A randomized, blinded-assessor, single center study to determine if administration of Sugammadex, when used to reverse deep neuromuscular blockade (NMB) after open or closed abdominal surgery, impacts hospital efficiency

Study Site: Tampa General Hospital, Tampa, FL

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Study Summary

Title	A, randomized, blinded-assessor, single center study to determine if administration of Sugammadex, when used to reverse deep neuromuscular blockade (NMB) after open or closed abdominal surgery, impacts hospital efficiency
Short Title	Deep NMB Reversal and Hospital Turnover Efficiency
Protocol Number	TGH015
Phase	Phase 4
Methodology	Randomized, blind-assessor, parallel, active control trial
Study Duration	12 months
Study Center(s)	Single-center (Tampa General Hospital, Tampa, FL)
Objectives	Primary Objective: To measure operating room (OR) turnover when using Sugammadex instead of combination of Neostigmine and Glycopyrrolate. Secondary Objectives: To evaluate the impact of reversal with 4.0 mg.kg-1 of Sugammadex after sustained deep neuromuscular blockade induced by rocuronium on patients reversal timing in comparison with standard reversal with Neostigmine 0.06 mg/kg and Glycopyrrolate 0.004mg/kg iv To determine the incidence of side effects, including postoperative nausea and vomiting, post-operative pain, and post-operative complications
Number of Subjects	50 Patients (25/group)
Diagnosis and Main Inclusion Criteria	Open or Closed Ventral Hernia Repair or Open or Closed Colectomy
Study Product, Dose, Route, Regimen	Sugammadex 4.0 mg/kg iv, single bolus Neostigmine 0.06 mg/kg and Glycopyrrolate 0.004mg/kg iv
Duration of administration	The bolus dose of Sugammadex will be administered within 1 minute into a fast running venous infusion. Sugammadex is dosed on the actual body weight of the subjects. Neostigmine plus Glycopyrrolate will also be injected over 1 minute.
Reference therapy	
Statistical Methodology	Analysis of Variance (ANOVA) Mixed Models Pearson Chi-squared/Fisher Exact Test

A. Background/Rationale for Study

In some patients, optimal clinical management requires continuing neuromuscular paralysis until conclusion of the surgical procedure. Reversal of residual neuromuscular paralysis at the end of a surgical procedure is an important step in reconstituting spontaneous muscle tone and re-establishing effective spontaneous ventilation and patient motility, cough effectiveness and natural muscular defenses. Slow reversal of muscle paralysis delays post-operative turnover time in the operating room (OR).

The cholinesterase inhibitor neostigmine remains the most commonly used neuromuscular blocking agent antagonist, but neostigmine causes bradycardia, alteration of gastrointestinal motility and increased gastric secretions. Furthermore, neostigmine has a slow onset, and slow peak-effect, up to 10 to 15 min, and is thought to increase the risk of postoperative nausea and vomiting (PONV) [1,2], possibly by provoking gastric spasms. The frequent addition of atropine or glycopyrrolate to the neostigmine attenuates the onset of bradycardia, though the combination of neostigmine and atropine may be emetogenic [3]. Neostigmine alone in doses larger than 2.5 mg increases the incidence of PONV [4].

A newer reversal agent called Sugammadex is available in the United States and has previously been available in Europe and other countries. Sugammadex is a new selective relaxant-binding agent thathas a different mechanism of action from anticholinesterase neuromuscular antagonists, based on physico-chemical characteristics. Specifically, Sugammadex encapsulates in a rapid and selective way steroidal neuromuscular blocking agents, leading to ultra-rapid clearance of free neuromuscular agent from the tissues into plasma and rapid renal elimination, devoid of parasympathetic side-effects: nevertheless Sugammadex has been reported to cause other minor various side effects in less than 10% of patients, including mild headache, nausea, injection site irritation, dry mouth, fatigue, a cold sensation at the injection site, and oral discomfort [5-8]. Furthermore, the most common adverse effect of Sugammadex is also nausea [10]. A systematic review evaluating the use of

