A double-blind, randomized, parallel group study to compare Rocuronium reversal with Sugammadex (Bridion®) versus Neostigmine/Glycopyrrolate and the incidence of urinary retention after elective ambulatory posterior lumbar spine surgery.

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Investigator Studies Program (MISP) Clinical Protocol	
Section #1 - MISP Protocol Identification	
Study Title:	A double-blind, randomized, parallel group study to compare Rocuronium reversal with Sugammadex (Bridion®) versus Neostigmine/Glycopyrrolate and the incidence of urinary retention after elective ambulatory posterior lumbar spine surgery.
Request Date:	1/4/2023 – v1; 8/2/2023 – v2; 1/16/2024 – v3; 5/10/2024 – v4; 07/16/2024 – v5; 07/21/2025 – v6
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1.1 Objectives The primary objective is the difference between Sugammadex and Neostigmine/Glycopyrrolate on the incidence of urinary retention defined as no void more than 6 hours after posterior lumbar spine surgery in ambulatory/short stay patients. The secondary objectives between patients who received Sugammadex and Neostigmine/Glycopyrrolate are: 1) To compare actual times of micturition we will analyze the proportion of patients (percentages) voided at 6, 9, 12 and 24 hours. 2) To compare bladder urine volumes in milliliters (mL) we will perform a bladder ultrasound scan at around 6 hours postoperatively if patients did not void. 3) To compare urinary retention symptoms, we will administer a questionnaire at around 6 hours postoperatively and on postoperative day (POD) 1. Urinary retention scoring: • Feeling pressure (0=no, 1=mild, 2=moderate, 3=severe) • Bladder discomfort (0=no, 1=mild, 2=moderate, 3=severe) • Urge to urinate (0=no, 1=mild, 2=moderate, 3=severe) • Hesitancy (0=no, 1=mild, 2=moderate, 3=severe) 4) To compare need for bladder catheterization (straight or Foley) 5) Length of stay 2.1.2 Clinical Hypotheses Our hypothesis is that Sugammadex will decrease the incidence of urinary retention compared to Neostigmine/Glycopyrrolate after lumbar spine surgery.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	2.2.1 Background Urinary retention is common after anesthesia and surgery, with a reported incidence of between 5% and 70%. (1) The incidence of postoperative urinary retention (POUR) is increased after general anesthesia in patients undergoing spine surgery. A case-control study conducted at the Cleveland Clinic found the incidence of POUR was over 20% after spine surgery. (2) Although the exact mechanism for how general anesthesia influences POUR is not fully understood, commonly used anticholinergic drugs such as atropine and Glycopyrrolate block detrusor muscle contractions and cause bladder hypotonia, also resulting in urinary retention. (1) Further, Neostigmine/Glycopyrrolate has been routinely used for neuromuscular blockade (NMB) reversal potentially increasing POUR. In contrast, Sugammadex does not have anticholinergic effects since its mechanism of NMB reversal is by encapsulation of Rocuronium. Therefore, we hypothesized that Sugammadex will reduce the incidence of POUR. We choose to investigate POUR in patients undergoing posterior spine surgery as the incidence of POUR is high for this population and many patients who receive lumbar spine surgery have them performed as ambulatory procedures (i.e., going home the same night) or as short stay procedures (i.e., going home the next morning). Increased incidence of POUR could lead to delayed discharge. 2.2.2 Medications Used - Sugammadex, Bridion® Merck - Neostigmine, Bloxiverz®, Exela Pharma Sciences - Glycopyrrolate, Glycopyrrolate Injecting, USP, Somerset Therapeutics

