The effect of deep neuromuscular blockade with Sugammadex reversal on shoulder pain of elderly patients undergoing Robotic Prostatectomy: A single-center double-blinded randomized controlled trial

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The effect of deep neuromuscular blockade with Sugammadex reversal on shoulder pain of elderly patients undergoing Robotic Prostatectomy: A single-center double-blinded randomized controlled trial	
Objectives	**Primary:** To compare the effect of deep neuromuscular blockade with Sugammadex reversal versus moderate neuromuscular blockade with neostigmine reversal (standard of care) on postoperative shoulder pain. **Secondary:** To assess the effect of deep neuromuscular blockade with Sugammadex reversal versus moderate neuromuscular blockade with neostigmine reversal on intraoperative insufflation pressures, perioperative recovery and morbidity for robotic prostatectomy.
Hypothesis	1. Elderly patients undergoing robotic prostatectomy who receive continuous deep neuromuscular blockade and its reversal with Sugammadex will have adequate surgical exposure with lower insufflation pressures which will be associated with lower postoperative shoulder pain, less morbidity and a faster recovery when compared to patients receiving moderate neuromuscular blockade. 2. The adoption of continuous deep neuromuscular blockade combined with lower insufflation pressures during robotic prostatectomy will have the most significant effects for patients with multiple comorbidities, such as obesity, age greater than 65, history of congestive heart failure, chronic obstructive pulmonary disease, chronic renal insufficiency, diabetes mellitus, peripheral vascular disease and sarcopenia.
Study Design	Single-center randomized controlled double-blind trial. Patients will receive either the Deep Neuromuscular Blockade (DNMB group) with Sugammadex reversal or Moderate Neuromuscular Blockade (MNMB group) with neostigmine reversal.
Number of Patients	100
Site	M. D. Anderson Cancer Center
Duration of Study	December 2017 to December 2019
Duration of Patient Participation	Until postoperative day 7 or discharge
Primary Endpoints	Incidence of postoperative shoulder pain

Secondary Endpoints	1. Quantitative grading of Shoulder Pain using Visual Analog Scale (VAS) for pain score 2. Cumulative intraoperative insufflation pressure (mmHg min) during the surgery 3. Subjective grading of quality of surgical exposure expressed by surgeon at end of case using Surgical Rating Scale (Martini, Boon, Bevers, Aarts, & Dahan, 2013) 4. Readiness to discharge from the PACU as determined by a modified version of the DASAIM discharge criteria scoring system to be completed at 15, 45 and 90 minutes after admission to the PACU 5. Degree of PONV per Visual Analog Scale and number of episodes of emesis per nurse in PACU 6. Length of ICU & Hospital stay, 30-Day Mortality and Readmission Rate 7. Measures of organ dysfunction and perfusion by the Postoperative Morbidity Survey (De novo need for oxygen supplementation, ability to tolerate an enteral diet, oliguria or Acute Kidney Injury, Delirium or new neurological deficits) and postoperative lactate Exploratory Outcomes: 1. Optional: Incidence of residual muscle relaxation upon admission to PACU as defined by TOF ratio <0.9, if TOF-Watch® SX is available 2. Optional: Subgroup analysis on elderly patients with comorbidities including laboratory evidence of sarcopenia (creatinine/cystatin c ratio)
Inclusion Criteria	1. Patients 65 years of age or older 2. Patients having robotic prostatectomy 3. Written informed consent
Exclusion Criteria	1. Patient with known hypersensitivity to Rocuronium, Sugammadex or its components 2. Patients with severe renal insufficiency, defined and confirmed by an estimated creatinine clearance equal or lower than 30 mL/min 3. Patients with history of severe liver disease, defined as and confirmed by elevated ALT and AST greater than 1.5 times the Upper Limit of Normal along with Albumin less than 3 OR INR 1.5 or greater per institutional laboratory.

