or enrollment: 100 for the intervention arm and 100 for the control arm. These envelopes will be randomized without stratification via a computer generated random allocation sequence and numbered in ascending order from 1 to 200. Subjects enrolled in the study will be assigned to the next free envelope and given the corresponding treatment contained therein. All researchers involved in patient recruitment, allocation, and assessment will be kept blind to the allocation sequence.

Research Integrity: The study will be assessed for initial approval by the Institutional Review Board (IRB) at OHSU, Portland, OR, USA, and given a unique identifier for ongoing review.

Setting

Study Location: Single center study performed at OHSU in Portland, OR, USA. Subjects will be enrolled in the preoperative area of the South Operating Room Suite. All study interventions will occur in the South Operating Room preoperative area, the operating rooms, or in the Post-Anesthesia Care Unit. Data collection will continue to occur throughout the subject's hospitalization.

Timeline

In a review of subjects ≥ 70 years old that had surgery ≥ 3 hours in length during the standard work week (Monday through Friday) in 2015, a total of 713 patients were found. Assuming 25% enrollment we should be able to enroll the necessary 200 subjects in 14 months, with a projected enrollment of 3 to 4 subjects enrolled per week.

SUBJECTS

Number of Subjects

Study Size: 100 subjects will be enrolled in the intervention (sugammadex) arm and 100 patients will be enrolled in the control (neostigmine) arm.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Subjects ≥ 70 years of age having surgery in the South Operating Rooms of Oregon Health and Science University (OHSU) of expected duration ≥ 3 hours.
- Only subjects having elective surgery scheduled on Monday through Friday with planned general endotracheal anesthesia will be eligible.

Exclusion Criteria

- Subjects having surgery for which neuromuscular blockade is contraindicated (e.g. neurosurgical, orthopedic, and head and neck surgery in which nerve monitoring will be employed).
- Subjects with known neuromuscular disorders, stage 4 chronic kidney disease or worse (eGFR < 30 ml/min), significant hepatic dysfunction, or allergies to drugs required for this protocol.
- Subjects taking the selective estrogen receptor modulator toremifene.
- Non-English speaking.

Vulnerable Populations - The following populations will be excluded from the study

- Prisoners
- Decisionally impaired adults

Recruitment Methods

Most subject recruitment is expected to occur by an approved study staffer as early as two months prior to a potential subject's scheduled surgery via a review of the OHSU South Operating Room surgical schedule as posted in Epic (Verona, Wisconsin). The study staff will work with surgical providers to identify and screen for potential eligible subjects (≥ 70 years old) scheduled for surgery expected to be ≥ 3 hours in length. We will review all the inclusion/exclusion criteria as early as two months prior to a potential subject's scheduled surgery. If a potential subject has been identified as meeting all inclusion criteria and none of the exclusion criteria, an approved study staffer will call the subject, using an approved phone script (included in 'Consent Form and Recruitment Materials' section of application) to introduce the study. If the subject is amenable to the study, study staff will make arrangements to meet with the subject to provide formal consent materials and signature at their pre-op visit or day of surgery. If the subject is not interested in participating in the study, the inclusion/exclusion criteria and any other information related to this subject will be destroyed.

The study will be listed on ClinicalTrials.gov to provide subjects, family members, and the public background information on the study.

Other than posting this study on OHSU Study Participation Opportunities, we do not expect to create advertisements for the study.

There will be no payments to subjects, we do not have funds to offer subjects payment for participation in the study.

Consent Process

The consent process will take place in a private and confidential area. All subjects that are approached for recruitment will hear a description of the study, reasons for pursuing this research study, options for opting out the research protocol or not completing data collection, and potential risks, advantages, and disadvantages from participating. We will ask subjects to reiterate their understanding of how the study will affect their care and allow time for questions before collecting a signature for consent. Subjects that agree to participate in the study will be asked to sign a written informed consent that has been approved by our Institutional Review Board. An electronic copy of the signed consent will be scanned into the subject's medical records system. A copy of the signed consent, describing the research study and providing contact information for the principal investigators will be given to subject.

