1. Protocol Title

Comparison of Multimodal Analgesic Regimen with Intravenous Acetaminophen to Standard Oral Multimodal Therapy in Primary Total Hip Arthroplasty: A Randomized Controlled Double Blind Trial

2. Purpose of the study

To determine the efficacy of intravenous versus oral acetaminophen in reducing opioid consumption and pain intensity when used as part of a standardized multimodal protocol for primary total hip arthroplasty.

3. Background and Significance

Multimodal analgesic regimens utilizing a variety of agents have become a standard of care for postoperative pain control following a wide variety of surgical procedures. With an increasingly greater emphasis on enhanced recovery and accelerated return to function, the opioid-sparing effect of these agents has been shown to result in improved patient outcomes such as mobilization, bowel recovery, satisfaction and hospital length of stay.[1,2] Typical multimodal agents used for orthopedic surgery include acetaminophen, NSAIDs/COX-2 inhibitors, gabapentinoids, ketamine, and dexamethasone.

Many of the agents that are used in these regimens are administered via the oral route. However, the oral route is associated with limitations: hospitalized patients are frequently *nil per os*, or unable or unwilling to swallow a large number of tablets. In addition, scheduling of oral medications can be difficult, especially when patients are asleep. Most importantly, bioavailability of orally administered agents that rely on absorption from the small intestine (e.g. acetaminophen) in the post-operative setting has been shown to be significantly reduced compared to preoperative levels in the same subjects.[3] This is likely related to impaired gastric transit due to the surgical stress response as well as the effect of opioids and/or volatile anesthetics on gut motility. In contrast, a similar drug administered via the intravenous route has 100% bioavailability.

While many anesthesiologists and surgeons anecdotally believe that intravenous acetaminophen leads to improved patient comfort and satisfaction with reduced opioid consumption compared to the oral route, this has not been investigated rigorously. This aim of this study is to compare these two routes over the first 24 hours following total hip arthroplasty. This is a moderately painful procedure for which both the surgical approach and the perioperative analgesic regimen is highly standardized at Duke University Medical Center. This standardization confers an opportunity to answer this research question with minimal confounders. Our hypothesis is that the group receiving 4 doses of intravenous acetaminophen will consume at least 20% less opioid medication compared to the group receiving an equivalent dose of oral acetaminophen.

4. Design and Procedures

This is a single center, prospective, randomized controlled study. 90 subjects will be recruited (see #6 Recruitment and Compensation below). On the day of surgery, subjects will be randomized to receive either the study intervention (intravenous acetaminophen and placebo tablets) or the control intervention (intravenous saline and active acetaminophen tablets). The Investigational Drug Service will prepare each intervention package, which will include one intravenous and one oral medication dose. Only one of these routes will be active (determined by randomization). Subjects will receive doses of both an intravenous and oral study drug every 6 hours in order to maintain blinding, and will receive a total of 4 doses of each (at 0, 6, 12 and 18 hours). The dose of acetaminophen in all cases will be 1000 mg. The volume of intravenous acetaminophen (and saline) will be 100 mL. The oral dose will consist of two (2) tablets of 500 mg each (or two matching placebo tablets).

All subjects will receive a standardized anesthetic regimen for total hip arthroplasty, as follows:

A) Preoperative phase

Subjects will receive the following preoperative multimodal drugs:

- Pregabalin 75 mg PO
- Celecoxib 200 mg PO
- The interventional drugs, both IV and PO

. The time that these drugs are administered will be recorded as time zero. Patients will then receive a spinal anesthetic with 12.5 mg of isobaric bupivacaine. No peripheral nerve blocks will be performed.

B) Intraoperative phase

All subjects will be receiving propofol infusion beginning at 50 mcg/kg/min and titrated to a Richmond Agitation-Sedation Scale score of -1 to -3 (drowsy to moderate sedation). Dexamethasone 10 mg IV and ketamine 0.25 mg/kg IV up to 40 mg total will be administered as part of the standard multimodal regimen. If required, subjects may receive fentanyl 25 mcg IV as needed to treat discomfort. No joint infiltration will be performed by the surgeon.

C) Postoperative phase

In the Post-Anesthesia Care Unit (PACU), subjects will have an intravenous patient-controlled analgesia (IVPCA) device connected and loading doses of hydromorphone administered by the PACU nurse as necessary (0.2 mg q 8 min

prn).