Sugammadex instead of Neostigmine for reversal found Sugammadex to reduce all signs of residual postoperative paralysis. Furthermore, there were no differences observed in critical respiratory events, though this result was not statistically significant. Sugammadex was also noted to reduce drug-related side effects but no difference was noted in the rate of postoperative nausea or the rate of postoperative vomiting [10]. In summary, selective relaxant binding agent antagonism with Sugammadex speeds recovery of neuromuscular strength. Improvement to PONV compared with neostigmine and atropine might be small. There was also no benefit in terms of time to oral intake, recovery of gastrointestinal function, or ambulation [11]. Non-depolarizing neuromuscular blocking agents (ND-NMBAs) are used during general anesthesia to facilitate tracheal intubation and to optimize surgical conditions. However, due to the variability of their duration of action, residual effects of ND-NMBA can last longer than clinically necessary.

Patients with large abdominal open wounds, such as patients requiring repair of large abdominal hernias or open colectomies, need profound neuromuscular relaxation during the crucial closure time, until the end of fascia closure, while the surgeon approximates the abdominal muscles or completes the fixation of fascial mesh insertion; conversely, the speed of recovery from neuromuscular blockade after the end of surgery is important to minimize delays to reach a steady spontaneous ventilation, extubation and a speedy recovery after the end of surgery. This group of patients is rapidly increase in number, both for the prevalence of obesity and of elderly patients, but also for the iatrogenic causes of multiple surgery with laparoscopy techniques operated in recent years, with exiting complications resulting in large abdominal hernias.

There is a growing body of evidence that postoperative residual neuromuscular blockade, defined as a train-of-four ratio (T4/T1) less than 0.9, places patients at higher perioperative risk for respiratory complications [12–14] and may increase hospital costs.

In order to reduce or avoid postoperative residual paralysis, anesthesiologists typically monitor intraoperative neuromuscular transmission blockade and reverse residual neuromuscular blockade with acetylcholinesterase inhibitors.

A recent publication (12) reported that the intraoperative use of ND-NMBA is associated with postoperative respiratory failure primarily due to pulmonary edema, pneumonia, and atelectasis. In addition, they observed that neostigmine reversal did not decrease the incidence of postoperative respiratory failure but was associated with a higher incidence of postoperative oxygen desaturation. However, in these patients who received neostigmine, qualitative neuromuscular transmission monitoring appeared to have a protective effect against hypoxia as the incidence of oxygen desaturation below 90% occurred less frequently when compared with those who received neostigmine without qualitative neuromuscular transmission monitoring. In this last study (12) it was important to define efficiency of turn-over and recovery in PACU or in the OR. PACU times were determined and documented by PACU nurses not involved with the study. PACU length of stay until discharge readiness was defined as time from PACU admission to the time the patient no longer required postoperative monitoring in the PACU. Actual PACU length of stay was defined as time from PACU admission until actual departure from the PACU. The occurrences of postoperative respiratory complications (i.e., atelectasis, pneumonia, and pulmonary edema) and mortality were retrieved from hospital billing data within 30 days after the index surgery. Reintubation was defined as the replacement of an endotracheal tube within 7 days of the index procedure following initial extubation in the operating room. Any patient who required replacement of an endotracheal tube for a second surgical procedure was excluded. The secondary outcomes were postoperative hospital length of stay, incidence of postoperative atelectasis, and unplanned postoperative intensive care utilization including surgical intensive care unit, reintubation, and length of PACU admission until discharge and discharge readiness. Exploratory outcomes were related to signs and symptoms of postoperative respiratory failure including pneumonia, pulmonary edema, reintubation, and mortality. In this study, Neostigmine reversal did