Dr. Michael Aziz will serve as medical monitor and will conduct periodic reviews to ensure that proper consent devoid of coercion is being collected as the study progresses.

Study Procedures

We will enroll eligible subjects ≥ 70 years of age with a scheduled surgical length of ≥ 180 minutes on Monday through Friday in the OHSU South Operating Room Theatre.

See the collection variables data collection sheet for a list of the variables to be collected from the medial records of participants that provided signed consent.

Subjects will be allocated to either neuromuscular reversal with sugammadex or neostigmine. Before study activation a sample of 200 sequentially numbered opaque envelopes will be prepared by a researcher not involved in patient recruitment, allocation, consent, or assessment: 100 for the sugammadex arm and 100 for the neostigmine arm. Patient allocation will occur in the operating room when the anesthesia provider responsible for patient care opens the lowest remaining numbered free envelope. Group assignment will be determined by a computer generated random number sequence [Excel, Redmond WA]). The random number sequence will be generated by a researcher not involved in either patient enrollment or patient assignment. Reversal of rocuronium neuromuscular blockade (i.e. sugammadex or neostigmine) will be defined in the opened opaque envelope. Once a study subject signs a consent form, a unique number corresponding to the opened opaque envelope will be assigned to that subject. The envelope will not be opened until the anesthesia provider is ready to prepare and administer reversal of neuromuscular blockade. This subject number will never be reused and will remain with the subject for the entirety of the study. No subject will ever be allowed to have more than one unique subject number.

The patient, anesthesia providers, and surgeon will not be blinded to the study drug. The anesthesiologists will not be blinded for reasons of patient safety. The assessor of PPCs, residual neuromuscular blockade, secondary outcomes, exploratory outcomes, and adverse event accounting will be blinded to study drug and will not be allowed in the operating room after the opaque envelope containing patient assignment is opened. The research coordinator (assessor of PPCs) will not allowed to access the anesthesia record for the study participants. We plan for a different research coordinator, not involved in the assessment, to do the data collection.

All patients will have standard ASA monitors plus five lead EKG applied. Additional monitoring needs will be left up the anesthesia team directing patient care. Decisions with regards to induction and maintenance of anesthesia will also be left up to the direction of the anesthesia team with the exception that rocuronium will be mandated for maintenance of neuromuscular blockade. Decisions on when to dose and what quantity of rocuronium should be dosed for maintenance of neuromuscular blockade will be left to the discretion of the anesthesia team in the operating room. The level of neuromuscular blockade will be monitored in the operating room at the adductor pollicis muscle with a basic peripheral nerve stimulator monitor that does not have TOF ratio capability. TOF counts will be mandated every 15 minutes, which is our current practice at OHSU. Anesthesia providers will be asked to maintain neuromuscular blockade at a T2 level throughout surgery and reverse neuromuscular blockade at as close to a T2 level as safely possible. Administration of sugammadex or neostigmine will occur into a fast flowing IV that is running wide open. Sugammadex will be dosed at 2 mg/kg and neostigmine will be dosed at 0.07 mg/kg to a maximum of 5 mg. Glycopyrrolate will be co-administered in the neostigmine arm at a dose between 0.1 to 0.2 mg of glycopyrrolate per 1.0 mg of neostigmine administered.

In accordance with standard of practice at our institution all patients will have convective warmers used during the case and patient temperature will be monitored. Ventilation parameters will be left to the discretion of the anesthesia team in the operating room.

