**TITLE:** Prospective, Randomized, Controlled Trial of An Opiate Sparing Protocol Versus Standard Opiate-Based Protocol Following Shoulder Arthroplasty

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**BACKGROUND:**
Recently, the opioid epidemic has been the center of focus for healthcare providers and governmental agencies due to rising rates of opioid abuse, opioid-related fatalities, and overall economic burden of treating the opioid epidemic. The prescribing patterns of opioid pain medications have fallen under scrutiny and healthcare providers have sought alternative pain management strategies that have limited opioid pain medication use. As orthopaedic surgeons account for 7.7% of all dispensed opioid prescriptions within the United States, surgeons have investigated multimodal pain management strategies to assess effectiveness in controlling postoperative pain as well as limiting opioid use and opioid related complications. Currently, there remains no clear consensus on the ideal pain management strategy following shoulder arthroplasty and the vast majority of strategies are based on opiate-driven protocols. We are investigating the effectiveness of an opiate sparing protocol following shoulder arthroplasty on 2 week postoperative pain scores and 12 week opiate consumption. We will also collect pain scores, patient satisfaction, and complications, reoperations, and readmissions during the 12 week episode-of-care. We are confident in the safety and effectiveness of an opiate sparing, multimodal pain management protocol in properly selected patients undergoing shoulder arthroplasty[1]. Continuous circulating flow cryotherapy is expected to be advantageous as part of our multimodal protocol for demonstrating better outcomes and significantly lower pain scores as compared to standard cold therapy[2,3]. Additionally we anticipate patients randomized to continuous circulating flow cryotherapy multimodal opioid protocol to use a significantly lower number of opioids[4].

The protection of our patient's safety and welfare has prompted this investigation. We believe that minimizing a patient's exposure to opiates can help prevent respiratory depression, nausea, vomiting, constipation, and most significantly, opiate addiction.

**PURPOSE:**
To investigate the difference in Visual Analog Scale (VAS) pain scores between two protocols following shoulder arthroplasty at the 2 week postoperative time point. The differences between opioid consumption, postoperative pain scores, patient satisfaction, and episode-of-care factors (reoperations, readmission, and complications) will be evaluated at the 12 week (90-day) postoperative time point. The two protocols are:

**Group 1 (opiate sparing protocol)**-a multimodal postoperative opiate sparing pain management protocol including continuous circulating flow cryotherapy versus

**Group 2 (opiate-based protocol)**-a standard postoperative opiate-based pain management protocol including standard cold therapy.

**HYPOTHESIS:**
A multimodal postoperative opiate sparing pain management protocol including continuous circulating flow cryotherapy (Group 1) will be non-inferior in the 2 week postoperative VAS pain scores using a non-inferiority margin of 2, as compared to a standard postoperative opiate-based pain management protocol including standard cold therapy (Group 2).

**STUDY DESIGN/DURATION:**
This is a single center, investigator initiated, prospective, randomized, controlled trial conducted among subjects who have given voluntary consent to participate. Participation will last until the completion of the 12 week standard of care follow up visit. The entire study will last for 2 years. Randomization will occur following signing of the informed consent document. No parties involved in the study will be blinded to randomization assignment.

**STUDY SETTING:**
Preoperative and postoperative office visits will be conducted at Campbell Clinic Collierville (1458 W. Poplar Ave., Ste. 100, Collierville, TN 38017) or Germantown Office (1400 S. Germantown Rd., Germantown, TN 38138). Perioperative care will be conducted at Baptist Memorial Hospital-Collierville (1500 W. Poplar Ave., Collierville, TN 38017).

**SAMPLE SIZE:**
76 subjects with 1:1 randomization (38 in opiate sparing and 38 in opiate-based) to account for a 20% lost to follow-up. Group sample sizes of 31 will achieve minimum 80% power to detect a one-sided non-inferiority margin of 2 on the VAS scale, where the true difference is assumed to be 0, the significance level (alpha) is set at 5%, and data are drawn from populations with standard deviations of 3. The standard deviations of 3 and non-inferiority margin of 2 were derived from the Hattrup article that compared liposomal bupivacaine nerve block to standard bupivacaine.[5] Power was determined using PASS 2008 software version 08.0.6. Because postoperative VAS pain scores reported in the literature vary greatly, if a difference in VAS pain scores is observed, then a superiority test comparing the two groups will be allowed to be conducted per The European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use.[6]

**PRIMARY OUTCOME:**
Primary outcome measure will be VAS pain scale at 2 weeks where the opiate sparing group pain is expected to be no worse than the standard opiate-based group using a non-inferiority margin of 2 points. VAS pain scale ranges from 0-10 with 0 indicating no pain and 10 indicating most intense pain.

