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Quality of Recovery after Reversal with Neostigmine or Sugammadex
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Title:
Pulmonary function, muscle strength, time to extubation and quality of recovery in the post anesthesia care unit after reversal of neuromuscular blockade with neostigmine or sugammadex.

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A. Background & Significance

Residual neuromuscular blockade after surgery can result in airway compromise, pulmonary complications, and possible need for reintubation and can be a negative experience for patients. Reintubation after surgery is currently a quality measure in NSQIP (National Surgery Quality Improvement Program) A Train of Four (TOF) monitor ratio of <0.9 has been identified as a marker of residual neuromuscular blockade in the PACU. Several clinical trials have shown that reversal of neuromuscular blockade with sugammadex results in a faster and more reliable return to TOF ratio of >0.9 when compared to neostigmine. However most of these studies primarily report on TOF ratios. There are scant data on clinical outcomes after reversal with neostigmine versus sugammadex. Incentive spirometry is a clinically meaningful measurement of postoperative pulmonary function, i.e. the ability to breathe deeply, which minimizes atelectasis and risk of postoperative pneumonia.

Our hypothesis is that sugammadex (2 mg/kg for intermediate blockade and 4 mg/kg for deep blockade per manufacturer's package insert) will be associated with and a better recovery profile in the PACU when compared to a standard practice dose of neostigmine (70 mcg/kg). Our primary outcome is incentive spirometry in the PACU, which is a validated measure of postoperative pulmonary function. We also hypothesize that sugammadex will also be associated with a shorter time to extubation. Recent publications by Masursky (2013) have defined prolonged times to extubation as 15 minutes from the end of surgery. A prolonged time to extubation negatively affects OR workflow.

Regarding dose selection, the dose finding study by Groudine (2007) found that there was significant variability in recovery times to TOF ratio of >0.9 when patients were reversed from profound neuromuscular blockade with Sugammadex 2 mg/kg. A study by Breuckmann (2015) used Sugammadex (2 or 4 mg/kg) and in comparison with neostigmine found elimination of residual neuromuscular blockade in the PACU (TOF ratio >0.9), and shorter times from study drug to extubation and OR discharge.

We have designed this study to reflect routine anesthesia practice. Providers will be instructed to aim for a level of neuromuscular blockade (using rocuronium) of 1-2 twitches on TOF during the intraoperative period, and data reflecting dosing and the depth of NMB will be recorded in the case report form. The administration of opiates and benzodiazepines will be standardized.

Previous studies have not measured pulmonary function or objective measures of strength in the PACU. Bastin (1997) reported the use of incentive spirometry as a simple means of assessing lung function in postoperative lobectomy patients showing good correlation with vital capacity and inspiratory reserve volume. A recent study by Bennett-Guerrero (2011) also had used incentive spirometry as the primary outcome for pulmonary function in a randomized clinical trial of sternal closure devices after cardiac surgery.

Hand Grasp will be measured using a Jamar Dynamometer. This will be measured preoperatively and postoperatively in the PACU. This mode of assessing hand grasp has been used in a previous Sugammadex study by Baumuller (2015) to assess muscle strength in post anesthesia patients.

Quality of recovery will be assessed using the QOR 15 described by Stark (2013). This is a validated, extensive and efficient tool to assess a patient's quality of recovery.

B. Objectives & Hypotheses

Primary outcome:
Strength to breathe deeply (inspiratory reserve capacity) using incentive spirometry in PACU – 30 min, 60 min and 120 min after reversal of neuromuscular blockade.

Secondary outcomes:
1. Grip strength in PACU – 30 min, 60 min, and 120 min after reversal
2. Able to sit up unaided in PACU – 30 min, 60 min and 120 min after reversal
3. Time to extubation (Percentage of prolonged extubation)
4. Time to readiness for PACU discharge (Aldrete score)
5. Reintubation in PACU
6. Adverse Events
7. TOF Ratio upon PACU admission
8. QOR 15 Survey

Clinical Hypotheses
Sugammadex has been shown to have a faster onset and more reliable reversal of neuromuscular blockade when compared to neostigmine as measured by return of TOF ratio to >0.9. Our hypothesis is that sugammadex will be associated with improved deep breathing as measured by incentive spirometry in the PACU.

