A Pilot Study Comparing the Effectiveness of an Opioid- Sparing Analgesic Regimen and an Opioid Based Regimen on Post- Operative Pain Control in Cardiac Surgery Patients (INOVA OPIOID)

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Site of Investigation: Inova Heart and Vascular Institute
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ABSTRACT

Title: A Pilot Study Comparing the Effectiveness of Opioid- Sparing Analgesic Regimen and an Opioid Based Regimen on Post- Operative Pain Control in Cardiac Surgery Patients

Short Title: Opioid Sparing in Post-Operative Cardiac Surgery Pain (INOVA OPIOID)

Rationale: To demonstrate the effectiveness of an opioid sparing pain regimen post cardiac surgery to provide optimal pain relief as well as to minimize opioid related side effects.

Objectives: We hypothesize that an opioid- sparing regimen consisting of scheduled acetaminophen and gabapentin for 72 hours post- operatively, will reduce opioid consumption, reduce opioid related side effects, and result in a decrease in overall healthcare costs.

Study Type: Single center, open label, prospective, randomized clinical trial.

Study Design: A total of 20 patients between the ages of 18-85 years old that have undergone sternotomy procedures in the context of cardiac surgery will be randomized to one of two treatment groups.

Study Methodology: We will analyze the total opioid consumption and pain scores of sternotomy patients beginning with admission to CVICU post-surgery (day 0) through post-operative day three (day 3) in patients receiving acetaminophen IV paired with gabapentin pro ora (PO).
Also analyzed will be hospital length of stay, incidence of ALT/AST >3X ULN (AST >168, ALT >105), occurrence of ileus during hospitalization, pre and post-surgical incentive spirometry tidal volume values; pre surgery and through post- operative day three (3), number of hours post CVICU arrival to extubation and perform cost analysis assessment of medication and hospitalization costs.

Statistical Methodology: Although underpowered for this pilot, our statistical analysis plan is designed to similarly assess the feasibility of the larger study to follow. Primary analyses for this pilot will be to determine feasibility of larger study and determine estimates of primary outcome (e.g., total opioid consumption, pain scores, etc.) mean and variance parameters for sample size calculation. Estimates for study attrition, and secondary outcomes of hospital length of stay, incidence of AST/ALT > 3x ULN (AST >168, ALT >105), etc. will be calculated. All analyses will be conducted as intent-to-treat.

1. INTRODUCTION

1.1. Specific Aims

The management of post-operative cardiac surgery pain representative of many etiologies remains a challenge to clinicians. Opioid pain medications can cause or exacerbate side effects which directly contribute to morbidity and mortality in post- operative cardiac surgery patients, as well as cost of medication and hospitalization. In this study we will demonstrate that an opioid sparing, multimodal pain regimen consisting of intravenous acetaminophen paired with PO gabapentin will reduce opioid consumption in addition to providing optimal pain relief, reduce opioid related side effects, and decrease the cost of medication and hospitalization. Reduction in opioid consumption and pain relief will be demonstrated by decreased patient self-report of pain and requests for breakthrough opioid pain medication. Reduction of opioid related side effects will be demonstrated by lack of incidence of ileus during hospitalization, tidal volumes that return and are maintained at pre surgical levels through post- operative day 3, and decreased time to extubation from Cardiovascular Intensive Care Unit (CVICU) arrival. Increase in AST/ALT will be monitored as a safety assessment. Additionally, we will demonstrate a reduction in total cost of hospitalization via decreased length of stay, as well as decreased medication costs.

1.2. Hypothesis

We hypothesize that an opioid- sparing pain regimen consisting of scheduled IV acetaminophen and PO gabapentin for 72 hours post- operatively will reduce opioid consumption while maintaining adequate pain relief as evidenced by pain scores less than two (2), and minimal request for breakthrough opioid medication, and that reduced opioid consumption will lead to a reduction in the incidence of ileus, rapid return to pre-surgical respiratory tidal volumes, and timely extubation, AST/ALT within normal limits, and demonstrate a positive effect on the cost of medication and hospitalization.

