Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	The title of the protocol should include study design, indication and, where applicable, dosage, dosage form, and comparative agent(s). A randomized prospective study to compare the effectiveness of Neostigmine versus Sugammadex in length of PACU stay in ASA II and III patients undergoing sleeve gastrectomy bariatric surgery
Request Date:	May 1
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1 List the objectives. Objective 1: Determine the difference in length of PACU stay from PACU arrival until ready for PACU discharge for ASA II and III patients reversed with Sugammadex versus Neostigmine in sleeve gastrectomy surgeries. Objective 2: Assess the incidence of PONV in ASA II and III patients reversed with Sugammadex versus Neostigmine, with the prediction that there will be a lower incidence of PONV in the Sugammadex group. Objective 3: Assess the incidence of respiratory complications postoperatively specifically looking at oxygen saturation at 10 minutes after patient arrival to PACU and 60 minutes after arrival to PACU and any intervention necessary. 2.1.1 List the clinical hypotheses. The main hypothesis is that Sugammadex given to reverse non-depolarizing muscle relaxants will expedite patients having bariatric surgery out of the PACU Bariatric patients receiving Sugammadex will have less PONV due to the fact that an adverse effect of Neostigmine is nausea and/or vomiting. Patients' status post sleeve gastrectomy surgeries who receive sugammadex will have less respiratory complications than their counterparts who receive neostigmine and thus show a higher PACU oxygen saturation since sugammadex binds and reverses the non-depolarizer muscle relaxants more effectively.
t2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Sugammadex has been demonstrated to shorten the time to reach a train-of-four ratio of 0.9 as well as the extubation time, resulting in improvement of operating room turnover in clinical anesthesia settings, including neuromuscular monitoring. Sugammadex may be recommended for the reversal of neuromuscular block in surgery that requires deep blockade to facilitate surgical procedures. From this point of view, bariatric surgery meets the indications for sugammadex use. Therefore, we frequently use this agent for the reversal of neuromuscular block in sleeve gastrectomy's, duodenal switches, and gastric bypasses. We aimed to investigate whether sugammadex shortens recovery time in the PACU. Currently the average length of stay for our sleeve gastrectomy's performed by one of our bariatric surgeons, Dr. Wasser, is 112 minutes over the last 17 months for ASA II and III patients. A secondary endpoint we want to measure is the incidence in postoperative nausea and vomiting with Sugammadex as compared to neostigmine. We hypothesize that sugammadex will shorten PACU recovery time, and that it will reduce PONV in patients undergoing sleeve gastrectomy bariatric surgeries. Morbid obese population is increasing every year worldwide, and laparoscopic bariatric surgery has a central role in their treatment. The postoperative period of these patients is not free from complications. The introduction of sugammadex has brought huge developments in patient's safety and now laparoscopic sleeve gastrectomy surgery is performed with better care and quality

	The rationale for conducting this study is to show that Sugammadex is more effective than Neostigmine in reversing non-depolarizing muscle relaxants. This will be demonstrated by the shorter ready for PACU discharge time leading to less cost. It will also show that there will be less post-operative respiratory complications in the Sugammadex group, including but not limited to PONV. A study by Park ES in the BMC Anesthesiology showed that sugammadex can shorten anesthesia and extubation times as well as recovery time in the PACU and reduce postoperative hemodynamic complications in a clinical setting in the absence of neuromuscular monitoring. This may enhance the patients' recovery in the OR and PACU while improving the postoperative condition of patients (1). Sugammadex has been demonstrated to decrease the incidence of post-operative respiratory complications and related costs in patients with OSA. After extubation, desaturation which is defined as spO2 <90% was observed in 32.4% of the neostigmine group and in 10.8% in the sugammadex group (2). It was also shown that patient receiving sugammadex over neostigmine had a shorter PACU stay (2). A comparison of sugammadex and neostigmine in children for reversal of rocuronium-induced neuromuscular blockade in children demonstrated a faster recovery and extubation times and lower incidence of adverse events compared with neostigmine (5). Sugammadex has been associated with less PONV and a faster discharge from the PACU in laparoscopic bariatric surgeries. In the first hour postoperatively, 27% of patients in the neostigmine group had PONV versus only 8% in the sugammadex group were observed to have nausea and/or vomiting (3). A retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade in the Eur J Anaesthesiol showed that neuromuscular blockade reversal with sugammadex was associated with lowest rate of PONV and may reduce the risk of pulmonary complications in elderly ASA 3/4 patients (4).
