Statistical Analysis Plan

Single Shot Liposomal Bupivacaine (EXPAREL®)/bupivacaine versus Continuous Erector Spinae Plane Block Catheter in Patients Undergoing Video Assisted Thoracoscopic (VAT) Surgery; Single Center Noninferiority Open Label Prospective Randomized Clinical Trial

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1. Introduction

a. Background and Rationale

Roughly 51 million Americans undergo various inpatient surgeries with opioids being the mainstay of acute pain management.[1] Excessive opioid prescriptions for postoperative pain control have been connected to the opioids crisis.[2,3] Preoperative opioid use, lower socioeconomic status, medical comorbidities and preexisting depression have been shown to cause chronic persistent opioid use after surgery.[4] Over 60% of people with opioid abuse obtain the medication from friends or relatives with unused prescriptions.[5] Thus, an effective acute pain management technique that mitigates opioid consumption for post-operative pain management warrants research.

In the perioperative period, a multidisciplinary approach that emphasizes various opioid sparing techniques can mitigate the risk of persistent chronic opioid use after surgery[6,7]. Anesthesiologists are at the forefront in providing effective pain control strategies in the perioperative period. Nerve blocks have been shown to effectively provide pre-emptive analgesia and acute post-operative pain relief, while preventing central sensitization and chronic neuropathic pain.[8]

Video assisted thoracoscopic (VAT) surgery has gained popularity among thoracic surgeons. This technique has been shown to be superior in improving post-operative lung function, decreasing hospital stays and has better patient satisfaction compared to traditional open thoracotomy.[9,10.] This minimally invasive technique has been widely used in various thoracic surgeries; lobectomy, wedge resection, decortication and pleurodesis. Some patients undergoing VAT surgery have been known to develop acute and chronic neuropathic pain.[11,12] The intercostal injury has been proposed as mechanism of chronic pain and numbness following VAT surgery.[13]

Although thoracic epidural was once considered a gold standard for acute pain management following thoracic surgery, this technique is becoming less popular in the VAT surgery.[14] While shown to be effective in acute post-surgical pain control, paravertebral block and intercostal block require an experienced operator, multiple level injections and risk of pneumothorax.[15] Recently, fascial plane block (erector spinae plane block, serratus anterior plane block, PEC, transverse thoracic plane block) have gained wide popularity in thoracic wall analgesia. Of interest is ultrasound guided Erector Spinae Plane (ESP) block, a novel technique first described by Forero et

al. (2016)[16]. The uniqueness of this technique is the minimal risk compared to neuraxial blockade because of the myofascial location of this block. ESP block has been utilized for thoracic, cardiac, shoulder and abdominal surgeries with excellent pain control post operatively.[17-20] ESP blockade at the level of T5 spinous process provides analgesia from T2 to T10 sensory level.[21] The proposed mechanism of action of ESP block is due to diffusion into paravertebral space, effectively blocking the dorsal and ventral rami of the spinal nerves, as well as the rami communicantes that transmits sympathetic fibers as well as the intercostal nerves.[22-24]

The Food and Drug Administration (FDA) has approved liposomal bupivacaine for interscalene block, bunionectomy, hemorrhoidectomy, transversus abdominis plane block and wound infiltration. Liposomal bupivacaine, or EXPAREL® the brand name, is a long-acting extended-release liposomal bupivacaine with microsomal liposomes (DepoFoam drug delivery system) containing multiple aqueous chambers of encapsulated bupivacaine. Bupivacaine is slowly released from the liposomes by diffusion as the unprotonated (uncharged) form of bupivacaine. This preparation allows sustained release of bupivacaine at the site of injection without exposing patients to toxic plasma concentrations. [25-26]

This open label noninferiority prospective randomized clinical trial is important to test the hypothesis that Single Shot Liposomal Bupivacaine (EXPAREL®)/Bupivacaine in erector spinae plane block is noninferior compared to continuous erector spina plane block catheter group. The comparison of single shot ESP blockade using long-acting local anesthetic with a continuous catheter is important to identify single shot ESP block using liposomal bupivacaine/bupivacaine as an acceptable method of pain relief. Currently, to the best of our knowledge, there is no prospective randomized clinical trial comparing Single Shot Liposomal Bupivacaine (EXPAREL®)/Bupivacaine in erector spinae plane block in patients undergoing VAT surgery.

b. Study Objectives

The objectives of this study are to assess the efficacy of the erector spinae nerve block using Single Shot Liposomal Bupivacaine (EXPAREL®)/Bupivacaine and establish the incidence of adverse events in order to determine if this is a safe regimen for routine use in patients undergoing video-assisted thoracic surgery (VATS).