1.3. Background and Significance

Post-Operative Cardiac Surgery Pain

The management of pain resultant from cardiac surgery necessitating a sternotomy is a challenging clinical quandary. Post cardiac surgery pain is associated with a variety of etiologies; sternotomy incision, retraction of the ribs and sternum with possible rib dislocation or fracture, pericardotomy, internal mammary and or saphenous vein harvesting, operative trauma to the parietal pleura, insertion of chest tubes, reactions to pacemaker wires, brachial plexus injury, insertion of mediastinal and pleural drains, and other body trauma occurring as a result of surgery [1, 2]. Cardiac surgery patients may experience severe pain in post anesthesia recovery as well as upon transfer to the Cardiovascular Intensive Care Unit [3]. Well controlled pain postoperatively is associated with positive physical and psychological outcomes. Well controlled pain facilitates early extubation, improves hemodynamics, improves myocardial oxygenation, improves hemostatic and immunologic modulation, decreases the incidence of ischemic events, maximizes chest expansion during respiration, enables early ambulation [2,4,5] and is responsible for the ensuing positive clinical outcomes that are associated with early ambulation (eg. deep vein thrombosis prophylaxis). Optimal pain control is associated with lower rates of cardiovascular complications, pneumonia, and avoidance of hypercoagulability in the postoperative recovery period [3, 6]. Equally, poorly controlled pain is responsible for elevated catecholamine levels which can progressively trigger myocardial ischemia, stroke, and bleeding complications [4, 25] post cardiac surgery. Cardiac surgery has the potential to disrupt the normal process of coagulation which could predispose a patient to thrombosis, this process may be attenuated by the increased physiologic benefit of adequate pain relief and its effect on increasing blood flow [6].

The Use of Opioids for Pain Management and Their Myriad Side Effects

Opioid analgesics have traditionally been the mainstay of treatment for postoperative cardiac surgery pain despite the myriad negative side effects of these medication regimens which constitute major barriers to their use [4, 7]. These side effects are frequently dose dependent and exert a profound negative influence on patient recovery, early discharge, safety, and associated morbidity and mortality [1, 7]. Perhaps the most significant effects involve the incidence of post-operative nausea and vomiting (PONV) and paralytic ileus [2, 8, 9, 10].

Paralytic ileus [ileus] refers to a state of low or absent peristalsis which results in secretion accumulation in the gastrointestinal tract leading to symmetric abdominal distension and vomiting [11]. Paralytic ileus is a significant contributor to mortality post cardiac surgery. Paralytic ileus etiology is multifactorial. Most commonly ileus results from a low gastrointestinal flow state during the perioperative period [12]. Surgical stress may disrupt the natural arrangement of the bowel and thus impair the function of the gastrointestinal tract [10]. PONV rates post cardiac surgery can range from 42- 71% of cardiac surgery patient utilizing opioids for post- operative pain [9]. PONV is associated with aspiration pneumonia, dehydration, electrolyte imbalances, which in turn may lead to or contribute to dysrhythmia, fluid overload, and uncontrolled pain secondary to absorption anomalies [9]. PONV has a profound impact on a patient's ability to participate in their recovery [1, 9] Other harmful effects of post-operative opioid consumption include; constipation, profound sedation, dizziness and confusion especially in elderly patients, suppression of gastrointestinal motility, and respiratory depression [1, 13]. Also concerning is that severe acute pain post sternotomy is a significant predictor of chronic pain which is fraught with profound psychological, physical, and financial costs [3, 14, 15], including chronic incisional pain and the potential for post-operative opioid addiction[16] which has of late reached epidemic proportions[25]. More than 2 million Americans suffer from substance abuse related to opioid consumption [25].Opioid induced hyperalgesia (OIH) is also a significant complication of an opioid based pain regimen. OIH is the direct sequlae of chronic opioid administration and results in patients developing a heightened sensitivity to pain [13]. Finally, scholarly evidence for the use of chronic opioids in the treatment of non-cancerous pain does not exist. In fact eminent pain societies recommend the use of opioid medications with "great restraint and caution" [3, 17,25]. Indications for responsible, effective pain management favor a plan based on the individual's unique history and condition, a multimodal regimen, and multidisciplinary collaboration [1, 3, 18].

Multimodal Analgesia Regimens

Multimodal pain regimens offer significantly better relief in post cardiac surgery patients [1]. Selection of a multimodal approach for post cardiac surgery pain is advocated to reduce opioid requirements. These regimens should include regional anesthesia, non-narcotic medication, and additional complimentary regimens[2]. Multimodal analgesia is the mainstay of responsible comprehensive individualized pain management [13]. Multimodal analgesia is the combination of different pharmacologic agents and routes of administration in order to produce analgesic effects along multiple pain pathways [13]. The use of multimodal analgesia provides pain relief that is both potent and synergistic while minimizing possible adverse effects of the medication [13]. Multimodal pain regimens combine agents to provide both central and peripheral analgesia [4]. The use of a multimodal pain regimen as opposed to an opiate based regimen offers significantly better pain relief [1, 17].