2.3 Study Design	The study is a randomized, interventional, controlled, blinded, single center study. There will be a minimum of 126 study patients, with 63 patients in the neostigmine group and 63 patients in the Sugammadex group. Inclusion criteria: • Patients having sleeve gastrectomy • Surgeries performed by Dr. Sam Wasser • BMI >35 • ASA II and III patients • +/- hiatal hernia repairs with the sleeve gastectomy Exclusion criteria: • Patients having a different type of bariatric surgery including but not limited to duodenal switch, gastric bypass, hand-assisted laparoscopic sleeve gastrectomy • Sleeve gastrectomy's performed by other surgeons than Dr. Sam Wasser. • Pregnancy • Allergic to sugammadex, Zofran or scopolamine • COPD or Asthma that is uncontrolled • ASA I, IV, V patients Primary parameter: • Assess the difference in length of PACU stay from PACU arrival until medically ready for PACU discharge and also from time of administration of reversal agent (which will be start of skin closure) until medically ready for PACU discharge Secondary parameter: • Assess the incidence of PONV in patients by asking the patients every 15 minutes after arrival to PACU if they are having nausea or vomiting Exploratory parameter:

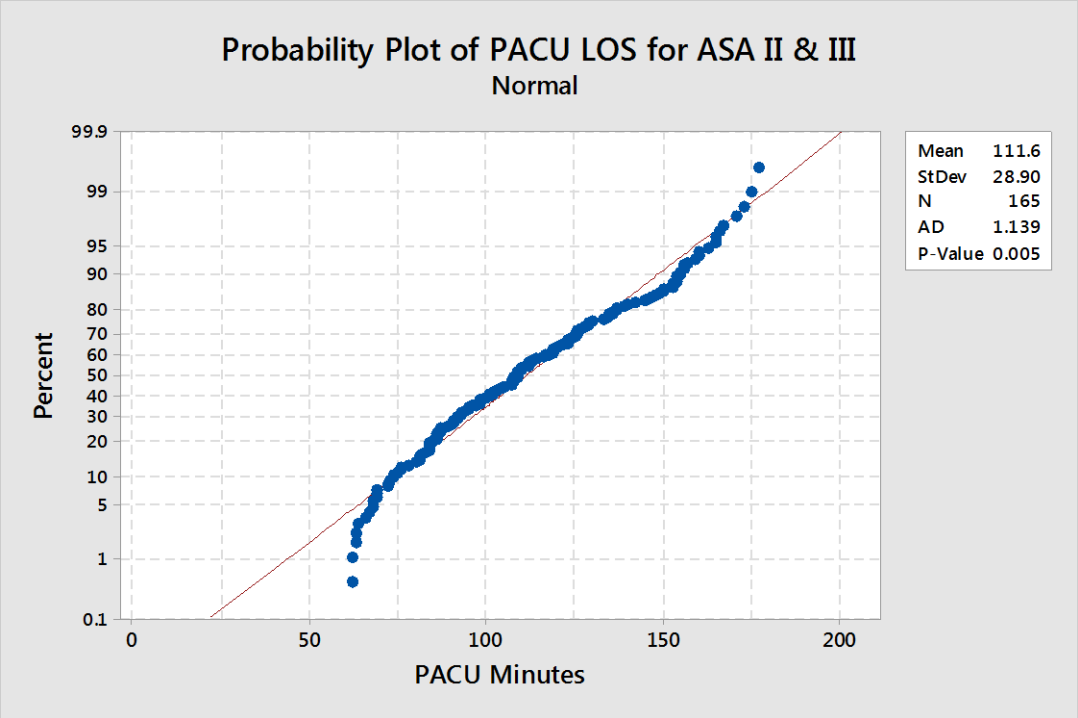
	• Assess the incidence of respiratory complications postoperatively looking at oxygen saturation every 15 minutes after PACU arrival and any intervention necessary
2.4 Study Flowchart	The bariatric surgeon, Dr. Sam Wasser, has already agreed to have their patients in the study. The next step is to get IRB approval. The patients will be consented prior to surgery and their signed consents would be kept in our study records. We will track these patients after the surgery in the PACU until discharge and assess their length of stay and possible nausea / vomiting. The exact time we are looking for is patient arrival to PACU until patient ready for discharge when the anesthesiologist writes the anesthesia evaluation. We will also take into account the time the reversal agent is administered during the start of skin closure until patient medically ready to leave the PACU. Blinded to the treatment group, an individual will ask each patient every 15 minutes after arrival to PACU if they are experiencing nausea or vomiting. As an exploratory measure, we will assess the patient at these same times (every 15 minutes) and determine their oxygen saturation. Then we will take all the results and use statistical means to measure what is significant. A discussion and conclusion will follow. Finally I will submit this to an anesthesia journal.