	2.2.3 References 1. Baldini G, Bagry H, Aprikian A, Carli F. Postoperative urinary retention: Anesthetic and perioperative considerations. Anesthesiology. 2009;110(5):1139-1157. 2. McLain RF, Kalfas I, Bell GR, Tetzlaff JE, Yoon HJ, Rana M. Comparison of spinal and general anesthesia in lumbar laminectomy surgery: a case-controlled analysis of 400 patients. J Neurosurg Spine. 2005;2(1):17-22.
2.3 Study Design	2.3 Study Design This is a prospective, double-blind, randomized, parallel group, single center study. Patients will be randomized into one of two groups according to NMB reversal agent (Sugammadex versus Neostigmine/Glycopyrrolate). The randomization will be conducted using permuted block randomization with blocks of 10. Note that this ensures that for each group of ten participants, the sequence or permuted block, the treatments are approximately evenly distributed. As the "block" here is **not** a *statistical* block, there is no need to include block effects in the analysis plan. Sequence generation will be done using SPSS and at least one extra block will be included to account for patient drop-out, screen failures, or other unintended enrollment issues. Sequence generation will be provided using an Excel file or other preference of the investigational pharmacist, in full, so that the compounds can be created and numbered accordingly. The surgeons, anesthesiologists, patients, analysts and individuals performing the postoperative assessments will be blinded to the study group assignment. All subjects will receive a standardized general anesthetic. Anesthesia induction will be dosed based on actual body weight with Propofol, 1.5-2 mg/kg intravenous (IV), Fentanyl, 100 mcg IV, and Rocuronium, 0.6 mg/kg IV, and maintained with sevoflurane in oxygen/air. Additional Rocuronium

will be given to maintain surgical muscle relaxation at train-of-four (TOF) count 1-3 twitches. Additional Fentanyl will be given during anesthesia and at the end of surgery per the clinical team.

NMB will be reversed (per the randomization schedule) using dosage based on actual body weight with either Sugammadex, 2 mg/kg IV, or Neostigmine, 50 mcg/kg IV (not to exceed 5 mg) and Glycopyrrolate, 10 mcg/kg IV (not to exceed 1 mg). The NMB reversal agent will be prepared in a blinded fashion by the University of Missouri (MU) Investigational Drug Services (IDS) Pharmacy.

All patients will receive Ondansetron and Dexamethasone for post-operative nausea and vomiting (PONV) prophylaxis. Patients who have history of PONV and require Scopolamine patch will not be included in the study. PONV treatment in PACU will be repeated dose of Ondansetron or Amisulpride.

2.3.1 Study Population

All adult patients undergoing elective posterior lumbar spine surgery at the Missouri Orthopedic Institute (University of Missouri Health Care, Columbia, Missouri, USA).