The Use of Gabapentin and Intravenous Acetaminophen

Gabapentinoids are effective on centrally mediated pain pathways and thus successful in the treatment of neuropathic pain, they have demonstrated a reduction in acute pain and have beneficial effects on the development of chronic pain and pain scores post-surgery [13, 14, 19, 20, 21, 22,25]. Gabapentin with its anti-inflammatory properties offers relief superior to opiates or acetaminophen alone in cardiac surgery patients [1, 5, 20, 21]. High quality evidence confirms the effectiveness of a multimodal regimen which includes acetaminophen[17] IV (IV APAP) is a powerful potential constituent of a multimodal pain management regimen post cardiac surgery. Without serious side effects and when used as recommended this medication is devoid of platelet, kidney, or gastrointestinal sequelae and therefore is beneficial to the cardiac surgery patient in a variety of ways. The intravenous route (IV APAP) ensures more efficient absorption and avoids the first- pass metabolism effect.

Post- Operative Pain Assessment

The Numeric Rating Scale is a one dimensional measurement of pain intensity in the adult patient. Various versions of this scale exist although the most commonly used version involves a 1-10 scale for scoring pain. Zero (0) represents no patient reported pain and 10 represents the patient reporting [the] "worst pain imaginable". The scale is administered verbally and the patient translates their pain intensity to a number on the scale. Higher scores indicate extreme pain[23, 24].

Study Procedures

The Cardiovascular Intensive Care Unit (CVICU) will be the setting for our clinical trial involving two groups of subjects and comparing the post cardiac surgery opiate based standard of care regimen in effect at the time of protocol development (Group 1) within the IHS/IHVI at the Inova Fairfax Medical Campus (IFMC)with a treatment group (Group 2). Group 2 will receive a scheduled multimodal pain regimen consisting of PO gabapentin paired with intravenous acetaminophen. Opiates will be available for breakthrough pain in the treatment group for pain scores greater than 4. The outcomes of total opioid consumption and minimum/ maximum pain scores will be assessed at the 24 hours, 48 hours, 72 hours, and PRN timepoints. Assessment will include amount of opioids consumed in both groups as well as number of requests for breakthrough pain medication in Group 2.

The term 'Standard of Care' in this protocol will refer to the adapted regimen of opioid based pain relief prescribed at the time of protocol development at the IHS/IHVI/IFMC.

Standard of Care regimens at the IHS/IFMC are revised regularly based on advances in evidence based practice, patient response, continuously evolving safety information, issuance of professional society practice guidelines, and physician recommendations.

While the post cardiac surgery pain standard of care regimen currently differs from the regimen to be administered to the Group 1 subjects in this clinical trial there is no change to the risk benefit ratio and is addressed in this protocol to provide transparency of practice. Also, this study will contribute meaningful evidence for future modifications to the standard of care at the IHS/IHVI/IFMC.

Minimum and maximum pain scores in all study groups will be assessed via Numeric Rating Scale (0-10) as per Inova Health System (IHS) policy; *'Pain Management for the Adult Population'*, at 24 hours, 48 hours, 72 hours, and PRN with opioid requests in all groups and opioid administration follow up within one hour as per IHS inpatient medication administration policy. Follow up medication administration scores will not be recorded as part of study results.

Secondary assessments will include the incidence of ileus both during hospitalization, increase in AST/ALT, post-operative tidal volumes as assessed by incentive spirometry as compared to pre- surgical values, time from CVICU arrival to extubation in both groups, and the effects of an opioid based regimen versus an opioid sparing regimen on cost of medication and hospitalization.

We hypothesize that a scheduled opioid- sparing pain regimen consisting of IV APAP and PO gabapentin for 48 hours post- operatively will reduce opioid consumption while maintaining adequate pain relief as evidenced by pain scores less than two (2), and a reduction in opioid consumption, and that reduced opioid consumption will lead to a reduction in the incidence of ileus, an opioid related side effect, no increase in AST/ALT, post-operative tidal volumes as assessed by incentive spirometry comparable to pre- surgical values, and demonstrate a positive effect on the cost of medication and hospitalization.

1.4 Preliminary Studies

The objective of this pilot study is to provide evidence that multimodal pain therapy utilizing IV APAP and PO Gabapentin will provide more effective pain relief than standard of care opioids as evidenced by pain scores <2. And the reduced consumption of opioids will lead to a reduction in ileus, no increase in AST/ALT, post-operative tidal volumes as assessed by incentive spirometry comparable to pre- surgical values, while also showing a positive effect on the cost of medication and hospitalization.