2. Study Design

a. Study Overview

Research location

This trial will be done at Robert Packer Hospital in Sayre, PA. The Department of Anesthesiology will be conducting the research in the operating room (OR) and post-operative cardiothoracic surgical unit at Robert Packer Hospital. The erector spinae block will be done in the preoperative area, a fully monitored area with immediately available resuscitation and airway equipment. The VAT surgery will be done in the general operating room and, upon completion of the surgery, study subjects will be transferred to Prep and Recovery Unit for immediate post-operative care.

Brief description of clinical intervention

In the Single Shot Liposomal Bupivacaine (EXPAREL®) plus Bupivacaine (SS group), the study drug will be 10 mL of EXPAREL® (133mg) mixed with 20 mL Bupivacaine HCL 0.25% (50mg). A total volume of 30 cc will be injected into the erector spinae plane on the operative side at level of T5 transverse process.

- EXPAREL® (bupivacaine liposome injectable suspension) is an FDA-approved prescription drug that will be administered at a dose in accordance with the package insert, but the site of the injection will be investigational.

In the continuous erector spinae plane block catheter using ropivacaine intermittent automatic bolus (CC group), the study drug to be used is 20-30 cc of bolus Ropivacaine 0.5 % into the erector spinae plane via catheter placement. Subsequent analgesia will be maintained by using electronic infusion pump (Sapphire ™ Multitherapy Pump; San Clemente, CA, USA) which will be programmed to deliver 20 cc intermittent Ropivacaine 0.2% automated bolus every 3 hours, with an additional patient demand bolus of 5 cc ropivacaine 0.2% with a lockout period of 30 min in the postoperative period at the Prep and Recovery Unit.

Design and Hypotheses

The study is a noninferiority, prospective, open label, randomized, double arm clinical trial comparing the effectiveness of Single Shot Liposomal Bupivacaine (EXPAREL®) plus Bupivacaine

(SS) and continuous erector spinae plane block catheter using ropivacaine intermittent automatic bolus (CC) in patients undergoing VAT surgery. The noninferiority limit was set as a between-group difference of two on the 11-point Numerical Rated Pain scale, representing a clinically meaningful change.

Null Hypothesis (H_0): The experimental treatment [Single Shot Liposomal Bupivacaine (EXPAREL®)/Bupivacaine in erector spinae plane block (SS)] is inferior to the control treatment [continuous erector spina plane block catheter group (CC)] by two or more points on the 11-point Numerical Rated Pain Scale

Alternative Hypothesis (H_1): The experimental treatment [Single Shot Liposomal Bupivacaine (EXPAREL®)/Bupivacaine in erector spinae plane block (SS)] is not inferior to the control treatment [continuous erector spina plane block catheter group (CC)] by two or more points on the 11-point Numerical Rated Pain Scale.

$\mathbf{H_0} = \mu$ experimental (SS) - μ control (CC) ≤ -2

$\mathbf{H_1} = \mu$ experimental (SS) - μ control (CC) > -2

μ experimental is the mean pain score for the experimental treatment (SS) group

μ control is the mean pain score for the control treatment (CC) group

If the difference of the mean Numerical Rated Pain Score between the groups is less than the noninferiority margin of two on the 11-point numeric pain scale, then the null hypothesis will be rejected.

Summary of Endpoints

The primary endpoints are:

- Numerical Rated Pain Score (0-10) while at rest at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery.

- Numerical Rated Pain Score (0-10) with cough at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery.

The secondary endpoints are:

- Post-operative cumulative opioid consumption at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery.
- Total intraoperative opioid, defined as total opioids administered in the operating room.
- Adjunct pain medication consumption (acetaminophen, gabapentin and ketorolac) at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hour and 48-72 hours postoperatively
- Postoperative incentive spirometry changes from preoperative baseline at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours and 48-72 hours.
- Number of days ESP catheter in place
- Postoperative quality of recovery score (QOR-15) measured at 12-24 hours, 24-48 hours (day 1) and 48-72 hours (day 2) post operatively (scored as the mean of 15 items).
- Adverse events associated with erector spinae block and Single Shot Liposomal Bupivacaine (Exparel)/Bupivacaine.