1. Background

Along with other minimally invasive techniques, the use of robotic laparoscopic surgical techniques require smaller incision sites, are often associated with lower intraoperative blood loss, postoperative pain and shorter recovery when compared with open techniques. (O'Neil, et al., 2016) (Sert, et al., 2016) The use of **insufflation pressure** (IP) required to maintain adequate pneumoperitoneum during robotic surgery can have numerous deleterious effects that are directly correlated with higher pressures (10-15 mmHg or more). These effects include lower respiratory compliance and higher inspiratory pressures, impaired cardiac function, systemic and portal venous stasis, hypercoagulopathy, decreased urine output, decreased organ perfusion and postoperative pain. Shoulder pain is common following laparoscopic abdominal surgery and is thought to be caused by irritation of the diaphragm by the carbon dioxide used for abdominal insufflation. (Fredman, Jedeikin, Olsfanger, Flor, & Gruzman, 1994) The intraoperative maintenance of deep **neuromuscular blockade** (NMB) has the advantage of potentially decreasing the insufflation pressure required by the surgeon to maintain adequate visualization. (Staehr-Rye, et al., 2014) (Koo, et al., 2016) (Kim, Lee, Lee, Min, & Yoo, 2016) By lowering the patients' cumulative exposure to pressurized carbon dioxide pneumoperitoneum, it is possible to decrease the incidence of shoulder pain during the recovery period. (Kim, Lee, Lee, Min, & Yoo, 2016) (Madsen, et al., 2016) Historically, the practice of maintaining deep continuous neuromuscular blockade was limited because excessive NMB would prevent timely extubation of the patient at the end of surgery.

Several studies have demonstrated decreased morbidity from laparoscopic surgery with the use of deep neuromuscular blockade (DNMB). Using data from laparoscopic colorectal surgery, patients in the DNMB vs. moderate NMB (MNMB) group had IP of 9.3 +/- 1.3 vs. 12.0 +/- 0.5 mmHg group respectively. The DNMB group had lower Numeric Rating Scale (NRS) pain scores [2.3(0.6) to 2.9(0.3)], incidence of shoulder pain (3.3% to 25.8%; a reduction of 87%) Gas Passing Time in hours [40(11.3) to 64(31)] and estimated blood loss (20.2 +/- 13.7 vs 60 +/- 95.3 mL). (Kim, Lee, Lee, Min, & Yoo, 2016) In another study which focused on 99 patients undergoing laparoscopic hysterectomy, 28.6% of the DNMB group (IP 8mmHg) vs. 60% in the MNMB group (IP 12mmHg) experienced shoulder pain. (Madsen, et al., 2016) Robotic surgery may differ from conventional laparoscopic surgery in that the duration of surgery is often more prolonged and the patient may be maintained in different positions (steep Trendelenburg or reverse Trendelenburg), both of which may increase the physiologic effects of pneumoperitoneum.

Sugammadex is a gamma cyclodextrin which directly encapsulates steroid NMB agents such as Vecuronium and Rocuronium thus allowing for safe, rapid and more complete reversal of muscular paralysis. (Flockton, et al., 2008) (Geldner, et al., 2012) With the use of Sugammadex, it is now possible to maintain a continuously deep level of muscular relaxation while also extubating the patient at the end of the operation in a safe and efficient manner. (Carron, Baratto, & Ori, 2016) (Ledowski, et al., 2014) (Duvaldestin, et al., 2010)

The Train of Four (TOF) ratio (or TOFR) is a technique for monitoring the degree of blockade by non-depolarizing neuromuscular blocking agents at the nicotinic acetylcholine receptors (neuromuscular junction). An electrical stimulus is applied by transcutaneous nerve stimulator as a group of four stimuli. The quantity and quality of muscular response to nerve stimulation correlates with the degree of neuromuscular blockade. The number of muscular responses to stimulation (TOF count) of 4, 3, 2 and 1 correlates with approximately 75%, 85%, 90% and 95% neuromuscular blockade. The TOF ratio of T4/T1 is a more objective and sensitive method to quantify the degree of neuromuscular blockade calculated by comparing the strength of muscular response of the last TOF stimuli compared to the first. It was previously thought that a

TOFR greater than 0.7 indicated sufficient neuromuscular recovery for extubation. Evidence now suggests that one can have an increased risk of upper airway obstruction and aspiration due to residual neuromuscular blockade with a TOFR less than 0.9, though more prospective studies are needed.

Elderly patients compared to the general population may receive more benefit from the reversal of NMB with Sugammadex as opposed to neostigmine but more prospective studies are needed. In a large retrospective study of 1444 patients, those who had an age greater than 60 and an ASA score of 3 or 4 had a small but significantly higher incidence of postoperative pulmonary complications when treated with neostigmine compared to Sugammadex. (Ledowski, et al., 2014) Additional investigation may identify subgroups within the elderly population who are the highest risk for complications of elevated insufflation pressures or residual neuromuscular blockade.

