Postoperative urinary retention in hip and knee surgery after reversal of neuromuscular block by neostigmine or sugammadex: A randomized controlled trial

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The Sponsor- Investigator and trial statistician have approved the protocol version 13.0 (date 1/AUG/2022) and confirm hereby to conduct the study according to the protocol and the legally applicable requirements.

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Place/Date	Signature

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1. STUDY OBJECTIVES

1.1 Primary Aims & Hypothesis

Aim: To investigate postoperative urinary retention after hip and knee surgery in patients in whom neuromuscular blocks are reversed by sugammadex or neostigmine with glycopyrrolate.

Hypothesis: Post-void bladder volume 1 hour after surgery is smaller when neuromuscular blocks are reversed with sugammadex than neostigmine with glycopyrrolate.

1.2 Secondary Aims & Hypothesis

1.2.1 Urinary Retention Related

Aim: To investigate complications related to postoperative urinary retention after hip and knee surgery in patients in whom neuromuscular blocks are reversed by sugammadex or neostigmine. Complications of interest include need for a urinary catheter and development of urinary tract infections.

Hypothesis : Complications related to urinary retention are less common when neuromuscular blocks are reversed with sugammadex than neostigmine with glycopyrrolate.

2. BACKGROUND AND RATIO NALE

2.1 Background and Rationale

Neuromuscular blocking agents are widely used to facilitate endotracheal intubation, ease mechanical ventilation, and optimize surgical conditions.[1] Most surgical patients are therefore given a non-depolarizing neuromuscular blocking agents such as rocuronium or vecuronium.[2] Residual neuromuscular block at the end of surgery is common, occurring in up to 60% of patients, and is independently associated with postoperative morbidity and mortality.[3-6] It is therefore routine to pharmacologically antagonize or reverse neuromuscular blocking agents before extubation, usually by giving neostigmine or sugammadex.[7]

Neostigmine is a commonly used acetylcholinesterase inhibitor, which competitively antagonizes residual neuromuscular blockade by preventing metabolism of acetylcholine.[3] Because the competitive mechanism is limited, neostigmine only reliably reverses mild-to-moderate neuromuscular blocks. The anticholinesterase neostigmine is routinely co-administered with a muscarinic receptor antagonist such as glycopyrrolate or atropine to prevent bradycardia that would otherwise occur with elevated plasma acetylcholine concentrations. Sugammadex, in contrast, reverses neuromuscular blocks by encapsulating and binding rocuronium and vecuronium molecules.[8] The mechanism is effective and sugammadex provides complete and rapid reversal even from deep neuromuscular blocks.

Major complications in the post anesthesia care unit (PACU) are rare, but even minor complications contribute to increased morbidity and mortality.[5] Postoperative urinary retention, a potential serious complication, is reported in about 4% of patients having general surgery, but is far more common in patients who have leg surgery.[9,10]

Postoperative urinary retention requiring urethral catheterization is uncomfortable for patients and indwelling catheters markedly augment the risk of urinary tract infection (UTI).[11-13] Urinary catheters can provide an opportunity for gram negative bacterial infections that can lead to further urological and infectious manifestations (e.g. pyelonephritis, urosepsis, and death).[14] Catheter-related UTI is responsible for 13% of 100,000 nosocomial infection related deaths each year.[15] It affects about one million Americans annually and is a significant source of morbidity and mortality. It is the most common “preventable” nosocomial infection that accounts for over $400 million spent annually in the U.S. alone.[14,16] Bacteria causing the UTI can potentially hematogenous spread and lead to surgical site infection.[17] Bacterial seeding from UTI is a special concern after certain type of surgery, especially those with prosthetic hardware implanted. For instance, ample evidence relates UTIs with deep joint infection after orthopedic procedures which carries significant morbidity and financial costs.

