Sugammadex VS Neostigmine and Glycopyrrolate reversal of neuromuscular relaxation for time to return of bowel function after bowel resection: prospective, randomized, triple-blinded clinical trial for quality improvement

Study Short-name: GI-2 Study

Protocol Version	*Version 1.5*
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Sponsor:	*Merck Sharp & Dohme LLC*

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Summary

PROTOCOL SYNOPSIS

Rationale	Neuromuscular blocking agents are essential during surgical procedures to paralyze the body to avoid unnecessary movement during surgery. There are various medications, such as Sugammadex that are later used to reverse the effects of the neuromuscular blockade. The U.S. performs approximately320,000 colectomies per year for benign and malignant conditions such as Ulcerative Colitis (UC). Bowel resection surgery removes a portion of your small or large intestine. Currently, there is little available prospective outcomes data regarding the use of Sugammadex versus Neostigmine with Glycopyrrolate in colorectal surgery as it relates to its effects on post-surgical time (hr) to first bowel movement and tolerance for solid food (aka GI-2recovery) following bowel resection surgery. The study team will be conducting a randomized triple-blind study (patient's assigned group is hidden from the patient, provider, and research team). Randomization is created by using an electronic randomizer. Upon consent, the patient's assignment (per the randomizer) will be submitted to the Investigational Drug Service (IDS) Pharmacy by a department employee with no direct patient interaction.
Study Design	Randomized, prospective, triple-blinded, controlled clinical trial
Inclusion Criteria	We will include all adult (≥18 years old) patients undergoing laparoscopic bowel section surgery under general anesthesia with nondepolarizing neuromuscular blockade with rocuronium or vecuronium, and requiring inpatient admission
Exclusion Criteria	• Allergy to Rocuronium, Vecuronium, or Sugammadex • Bowel resection surgery requiring an ostomy • No severe valvulopathy, no systolic heart failure with reduced ejection fraction (HFrEF), no coronary artery disease with positive stress test for ischemic regional wall motion abnormality • No autoimmune pulmonary disease, no severe pulmonary fibrosis, no severe pulmonary hypertension, no COPD with requirement of home oxygen, no pulmonary cancer of primary or metastatic origin

	• Creatinine Clearance (CrCl) of less than 30 • Pregnancy • Incapable of providing consent or understanding the research project
Primary Outcome	The primary endpoint will be GI-2 recovery as defined as hour to first bowel movement and toleration of oral diet.
Secondary Outcomes	• Patient demographics (age, sex, race/ethnicity, etc.) • Total cost of stay • Total length of stay • 30-day morbidity and mortality • Post reversal bradycardia prior to PACU discharge • Duration of PACU stay not owing to bed availability • Time to out of bed • Amount of fluid administration • Presence of bowel adhesions • PONV
Study Duration	12 Months
Sample Size	128 Patients
Statistical Analysis	The primary outcome will be analyzed using Kaplan-Meier . Baseline characteristics of patients will be analyzed using chi-squared tests for categorical variables and unpaired Student's t-tests for continuous variables. Multivariable linear regression will be performed for continuous variables, multivariable logistic regression for dichotomous variables, and chi-square test for categorical variables.

LIST OF ABBREVIATIONS

Pre-Op	Preoperative Care Unit
PACU	Post Anesthesia Care Unit
OR	Operating Room
IDS Pharmacy	Investigational Drug Services Pharmacy
PONV	Postoperative nausea and vomiting
NMB	Neuromuscular Blockade
EMR	Electronic Medical Records

RATIONALE

Acetylcholinesterase inhibitors such as Neostigmine are most commonly administered to reverse a patient's inability to move during surgery. Neostigmine was introduced in 1931 and by the 1990s several milestone clinical trials reinforced its effectiveness and safety. They are considered the “Gold Standard” in clinical settings. Neostigmine increases Acetylcholine (a neurotransmitter) in the neuromuscular junction (chemical synapse between a motor neuron and a muscle fiber), which allows for muscles to contract with full strength and allows you to breathe on your own following surgery.

Sugammadex was first produced in 1999 and created a new class of drug called selective relaxant binding agents. Following extensive clinical trial testing, the FDA approved Sugammadex in 2015. It was approved to reverse a patient's inability to move during surgery. But unlike Neostigmine, Sugammadex surrounds the muscle relaxer so it cannot bind to the receptors (cells that receive signals) that keep patients from moving. Due to the binding, the amount of free muscle relaxer in the plasma (amber-colored liquid component in the blood) decreases and allows patients to move and breathe on their own.