While there is no universal age which defines the elderly, we chose the age of 65 years or greater to be our threshold based on the Phase 3 trial which demonstrated the safety and efficacy of Sugammadex in the elderly population. Overall, 150 patients were treated and had at least one post-baseline efficacy assessment; 48 were aged 18-64 yr (adult), 62 were aged 65-74 yr (elderly), and 40 were aged 75 yr or older (old-elderly). The geometric mean time (95% confidence interval) from Sugammadex administration to recovery of the TOF ratio to 0.9 increased with age, from 2.3 (2.0-2.6) min (adults) to 2.9 (2.7-3.2) min (elderly/old-elderly groups combined). Recovery of the TOF ratio to 0.9 was estimated to be 0.7 min faster in adults compared with patients aged 65 yr or older ($P = 0.022$). Sugammadex was well tolerated by all patients. (McDonagh DL, 2011)

One possible subgroup that may receive the greatest benefit from the use of Sugammadex are cancer patients with sarcopenia and sarcopenic obesity. Cancer cachexia affects 60-80% of patients with advanced cancer and is associated with increased morbidity and mortality. (Baracos, 2011) Though criteria for cancer cachexia has traditionally varied, an international panel of cachexia experts recently agreed upon a common definition which includes recent weight loss, BMI and sarcopenia. Among 1,077 cancer patients, those classified as cachectic, as defined by weight loss greater than 5% over the last 6 months or greater than 2% with a BMI less than 20 kg/m2, had a shorter median survival than for non-cachectic patients. (139 versus 269 days; $P < 0.001$) (Blum, 2014) Among cancer patients to receive chemotherapy, those with sarcopenia had a mortality hazard ratio of 5.19 when controlled for BMI, age and tumor stage. (Gonzalez, 2014)

A laboratory indicator of sarcopenia is the creatinine to cystatin c ratio, which can account for the majority of individual variability of total body muscle mass and has been used to detect sarcopenia and sarcopenic obesity. (Kim, et al., 2016) Cystatin C also has greater prognostic value than creatinine. (K Suzuki, 2015) (Y Otaki, 2015) (Graf, 2015) (Wannamethee, 2015)

The Postoperative Morbidity survey is a 9-point scale used to systematically assess short-term morbidity and multi-organ dysfunction following surgery. (Bennett-Guerrero, et al., 1999) (Davies, et al., 2013) It has been shown to have good reliability and validity with an association with greater hospital length of stay in the general population and increased mortality in the elderly. (Howes, et al., 2015)

2. Hypotheses

2.1 Elderly patients undergoing robotic prostatectomy who receive continuous deep neuromuscular blockade and its reversal with Sugammadex will have adequate surgical exposure with lower insufflation pressures which will be associated with lower postoperative shoulder pain, less morbidity and a faster recovery when compared to patients receiving moderate neuromuscular blockade.

2.2 The adoption of continuous deep neuromuscular blockade combined with lower insufflation pressures during robotic prostatectomy will have the most significant effects for patients with multiple comorbidities, such as obesity, age greater than 65, history of congestive heart failure, chronic obstructive pulmonary disease, chronic renal insufficiency, diabetes mellitus, peripheral vascular disease and sarcopenia.

3. Objectives

3.1 Primary: To compare the effect of deep neuromuscular blockade with Sugammadex reversal versus moderate neuromuscular blockade with neostigmine reversal (standard of care) on postoperative shoulder pain.

3.2 Secondary: To assess the effect of deep neuromuscular blockade with Sugammadex reversal versus moderate neuromuscular blockade with neostigmine reversal on intraoperative insufflation pressures, perioperative recovery and morbidity for robotic prostatectomy.

4. Study Design

4.1. Primary Outcome

Incidence of postoperative shoulder pain

4.2. Secondary Outcomes

4.2.1 Quantitative grading of Shoulder Pain using Visual Analog Scale (VAS) for pain score

4.2.2 Cumulative intraoperative insufflation pressure (mmHg min) during the surgery

4.2.3 Subjective grading of quality of surgical exposure expressed by surgeon at end of case using Surgical Rating Scale (Martini, Boon, Bevers, Aarts, & Dahan, 2013)

4.2.4 Readiness to discharge from the Post-Anesthesia Care Unit (PACU) as determined by a modified version of the Dansk Selskab for Anæstesiologi og Intensiv Medicin (DASAIM) discharge criteria scoring system to be completed at 15, 45 and 90 minutes after admission to the PACU