Perioperative characteristics including the type of surgery – especially anorectal and pelvic surgery, or joint arthroplasties, type of anesthesia – especially neuraxial anesthesia, use and dose of anticholinergic drugs, and comorbidities are thought to increase the risk of postoperative urinary retention.[18-21] Additional potential causes for postoperative urinary retention include advanced patient age, diabetes mellitus, pre-operative voiding dysfunction, prolonged surgery, large amounts of intraoperative fluid,

perioperative use of opioids, and administration of anticholinergic medications.[10] Anticholinergics are routinely used during surgery for several indications including to decrease of oral secretions, treatment of bradycardia, and to antagonize the side effects of anticholinesterases used to reverse neuromuscular block at the end of the surgery. Anticholinergics have an inhibitory effect on bladder contraction in the presence of outlet obstruction, an affect achieved primarily by antagonizing post-junctional excitatory muscarinic receptors in the detrusor muscle, thereby promoting urinary retention.[22-24] After intravenous administration, the plasma half-life of neostigmine ranges from 24 to 113 minutes, with a mean elimination half-life of 80 ± 49 minutes (neostigmine FDA prescribing information, appendix 1).

Delirium is a common after surgery, and is associated with morbidity and mortality.[25-29] The reported incidence of delirium after major non-cardiac surgery is typically about 10%, and increases markedly as age increases beyond 65 years.[30] Even after adjustment for baseline factors, attributable costs associated with postoperative delirium are remarkable.[31] The pathophysiology of delirium is multifactorial.[32] Disturbances in neurotransmitters are postulated to be contributing factors. Acetylcholine plays an important role in neurocognition with decreased acetylcholinesterase activity in brain being associated with an increased risk of delirium.[33] Decreased endogenous acetylcholinesterase concentrations is a reliable predictor of postoperative delirium after hip and knee arthroplasty.[34] There is thus considerable reason to expect that administration of anticholinesterase medications to reverse neuromuscular blocks will promote delirium. Taking the pharmacokinetics of neostigmine into consideration (neostigmine FDA prescribing information, appendix 1), we would expect this effect to be the most prominent in the first hours after emergence while neostigmine plasma levels are the highest. A single small randomized trial reported that the use of sugammadex instead of neostigmine to reverse neuromuscular blocking agents in children decreased emergence agitation.[35] However, no randomized trial of sugammadex and neostigmine on emergence delirium in adults has been published.

Available evidence thus suggests that use of sugammadex instead of the anticholinesterase neostigmine and the routinely co-administered anticholinergic medication is likely to reduce postoperative urinary retention and related complications, as well as emergence delirium. An analysis of reversal strategy on urinary retention and emergence delirium in adults is therefore warranted.

2.2 Significance

The burden of urinary retention and subsequent complications on patients and the health care system is large. Delirium is also common, and imposes a substantial burden on patients and health care systems. It would be a considerable advance if a simple change in block reversal strategy, from neostigmine to sugammadex, prevented either or both complications.

3. STUDY DESIGN

3.1 General study design

We propose a randomized trial comparing sugammadex and neostigmine for the reversal of neuromuscular blocks induced by rocuronium or vecuronium in adults having general anesthesia with muscular block for hip and knee orthopedic surgery. The primary outcome will be urinary retention 1 hour after surgery. Secondary outcomes will be complications related to urinary retention and emergence delirium.

3.1.1 Randomization

Patient will be randomly assigned (1:1 block randomization, stratified for knee or hip surgery) to neuromuscular block reversal with neostigmine vs. sugammadex. Randomization will be web based, and accessed through Redcap after induction of anesthesia. Allocation will thus be concealed as long as practical.

3.1.2 Blinding procedures

Patients will be blinded, but anesthesiologists will not be. Postoperative assessments will be evaluated by an independent team of investigators who will be unaware of randomization or actual block reversal strategy. All post-discharge assessments will be made by investigators blinded to randomization and treatment; adjudicators will be similarly masked. The trial will thus be patient, assessor, and adjudicator blinded.

3.2 STUDY POPULATION

3.2.1 Eligibility criteria

There will be no restriction on sex, race, or ethnicity; all qualifying patients will be asked to consider the trial. We will restrict this trial to adults having hip or knee arthroplasties with general anesthesia that require neuromuscular blocks at the Cleveland Clinic, Main Campus.

The study sample will focus on an at risk population. Orthopedic joint surgery on the lower extremity is a precipitating factor for urinary retention. To increase external validity, we do not restrict the study population to a single joint and will thus enroll both hip and knee arthroplasties. Patients at the Cleveland Clinic Main Campus are generally elderly and have various comorbidities, which also are risk factors for postoperative urinary retention. They are typically hospitalized for 2-3 days postoperatively.