On the floor, subjects will receive:

- Pregabalin 75 mg PO BID until discharge
- Celecoxib 200 mg PO BID until discharge
- Dexamethasone 10 mg IV x 1 on postoperative day 1 (24 hours after the first dose)
- Intravenous patient-controlled analgesia (IVPCA) with hydromorphone (0.2 mg q 8 min).

The remaining 3 intervention packages (IV and PO) will be administered at 6, 12 and 18 hours following the first dose. At time point 24 hours (i.e. the ***fifth*** dose of acetaminophen), all subjects will begin to receive 975 mg of oral acetaminophen, continuing every six hours until discharge.

Assessments

Assessments will be performed by a blinded research assistant.

i. Opioid consumption. Opioid consumption at 24 hours is the primary outcome measure. Data will be drawn from PACU records and from the IVPCA infusion pump on a daily basis. Related secondary outcomes will include PACU opioid consumption, and at time points 12 hours, 24 hours, 36 hours and 48 hours. On discharge, patients will be provided with an analgesic diary in order to record their pain medications and daily worst pain scale out to 30 days postoperatively.
ii. NRS-11. The 11-point Numeric Rating Scale (0-10) will be used as a secondary outcome measure. Two measures will be taken with each assessment, one at rest and one with active hip flexion. These will be conducted preoperatively, 1 hour after arrival to PACU, and at time points 8 hr, 24 hr, 36 hr and 48 hr.
iii. Satisfaction. Overall subject satisfaction will be recorded on postoperative day 1 and 2.
iv. Straight leg raise. Subjects will undergo straight leg raise test in the presence of a physical therapist. Maximum range of motion will be recorded using a goniometer. (POD 1 and 2)
v. Heel slide test. This test assesses range of motion. Subjects will be asked to bend their knee and hip while sliding their heel along the bed.
vi. Self-paced walk test. This measure of overall physical performance is typically used in patients with osteoarthritis. Subjects are asked to walk quickly and safely without overexerting themselves along a hallway to a

line marked at 20 meters, turn around, and return to the starting point. Time required to perform this task is recorded.

vii. Supine to sit test. This measure of overall physical performance is typically used in patients with osteoarthritis. Subjects will be assessed on how easy it is, for them, to change from lying down to sitting on the side of the bed. Subjects may use assistance, if needed. The assessment will test overall function and strength of hip, lower limbs, and trunk.

Subjects will be assessed daily for opioid-related adverse events including the incidence of respiratory desaturation events overnight, nausea, vomiting, ileus, orthostasis and pruritis.

Hospital costs including pharmacy-related costs, costs due to opioid-related adverse events, the cost associated with nursing interventions and drugs to treat opioid-related adverse events, and overall hospital admission costs will be calculated. Hospital length of stay will be measured by both raw length of stay in hours and by time required to achieve discharge readiness. This is defined by the presence of 3 criteria: a pain score of 3 or less with ambulation, no intravenous opioids required in the preceding 6 hours, and the ability to perform self-care (go to the toilet, dress, and shower).

5. Selection of subjects

Criteria for inclusion:

- Patients scheduled for elective, primary total hip replacement for osteoarthritic disease
- Age 56-85 years
- American Society of Anesthesiologists (ASA) Physical Class I-III
- Weight ≥50 kg
- BMI 18-40 kg/m^2

Criteria for exclusion:

- Inability to consent
- Inability to speak English
- Pregnancy
- Weight <50 kg
- Revision hip replacement
- Emergency surgery
- Contraindications to regional blockade: coagulopathy or bleeding diathesis, local infection, allergy to local anesthetics
- Allergies/intolerances/contraindications to any of the multimodal agents (acetaminophen, pregabalin, celecoxib, ketamine or dexamethasone)
- Chronic pain from a separate source other than operative hip

- Daily opioid equivalent use of 30 mg of morphine or greater at time of consent
- History of heart failure
- History of drug or alcohol abuse
- Rheumatoid arthritis
- Uncontrolled anxiety, schizophrenia or other psychiatric disorder that, in the opinion of the investigator, may interfere with the study assessments of compliance
- History of alcoholism, chronic malnutrition, renal or liver impairment
- Hypersensitivity to acetaminophen or any of its excipients

6. Subject recruitment and compensation

Potential subjects (see inclusion criteria above) will be identified and screened in the Pre-Anesthetic Clinic by a research assistant. Only patients scheduled for primary total hip arthroplasty will be eligible for this study. There will be no compensation for subjects for their participation.

