Efficacy of IV Acetaminophen Versus Oral Acetaminophen

Study Protocol and Statistical Analysis

NCT03365622

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Randomized, Double-Blind Clinical Study Evaluating Efficacy of Intravenous versus Enteric Acetaminophen in Donor Nephrectomy and Robot-Assisted, Laparoscopic Nephrectomy.

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1. BACKGROUND, PURPOSE and OBJECTIVES OF THE STUDY

1.1 Background:

Obtaining effective postoperative analgesia following major surgery can be difficult. Nonnarcotic regimens have been applied to specific procedures to improve outcomes. Intravenous acetaminophen may be more efficacious for the management of postoperative pain than oral acetaminophen.

There is not a large body of literature addressing this subject. A literature search was done through Miner Library through PubMed and Embase using the following strategies: "Infusions, Intravenous" [Mesh] OR "Administration, Intravenous" [Mesh] OR "Injections, Intravenous" [Mesh] AND "administration, oral AND elective surgery AND acetaminophen" yielded only 12. Of those, only two were relevant. One study compared plasma levels following IV or oral administration of acetaminophen. Another study was similar to our proposed trial but compared IV versus oral tramadol.

A search through Clinicaltrials,gov showed that several groups (12 trials) are studying this topic (comparing IV versus oral acetaminophen) but are studying different populations (laparoscopic cholecystectomy, hip fracture, total hip replacement, total knee replacement, lumbar discectomy, cesarean section). Of these, only 4 are double blind.

In summary, we feel that the proposed study will add knowledge to the field.

1.2. Purpose of the Study:

The aim of this study is to compare pain control for oral and intravenous acetaminophen for post-operative pain control in patients who undergo either (1) donor nephrectomy, or (2) nephrectomy for cancer. Many clinicians believe that intravenous acetaminophen is superior to enteral acetaminophen for the management of perioperative pain. However, the intravenous formulation of acetaminophen is six-hundred times more expensive than the enteral form. To date, there is no empiric evidence that IV acetaminophen provides superior pain relief than PO acetaminophen which could be used to justify the higher cost of the IV formulation. Our objective is to conduct a pragmatic RCT to determine whether IV acetaminophen provides superior pain control compared to PO acetaminophen in the setting of routine clinical practice.

Patients undergoing laparoscopic donor nephrectomies or robot-assisted donor nephrectomies were chosen to be included in this study for the following reasons:

1. These two procedures are associated with similar levels of surgical stress and tissue trauma.

2. Patients undergoing these procedures are not treated with NSAIDs due to the nephrotoxic risk of NSAIDs to the remaining kidney.
3. These patients are at minimal risk for post-operative ileus and are thus able to take enteral medications in the immediate post-operative period.
4. The surgical procedures are generally well under 6 hours duration enabling patients to take enteral medications 6 hours after the initial pre-operative dose.

1.3. Primary Objective.

The primary objective of this study is to compare pain control for oral and intravenous acetaminophen for post-operative pain control. The primary outcome is the total opiate dose used from the study start (when the first dose of acetaminophen is administered in the pre-anesthesia holding area) to 24 hours post-operatively (in morphine equivalents). This will include opiates administered intra-operatively.

1.4. Secondary Objectives.

The secondary outcomes are:

1. Average surgical pain intensity on a 0-10 numeric rating scale (NRS) administered between 20 and 24 hours post-operatively.
2. Average surgical pain intensity on a 0-10 numeric rating scale (NRS) administered between 1 and 2 hours post-operatively.
3. Inspiratory capacity at the time of pain intensity assessments (between 1-2 hours postoperatively and between 20-24 hours post-operatively). The inspiratory capacity will be presented as a percentage of the subject's baseline (pre-operative) inspiratory capacity
4. Dynamic pain score with incentive spirometer use taken during pain intensity assessments at 1-2 hours and 20-24 hours post-operatively.
5. Surgical pain score on a 0-10 numeric rating scale (NRA) obtained during the 20-24 hour assessment.
6. Time to first narcotic use post-operatively.
7. Incidence of nausea post-operatively
8. Time to discharge from post-anesthesia care unit
9. Time to hospital discharge

2. CHARACTERISTICS OF THE RESEARCH POPULATION

2.1. Number of subjects.

We will enroll 265 subjects.