2.5 Study Procedures	The initial screening period will identify the patients that fit in the inclusion criteria and get their consent to be in the study. There will be two measurements of length of time to assess. One measurement will be from the time the reversal agent is administered which will be the start of skin closure to the patient ready for discharge from the PACU. The second duration of treatment will be the patients' stay in the PACU from arrival from the operating room until ready for discharge based on anesthesia evaluation completed. The criteria for readiness for discharge are based on a modified Aldrete Score >8. The assessor will be blinded to the study group. Readiness will be assessed every 5 minutes. The control group will be the patients who receive the Neostigmine in a dose of 5mg, along with the anti-cholingeric Glycopyrolate 0.6mg. Sugammadex will be given in a dose of 2mg/kg if the train of four twitch count is 2 and 4mg/kg if the twitch response has reached 1-2 post-tetanic counts with no twitch response to train of four. Monitoring neuromuscular response will be with the device SunStim Plus by SunMed. The end point when we will give the reversal agent is a T1 or T2 block of the adductor policis muscle on the twitch monitor. Our standard criteria for extubation include full reversal of muscle relaxation with sustained tetany and a TOF ratio of > .9. We also require adequate oxygenation SpO2>92%, adequate ventilation with tidal volumes >5 ml/kg, spontaneous RR >7bpm, and the patient to be hemodynamically stable. All patients in both the control and study group will receive a Scopolamine 1.5mg patch instructed to place behind the ear the night prior to coming in for surgery and Ondansetron 4mg given 30 minutes prior to the end of the surgery. . All patients will be induced with the standard medications of Lidocaine, Fentanyl, Propofol and Rocuronium unless clinically indicated. The patients will be standardized to receive the volatile anesthetic Sevoflurane. Nitrous Oxide will not be given to any patient since this can increase the likelihood of PONV. From a pain management standpoint, fentanyl and hydromorphone will be administered intraoperatively based on the patient's requirements at the discretion of the anesthesia team. The standard inflation pressure at our institution is 18mmHg. The surgeon makes a judicious effort to remove CO2 at the end of the surgery as well to help this cause because residual CO2 can lead a patient to have nausea. The individual who assesses the PONV in the PACU will do so at q 15 minute intervals when VS are checked. They will be blinded to neostigmine and sugammadex treatment. If the patient has PONV, the RN will administer Ondansetron 4mg. If the patient still has PONV then they will administer 25 mg of Diphenhydramine and a third option would be Promethazine 12.5 mg.