**SECONDARY OUTCOME:**

The secondary outcome measure will be Oral Morphine Equivalents (OME) which will be collected in hospital on day of surgery, POD #1-7 via home diary, and 2 week, 6 week, and 12 week at in-office visits. Because this is an important outcome, a power analysis was conducted to ascertain if the minimal planned sample size of 38 subjects in each group would be sufficient to conduct a superiority analysis comparing OME between the two groups. Using the observed 24-hour median difference of 16mg OME observed between the acetaminophen+ibuprofen (median=20mg) and acetaminophen only (median=36mg) groups in the Thybo paper[7], along with the provided standard deviations of 20mg, a sample size of 26 in each group will achieve minimum 80% power using an alpha of 5%. Therefore, this secondary endpoint should be adequately powered with the planned sample size of 38 subjects in each group.

**INCLUSION/EXCLUSION CRITERIA:**

1) Inclusion Criteria
    a) 18-85 years old
    b) BMI <45
    c) Primary total shoulder arthroplasty scheduled (anatomic or reverse total shoulder arthroplasty) based on physical exam, medical history, and failed nonoperative treatment
    d) Willing and able to provide written informed consent
    e) Willing and able to cooperate in the required postoperative therapy
    f) Willing and able to complete scheduled follow-up evaluations/questionnaires
    g) Fluent in verbal and written English
2) Exclusion Criteria
    a) Less than 18 years of age or greater than 85 years of age
    b) Unable to provide written informed consent, cooperate with postoperative therapy, or complete follow-up evaluations/questionnaires
    c) Known sensitivity, allergy, or intolerance to medications within protocols
    d) Renal disease as defined by active or impending dialysis within 6 months or kidney transplant
    e) Concomitant ipsilateral upper extremity injury or condition other than shoulder that compromises function
    f) Chronic pain syndrome
    g) Five consecutive days of opioid use within the previous 90 days
    h) Worker's compensation
    i) Women who are pregnant, planning to become pregnant, or breastfeeding

**CONSENT PROCESS:**

A member of the study team will review the Campbell Clinic health history of the prospective subject from the Campbell Clinic EMR to determine inclusion and exclusion criteria. If determined to be eligible, subject will be contacted by one of the study team either at Campbell Clinic or on the phone to determine interest in study participation.

The informed consent document will be utilized as a tool to direct the informed consent discussion with ample time allowed for questions and answers with the study team. A copy of the signed consent will be given to the subject and a copy placed in the medical record.

**METHODS:**

Randomization:

A computer-generated randomization table will be created to employ a simple 1:1 randomization strategy with each code placed in sealed, numbered envelopes. Subjects will be randomized into one of the 2 groups following consent.

Randomization Arms:

**Group I**: Subject will receive **opiate sparing protocol**

Pre-Med Orders

1. Acetaminophen (Tylenol) 1000mg PO x 1
2. Gabapentin 300 mg PO x 1
3. Celecoxib (Celebrex) 200 mg PO x 1
    a. If allergic to sulfa, give Meloxicam (mobic) 15 mg PO x 1

Intraoperative/PACU Orders-per Anesthesia provider

In-patient Orders

1. Continuous circulating flow cryotherapy to operative shoulder: 2 hours on and 1 hour off when awake
2. Acetaminophen (Tylenol) 1000 mg PO every 6 hours
3. Gabapentin 100 mg PO TID
4. Ketorolac (Toradol) 15 mg IV every 6 hours (8 doses max)
5. Esomepraxole (Nexium) 20 mg PO daily
6. Ondansetron (Zofran) ODT (orally disintegrating tablet) 4 mg PO every 8 hours PRN nausea/vomiting
7. Oxycodone 5 mg PO every 6 hours PRN pain unresponsive to other medications and Cryotherapy
    a. If unable to take oxycodone, give Codeine 30 mg PO every 6 hours PRN pain or Hydromorphone (Dilaudid) 2 mg PO every 6 hours PRN pain

Discharge Orders

1. Continuous circulating flow cryotherapy to operative shoulder
    a. POD #2-#3: 2 hours on and 1 hour off when awake
    b. POD #4-#14: 1 hour on four time per day when awake
    c. Return cryotherapy unit to office at 2 week follow-up visit
2. Acetaminophen (Tylenol) 1000 mg PO every 6 hours X 14 days
3. Gabapentin 100 mg PO TID X 30 days

