Use Of Perioperative Pain Blocks In Urological Surgery
A Phase III Randomized single blind single center three arm non-inferiority trial
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Mount Sinai *The Tisch Cancer Institute*

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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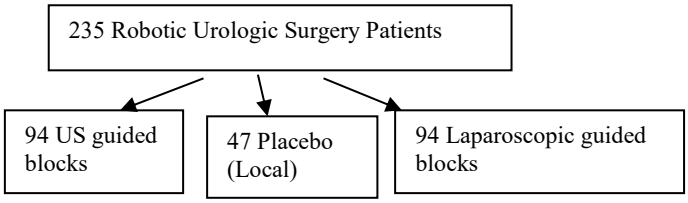
LIST OF ABBREVIATIONS

TAP	Transversus abdominis plane
US	Ultrasound
UTAP	ultrasound-guided transversus abdominis plane
LTAP	laparoscopic-guided transversus abdominis plane
SD	Standard deviation
VAS	Visual Analog Scale
PCAS	Patient-controlled analgesia system
NRS	Numeric Rating Scale

STUDY SCHEMA



Title	Use of perioperative pain blocks in urological surgery
Short Title	Use of perioperative pain blocks in urological surgery
Protocol Number	IF2449510
Phase	Phase III
Methodology	Single Blind, Stratified Randomization, Three Arm Non-inferiority
Study Duration	One Year
Study Center(s)	Single Center
Objectives	Primary Objectives • To verify assay sensitivity by demonstrating that UTAP (the active reference) is superior than local bupivicaine at controlling 24 hour postoperative pain. • To demonstrate non-inferiority of LTAP (the experimental approach) to UTAP (the active reference) with respect to 24 hour postoperative pain control. Secondary Objectives • To determine the efficacy of regional blocks on postoperative pain control. • To determine whether the LTAP ability of regional blocks to reduces narcotic 24 hour cumulative postoperative opioid analgesic requirement usage in the perioperative period compared to UTAP and Placebo. • To determine the rate of antiemetic medication use during postoperative course in UTAP, LTAP, and Placebo groups. • To determine the days to return of bowel function in the UTAP, LTAP, and Placebo groups. • To determine the length of hospital stay in the UTAP, LTAP and Placebo groups. • To determine the time taken to complete the surgical block, operating room time, and surgical time in the UTAP, LTAP and Placebo groups. • To determine whether determine the efficacy of LTAP is non-inferior to UTAP ultrasound and laparoscopic regional blocks in obese patients. • To determine procedure related complications and adverse events including bleeding or injection of anesthetic intravascular
Number of Subjects	235 (94 LTAP, 94 UTAP, 47 Placebo)
Diagnosis and Main Inclusion Criteria	Robotic Prostatectomy and Partial nephrectomy patients
Study Product(s), Dose, Route, Regimen	None

Duration of administration	None
Reference therapy	None
Statistical Methodology	

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Currently, ultrasound-guided transversus abdominis plane (UTAP) blocks (regional anesthetic blocks) are being employed for the care of urological surgery patients. Local and regional anesthesia is commonly used throughout surgical fields. However, ultrasound-guidance can be challenging, particularly in larger, obese patients. It is unknown how such techniques compare to laparoscopic-guided blockade, with respect to time to perform, learning curve, and postoperative analgesia. The transversus abdominis plane lies deep within the abdominal wall, potentially allowing for greater ease of access from a laparoscopic approach from within than the ultrasound guided percutaneous approach.