The Principle Investigator Ramesh Singh is a cardiothoracic surgeon at the Inova Heart and Vascular Institute (IHVI) with over 25 years of experience and well qualified for the design and conduct of the study. Dr. Singh has performed over 177 cardiothoracic surgeries at the IHVI in 2017 alone.

2. STUDY DESIGN AND SUBJECT SELECTION

2.1 Study Type

Single center, open label, prospective, randomized clinical trial.

2.2 Setting/Location
Inova Heart and Vascular Institute (IHVI)
3300 Gallows Road
Falls Church, Virginia 22042

2.3 Duration of Study
Consented and randomized subjects will participate for three (3) days starting at admission to CVICU (day 0). Biological specimens will not be collected for the purposes of this study.

2.4 Number of Subjects
A total of 20 patients, 10 per study arm are expected to participate in this study.

2.5 Study Population
2.5.1 Gender of Subjects
The study population is inclusive of both genders (male and female).

2.5.2 Age of Subjects
Subject enrollment will be comprised of subjects 18- 85 years of age.

2.5.3 Racial and Ethnic Origin
The study population will be inclusive of all racial and ethnic subgroups.

2.5.4 Vulnerable Populations
Children, pregnant women, institutionalized persons, and persons with decisional incapacity will not be enrolled in this study.

2.6 Recruitment
Patients will be recruited upon first contact with the cardiac surgery service either while inpatient pre-surgery or outpatient at the Cardiac and Thoracic Surgery Associates office located at 2921 Telestar Court, Falls Church, Virginia during the preoperative consult/ visit. Patients will not be consented less than 24 hours before surgery to provide adequate time for participation consideration.

2.7 Inclusion Criteria
1. Patient between 18 and 85 years old.
2. Elective or urgent surgery requiring sternotomy approach
3. Subject is able to read and has signed and dated the informed consent document including authorization permitting release of personal health information (PHI) approved by the Inova Institutional Review Board (IRB).

2.8 Exclusion Criteria
1. Patients lacking enteral access on post-operative day 0
2. Inability to communicate
3. Active chronic pain with opioid therapy
4. Active chronic use of gabapentin or pregabaldin
5. Active substance abuse
6. Current self- report of alcoholism
7. End stage renal disease
8. Active renal dialysis therapy

3. STUDY METHODS AND PROCEDURES

3.1 Schedule of Assessments

<table>
<tr><th colspan="2">Schedule of Assessments</th></tr>
<tr><th>Group 1:Standard of Care</th><th>Group 2: Total 48[5] hours</th></tr>
<tr><td>PRN opiates per patients self- report of pain. Dosing based on patient pain score report.</td><td>Scheduled post-op loading dose of IV acetaminophen 1000mg X 1 dose AND Gabapentin 600 mg PO X 1 dose upon arrival to the Cardiovascular Intensive Care Unit (CVICU)</td></tr>
<tr><td>Pain will be assessed in standard of care group every 12 hours or twice per day for 72 hours by study personnel.</td><td>Pain will be assessed in standard of care group every 12 hours or twice per day for 72 hours by study personnel.</td></tr>
<tr><td>Assessment of tidal volume via incentive spirometry q day by study personnel.</td><td>Assessment of tidal volume via incentive spirometry q day by study personnel.</td></tr>
<tr><td>1-3 (Mild pain) Acetaminophen 650 mg PO q4 hours (Mild pain) PRN</td><td rowspan="3">Scheduled Acetaminophen 1000 mg IV q6[1,4] X 42 Hours and PO Gabapentin 300 mg[2] q8 hours X 40 Hours then discontinue[2]
Then:
Acetaminophen 1000 mg PO q6 hours PRN for pain scores 4-10 (Moderate to severe)[4]

Patients with moderate hepatic disease and/or severe renal impairment will receive Acetaminophen 1000 mg PO q 12 hours X 48 hours, then q12 hours PRN for pain scores 1- 10 (mild to severe)

Patients with Creatinine clearance <30mL/min will receive 100 mg Gabapentin PO q8 hours X 40 hours[2]</td></tr>
<tr><td>First line:

4-6 (Moderate pain): Tramadol 50mg PO q4 PRN</td></tr>
<tr><td>Second line[3]: If first line is ineffective X 2 doses

