Comparison of time to full recovery of muscle paralysis (TOF>0.9) and extubation using Sugammadex versus Neostigmine/Glycopyrrolate in patients with pulmonary disease in the outpatient Bronchoscopy Suite

1) Abstract of the study

Patients who have chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) are known to experience more postoperative pulmonary complications (PPC) such as re-intubation, COPD or ILD exacerbation, pulmonary infection and even respiratory failure than those without this diagnosis. Studies have suggested that respiratory muscle strength may be a contributing factor to such complications. These patients often require outpatient bronchoscopic procedures such as lung biopsies, tracheal and bronchial dilations, and bronchoalveolar lavage. These procedures are conducted either under conscious sedation, or general anesthesia. Our study will focus on lung patients in the bronchoscopy suite undergoing procedures requiring general anesthesia. Due to these patients' health status, it is important to ensure appropriate neuromuscular reversal and extubation time. We propose the following hypotheses to improve the efficiency of patient care in the bronchoscopy suite. If Sugammadex is used to reverse neuromuscular blockade after outpatient bronchoscopy in patients with COPD or ILD, they will recover from the neuromuscular blockade completely and more efficiently (faster) than if neostigmine and glycopyrrolate are given for the same purpose. In addition, if Sugammadex is used to reverse neuromuscular blockade after outpatient bronchoscopy in patients with COPD or ILD, they will be extubated sooner than if neostigmine and glycopyrrolate are given for the same purpose. Finally, if Sugammadex is used to reverse neuromuscular blockade after outpatient bronchoscopy in patients with COPD or ILD, these patients will be discharged from the bronchoscopy suite sooner than if neostigmine and glycopyrrolate are given for the same purpose. The latter two hypotheses are secondary to the first listed hypothesis.

2) Protocol Title

Comparison of time to full recovery of muscle paralysis (TOF>0.9) and extubation using Sugammadex versus Neostigmine/Glycopyrrolate in patients with pulmonary disease in the outpatient Bronchoscopy Suite

3) Sponsor / Funding

Merck Investigator Studies Program Review Committee approval #59676

4) IRB Review History

None.

5) Investigator

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6) Objectives

The objective of this study is to compare time to full reversal of neuromuscular blockade between use of Sugammadex or neostigmine/glycopyrrolate as determined by train of four >0.9 in patients with pulmonary disease in the outpatient bronchoscopy suite. A secondary outcome measured will be time to extubation.

7) Background

Patients with COPD and ILD are more likely to have PPC. Severity of their disease and length of the operative procedure both correlate with an increase in these complications [1-5]. This patient population has also been shown to develop progressive atrophy of their respiratory muscles: thoracic accessory muscles in those with COPD and the diaphragm in those with ILD [6,7]. Studies have shown that pulmonary rehabilitation can reduce dyspnea and improve pulmonary function [8], suggesting that respiratory muscle strength is a possible factor contributing to adverse events. In support of this hypothesis, one study looking at ASA 3 patients having noncardiac surgery under general anesthesia, found that those patients who had a PPC required higher doses of neostigmine prior to extubation, although their dose of neuromuscular blockade was not different from those who did not have a PPC [9]. It is these chronic lung disease patients that come to the bronchoscopy suite for outpatient procedures, commonly lung biopsies. While some bronchoscopic procedures are performed under conscious sedation (no anesthesiologist, midazolam and fentanyl only), many others require general anesthesia with endotracheal intubation and neuromuscular blockade. Given these patients' compromised respiratory muscle strength, it is logical that full and timely reversal of neuromuscular blockade is essential to the prompt recovery of these patients after bronchoscopy.

In addition to the respiratory compromise of outpatients for bronchoscopy, reliable timely extubation is essential to the efficiency of the bronchoscopy suite. These cases run for highly variable periods of time (20 minutes to 2 hours) and the neuromuscular blockade should be reversed in an efficient manner. Given the need for general anesthesia with neuromuscular blockade and the unpredictability of the duration of the bronchoscopic procedure, there

is a need for prompt reversal of neuromuscular blockade not dependent on the depth of the neuromuscular blockade at the end of the procedure.