Prior randomized studies have been completed comparing UTAP and Placebo. In 2012 Hosgood et al. compared UTAP and placebo (UTAP w/ saline) in 46 live-donor laparoscopic nephrectomy patients (24 UTAP vs. 22 placebo). Pain control (measured using the 0-10 VAS scale) was greater on post-operative day (POD) 1 in patients receiving UTAP than in controls, 19 (15) vs. 37 (20) (presented as mean (SD)), respectively.[1] A similar randomized study in 2014 compared UTAP and placebo (UTAP w/saline) in 21 hand assisted laparoscopic nephrectomy patients (10 UTAP vs. 11 placebo). The study was initially powered for 50 patients but with decreased accrual secondary to a surgeon taking a leave of absence during the study period. Pain scores were recorded using the 0-10 VAS score. Postoperatively at 24 hours (median (IQR)) UTAP patients demonstrated decreased postoperative pain than placebo patients (1 (0-2) vs. 4 (2-6)) on the VAS score, respectively.[2]

A larger study, done in 2016, with 80 randomized patients undergoing retroperitoneal laparoscopic urologic surgery compared UTAP (40) and saline UTAP (40). Pain scores were assessed using the 0-100 VAS score scale. On POD1, UTAP group had lower pain scores (mean (SD)) of 8.4 (5.9) vs. placebo 28.3 (12.2).[3]

The most recent study, done in 2018, examined 100 randomized patients undergoing robotic-assisted laparoscopic prostatectomies. Fifty patients were given UTAP blocks while the others received no block. A Numerical Rating Scale (assumed to range from 0-10 as not otherwise specified) was used to assess pain. Patients receiving the block at 24 hours had better pain control (mean (SD)) (1.8 (0.82) vs. 3.57 (0.64)).[4]

While all of these studies point to potential efficacy of UTAP, no data has been published to date comparing laparoscopic administration of the TAP block (LTAP) to ultrasound guided administration. While these regional anesthetic blocks carry a theoretical risk of hematoma or damage to surrounding structures, none of the above studies report any complications with the injections.

1.2 Study Agent(s) Background and Associated Known Toxicities

N/A

1.3 Other Agents

N/A

1.4 Rationale

We aim to prospectively compare Placebo (local administration), UTAP, and LTAP blocks in patients undergoing surgery of the prostate and kidney. We expect to be able to equally efficiently administer the blocks using direct visualization and ultrasound guidance. We expect that a negative result would obviate the need for longer operative time by eliminating the need for the separate ultrasound guided block while a positive result would demonstrate the increased utility of preoperative ultrasound blocks in managing postoperative pain.

1.5 Correlative Studies

None

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To verify assay sensitivity by demonstrating that UTAP (the active reference) is superior to placebo (local administration) at controlling 24 hour postoperative pain.
2.1.2 To demonstrate non-inferiority of LTAP (the experimental approach) to UTAP (the active reference) with respect to 24 hour postoperative pain control.

2.2 Secondary Objectives

2.2.1 To determine whether LTAP reduces 24 hour cumulative postoperative opioid analgesic requirement in the perioperative period compared to UTAP and Placebo.
2.2.2 To determine the rate of antiemetic medication use during postoperative course in UTAP, LTAP, and Placebo groups.
2.2.3 To determine the days to return of bowel function in the UTAP, LTAP, and Placebo groups.
2.2.4 To determine the length of hospital stay in the UTAP, LTAP and Placebo groups.
2.2.4 To determine the time taken to complete the surgical block, operating room time, and surgical time in the UTAP, LTAP and Placebo groups.
2.2.5 To determine whether LTAP is non-inferior to UTAP in obese patients.
2.2.6 To determine procedure related complications and adverse events including bleeding or injection of anesthetic intravascular

2.3 Exploratory Objectives

2.4 Endpoints

Primary:
The primary endpoint is 24 hour postoperative pain scores recorded using the visual analog scale (VAS) described in section 6.1.1.

Secondary:
The secondary endpoints include:

- The 24-hour cumulative postoperative opioid analgesic requirement described in Section 6.2.
- Use of antiemetic medications during the postoperative course
- Days to return of bowel function
- Length of hospital stay
- Intraoperative time taken to complete surgical blocks
- Operating Room time
- Surgical Time
- Procedure related complications and adverse events including bleeding or injection of anesthetic intravascular will be determined according to Common Terminology Criteria for Adverse Events (CTCAE v 4.0)