The U.S. performs approximately 320,000 colectomies per year for benign and malignant conditions such as Ulcerative Colitis (UC) and colon malignancy. Following the 2004 published data from the Clinical Outcomes of Surgical Therapy (COST) trial, a greater percentage of colectomies are performed using minimally invasive techniques. Various studies continue to show decreased hospital length of stay and complications with laparoscopic colectomy. A major cost increasing complication of bowel resection can be prolonged ileus, increasing cost by overall treatment expense and length of stay.

Currently, there is little available prospective outcomes data regarding the use of Sugammadex in colorectal surgery as it relates to its effects on post-surgical bowel motility following bowel resection surgery. The purpose of this study is to see the outcome of Sugammadex versus Neostigmine with Glycopyrrolate in colorectal surgery as it relates to its effects on post-surgical time (in hours) to first bowel movement and tolerance to solid food (GI-2 recovery) following bowel resection surgery.

STUDY DESIGN

Randomized, prospective, triple-blinded, controlled clinical trial.

POPULATION

Inclusion Criteria

We will include all adult (≥18 years old) patients undergoing laparoscopic bowel section surgery under general anesthesia with nondepolarizing neuromuscular blockade with rocuronium or vecuronium, and requiring inpatient admission.

Exclusion Criteria

- Allergy to Rocuronium, Vecuronium, or Sugammadex
- Bowel resection surgery requiring an ostomy
- No severe valvulopathy, no systolic heart failure with reduced ejection fraction (HFrEF), no coronary artery disease with positive stress test for ischemic regional wall motion abnormality

- No autoimmune pulmonary disease, no severe pulmonary fibrosis, no severe pulmonary hypertension, no COPD with requirement of home oxygen, no pulmonary cancer of primary or metastatic origin
- Creatinine Clearance (CrCl) of less than 30
- Pregnancy
- Incapable of providing consent or understanding the research project

PRIMARY OUTCOME

The primary endpoint will be GI-2 recovery as defined as hour to first bowel movement and toleration of oral diet.

SECONDARY OUTCOMES

*Potential confounders **C**, Secondary Endpoints **E***

• Patient demographics (*age, sex, race/ethnicity, etc.) pulled from EPIC*	C
• Total cost of stay i*n USD (pulled from billing*	E
• Total length of stay *in days*	E
• 30-day morbidity (*yes/no, as a patient having 1 or more of the 21 specific NSQIP postoperative complications*)	CE
• 30-day mortality (*yes/no*)	
• Post reversal bradycardia prior to PACU discharge (*yes/no, defined as heart rate <50*)	CE
• Duration of PACU stay not owing to bed availability *in hours*	CE
• Time to out of bed *in hours*	CE
• Amount of fluid administration (*preop to PACU discharge to include but not limited to intraoperative fluid management*)	C
• Presence of bowel adhesions (*yes/no, defined as pre-existing adhesions*)	C
• PONV (*yes/no, defined as postoperative nausea and vomiting in PACU*)	CE

STATISTICAL ANALYSIS

The primary outcome will be analyzed using Kaplan-Meier.

Baseline characteristics of patients will be analyzed using chi-squared tests for categorical variables and unpaired Student's t-tests for continuous variables. Multivariable linear regression will be performed for continuous variables, multivariable logistic regression for dichotomous variables, and chi-square test for categorical variables.

In the uneventful likelihood that there are differences in our baseline characteristics, not accounted for by randomization, we will analyze for an absolute standardized difference of less than 0.1. Any absolute standardized difference that is greater than 0.1 will be individually analyzed for impact on the results obtained. We may elect to choose alternative statistics to account for any characteristics where randomization failure occur.

Sample Size

To look at GI-2 recovery as primary outcome, we find the most recent data showing a mean in control patients of 112 hours. We assume a standard deviation of 48 hours around that time. To show a

reduction of 18 hours inGI-2 time, we find an estimated effect size of 0.5. With that effect size of0.5, power of 0.8, and an alpha of 0.05, we find that 63.7 patients are needed per group, or a total of 128 patients. Neo/Glyco group assumed mean & SD: 112 +/- 48 hours Sugammadex group assumed mean & SD: 88+/- 48 hours Group difference to detect: 24 hours Cohen's d of 0.5. From there 80% power and alpha of 0.05 gives us 63.7 per group.

STUDY PROCEDURES

Triple Blinding

The study team will be divided into blinded and unblinded members. Some research personnel and the IDS Pharmacy team will be unblinded. The patients, researchers, and data analysts will be blinded. This ensures that the anesthesiologists do not behave differently intraoperative, the surgeons and patients do not behave differently post-operatively and eliminates any placebo effect for the patient. It also reduces research bias during the analysis and manuscript writing phase.