Patients who are reversed with sugammadex have a lower incidence of residual postoperative residual neuromuscular blockade when compared to neostigmine. We hypothesize that patients reversed with sugammadex will have better recovery profiles in the PACU as measured by strength and PACU discharge readiness. Additionally, we hypothesize that sugammadex will be associated with shorter time to extubation compared to neostigmine.

C. Study Design

This will be a single-center, prospective, randomized, assessor blinded, controlled trial.

Patients will be randomized to either receive sugammadex or neostigmine for the reversal of neuromuscular blockade. The anesthesiologist will be unblinded to the study drug however the assessor in the PACU will be blinded.

Inclusion Criteria

The participant must fulfill all the criteria listed below for entry.

1. Each participant must be willing and able to provide written informed consent for the study
2. Each participant must be greater than or equal to 18 years of age
3. Each participant must be ASA class I, II or III
4. Planned used of neuromuscular blocking drugs
5. Planned use of endotracheal intubation
6. Planned for extubation to occur in the OR

Exclusion Criteria

1. ASA Class IV
2. Age <18 years old
3. Inability to give oral or written consent
4. Known or suspected neuromuscular disorder impairing neuromuscular function
5. True allergy to muscle relaxants
6. A (family) history of malignant hyperthermia
7. A contraindication for neostigmine or sugammadex administration
8. Serum creatinine level of greater than 2.0 mg/dL
9. Surgery where the patient's arm is not available for neuromuscular monitoring
10. A plan to extubate under deep anesthesia

Anesthesia: Induction and maintenance of anesthesia will be at the discretion of the providing anesthesiologist. Midazolam (max 2 mg) can be administered prior to induction of GA. Fentanyl (1-3 mcg/kg) will be administered around the time of induction and intubation, and can be administered as needed (1-2 mcg/kg/hour). Additional fentanyl, or other opiates, can be administered if determined to be appropriate by the anesthesiologist. For patients who receive dilaudid, a conversion of dilaudid 1.5 mg to fentanyl 100 mcg will be used to calculate total opiate received during data analysis. Rocuronium will be the only nondepolarizing neuromuscular blocking agent utilized in all study patients. Succinylcholine may be given for induction per the anesthesiologist discretion. Anesthesiologists will be asked to aim for a depth of neuromuscular blockade of 1-2 twitches on train of four (TOF) nerve stimulation. Train of four monitoring via peripheral nerve stimulator at the ulnar nerve will be used.

Patients will be assigned a randomization group prior to surgery, however the anesthesiologist will only be notified of study arm assignment 15 minutes prior to expected end of surgery to avoid bias/confounding due to possible differences in patient management earlier in the case if assignment was known earlier.

Group 1: Sugammadex: 2 mg/kg for moderate to shallow block (2-4 twitches on TOF), 4 mg/kg for profound block (1-2 post tetanic twitches only)
Group 2: Neostigmine: 70 mcg/kg with Glycopyrrolate 10 mcg/kg.

Patients will receive reversal of neuromuscular blockade immediately after closure of the surgical wound, as defined as the last staple or the last suture. This is consistent with routine anesthesia practice.

Before extubation, the patient should be awake and hemodynamically stable. The patient should have regained full muscle strength (5 second head lift or sustained tetanus without fade), follow simple verbal commands (e.g. lift head), and breathe spontaneously with acceptable oxygenation and ventilation (At least 8 breaths per minute, and a tidal volume of greater than 5 mL/kg).

Additional neuromuscular blockade reversal can be administered at the discretion of the primary anesthesiologist. This additional reversal can be given if the patient demonstrates residual neuromuscular blockade that is preventing extubation 15 minutes after administration of the initial dose of reversal. After extubation, if the patient demonstrates respiratory distress secondary to residual neuromuscular blockade, additional neuromuscular reversal can be given. There is no time restriction for additional neuromuscular reversal after extubation. Either neostigmine or sugammadex may be given for this additional reversal at the discretion of the anesthesiologist. Need for additional reversal agent and drug crossovers will be collected as an outcome between groups.

