

Reducing Postoperative Opioids in
Patients Undergoing Laparoscopic
Hiatal Hernia

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Title: Reducing Postoperative Opioids in Patients Undergoing Laparoscopic Hiatal Hernia

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Funding: Departments of Surgery and Anesthesia

Type of Research: Prospective randomized double-blinded control trial

Intervention: Patients undergoing laparoscopic hiatal hernia repairs will be randomized to:

Experimental Group: Opioid Sparing Anesthesia Protocol vs. **Control Group:** Opioid Based Anesthesia Protocol

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I. Introduction: Background and Rationale:

The administration of perioperative opioids to nearly 80% of surgical patients leaves approximately 6 million Americans susceptible to becoming opioid-dependent.¹ This practice has been hypothesized as a contributing factor to the ongoing opioid crisis, where currently more than 136 Americans die from an opioid overdose every day.² Recent data suggest a potential benefit of reducing perioperative opioid use, while improving the quality of surgical recovery when employing an Opioid Sparing Anesthesia (OSA) protocol with non-narcotic analgesics.³⁻⁷

More than a million hernia repairs are performed each year in the US.⁸ With the significant nationwide obesity epidemic, it is estimated that the prevalence of hiatal hernias in the western population is approximately 20%.⁹ We perform hundreds of laparoscopic hiatal hernia repairs annually at Endeavor Health. Patients routinely receive fentanyl and other opioids during this surgery to reduce pain, but opioids also increase the risk of nausea, vomiting, and ileus. In addition, these patients are often times prescribed opioids upon discharge from the hospital. Preliminary results from a small, retrospective study among laparoscopic hiatal hernia surgical patients suggested that an OSA protocol with non-narcotic analgesics (that included dexmedetomidine and ketamine) resulted in a 33% reduction in those patients requiring opioids post-discharge.⁷ Moreover, these same patients had a significant reduction in hospital length of stay and nausea/retching.⁷ Therefore, we propose a double-blinded randomized controlled trial to compare the number of patients in OSA protocol vs. Opioid Based Anesthesia (OBA) protocol groups, who require no opioids within 7 days postoperatively, (a time period where our quality data suggest nearly all patients receive postoperative opioids in this population).

II. Hypothesis: Key Questions

The investigators hypothesize that use of an OSA protocol will result in a significant decrease in post-discharge opioid use, postoperative pain scores, total hospital opioid consumption, PACU and hospital length of stay, the incidence of significant nausea and vomiting in the PACU and on postoperative day 1, the number of patient calls to the surgeon for severe pain in the first 7 days postoperatively, rate of emergency room visits and re-hospitalizations, equivalent surgical conditions, and a reduced hospital cost.

III. Inclusion Criteria:

- a. Patients from 18-90 years old who are undergoing laparoscopic hiatal hernia surgery
- b. Elective Laparoscopic hiatal hernia repair

IV. Exclusion Criteria:

- a. Patients receiving urgent or emergent hiatal hernia surgery
- b. Patients receiving hiatal hernia surgery without laparoscopy.

- c. Patients with adverse reactions (e.g., anaphylaxis, rash) to any of the drugs in the OBA or OSA protocols.

V. Objectives: Primary and Secondary Outcomes

Primary Outcome:

- 1) The difference in discharge opioid consumption in morphine milligram equivalents (MMEs) through postoperative day 7 in patients in the Opioid Sparing Anesthesia (OSA) protocol vs. Opioid Based Anesthesia (OBA) protocol.

Secondary Outcomes:

- 1) Postoperative VAS pain scores upon PACU arrival
- 2) Postoperative VAS pain scores upon PACU discharge
- 3) Postoperative VAS pain scores upon hospital discharge
- 4) Total hospital opioid consumption (MMEs)
- 5) PACU length of stay
- 6) Hospital length of stay
- 7) Incidence of PONV in PACU
- 8) Incidence of PONV postoperative day 1
- 9) Incidence of PONV during hospital stay
- 10) Rate of rehospitalization within 30 days
- 11) Rate of reoperation within 30 days
- 12) Rate of emergency room visit within 30 days
- 13) Surgeon satisfaction with surgical conditions using 5 point Likert Score
- 14) Hospital Cost Differential between groups while in hospital using direct operating cost.
- 15) Patient-Reported Outcome Measures (PROs) following surgery
 - a. Gastroesophageal Reflux Disease Health-Related Quality of Life questionnaire (GERD-HRQL) score
 - b. Reflux Symptom Index (RSI) score
 - c. Quality of life metrics
 - d. Satisfaction with surgery
 - e. Bowel function