2.2 Sex of Subjects.

We will enroll both males and females. The sex of the subjects will represent the sex distribution of the patients who have donor nephrectomies or robot-assisted laparoscopic nephrectomies.

2.3. Age of Subjects.

We will enroll subjects 18 years of age and older.

2.4. Racial and Ethnic Origin.

Subjects will be enrolled without racial or ethnic restrictions. We expect enrolled subjects to represent the racial/ethnic composition of the patients at the URMC.

2.5. Inclusion Criteria. The subject must:

1. Be at least 18 years old
2. Be scheduled for donor nephrectomy or robot-assisted or laparoscopic nephrectomy for cancer at URMC
3. Have cognitive ability to verbally rate their pain on the Numeric Rating Scale (NRS).

2.6. Exclusion Criteria. The subject must not:

1. Age younger than 18 years old or older than 90 years old
2. Pregnancy (Pre-operative pregnancy test is routinely performed for all elective operating room cases)
3. Weight less than 50 kg (lowest weight for safe dosing of 1000mg of acetaminophen) 4. Epidural use
5. Known liver disease (i.e. cirrhosis, liver failure).
6. Patient unable to take enteral medications (i.e. cannot swallow pills, have a feeding tube, or are on TPN). However, patients who become NPO postoperatively due to ileus, persistent nausea and vomiting will be included in the analysis. These results will be evaluated using intention-to-treat analysis.
7. Previous adverse reaction to acetaminophen

2.7. Vulnerable Subjects.

This study design excludes many vulnerable subjects, including children, pregnant women, and subjects with impaired cognition (who cannot provide accurate and consistent reports of their pain scores). Other potentially vulnerable subjects, such as employees, or the elderly, may enter the study; those who do will be afforded the same protections from risk as subjects not considered specifically vulnerable, and all subjects will be treated and monitored according to the same protocols and by the same personnel. Prisoners will not be included in the study given limitations in access prior to surgery and additional screening required for this population.

3. METHODS AND PROCEDURES

3.1 Overview.

This is a single center, randomized, double blinded study (pre, peri and post-operative days) clinical trial. Subjects will be randomized to receive: 1.) IV acetaminophen and placebo pills or 2) placebo IV (normal saline) and PO acetaminophen. It is expected that this trial will take approximately 1-2 years to complete.

3.1.2 Study medication pharmacokinetics

3.1.2.1 Intravenous and Enteric Acetaminophen.

Physical description – Capsules, Tablets, Gel, Liquid, Suspension, Solution
Pharmacodynamics –
Onset of action: Oral: <1 hour.
IV: Analgesia: 5 to 10 minutes; Peak effect: IV analgesic: 1 hour Antipyretic: within 30 minutes

Absorption – Primarily absorbed in small intestine (rate of absorption dependent on gastric emptying; minimal absorption from stomach. Absorption varies by dosage form.

Distribution – 1 L/kg at therapeutic doses.
Time to peak, serum: Oral: Immediate release: 10 to 60 minutes. IV: 15 minutes

Metabolism – At normal therapeutic dosages, there is primarily hepatic metabolism to sulfate and glucuronide conjugates; a small amount is metabolized by CYP2E1 to a highly reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQ1), which is conjugated rapidly with glutathione and inactivated to nontoxic cysteine and mercapturic acid conjugates.