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Aged 18 years or older
3.1.2 Undergoing Robotic Assisted Laparoscopic Partial Nephrectomy or Robotic Assisted Laparoscopic Prostatectomy
3.1.3 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Prior Partial Nephrectomy or Subtotal Prostatectomy Surgery (organ specific)
3.2.2 Conversion to open surgery
3.2.3 History of chronic pain
3.2.4 History of opiate or alcohol dependence
3.2.5 Allergies to local anesthetic
3.2.6 Retroperitoneal surgery
3.2.7 Single Port Surgery

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 30mL of 0.25% bupivacaine will be administered to bilateral TAP using ultrasound or laparoscopic guidance in prostatectomies. 40ml 0.25%

bupivacaine unilateral will be administered in nephrectomy patients (weight based dosage permitting). Placebo groups will receive direct injection of bupivacaine into surgical wounds.

4.1.2 The anesthesia protocol will be at the discretion of the anesthesiologist, including premedication, induction of anesthesia, endotracheal intubation, and maintenance of sedation and neuromuscular blockade. Similarly, all patients will undergo standardized procedure for obtaining pneumoperitoneum and insertion of laparoscopic ports.

Patients in the UTAP group will receive abdominal wall nerve block by the anesthesia team with 30 cc of 0.25% Bupivacaine in bilateral TAP regions under ultrasound guidance (percutaneously) after obtaining general anesthesia. (unilateral 40ml for nephrectomies) Conversely, patients in the LTAP group will undergo bilateral nerve blocks by the surgical team under direct vision from an intraabdominal access after creating pneumoperitoneum and inserting the laparoscope. Patients in the Placebo will receive injection of bupivicaine directly into the surgical wound.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

N/A

4.3 Concomitant Medications/Treatments

Pain medication will be given according to the level of pain expressed by the patient. 1 tab of Percocet (325-5mg acetaminophen-oxycodone) will be given for moderate pain, 2 tabs of Percocet for severe pain. For breakthrough pain 4mg of morphine sulfate will be given.

4.4 Other Modalities or Procedures

In the laparoscopic arm, administration of the block will take place through a laparoscopic port after pneumoperitoneum has been established.

4.5 Duration of Therapy

The block will be administered in the perioperative period. Bupivacaine is expected to last up to 8 hours.

4.6 Duration of Follow Up

The patient will be followed while an inpatient postoperatively, as well as at the first postop visit at which time the protocol will conclude.

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.8 Patient Replacement

If any patient expires, is converted to open surgery, or requires a return to the operating room they will be removed from the study.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 0 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, history of infections

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Adverse event assessment*

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.8 *Hematology*

5.1.9 *Blood draw for correlative studies*

None

5.1.10 *Serum chemistries*

5.1.11 *Pregnancy test (for females of child bearing potential)*

See section 3.1.6.1 for definition. Distinguish between blood and urine tests for pregnancy. If pregnancy test is completed at more than one visit, it should be detailed for each visit and include which type of test is being conducted (urine or blood).

5.2 Procedures during Treatment

5.3 Follow-up as in 5.4

5.4 Time and Events Table

	Pre-study	Postop 4-6 hours	Postop 12 hours	Postop 24 hours	Follow up Visit
VAS Pain Assessment		X	X	X	
Informed Consent	X				
History and PE	X			X	X
Other required labs		X			X
Narcotic Use	X				X
Monitoring for Adverse Events		X	X	X	X

5.5 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

6.0 Measurement of Effect

6.1 Pain Scale

6.1.1 Definition

Patient solicited pain scores will be assessed using the Visual Analogue Pain Scale (VAS-Pain). VAS is a pain rating scale where scores are based on self-reported measures of symptoms that are recorded with a single handwritten mark placed at one point along the length of a 10-cm line that represents a continuum between the two ends of the scale—"no pain" on the left end (0 cm) of the scale and the "worst pain" on the right end of the scale (10 cm). Measurements from the starting point (left end) of the scale to the patients' marks are recorded in centimeters and are interpreted as their pain intensity. This will be administered by asking the patient to place a line perpendicular to the VAS line at the point that represents the pain intensity. This pain scale is commonly used throughout the pain literature and takes <1 minute to complete.