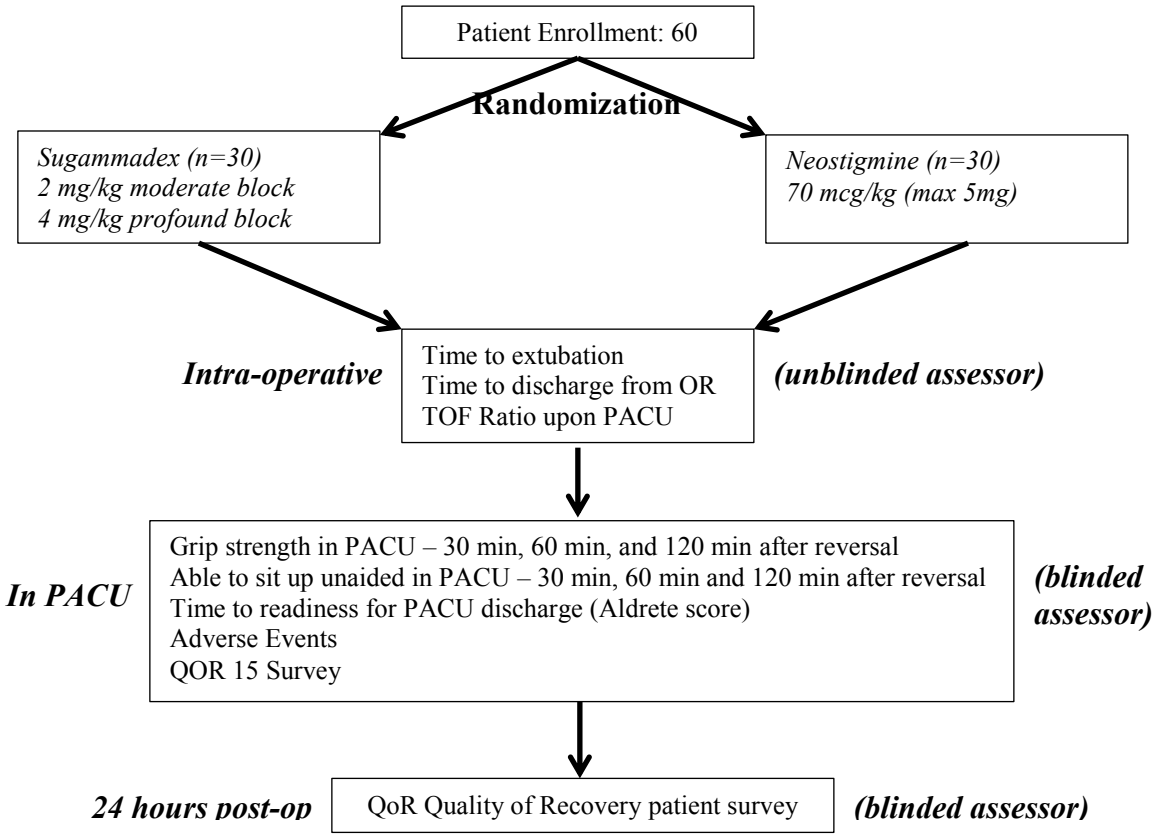
Data Collection: Preoperative information will be collected for each patient including age, BMI, medical comorbidities, sex, ASA class, race/ethnicity. In the pre-operative holding area, baseline measurements of hand grip and incentive spirometry will be measured.

Intraoperative data will be collected by an unblinded research coordinator or team member. Intraoperative data will include total dose of rocuronium, time of last rocuronium dose, TOF prior to administration of reversal, time of reversal agent, time of extubation, time of OR discharge, surgical procedure, duration of surgery (surgery start to surgery stop) and duration of anesthesia (anesthesia start to anesthesia stop). TOF ratio will be measured with TOF-watch SX acceleromyograph. The unblinded research coordinator will accompany the patient from the OR to PACU and measure TOF ratio upon PACU admission.

The patient will be assessed in the PACU by a research coordinator/assistant blinded to the patient's randomization. The research coordinator/assistant will not be directly involved in the patient's care. Incentive spirometry (measured with an incentive spirometer), hand grip strength (measured with a Jamar dynamometer), and ability to sit independently will be assessed at 30, 60 and 120 minutes from reversal of neuromuscular blockade. Level of sedation will be measured at 30, 60 and 120 minutes using the RASS sedation scale. Time to PACU readiness will also be assessed using the Aldrete score.

The 120-minute measurement will be completed even if the patient has been discharged from the PACU prior to this time. If a patient is ready for discharge home prior to 120 minutes, they will remain longer in the holding area to complete the 120-minute assessment. The patient consent will allow for this provision.

24 hours after surgery, patients will complete a QOR15 survey either in person (if still hospitalized) or via telephone from a research coordinator/assistant blinded to the patient's study arm assignment.