Excretion – Urine (<5%; 60-80% as glucuronide metabolites; 20% to 30% as sulphate metabolites; ~8% cysteine and mercapturic acid metabolites.
Half-life elimination: Prolonged following toxic doses.
Adolescents: ~3 hours (range: 2 to 4 hours)
Adults: ~2 hours (range: 2 to 3 hours); may be slightly prolonged in severe renal insufficiency (CrCl<30mL/minute): 2 to 5.3 hours

Common side effects—
Oral, Rectal:
Dermatologic: skin rash.
Endocrine & metabolic: decreased serum bicarbonate, decreased serum calcium, decreased serum sodium, hyperchloremia, hyperuricemia, increased serum glucose.
Genitourinary: Nephrotoxicity (with chronic overdose)
Hematologic & Oncologic: Anemia, leukopenia, neutropenia, pancytopenia
Hepatic: Increased serum alkaline phosphatase, increased serum bilirubin
Hypersensitivity: rare
Renal: Hyperammonemia, renal disease (analgesic)

IV: >10%: Gastrointestional: Nausea (adults 34%), vomiting (adults 15%) 1% to 10%:
Cardiovascular: hypertension, hypotension, peripheral edema, tachycardia
Central nervous system: headache (adults 10%), insomnia (adults 7%), anxiety, fatigue, trismus

Dermatologic: Pruritus, skin rash
Endocrine & metabolic: hypervolemia, hypoalbuninemia, hypokalemia, hypomagnesemia, hypophosphatemia
Gastrointestinal: Constipation, abdominal pain, diarrhea
Genitourinary: Olguria
Hematologic & oncologic: Anemia
Hepatic: Increased serum transaminases
Local: Infusion site reaction (pain)
Neuromuscular & skeletal: Limb pain, muscle spasm
Ophthalmic: Periorbital edema
Respiratory: Atelectasis, abnormal breath sounds, dyspnea, hypoxia, pleural effusion, pulmonary edema, stridor, wheezing
All formulation: <1% (Limited to important or life-threatening): Anaphylaxis, hepatic injury (dose-related), hypersensitivity reaction, severe dermatological reaction (acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis.
(https://www.uptodate.com/contents/acetaminophen-paracetamoldruginformation?source=preview&search=acetaminophen&anchor=F129376#F1 29376)

Active blinded acetaminophen capsules will consist of a single 500mg acetaminophen tablet over-encapsulated into a size 00 colored, opaque capsule which is then backfilled with inert powder (lactose USP)

Each 1,000mg dose to consist of 2 x 500mg blinded capsules (sig: take 2 capsules POq6h)

Active Acetaminophen IV doses will consist of a single 1,000mg/100 ml IV dose with contents of commercial vials transferred to an empty sterile IV bag.

3.1.2.2. Placebo IV

Placebo IV doses will consist of 100ml of normal saline transferred to an empty sterile IV bag.

3.1.2.3. Placebo PO tablets

Placebo oral doses will be the same size 00 colored, opaque capsules that have been filled with inert powder (lactose USP)

3.1.3 Treatment protocol.

This single site randomized double blind study will include a Screening Visit, Surgical Day (Pre and intra-operative dosing) and continued follow-up study interventions through Post-Operative Day 1.

3.1.3.1 Blinding procedures**.** The research pharmacist will establish the blinding code sequence and maintain this independent of any research staff that have direct interactions with study subjects. After consent has been signed, on surgical day, the research pharmacist will dispense blinded IV and PO study medication to be dispensed

to study subjects in the pre-operative suite. Subsequent dosing of subjects' blinded medication will be dispensed from the inpatient Pyxis system. All blinded study medication will be labelled as required.

3.1.3.2 The University of Rochester Medical Research Pharmacist will be overseeing the randomization scheme incorporating blocks of 8 for study medication versus placebo. The randomization scheme code will only be available to research pharmacy staff and kept in a locked office. The Research Pharmacist will send a sealed envelope with unblinding information if needed for clinical safety information. This sealed envelope will be kept in a locked cabinet in the clinical research locked office which will only be available to Principal and Sub-Investigators if needed for subject safety.

