The POUR Study: Effects of Neuromuscular Reversal Agents on Postoperative Urinary Retention (POUR) Following Laparoscopic Inguinal Hernia Repair

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Funding Source:

This project has received preliminary approval from the Merck Investigators Studies Program (MISP) with a budget of $72,146.78. The budget for the study includes cost of the drug (Sugammadex), pharmacy and IRB fees, and payment for the research team. We will provide the budget for the study along with the rest of the protocol.

Study Summary:

Postoperative urinary retention following laparoscopic inguinal hernia repair occurs in approximately one out of ten patients.[1] The more rapid reversal of neuromuscular blockade with Sugammadex has empirically been associated with low rates of postoperative urinary retention. In this study, patients will receive Sugammadex following laparoscopic inguinal hernia repair and then be retrospectively matched against a group of patients who did not receive Sugammadex. The primary aim of this study will be to compare the rate of postoperative urinary retention between patients receiving Sugammadex and those receiving traditional reversal agents (e.g. neostigmine which has a retention rate of 5-11%). We will also examine difference in cost and quality of life between the two groups. Our hypothesis is that the use of Sugammadex will decrease rate of postoperative urinary retention, decrease associated cost, such as need for admission, and not negatively impact quality of life.

Background and Rationale:

Urinary retention is a common complication following laparoscopic inguinal hernia repair, with recent studies citing the rate of postoperative urinary retention anywhere from 5-11%.[1–4] Age, history of benign prostatic hypertrophy, general anesthesia, male gender and postoperative narcotic use have been associated with urinary retention following laparoscopic inguinal hernia repair.[1,5] The exact effects of general anesthesia and a systemic paralytic agent on bladder function and urinary retention are not completely clear. However, it is strongly suggested that the lack of complete bladder musculature recovery and function in the immediate postoperative period and may lead to urinary retention.[6]

Our institutional database contains over 2,500 patients who have undergone either unilateral or bilateral laparoscopic inguinal hernia repair. Currently our overall rate of urinary retention in all patients in our database is 7.3%, or 185 of the 2,551 patients. In the 90 patients who were both over the age of 60 and had benign prostatic hypertrophy symptoms, the rate was 15.6%. Postoperative urinary retention potentially requires prolonged post-anesthesia care unit (PACU) stay, overnight hospital admission, return to the emergency department, need for an indwelling catheter and further physician assessment,

prolonged micturition difficulties, and urinary tract infection and other catheter-related complications.[7] Urinary retention can be detrimental to the overall health of our surgical patients.

Sugammadex has been anecdotally reported to decrease rates of postoperative urinary retention following laparoscopic inguinal hernia repair. The more rapid reversal of neuromuscular blockade helps to explain this claim. In other areas of surgery, such as orthopedics, Sugammadex has already been associated with reduced anticholinergic usage and decreased rates of postoperative urinary retention.[8] The cost efficacy of Sugammadex has yet to be determined as it is more expensive than traditional reversal counterparts; however, if it significantly decreases rates of postoperative urinary retention it could reduce healthcare costs that are downstream.[9] Given that the reported incidence of postoperative urinary retention is high after laparoscopic inguinal hernia repair, and given this is one of the most common general surgery operations performed, the results of this study will certainly be widely applicable.[10]

Study Objectives

Objectives –

1. The primary objective of this study will be to compare urinary retention rates when using Sugammadex for neuromuscular reversal compared to neostigmine. The patients receiving Sugammadex will be enrolled prospectively and those who received neostigmine will be identified retrospectively on chart review.
2. We will secondarily evaluate length of stay (in postoperative recovery or in the hospital), charges accrued by patients, and quality of life compared to patients who received neostigmine.

Hypotheses –

1. We hypothesize that the use of Sugammadex as a neuromuscular reversal agent will decrease postoperative urinary retention after laparoscopic inguinal hernia repair compared to patients who received neostigmine.
2. We also hypothesize that there will be decreased postoperative length of stay, total hospital charges accrued by patients, and no negative impact on quality of life compared to patients who received neostigmine.

Study Design/Methods:

In this study, a prospective cohort of patients undergoing laparoscopic inguinal hernia repair will receive Sugammadex and then retrospectively be matched against a cohort of patients who did not receive Sugammadex. The patients will be matched based on age, gender, history of BPH, bilateral vs. unilateral hernia, opioid usage with morphine milliequivalents, and operative time. The patients will be consented when they present to clinic for the evaluation of their inguinal hernia as the primary means of consent or in the preoperative area as a secondary means of consent. The operating surgeon will notify the research team, consisting of a resident physician and two full time research analysts, when the patient is in clinic and expresses interest in the study. One of the members of the research team will see the patient and consent them for the study as the primary consent process. Patients will be identified prior to the day of surgery and, if not previously contacted in clinic, will be contacted via telephone about participating in the study. If the patient agrees to participate prior to the day of surgery, a member of the aforementioned research team will consent the patient on the day of surgery prior to the procedure as the secondary consent process. Inclusion and exclusion criteria are defined below. Neither the patient nor the surgeon will be blinded in this study, but we do not anticipate that this will in any way change management.