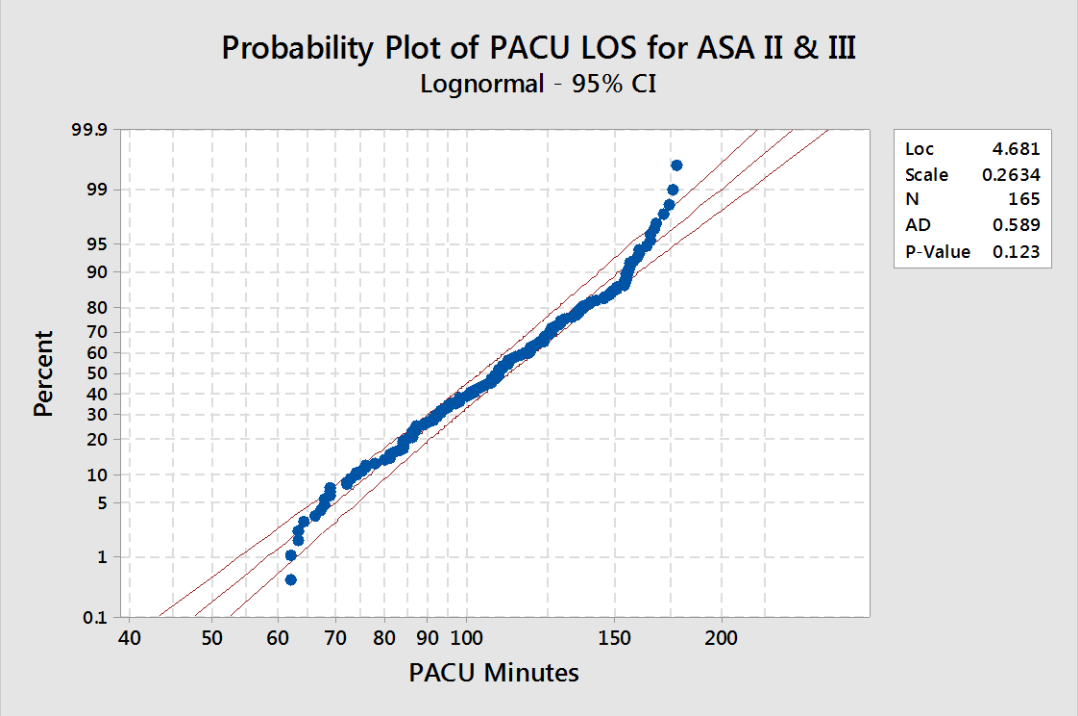
2.6 Study Duration	At our institution Dr. Sam Wasser currently averages about 13 ASA II and III sleeve gastrectomy bariatric surgeries a month. We therefore anticipate that it will take approximately 10 months for patient recruitment and study completion.
2.7 Statistical Analysis and Sample Size Justification	Both a statistician and I will be responsible for analyzing the study data. The PONV data will be blinded, with the individual(s) responsible for asking the patient if they're experiencing nausea not made aware of which reversal agent was given. <u>Variables/Time Points of Interest</u> The assessment of PONV: • A blinded individual will ask patients at 15 minute intervals in the PACU after arrival to the recovery room until ready for discharge • It will be a check box with yes and no being the only outcome. • If the patient has PONV at any point in the PACU it is considered positive for PONV. The assessment of time spent in the PACU: • Defined as the time from arrival in PACU to ready for PACU discharge (Anesthesia Evaluation completed). The other time measurement is from administration of the reversal agent during the start of skin closure to the patient being ready for PACU discharge. Cost Analysis • Knowing the cost per 30 minute increment after the first hour stay in the PACU Phase 1 is $59.32, the prediction of a 15 minute decrease in PACU stay will equate to a cost savings of approximately $30/patient in time spent in the PACU <u>Statistical Methods</u> The primary outcome measure is the difference in mean PACU Phase 1 LOS minutes between the two groups for which the two sample t-test will be utilized. While the historical (January 2016 to May 2017) PACU Phase 1 LOS (minutes) data did not appear to follow a normal distribution (P-Value = 0.005), they were however found to be lognormally distributed (P-Value = 0.123) [see appendix]. The t-test will therefore be conducted using the log-transformed data. A two sample t-test on the log-transformed PACU data showed that there was no significant difference in geometric mean PACU LOS between ASA II (101.19 minutes) and III (109.62 minutes) patients (P-Value = 0.131). We therefore find it reasonable to include ASA II and III patients in the study. The secondary analysis will use the z-test for proportions since we are looking at the percentages of PONV "yes" outcomes. The exploratory parameter analysis will use the z-test for proportions since we are looking at the percentages of post op respiratory "yes" outcomes. <u>Power/Sample Size:</u> Based on an 80% power to detect a 15% difference in PACU LOS minutes between the two groups and a standard deviation of 0.2634 for the log-transformed data, a minimum sample size of 57 patients per group is needed. Applying a 10% markup against the derived minimum sample size, we will enroll a minimum of 63 patients in each group for a total of 126 study patients. A documented study in the literature (3) revealed that in the first hour postoperatively, 27% of patients in the neostigmine group had PONV versus 8% in the sugammadex group. According to another study (2), after extubation, desaturation (spO2<90%) was observed in 32.4% of the neostigmine group versus 10.8% in the sugammadex group. With 63 patients in each study group, statistical

	powers of 80.9% and 84.7% are estimated for the PONV test and respiratory complications test respectively.