4.2.5 Degree of Post-Operative Nausea and Vomiting (PONV) per Visual Analog Scale and number of episodes of emesis per nurse in PACU

4.2.6 Length of Intensive Care Unit (ICU) & Hospital stay, 30-Day Mortality and Readmission Rate

4.2.7 Measures of organ dysfunction and perfusion by the Postoperative Morbidity Survey (De novo need for oxygen supplementation, ability to tolerate an enteral diet, oliguria or Acute Kidney Injury, Delirium or new neurological deficits) and postoperative lactate

4.3. Exploratory Outcomes

4.3.1. Optional: Incidence of residual muscle relaxation upon admission to PACU as defined by Train-Of-Four (TOF) ratio <0.9, if TOF-Watch® SX is available

4.3.2. Optional: Subgroup analysis on elderly patients with comorbidities including laboratory evidence of sarcopenia (creatinine/cystatin c ratio)

4.4. Design

Single-center randomized controlled double-blind trial. Patients will be randomized to receive either the Deep Neuromuscular Blockade (DNMB group) or Moderate Neuromuscular Blockade (MNMB group).

4.5. Eligibility

4.5.1. Inclusion Criteria:

- Patients 65 years of age or older
- Patients having robotic prostatectomy
- Written informed consent

4.5.2. Exclusion Criteria:

- Patient with known hypersensitivity to Rocuronium, Sugammadex or its components
- Patients with severe renal insufficiency, defined and confirmed by an estimated creatinine clearance equal or lower than 30 mL/min, per institutional laboratory.
- Patients with history of severe liver disease, defined as and confirmed by elevated ALT and AST greater than 1.5 times the Upper Limit of Normal along with Albumin less than 3 **OR** INR 1.5 or greater per institutional laboratory.

Patients will be identified when scheduled for Robotic Prostatectomy. Eligible subjects will be approached before scheduled surgery to obtain Informed Consent. Consent will be obtained by Investigator, Co-Investigator and/or Collaborators; the process will be documented in EPIC.

After Informed Consent is obtained, we will collect Demographics, Laboratory Test results of interest for the study, Concomitant Medications taken within 30 days prior surgery and Neoadjuvant Chemotherapy if any.

4.6. Randomization

Once it has been determined that the patient meets all eligibility criteria, they will be randomized on a 1:1 ratio for Deep Neuromuscular Blockade and Sugammadex or Moderate Neuromuscular Blockade and neostigmine administration. Randomization will be done the morning of surgery by using REDCap randomization tool.

4.7. Blinding, Allocation and Concealment

Patients and TOF-watch assessors will be blinded to the study drug. The assessor of the primary outcome will not be involved in randomization, or allowed in the operating room during surgery. Anesthesiologists will not be blinded to study drug but he/she will be blinded to the TOF watch response. The surgeon and PACU staff will be blinded to the group assignment.

4.8. Sample Size Justifications

For 99 patients undergoing laparoscopic hysterectomy, 28.6% of the DNMB group (IP 8mmHg) vs. 60% in the MNMB group (IP 12mmHg) experienced shoulder pain. (Madsen, et al., 2016)

Using the data from the aforementioned study, a sample size of 48 per group will enable the study 88% power to detect the decrease in the rate of postoperative shoulder pain from 60% for the control group to 28.6% for the group with deep Neuromuscular Blockade and Sugammadex, assuming a two-sided type I error rate of 0.05 using a two-group Chi-square test (nQuery Advisor 7.0). Postoperative shoulder pain is defined as any shoulder pain recorded before the discharge from PACU. We predict that the typically increased length of robotic surgery in combination with potentially lower insufflation pressures (6-7mmHg) may result in an even greater difference between the two groups. We want to factor in a 4% drop-out rate, therefore, we will enroll a total of 100 patients.

4.9. Analysis Plans

Patients' demographic information, laboratory test results and concomitant medications, including neoadjuvant chemotherapy at baseline will be analyzed, with data summarized in tables listing the distributions of the variables along with the number of subjects per treatment arm in order to assess comparability. Patients' information on post-operative shoulder pain, nausea, vomiting, intubation and measures from Postoperative Morbidity Survey will be collected. The Fisher's exact test or Chi-square test will be applied to assess the association between two categorical variables. We will summarize the distribution of average and cumulative intraoperative insufflation pressure, Post Anesthesia discharge DASAIM scores, length of ICU and hospital stay by each treatment. We will use the student t-test or the Wilcoxon rank sum test to compare continuous variables between two different patient groups. Logistic regression will be utilized to assess the effects of patient prognostic factors, comorbidities and treatment on postoperative shoulder pain and postoperative morbidity.