not affect oxygenation but was associated with increased atelectasis. Exploratory analysis revealed that high-dose neostigmine was associated with longer postoperative length of stay. Unwarranted use of neostigmine, and neostigmine administration without appropriate guidance from neuromuscular transmission monitoring, was associated with increased respiratory morbidity. Neostigmine is effective in reversing shallow and moderate nondepolarizing neuromuscular blockade [13] by inhibiting acetylcholinesterase [14] and increasing the amount of acetylcholine in the neuromuscular junction. [15] Neostigmine does not reverse deep neuromuscular blockade [16] and neostigmine should not be given to patients who present with deep neuromuscular blockade because it can result in incomplete reversal of neuromuscular blockade.

We are advancing the hypothesis in this proposal, that the administration of high-dose neostigmine could be associated with additional side effects in these patients who are reversed from deep levels of paralysis to awake, leading to greater utilization of hospital resources, and we believe that this association is due to the increased incidence of signs and symptoms of postoperative respiratory failure. We speculate that some of our anesthesia providers attempt to reverse deep neuromuscular blockade with a "full-reversal" dose of neostigmine (heuristically 5 mg at our institution for a patient of average weight) and then transfer extubated and weak patients to the PACU. High-dose neostigmine was a strong predictor of atelectasis and was associated with longer postoperative hospital length of stay. Unwarranted use of neostigmine, and neostigmine administration without appropriate guidance from neuromuscular monitoring, was associated with increased respiratory morbidity. Our plan to administer Sugammadex to half of our study population to reverse neuromuscular blockade in these high-risk patients will allow us to determine if Sugammadex leads to better OR turnover, duration in PACU, and hospital utilization by inducing faster recovery and fewer side effects.

Study Paradigm: we are planning to study the neuromuscular reversal process in patients who need open or closed abdominal wound closure of medium to large size: the surgical process benefits from and requires deep neuromuscular paralysis during abdominal muscle apposition and fascia closure, to result in a solid abdominal wall: we selected abdominal hernias and possibly open or closed abdomen colectomy, both groups of patients experiencing rather large wound closures. After completion of the muscular closure the superficial skin layers are completed quickly and anesthesia reversal, patient awakening and extubation will benefit from rapid reversal, restoration of spontaneous ventilation and reappearance of upper airway reflexes and strong cough responses. This will facilitate rapid transfer to PACU, turn-over in the OR and increase efficiency in this costly hospital area. The comparison will be between Sugammadex reversal vs. traditional Neostigmine/Glycopyrrolate reversal.

B. Objectives

Primary Objective:

- To measure operating room (OR) turnover when using Sugammadex instead of combination of Neostigmine and Glycopyrrolate.

Primary Objective Endpoint:
Time from injection of neuromuscular block reversal medication to start of next case (OR Turnover)

Primary Data Points:

1. Time of operating room (OR) admission (physical placement of subject in the OR);
2. Time of initial rocuronium dose and time of maintenance dose, if any;
3. Time of sugammadex or neostigmine/glycopyrrolate administration;
4. Time from sugammadex or neostigmine plus glycopyrolate administration to TOF of 0.9
5. Time of extubation;
6. Time of patient first eye opening, measured after question from provider
7. Time of headlift, also measured from questions from provider
8. Time of the end of surgery (end of skin suturing);
9. Time of OR-discharge ready;
10. Time of actual OR discharge;
11. Time of post anesthesia care unit (PACU) admit;

12. Time of PACU discharge ready
13. Length of hospital stay

Secondary Objectives

- To evaluate the impact of reversal with 4.0 mg.kg-1 of Sugammadex after sustained deep neuromuscular blockade induced by rocuronium on patients reversal timing in comparison with standard reversal with Neostigmine 0.06 mg/kg and Glycopyrrolate 0.004mg/kg iv
- To determine the Incidence of side effects, including postoperative nausea and vomiting, post-operative pain, and post-operative complications

Secondary Endpoint: Time from PACU discharge to Discharge from hospital

Secondary Data Points:

1. Post-operative pain measured on the Visual Analog Scale (VAS) 0 – 10 centimeter line.
2. Total amount of required supplemental analgesia during the postoperative period for both treatment groups
3. Post-operative complications

Exploratory Objectives

- To determine the Incidence of postoperative nausea and vomiting in both groups, to verify the superiority of Sugammadex reversal by adding Apfel's postoperative nausea and vomiting (PONV) risk factors assessment

C. Methods

Study Design

This is a parallel, blinded-safety assessor, randomized, active control study.