4. Celecoxib (Celebrex) 100 mg PO BID X 30 days
    a. If allergic to sulfa, give Meloxicam (mobic) 15 mg PO daily X 30 days
5. Esomepraxole (Nexium) 20 mg PO daily X 30 days
6. Ondansetron (Zofran) ODT 4 mg (#20) PO every 8 hours PRN nausea/vomiting
7. Oxycodone 5 mg (#10) PO every 6 hours PRN pain unresponsive to other medications and Cryotherapy
    a. If unable to take oxycodone**,** give Codeine 30 mg (#16) mg PO every 6 hours PRN or Hydromorphone (Dilaudid) 2 mg (#10) PO every 6 hours PRN)
8. Colace 100 mg PO twice per day while taking oxycodone (or Codeine/Hydromorphone as prescribed)

**Refills and/or additional medications will be processed at scheduled office visits or as needed via the 24 hr/7 day answering service.**

**Group II**: Subject will receive **standard opiate-based protocol**

Pre-Med orders

1. Acetaminophen (Tylenol) 1000mg PO x 1
2. Gabapentin 300 mg PO x 1
3. Celebrex 200 mg PO x 1
    a. If allergic to sulfa, give Meloxicam (mobic) 15 mg PO x 1
4. Oxycontin 10mg PO x 1 (if able to take)

Intraoperative/PACU Orders-per Anesthesia provider

In-patient orders

1. Standard cold therapy
2. Acetaminophen 1000 mg PO every 6 hours
3. Gabapentin 100 mg PO TID
4. Celecoxib (Celebrex) 100 mg PO BID
    a. If allergic to sulfa, give Meloxicam (mobic) 15 mg PO daily
5. Oxycodone 5 mg PO 1-2 tabs every 4-6 hours PRN pain
    a. If unable to take oxycodone, give Codeine 30 mg PO every 4-6 hours PRN pain or Hydromorphone (Dilaudid) 2 mg PO every 4-6 hours PRN pain
6. Hydromorphone (Dilaudid) 0.5 mg IV every 3 hours PRN pain
    a. If unable to take Hydromorphone (Dilaudid), give Morphine 2 mg IV every 3 hours PRN pain
7. Esomepraxole (Nexium) 20 mg PO daily
8. Ondansetron (Zofran ) ODT (orally disintegrating tablet) 4 mg PO every 8 hours PRN nausea/vomiting

Discharge Orders

1. Oxycodone 5 mg PO 1-2 tabs every 4-6 hours PRN pain (#40)

   a. If unable to take oxycodone, give Codeine 30mg (#40) PO every 4-6 hours PRN pain or Hydromorphone (Dilaudid) 2 mg (#40) PO every 4-6 hours PRN pain
2. Acetaminophen 1000 mg PO every 6 hours X 14 days
3. Gabapentin 100 mg PO TID X 30 days
4. Celecoxib (Celebrex) 100 mg PO BID X 30 days
   a. If allergic to sulfa, give Meloxicam (mobic) 15 mg PO daily X 30 days
5. Esomeproaxole (Nexium) 20 mg PO daily X 30 days
6. Ondansetron (Zofran) ODT 4 mg (#20) PO every 8 hours PRN nausea/vomiting
7. Colace 100 mg PO twice per day while taking oxycodone (or Codeine/Hydromorphone as prescribed)

**Refills and/or additional medications will be processed at scheduled office visits or as needed via the 24 hr/7 day answering service.**

Study Procedures:

| Procedure | Preop | Periop Care | POD # 0-7 | 2 week visit | 6 week visit | 12 week visit |
|---|---|---|---|---|---|---|
| I/E Review | X | | | | | |
| Office or phone contact | X | | | | | |
| Informed Consent | ● | | | | | |
| Randomization | X | | | | | |
| Demographics | X | | | | | |
| Perioperative Care | | X | | | | |
| Hours of hospital stay | | X | | | | |
| Home Diary | | | ● | | | |
| VAS | ● | | ● | ● | ● | ● |
| Return home diary | | | | ● | | |
| ASES | ● | | | | | ● |
| SANE | ● | | | ● | ● | ● |
| Patient Satisfaction | | | ● | ● | ● | ● |
| Pill Counts | | | | X | X | X |
| ROM/MD exam | X | | | | | X |
| Safety/Complications | X | X | X | X | X | X |

X=Completed by Study Member
●=Completed by Subject

**BENEFITS:**
There are no promises of benefits to taking part in this research. However, it is possible that postoperative pain can be controlled with minimal or no opiate use.