Adverse event (AE) data will be summarized by frequency tables. The association between the types and severity of AE and the treatment will be evaluated.

5. Study Drug Information

Since both Sugammadex and Neostigmine are FDA approved, Insert recommendations and Institutional Standards will be followed for all study agents.

5.1. Sugammadex

5.1.1. Dosage Forms And Strengths: 200 mg/2 mL (100 mg/mL) in a single-dose vial for bolus injection and 500 mg/5 mL (100 mg/mL) in a single-dose vial for bolus injection.

5.1.2. Recommended Dose and Administration: 4 mg/Kg, intravenously as a single bolus injection.

5.2 Neostigmine

5.2.1 Dosage Forms and Strengths: 0.5 mg/mL, 5 mg of Neostigmine in 10 mL vials and 1 mg/mL, 10mg of Neostigmine in 10 mL vials.

5.2.2 Recommended Dose and Administration: 70 mcg/Kg up to a total of 5 mg, intravenously slowly over a period of at least 1 minute.

6. Study Procedures

6.1. Intraoperative Anesthesia Care

All patients will receive a balanced general anesthesia with endotracheal intubation and volatile anesthetic agents. In order to avoid excessive sedation in the PACU, no long acting anesthetic agents (ketamine, dexmedetomidine, etc.) or narcotics (hydromorphone, morphine) will be allowed. Short acting narcotics (fentanyl) are allowed.

Patients will be randomized to receive either the Deep Neuromuscular Blockade (DNMB group) with Sugammadex reversal or Moderate Neuromuscular Blockade (MNMB group) with neostigmine reversal. The patients will be started on a continuous Rocuronium intravenous infusion following intubation. Insert recommendations and Institutional Standards will be used for Rocuronium. For the DNMB group, the rate will be adjusted and boluses given to maintain 1-2 post tetanic responses during the pneumoperitoneum. NMB will be reversed with Sugammadex at the end of surgery. For the MNMB group, the Rocuronium infusion rate will be adjusted to maintain 1-2 TOF responses and will be reversed with neostigmine at the end of surgery. The level of NMB will be assessed by the anesthetist with a standard nerve stimulator at 20 minute intervals for both groups.

During the surgical time-out and at the time of insufflation, the surgeon will be instructed to maintain the lowest insufflation pressure necessary for good surgical exposure and safety throughout the operation. All adjustments to the insufflation pressure will be directed by surgeon.

A clinical coordinator will calibrate the acceleromyography (TOF-Watch® SX, Organon Ireland Ltd., a subsidiary of Merck & Co., Inc., Swords, Co. Dublin, Ireland; pending availability due to product discontinuation by manufacturer) at the adductor pollicis muscle during induction prior to neuromuscular blockade, will record insufflation pressure changes during surgery and acquire the TOF ratio (TOFR) with the TOF-Watch® SX upon arrival of each patient to the PACU. Data will be collected from the electronic medical record (Anesthetic Record, PACU notes, Progress notes, Discharge summary, etc.) as well as a PACU survey.

6.2. Assessment of Outcomes

6.2.1. Depth of Neuromuscular Blockade: When possible, acceleromyography (TOF-Watch® SX, Organon Ireland Ltd., a subsidiary of Merck & Co., Inc., Swords, Co. Dublin, Ireland) at the adductor pollicis brevis muscle will be calibrated during induction but prior to muscle relaxation. The responses from the peripheral nerve stimulator and the site of application used by the anesthetist will be recorded at 20 minute intervals throughout the procedure. A TOF ratio per acceleromyography will be measured upon arrival to the PACU.

6.2.2. Insufflation pressure: Intra-abdominal insufflation time and pressure will be directed by the surgeon and recorded continuously by the clinical coordinator until the time of desufflation.