D. Study Procedures

Patients who are scheduled for surgery at Stony Brook Hospital will be identified based on inclusion/exclusion criteria. Explanation of the research protocol and consent will be obtained during the preoperative period allowing patients sufficient time to decide if they wish to participate in this study. Once patients have consented to participate, they will be assigned a unique identification number.

Patients will be randomized (1:1) to either the neostigmine or sugammadex group. When enrolling patients, we will divide patients into short (expected < 2 hours) or long (expected > 2 hours) surgical groups and have separate randomization lists for these two durations of surgery. This will allow us to ensure balance of this important confounding variable between study groups.

Patients will be evaluated in the preoperative area to obtain their medical history, demographic information, and type of surgery. Preoperatively, we will obtain hand grasp, and incentive spirometry measures. For each incentive spirometry measurement, patients will use the device three times. Each volume will be recorded and the largest volume will be used for analysis. To avoid confounding factors of patient position, we will standardize our measurements: patients will be sitting at a 45-degree angle in a stretcher, unless there are medical contraindications to this positioning.

The patients will undergo anesthesia and surgery and receive either neostigmine or sugammadex based on their group assignment. Intraoperative information will be collected regarding the duration of surgery, time to extubation, and information about use and depth of neuromuscular blockade. In the PACU, patients will be assessed by a blinded assessor for hand grip strength, incentive spirometer measures, and ability to sit independently. Time to PACU discharge readiness will be assessed using the Aldrete score. The patients will be surveyed 24 hours after surgery using the QOR 15 to assess their quality of recovery.

This will then complete their participation in the study.

E. Statistical Analysis and Sample Size Justification

Statistical procedures/analysis will be performed by the trial's biostatistician.

Randomization: Randomization will be performed using a sealed envelope technique. Envelopes will not be reused in any case. Two computer generated randomization schema, in permuted blocks, will be provided by the trial's statistician, one for short cases and one for long cases.

Unblinding Process: The investigator and the PACU assessor will remain blinded to patient allocation during this study. The primary anesthesiologist conducting the anesthesia for these patients will not be blinded to their allocation, for purposes of appropriate and safe reversal of neuromuscular blockade. An unblinded member of the study team will record intraoperative information for each patient to which the primary investigator will blinded to until final analysis. After all patients have completed the study and all data has been collected, the clinical database will be locked and unblinded for statistical analysis.

Variables/Time Points of Interest: All variables will be collected on the day of surgery with the exception of the QOR 15 which will be collected on postoperative day one.

Preoperative variables collected include:
1. Age
2. ASA Classification
3. Ethnicity
4. BMI
5. Surgery
6. Surgical Division (Ortho, General, GYN, Urology, ENT, Neuro, Plastics)
7. Hand Grip Strength
8. Incentive Spirometry Measure
9. Ability to sit independently

Intraoperative variables collected include:
1. Duration of surgery (surgery start to surgery stop)
2. Time to extubation (surgery stop to extubation time)
3. Time to OR discharge (surgery stop to time out of OR)
4. Total dose of rocuronium
5. Time of last dose rocuronium

6. Time of reversal of neuromuscular blockade
7. # of twitches of TOF prior to reversal

Postoperative variables collected include:
1. Incentive spirometry at 30, 60 and 120 min after reversal
1. TOF ratio measured by TOF watch on PACU admission
2. Hand Grip at 30, 60 and 120 min after reversal
3. Independent sitting ability at 30, 60 and 120 min after reversal
4. Time to PACU discharge readiness (PACU admit to Aldrete score of 10)
5. QOR 15 Survey after surgery
6. RASS sedation score at 30, 60 and 120 min

These variables will be analyzed after all patients have completed this study and all medical data has been collected. Preoperative data and intraoperative data (duration of surgery, amount of rocuronium) will be used to compare that both study groups have similar characteristics. Incentive spirometry measures in the PACU will be our primary outcome. Secondary outcomes will look at time to extubation and measures of PACU recovery with relation to agent used for reversal of neuromuscular blockade.

Statistical Methods

Primary Outcome: Spirometry readings at baseline, PACU 30, 60 and 120 minutes after reversal of neuromuscular blockade

A "change from baseline" spirometry score will be calculated for the PACU 30, 60 and 120 time points for each patient. A repeated measures (mixed) ANOVA will be performed comparing the mean spirometry change scores at 30, 60 and 120 time points, by treatment group. This ANOVA design will allow us to test 3 things: 1 – is there a difference in mean spirometry change score by treatment group; 2- does spirometry measurement change over time; and 3 – is there a group/time interaction, specifically, does the sugammadex group spirometry measurement change differently over time compared to the neostigmine group? Alpha will be set at 0.05.