Inclusion/Exclusion Criteria

Inclusion Criteria
• Patients scheduled for open or closed ventral hernia repair or open or closed colectomy
• ASA class I-III
• 18 years and older
• Subjects with a Body Mass Index (BMI) of < 45 kg/m2 and weight less than 150 kg
• Subjects who have given written informed consent

Exclusion criteria
• Subjects with medical conditions and/or undergoing surgical procedures that are not compatible with the use of the TOF-Watch® SX (e.g., injuries to the thumbs/distal forearms, bilateral ulnar nerve damage or subjects with cardiac pacemaker
• Subjects known or suspected to have neuromuscular disorders impairing neuromuscular blockade (e.g., subjects with myasthenia gravis)
• Subjects known or suspected to have significant renal dysfunction (e.g. creatinine clearance < 30 mL.min-1
• Subjects known or suspected to have significant hepatic dysfunction
• Subjects known or suspected to have a (family)history of malignant hyperthermia;
• Subjects known or suspected to have an allergy to opiates/opioids, muscle relaxants or other medications used during general anesthesia;
• Subjects known or suspected to be hypersensitive to Sugammadex or other cyclodextrins or Rocuronium or any of its excipients
• Subjects who have a contraindication to, Rocuronium or Sugammadex
• Female subjects who are pregnant • Morbidly obese subjects with a BMI > 45 kg/m2 or weight more than 150 kg

Consent Process

All patients that are scheduled to have an open or closed colectomy or ventral hernia repair will be evaluated for study eligibility in the preoperative assessment center at Tampa General Hospital during their visit with the anesthesiologist. The pre-operative assessment takes place 3-7 days prior to the scheduled surgery. Standard pre-operative orders include CBC, CMP, and PT/PTT. Patients who qualify for the study and give informed consent will be entered into the study during their pre-operative visit or the patient may take the consent form home to review and sign on the day of surgery. All study discussions will take place in a private exam room in the preoperative clinic. All subjects will be given the opportunity to ask questions. If the investigator feels that the subject understands the research parameters and the subject is willing to sign the consent form, the patient will be enrolled in the study. On the day of the surgical procedure, the study subject will present to the surgical prep unit. It is here that the

subject will be re-evaluated for willingness to participate. Any additional questions will be answered prior to surgery.

Screening & Baseline Visit:

After the patient signs the consent form, patient demographics and medical history will be collected from the medical record. A clinical examination, including vital signs (blood pressure, heart rate, and respiratory rate); physical measurements (body weight and body height) and a physical examination will be completed. Patients will be assessed for postoperative nausea and vomiting (PONV) risk factors using the Apfel's assessment. All laboratory results will be reviewed to ensure that the patient meets the study criteria.

After confirming that the patient meets the study criteria, the pharmacy will be notified by a member of the research team to start the randomization and drug preparation process.

Stratification:

The randomization procedure will minimize the imbalance between treatment arms within each of the following stratification factors: Age; <60 years and ≥60 years

Randomization/ Blinding/ Unblinding

A 1:1 computer-generated randomization schedule will be provided by the biostatistician and delivered to the research pharmacist. The research pharmacist will assign the patient to the next available treatment on the randomization list and prepare the study drug. Patients will be randomized to receive Sugammadex or neostigmine plus glycopyrrolate using a two-block design in which patients will be assigned to one of two groups. One group of 25 patients will receive Sugammadex and the second group of 25 patients will receive a combination of Neostigmine and Glycopyrrolate. Study personnel will provide the pharmacy with a copy of the signed informed consent and signed physician orders as

well the patient's actual body weight (ABW). In return, the pharmacist will prepare the study drug and provide the study staff with a red travel box that contains the study drug. The travel box is designed to maintain the blind. The study medications will be delivered to the operating room by the study staff and will be administered to the patient by the anesthesiologist or CRNA assigned to the case.