4-6 (Moderate pain): Oxycodone/acetaminophen 5/325 mg PO q4 hours PRN

7-10 (Severe pain): Hydromorphone 0.25 mg IV q3 hours PRN</td></tr>
<tr><td></td><td>Administered in conjunction with an opioids for moderate to severe breakthrough pain (Scores 4-10)</td></tr>
<tr><td></td><td>Schedule for breakthrough pain Group 2:
1st line: Score 4-6 Tramadol 50 mg q4 PRN
2nd line[3]: Score 4-6 Oxycodone 10 mg PO q4 hours PRN
Severe pain Score 7-10: Hydromorphone 0.25 mg IV q3 hours PRN</td></tr>
</table>

[1] *Start 6 hours post CVICU arrival loading dose*
[2] *Start 8 hours post CVICU arrival loading dose*
[3] *If first line ineffective X 2 doses*
[4] *Acetaminophen administrations will not exceed 4000 mg per 24 hour period.*
5 *Experimental regimen will be administered to Group 2 for 48 hours. Pain assessment will be for 72 hours beginning at time of CVICU arrival.*

3.2 Randomization

Allocation of study treatment will be performed via a web-based interactive randomization system, based on a computer-generated random sequence with a random block size.

3.3 Endpoints/Outcomes Measurements

3.3.1 Primary Outcomes.

The primary outcome will be reported as total opioid consumption in Group 2.Total opioid consumption in Group 2 will be assessed at 24 hours, 48 hours, and 72 hours from the initial dose of IV acetaminophen and PO gabapentin received upon arrival in the CVICU. Assessment will include amount of opioids consumed as well as number of requests for breakthrough opioid pain medication in Group 2.

Minimum and maximum pain scores in all study groups will be assessed via Numeric Rating Scale (0-10) as per Inova Health System (HIS) policy *'Pain Management for the Adult Population'* at 24 hours, 48 hour, 72 hours, and PRN with opioid request in all groups and administration follow up within one hour as per IHS inpatient medication administration policy Follow up scores will not be recorded as part of study procedure.

3.3.2 Secondary Outcomes

Secondary outcomes include decreased incidence of ileus, AST/ALT > 3x ULN (AST >168, ALT >105), post-operative tidal volumes as assessed by incentive spirometry, number of hours post CVICU arrival to extubation and analysis of medication and hospitalization costs.

3.4 Consent/Assent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB -approved informed consent. If the subject is capable of doing so, he/she will indicate assent by personally signing and dating the written informed consent document. Informed consent must be obtained by the Principal Investigator, Sub-Investigator, or the Study Coordinator; individuals qualified to obtain informed consent before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent will be documented in the subject's medical record as well as clinical trial source documents.

3.4 Criteria for Withdrawal of Subjects from the Study.

Subjects in the experimental groups will be withdrawn from the study if there is no enteral access beyond post- operative day 0, and for increased serum liver function values.

4. STATISTICAL CONSIDERATIONS/DATA ANALYSIS

4.1 Sample Size

Twenty subjects, 10 per arm (Group 1opiate based standard of care, and Group 2 multimodal regimen of IV APAP and PO gabapentin) to determine feasibility of larger study and determine estimates of primary outcome (i.e., total opioid consumption, pain scores, etc.) mean and variance parameters for sample size calculation for larger study to follow. Estimates for study attrition, and secondary outcomes of hospital length of stay, incidence of AST/ALT > 3x ULN, (AST >168, ALT >105) etc. will be calculated.

4.2 Method of Data Analysis

Although underpowered for this pilot, our statistical analysis plan is designed to similarly assess the feasibility of the larger study to follow. Primary analyses for this pilot will be to determine feasibility of larger study and determine estimates of primary outcome (e.g., total opioid consumption, pain scores, etc.) mean and variance parameters for sample size calculation. Estimates for study attrition, and secondary outcomes of hospital length of stay, incidence of AST/ALT > 3x ULN (AST >168, ALT >105) , etc. will be calculated. All analyses will be conducted as intent-to-treat. Data will be presented as mean ± standard deviation or frequency and percent, where appropriate. Data will be assessed for departures from normality using Kolmogorov-Smirnov tests. Departures from normality will be treated using nonparametric tests (e.g., Wilcoxon, Kruskal-Wallis, etc.). However, given the short duration of the total patient enrollment and total patient time in study, we anticipate minimal missing data or patient attrition. Subjects with missing data ≥ 10% will be examined to determine if missing data is non-random.