VI. Study Design: Prospective Randomized Double-blinded Control Trial

We plan to approach 75 study subjects undergoing laparoscopic hiatal hernia repair, with a target of 46 enrolled subjects. Subjects will be presented with the option to be a part of the study during their pre-operative appointment with the surgeon and team. At that time, if they are interested, they will be given a patient recruitment letter with more detail and a copy of the informed consent. With approval from the surgeon, subjects may also be sent the physician signed recruitment letter via Endeavor Health Connect by the research team. For patients that follow this workflow, they will only be contacted further after reading the NorthShore Connect message. Patients will be given 24 hours from the initial introduction of the study to review the consent form prior to recontact by research

staff, they may sign of their own accord within 24 hours. The patients will then either meet with or be contacted by trained research staff to further explain the study and go through the informed consent process. This will be done in person using an iPad with a secure REDCap consent form or remotely using an electronic consent with a dedicated REDCap database that will also be used for the patient data collection. iPads used during the consent process were purchased by Endeavor Health and set up by the IT Department according to Endeavor Health IT standards. A copy of consent forms signed through REDCap will be emailed to the subject automatically by the system. Additionally, patients who would prefer a paper copy of the consent form will be provided with such. A randomization allocation table will be generated by the study biostatistician and used by the Investigational Drug Services pharmacy team for assigning the participants to the treatment groups.

Pain levels will be measured using the VAS scale with patients entering their average pain over the last 24 hours. Subjects will rate their pain level on a scale of 0-10. Number "0" indicates no pain and number "10" indicates the worst experienced pain. The REDCap survey instrument will also ask the patient to fill out a survey everyday asking questions about their recovery and pain management. The REDCap surveys are attached. Patients will receive an electronic version viewable on mobile device or computers.

We collaborated with key perioperative team stakeholders to create OSA and OBA protocols based on a systematic review of the literature. The major difference in the OSA and OBA protocols (see p. 9-10) is that the OSA protocol will include boluses of dexmedetomidine and ketamine at anesthesia induction, followed by a ketamine infusion that will continue until PACU discharge. Another bolus of ketamine will be administered upon surgical incision and another dexmedetomidine bolus will be given at surgical closure to reduce the use of opioids. The OBA group will be administered a saline infusion at the same rate of the ketamine infusion (only while in the PACU) up until PACU discharge so that surgeons, patients, and PACU nurses will be blinded. The OBA group will be administered fentanyl 100 mcg IV for anesthesia induction followed by 50 mcg IV boluses when heart rate or systolic blood pressure is 20% above baseline throughout the case. Postoperative care will be the same in both groups.

The study investigators will develop a double-blinded (surgeons, PACU nurses, and patients) randomized controlled trial comparing the number of patients undergoing laparoscopic hiatal hernia repair who require no post-discharge opioids in the first 7 days postoperatively in the OSA vs. OBA groups. It is impractical to blind the anesthesia team as they are administering opioids or the non-narcotic analgesics based on the differences in heart rate and blood pressure and therefore need to know what they are administering for the safe delivery of the anesthetic in the operating room. The anesthesia team will not be involved with any of the evaluation processes in the postoperative period.

In the PACU, nurses will assess the subjects' pain by using VAS (0-10). When subjects experience of VAS > 4 they will receive hydromorphone in aliquots of 0.25mg IV until VAS is $\leq$ 4.

The discharge pain management regimen is as follows:

Mild pain (0-4) – acetaminophen 1000mg po q6hr or ibuprofen 400mg po q6hr (alternating between the two drugs)

Moderate pain (5-7)- tramadol 50mg po or Norco 5/325 (hydrocodone/acetaminophen) po q6hr