6.2.3. Surgical Exposure: At the end of the procedure, the surgeon will use the Surgical Rating Scale to describe the quality of surgical exposure. (Martini, Boon, Bevers, Aarts, & Dahan, 2013)

Table 1

The surgical rating score

1	*Extremely poor conditions*: the surgeon is unable to work because of coughing or because of the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Additional neuromuscular blocking agents must be given
2	*Poor conditions*: there is a visible laparoscopic field, but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions, movements, or

both with the hazard of tissue damage. Additional neuromuscular blocking agents must be given

3 *Acceptable conditions*: there is a wide visible laparoscopic field but muscle contractions, movements, or both occur regularly causing some interference with the surgeon's work. There is the need for additional neuromuscular blocking agents to prevent deterioration

4 *Good conditions*: there is a wide laparoscopic working field with sporadic muscle contractions, movements, or both. There is no immediate need for additional neuromuscular blocking agents unless there is the fear of deterioration

5 *Optimal conditions*: there is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional neuromuscular blocking agents

6.2.4. Postoperative Pain: A Survey will be completed by the PACU nurse. The patient will be asked if INCISIONAL, VISCERAL and/or SHOULDER PAIN are present. The nurse will record Visual Analog Scale (VAS) pain score (1-10) for pain in general and for Shoulder Pain if present, recording these separately. All these will be recorded at 15, 45 and 90 minutes (if patient not previously discharged). Opioids administrated by the PACU nurse will be measured in morphine equivalents.

6.2.5. Readiness to Discharge from PACU: Readiness to discharge from the PACU as determined by a modified version of the DASAIM discharge criteria scoring system (Gartner, Callesen, Kroman, & Kehlet, 2010) (Phillips, Street, Kent, Haesler, & Cadeddu, 2013) to be completed at 15, 45 and 90 minutes (if patient not previously discharged) after admission to the PACU. A patient will be considered ready for discharge if cumulative score is 4 or less and no single category has a score greater than 1.

DASAIM Discharge Criteria Scoring System (Gartner, Callesen, Kroman, & Kehlet, 2010)		
Sedation	0	Patient is fully awake
(Nurse Evaluation)	1	Patient is asleep, aroused by verbal stimulation
	2	Patient is asleep, aroused by physical stimulation
	3	Patient is asleep, cannot be aroused
Respiratory Rate	0	Respiratory rate > 10
(Nurse count)	1	Snoring, 10 < RR <30
	2	RR < 10 or RR > 30/min
	3	Periods of apnea or obstructive patterns
Oxygen Saturation	0	SpO2 $\geq$ 94%
(No supplemental oxygen for 10 minutes)	1	90% $\leq$ SpO2 < 94%
	2	85% $\leq$ SpO2 < 90%
	3	SpO2 < 85%

Systolic Blood Pressure	0	SBP ≥ 100mmHg
	1	90mmHg ≤ SBP < 100mmHg
	2	80mmHg ≤ SBP < 90mmHg or SBP > 220mmHg
	3	SBP < 80mmHg
Heart Rate	0	50 < HR ≤ 100
	1	100 < HR ≤ 120
	2	40 < HR ≤ 50 or 120 < HR ≤ 130
	3	HR < 40 or HR > 130
Pain at rest	0	No pain
(Patient evaluation)	1	Light pain
	2	Moderate pain
	3	Severe pain
Nausea	0	No nausea or vomiting
	1	Light nausea or vomiting without previous nausea
	2	Moderate nausea and/or vomiting
	3	Severe nausea and/or vomiting

6.2.6. Postoperative Morbidity: Cystatin C will be drawn during pre-procedure and sent to external laboratory for analysis and calculation of the Cystatin C/Creatinine Ratio, to determine if the patient shows laboratory evidence of Sarcopenia. Postoperative lactate level will be drawn in the PACU as well as an arterial blood gas when an arterial line catheter is present. Overall postoperative morbidity will be recorded on POD 1, 3, 5 and 7 using the Postoperative Morbidity Survey assessed by chart review.

Morbidity type	Criteria
Pulmonary	*De novo* requirement for supplemental oxygen or other respiratory support (e.g., mechanical ventilation or CPAP)
Infectious	Currently on antibiotics or temperature >38 °C in the last 24 h
Renal	Presence of oliguria (<500 mL/d), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for a nonsurgical reason
Gastrointestinal	Unable to tolerate an enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting, and abdominal distention
Cardiovascular	Diagnostic tests or therapy within the last 24 h for any of the following: *de novo* myocardial infarction or ischemia, hypotension (requiring pharmacological therapy or fluid therapy >200 mL/h), atrial or ventricular arrhythmias, or cardiogenic pulmonary edema
Neurological	Presence of a *de novo* focal deficit, coma, or confusion/delirium
Wound complication	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms
Hematological	Requirement for any of the following within the last 24 h: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate
Pain	Surgical wound pain significant enough to require parenteral opioids or regional analgesia

CPAP = continuous positive airway pressure.