Our proposed study hopes to determine the efficacy of the use of Sugammadex as compared to neostigmine and glycopyrrolate to reverse neuromuscular blockade with respect to the predictability of both timing and completeness of such reversal. Completeness of reversal will be measured using the TwitchView monitor, an electromyography (EMG)-based device to detect muscle twitch strength after delivery of electrical stimulus. Patients will be randomized to receive one reversal treatment or the other, and the time to full reversal of neuromuscular blockade as well as the time to extubation will be followed.

7) Setting of the Human Research

This study will be conducted in the bronchoscopy suite at Temple University Hospital, Philadelphia PA. The potential subjects will be recruited during their preoperative anesthetic examination in PAT. All investigators and research staff will have valid CITI training.

8) Resources Available to Conduct the Human Research

Merck, Sharp & Dohme, Corp. will provide the following drugs:

Drug Name: Sugammadex

Amount: up to 4mg/kg for 40 patients

Drug Name: Neostigmine and glycopyrrolate

Amount: 5mg vial and 0.6mg respectively for 40 patients

9) Prior Approvals

Merck Investigator Studies Program Review Committee approval.

10) Study Design

a) Recruitment Methods

Patients will be recruited during their Pre-Admission Testing visit on the first floor of Temple University Hospital. A member of the research team will approach a patient who is scheduled for an outpatient bronchoscopic procedure requiring general anesthesia. The patient will be given enough time to make an informed decision about their participation and will be given a copy of all signed consent documents.

b) Inclusion and Exclusion Criteria

i) Inclusion:

a. Patients older than 18
b. Have a diagnosis of COPD and/or ILD
c. ASA 3 or ASA 4
d. Requiring general anesthesia for a bronchoscopy suite biopsy procedure
e. English speakers
f. GFR greater than 30 cc/minute

ii) Exclusion:
a. Vulnerable populations
b. Patients undergoing non biopsy procedures
c. Monitored Anesthesia Care (MAC) procedures
d. Non-English speakers

c) Study-Wide Number of Subjects

80 patients

d) Study Timelines
It is expected to take 1 year after approval to enroll a total of 80 subjects. With an additional 6 months for data analysis and study closure. A total of 18 months from approval.
We also would like to acknowledge the COVID-19 pandemic and will not begin enrollment or other study procedures until normal hospital procedures are resumed.

11) Procedures Involved in the Human Research

This research study will have the design of a blinded randomized clinical trial. The pharmacist will not be blinded to the study medication given. The anesthesia provider cannot be blinded because he/she will need to determine the proper dose and timing of the neuromuscular blocker reversal medication (the study medications) given at the end of the procedure. The study will recruit 80 patients coming to Temple University Hospital for an outpatient bronchoscopy biopsy procedure that requires general anesthesia with neuromuscular blockade. Rocuronium will be the neuromuscular blockade medication given in this study. Inclusion criteria for these patients will include those age >18 who have a diagnosis of COPD and/or ILD and who require medical treatment for the same. Patients who belong to a vulnerable population will be excluded (pregnant women, prisoners, patients with dementia or otherwise not able to consent themselves). Requiring medical treatment for these conditions will place the patients in the ASA 3 or ASA 4 health status category based on their pulmonary disease. The patients will then be randomly assigned to one of two study arms (40 per arm). Patients in one arm of the study will receive Sugammadex and patients in the other arm

will receive neostigmine/glycopyrrolate for reversal of neuromuscular blockade. Due to the nature of bronchoscopy for biopsy, the depth of anesthesia at the end of the case will be difficult to predict; the length of the cases may vary some (although most will be approximately one hour), and patients' metabolism of neuromuscular blocking agents is very much dependent on their personal medication regimens and liver function. We plan to follow each patient's depth of neuromuscular blockade using the TwitchView monitor, a commercially available, EMG-based monitor. The TwitchView measures muscle response to delivered electrical stimuli (2Hz) which are sent in sets of 4 0.5 seconds apart(most commonly). The muscles controlled by the ulnar nerve are most commonly followed, and will be during this study. These set of electrical stimuli are called a train of four. Return of muscle strength after reversal agents are given is considered complete when the ratio of the strength of the response to the fourth electrical stimulus to the first stimulus is 0.9. The device can also deliver one long electrical stimulus of 50 Hz over 5 seconds which is called a tetanic stimulus. This causes a large release of acetylcholine into the muscle synapses so that the muscle fibers are more sensitive to the train of four stimuli and can be used to detect weaker muscle strength response. This only occurs if recovery from neuromuscular blockade has begun. Multiple time points will be recorded, including train of four measurement (TOF) every 5 minutes during the procedure, time and TOF at the end of the procedure, time of reversal medication dosing, time of TOF>0.9 and time of extubation. The TwitchView monitor will deliver a train of four stimulus to the patient every 5 minutes during the procedure until full reversal of neuromuscular blockade is detected. Reversal medication will be given as soon as each patient's procedure is complete and the patient meets appropriate criteria for reversal for each respective medication. This means that upon completion of the procedure, patients in the Sugammadex arm will be reversible from the point of 1-2 post tetanic muscle twitches or better. Depending on the results from the TwitchView monitor, the dose of Sugammadex given will be appropriate for the finding of deep (4mg/kg) or moderate block(2mg/kg). Those in the Neostigmine/glycopyrrolate arm will be reversible from the time of detection of 1-2 twitches. Comparison of the data from the two arms of the study will then be made.