3.1.3.3 Data Collection

Subject demographics:

1. Encrypted patient identifier
2. Encrypted regional anesthesia attending provider
3. Age
4. Sex
5. Race and ethnicity

Subject clinical characteristics:

6. Height and weight
7. BMI
8. Medical Comorbidities
9. Patients' current pre-surgical opioid use
10. Diagnosis

Characteristics of acetaminophen use:

11. Pre-surgical procedure use of acetaminophen (oral or IV) including dosing
12. Post-surgical procedure use of acetaminophen (oral or IV) including dosing

Outcomes:

13. Total opiate dose used from the study start (when the first dose of acetaminophen is administered in the pre-anesthesia holding area) to 24 hours post-operatively in morphine equivalents.
14. Average surgical pain intensity on a 0-10 numeric rating scale (NRS) administered between 20 and 24 hours post-operatively.
15. Average surgical pain intensity on a 0-10 numeric rating scale (NRS) administered between 1 and 2 hours post-operatively.
16. Pain Intensity at 20-24 hour assessment prior to incentive spirometry use.
17. Inspiratory capacity at the time of pain intensity assessments (between 1-2 hours post-operatively and between 20-24 hours post-operatively. The inspiratory capacity will be recorded in milliliters (nearest 250 ml mark on the

incentive spirometer) and as a percentage of the subject's baseline (preoperative) inspiratory capacity.
18. Dynamic pain (NRS) with incentive spirometer use.
19. Post-procedure adjuvant analgesic use (other than opioids and acetaminophen; for example, neuromodulators, muscle relaxants, and NSAIDS)
20. Incidence of nausea
21. Any side effects related to use of acetaminophen22. Length of time from PACU arrival to discharge.
23. Number of days to discharge from hospital

3.1.4. Drug packaging and labeling.

All study medications will be supplied to the investigators by the University of Rochester Investigational Drug Service (UR-IDS). Enteral acetaminophen and IV acetaminophen will be purchased. Oral and intravenous placebo will be provided by the UR-IDS.

Preparation of placebo IV and PO acetaminophen, packaging, labeling, distribution, and randomization of study medications will be completed by the UR-IDS, and labels on each study medication will include the following information:

1. Protocol number
2. Medication identification
3. Tablet or patch content number
4. Storage instructions
5. Cautionary statement, "For investigational use only"

3.1.5. Storage.

The principal investigator will ensure that the study medications are stored and dispensed in accordance with FDA regulations concerning the storage and administration of investigational drugs. All study medications will be stored at room temperature and will be protected from any extremes of temperature, light, and humidity. All drug supplies must be kept under locked conditions with access limited to those authorized by the principal investigator.

3.1.6. Dispensing of medications to study subjects.

Study investigators will initiate an Epic Investigational Study Medication order. Subjects will then be dispensed the randomized study medication just prior to surgery and every 6 hours thereafter for the subsequent 24 hours (total of 5 doses) *by* surgical nursing and medical staff. Study medication will be dispensed to the inpatient unit and kept in the Pyxis system with all appropriate subject information for staff dispensing at appropriate timeframes.

3.1.7. Drug accountability.

The principal investigator and UR research pharmacist will maintain accurate records of all study medication. Current dispensing records will be maintained, including the date and amount of medication dispensed per study subject. All unused and returned study drug not required by

applicable federal and state regulations to be held by the clinical facility must be destroyed in accordance with applicable federal and state regulations or be returned to the UR-IDS immediately after the study is completed.

3.1.8. Study evaluations and procedures.

3.1.8.1 Baseline; Pre-Surgical Anesthesia Assessment

- Study rationale, inclusion and exclusion criteria, and procedures will be described in lay terms to potential subject.
- If subject is interested in participating, obtain written informed consent and copy given to subject.
- Pre-anesthesia evaluation will be conducted per standard of care (SOC).
- Incentive Spirometer instructions and baseline measure will be obtained by a study investigator.

3.1.8.2 Surgical Day & Post-Operative Day 1

- Research staff review inclusion/ exclusion criteria
- Per Epic order set, research pharmacist dispenses blinded study medication of 1000mg acetaminophen (IV acetaminophen/ PO placebo or IV placebo/PO acetaminophen) for administration prior to transfer to operating room
- Note: per Standard of Care at University of Rochester Medical Center, the Epic ordering system will flag any potential order for additional acetaminophen to notify the provider of this duplication of therapy
- Blinded study medication administered every 6 hours for 24 hours post-surgery
- Standard of care for all pre-operative, intra-operative, and post-operative care to be maintained including usual post-operative IV opioid medications ordered.