(Bennett-Guerrero, et al., 1999)

6.2.7. 30-Day Mortality and Readmission Rate: Patients will be contacted via phone 30 days after being discharged from the Hospital to collect mortality and readmission data. If research staff is not able to contact the patient, this data will be obtained from available medical records.

7. Adverse Events

7.1. General

All adverse events (AE) and serious adverse events (SAE) from study drug administration until hospital discharge. An AE is defined as an undesirable clinical outcome regardless of whether it was directly caused by the study drug. An AE applies to any unintended event with an onset during the study or an exacerbation in the severity of a preexisting condition. All reported AEs will be recorded in the database with their respective description, date, actions taken, outcomes and assessment of the relationship with the study drug and protocol. AEs will be categorized using the Common Terminology Criteria for Adverse Events (CTACE) version 4.0. For the events not characterized by CTACE, the following definitions for severity will be applied:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate Interferes with the patient's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

A Serious Adverse Event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

All SAE's will be reported.

7.2. Drug-Related Adverse Event

An adverse event that may be reasonably attributed, in the judgment of the Investigator, to the study drug based on the time sequence of drug administration and is unlikely to be attributed to concurrent disease or another source.

7.3. Procedure-Related Adverse Event

An adverse event that may be reasonably attributed to the procedure itself and not to the study drug. Other anesthesia or surgical techniques are more likely to have contributed to the occurrence of the adverse event.

7.4. Concomitant Medication-Related Adverse Event

An adverse event that may be more reasonably attributed to the use of another medication and not to the study drug.

7.5. Pre-Existing Condition-Related Adverse Event

An adverse event that may be more reasonably attributed to the existence of a pre-existing condition and not to the study drug. Pre-existing conditions with an increase in severity during the study will be evaluated to determine whether the study drug was likely responsible for the exacerbation.

The Investigator should assess all adverse events considered to be drug-related for potential reportability to the FDA.

The Investigator should follow all unresolved serious adverse events until their resolution, the patient is lost to follow-up, the patient has withdrawn consent or the adverse event is otherwise explained.

For purposes of this study, the following events are not considered adverse events, because they are expected to normally occur in conjunction with surgical procedures:

- Early postoperative pain (within 24 hours post-procedure)
- Chest or shoulder pain without associated ECG changes
- Hematocrit changes not to exceed a 30% change from baseline or requiring a blood transfusion
- Electrolyte imbalance without clinical sequelae, even if requiring correction
- Low grade temperature increase (≤38.3°C/≤101°F)
- Any pre-planned surgical procedures or interventions

7.6. Reporting of Serious and Non-Serious Adverse Events

Sugammadex is FDA-approved for the reversal of steroidal neuromuscular blocking drugs and the potential risks are well-documented. We will only collect adverse events that rise to the level of grades 3 and 4 with an attribution of possible, probable, or definitely related to the device. Serious Adverse Events, regardless of attribution, will be reported per MDACC's standard practice and requirements, and per sponsor guidelines.

8. Ethical considerations

8.1. Institutional Review Board

A copy of the proposed protocol, Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent form must be received by Merck Inc. before recruitment of patients into the Study and shipment of product.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB of deviations from the protocol or SAEs.

8.2. Informed Consent form

The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The IRB must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki and the International Conference on Harmonization (ICH).

Prior to participation in the clinical Study, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's, or their legal representative's dated signature. The patient will receive a copy of the Informed Consent form.

8.3. Amending the Protocol

An Investigator may not make protocol changes without prior approval by Merck, Inc. All significant protocol changes that may affect the following must be submitted and approved by the IRB before initiating the change:

- validity of the data or information resulting from the completion of the approved protocol;
- relationship of the likely patient risk to benefit relied upon to approve the protocol;
- scientific soundness of the investigational plan, or;
- rights, safety, or welfare of the human patients involved in the investigation.