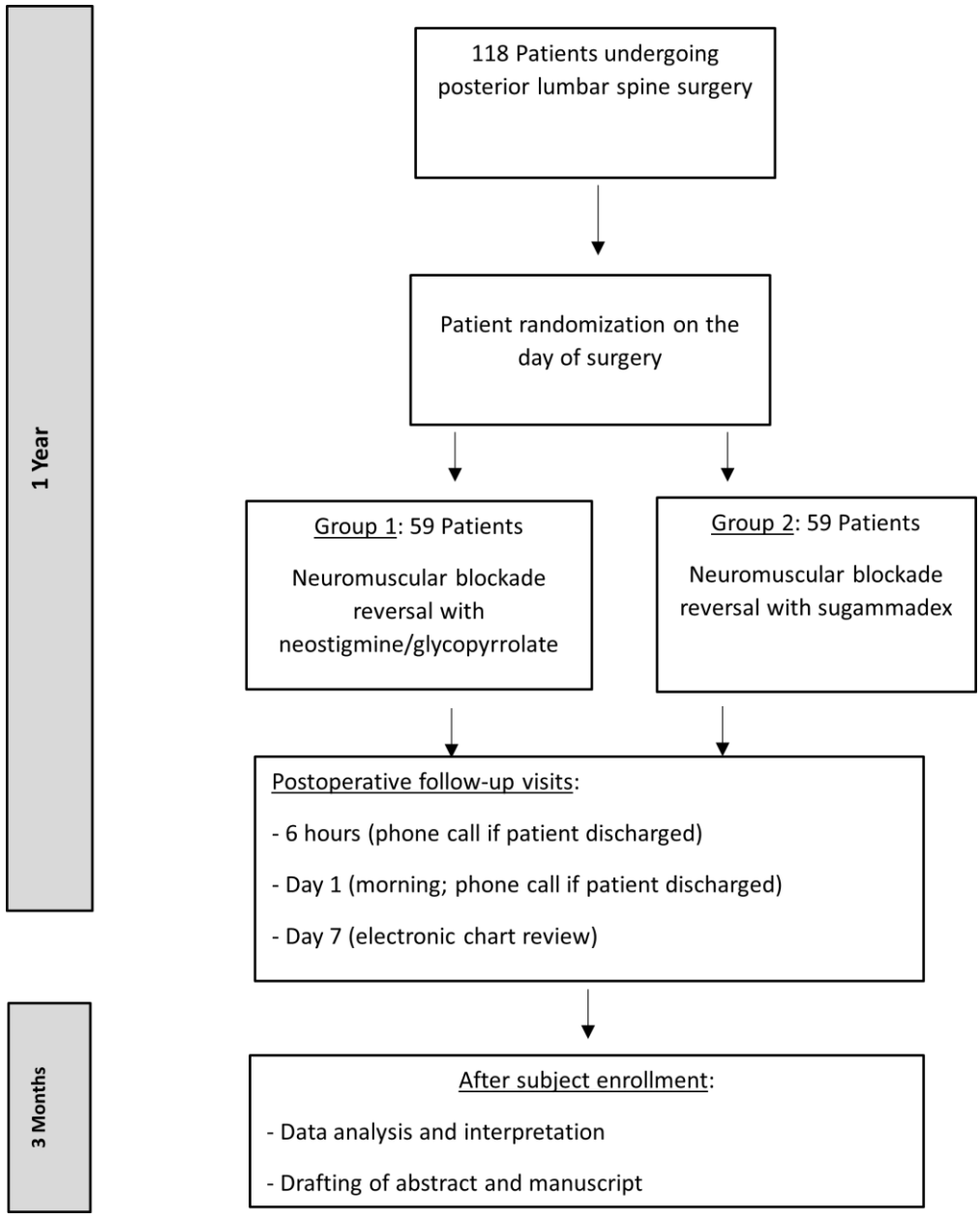
2.3.2 Inclusion Criteria

- Age 18 ≥ years
- ASA Physical Status I-III

2.3.3 Exclusion Criteria

- Inability to obtain written informed consent.
- Allergy to medications used in the protocol.
- Known or suspected neuromuscular disorders.
- Significant renal disease with a serum creatinine ≥ 2 mg/dL.
- Significant liver disease.
- A family history of malignant hyperthermia.

	- History of genitourinary surgery, cancer, or radiation within the last year. - Currently prescribed urological medications or diuretics. - BPH or symptoms of BPH (interrupted or weak urine stream or wake up to urinate more than two times per night). - History or diagnosis of urinary incontinence or urinary retention. - History of PONV with use of Scopolamine. - Use of Foley catheter pre- or intra- operatively - Perioperative medications that influence micturition (e.g., diuretics or intraoperative anticholinergic medication use other than NMB reversal)
2.4 Diversity & Inclusion	All patients eligible for study enrollment will be approached to participate in the study regardless of age, race, ethnicity, and sex pursuant to available randomization slots.

2.5 Study Flowchart	
2.6 Study Procedures	2.6.1 Experimental Design - A prospective, double-blind, randomized, parallel design, single center study. - Patients undergoing ambulatory/short stay lumbar spine surgery.

- Patients will be randomized into one of two groups to receive either Sugammadex or Neostigmine/Glycopyrrolate for NMB reversal.
    - Group Neostigmine/Glycopyrrolate: 59 patients
    - Group Sugammadex: 59 patients