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Informed Consent as documented by signature;
- Adults having orthopedic surgery on the lower extremity with expected surgery duration ≥ 2 hours;
- General anesthesia requiring endotracheal intubation and neuromuscular block with rocuronium or vecuronium;
- Planned administration of sugammadex or neostigmine for reversal of the neuromuscular block at the end of surgery;
- American Society of Anesthesiologists (ASA) physical status 1-3.

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Contraindications to the class of drugs under study;
- Preoperative urinary catheter;
- Planned intraoperative insertion of a urinary catheter;
- Planned postoperative admission to the ICU;
- Severe preoperative hepatic impairment (≥3 times increase in aspartate aminotransferase or alanine aminotransferase as per reference range) or renal impairment (estimated GFR < 30 ml/min or end-stage renal disease requiring scheduled dialysis.);
- History of bladder cancer;
- Presence of a sacral nerve stimulator;
- Current use of anticholinergic medications such as antihistamines, phenothiazines, antidepressants or antipsychotics;
- Urinary tract infections or other urogenital comorbidity (incontinence, cysto-ureteric reflux, known bladder retention) or conditions which promote urinary retention;
- Known or suspected neurological conditions such as Alzheimer's disease, stroke, poliomyelitis, cerebral palsy, multiple sclerosis, spinal lesions, or Parkinson's disease.

3.2.2 Recruitment and screening

Participants will be evaluated for eligibility by investigators during the preoperative anesthesia consultation. Patients will be given the option to review the informed consent form for at least a full day, if they wish to do so. Written consent will be obtained. Participants will not receive any compensation for their participation.

4. STUDY PROCEDURES

4.1 Table of study procedures and assessments

	Screening (-30 days up to surgery)	Day 0 Surgery (Visit 1)	Day 0 PACU (Visit 2)	Day 0 ward (Visit 3)	POD 1 (Visit 4, 5)
Informed Consent	✓				
Questions and review of medical record - demographics, medical, social and education	✓	✓			✓
Randomization		✓			
Post-void residual		✓[1]	✓[2]	✓	✓
3D-CAM questionnaire		✓[1]	✓	✓	✓
Abdominal discomfort		✓[1]	✓	✓	✓

[1] Baseline assessment in the preoperative area

[2] Primary Endpoint

4.2 Protocol

All patients will be asked to void before they are transferred to the operating room. Patients will be seen shortly before anesthetic induction (baseline, Visit 1). As this is a pragmatic trial, no restrictions to anesthetic management other than the random allocation to sugammadex or neostigmine are planned.

As part of local standards, it is recommended to maintain a moderate block of 1 to 2 twitch responses to train-of-four (TOF) stimulation throughout surgery. Further, local standards on pain management include a single shot adductor canal block with a long acting local anesthetic with possibility of adding a catheter for knee surgery. Hip surgeries may receive a fascia iliaca block, if pain is severe.

Randomized treatments will be implemented by clinicians in collaboration with research personnel. Patients will be randomized shortly before the reversal of the neuromuscular block. At the time of randomization the administration of either neostigmine or sugammadex need to be possible. If e.g. the neuromuscular block is too deep to be reversed with neostigmine, patients will not be randomized and excluded from the study.

The anesthesiologist in charge will be informed on the patient's allocation to either the sugammadex or neostigmine group by an unblinded investigator. Patients will be monitored for twitch responses towards the end of surgery to determine the timing and dose for the reversal agent. The twitch response will be measured using a quantitative, acceleromyographic monitoring device. For sugammadex, 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to (TOF) stimulation. Alternatively, 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation. In the neostigmine group, neostigmine 2.5 mg with glycopyrrolate 0.5 mg will be administered as an initial dose. Neostigmine and glycopyrrolate are to be administered in a fixed ratio, and only if the second twitch in response to TOF stimulation has appeared. The initial dose can be repeated up to a ceiling dose of 5 mg neostigmine with 1 mg of glycopyrrolate. However, the final decision of the dose will be up to the attending anesthesiologist. The administered dose will be recorded. All patients are required to have a documented TOF ratio > 0.9 before extubation

Visit 2 is one hour after surgery in the post anesthesia care unit (PACU). The third Visit is within 4 to 6 hours after surgery on the regular ward. Visit 4 and 5 will be in the morning and afternoon of the first day after surgery (postoperative day (POD) 1). Visit 5 on the afternoon of POD 1 will be the last follow-up and the end of a patient's participation in the study. Thereafter, data will be recorded from electronical medical records until POD 4 or discharge, whichever comes first.