Further explanation may be found here:
https://onlinelibrary.wiley.com/doi/full/10.1002/acr.20543

6.2 Cumulative Morphine Equivalent Dose Requirement

6.2.1 Definition

The 24-hour cumulative postoperative opioid analgesic requirement will be calculated for each patient. The administered medications over the 24 hour period will be recorded in each patient's medication administration record, ensuring that all opiates used within the hospital stay are recorded. The only opiates the patients on this trial will receive are morphine and/or Percocet (oxycodone). The standard of care for these patients is 1 Percocet for moderate pain, 2 for severe pain, and 4mg of morphine for breakthrough pain. Oxycodone 5mg is considered equivalent to morphine 7.5mg. Ideally, only morphine sulfate will be used for breakthrough pain. If another opioid is administered, we will convert the dose, using standard tables to morphine equivalents (https://www.oregonpainguidance.org/opioidmedcalculator).

6.3 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or death.

6.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

6.3.2 Definition of Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

6.3.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

6.3.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

6.3.3.2 Is life-threatening.

(The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

6.3.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

6.3.3.4 Results in persistent or significant disability or incapacity.

6.3.3.5 Is a congenital anomaly/birth defect

6.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

6.3.4 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;

- the drug package insert;
- the current Investigator's Brochure

6.3.5 Reporting Requirements for Adverse Events

6.3.5.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

- The IRB/PPHS must be notified within 5 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR

  a. Any new information that indicates a new or increased risk, or safety issue (e.g., interim analysis, safety monitoring report, publication, updated sponsor safety report), that indicates an unexpected change to the risk/benefit ratio for the research.

  b. An investigator brochure, package insert, or device labeling is revised to indicate an increase or magnitude of a previously known risk, or describes a new risk.

  c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in research protocol

  d. Protocol deviation or violation that harmed subjects or others or that indicated subjects or others might be at increased risk of harm.

  e. Complaint of subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm

  f. Any breach in confidentiality that may involve risk to the subject or others.

  g. Any harm experienced by a subject or other individual that in the opinion of the investigator is unexpected and at least probably related to the research procedures.

6.3.5.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

6.4 Unblinding Procedures

Patients will be informed of their method of anesthetic administration if they request removal from the trial.

6.5 Stopping Rules

7.0 As none of the prior trials report any complications with TAP procedures, an acceptable AE rate would need to be very low i.e. <5% and include theoretical complications such as bleeding, or injection of anesthetic intravascularly. Most recent randomized trials[3,4] do not report any complications with these injections. This trial will be monitored by the DSMB on a biannual basis and if a TAP procedure related serious complication occurs then accrual will be halted for safety considerations and a DSMB meeting requested.

8.0 DRUG INFORMATION

8.1 0.25% Bupivacaine

- Other names for the drug(s):

Marcaine

- Classification - type of agent:

Anesthetic

- Mode of action:

Sodium Channel blocker

- Storage and stability: Room Temperature
- Protocol dose: 30x2/40mL
- Preparation: None
- Route of administration for this study: Laparoscopic versus percutaneous versus local
- Incompatibilities:

Allergy to local anesthetic

- Availability: Commercially available
- Side effects: Please refer to a complete list of side effects available from the manufacturer
- Nursing implications:

8.1.1 Return and Retention of Study Drug

N/A

7.1.2 Pain scale is asked as part of standard postoperative treatment and is used in order to treat patient's pain.

9.0 CORRELATIVES/SPECIAL STUDIES

N/A

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a single-center, single-blinded, (stratified) randomized placebo-controlled three-arm non-inferiority trial with 2:2:1 allocation ratio.