A TOF ratio will be obtained on all patients within 5 minutes of arrival to the PACU, which is *not* currently standard of care at OHSU, with a TOF-Watch SX acceleromyograph,. The accelerometer sensor will be attached to the patient's thumb. The patient's fingers and forearm adjacent to the thumb attached to the accelerometer sensor will be fixed with tape to an arm board to minimize artifact. Ulnar nerve stimulation of the adductor pollicis muscle will be measured via the TOF-Watch. A TOF ratio of less than 0.7 will be considered residual neuromuscular blockade.

Active monitoring of adverse events (desaturation, hypoxemia, upper airway obstruction, aspiration pneumonitis, bronchospasm, laryngospasm, drug hypersensitivity reaction, and recurarization) will be conducted on an ongoing basis until discharge with daily assessments by the research coordinator and/or principal investigator. Assessment of PACU phase 1 recovery time will occur on POD#0 or POD#1. Assessment of hospital length of stay will be assessed within a week of discharge by electronic medical record review. Hospital readmission data will be assessed within 1 to 2 months of hospital discharge. NSQIP 30-day postoperative risk-adjusted respiratory complications will be assessed and recorded prior to data analysis at the conclusion of patient enrollment and study implementation.

To gather information on hospital readmission within 4 weeks of hospital discharge subjects will be called between 4 weeks and 3 months after discharge from Oregon Health & Science University. The attached script titled "Post-Discharge Phone Call" will be used to obtain this data.

Subjects enrolled that do not get neuromuscular relaxant during surgery, for any reason, may be withdrawn from the study without their consent. In addition, a subject's may be removed from the study if the investigator or funder stops the study, the subject's clinical status changes, or if the subject does not follow study instructions. In the event that such a situation occurs the subject would be informed at the earliest reasonable time.

The subject's status in the research project will show up clearly in their electronic medical record problem list, until the subject's participation is complete. A progress note will be placed in the subject's chart to allow other providers to easily contact study investigators.

Subjects that enroll in the study and then decide to withdraw before randomization and assignment occur will be excluded from further data collection and analysis.

DATA and SPECIMENS

Handling of Data and Specimens

Study subjects will be assigned a unique study number after enrollment in the study. All data points, procedure related data, and electronic files for data analysis will be linked only to this unique study number. This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in a cloud location with special protection for confidential and restricted health information (the OHSU Box). Only the principal investigator and other study staff will have access to this key.

Data collected in the course of the study will be stored using OHSU's secure Research Electronic Data Capture (REDCap). Again, this data tool will be only be made available to study personnel though a secure online log-in. Secure data will be stored in REDCap for indefinite use. Data in REDCap will be linked only to subject study code, not to any of the 18 HIPAA identifiers.

Any data that is shared will be transmitted in an encrypted manner over a secure network. Transmitted data will be labeled only with the study code, none of the 18 HIPAA identifiers. When data is transmitted, the transmitter (research personnel with access to REDCap) will be responsible for sending the data in a protected manner. Any person receiving data will then assume responsibility for patient confidentiality and data integrity.

There will be no specimens collected in this study.

Sharing of Results with Subjects

Study results will not be available to subjects at the time of participation. All subjects will be given the contact information of the principal investigator (Brandon Togioka) and told that they may contact him to obtain conglomerated de-identified data at the conclusion of the study. Patients will also be able to obtain a free copy of any published data should they indicate interest. The study will not generate any additional laboratory data, genetic information, or imaging studies.

Data and Specimen Banking

Data will not be stored in a repository.

Data Analysis - Power/Sample Size:

Based upon a sample size of $n=100$ patients in each arm and an expected incidence of PPC of 42% in the control arm, based upon previously published studies, this study has 80% power to detect a 19% difference (for a two-sided alpha level of 5%) in the incidence of PPC between patients given sugammadex and neostigmine. That is, to find a statistically significant result we would need to find an incidence of PPC in the sugammadex arm of less than 23%.

Primary analysis: The analyses will be intention-to-treat. We will use relative risk with 95% confidence interval to test the hypothesis that rocuronium reversal with sugammadex reduces the proportion of PPCs, compared to neostigmine. To determine statistical significance for the difference in proportions, we will use the chi-square statistic.