The operating room team, including the surgeon, nurses, anesthesiologist, nurse anesthetists and research coordinator will be blinded to the study drug. The research coordinator will be the post-operative assessor. Each study drug will be administered intraoperatively as standard of care. Intraoperative notes in the electronic medical record (Epic) will be listed as 'neostigmine plus glycopyrrolate/Sugammadex given so that the blinded assessor cannot view the study drug in the patient's record. If necessary for the clinical management of the patient, the clinical team treating the patient can request un-blinding from the pharmacist.

Table 2 Study Groups

Group	Drug
S	Sugammadex 4mg/kg
NG	Neostigmine 0.06 mg/kg and Glycopyrrolate 0.004mg/kg iv

Preoperative Management The preoperative course will follow our standard of care practices

Intraoperative Management: The intraoperative course will follow our standard of care practices. Doses/concentration of medications/agents used for the anesthetic management of the subjects enrolled in this trial may be adjusted when necessary to provide optimal subject care. Anesthesia will be induced with propofol, intravenous opioids, and other medication(s)/agent(s) at a concentration range/dose(s) based on the clinical need of the subject.

After induction of anesthesia but before administration of the intubation dose of

Rocuronium, continuous neuromuscular transmission monitoring will be performed using the TOF-Watch® SX until the end of anesthesia, at least until recovery of the T4/T1 ratio to 0.9 and full recovery of neuromuscular function has occurred as determined by the anesthesiologist. The TOFWatch® SX will be affixed to the forearm/hand. Stabilization and calibration of the TOFWatch® SX will be done in the operating room.

Rocuronium 0.6 mg/kg will be given intravenously to facilitate tracheal intubation; additional boluses of rocuronium, 0.15 mg/kg will be given to maintain 1-2 twitches in response to supramaximal electrical stimulation of the ulnar nerve as determined by a TOF-Watch SX (Schering-Plough Ireland, Dublin, Ireland). In addition to the TOF-Watch-SX, depth of anesthesia will be measured with BIS-monitoring of all patients and a standard approaching 50% suppression will be maintained throughout the main duration of surgery. Reversal agent will be administered at a post-tetanic count of 1 or 2 (PTC 1,2 defined as deep block).

Anesthesia will be maintained in both groups with intravenous opioids, propofol and/or medication(s)/agent(s), including inhalation anesthetic agents, at a concentration range/dose(s) based on the clinical need of the subject.

Tracheal extubation will be performed at the end of anesthesia after administration of Sugammadex or neostigmine/glycopyrrolate and a T4/T1 ratio of 0.9 has been measured by means of the TOF-Watch® SX. After extubation, the investigator will determine when the subject is OR discharge ready (subject is extubated, wound dressing is in place, and vital signs are stable). The actual time the subject was physically transferred from the OR to the PACU will also be recorded.

Postoperative Management: Upon arrival in the PACU, the (sub)investigator (blinded safety-assessor), using the visual analog scale, will clinically assess post-operative pain.

Assessment of patient pain levels involve a series of VAS testing postoperatively (upon arrival and every 30 minutes postoperatively until discharge from the PACU) using a 10 cm line. Patients that complain of pain intensity >5 cm/10 cm, will be given a standardized rescue intravenous dilaudid regimen, IV dilaudid at 0.4mg up to a max

dose of 2mg prn q 2 hours or until a VAS of <5 is obtained. If a VAS score of <5 cannot be obtained, the PI may withdraw the patient from the study and administer another pain medication. Post-operative PACU narcotic consumption will be recorded and quantified.