Severe pain (8+)- Patient will call surgeon

Patients are informed on how to rate their pain and the associated post discharge pain management regimen prior to discharge. Post-discharge data will be collected via electronic REDcap surveys (VAS and MME surveys) every day up to 7 days post-discharge. Patients will be provided with a pain medication diary for postoperative days 1-7 to help track their pain score and medications throughout the day before entering responses in the REDCap VAS and medication surveys. Morphine Milligram Equivalents (MMEs) will be calculated using our hospital's opioid conversion scale¹⁰⁻¹²(see p. 11). The investigators will prospectively evaluate the following differences between groups: VAS scores upon PACU arrival/discharge, and upon hospital discharge, total hospital opioid consumption, incidence of clinically significant nausea and vomiting in the PACU and on postoperative day 1 using the PONV Intensity Scale¹³ (see p. 12), duration of PACU and hospital length of stay, rate of readmissions, reoperations, and emergency room visits within 30 days of discharge, number of patients who call surgeon's office for severe pain, surgeon satisfaction with surgical conditions using a 5-point Likert Score, and hospital cost during hospital stay differential between groups.

The study investigators, research coordinator, and research assistant will collect data using REDCap to send VAS and MME surveys beginning the day after discharge. For patients having same-day surgery, this will be the first postoperative day. Patients will receive an e-mail daily covering the first seven days after surgery generated automatically in REDCap that contains a link to the survey. If subjects do not fill out the survey, they will be contacted by the research staff reminding them to fill out the survey with the option to answer the questions over the phone.

The electronic medical record will be utilized to record demographic and surgical information on patients. The demographics data will include: age, sex, race, BMI, medical history, surgical history, prior and current medications, alcohol and tobacco use, and ASA status. Surgical information will include: the type of surgery, length of surgery, hospital admission/outpatient surgery, whether there

was a need for a return to the operating room, hospital length of stay, surgical complications, and block complications.

The subject's surgeon will be asked to fill out a paper 5-point Likert Score survey about the surgical conditions for each study subject. The surgeons will be verbally consented in-person prior to filling out the survey.

Additionally, the Endeavor Health Gastroesophageal Registry will be used to extract data regarding Patient-Reported Outcome Measures (PROs) following surgery. This data will include Gastroesophageal Reflux Disease Health-Related Quality of Life questionnaire (GERD-HRQL) score, Reflux Symptom Index (RSI) score, Quality of life metrics, Satisfaction with surgery, and Bowel function following surgery.

VII. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

The following steps will be used to keep all PHI confidential:

- The investigators will use an encrypted and password protected anesthesiology research collaboration portal and Endeavor Health REDCap data warehouse for the data collection forms will only be accessible to the PI, co-investigators, and research coordinator. The MRN's and subject numbers will be decoupled from the data collection forms and be stored on the collaboration portal at Endeavor Health.
- The data will be stored for three years after the study is published. It will be stored on the same password protected and encrypted Endeavor Health anesthesiology research collaboration portal for the specific decoupled MRNs and subject #s.

VIII. Statistical Considerations:

Data will be summarized using descriptive statistics. Continuous variables will be compared using the independent samples t-test or Wilcoxon rank-sum test. Categorical variables will be compared using chi-square or Fisher's exact tests. Patient demographics will be compared between those with missing data and those who completed all surveys. If there is potential bias due to missing data concerns, multiple imputation by chained equations techniques will be used along with full case analysis. All data will be analyzed with two-tailed tests and a significance level of $p < 0.05$ using SAS 9.4 (Cary, NC). Assuming that 100% of the opioid based group will receive post-discharge opioid and we expect 70% of the opioid sparing group to receive post-discharge opioids (30% absolute

difference between groups), 23 patients in each group would be needed to power this study with a 90% power and a significance level of $\alpha=0.05$. Therefore, a total of 46 patients would be needed who undergo elective laparoscopic surgery. We plan on approaching 75 total patients over a 1-year time period as we project a 61% eligible enrollment success rate from experience with other studies.

IX. Foreseeable Risks and Benefits:

Benefits:

This study will provide valuable insight into opioid reduction during anesthesia. This could lead reduced postoperative nausea and vomiting, potentially reducing cases of postoperative ileus in laparoscopic hiatal hernia repair, which may prolong patient hospital stay.

Risks:

There are always risks associated with general anesthesia. Opioids have a potential for side effects including: severe nausea, high risk of addiction, urinary retention, severe confusion, hallucinations, spasm of the airway, skin rash, hypotension, bradycardia, and increased liver enzymes. The OSA group modifies the standard anesthetic/analgesic approach by providing dexmedetomidine and ketamine in lieu of opioids. Both of these drugs are FDA approved for use in anesthesia and have been used in practice for decades. The side effects of these medications include hypotension or hypertension, bradycardia or tachycardia, constipation, nausea, delirium, double vision, and temporary memory loss. Anesthesia professionals are trained to manage all of these symptoms and these side effects are rare at the low doses being used in the present study.