Data Collection

At the time of consenting, baseline incentive spirometry will be done, baseline quality of recovery questionnaire (QOR-15) will be administered, and the patient will be educated on how to use the pain assessment tool during the study.

On the day of the surgery, the participant's history, physical, and laboratory results will be reviewed to confirm study eligibility by the study coordinator and the principal investigator/sub-investigators.

Data collection will occur in the operating room, Prep and Recovery Unit and the post-operative cardiothoracic surgical floor at Robert Packer Hospital. If the participant is discharged prior to 72 hours the surveys will be completed in their outpatient location.

Following home discharge, a telephone call will be made by the investigator team every 24 hours until 72 hours during the post-operative period to collect data on opioid consumption, QOR-15 questionnaire, numerical pain score, and adverse events.

All data will be documented in Epic® electronic medical records. An IT/ Epic® data analyst will develop flowsheets in Epic® for data collection. After the first patient is enrolled, an independent statistician will validate that the flowsheet includes each data point to be collected. Upon completion of the overall intervention, data will be downloaded from the Epic® electronic health

record with the help of Epic® consultants from the database by an analyst not involved in the research.

Data will be stored for five years after the conclusion of the trial in a secure location and access will be allowed to investigators. In compliance with the ICH/GCP guidelines, the investigator will maintain all source documents that support the data collected from each subject, as well as all study documents.

Data Safety Monitoring

A Data Safety Monitor (DSM) will be appointed to monitor and identify alarming trends in adverse events involving the study subjects. The DSM will not be involved in data collection or patient interaction. The DSM will be unblinded to assist in detecting trends of serious events that may warrant modification or stopping the study. The DSM will conduct periodic reviews on every 5 patients enrolled in the study. If enrollment is slow, then the DSM will review at least annually.

The Clinical Monitor will review all adverse events in each study subject. This will also ensure that the adverse events occur with reasonable expectation within the study. The Clinical Monitor will contact the DSM within 24 hours of recognizing the occurrence of adverse events or serious adverse events. The DSM will review the unblinded events and if there is an alarming trend significant enough to modify or suspend the trial, then the DSM will notify the Principal Investigator.

The study will be stopped if one death where a clear alternate cause is not readily apparent, two non-fatal serious adverse events where a clear alternate cause is not readily apparent and two moderate to severe symptoms related to local anesthetic systemic toxicity.

b. Study Groups

In patients undergoing video assisted thoracoscopic (VAT) surgery, the study evaluates pain relief for two groups:

1) Single Shot Liposomal Bupivacaine (EXPAREL®) plus bupivacaine (SS)
2) Continuous erector spinae plane block catheter using ropivacaine 0.2% intermittent automatic bolus technique (CC).

Recruitment and Consent

Patients at Robert Packer Hospital who are undergoing video assisted thoracoscopic (VAT) surgery who meet inclusion/exclusion criteria will be invited to take part. Participants will be screened for eligibility once a decision has been made for thoracoscopic surgery. The cardio-thoracic surgery department will screen for potential recruitment. The study will be introduced by the surgeon and a consent document offered for review.

Written consent will be required for all study participants prior to participation and will be obtained by the principal investigator (PI) or a sub-investigator during the preoperative period. After fulfilling the inclusion and exclusion criteria, consent will be obtained by the anesthesiologist sub investigator at the pre-admission appointment for the surgery. If the subjects need more time to review before deciding to participate, a consent form will be given for review before a decision is made at a later time.

Randomization and Allocation Concealment:

Subjects are randomized by block randomization with random blocks. Block size (4, 6 or 8) remained concealed from the researchers until the end of enrollment. Randomization was done by a random number generated computer program using Sealed Envelope Ltd. by someone not involved in the research. The randomization schedule was placed in sealed envelopes to be concealed from the researcher until time of consent.

> Sealed Envelope Ltd. 2020. Simple randomisation service. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/ [Accessed 2 Sep 2020].

The pharmacy department of the Robert Packer Hospital maintains the randomization table. The day prior to the planned surgery the instructions to randomize the participant is sent to the pharmacy. The anesthesiologist advances the treatment allocation orders for the study. The pharmacist prepares the study medication on day of surgery. The randomization is sequential to the actual surgery date.