Adverse events will be reported using the adverse event reporting document attached. Adverse events will also be subjected to statistical analysis as

described below. This report is copied from the AE form provided our study team for the Merck 8616-145 study.

Determination of deep vs moderate blockade:
In order to provide neuromuscular blocking reversal medications at the proper time and dose, the degree of neuromuscular blockade for each patient must be monitored. The monitor we will use is called the TwitchView monitor. It will be attached by stickers to one hand/thumb of the patient, and every 5 minutes small electrical stimuli will be given through the device and the muscle responses or twitches measured by the device. The electrical stimuli are given as four impulses of 50 Hz, 100milliseconds apart. This set of stimuli is called the train of four. The depth of the neuromuscular blockade is measured by how many twitches the patient's muscles have to these stimuli (1,2 ,3 or 4) and how strong the 4^{th} twitch is compared to the 1^{st} twitch. A moderate level of neuromuscular blockade is defined by the detection of at least two twitches (no ratio needed here). If the TwitchView does not register any muscle response to the stimuli, it sends a single 100Hz stimulus followed by the standard train of four stimuli. A deep neuromuscular blockade is defined as at most 1 or 2 twitches in response to this set of stimuli. Full reversal of neuromuscular blockade is defined at four twitches with a ratio of at least 0.9 of the 1^{st} twitch to the 4^{th} twitch.

Treatment:
Medication dosing for each arm of the study will be as follows:

Sugammadex arm: 4mg/kg for deep block or 2mg/kg for moderate block given intravenously once procedure is complete and reversal criteria are met.

Neostigmine/glycopyrrolate arm: 0.05mg/kg neostigmine up to a maximum dose of 5mg and 0.6mg glycopyrrolate once procedure is complete and reversal criteria are met.

Study Limitations:
Limitations of this study are that it will be performed in a single academic medical center (not a multi-center study) and that our population is an inner city, lower socioeconomic population and results may not be fully generalizable to other populations. In addition, we will be limiting our study to a narrow range of procedures often done in the bronchoscopy suite in order to have each procedure last approximately an hour. Procedures to be included will be biopsy based procedures (some of these are done with ultrasound, some with fluoroscopy).

a) Data and Specimen Banking

This study will not disclose subjects' Protected Health Information. HIPAA authorization will be obtained from each participating subject. Patients will be informed during the consent process that any data collected from his/her chart will be de-identified so that the subject's identity is protected. See attached data sheet for data collection variables.

Data will be de-identified at the time of collection and kept in a password protected and encrypted file. The file will be accessible only to study personnel as needed. The key to the de-identified data will be kept in a password protected and encrypted file accessible only to the study's principal investigator. This key will be destroyed once full data analysis is complete.

De-identified data will be stored and kept in a password protected and encrypted file. This file will be on the U Drive of Dr. Ellen Hauck in room B307 of the Department of Anesthesiology office that is locked behind two doors.