Secondary outcomes: There will be six secondary outcomes:
1. Grip strength in PACU – 30 min, 60 min and 120 min
2. Able to sit up unaided in PACU – 30 min, 60 min and 120 in
3. Time to extubation (Percentage of prolonged extubation)
4. Time to readiness for PACU discharge (Aldrete score)
5. TOF ratio upon PACU admission
6. QoR 15

We will use a Bonferroni correction for multiplicity, thus, each secondary outcome will be tested at the alpha of 0.008 (0.05/6 = 0.008) level for significance. We plan to test the 6 secondary outcomes even if the primary outcome does not show a difference. All continuous outcomes will be first tested for normality using a Shapiro-Wilk test, and appropriate analytical methods will be used. A repeated measures ANOVA (or Friedmen's test) will be used to test for group differences in grip strength over time. T-tests or Wilcoxon rank sum tests will be used to test for differences in treatment groups for Aldrete score and QOR15 score. Chi-Square and Fisher exact tests will be used to examine for group differences in proportion of first sit time, prolonged extubation and TOF ratio upon PACU admission.

1. Grip strength in PACU – 30 min, 60 min and 120 min – A repeated measures ANOVA will be used to test for group differences in grip strength over time.
2. Able to sit unaided in PACU – 30 min, 60 min, and 120 min – A chi square/fisher's exact test will be used to see if there is a difference between the 2 groups' ability to sit independently.
3. Time to extubation (Percentage of prolonged extubation) – Prolonged extubation is defined as 15 minutes after end of surgery. Time to extubation will be dichotomized into either YES- prolonged, or NO- normal. Chi Square or Fisher's exact tests will be performed to test for significant differences in proportion between groups.
4. Time to readiness for PACU discharge (Aldrete score) – Either t-tests or Wilcoxon rank sum tests will be performed to assess the difference in mean/rank Aldrete score.
5. TOF Ratio upon PACU admission – Chi-square or Fisher's exact tests will be performed to test for significant differences in proportion between groups.
6. QoR 15 – Either t-tests or Wilcoxon rank sum tests will be performed to assess the differences in mean/rank QoR15 score.

Reintubation in PACU: Because we anticipate reintubation rates to be 0% for both groups, this variable will not be a secondary outcome, but rather an adverse event worth reporting.

Drug crossover: We will collect and analyze the incidence of drug crossovers for each group. This is defined as patients who received the initial neuromuscular reversal, but then were given the other neuromuscular reversal agent due to residual paralysis.

Analysis Population: Our primary population for data analysis will be a "modified intention to treat" grouping. Any patient who received a neuromuscular blockade reversal agent (neostigmine or sugammadex) will be included in this population. Patients who received neither reversal agent (i.e. patients who remain intubated after surgery) will be excluded from this primary population analysis. Our secondary population for analysis will be "actual medication received." Patients will be included in the group of which reversal agent they actually received, in the event that the wrong reversal agent is given. Patients who receive both reversal agents (drug crossover) will be excluded from this secondary population analysis. Drug crossovers will be collected as a separate outcome measure.

Power/Sample Size

We believe that a 20% difference in incentive spirometry volumes is clinically relevant. We anticipate that patients will have a preoperative incentive spirometry volume of 2200mL and a postoperative incentive spirometry of 1540 mL with regular care. A 20% difference with sugammadex would translate to 300 mL increase in inspiratory reserve capacity (1840 mL vs 1540 mL):

300 mL difference in volume (assuming a standard deviation of +/- 400 mL):
Group 1: 1540 mL +/- 400 mL
Group 2: 1840 mL
Enrollment Ratio 1:1, alpha 0.05 and power 80% → Total sample size required is 60 patients. The study expects to enroll about 80 subjects to end with 60 "randomizable" subjects after accounting for screen failures, withdrawals or surgery cancelations.

F. Adverse Experience Reporting

Safety evaluation: For this Phase 4 (post marketing) study serious adverse events (SAEs) that may occur during the study will be recorded in the case report form. The AE record in the case report form includes the nature of the event (with onset date and time, end date and time) severity, treatment, outcome, and the relationship to the treatment given. All serious AEs that require reporting will be reported to the medical ethics committee and authorities as required by GCP/GRP guidelines.

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