Blinding

Blinding is not possible in this study because the CC group has an indwelling nerve catheter whereas the SS group does not.

Inclusion Criteria

Subjects who are age > 18, undergoing video assisted thoracoscopic (VAT) surgery, and following Robert Packer Hospital's Enhanced Recovery After Surgery (ERAS) protocol for Thoracic Surgery will be included in this study.

Exclusion Criteria

The exclusion criteria is weight < 50 kg, pregnant subjects, left ventricular ejection fraction < 30%, history of drug or narcotic abuse, history of allergic to amide local anesthetic, presence of contraindication for erector spinae plane block (local skin infection, sepsis, severe coagulopathy) unable to provide consent, unable to use pain rating scales as demonstrated by verbal feedback, preoperative chronic pain on narcotics, history of renal insufficiency (Creatinine > 1.5 mg/dl), preoperative mild liver impairment (i.e. AST/ALT above 1.5 times the upper normal limit) and lactating women. A urine pregnancy test will be done on all female patients of childbearing age to exclude pregnancy unless there is a history of hysterectomy.

The following subjects will be withdrawn from study data analysis but will remain in the study for safety monitoring and study data collection as they have received the treatment: subjects that require conversion into open thoracotomy, and subjects who failed nerve block, defined by inability to determine the local anesthetic spread in the erector spinae plane on the ultrasound image. A screen failure is a participant who does not meet eligibility criteria after consenting or chooses to withdraw prior to surgery.

c. Intervention

The erector spinae block will be done in the preoperative area, a fully monitored area with immediately available resuscitation and airway equipment. The VAT surgery will be done in the general operating room and, upon completion of the surgery, study subjects will be transferred to Prep and Recovery Unit for immediate post-operative care.

In the SS group, the study drug will be 10 mL of EXPAREL (133mg) mixed with 20 mL Bupivacaine HCL 0.25 % (50mg). A total volume of 30 cc will be injected into the erector spinae plane on the operative side at level of T5 transverse process.

In the CC group, the study drug to be used is 20-30 cc of bolus Ropivacaine 0.5 % into the erector spinae plane via catheter placement. Subsequent analgesia will be maintained by using electronic infusion pump (Sapphire ™ Multitherapy Pump; San Clemente, CA, USA) which will be programmed to deliver 20 cc intermittent Ropivacaine 0.2% automated bolus every 3 hours, with an additional patient demand bolus of 5 cc ropivacaine 0.2% with a lockout period of 30 min in the postoperative period at the Prep and Recovery Unit.

The Video Assisted Thoracic (VAT) Surgery is done in a standard fashion. Thoracic surgery multimodal analgesia as per the ERAS protocol will be utilized in all subjects. Preoperatively, acetaminophen 1000mg orally, gabapentin 300mg orally and celecoxib 200mg orally will be given on the preoperative holding area. Postoperatively, acetaminophen 1000 mg Q8 hour prn, Gabapentin 100mg orally TID, Oxycodone 5 mg orally Q4H PRN for moderate pain, Oxycodone 10 mg orally Q6H PRN severe pain and morphine IV 2mg (moderate pain) and 4mg (severe) pain will be given for breakthrough pain as needed.

On arrival in the Prep and Recovery Unit, subjects will be attended by nursing staff and placed on monitors. Intravenous fentanyl or hydromorphone as needed will be given based on the numerical rated pain ratings. Chest x rays will be taken and reviewed in the Prep and Recover Unit, and signs of local anesthetic toxicity (LAST) will be screened. The ESP catheter in the CC study group will be connected to electronic infusion pumps in the Prep and Recovery Unit. (Sapphire ™ Multitherapy Pump; San Clemente, CA, USA) which will be programmed to deliver automatic intermittent bolus of 20 cc of ropivacaine 0.2% every 3 hours. Patient controlled bolus of 5 cc of ropivacaine 0.2% will be allowed at a lockout period of every 30 minutes.

All study subjects will be admitted and observed in the cardiothoracic surgery floor at least for 24 hours post VATS with telemetry monitoring. If the study subjects are deemed suitable for discharge home in less than 72 hours, the continuous catheter in the CC group will be removed. Subjects will be screened for LAST signs and symptoms for 8 hours after removal of the catheter and before being sent home. Subjects will be educated on signs and symptoms of LAST (metallic taste, ringing in the ears, perioral tingling, agitation, seizure and cardiac arrythmias) and if these signs are present, subjects will be instructed to go to the nearest emergency department for medical evaluation.