For the secondary endpoints, two-sample Student's t-test will be used for continuous variables and the chi-square statistic for categorical variables, as appropriate.

We will not conduct an interim analysis since we will need the full sample to evaluate efficacy. A two-sided alpha level of 5 percent will be required for statistical significance. The statistical software STATA (Stata Corporation, College Station, TX) will be used for all analyses.

PRIVACY, CONFIDENTIALITY AND DATA SECURITY

The results of the study as well as all other information collected on the data collection sheet will be stored on site at OHSU in the office of the principal investigator. This office requires a key for entry and the corridor to the office requires a passcode for entry. The office is not shared with any other individuals. No protected health information or other data collected during the completion of this randomized controlled trial will be taken off campus. All data gathered for this study will be coded before any analysis or publication occurs.

This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in a cloud location with special protection for confidential and restricted health information (the OHSU Box). Only the principal investigator and other study staff will have access to this key.

Data collected in the course of the study will be stored using OHSU's secure Research Electronic Data Capture (REDCap). Again, this data tool will be only be made available to study personnel though a secure online log-in. Secure data will be stored in REDCap for indefinite use. Data in REDCap will be linked only to subject study code, not to any of the 18 HIPAA identifiers

In order to maintain patient privacy, data capture tools, study drug accountability records, study reports, and communications will identify the patient only by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authorities access to the patient's original medical records, including medical history, laboratory studies, and medication administrations, for verification of data gathered and to audit the data collection process. This information will be accessed for the duration of the research study, including the follow-up period, for the purpose of data reconciliation. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

DSMP submitted as a separate document.

RISKS AND BENEFITS

Risks to Subjects

As with all studies, breach of confidentiality is a common risk. In addition, there is the possibility of slightly increased anxiety on the day of surgery for patients approached for inclusion in the study. There is also likely to be a loss of free time in the preoperative area as consent will likely take 15 minutes to complete. A TOF ratio will also be obtained in the Post-Anesthesia Care Unit (PACU), which is not currently standard of care at OHSU. This TOF ratio may result in a slight discomfort. Every attempt will be undertaken to perform this TOF ratio while the patient is still under a significant depth of anesthesia upon first arrival (within 5 minutes) to the PACU. Patients greater than or equal to 70 years of age having just completed surgery lasting over 3 hours are very unlikely to remember the slight stimulus of a TOF ratio. As data collection will continue to occur throughout the patient's hospitalization inconvenience is possible.

Sugammadex is a novel method of reversing neuromuscular relaxant in the operating room just approved by the FDA on December 15, 2015. There is a history of safe Sugammadex use in Europe since its initial approval by the European Union on July 29, 2008. As Sugammadex is a new drug in the United States there is a possibility of unknown or understated adverse events associated with its use. To this extent adverse experience reporting will include monitoring for and publishing the occurrence of any of the following adverse events associated with sugammadex or neostigmine administration:

- Bronchospasm within minutes of drug administration
- Laryngospasm within minutes of drug administration
- Marked bradycardia within minutes of drug administration

- Drug hypersensitivity reaction, including any reaction ranging from mild skin changes to anaphylaxis
- Recurarization occurring in the postoperative period
- Postoperative cough
- Postoperative headache
- Postoperative nausea or vomiting
- Postoperative pruritus – a temporary condition causing severe itching of the skin
- Postoperative complaints of dysgeusia – a temporary condition in which a foul, salty, rancid, or metallic taste sensation will persist in the mouth.

Participants will not incur any additional cost for participating in this study.

Potential Benefits to Subjects

We are performing this study because the incidence of postoperative pulmonary complications in the study population is undesirably high (around 40%). Whether the study drug is better than the current standard of care at preventing these complications is unknown. We anticipate that patients that receive Sugammadex will have a decreased rate of postoperative pulmonary complications. This decrease in the incidence of postoperative pulmonary complications may translate to a shorter PACU length of stay, shorter length of hospitalization, and possibly a decreased hospital readmission rate.