In the event that a potential subject is not feasible for in-person approach to occur, the subject will be introduced to research by a provider. The research staff will follow-up with a phone call using the IRB approved phone script. Subjects will be asked for permission for their electronic records to be viewed by research staff for inclusion/ exclusion criteria. If the subject qualifies and is interested in participating, research staff will meet the subject at the next visit to Duke for a formal consent. If the patient is not interested in the study, or does not meet inclusion/exclusion criteria, then information collected from the patient will be destroyed.

7. Consent process

Subjects permission to be approached for research will be obtained by the primary care team involved with the patient. The consent process will be conducted by the research personnel or one of the physicians involved in the study. The consent process will take place in the pre-operative screening or the surgical clinics. Throughout the consent process, measures will be taken to maintain privacy, such as by conducting face-to-face conversations in private rooms. As much time as necessary will be spent with each potential subject to sufficiently explain and answer all questions, and address all concerns they may have in regard to the study and/or consent process. Under HIPAA waiver, the study team will identify potential subjects from clinic schedules, OR schedules and Maestro Care.

8. Subject's Capacity to Give Legally Effective Consent

Subjects who do not have the capacity to give legal consent will not be approached for participation in this study.

9. Study interventions
See #4.

10. Risk/benefit assessment
Risk to the subject
Risks of the study intervention are minimal. Both IV and PO acetaminophen are FDA approved for treatment of pain in doses up to 4000 mg/day. Acetaminophen is a standard drug used in our multimodal pathway for total joint replacement. Subjects will receive an additional 400 ml of fluid (either acetaminophen or saline) over the first 24 hours, which may result in peripheral or pulmonary edema. There may be intolerances to excipients in either the IV acetaminophen preparation or the placebo tablets.

Benefits to the subject
There are no routine benefits to the subject for participation.

11. Costs
There will be no costs to the subject for participation in the study. Subjects will not be compensated for their participation.

12. Data analysis and statistical considerations

We will use descriptive statistics (mean (SD) or frequency (%)) and group comparisons via Wilcoxon rank sum or fisher exact tests to measure differences between groups in opioid consumption, pain scores with rest and activity, and other secondary outcome measures.

Sample Size Justification

Our typical mean opioid consumption following primary total hip arthroplasty in the first 24 hours is approximately 35 morphine equivalents. To address the primary hypothesis, that the opioid consumption in the intravenous group will be reduced by 20% compared to the oral group, we would need 27 subjects per group (80% power and alpha=0.05), or 54 total. To allow for participant drop-out, we will enroll a total of 90 subjects.

13. Data & Safety Monitoring
In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR

56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies. PI will be monitoring all AEs and submitting reports to the IRB per DUHS IRB policy.

Privacy, Data Storage and Confidentiality

Potential subjects and their families will be approached in private rooms. Any guests not involved in the consent process will be asked to leave the room during any communications, unless the patient allows them to be present. Data will be collected and stored in Redcap. Efforts to maintain subject confidentiality will include assignment of following Federal Privacy Regulations which provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). Subjects will be not be revealed in any reports or publications resulting from this study. For records disclosed outside of DUHS, subjects will be assigned a unique code number. The paper/electronic data will be stored as per the RDSP.

References

1. Parvizi J, Miller AG, Gandhi K: Multimodal pain management after total joint arthroplasty. J Bone Joint Surg Am 2011; 93:1075–84
2. Peters CL, Shirley B, Erickson J: The effect of a new multimodal perioperative anesthetic regimen on postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint arthroplasty. J Arthroplasty 2006; 21:132–8
3. Petring OU, Dawson PJ, Blake DW, Jones DJ, Bjorksten AR, Libreri FC, Leadbeater M: Normal postoperative gastric emptying after orthopaedic surgery with spinal anaesthesia and i.m. ketorolac as the first postoperative analgesic. Br J Anaesth 1995; 74:257–60