Randomization:
People who meet eligibility requirements and provide informed consent will be randomly allocated to 3 groups to receive either UTAP, LTAP or Placebo with a 2:2:1 allocation ratio. The allocation sequence will be stratified by type of surgery (prostatectomy or partial nephrectomy) using stratified block randomization with randomly varying block sizes. Random permuted blocks sizes within stratification groups will be used to minimize the chance of selection bias. Investigators will be blinded to the size of each block with only the study statistician responsible for generating the randomization list knowing this information. A randomization service called Sealedenvelope.com available at https://www.sealedenvelope.com/simple-randomiser/v1/ will be used for allocation concealment to ensure that retrieval of the treatment group assignment is only revealed to appropriate team members on a real time basis after each new patient has been screened and consented. This service allows for allocation concealment that would not be possible if the entire randomization list was made available to team members at the beginning of the study. The security and integrity of the codes used by Sealedenvelope.com follows the Food and Drug Administration (FDA) standards for electronic records and follows the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

The following is an overview of the randomization generation and management process. The trial coordinator will create an administrator account with sealedenvelope.com. Only the email address given when setting up the trial will be registered as the administrator email address and it can be used to change the password, delete the trial, or receive a list of all randomizations performed at any time. The study statistician will generate the randomization list in Sealedenvelope.com. Once the account for the trial has been opened and the randomization list generated; any designated user (designated by the account administrator) with the single password for the trial can carry out new randomizations. Online randomization is achieved by the user completing a form with the trial ID and password after providing a patient ID as well as surgical type for stratification purposes. An email notification is then generated displaying the next sequential treatment group assignment from the randomization list and sent to the email address given by the user randomizing and the administrator. Data and randomizations held by the sealed envelope randomization system cannot be

changed or edited by users. Sealed Envelope will not edit or delete any data held by the system.
Participants will be blinded from the type of block given. Investigators cannot be blinded due to the nature of the intervention; however allocation concealment will be implemented by use of the sealed envelope service described above.

Blinding:
Participants will be blinded to group allocation throughout the study. Due to the nature of the intervention, it is not possible to blind the investigator to group allocation.

10.2 Sample Size and Accrual

For two-arm non-inferiority trials, issues such as choice of non-inferiority margin, constancy assumption, and assay sensitivity have been debated for years, and the statistical methodology has been challenged. Three-arm trials including the experimental treatment, an active reference treatment and a placebo are recommended in the guidelines of the ICH[5] and EMEA/CPMP[6] as a useful approach to the assessment of assay sensitivity providing the trial with internal validation. The placebo group affords an opportunity to test for non-inferiority directly without use of a fixed pre-specified non-inferiority margin thereby making the constancy assumption an irrelevant point and allows for direct testing of assay sensitivity by comparing the active reference to the placebo.

The objectives of this trial are two-fold: 1. to verify assay sensitivity by demonstrating that UTAP (the active reference) is superior to placebo at controlling 24 hour postoperative pain and 2. to demonstrate non-inferiority of LTAP (the experimental approach) to UTAP (the active reference) with respect to 24 hour postoperative pain control.

A step-down hierarchical hypothesis testing approach will be used to test the two hypotheses (co-primary endpoints). In the first step, to establish assay sensitivity, the alternative hypothesis that UTAP is superior to placebo will be tested:

$$H_{01}: \mu_{UTAP} \geq \mu_{Placebo}$$

$$H_{A1}: \mu_{UTAP} < \mu_{Placebo}$$

If and only if we reject the null hypothesis, H_{01}, thereby establishing assay sensitivity will we proceed to the second step, to demonstrate non-inferiority of LTAP to UTAP.

In the second step, to establish non-inferiority, the alternative hypothesis that LTAP is non-inferior to UTAP will be tested using the ‘fractional approach’

introduced by Pigeot I et al (2003) where the effect estimate is based on the ratio of the differences in means between LTAP and placebo and UTAP and placebo[7] :

$$H_{02}: \frac{\mu LTAP - \mu Placebo}{\mu UTAP - \mu Placebo} \leq \theta$$

$$H_{A2}: \frac{\mu LTAP - \mu Placebo}{\mu UTAP - \mu Placebo} > \theta$$

θ is a pre-specified fixed fraction of active reference effect (retention of effect). Koch and Tangen[8] provide reasonable regions of θ for non-inferiority testing between 0.5 and 0.99.