4.3 Measurements

4.3.1 Assessment of primary outcome

Post-void residual volume will be measured by ultrasound bladder scan after patients spontaneously void. Voiding can be into a urinal, bedpan, or toilet per patient ability and preference. There is a good correlation between the volumes measured by bladder catheterization and by ultrasound.[36]

Residual post-void urine will be measured with ultrasound on:

- Visit 1: before surgery (baseline assessment in preoperative area right before surgery);
- Visit 2: in the PACU around 1 hour after extubation;
- Visit 3: within 4-6 hours after end of surgery on the regular ward;
- Visit 4 and 5: in the morning and afternoon of the first day after surgery.

Residual volume will be measured within 30 minutes after urination using the battery-powered, portable Bladder scan BVI 3000 (Verathon, Bothell, WA, USA). If a patient - despite his or her best efforts - cannot adequately void at the time of the visit, the urine volume will be measured as such and recorded as post void because the patient gave his or her best effort to void. The BVI 3000 shows high correlation between measurements (intraclass correlation coefficient 0.95) and a mean difference from the true residual volume by less than 4 ml.[37]

The scanner will be placed on the suprapubic area and held stationary during measurement scanning. The diameter of the bladder and volume of urine will be calculated from the scan data. Scans will be repeated three times to ensure accuracy in measurements, with only one volume (the average of the three measurements) being recorded for each visit. The average of the measurements at each measurement time will be analyzed. All clinical procedures will be performed by trained physician investigators. Surgical team will be blinded to volume determined by scanning and we will also record if they had ordered indwelling catheterization.

For visit 1 it will also be assessed when the patient's last intake of fluids was. Per local standards patients are allowed to drink clear fluids up to 2 hours before surgery.

4.3.2 Assessment of secondary outcomes

4.3.2.1 Catheterization

A fraction of patients requiring bladder catheterization within 24 hours after surgery. Per institutional policy, a bladder catheter is inserted in patients with a post-void urine volume > 300 ml as requested by surgeons. Based on results from a previous randomized trial in the same population, we expect the incidence of postoperative catheterization to be 15%.[38] This will be assessed on an ongoing basis during the patients' enrollment in the trial.

4.3.2.2 Urinary tract infections during hospitalization

A urinary tract infection with (Catheter-Associated Urinary Tract Infection, CAUTI) or without (urinary tract infection, UTI) indwelling catheter will be recorded based one of the following criteria:

- Organisms isolated from an aseptically obtained urine culture
- Diagnosis of a urinary tract infection by a surgeon or attending physician.

This will be assessed on an ongoing basis during the patients' enrollment in the trial.

4.3.3 Asses sment of exploratory outcom es

4.3.3.1 Emergence Delirium

Baseline for delirium will be assessed in the preoperative are as part of Visit 1. Patients with a positive delirium test at baseline will be excluded from this exploratory analysis. Emergence delirium then will be evaluated directly after surgery in the PACU and on the ward (Visit 2 & 3).

There is no validated tool available to specifically assess emergence delirium, but other general delirium screening tools have been used in this context.[39] We will use the 3D-CAM (Appendix) which is based on a three-minute questionnaire, and has a sensitivity of 95% (95% CI, 84, 99), and specificity of 94% (CI: 90, 97) compared with formal psychometric evaluation.[40] The 3D-CAM also shows excellent inter-rater agreement of 95%.[40] The test works well in patients with dementia.[40] Delirium will be assessed by investigators trained in the methods. Any positive CAM test will be considered evidence of delirium which will be analyzed dichotomously.

Immediately before assessing delirium, patients will be evaluated for sedation and agitation with the Richmond Agitation and Sedation Scale (RASS). Scores ranging from –5 (unarousable) to +4 (combative), with 0 indicating alert and calm.[41] When patients are deeply sedated or unarousable (RASS –4 or –5), delirium will not be assessed and the patient recorded as comatose. The RASS score will be recorded.

4.3.3.2 Ward Delirium

Baseline for delirium will be assessed in the preoperative are as part of Visit 1. Patients with a positive delirium test at baseline will be excluded from this exploratory analysis. Ward delirium will be formally assessed in the morning and evening on POD 1 (Visit 4 & 5) using the 3D-CAM. Thereafter formal assessment by study personnel will conclude. Delirium will continue to be assessed per routine by ward nurses until POD 4 or discharge. The hospital's caregivers on regular wards do asses delirium daily with the Brief Confusion Assessment Method (bCAM). Observed delirium at other times will be recorded and considered as an outcome. Any positive CAM test will be considered evidence of delirium which will be analyzed dichotomously.