8.4. Emergency Actions

Merck, Inc. accepts the right of the Investigator to deviate from the protocol in an emergency and/or break study drug blinding when necessary to safeguard the life or the physical well-being of a study patient. If a patient is displaying signs and/or symptoms of residual neuromuscular blockade that jeopardizes the safety of the patient, the anesthesiologist may decide to administer an additional amount of Sugammadex. In such an event, the patient will remain in the intention to treat group but will be excluded from the analysis between the two treatment groups. The Investigator must give notice of any emergency deviations and justification for the deviation to Merck and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

8.5. Protocol Deviations

A protocol deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the protocol. Investigators shall be required to obtain prior approval from Merck, Inc clinical study management before initiating deviations from the protocol, except where necessary to protect the life or physical well-being of a patient in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. patient was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Deviations will be reported to Merck, Inc. regardless of whether medically justifiable, pre-approved by Merck, Inc. or taken to protect the patient in an emergency. Patient specific deviations will be reported on the Protocol Deviation case report form. The investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

8.6. Coverage of Expenses

The treated patients will not be reimbursed or compensated for participating in the Study.

Patient or insurance provider is responsible for all costs of surgery, including anesthesia and hospitalization. This includes all drugs involved in the study including Rocuronium, which is used as a neuromuscular blocking agent.

The study/treatment drugs Sugammadex and Neostigmine will be covered by the Sponsor and not billed to the patient. Other drugs utilized in this study will be used as per standard routine care. The site institution's research pharmacy department will maintain study supplies and record documentation. Additionally, they will also be responsible for the destruction of the supplies at the end of the study as per ICH/GCP guidelines, local regulations, and institutional policies. Supply should be shipped in marked vials to allow for non-blinded administration by the anesthesiologist.

Note: At conclusion of the study or upon drug expiration, the Merck GRS will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies.

8.7. Confidentiality

Confidentiality of patients will be maintained throughout the study. A unique identification number will be assigned to each patient participating in this study.

8.8. Documentation

The Principal Investigator must maintain detailed source documents on all study patients who are enrolled in the study or who undergo screening. Source documents include patient medical records, hospital charts, clinic charts, Investigator's patient Study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the patient's medical records:

- The date the patient entered the Study and the patient number
- The Study protocol number
- The date that informed consent was obtained
- Evidence that the patient meets Study eligibility requirements (e.g.,medical history, Study procedures and/or evaluations)
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used, if any
- All lab reports taken for this study
- Occurrence and status of any Adverse Events
- The date the patient exited the Study, and a notation as to whether the patient completed the Study or was discontinued, including the reason for discontinuation.

8.9. Record Retention

The Investigator will maintain all essential Study documents and source documentation, in original format, that support the data collected on the study patients in compliance with the ICH/GCP guidelines. Following publication study data will be archived in REDCap. Since study data may be useful for future research studies performed under separate IRB approved protocols, study data will be archived indefinitely in REDCap. Since REDCap is a secure electronic database with controlled access, and because patient identifiers may be needed to link study data to data from other sources under future IRB approved protocols, patient identifying information will be retained in the archived database.

8.10. Criteria for Terminating Study

The Investigators reserve the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of Merck to suspend or discontinue development of Sugammadex.

8.11. Investigator Responsibilities

- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP
- Complete all CRFs

8.12. Publication Policy

The information in this document and regarding this Study might contain commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Patient to the foregoing, this information may be disclosed only to those persons involved in the Study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information provided that is indicated as confidential. **All manuscripts associated with the data collected on this study are not to be submitted for publication without the written consent of the MD Anderson Principal Investigator**.

9. Regulatory Considerations

9.1. Role of Investigator and collaborators

The Investigator has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA).

Investigators or collaborators are responsible for obtaining IRB approvals prior to start of the study. The Investigator is required to obtain signed study agreements, to provide the Investigators with the information necessary to conduct the study and adequate on-site training to conduct the Study, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators, and IRBs.

The investigator will be responsible for providing quality data that satisfies publication requirements and informing of serious unanticipated adverse events and deviations from the protocol.

9.2. Monitoring

The Investigator will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the IRB.

9.3. Maintaining Records

The Investigator will maintain copies of correspondence, data, shipment of devices, serious adverse device effects and other records related to the clinical Study. The Investigator will maintain records related to the signed Investigator Agreements.

9.4. Informed Consent & Institutional Review Board (IRB)

All patients must provide written informed consent / Assent in accordance with the MD Anderson Cancer Center IRB. All Protected Health Information (PHI) to be collected in the study will be described in the informed consent form, and all study data will be managed in accordance with the Privacy Law (HIPAA).

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