If the null hypothesis, H_{02} is rejected for a given θ, we will claim that LTAP (the experimental approach) retains more than θx100% efficacy of UTAP (the active reference) compared with the placebo, and non-inferiority of LTAP to UTAP will be declared.

With a hierarchical step down closed testing procedure (which can occur when one has two or more endpoints for which demonstration of an effect on each is needed to support regulatory approval), the familywise type I error rate is controlled at the level α as there is only one way to succeed, however, the type II error rate is inflated thereby decreasing the overall power to show success on both endpoints. To account for inflation of the type II error rate, the sample size will be calculated to provide an overall power (to detect both endpoints) of 80% by setting the power for each hypothesis test at 90% (90%x90%=80%)[9] corresponding to β=0.10.

The statistical methodology for a test problem based on the ratio of (differences in) population means was published by Koch et al. (1998).[10] The null hypothesis $H_{02,}$ referred to above as our second hypothesis, can be rejected, if the lower limit of Fieller's one-sided 100 (1-α)% confidence interval for the ratio of differences in means is greater than θ. Pigeot et al. (2003) investigated Fieller's confidence interval and derived formulas for power and hence sample size calculation. The R package 'ThreeArmedTrials' developed by Tobias Muetze (2016)[11] provides a collection of functions for statistical inference in three-arm trials using the formulas derived by Pigeot et al. for a normally distributed outcome. For a study assessing non-inferiority of an experimental approach compared to an active reference, tools to: determine optimal sample size allocation among groups (UTAP, LTAP, Placebo), compute total (and group) sample size required to detect a particular non-inferiority fraction θ at a particular power and alpha level, as well as analyze the final data set are provided. For a normally distributed endpoint the group means, variances as well as power, alpha, group allocation ratios and non-inferiority fraction θ need to be specified for computation of sample size. It is recommended by Muetze to use estimates of means and variances from a random effects meta-analysis of the historical placebo-controlled trials comparing UTAP to placebo (presented in Section 1.1). Based on meta-analysis of the four

historical placebo-controlled trials with parameters listed in the table below and discussed in the introduction, the estimated pooled mean pain scores and (total variance) was 3.4 (1.50) in the placebo and 1.49 (1.77) in the UTAP groups. The random effects meta-analysis was conducted with the Comprehensive Meta-Analysis Software Version 3.3.070 (2013).[12]

Study name	Treatment	Mean	SD	Variance	Sample size
Hosgood (2012)	*Placebo*	3.70	2.00	4.00	22
Aniskevich (2014)	*Placebo*	4.00	2.30	5.29	11
Qu (2016)	*Placebo*	2.80	1.20	1.44	40
Fabrizio (2018)	*Placebo*	3.57	0.64	0.41	50
Random	**Placebo**	**3.40**		**1.50**	
Hosgood (2012)	*UTAP*	1.90	1.50	2.25	24
Aniskevich (2014)	*UTAP*	1.50	1.20	1.44	10
Qu (2016)	*UTAP*	0.84	0.59	0.35	40
Fabrizio (2018)	*UTAP*	1.80	0.82	0.67	50
Random	**UTAP**	**1.49**		**1.77**	

In accordance with ICH guidelines on statistical principles for clinical trials a type I error rate of 0.025 was used for this sample size calculation. Optimal sample size allocation was determined to follow a 2:2:1 ratio of LTAP:UTAP:Placebo. A total sample size of 235 is required with a 2:2:1 allocation ratio (94 LTAP, 94 UTAP and 47 Placebo) to achieve 90% power to establish non-inferiority of LTAP to UTAP with a fixed fraction of 0.50 (LTAP has to achieve more than 50% of the effect of UTAP compared to placebo to claim as non-inferior) assuming means and variances of 1.49 (1.77), 1.49 (1.77) and 3.40 (1.50) in the LTAP, UTAP and Placebo groups, respectively. This sample size calculation was performed using the PowerRet function of the 'ThreeArmedTrials' package with the following parameters:
power_RET(experiment = c(1.49,1.77), reference = c(1.49,1.77), placebo =c(3.4,1.5),Delta = 0.7, sig_level = 0.025, power= 0.9,allocation = c(2,2,1) /5,distribution = "normal")