4.3.3.3 Abdominal discomfort

Abdominal patient discomfort / pain likely associated with urinary retention will be assessed by the use of a numeric rating scale (NRS), specific to bladder pain (e.g. "Do you feel pain, discomfort or pressure in your lower abdomen, where your bladder is located?"). Patients will be asked to communicate a number between 0 and 10 that fits best to their pain intensity, with 0 representing 'no pain or discomfort at all' and 10 'the worst imaginable pain'. After a baseline assessment on Visit 1, this will be assessed on Visits 2 to 5.

4.3.3.4 Time to PACU discharge

The time to PACU discharge will be assessed and is defined as time from extubation to readiness for discharge from PACU. Readiness for PACU discharge is determined by the treating physician and will be noted as the time the discharge order is submitted.

4.3.4 Assessment of other outcomes of interest

4.3.4.1 Baseline data

Demographic data will be obtained during screening and Visit 1 and includes height (cm), weight (kg), age (yr), gender, physical status (ASA), and self-declared ethnicity. Patients will be questioned for social history (tobacco) and medical history (pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, illegal drug usage, alcohol abuse, myocardial infarction, previous surgery or stent placement and medications usage).

The most recent baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including creatinine, estimated glomerular filtration rate, sodium, potassium, C-reactive protein and hemoglobin.

4.3.4.2 Data obtained from electronic medical records

Data obtained from electronic medical records will include: operation time, surgery type, all intraoperatively administered medications, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of oxygen in PACU and ward, nausea and vomiting, requirement of antiemetics, ambulation time and length of stay. Preoperative and postoperative laboratory data relevant to postoperative kidney function or urinary tract infection will also be collected from electronic medical records.

4.3.5 Assessment of safety outcomes

Adverse events and serious adverse events occurring at any time during the study period will be recorded on a specific form in the CRF.

5. STATISTICAL METHODS

5.1 Hypothesis

The primary hypothesis is that post-void bladder volume 1 hour after surgery is smaller when neuromuscular blocks are reversed with sugammadex than neostigmine.

A 40% reduction and a difference of at least 50 ml in post-void urine volume will be considered clinically meaningful if the data appears normal.[38] A mean ratio of 0.7 will be considered a smallest clinically meaningful effect size since we expect the post-void urine volume will not be normally distributed.

5.2 Determination of Sample Size

The sample size calculation is based on expecting the data will not be normal. Based on a previous randomized clinical trial investigating the post-void urine volume in surgical patients in the morning of postoperative day 1, the urine residual had an observed coefficient of variation (CV) of 1.2.[38] The coefficient of variation is a measure of relative variation, which is defined by the ratio of standard deviation and mean where higher CV means higher relative variation. With a sample size of 286 we have a power of 0.9 at a type one error level of 0.05 to detect a minimum clinical meaningful mean ratio of 0.70 for the primary outcome.

5.3 Planned Analyses

5.3.1 Datasets to be analyzed , analysis populations

The analysis will be based on modified intent-to-treat rule, where patients received at least some intervention will be included in the analysis and patients will be analyzed based on their randomization regardless what actual treatment they received. The treatment and control group will be compared for balance on baseline characteristics using standard descriptive statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%) as appropriate) and standardized difference. If there are any characteristics that has standardized difference larger than 0.1 will be additionally adjusted for as a sensitivity analysis.

If the randomization has stratification, the stratification factor will be adjusted in the following analyses.

5.3.2 Primary Analysis

The primary outcome is the urine residual at visit 2 (PACU after surgery). If the data is normal, a two-sample t test would be conducted to test the mean difference. If the data is not normal, a log transformation would be applied and a simple regression would be conducted to estimate the geometric mean ratio. As a sensitivity analysis, a Wilcoxon signed-rank test would be conducted. Any imbalanced baseline characteristics would be additionally adjusted as a sensitivity analysis too. The significance level for primary analysis is 0.05.