**RISKS:**
Randomization will expose the subjects to the specific risk associated with either of the medication regimens laid out in this protocol. All medications included in the protocol are approved by the Federal Drug Administration (FDA). The most common side effects of each medication (and the continuous circulating flow cryotherapy if applicable) will be communicated in the informed consent document.

There is a rare risk of bowel perforation resulting from constipation with opioid use. This information has been added to the ICF and a bowel regimen was prescribed with discharge medications.

A subject may experience uncomfortable or troublesome feelings in conjunction with completion of the home diary.

Loss of confidentiality is a potential risk.

**RISK MINIMIZATION PLAN:**
1. Subject selection based upon inclusion/exclusion criteria to safeguard enrollment of medically cleared patients.
2. A detailed disclosure of the side effects of each medication is communicated to the Subject in the consent form.
3. Emergency contact with a Campbell Clinic Physician 24 hour/7 day through answering service.
4. If a Subject does not achieve adequate pain control per self-reported VAS, additional opiate medications will be prescribed, regardless of randomization assignment, to protect the welfare of the Subject. These additional opiates will be included in data analysis.
5. If a subject randomized to the opiate sparing group consumes all of the prescribed opiate pills in the first fourteen (14) days following surgery, the subject will be grouped into the opiate-based group for analysis of VAS score.
6. The information requested in the home diary is the minimum required to evaluate study outcomes.
7. All paper and electronic research records are securely stored and accessible only to study personnel.

**SUBECT STIPENDS:**
Subjects will receive a $25 pre-paid card at completion of the 2 week office visit and a $50 pre-paid card at completion of the 12 week office visit. These two stipends are to offset any

incidental expenses for time and travel. The amounts were determined based upon previous studies conducted at Campbell Clinic.

**PROTECTION OF PRIVATE HEALTH INFORMATION (PHI):**
Multiple layers of security will be in place to insure protection of confidential information. All paper records will be locked in the Research Office at Campbell Clinic. Electronic records will be stored within the Campbell Clinic secure server. Only authorized study team members will have access to paper and/or electronic study records.

**OPERATIONAL OVERSIGHT/SAFETY MONITORING:**
All adverse events will be monitored by the Principal Investigator and reported accordingly to the IRB at Baptist Memorial Hospital. Appropriate treatment will be given to protect the rights and welfare of all subjects.

**PREMATURE WITHDRAWAL OF SUBJECTS:**
A subject may withdraw his/her consent through a verbal request or by sending a letter to the Principal Investigator. This information is included in the informed consent document. Participation is voluntary. Early withdrawal from the study does not result in a loss of rights or privileges.

A subject may be withdrawn by the study team without his/her consent if he/she does not show up for visits or does not follow the physician's instruction.

**OUTCOME MEASURES:**
1) Subject Demographics
    a) Age
    b) Sex
    c) Body mass index
    d) Medical comorbidities
    e) Hand dominance
    f) Occupation
2) Perioperative information
    a) Procedure performed
    b) Intraoperative complications
    c) Intraoperative blood loss
    d) Postoperative VAS and medication administration
3) Outcomes
    a) VAS pain scores collected on a scale from 0 to 10 where 0 indicates no pain and 10 indicates disabling pain will be collected on Postoperative Day (POD) #1-7 (collected via home diary), 2 week, 6 week, and 12 week

b) Oral Morphine Equivalents (OME) in hospital (POD #0), POD #1-7 (collected via home diary), and in 12 week postoperative period (subject will be asked to bring opiate pill containers at 2 week, 6 week, and 12 week office visit)
c) Patient satisfaction score regarding pain management (ordinal scale 0-10) at 1 week (collected via home diary), 2 week, 6 week, and 12 week
d) Preoperative and 12 week Postoperative outcomes scores
   i) VAS pain score
   ii) American Shoulder and Elbow Surgeon (ASES)
   iii) Single Assessment Numerical Evaluation (SANE)
e) Range of motion measurements (forward elevation, external rotation, internal rotation) at preoperative and 12 week
f) 90-day (12 week) episode-of-care measures including all complications, reoperations, and readmissions
g) Length of hospital stay (hours)

**STATISTICAL ANALYSIS:**

Statistical methodology will consist of summarizing collected data descriptively using percentages (numerator/denominator) for categorical outcomes, and means, medians, standard deviation, minimum, and maximum for continuous variables over the 12 week period of interest. Return to function using established outcome assessment tools will be used to compare the two groups using parametric or nonparametric methods, as appropriate.

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