3.1.9 Measures

3.1.9.1 Recruitment: Subjects will be referred by surgical providers. An informational letter and a copy of the consent form will be given to the potential subject by surgical providers or by Peri-operative Evaluation Center (PEC) staff outlining general information regarding this clinical study.

If the subject is interested in getting more information, they can contact the U of R Anesthesia research line at 585-273-5199 and a study coordinator will return their call.

The informed consent may also l be reviewed and questions answered at the PeriOperative Medicine Clinic appointment by PEC staff who are approved study staff, or on the day of surgery by a study investigator.

3.1.9.2 Demographic and clinical variables. Basic demographic information and clinical variables (ie diagnosis, medical comorbidities) will be obtained from the medical record as charted by surgical and nursing attendants during the standard of care for pre-, intra-, and post-operative treatment. See Appendix 1 data collection sheet.

3.1.9.3 Total opiate administered: The total amount of opiate administered from the time of the study start (administration of IV or oral acetaminophen) to 24 hours postoperatively will be recorded and converted to morphine equivalents.

3.1.9.4 Pain intensity. The standard of care pain rating scale will be used to quantify pain intensity. Subjects will be asked to rate their pain on the 11-point rating scale ranging from 0 ('no pain') to 10, (worst pain possible). Subjects will be asked to rate their average surgical pain intensity on a 0-10 numeric rating scale (NRS) assessment of pain from the time of waking up after surgery to a point in time between 1 and 2 hours postoperatively. Similarly, subjects will be asked to rate their average surgical pain intensity on a 0-10 numeric rating scale (NRS) assessment of pain from the time of waking up after surgery to a point in time between 20 and 24 hours post-operatively. Both nursing staff and post-surgical team will assess pain intensity as standard of care.

3.1.9.5: Inspiratory capacity: Inspiratory capacity is measured using a Voldyne 5000 incentive spirometer (Hudson RCI, Teleflex Medical). Inspiratory capacity will be recorded pre-operatively and at the time of pain assessments (1-2 hours and 20-24 hours post-operatively). Inspiratory capacity will be recorded to the nearest 250 cc mark on the incentive spirometer. Proper use of the incentive spirometer will be demonstrated to the patient in the pre-anesthesia holding area by a study investigator. Research staff will assist in collection of incentive spirometer data at 1-2 hours and 20-24 hours postsurgical time.)

3.1.10 Adverse events and serious adverse events

3.1.10.1 Definitions

3.1.10.2. Adverse event (AE). An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that develops or worsens in severity during the course of the study which is temporally associated with the use of a treatment, whether or not considered related to the treatment. Adverse events may be reported by the patient, or detected by the investigator or other observers. For the purpose of adverse event recording, the study period will begin with the initiation of study procedures (including pretreatment procedures) and will continue to the end of the trial.

3.1.10.3. Intensity of adverse events. The intensity or severity of adverse events will be graded as follows:

Mild: Awareness of sign or symptom, but easily tolerated. Not expected to have a clinically significant effect on the patient's overall health and wellbeing. Not likely to require medical attention.

Moderate: Discomfort enough to cause interference with usual activity or affects clinical status. It may require medical intervention.

Severe: Incapacitating or significantly affecting clinical status. Likely requires medical intervention and/or close follow-up.

3.1.10.4. Relationship to study medication. The principal investigator or a delegated sub investigator will be responsible for assessing relationship of AEs to study medication using the following definitions:

Probable: a clinical event, including a laboratory test abnormality, in which a relationship to the study drug seems probable because of such factors and consistency with known effects of the drug, a clear temporal association with the use of the drug, improvement upon withdrawal of the drug, lack of alternative explanations for the experience, or other factors.

Possible: a clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could not be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.

Unlikely: a clinical event, including a laboratory test abnormality, with a temporal relationship to study drug administration, which makes a causal relationship improbable and in which other factors suggesting an alternative etiology exist. Such factors include a known relationship of the adverse experience to concomitant medication, the patient's disease state, or environmental factors including common infectious diseases.