DRUGS OR DEVICES

We expect to use 60 vials of open label 200 mg/2 mL Sugammadex solution and 60 vials of open label 500 mg/5 mL Sugammadex solution during the study.

The study drug, Sugammadex, is now FDA approved as well as approved for OHSU use by the Pharmacy and Therapeutic Committee. Thus, the study will not require that OHSU's research pharmacy be responsible for either preparing or dispensing the study drug.

Neostigmine is a standard of care drug that has been approved by the FDA for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery. Neostigmine is a cholinesterase inhibitor, meaning that it inhibits the breakdown of acetylcholine. As acetylcholine is the molecule responsible for action at the neuromuscular junction, a build up of acetylcholine allows for muscle activation. Neostigmine is a commonly used drug in anesthesia to reverse non-depolarizing neuromuscular blocking agents at the end of surgery. Because neostigmine nonspecifically increases acetylcholine levels throughout the body another drug, glycopyrrolate, is typically given immediately prior to neostigmine administration to counteract some of neostigmine's undesired side effects, such as bradycardia. Glycopyrrolate is an anticholinergic, meaning that it blocks the action of acetylcholine. Glycopyrrolate is very similar in action to atropine other than the slower onset of action (which better matches the speed of onset of neostigmine) and the fact that it does not cross the blood-brain barrier. Neostigmine and glycopyrrolate are almost always given within minutes of one another in the operating room. Glycopyrrolate is also a standard of care drug that has been approved by the FDA for the intended use (i.e., protecting against the peripheral muscarinic effects of cholinergic agents such as neostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants).

The TOF-Watch SX acceleromyograph is a device for measuring the degree of neuromuscular blockade during surgery and in the acute postoperative period. The TOF-Watch allows for a more

accurate assessment of neuromuscular function than clinical observation of muscle function when using a peripheral nerve stimulator. Subjects given a non-depolarizing neuromuscular blocking agent will exhibit a fade in muscle contraction when nerve stimulation is repeated in short intervals. As opposed to a peripheral nerve stimulator, which gives an assessor *qualitative* feedback on the strength and presence of a muscle twitch, the TOF-Watch can give a *quantitative* ratio indicative of muscle force. The TOF-Watch is used by applying two electrodes on the volar and ulnar side of the forearm about 2-3 cm apart. A force transducer is then placed against the flat side of the thumb held in place by a hand adaptor. When the train-of-four button is pushed four 0.2 millisecond pulses are spaced 0.5 seconds apart. The ratio of the force of the fourth twitch to the force of the first twitch is the train-of-four ratio.

As an open label study, the anesthesia provider, surgeon, and patient will not be blinded. In order to improve the quality of the study, the assessor of PPCs, residual blockade, secondary outcomes, exploratory outcomes, and adverse events will be blinded. Anesthesia providers taking care of patient's randomized to sugammadex will be able to obtain one vial of Sugammadex from the OMNICELL (automated medicine dispensing cabinet). Providers will obtain a 500 mg/5 ml vial for patients >100 kg and a 200 mg/2 ml vial for patients ≤100 kg. For research billing purposes, Sugammadex administered to study participants will be ordered and identified as a research medication in EPIC (electronic medical record). The anesthesia provider would be responsible for drawing up, labeling, checking, and administering the study drug. Drug accountability will be tracked based on the use of the specific research order.

Accurate records of drug quantities drawn up, administered, wasted, and disposed of at the end of the study will be kept by the principal investigator. Any unused drugs (either left over after patient administration or at the conclusion of the study) will be destroyed at OHSU in a manner consistent with ICH/GCP guidelines, city of Portland regulations, state of Oregon regulations, federal policy, and OHSU institutional policy.