Recruitment/Consent

1. The study team will review the surgical schedule and coordinate with the surgical team to pre-screen patients within the electric medical record (EMR). The Colon & Rectal Surgery team may refer patients who are eligible for the study that meet the inclusion/exclusion criteria.
2. The study team will call prescreened patients and email the consents in advance to allow the patient ample time to review the consent. The study team may also attend the pre-surgical appointment and work with the surgical team to discuss the study and obtain full written consent. If the patient requests additional time to review the consent forms, the team will try to obtain written consent on the day of surgery.

Day of Surgery and Discharge

1. All UCI Colorectal patients are part of the ERAS protocol. Prior to surgery, patients are given oral antibiotics in addition to mechanical bowel preparation. They are also educated on dehydration avoidance and encouraged to carbohydrate load prior to surgery.
2. Once subjects have been fully consented, the subject will be randomized via a sealed envelope or electronic randomizer into either the Sugammadex arm or Neostigmine plus Glycopyrrolate arm by an unblinded member of the study team.
3. On the day of surgery, patients are given anti-nausea drugs and their dose of pain medication with the Pre-Op area. The unblinded study member will inform IDS Pharmacy about the randomization and the PI or a Co-investigator will put in a blinded order set based upon said randomization.
4. The patient will under surgery per standard-of-care (SOC)
    a. Intraoperatively, the anesthesiologist will monitor the pharmacological effects of NMB and the dose can be titrated to effect. Provider will maintain a moderate level of blockade throughout the case.
        i. Group A: Sugammadex
            1. Patient will receive 2 mg/kg of Sugammadex plus equivalent volume of saline (0.9% sodium chloride)
        ii. Group B: Neostigmine with Glycopyrrolate

1. Patient will receive 0.07 mg/kg Neostigmine plus equivalent volume of glycopyrrolate (0.014 mg/kg)

iii. The anesthesiologist will check twitches at emergence (3-4 twitches are present).

iv. Both groups will receive rocuronium

b. Once the patient has adequately recovered from the effects of the neuromuscular blocking agents, can breathe on their own, follow commands, demonstrate purposeful movement, and can protect their airway, they will be extubated.

c. If for any reason patient safety is threatened, the team should use Sugammadex where appropriate and exclude the case from the data set. While the anesthesiologist will not initially know the medicine being administered, they may have a suspicion following administration. We ask that they do not share any suspicions with any influencing parties (i.e., surgeon or patient)

5. Once the surgery ends, the subject will go into the post-anesthesia care unit (PACU), where they will be accessed according to standard-of-care. This includes the standard ileus prevention strategy of offering patients a regular diet within 30 minutes of surgery.
6. Patients are not required to have a bowel movement prior to discharge but all patients will undergo a standard post-surgical assessment. Any patients that do not have a bowel movement prior to discharge will be contact post-discharged daily and educated to note the date/time of first bowel movement following discharge

Post-Op Data Analysis

1. The unblinded study members will pull the study data from EPIC or put in a data request with the Honest Broker. Data will be de-identified prior to blinded study member analysis.

Data Collection

The subject's medical record will be reviewed by the study team to collect and review the rest of the study endpoints. The study team will have access to the entire medical record which includes:

- Lab & Pathology Reports (surgical site infection)
- Operative Reports (presence of bowel adhesions)
- Discharge Summary (total length of stay)
- Financial Reports (total cost of stay)
- Imaging Reports
- History & Physical Exams (demographics)
- Progress Notes (time out of bed, PONV, etc.)

ADVERSE EVENT REPORTING

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Serious adverse event or suspected adverse reaction refers to an event or reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- in-patient hospitalization or prolongation of existing hospitalization,

- a persistent or significant incapacity or substantial disruption of the ability to
- conduct normal life functions, or,
- a congenital anomaly or birth defect.

Mandatory Safety Reporting

The study team will submit an Unanticipated Problems (UP) form to the UCI IRB within 5 business days of the occurrence or within 5 business days from the date in which the lead researcher learned of the occurrence. The UP Report is an online, electronic application that can be drafted by any member of the study team but can only be officially submitted by the lead researcher or IRB-approved co-researcher. If the adverse event changes the risk/benefit profile of the study, a modification will be submitted to the IRB to update the protocol and consenting documentation.