Post-operative nausea and vomiting (PONV) will be assessed using a PONV rating scale every 30 minutes until PACU discharge. PONV will be rated as 0, no nausea; 1, mild nausea ≤ 15 minutes; 2, nausea ≥ 5 minutes and 3, vomiting. PONV will be treated with ondanestron 4 mg intravenously and, if persistent, with metoclopramide 10 mg intravenously.

All patients will be monitored with continuous pulse-oximetry. All post-operative complications will be captured.

Follow-up Period: All patients will have a planned hospital admission from the PACU. Pain and PONV will be assessed every 2 hours for the first 24 hours followed by every 4 hours until hospital discharge using the VAS scale. All post-operative complications will be captured. Post-PACU narcotic consumption will be recorded and quantified.

CLINICAL MEASUREMENTS

1. **Hospital Efficiency:** Time delay between injection of reversal drug (Sugammadex or Neostigmine and Glycopyrrolate) and time of extubation.

2. **Analgesia quality and management**: Analysis of patient outcome will involve a series of Visual analog scale pain assessed both preoperatively and postoperatively. The participant's pain level will then be assessed every 30minutes in the post-anesthesia care unit (PACU) until the time of discharge using the Visual Analog Pain Scale. If a delay in transfer is observed, the reason for the delay will be noted.

3. **Supplemental Analgesics**: Data involving the time to first intravenous dilaudid rescue and total dilaudid requirements will be obtained and recorded. This data will be reviewed upon study completion.

4. **Post-operative adverse events**: Analysis of adverse events will be measured to include: postoperative nausea and vomiting, constipation, respiratory depression, and sedation. All side effects will be assessed based upon physical symptoms and clinical assessment. This data will be reviewed upon study

completion.

Duration of study participation
The entire length of surgical procedure and length of hospital stay for each patient. The total study duration will be approximately 6 months from the start, in order to enroll the planned patients.

Statistical Plan

Sample Size
As reported in a study by Della Rocca et al. (2013) **time from reversal administration to TOFr to 0.9 is significantly faster in the Sugammadex group than in the neostigmine group (deep block: 2.7 vs. 16.2 min, respectively; $P < 0.0001$). [17]. Based on data from this study published in Acta Scandinavica, the standard deviation for the primary outcome measure is assumed to be 18 min and in order to be able to detect a difference of 16 min between the treatment arm and control arm using t-test with alpha of 0.05 and power of 80%, 21 patients are needed per study arm. To account for the possibility of not meeting the assumptions of t-test and the need of using non-parametric tests, this sample size is further adjusted to 25 per arm or 50 total according to the Pitman Asymptotic Relative Efficiency (ARE) method.

Statistical Methods
All data will be analyzed using Stata 11.0 (StataCorp LP, College Station, TX). Patients will be randomized to receive Sugammadex or Neostigmine/Glycopyrrolate for muscle paralysis reversal at a 1:1 ratio (25 patients will be in each arm). Before the start of the study, a sample of 50 sealed envelopes will be prepared by the biostatistician: 25 for the Sugammadex group and 25 for the Neostigmine/Glycopyrrolate group. Patients who meet the criteria for inclusion will be assigned to the next available subject number and

corresponding treatment as defined in the randomization envelope, in ascending sequence of subject numbers. Each subject number was only assigned once during the study. Only unblinded research staff will have access to the randomization process. Analysis of Variance (ANOVA) or mixed effects model will be used to analysis multiple VAS scores from the same patient. Categorical variables will be analyzed using either Chi-square or Fisher Exact tests. Results will be expressed as mean ± SD (medians for nonparametric) for continuous variables and as frequencies and percentages for categorical variables. A *p* value of <0.05 will be considered statistically significant. For secondary data points, post-operative pain, total amount of required supplemental analgesia during the postoperative period for both treatment groups, and post-operative outcomes will be analyzed for covariance where the assigned treatment group will be the main predictor in the model. All statistical analyses and tests will be performed using SAS (v 9.1.1, Cary, NC). A two-sided P-value of <0.05 was considered statistically significant.