2.6.2 Study Periods

1. Study preparation: Protocol budget, departmental and hospital meetings, institutional review board (IRB) preparation, registration to clinicaltrials.gov, coordinator and co-investigator training, permuted block randomization sequence generation, source document development, drug storage and documentation by MU IDS Pharmacy.
2. Ongoing study maintenance: Departmental and hospital meetings, coordinator and co-investigator training, IRB maintenance, clinicaltrials.gov maintenance.
3. Day(s) before surgery: Patient pre-identification.
4. Day before surgery: Patient screening, notification of study physicians, coordinators, and pharmacy of potential patients.
5. Day of surgery: Confirmation of inclusion and exclusion criteria, informed written consent, patient education with provision of examples for study measures and symptom grading criteria used in study questionnaires, provide patient a form to record the time of the first void and questionnaire, patient randomization, drug preparation by MU IDS Pharmacy, drug delivery to operating room, NMB reversal administration, medications, times, adverse events assessments.
6. Patient visit/phone call around 6 hours postoperatively: Urinary retention evaluation if patient voided or not, medications received, perioperative times, adverse events. Bladder scan if patient did not void till then and still in hospital. Patient education will be performed on the importance of accurate void time documentation. The retention

questionnaire will be administered in patients who did not void. The form to record the time of void that will be sent home with the patient, depending on void status at discharge, will also be reviewed again with the patient to minimize the potential impact of recall bias. They will be instructed to fill out the form immediately after voiding to decrease the chance of not remembering the time.

7. Patient visit/phone call around 9 AM on morning of POD 1: Urinary retention evaluation and questionnaire, record all medications, adverse events, and times for urination and hospital discharge.
8. Electronic chart review one week (POD 7) after the surgery: Record all adverse events, hospital discharge, and readmission/emergency room visits. Record pain medications given in the hospital and the time of discharge.

2.6.3 Anesthetic Management

1. Monitoring
   a. All patients will be monitored with standard American Society of Anesthesiologist (ASA) monitors including ECG, non-invasive blood pressure, pulse oximetry, esophageal temperature, and capnography.
   b. NMB monitoring per clinical team.
2. Anesthetic Technique
   All patients will receive standardized general anesthetic:
   a. Premedication: None.
   b. Preoxygenation with 100% oxygen for a minimum of 3 min.
   c. Induction: Propofol, 1.5 mg/kg IV, Lidocaine 1 mg/kg IV, and Fentanyl, 1 mcg/kg IV. Additional Propofol or Fentanyl may be administered at the discretion of the anesthesia provider.

d. Intubation: Rocuronium 0.6 mg/kg IV after loss of consciousness to facilitate tracheal intubation.

e. Maintenance: Ventilation with air/oxygen to achieve a fraction of inspired oxygen (FiO_2) = 0.6 and inhaled Sevoflurane. Additional Fentanyl, 25-50 mcg IV may be administered as determined by the anesthesia provider. The FiO_2 can also be increased if determined necessary by the anesthesia provider. LR for maintenance fluid per clinical team.

f. PONV prophylaxis: Dexamethasone and Ondansetron

g. Train-of-four (TOF) Monitoring: TOF will be checked per clinical team to maintain TOF 2-3 twitches. TOF monitoring will be performed per standard care until the end of anesthesia.

h. Reversal of NMB: Performed at the end of surgery when TOF is ≥3 twitches. The clinical team will be given an envelope with the blinded reversal drugs as described above.

i. Extubation: It will be per clinical team and our hospital standard care, following established hospital policies/procedures. Current standard is that patients are awake, following verbal commands (opening eyes, squeezing hands, head lift) and have adequate NMB recovery.

j. Should a patient not breathe adequately and/or remain weak after receiving the study drug, a rescue dose of sugammadex will be administered per standard of care, regardless of what the study drug was, following established hospital policies/procedures. Unblinding will be done immediately with IDS pharmacy telephonically and followed with written communication via email. Should this occur, the patient will be excluded from the study, data collection will cease immediately, and an event report

will be submitted to IRB. Data, of patients who require rescue medication, will not be included in the dataset for analysis.

2.6.3 Postoperative Pain Management

Postoperative pain management will be per clinical team and our hospital standard care: Fentanyl IV in PACU and Oxycodone PO after. Opioid requirements during hospitalization will be calculated in milligram morphine equivalents (MME). PONV postoperative treatment will be with repeated Ondansetron or Amisulpride if needed.