Following home discharge, a telephone call will be made by the investigator team every 24 hours until 72 hours post-operative period to collect data on opioid consumption, QOR-15 questionnaire, numerical pain score, and screening questions for signs and symptoms of LAST.

d. Sample Size

A power analysis was carried out using PASS 2022[27] to determine the appropriate sample size given power set at 1 - β = 0.90. One-tailed alpha was set at the Bonferroni-adjusted level 0.008 given six time points at which the two treatment groups will be compared. The noninferiority limit was set as a between-group difference of two on the 11-point numeric pain scale, representing a clinically meaningful change.[28] Assuming the standard deviation in each group is two, and that up to 20% of the sample may not complete the follow-up measures, the necessary sample size is 74 (n = 37 in each treatment group).

3. Outcomes

a. Primary Outcomes

The Primary Outcomes is the Numerical Rated Pain Score (at rest and with cough), which patients report on a scale that ranges from zero to ten. It will be collected at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours (day 2), and 48-72 hours (day 3) post VAT surgery by an independent provider (registered nurse) not directly involved in the research. Following home discharge, a telephone call will be made by the investigator team every 24 hours until 72 hours post-operation to collect pain scores. The value obtained within the specified time interval will be used for analysis. The highest score will be taken if multiple values are obtained within the specified time interval.

b. Secondary Outcomes

- "Post-operative cumulative opioid consumption at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery" is defined as the total opioid that was administered to achieve adequate pain control up to the specified time interval starting from the arrival in the Prep and Recovery Unit. All opioids will be converted to morphine equivalents to determine total morphine requirements for each interval.

- "Total intraoperative narcotic" is defined as total opioids administered in the operating room.
- "Adjunct pain medication consumption at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours and 48-72 hours postoperatively" is defined as all non-narcotic pain medications such as acetaminophen, gabapentin, and ketorolac measured in mg units.
- "Incentive spirometry changes post-extubation at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery" is defined as the change from preop incentive spirometry readings post VAT surgery. The value obtained within the specified time limit minus the value recorded preop will be used for analysis.
- QOR-15 consists of 15 questions related to five domains of patient reported health status (pain, physical comfort, physical independence, psychological support and emotional state). It will be administered at the time of consenting (baseline), and repeated on days 1, 2 and 3 post VATS surgery. The overall score, taken as the mean across the 15 questions, will be the measure used in the analysis.
- Common Terminology Criteria for Adverse Events (CTCAE) version 5, published November 27, 2017, will be used for standard classification of adverse events for this project. Additionally, any of the following will be recorded:
    - Cardiac: anginal, myocardial infarction, arrythmia suspected to be related to local anesthetic
    - Neurologic: Transient Ischemic attack (TIA), stroke, seizure, nerve injury from ESP block
    - Gastrointestinal: Nausea, vomiting, constipation, ileus, bowel obstruction
    - Pulmonary: pneumonia, pneumothorax
    - Infection at the site of the block
    - Local anesthetic systemic toxicity (LAST) necessitating use of Intralipid

4. Statistical Analysis

a. General Considerations

Both the intention-to-treat (ITT) and per protocol samples will be analyzed and reported if the full sample size identified in the power analysis section can be recruited. If full recruitment is not possible, and if incomplete post-operative data collection is common, the available data will be

insufficient for the per protocol analysis to yield reliable results. In such a case, only the ITT sample will be analyzed.

The primary outcomes will be summarized with means, standard deviations, and mean differences with 95% confidence intervals. For the two pain variables (at rest and with cough), the analysis will utilize independent samples t-tests with a noninferiority margin of two on the 11-point scale. With six time points, results will be considered statistically significant when p-values testing the null hypothesis of inferiority are less than a Bonferroni-adjusted 0.008. Cumulative morphine equivalents will be assessed in terms of superiority using independent samples t-tests, a null hypothesis of no difference, and p-values interpreted with the Bonferroni-adjusted cut-off of 0.008. Effect sizes (Cohen's d) will also be reported.