Data Analysis

We will perform a cost analysis to determine how changes in OR turnover time affect hospital costs and efficiency.

Ethical Obligations
Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed according to the IRB approved protocol, the Good Clinical Practice (GCP) guidelines, as well as any additional regulatory requirements. The requirement of pre-study informed consent and following of guidelines will provide assurance that the patients' rights and safety are protected.

Informed Consent Process

Each subject must provide written consent with full knowledge of the procedures involved with our research. The informed consent, approved by the IRB and in

accordance with regulatory guidelines, must be fully explained by the investigator or member of the study staff including the study aims, methods, benefits, and risks and signed by the subject before entry into the study. The subjects will be informed that the study is voluntary and that they may withdraw at any time. The subjects will be told that choosing against participation will not affect the care received for treatment. The subjects will be informed that they will be authorizing access of investigational staff to confidential medical records. The subject will be given sufficient time to read the consent and ask any questions. Once the informed consent is signed, the subject will be given a copy of the document. The subject will be given a second time to ask questions about the study on the day of their surgery while they are in the surgical prep unit and pre-operative area.

Privacy of Records and Data

All patients will be identified with a study number on clinical report forms provided by the pharmacy. Personal data of subjects used in the study will be limited to the necessary information needed. The collection of this data will be done in attempts to provide confidentiality and compliance with privacy protection regulations. Consent will be obtained from the subject before the collection of data. The data and subject identity will be kept confidential.

Risk/Benefit:
Risk to Participants

There may be side effects to taking part in this study.

Major side effects of sugammadex are: minor various side effects, including mild headache, nausea, the injection site irritation, dry mouth, fatigue, a cold sensation at the injection site, and oral discomfort

Major side effects of neostigmine are: bradycardia, salivation, muscle twitching, bowel cramps, or diarrhea.

Major side effect of glycopyrrolate are: dry mouth, vomiting; mild constipation; stuffy nose, sinus pain; or flushing (warmth, redness, or tingly feeling).

Data safety monitoring plan

All data will be monitored by the PI on a daily basis.

Stopping Guidelines / Stopping Rules: Safety

Termination may be recommended for any perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate (≥1%) for any component resulting in an unexpected SAEs.

Benefits to Participants

The benefits of participating in this study may be faster recovery, less postoperative pain and less nausea and vomiting.

Regulatory Documentation

Documentation that must be available prior to the start of the study is as follows:

- Copy of the IRB approval of the written protocol
- Copy of approved protocol and amendments
- Copy of the IRB approved informed consent
- Regulatory correspondence and FDA IND documentation
- Local regulatory documentation
- Financial disclosure of investigators
- Study and financial agreement
- Curriculum vitae for each investigator
- Verification of laboratory facility conducting experimental tests

Data Monitoring and Records

The primary investigator will monitor each individual CRF for completion and accuracy, as demonstrated by a provided signature following the review of each completed CRF. The investigator will maintain confidential individual records documented on CRFs for each subject.

Case Report Form Completion

CRFs must be completed for each subject. All data collected must be collected and entered in a timely manner to reflect the most recent observations at any point. Subjective evaluations of each subject should be performed and entered by the same investigator when possible.

Study Personnel and Responsibilities

Enrico Camporesi, MD	PI	Responsible for all study related issues
Devanand Mangar, MD, FFCP	Co-PI	Data collection and analysis
Than Tran, MMS	Biostatistician	Data Analysis and Interpretation
Prachiti Dalvi, MS	Research Coordinator	Data collection, Addresses IRB issues, communicates with IRB

Conflict of Interest
None

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