The statistical evaluation will be performed in the first step by a two sample t-test for demonstrating superiority of UTAP over placebo. Group sample sizes of 94 and 47 for UTAP and placebo groups achieve over 99% power to reject the null hypothesis of equal or worse means when the population VAS pain score means (SDs) in the UTAP and Placebo groups are 1.50 (1.33) and 3.4 (1.22), respectively, with a significance level of 0.025 using a one-sided two-sample unequal-variance t-test. The calculation was performed with PASS Version 15.

10.3 Data Analyses Plans

Analysis of Co-Primary Endpoints:

The distribution of VAS pain scores in each group will be examined and assessed for normality and homoscedasticity, visually, by generating probability-probability (P-P) plots, boxplots, stem-and-leaf plots and quantile-quantile (Q-Q) plots, and with the Shapiro-Wilk normality test. If necessary, a transformation of the data will be made to render appropriate for parametric testing. All analyses will be performed on patients who undergo surgery and have a 24 hour VAS pain score assessment. Balance on baseline characteristics (including gender, age at surgery, height, weight, BMI, and operative time) among the randomized groups will be assessed separately for each intervention, using the standardized difference. Any variable with an absolute standardized difference >0.52 (i.e., 1.96 × 1/n1 + 1/n2) for either intervention will be adjusted for in secondary analyses.[13,14]

A step-down hierarchical hypothesis testing approach will be used to test the two hypotheses (co-primary endpoints). In the first step, to establish assay sensitivity, the alternative hypothesis that the 24-hour post-operative mean VAS pain score in the UTAP group is superior to that in the placebo group will be tested by a one-sided two sample t-test at the 0.025 level of significance (H_{01}: $\mu_{UTAP} \geq \mu_{Placebo}$ vs. H_{A1}: $\mu_{UTAP} < \mu_{Placebo}$).

If assay sensitivity is demonstrated in the first step by rejecting the null hypothesis, H_{01}, we will proceed to the second step of testing for non-inferiority of LTAP to UTAP. To establish non-inferiority, the alternative hypothesis that LTAP is non-inferior to UTAP will be tested using the 'fractional approach' introduced by Pigeot et al (2003) where the effect estimate is based on the ratio of the differences in means between LTAP and placebo and UTAP and placebo (H_{02}: $\frac{\mu LTAP-\mu Placebo}{\mu UTAP-\mu Placebo} \leq \theta$: vs. H_{A2}: $\frac{\mu LTAP-\mu Placebo}{\mu UTAP-\mu Placebo} > \theta$).
θ is pre-specified as the fixed fraction of active reference effect (retention of effect) of 0.50 (LTAP has to achieve more than 50% of the effect of UTAP compared to placebo to claim as non-inferior). The second step will be carried out based on the Fieller's one-sided 97.5% lower confidence bound for the ratio of $\mu LTAP - \mu Placebo$ and $\mu UTAP - \mu Placebo$. If the lower bound of the confidence interval is greater than 50% then the null hypothesis, H_{02} is rejected (LTAP (the experimental approach) retains more than 50% efficacy of UTAP (the active reference) then non-inferiority of LTAP to UTAP will be declared. The formula for calculating Fieller's confidence bound is presented in Pigeot et al (2003) and will be implemented using The R package 'ThreeArmedTrials' developed by Tobias Muetze (2016).