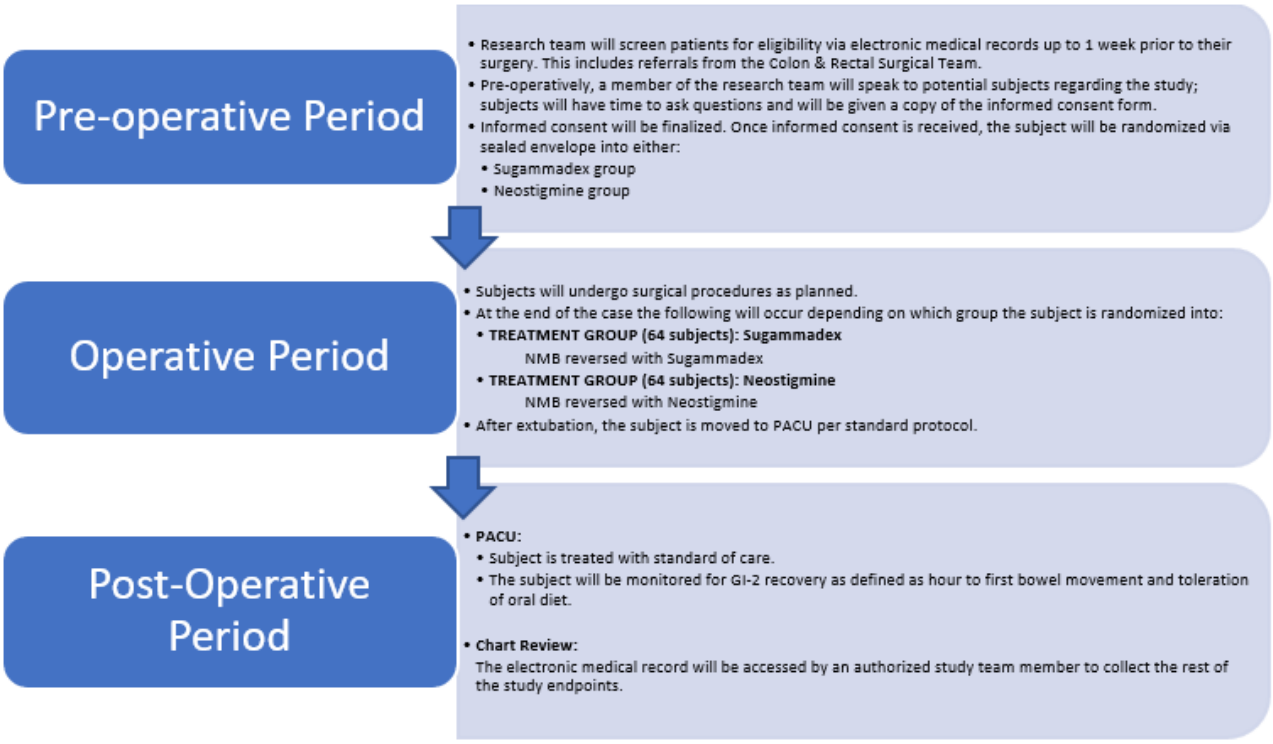
PUBLICATION PLAN

We anticipate 1-3 manuscripts generated from the present study, though the total number is largely dependent on study outcomes. The projected target date for manuscript submission would be September 2024 in Anesthesiology, Anesthesia, and Analgesia, Journal of Clinical Anesthesiology, and/or BMC Anesthesiology

We anticipate 2-3 abstracts to result with presentations at ASA and other relevant organizations. The PI would present at the American Society of Anesthesiologists (ASA) Annual Meetings. The future date and location currently listed is:

- October 18-22, 2024 Philadelphia, PA
- October 10-13, 2024 San Antonio, TX

APPENDIX 1 – STUDY FLOWCHART



APPENDIX 2 – STUDY DRUG AND PREPARATION | IDS PHARMACY

Reversal Agents (mg/kg)	
Neostigmine	0.07
Glycopyrrolate	0.014
Sugammadex	2.0
Muscle Relaxants (intubating doses in mg/kg)	
Rocuronium	0.60 or 1.20
Muscle Relaxants (maintenance bolus in mg)	
Rocuronium	10-20

1) Group A | SUGAMMADEX
   a) 2.0 mg/kg of Sugammadex plus saline equivalent
      i) 2 syringes numbered 1 and 2
         (1) Syringe #1: 0.9% sodium chloride
         (2) Syringe #2: full Sugammadex + 0.9 sodium chloride (QS to match volume)
2) Group B | Neostigmine with Glycopyrrolate
   a) 0.07 mg/kg Neostigmine plus 0.014 mg/kg Glycopyrrolate
      i) 2 syringes numbered 1 and 2
         (1) Syringe #1: Glycopyrrolate
         (2) Syringe #2: Neostigmine

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