To test the primary hypothesis that for significant differences between groups, we will use separate GLM for total opioid consumption (repeated measures [3 time points], dependent variable [DV]), total number of breakthrough pain medication requests (DV) and medication cost (DV). Time points (n=3) to assess total opioid consumption and breakthrough pain medication requests will be at 24, 48 and 72 hours. Medication cost will be assessed once following discharge. An interaction term will be included for the group (n=2)* time (n=3) models (DV=total opioid consumption and breakthrough pain medication requests). Pain (dichotomized, pain score < 2) will be assessed using an unconditional binary logistic regression approach. *Post-hoc* testing for group comparison (Group 1 vs. Group 2) and group by time interaction (e.g., total opioid consumption only, etc.) will be performed using Tukey's least significant difference test (LSD) for GLM models and estimation procedures (contrasts) for logistic regression (Group 1 vs. Group 2). To test the hypothesis that reduced opioid consumption will lead to a reduction in the incidence of ileus, incidence rates and 95% confidence intervals (CI) per group will be calculated and compared using conditional exact tests based on the binomial distribution. Secondary outcomes include

hospital length of stay (LOS, days), antiemetic requirement, the incidence of AST/ALT > 3x ULN(AST >168, ALT >105) , the incidence of ileus during hospitalization will be calculated using either methods described above; GLM (LOS), unconditional logistic regression (antiemetic) or exact tests (AST/ALT, ileus).

4.3 Data Storage

4.3.1 Data Management

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). Each subject screened and enrolled will be assigned a subject identification number (SID) and a list of subjects with their corresponding SID will be maintained separately from collected data. Physical case report forms (CRF's) will be stored at the research site in a locked office and electronic subject data will be locked in a password protected file on a secure internet server, accessed only by authorized research staff. Only members of the research team will be able to access to this data on the secure server and the file password.

4.3.2 Records Retention

The Investigator will maintain the records of drug disposition, final CRFs (CDROM copies), worksheets, source documents, and all other study-specific documentation in accordance with ICH Guidelines. Essential documents should be retained for at least three (3) years after the investigation is formally discontinued.

5. HUMAN SUBJECTS PROTECTION (RISKS, BENEFITS, AND ALTERNATIVES)

5.1.1 Potential Loss of Privacy

Protected health information (PHI) will be collected during the study. The risk for breach of confidentiality and privacy will be minimized by shielding the subjects unlinking his or her identity from his or her personal health information.

5.1.2 Potential Adverse Events

Aside from standard of care cardiac surgery practices and procedures, no other additional treatments or procedures will be given to subjects for this trial.

5.2 Benefits and Alternatives

There are no direct benefits to the patient. Participation in the study is entirely voluntary. The alternative is not to participate in the trial.

6. SUBJECT COMPENSATION

6.1 Costs

There are no costs to participate in the research study.

6.2 Payment

There will be no payment to the subject for participation in the research study.

7. ADVERSE EVENT REPORTING

7.1 AE Recording

Adverse events will be collected postoperatively. For the purpose of this study, only the following adverse events will be collected and reported:

- Nausea
- Vomiting
- Paralytic Ileus

7.2 Adverse Events Treatment

Patients will be followed for clinical outcomes. All AEs and SAEs will be collected from randomization through 72 hours after randomization.

7.3 Adverse Event Documentation

The principal investigator has the primary responsibility for SAE identification, documentation, grading, and assignment of attribution to the study intervention. SAEs must be recorded in the AE CRF with the following information:

- AE term
- The intensity grade (CTCAE v 4.03 grading)
- The relationship to study procedure
- Attribution
- Duration
- Occurrence (known risks for study procedure-expected, unexpected)
- Other contributing causes
- Actions in response to event
- Outcome
- Criteria for SAE

7.4 AE Grading Scale

The descriptions and grading scales found in NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be used for AE reporting. Each AE term is associated with a 5-point severity scale.

8. FUNDING

This is an investigator-initiated study sponsored by Inova Heart and Vascular Institute. There is no investigational product involved. Treatment received by the subject will be as according to main provider's discretion as according to standard of care.

9. CONFLICTS OF INTEREST

The investigators declare no conflicts of interest linked to this study.

10. FACILITIES AND EQUIPMENT

The Inova Heart and Vascular Institute (IHVI) will be the only setting for this clinical trial. IHVI equipment will be utilized as necessary per standard of care.

11. OUTSIDE CONSULTANTS/COLLABORATORS

There are no outside consultants/collaborators participating.

12. CONTRACTURAL AGREEMENTS

There are no contractual agreements in effect for this study.

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