Analysis of Secondary Endpoints:

The secondary endpoints of 24-hour cumulative post-operative opioid analgesic requirement expressed in morphine equivalent dose (MED), intraoperative time taken to complete the surgical block, total operating room time and surgical time will be summarized using median, 1st and 3rd quartiles and minimum and

maximum values. A Kruskal-Wallis analysis of variance will be used to compare the cumulative MED requirement (time to complete the surgical block, total operating room time and surgical time) among the three intervention groups with all pairwise comparisons made between groups using the Dwass-Steel-Critchlow-Fligner procedure (Dwass 1960; Steel 1960; Critchlow and Fligner 1991).[15–17]

The secondary endpoint of antiemetic medication use will be reported as the number and percentage of patients that require antiemetic medication during their hospital stay within each intervention group. A Chi-Square will be used to compare percentages across groups. A log-binomial regression model will be used to estimate and compare the prevalence ratios (PR) and corresponding 95% confidence intervals (CI) for antiemetic medication use among patients in the three intervention groups.

The secondary endpoints, including length of hospital stay and days to return of bowel function will be analyzed depending on existence of event censoring and/or occurrence of competing events at the time of analysis. Length of hospital stay will be calculated as the number of days between the date of surgery and the date of discharge from the hospital. Days to return of bowel function will be calculated as the number of days between the date of surgery and the date of first bowel movement. If the event is observed in all patients and there is no censoring at the time of analysis, the mean and standard deviation (if normally distributed) or median and IQR (if skewed) will be presented and an analysis of variance (or Kruskal-Wallis analysis of variance)will be used to compare means (or distributions) among groups, respectively. If the event is not observed in all patients (censoring at time of analysis) then the method of Kaplan-Meier will be used to estimate the median times to event and corresponding 95% confidence intervals will be constructed based on the method of Brookmeyer and Crowley.[18] Comparisons of time to event distributions among intervention groups will be made with the log-rank test. If competing events are observed, such as death prior to the event of interest, then cumulative incidence functions (CIF) will be estimated in a competing risk setting. In these analyses, discharge and first bowel movement will be the defining events in each analysis while death without discharge or prior bowel movement will be considered the competing event. Patients who are alive and have not yet been discharged or have not had return of bowel function as of the data analysis cutoff will be censored. CIF comparisons among intervention groups will be made with Gray's test.[19]

The secondary endpoint of procedure related complications including bleeding or injection of anesthetic intravascular will be determined according to Common Terminology Criteria for Adverse Events (CTCAE v 4.0) and presented as frequency at each grade. A Poisson regression model will be used to test the difference in adverse event rates between the two groups. In this model, the numerator is the number of adverse events and the denominator (offset) is the natural log of the person days followed.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any research personnel who have a conflict of interest with this study (patent ownership, intellectual property, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must declare their conflict of interest to the appropriate institutional review bodies. Local institutional conflict of interest policies will be followed for all research personnel associated with the research project.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Data Management and Monitoring/Auditing

10.3.1 Elements of a Data and Safety Monitoring Plan

List the name(s) of the individual(s) at the Icahn School of Medicine at Mount Sinai (ISMMS) who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information.

ISMMS Principal Monitor: (principal investigator)

Last Name: Mehrazin
First Name: Reza

Academic Title: Assistant Professor
Department: Urology
Mailing Address: 1468 Madison Ave
Phone: 212-241-4812
E-mail: reza.mehrazin@mountsinai.org

Dr. Mehrazin is closely involved in the care of his patients and cares deeply that his patients, as well as those of his colleagues, are receiving the best possible care regardless of their involvement in a study.

Specific items that will be monitored for safety include adverse events, drop outs, and patient concerns. This information will be regularly reviewed biweekly during recruitment period. As participant involvement lasts no more than one week, this will assure that all subjects are being carefully monitored. Data accrued throughout the project will also be evaluated with the same regularity to ensure accuracy and completeness in reporting.

Should a temporary or permanent suspension of your study occur, in addition to the
PPHS, the organization's IRB will be informed.

In addition, a DSMB of senior physicians in Urology and a biostatistician will monitor the study on a biannual basis.

11.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.4.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

11.4.2 Other Reportable New Information and Protocol Deviations/Violations

In accordance with local IRB requirements, the following information must be reported within five (5) business days.

- Non-compliance with federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance
- Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Breach of confidentiality

- Premature suspension or termination of the research by the sponsor or investigator.

11.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will

be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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