Inclusion Criteria:

- Over the age of 18
- Undergoing laparoscopic inguinal hernia repair at Carolinas Medical Center by attending surgeons within the Division of Gastrointestinal and Minimally Invasive Surgery
- Unilateral or bilateral inguinal hernia repair; may have concurrent umbilical hernia repair performed
- Agreeable to participation in the study

Exclusion Criteria:

- Patients who are having concurrent ventral or flank hernias repaired at time of operation or are having an inguinal hernia repair along with another operation (e.g. laparoscopic cholecystectomy)

- End-stage renal disease (Creatinine clearance less than 30)
- Neuromuscular disease
- Prior adverse reactions to Sugammadex
- Patients who do not provide consent for the study

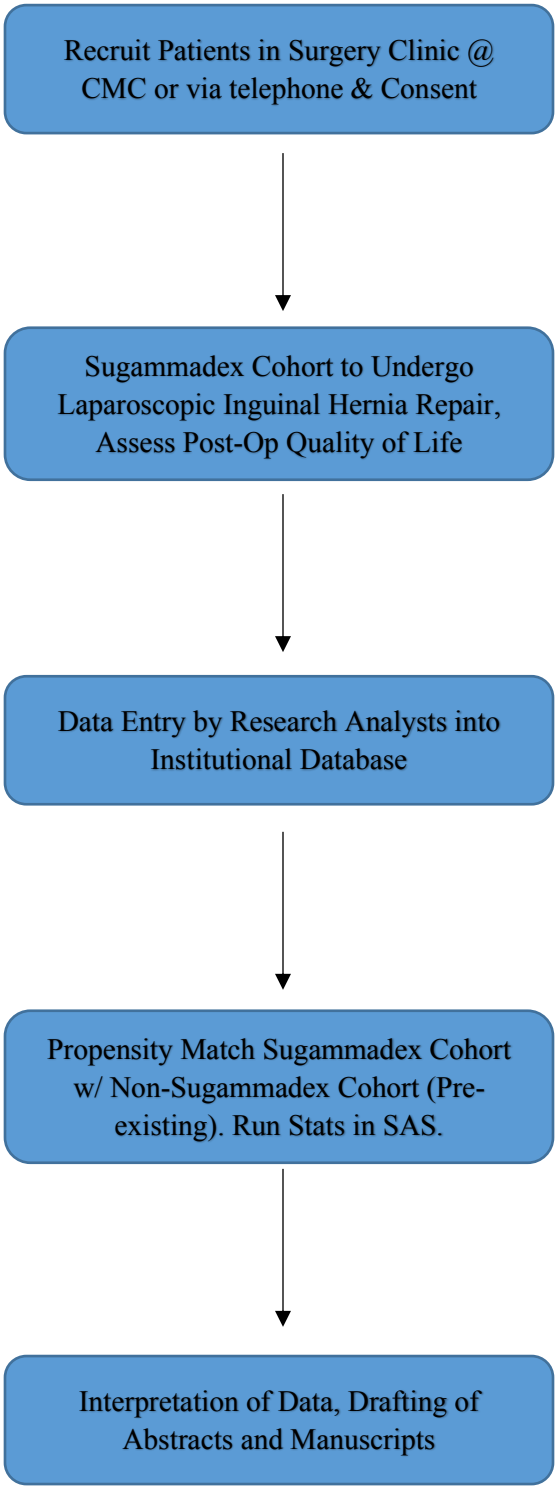
On the day of surgery, the research team will be present in the preoperative area and communicate directly with the anesthesia team that this is a patient who will be receiving Sugammadex; this communication is important because Sugammadex can only reverse vecuronium or rocuronium.[11] The Investigational Drug Service Department at Atrium Health will be notified the day before that there will be a patient included in the study the day prior to the operation. Their pharmacists will have the drug present for the anesthesiology team. This will not be a blinded study, so the anesthesia team and even the surgeon can know that the patient is receiving Sugammadex. In this study, patients will receive Sugammadex, in accordance with FDA approved labeling, following laparoscopic inguinal hernia repair and then be retrospectively matched against a group of patients who did not receive Sugammadex.