3.1.10.5. Serious adverse event (SAE). Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death
- life threatening complication
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

3.1.10.6. Assessment of adverse events. All adverse events that occur during the study period will be recorded, regardless of the severity of the event or judged relationship to the study drugs, and a diagnosis will be recorded whenever possible. The onset date, stop date, action taken with the study drugs, and outcome of each adverse event will be recorded. The relationship to study drug, severity, and seriousness of each adverse event as judged by the investigator will be recorded. In addition, subjects who experience an adverse event may be withdrawn from the study at any time at the discretion of the investigator. The subject will be monitored until the event has resolved or stabilized, determination of a cause unrelated to the study is made, or the subject is referred to the care of a local physician.

3.1.10.7. Reporting of adverse events. The principal investigator will report all SAEs to the Institutional Review Board (IRB) and to the FDA as required by applicable local and federal regulations.

4. DATA STORAGE AND CONFIDENTIALITY

The privacy of the subjects including their personal identity and all personal medical information including medical record numbers, date of birth, date of service will be maintained at all times. Subjects will be identified by a unique subject identification number and all data will be presented in aggregate reports.

Information about study subjects will be kept confidential and managed according to the requirement of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subject data will be entered into electronic spreadsheets. One spreadsheet will serve as the correlation tool and contain the subject name, medical record number and unique study subject identifier. The second spreadsheet will contain the unique study subject identifier as well as all the variables required for the study. The two spreadsheets will be stored as separate files, protected by unique passwords. Only the investigators and key study staff will have access to the files and their passwords. All the results of this research will be presented in the form of aggregate data.

5. SAMPLE SIZE JUSTIFICATION

The primary outcome is total opiate dose used during the study period (from the time of the administration of acetaminophen in the pre-anesthesia holding area to 24 hours postoperatively) in morphine equivalents. We assume that the IV acetaminophen is associated with a decreased opiate requirement during the surgical procedure and over the 24 hours postoperatively compared with oral acetaminophen. For a moderately clinically meaningful standardized treatment effect size of 0.4 with a significance level 0.05, a sample size of 200 achieves 80% power to reject the null hypothesis of no difference between the two groups in the mean values of total opiate dose. Assuming approximately 15% of participants will not complete the study after consenting (e.g., due to COVID cancellations, surgical changes, PI review or patient preference), we plan to enroll 265 subjects.

6. DATA ANALYSIS

All analyses of this study will be based on the principle of modified intention-to-treat (ITT). Patients who did not undergo surgery or who did not receive the study drug prior to surgery will be excluded from the analysis.

6.1 Analysis of primary outcome:

The primary outcome is the total opiate dose used from the study start (when the first dose of acetaminophen is administered in the pre-anesthesia holding area) to 24 hours post-operatively in morphine milligram equivalents (MME). Pain as measured by the average surgical pain intensity on a 0-10 numeric rating scale (NRS) administered between 20 and 24 hours postoperatively will be a second primary outcome, with gatekeeping used to control for multiplicity.

We anticipate some missing data in the study. Subjects who do not undergo surgery or who do not receive the study drug prior to undergoing surgery will be excluded from the analysis (the missing data here are assumed to be missing completely at random [MCAR]). For remaining missing data on the primary outcome, we will assume that the data are missing at random (MAR), which means that the missing data only depend on observed factors. In this case, we will model the probability that a patient's data are missing on the primary outcome with logistic regression conditional on patient demographics (age, sex, BMI), and the type of surgery (donor nephrectomy versus nephrectomy for cancer). For the primary analysis, inverse probability weighted (IPW) semiparametric linear regression analysis will be used to study the effect of group indicator, adjusting for, age, sex, BMI, type of surgery (donor nephrectomy versus nephrectomy for cancer) and block (yes vs. no). The primary analysis will be performed first for the total opioid dosage outcome. If the treatment effect for that analysis is positive, the similar analysis will be repeated for the pain score. Sensitivity analyses will be performed that do not include the block as a covariate because the block is often administered after the first dose of experimental Tylenol, although the choice to administer the block is not based on pain or distress or any other outcomes that are related to success of analgesia. We will also perform a per-protocol analysis in which only subjects who received all 5 doses of the Tylenol as indicated by the protocol will be included.