De-identified data will be available made available to Merck, Sharp & Dohme, Corp. and to any future peer-edited journal, or scientific peers requesting data for scientific purposes.

b) Data Management

Sample size and power considerations

We propose two-arm study with 40 subjects per group: group 1) Sugammadex 2 mg/kg for reversal of moderate neuromuscular blockade or 4 mg/kg for deep block and group 2) Neostigmine/glycopyrrolate for reversal of moderate neuromuscular blockade. To evaluate statistical power for primary endpoint of recovery time to TOF>0.9, the size of detectable standard deviation unit (SDU) was calculated. The SDU corresponds to a beta coefficient in a regression model when we assume the standard normal deviate (i.e. N(0,1)). Using the same assumptions above, this study will have 83.8% power to detect an SDU of 2/3 using a two group t-test with a 5% two-sided significance level.

The assumed SDU of 2/3 is considered as a moderate effect size. Based on Couto 2019 Current Clinical Pharmacology, the estimated SDU is 1 between Sugammadex for moderate blockade (mean 1.68 SD 0.47 minutes) and Sugammadex for deep blockade (mean 2.85 SD 1.17). When comparing Neostigmine to Sugammadex, the much larger SDU is expected based on Hristorska 2018 Anesthesia (recovery time to TOF>0.9 ranging from 8.43 to 16.7 minutes).

Statistical analysis plan

Descriptive analysis. The patient demographic and characteristics will be described using counts with percentages for categorical variables and means with standard deviations for continuous variables. These descriptive measures will be compared between two groups using chi-square tests for categorical variables and two sample t-tests for continuous variables, or comparable nonparametric tests.

Analysis of primary endpoint. The primary endpoint of recovery time to TOF>0.9 will be described for each treatment group using the mean and standard deviation. These means will be compared between groups using two sample t-test. If the randomization results in unbalanced treatment groups, the linear regression models will be used to test for treatment effects with any potential confounding variables.

Analysis of secondary endpoint. The secondary endpoint is time to extubation. This endpoint will be compared between groups using logrank test with Kaplan-Meier estimates. If the randomization results in unbalanced treatment groups, the Cox regression models will be used to test for treatment effects with any potential confounding variables.

Analysis of adverse event (AE). The counts and percentage of AE will be described overall and by treatment arms. The adverse event rates will be compared between two groups using Fisher's Exact test. This report is copied from the AE form provided our study team for the Merck 8616-145 study WIRB Protocol #20171782 24966.

c) Provisions to Monitor the Data to Ensure the Safety of subjects
   The PI, Dr. Ellen Hauck will be notified immediately about any complication during or after the bronchoscopy procedure. The PI will also monitor data to ensure no adverse events or to resolve any adverse events.
d) Withdrawal of Subjects
   Enrolled patients will be withdrawn from the research without their consent for any of the following reasons: if the surgery is converted to an open procedure or has other serious surgical complications as per surgeon, if a surgical complication results in the removal of the TwitchView monitoring system, or there is an impairment to the anesthesiologist's or nurse anesthetist's ability to follow protocol.
   The enrolled patient will be able to withdraw prior to induction of anesthesia on the day of the procedure. If a patient decides after awaking from anesthesia or at any time after his or her surgery to withdraw from the study they will be able to do so. If the patient desires their data be removed from the study, it will be destroyed and not used in the study.

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12)Risks to Subjects

Sugammadex (also known as Bridion®)
Muscles are activated by nerves that send signals to them. Neuromuscular blocking drugs bind at the nerve-muscle interaction site and stop the nerve signals from reaching the muscles. When used as part of standard of care treatment, Sugammadex binds to the neuromuscular blocking drug and prevents and disrupts binding to the nerve-muscle interaction site to the muscle can receive information from the nerves once again.

The following adverse events are noted in FDA label.
- Allergic reactions that can sometimes be serious or life-threatening.

These reactions can occur in persons who have not been previously treated with sugammadex.
Symptoms reported in studies or general use of sugammadex have included:

- Rash
- Hives
- Redness of the skin
- Swelling of the tongue and throat that may cause difficulty breathing or swallowing
- Fast heartbeat
- Low blood pressure
- Shortness of breath due to muscle cramps of the airways (bronchospasm).
- Slower-than-expected recovery of muscle movement after surgery or return of muscle weakness after surgery

The most common side effects in patients undergoing surgery are:
- Cough
- Airway difficulties
- Unwanted muscle movement or coughing during surgery
- Change in heart rate or blood pressure due to the operation