Ketamine Adverse Effects:

>10%: these adverse effects are typically seen more at higher doses than being used in the present study.

Hypertension (Increased blood pressure)

Increased Cardiac Output (Increased amount of blood pumped per minute)

Increased Intracranial Pressure (Increased pressure on the brain)

Tachycardia (Fast heart rate)

Tonic-clonic movements (Rigidity followed by violent shaking of muscles)

Visual hallucinations (Seeing things that are not there)

Vivid Dreams (Remembering dreams as if they were real)

1-10%:

Bradycardia (Slow heart rate)

Diplopia (Double vision)

Hypotension (Low blood pressure)

Increased Intraocular Pressure (Increased pressure around the eye)

Nystagmus (Repetitive, uncontrolled eye movements)

<1%:

Anaphylaxis (Severe allergic reaction)
Cardiac arrhythmia (Abnormal heart rhythm)
Depressed cough reflex (Inability to cough)
Fasciculation (Involuntary twitch of an individual muscle)
Hypersalivation (Increased production of saliva in the mouth)
Increased metabolic rate (Increased speed of breakdown of food)
Hypertonia (Muscles are too stiff)
Laryngospasm (Seizing of the vocal cords)
Apnea/Respiratory Depression (Stop/reduced breathing)

Dexmedetomidine Adverse Effects:

>10%:

Hypotension (25-28%) (Low blood pressure)
Hypertension (12-16%) (Increased blood pressure)
Nausea (9-11%) (Uneasiness in the stomach)

1-10%:

Bradycardia (5-7%) (Slow heart rate)
Pyrexia (4-5%)
Atrial fibrillation (4%) (Abnormal heart rhythm)
Dry mouth (3-4%)
Vomiting (3-4%)
Hypoxia (2-4%) (Reduced oxygen)
Hypovolemia (3%) (Reduced blood or fluid)
Atelectasis (3%) (Collapsed lung)
Tachycardia (2-3%) (Increased heart rate)
Post-procedural hemorrhage (2-3%) (Bleeding after your procedure)
Anemia (2-3%) (Reduced red blood cells)
Agitation (2%)
Hyperthermia (2%) (Increased temperature)
Pain (2%)
Hyperglycemia (2%) (Increased sugar level)
Chills or rigors (2%)
Oliguria (2%) (Production of small amounts of urine)
Thirst (2%)
Acidosis (1-2%) (Blood is acidic)
Pleural effusion (1-2%) (Buildup of fluid in the chest)
Pulmonary edema (1%) (Fluid in the lungs)
Hypocalcemia (1%) (Decreased calcium)
Urine output decreased (1%)
Sinus tachycardia (1%) (Normal, fast heart rate)

<1%:

Ventricular tachycardia (dangerous, abnormal heart rhythm)
Wheezing
Peripheral edema (fluid buildup in the arms and legs)

X. Equitable Selection of Subjects

Patients will not be categorically excluded from this research. The study population will be limited to those who are eligible based on the inclusion criteria for this study. We anticipate an equal number of males and females to be enrolled in this randomized trial. No patients will be excluded based on sex, religion, or culture beliefs.

XI. Recruitment and Consent Procedures

Physicians' clinical practices will be the basis of recruitment for this study. The subject's laparoscopic gastrointestinal surgeon will introduce the study to the subject at their pre-operative clinic appointment. The research team may also send the patient the recruitment letter via a NorthShore Connect message with approval from the patient's surgeon. Patients following this workflow will only be contacted further after reading this message. If the subject is interested in participating, they will receive the consent form for the study. This document will be read by the patients and reviewed by the subject with a licensed physician investigator or a research coordinator prior to participating in the study. The subject will be given as much time as they need to review the consent. They may choose to sign the form at the time of their appointment, or they may take the consent form home to review and later receive a phone call from an investigator or research coordinator to provide consent. Any questions, concerns, or ambiguities will be clarified by Dr. Steven Greenberg, and/or a research coordinator or co-investigators prior to the subject signing consent. Subjects will sign informed consent and only then will begin participation in the study.