Although the primary aim of this study is not to test non-inferiority, we have prespecified a standardized effect size of 0.3 as the smallest effect size that we would consider to be clinically meaningful to guide interpretation of a non-significant result on the primary outcome. Given the fact that IV Tylenol is more expensive, we believe that ruling out an effect size larger than 0.3 would support a conclusion that the disadvantages do not outweigh the benefits of using IV Tylenol. We will use the 95% confidence intervals of the primary (opioid MME) and key secondary outcome (pain score) to determine whether an effect size of 0.3 can be ruled out (i.e., the 95% CI excludes an effect size of 0.3). This interpretation will be limited as it is not the primary objective of the study, but will be more likely to be an accurate conclusion given the prespecification of the parameters upon which to conclude the study supports a truly negative result rather than an inconclusive result.

6.2 Analysis of secondary outcomes:

Inverse probability weighted semiparametric linear regression or logistic regression method, as appropriate, will be used to analyze the secondary outcomes, adjusting for age, sex, BMI, type of surgery (donor nephrectomy versus nephrectomy for cancer), and block (yes v. no).

6.3 The significance level is set at 0.05 for each analysis. All analyses will be implemented with SAS 9.4 (SAS Institute Inc., Cary NC).

7. RISK/BENEFIT ASSESSMENT

Potential Risk.

There are minimal risks to the subjects associated with this clinical study. The use of acetaminophen is currently used pre-, intra-, and post-operatively with various surgical procedures. Subjects will be excluded if they have any known co-morbidities that pose a risk

with use of this medication (i.e., hepatic issues) or previous adverse effects from use of acetaminophen).
The most common rare side effects that may occur are skin rash, shortness of breath, chest pain, problems with blood, headache and liver damage or failure (with chronic use). Subjects will be monitored throughout the post-surgical time and any potential side effects will be evaluated and treated as standard of care. If subjects have any concerns about potential side effects of the study medication subjects can discuss this with the study team.

Potential Benefits to the Subjects.

Subjects potentially may have improved pain control post procedure that can facilitate recovery time.

Alternatives to Participation.

Subjects can elect not to participate in this clinical study.

Costs

There will be no cost to research subjects to participate in this study. All study medications will be covered under this research protocol.

Payments

Research subjects will not be paid for participating in this study.

8. DATA SAFETY AND MONITORING:

The independent Data Safety Monitoring Board (DSMB) will be composed of:

Raymond Zollo, MD (Anesthesiology) Chair
Richard Wissler, MD, PhD (Anesthesiology) Biostatistician

After clinical data collection is complete for the initial 6-10 study subjects, one half of the clinical records completed will be randomly selected for review by the DSMB. Subsequent DSMB review meetings will occur every 4-6 months dependent on study enrollment and review by DSMB chair throughout the course of this clinical study.

The board will review individual subject data, including documentation of informed consent, information regarding any protocol deviations and all adverse events. They will make a preliminary determination of the likelihood of the adverse effect being related to participation in the study. Any determination that the adverse event is possibly or likely related to participation, or that the DSMB association of causality differs from the PI determination will be discussed with the PI and reported to the RSRB. The distribution of adverse events will be compared between the IV acetaminophen and placebo group (statistical testing may be deferred until sufficient completor data is available to reduce the possibility of Type I error). If it is determined that there is a statistical difference in the incidence of adverse events between groups, then enrollment in the study will be stopped with this reported to the RSRB. If the study is stopped by

the DSMB, the Principal Investigator and the DSMB will meet to determine the advisability of continuing the study. If it is determined that the risk benefit balance merits continuation of the study, the PI may resubmit the study for approval to the RSRB.
Adverse events will be considered likely related to drug administration if there is a temporal relationship consistent with cause and effect, no other and more likely explanation for the adverse event, and a clear casual mechanism linking drug to effect. Adverse events will be considered possibly related (ie a suspected adverse drug reaction) if there is a reasonable possibility that the adverse event was caused by the study drug.

All members of the DSMB have agreed to perform in this role and have no relevant conflicts of interest.

9. REFERENCES

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