Neostigmine

The following side effects by Neostigmine according to FDA label:
- Low blood pressure
- Slowed heart rate
- Increased heart rate
- Abnormal heart rhythm
- Difficulty breathing that can sometimes be serious or life threatening
- Increased mucous in the respiratory system
- Reduction of oxygen supply to a tissue
- Difficulty speaking

- Changes in the ability to see
- Headache
- Dizziness
· Fainting
- Inability to sleep
- Dry mouth or increased saliva
- Nausea and vomiting after the procedure
- Joint pain
- Itchiness, rash or redness
- Pain at the site of surgery; pain in the throat
- Muscle cramps or spasms
- Slower than expected recovery of muscle movement after surgery (your muscles may stay relaxed longer)
- Loss of bladder control
- Increased urine frequency
- Increased gas and increased bodily functions
- Abnormal heart rhythms or increase or slowing of the heart rate that can sometimes be serious or life-threatening
- Wheezing or contraction of the muscles of the airway (bronchospasm). This may be worse if you have asthma.
- Difficulty breathing or swallowing
- Convulsions
- Drowsiness
- Difficulty in speech
- Involuntary muscle twitches
- Loss of consciousness
- Blurred vision, and changes in vision.

Glycopyrrolate
Side effects of glycopyrrolate from FDA label may include:
- Abnormal heart rhythms, slow or fast heart rate and palpitations that can sometimes be serious or life threatening
- Nausea, vomiting, bloated feeling
- Constipation
- Difficulty urinating
- Difficulty breathing that can sometimes be severe or life threatening
- Blurry vision, large pupils, eye discomfort in bright light
- Dry mouth and skin
- Increased body temperature that can sometimes be serious or life threatening
- Headache
- Mental confusion
- Feeling nervous or restless

- Inability to sleep
- Dizziness
- Feeling drowsy
· Muscle weakness
- Increased pressure in the eye (glaucoma)
- Loss of sense of taste
- Impotence (erectile dysfunction)
- Hives, itching
- Decreased sweating
- Seizures
- Low or high blood pressure

13) Potential Benefits to Subjects

There is no direct benefit to subjects participating in the study. Information learned from this study could potentially help future patients.

14) Privacy and Confidentiality

The study will not use or disclose subjects' Protected Health Information (PHI). Appropriate steps will be taken to secure the data including CITI training of involved personnel, authorization of access, password protection, encryption, physical Certificates of Confidentiality, and separation of identifiers and data. During the intraoperative periods medication requirements, vital signs, operative time, and train-of-four information will be collected. During the recruitment process and on the morning of the procedure, subjects will be assured of the privacy of data collected and the expertise of their anesthesia team.

15) for Research-Related Injury

There is no compensation for research-related injury. If there are any complications or injuries patient will be referred to a specialist as appropriate.

16) Economic Burden to Subjects

There will be no cost of the study drugs billed to the subject.

17) Subject Compensation

Subjects will receive a $50 gift card for each visit for a total of $100.

18) Consent Process

Procedures recommended in the "INVESTIGATOR GUIDANCE: Informed Consent (HRP-802) document will be followed when obtaining informed consent. Patients listed for outpatient bronchoscopy biopsy procedure that requires

general anesthesia with neuromuscular blockade will be approached and consented during their preoperative anesthetic evaluation in PAT or in their hospital rooms if they are inpatients, at least one day before their day of surgery. Only study personnel will obtain consent. Assurances will be given that withdrawal from the study at any time is possible, and that all data will be de-identified. Patients will also sign a HRP 505 in English HIPAA authorization form.

Non-English Speaking Subjects

Non-English will not be recruited for this study.

19) Process to Document Consent in Writing

We will follow "INVESTIGATOR GUIDANCE: Documentation of Informed Consent (HRP-803)." As well, we will have an additional document "Informed Consent Process Documentation", requiring the staff obtaining consent and PI to sign and confirm the subject signed the IRB approved consent form and understood what he/she signed. This document is also attached.

20) Vulnerable Populations

The following populations will not be approached to be part of this study: Pregnant Women, Neonates of Uncertain Viability, Nonviable Neonates, Prisoners, Children, Wards, Adults Lacking Capacity

21) Sharing of Results or Incidental Findings with Subjects

If patients would like to see the data collected during his or her surgery, it will be provided to them. In addition, results from the study will also be made available to interested patients.

22) References

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