5.3.3 Secondary Analyses

For the binary secondary outcomes: (1) need for urine catheter within 24 hours after surgery (2) urinary infection during the hospitalization and (3) emergence delirium, a Chi-square test would be conducted to see if the incidence of each corresponding outcome is different across groups. The relative risk would be estimated with a confidence interval. For the continuous secondary outcome, quality of recovery score, a 2 sample t-test or Wilcoxon-sighed rank test would be done to compare the groups depending on the normality. The significance level for each test will be 0.05/3 = 0.017 after Bonferroni correction for multiple testing.

5.3.4 Exploratory analysis

For the exploratory outcomes abdominal pain and discomfort, the scores will be summarized in median [Q1, Q3] or mean (SD) depending on the normality at each visit from 1-5 by groups. For ward delirium incidence will be shown as number and percentage for both groups. If a patient has a positive delirium assessment at baseline, this patient will be excluded from both delirium related analyses. No formal testing will be conducted in exploratory analysis.

SAS software version 9.4 for Windows (SAS Institute, Cary, NC) or R studio will be used for all statistical analyses and graphics. All the analyses will be done by an assigned biostatistician in Outcome Research.

5.4 Handling of missing data a nd drop -outs

The missing pattern will mainly be explored for primary outcome. For the primary outcome, if the missing

proportion is below 5%, an imputation would be conducted using worst and best scenario in addition to the complete case analysis. If the missing proportion is between 5%-10%, a multiple imputation would be conducted in addition to complete case analysis if no sign of obvious missing not at random. For the secondary outcomes, we would explore the missing proportion and pattern, if missing is below 10% and it is reasonable to assume missing at random, a complete case analysis will be done. If missing is above 10%, imputation could be used with caution as a sensitivity analysis.

6. DRUG REQUIREMENTS

6.1 Identity and Administration of Investigational Products

BRIDION 2-mL single-dose vials containing 200 mg sugammadex (100 mg/mL) for intravenous injection is U.S. FDA approved for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery (FDA Reference ID: 3860969). It is manufactured by Merck & Co., Inc (Whitehouse Station, NJ, USA). Its properties and clinical evidence to date are described in the FDA Prescribing Information (appendix 2). Sugammadex will be administered according to the local standards.

Neostigmine is widely used cholinesterase inhibitor used to reverse the effects of muscle relaxants. It is FDA approved in different forms and doses. It will be given according to local standards.

6.2 Packaging, Labelling and Supply

Both study drugs used are commercial ware. No special packaging or labelling is planned as the anesthesiologist in charge who is administering the drug will not be blinded to the intervention. Supplies will be kept in a secure, limited access storage area according to the Cleveland Clinic's Anesthesiology Institute's standards for storage conditions. As all study drugs are being handled as standard commercial ware, no special drug accountability measures are planned.

Merck & Co., Inc will be asked to provide the study drug for the 145 patients in the sugammadex group. These will also be supplied as standard commercial ware, without special packaging or labelling.

7. ADVERSE EXPERIENCE REPORTING

During the entire duration of the study, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: is life-threatening; or requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect; or is a medically important event.

Suspected unexpected serious adverse reactions (SUSARs) are events that meet the following criteria: 1) suspected to be causally associated with sugammadex or neostigmine; 2) unexpected if the nature, severity, or outcome of the reaction(s) is not consistent with the reference information (i.e., product monograph for trial drugs); 3) serious (as defined above for an SAE); and 4) not a defined efficacy.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions), will not be regarded as SAEs. This pertains also to hospitalizations which are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study (e.g., patient returning to the hospital for chemotherapy), and which did not result in a worsening of the disease.

All SAEs need to be reported within 48 hours of knowledge of the event to the Sponsor-Investigator. For such events, research personnel will complete an SAE CRF in the database. The Sponsor-Investigator will then inform regulatory authorities in a timely manner, as necessary, according to the applicable regulations.

8. PUBLICATION AND DISS EMINATION POLICY

After the statistical analysis of this study, the Sponsor will make every endeavor to publish the data in a medical journal. The primary outcome combined with urinary retention related secondary outcomes will be evaluated and published separately from the delirium secondary outcome.

Some preliminary data may be presented as an abstract or oral presentation at a national or international conference.

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10. APPENDICES

1. Prescribing Information for neostigmine
2. Prescribing Information for sugammadex
3. 3D CAM delirium assessment
4. RASS sedation assessment

Summary of the revision history in case of amendments after IRB approval

Version Nr, Version Date	**Chapter**	**Description of change**	**Reason for the change**