2.6.4 Postoperative Follow-Up

1. Visit around 6 hours post-op (phone call if patient discharged):
    a. Determine if patients voided (time) or not.
    b. Need for bladder catheterization (yes/no).
    c. Bladder scan if not already voided and not discharged.
    d. Record medications, perioperative and discharge times.
    e. Patient re-education of remaining study measures and provision of answers to any follow-up questions.

2. Visit on around 9 AM on morning of POD 1 (phone call if patient discharged):
    a. Determine time when patient voided.
    b. Administer urinary retention questionnaire:
        - Feeling pressure (0=no, 1=mild, 2=moderate, 3=severe)
        - Bladder discomfort (0=no, 1=mild, 2=moderate, 3=severe)
        - Urge to urinate (0=no, 1=mild, 2=moderate, 3=severe)

	- Hesitancy (0=no, 1=mild, 2=moderate, 3=severe) c. Need for bladder catheterization (yes/no). d. Record adverse events, hospital discharge. 3. Electronic chart review one week (POD 7) after the surgery a. Record all adverse events, hospital discharge time, and need for any readmission/emergency room visits. b. Record pain medications given in the hospital.
2.7 Study Duration	The patients will be identified and approached regarding participation in preoperative clinic. Eligibility screening will be confirmed on the day before the surgery. The total study duration is 7 days. We estimate a recruitment rate of 1:3. Our institution has four orthopedic surgeons and three participating neurosurgeons each performing about 100 lumbar spine surgeries per year. We expect to complete the study within 1 year.
2.8 Statistical Analysis and Sample Size Justification	2.8.1 Blinding An IDS pharmacist will prepare the NMB reversal medications according to the randomization list in blindly fashion. After that, all personnel who conduct the study will be blinded. Medications will be in a syringe and capped to 10 ml with saline providing that reversal syringes in both groups look the same. All reversal medication are clear liquids. The syringe will be placed in an envelope and delivered to the operating room by a blinded study coordinator. Anesthesia providers will be given instructions when it is appropriate to give the reversal. The blinded study coordinator will measure the train-of-four (TOF) count (TOFC) before the reversal agent is given and a blinded Co-I anesthesiologist will supervise administration. Study coordinators who collect outcomes data will be blinded, including the statistician. If clinically needed, the NMB reversal medication will be unblinded by the IDS pharmacist.

2.8.2 Data Storage and Analysis

The blinded study data will be electronically coded in a database. Analyses will be performed by the investigator team (including statistician). R statistical software will be used for all analyses. Data will be summarized overall and by (blinded) treatment. Categorical variables will be compared by treatment using Chi-square or Fisher's Exact tests; continuous or ordinal variables will use t-tests or Wilcoxon Rank Sum tests, as appropriate. For the primary binomial outcome, urinary retention, a logistic regression analysis will be used, with known covariate age and suspected covariate sex (2). Additional covariates may be considered, if warranted (e.g., length of stay). Time to event analyses will be considered to compare the actual times of micturition by treatment, with covariates as previously stated.

2.8.3 Variables/Time Points of Interest

1. Demographics: Sex, age, weight, height, BMI, ASA PS classification, comorbidities especially ones listed in exclusion criteria (BPH, urinary problems, pelvic cancer, radiation).
2. Intraoperative: Use of narcotic, medications, reversal agents, fluids, blood loss/transfusion, duration of surgery and anesthesia.
3. Six hours postoperative: Time of urination, bladder scan in milliliters of urine, narcotics/pain medications in morphine equivalents, fluids, antiemetics, PACU length of stay.
4. POD 1: Time of urination, urinary retention scores, narcotics/pain medications, time of discharge from hospital (hospital length of stay).
5. POD 7: Any adverse events or complications.