XII. Data and Safety Monitoring

The research team will conduct weekly research meetings with study staff to review study progress, including recruitment strategies, enrollment numbers, protocol issues, and safety issues. Patients will be asked to contact an investigator or study staff member at any time during or after their participation in the study should they have any questions or concerns.

XIII. Monitoring and Quality Assurance

During the study, monitoring will be conducted by the PI, Dr. Steven Greenberg. Dr. Greenberg and the study coordinator will be responsible for monitoring the data collected as well as ensuring that the study is being executed in accordance with the protocol. Patient data will be monitored for significant adverse events by a group of three independent board-certified anesthesiologists. A review of significant adverse events will be performed after every 20 cases. The anesthesiologists will submit a summary report to the Endeavor Health's Institutional Review Board on a quarterly basis. If higher than expected complication rates occur, the study will be stopped. If serious complications such as anaphylaxis or seriously low blood pressure occur in 8 out of the original N of 75 patients, the study will be stopped. Based on current

literature, we do not expect this to occur. In a retrospective study of approximately 300 patients, it was determined that the overall surgical complication risk was reduced with opioid free anesthesia. There have been no reported deaths at any institution. Anticipated events include acute pain control. Unanticipated events include hypotension, bradycardia, myocardial infarction, and complete heart block. All serious events, including expected events are to be assessed as a matter of course by the three anesthesiologists. Expectedness is defined by reasonable possibility that an event may have been caused by the anesthetic regimen.

XIV. Financial Considerations

There are no financial incentives to participate in this study.

XV. Conflict of Interest

There is no conflict of interest about the conduct of this study.

XVI. Appendix

Opioid Conversion Chart

MEDICATION	PARENTERAL DOSE (MG)	ORAL DOSE (MG)
Morphine (Roxanol, MSIR)	10	30
Hydromorphone (Dilaudid, Hydrostat)	1.5	7.5
Fentanyl (Duragesic)	0.1	--
Oxycodone (Roxicodone, Percocet)	--	20
Methadone (Dolophine)	Refer to Lexicomp Consider expert consultation	Refer to Lexicomp Consider expert consultation
Hydrocodone (Vicodin, Lortab, Norco)	--	30
Oxymorphone (Opana)	--	10*
Tapentadol	--	100-150*

Codeine	--	200
Meperidine (Demerol)	75	Not Recommended
Buprenorphine (Buprenex)	0.4	--

*estimated conversion factor which is not supported by published evidence

- **Initially, decrease calculated dose by 25-50% when switching opioids**
- **Further dose adjustments should be based on clinical response**

PONV INTENSITY SCALE:

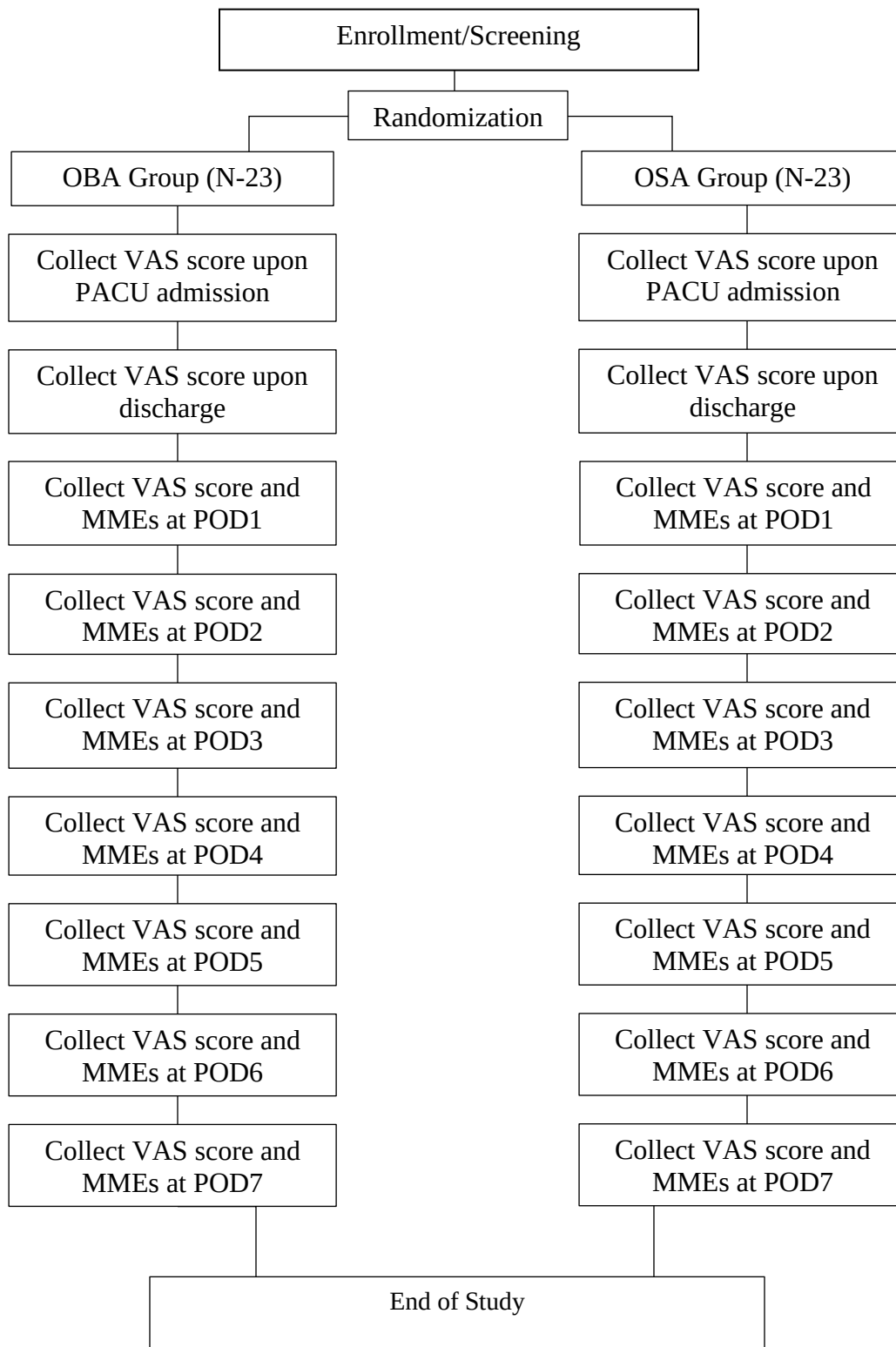
Assessment	Score
A. At 6 hours after surgery (or time of discharge if after ambulatory surgery)	
Q1 Have you vomited or had dry-retching*? a) No b) Once or twice c) Three or more times	0 2 50
Q2 Have you experienced a feeling of nausea (<i>"an unsettled feeling in the stomach and slight urge to vomit"</i>)? If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally or eating and drinking? a) No b) Sometimes c) Often or most of the time d) All of the time	0 1 2 25
Q3 Has your nausea been mostly: a) varying (<i>"comes and goes"</i>)? b) constant (<i>"is nearly or almost always present"</i>)?	1 2
Q4 What was the duration of your feeling of nausea (in hours [whole or fraction])?	___ · ___ h
For Part A, if answer to Q1 = c), score A = 50; otherwise, select the highest score of Q1 or Q2, then multiply x Q3 x Q4	PONV intensity score (0-6 h) A =

*Count distinct episodes: several vomits or retching events occurring over a short time frame, say 5 min, should be counted as one vomiting/dry-retching episode; multiple episodes require distinct time periods without vomiting/dry-retching

Scoring for Clinical Importance of PONV

Total Score	Score
Clinically important PONV is defined as a total score ≥ 50 at any time throughout the study period. Scores at 6 and 24 (and, if considered important in the clinical context, 72) hours can be added for quantification of the entire period, or sub-scales used for each period.	Final PONV intensity score (0-72 h)
A + B + C =	

XVII. Study Flowchart



XVIII. Budget

Overhead	
IRB Fees	
Initial Review	\$2,750
Annual Renewals	\$1,100
Revisions, Amendments, etc.	\$1,100
Coverage Analysis	\$1,200
Pharmacy Fees	
Start Up	\$3,000
Renewal	\$1,000
Close Out	\$250
Dispensing Fee	\$100/dosage x 60 patients = \$6,000
Study Personnel Time	
Research assistant	60 patients x \$20/hr. 4 hours per patient = \$4,800
Research coordinator	60 patients x \$50/hr. 4 hours per patient = \$12,000
Statistician	50 hours x \$100/hr. = \$5,000
Principle Investigator	416 hours x \$250/hr. = \$104,000
Total	\$142,200

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