The secondary outcomes of adjunct medication doses (in mg units), QOR-15, and change in incentive spirometry results from baseline will be reported as means, standard deviations, medians, interquartile ranges, and mean differences with 95% confidence intervals. Results of independent samples t-tests with a null hypothesis of no difference will be reported. Due to the likely nonnormal distributions of these variables, p-values from Mann-Whitney are also reported.

b. Baseline data

Demographic and clinical characteristics of the study groups will be reported as the number of observations (percentages) and mean (standard deviation) or median (range). Differences in baseline characteristics between treatments will be assessed using independent samples t-tests, Mann-Whitney tests, or chi-square tests, depending on the variable type and definitions.

Descriptive statistics for baseline demographics will include:

- Age in years- mean (standard deviation)
- Gender (male or female) – frequency, number of participants
- Tobacco History – frequency, number of participants
    - Quit more than 12 months ago
    - Never
    - Current

- Chronic Liver Disease (CLD) History - frequency, number of participants
- Chronic Obstructive Pulmonary Disease (COPD) History - frequency, number of participants
- Diabetes History - frequency, number of participants
- Primary Procedure - frequency, number of participants
    - Video Assisted Thoracic Surgery (VATS)
    - VATS with lobectomy
    - VATS with wedge biopsy
- American Society of Anesthesiology (ASA) Physical Status – frequency, number of participants.

  ASA Physical Status is a classification system to assess a patient's pre-anesthesia medical co-morbidities and helps predict perioperative risk when used with other risk factors such as frailty, level of deconditioning and type of surgery.
    - ASA 1 – a normal healthy patient
    - ASA 2 – a patient with mild systemic disease
    - ASA 3 – a patient with severe systemic disease
    - ASA 4 - a patient with severe systemic disease that is a constant threat to life
    - ASA 5 - a moribund patient who is not expected to survive without the operation.
- Length of Stay – Reported in hours. Due to its likely skew, length of stay will be summarized with medains and interquartile ranges.

For continuous variables, the two groups will be compared using independent samples two-sample t-tests (age) or Mann-Whitney (length of stay). For categorical variables, the two groups at baseline will be compared using chi-square tests.

c. Primary Outcomes

Primary outcomes are:

- Numeric pain score reported at rest – zero to ten scale collected at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery

- Numeric pain score reported with cough– zero to ten scale collected at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery

For both primary endpoints (reported separately), the means and standard deviations for each group will be reported along with the mean difference and its 95% confidence interval for each group. A one-sided independent samples t-test will be performed at each time point. The null hypothesis will be that the treated group report pain values of two or more points on average lower than the control group. 95% confidence intervals for mean differences that are bounded above -2.0, along with Bonferroni-adjusted p-values less than 0.008, will be considered as evidence to reject the null hypothesis of inferiority.

d. Secondary Outcomes

Secondary outcomes:

- Post-operative cumulative opioid consumption – reported in morphine equivalents at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery
- Total intraoperative narcotics - total opioid equivalent units administered in the operating room
- Adjunct pain medication consumption collected at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours and 48-72 hours postoperatively.
    - Acetaminophen (mg)
    - Gabapentin (mg)
    - Ketorolac (mg)
- Incentive spirometry changes post-extubation - The value obtained within the specified time limit minus the value recorded preop will be calculated at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery. The average spirometry value will be used if multiple values are obtained within each specified time interval.
- QOR-15 – Calculated as the mean across the fifteen items that ask questions about pain, physical comfort, physical independence, psychological support and emotional state. It will be administered at the time of consenting (baseline), and repeated on days 1, 2 and 3 post VATS surgery.

These secondary outcomes will be summarized using means, standard deviations, medians, interquartile ranges, and mean differences [95% confidence interval]. Tests of the null hypothesis of no difference will be assessed using both independent samples t-tests and (because of likely nonnormality) Mann-Whitney tests. The same Bonferroni adjustment for multiplicity of tests will be applied when interpreting p-values.

e. Adverse Events

A table of all recorded adverse outcomes will be reported showing the type of event, its level of severity, and the arm into which the participant was randomized. All patients, including those removed from the study for the reasons listed above under Exclusion Criteria, will have any adverse events reported. Differences between study arms in terms of the occurrence of an adverse event and, among those who experienced an adverse event, the event severity will be tested using Fisher's exact test and a Mann-Whitney test, respectively.

f. Software

Analysis will be performed using the most up-to-date version of R.

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