2.9.1 Statistical Power/Sample Size

- The incidence of POUR after spine surgery under general anesthesia is approximately 23%. (2)

	- For the power analysis, we consider age and sex as covariates using the information from previous studies (McLain 2005) with distributions age of the target population normal (47.5, 10), sex binomial (0.5, 200), and null distribution for the outcome binomial (0.236, 200). We assume the odds ratio for the predictor is 1.175 using a logistic regression framework. Consequently, using the Shieh-O'Brian approximation, we require 59 patients per treatment to identify such a difference in urinary retention with power 0.801, two-sided alpha of 0.05, and including the covariates age and sex. Proc power for logistic regression using SAS v9.4 was used. - Total of 118 patients + dropouts/protocol violations.
2.9 Specific Drug Supply Requirements	2.9.2 Drug Supply Merck will provide Sugammadex. Neostigmine and Glycopyrrolate will be purchased locally by the MU IDS Pharmacy as marketed product because Merck does not provide third party medications. 2.9.3 Drug List - Sugammadex, Bridion® Merck – 2 mg/kg, IV - Neostigmine, Bloxiverz®, Exela Pharma Sciences – 50 mcg/kg, IV (not to exceed 5 mg) - Glycopyrrolate, Glycopyrrolate Injecting, USP, Somerset Therapeutics - 10 mcg/kg, IV (not to exceed 1 mg) 2.9.4 Drug Preparation The MU IDS Pharmacy will prepare all NMB reversal medications according to the actual weight of the patients. It will be drawn up in 10 cc syringes and topped-up with saline such that all syringes contain the same amount of fluid. The blinded syringe will be placed in an envelope and delivered to the operating room prior to reversal of NMB.

2.10 Adverse Experience Reporting	All patient adverse events will be recorded and reported according to the study visit schedule. Postoperative complications including the need for postoperative mechanical ventilation, re-intubation, residual paralysis, pneumonia, infections, other adverse events during the hospital stay, and readmissions/emergency room visits during first week postoperatively.
2.11 Itemized Study Budget	Preliminary budget is uploaded as a separate file.
2.12 References	2.12.1 References 1. Baldini G, Bagry H, Aprikian A, Carli F. Postoperative urinary retention: Anesthetic and perioperative considerations. Anesthesiology. 2009;110(5):1139-1157. 2. McLain RF, Kalfas I, Bell GR, Tetzlaff JE, Yoon HJ, Rana M. Comparison of spinal and general anesthesia in lumbar spine surgery surgery: a case-controlled analysis of 400 patients. J Neurosurg Spine. 2005;2(1):17-22. 3. Chang Y, Chi KY, Tai TW, et al. Risk factors for postoperative urinary retention following elective spine surgery: a meta-analysis. Spine J. 2021;21(11):1802-1811. 4. Cremins M, Vellanky S, McCann G, Mancini M, Sanzari L, Yannopoulos A. Considering healthcare value and associated risk factors with postoperative urinary retention after elective spine surgery. Spine J. 2020;20(5):701-707. 5. Cha JE, Park SW, Choi YI, et al. Sugammadex use can decrease the incidence of post-operative urinary retention by avoiding anticholinergics: a retrospective study. Anesthesia and Pain Medicine. 2018;13(1):40-46. 6. Zakaria HM, Lipphardt M, Bazydlo M, et al. The Preoperative Risks and Two-Year Sequelae of Postoperative Urinary Retention: Analysis of the

	Michigan Spine Surgery Improvement Collaborative (MSSIC). World Neurosurg. 2020;133:e619-e626.
2.13 Publication Plan	After the completed data analysis (~3 months) we will submit an abstract(s) to the annual meeting for the American Society of Anesthesiologists (ASA) and in the same year submit a manuscript for peer reviewed publication according to the rules of the ASA conference embargo period (requirement of ASA scientific presentations) in a peer-reviewed anesthesiology or spine care journal.
2.14 Curriculum Vitae	Updated curriculum vitae is uploaded into Visiontracker.

2.15 Protocol Submission for Investigator-Initiated Studies	*U.S. protocols should be submitted by US investigators directly to Visiontracker at https://mrk.envisionpharma.com/ienv_mrk/visiontracker/portal/login.xhtml?pgm=ISR&windowId* *Non U.S. protocols should be submitted to the MSD office by the investigators.*