The definition that we will be using for urinary retention is the inability to void at six hours postoperatively which will be recorded in the postoperative recovery area and the same definition for urinary retention will be applied to the comparative retrospective cohort. Patients will be required to void prior to their discharge from the hospital. The requirement for urinary catheterization will be secondarily recorded. The details of the patient's operation, postoperative recovery, and potential admission encounter will be obtained and enter into the electronic health record into our pre-existing hernia database. Details about the cost to the patient will be obtained from a monthly billing statement that is generated for our department in Epic™ Systems. Patients will be seen in clinic postoperatively, typically within one to two weeks, and a quality of life questionnaire will be administered. This questionnaire is the same form that is typically used in our surgical clinics and will provide a means for retrospective comparison.

The data entry will be performed by two data analysts that are employed by our division. Once this data has been entered for all patients, our statistician will perform an analysis using Statistical

Analysis Software, version 9.4 (SAS Institute, Inc., Cary, NC) and send this data to the investigators for review. The principal investigator (PI) and co-investigators will be responsible for composing the abstracts and manuscript for this project.

Study Flow Chart (Overview):



Specific Drug Supply Requirements:

For the treatment group, 140 patients will require Sugammadex for reversal of their neuromuscular blockade. The dosing for Sugammadex is 4mg/kg for a deep reversal and a 2mg/kg for a standard reversal, which will be more common for this study. Sugammadex comes in 200mg/2mL and 500mg/5mL vials. Because of the variability in weight of the patients and the type of reversal needed (deep vs standard), 140 5mL vials will be required.

Study Duration:

Conservatively, the Division of Gastrointestinal and Minimally Invasive Surgery group performs five laparoscopic inguinal hernia repairs per week. A total of 140 patients will receive Sugammadex in the study. If all patients undergoing laparoscopic inguinal hernia repair agreed to participate in the study, then it would require 28 weeks for all patients to have surgery. Given that not all patients will not be agreeable to participation, and to allow time for statistical analysis, we estimate that 40 weeks will be required to complete the study.

Statistical Analysis and Sample Size Justification:

Variables/Time Points of Interest – Basic demographic information for each patient will be obtained from the medical record, such as age, gender, ASA class, and prior medical histories/surgeries. This information will aid in propensity matching for the study. The propensity match will be 1:1 with an equal number of patients in each group. The match will ensure that there is no statistical difference in data points between the groups and it will be performed by our statistician using SAS. The primary outcome variable, postoperative urinary retention, is a categorical variable (yes/no) that will be documented in postoperative recovery after the patient's operation. Length of stay and hospital cost, continuous variables, will be recorded at the completion of the patient's hospital stay. Information about quality of life will be obtained postoperatively in clinic. The demographic information, primary and secondary outcomes will be entered into our institutional database along with the other information that is typically recorded, such as operative characteristics and patient follow up.

Statistical Methods - Data will be analyzed using Statistical Analysis Software, version 9.4 (SAS Institute, Inc., Cary, NC); this task will be performed by the statistician employed by our division. Descriptive statistics will be reported as means with corresponding standard deviations for continuous variables and percentages for categorical variables. Continuous and ordinal variables will be evaluated with the Wilcoxon-Mann Whitney and the Kruskal-Wallis tests. The Wilcoxon-Mann Whitney test will be used when normality exists and there are two variables for comparison, otherwise, the Kruskal-Wallis test will be used. For categorical variables, a Pearson chi-square will be used, and a Fisher exact test will be utilized with a small sample size (i.e. less than five). A two-sided p-value of <0.05 will be used for all significance determinations.

Power/Sample Size – Using SAS, the power for our study was calculated using the postoperative urinary retention rate at our institution, 7%, compared to a current 0.5% postoperative urinary retention rate using Sugammadex. With 80% power, we would need to enroll 140 patients per group. The data for this project will be interpreted by the PI for the project as well as the co-investigators.

Risks and Benefits

The risk to the patient is minimal. Common side effects of Sugammadex are dizziness, tremor, lightheadedness, hypotension and tachycardia, but they are rare.[12] Patients will be excluded with renal disease or neuromuscular disease, which could be exacerbated by the use of Sugammadex. Women of childbearing age will be encouraged to use a second form of barrier contraceptive to prevent pregnancy. Adverse Experience Reporting will proceed in accordance with the policies and standards of Atrium Health. Patients in the study will be informed to report any adverse experiences related to this study directly to the research staff for the division. Reporting of such events can also be made directly to North Carolina Department of Health and Human Services.

Based on the limited amount of patients who have received Sugammadex to this point at CMC, we anticipate decreased rates of postoperative urinary retention. A decrease in urinary retention would be the main benefit for patients.

Confidentiality and Data Storage

Data will be collected electronically for this project and be stored on a secure server that is accessible only by password to the research team. Information for the study will be de-identified and names and medical record numbers will not be used in presentation or publication of the data. The data itself will be kept for a period of 5 years after study closure and destroyed by overwriting and deleting the file

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. Dr. Ronald Sing ((704) 355-3776) will serve as the DSMP for this study.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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