2.8 Specific Drug Supply Requirements	For US and non-US studies, the investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.
2.9 Adverse Experience Reporting	The study agreement outlines the requirement for adverse experience reporting. For clinical protocols, specific adverse experience reporting requirements must be identified in the protocol if the Model Study Agreement is not used (in general, this would apply to non-US. studies whose local requirements may prohibit the use of the agreement).
2.10 Itemized Study Budget	Please refer to the Budget spreadsheet for specifics.
2.11 References	1. Park ES, Lim BG, Lee WJ, Lee IO. Sugammadex facilitates early recovery after surgery even in the absence of neuromuscular monitoring in patients undergoing laryngeal microsurgery: a single-center retrospective study. BMC Anesthesiol. 2016 Aug 2;16(1):48. 2. Ünal DY, Baran İ, Mutlu M, Ural G, Akkaya T, Özlü O. Comparison of Sugammadex versus Neostigmine Costs and Respiratory Complications in Patients with Obstructive Sleep Apnoea. Turk J Anaesthesiol Reanim. 2015 Dec;43(6):387-95. doi: 10.5152/TJAR.2015.35682. Epub 2015 Dec 1 3. Castro DS Jr, Leão P, Borges S, Gomes L, Pacheco M, Figueiredo P. Sugammadex reduces postoperative pain after laparoscopic bariatric surgery: a randomized trial. Surg Laparosc Endosc Percutan Tech. 2014 Oct;24(5):420-3. 4. Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, De Mel A, Tiong WS, Phillips M. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: sugammadex, neostigmine or no reversal. Eur J Anaesthesiol. 2014 Aug;31(8):423-9. 5. Ammar AS, Mahmoud KM, Kasemy ZA. A comparison of sugammadex and neostigmine for reversal of rocuronium-induced neuromuscular blockade in children. Acta Anaesthesiol Scand. 2017 Apr;61(4):374-380.
2.12 Publication Plan	I plan on submitting to the Journal of Clinical Anesthesia. I would not be opposed to other suggestions for publication. Projected date of submission would be December 2018 time frame. I would also submit an abstract to the ASA and hopefully present my results at the national meeting.
2.13 Curriculum Vitae	Investigator should provide curriculum vitae in English and a listing of references to MSD.
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.

Appendix: A randomized prospective study to compare the effectiveness of Neostigmine versus Sugammadex in length of PACU stay in ASA II and III patients undergoing sleeve gastrectomy bariatric surgery

Jan 2016 to May 2017 PACU Data for Dr S. Wasser's Lscopic Gastrectomy Sleeve Cases


Probability Plot of PACU LOS for ASA II & III
Normal
Percent
99.9
99
95
90
80
70
60
50
40
30
20
10
5
1
0.1
0
50
100
150
200
PACU Minutes
Mean 111.6
StDev 28.90
N 165
AD 1.139
P-Value 0.005


Probability Plot of PACU LOS for ASA II & III
Lognormal - 95% CI
Percent
99.9
99
95
90
80
70
60
50
40
30
20
10
5
1
0.1
40
50
60
70
80
90
100
150
200
PACU Minutes
Loc 4.681
Scale 0.2634
N 165
AD 0.589
P-Value 0.123