Opioid-Free Shoulder Arthroplasty

NCT03540030

Protocol Date: July 5, 2017

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Protocol# SPORT049

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1. .**Title:** Opioid-Free Shoulder Arthroplasty

2. **Principal Investigator:**
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4. **Purpose of Study:**
To identify and provide a safe, opioid-free treatment pathway for shoulder arthroplasty with a focus on perioperative pain control and postoperative symptoms from treatment

5. **Background and Significance:**

Opioid-based analgesia has been a cornerstone of patient care in the setting of acute pain for the last century and has undergone logarithmic increase over the past twenty years. Unfortunately, the rise in utilization has brought with it a rise in opioid-induced side effects. These include constipation, nausea/vomiting, hyperalgesia [1, 2], delirium [3], addiction/withdrawal (with 67% of those prescribed a long-term opioid program still on opioids at an average of 4.8 years of follow-up [4]), and in some cases even respiratory depression/death. Patient expectations of opioid-based pain medication has driven a rapid rise in outpatient opioid prescriptions including both short and long-acting opioids [4]. These prescriptions have in turn become a source of significant mortality in the United States, with nearly 20,000 deaths due to opioid overdose in 2014 alone.

There have been momentous efforts made in identifying synergistic compounds to use for acute pain management in the perioperative time period to begin to minimize the opioid requirement for pain control. These studies have focused on nerve modulation with gabapentinoids [5-7], intravenous and local administration of sodium-channel blockers such as lidocaine and bupivacaine [8-10], and even increased interest in non-steroidal anti-inflammatories and acetaminophen [11-15]. At this time, no study has looked at the possibility of utilizing a multi-modal acute post-surgical pain control pathway that did not include some form of opioid medication for the general population.

Arthroplasty continues to be a dominant procedure in the orthopaedic armamentarium and accounts for well over a million surgeries done in the United States per year. With the ability to utilize targeted nerve blocks by anesthesia [16-18], and the increasing data showing efficacy of multi-modal therapy for acute pain [19-24], we propose a patient care pathway that is completely free of all opioid-based medications. From the time that patients are checked in until the time the patient follows up in clinic, they will utilize a pathway designed to eliminate pain and opioid-related side effects following shoulder arthroplasty. Our hope is that a well-designed pathway for total shoulder arthroplasty can quickly be modeled for other surgical procedures in an attempt to minimize the negative effects of opioid utilization both acutely and on a societal level.

6. References: See part C.

7. Study Design:

A. **Type of Study**: Prospective Cohort Study

B. **Study Population**

1. **Inclusion Criteria**
   a. Patient undergoing elective primary total shoulder or reverse total shoulder arthroplasty for osteoarthritis, avascular necrosis, cuff tear arthropathy, or inflammatory arthritis etiologies
   b. Age greater than or equal to 50.

2. **Exclusion Criteria**
   a. Revision total shoulder arthroplasty
   b. Chronic opioid therapy – per investigator discretion
   c. Liver or renal insufficiency – per investigator discretion
   d. Arthroplasty for fracture
   e. Sickle cell disease
   f. Workers compensation
   g. Inability to receive block
   h. Intervention Arm Only: Creatinine clearance less than 30 mL/min
   i. Intervention Arm Only: Allergy to non-steroidal anti-inflammatory medications (NSAIDs).

C. **Definition of Variables**

1. **Primary Outcome Variable**
   a. Pain at patient discharge or 24-hours, whichever comes first – measured on a 0-10 numeric rating scale (NRS).

2. **Secondary Outcomes Variables**
   a. Pain at 6hr, 12hr, 2 weeks, and 2 months post-operatively measured on a 0-10 NRS
   b. Rate of nausea
   c. Rate of constipation
   d. Continued use of pain medications
   e. Delirium score
   f. Falls
   g. Morphine milli-equivalents (In-hospital operative, In-hospital post-operative, and post-discharge)
   h. Satisfaction with overall pain
   i. American Shoulder and Elbow Surgeons (ASES) Shoulder Score
   j. Simple Shoulder Test
   k. VR-12

3. **Additional Data Points**
    a. Age
    b. Gender
    c. Height/Weight/Body Mass Index (BMI)
    d. Tobacco Use (current, former, never)
    e. Medical Comorbidities (based on the Charlson Comorbidiy Index)
    f. Primary Diagnosis
    g. Pre-Operative Opioid Use
    h. Pre-Operative current and average pain score (NPS)
    i. Pre-Operative creatinine level
    j. Surgeon
    k. Surgical Approach (Total Shoulder Arthroplasty, Reverse Total Shoulder Arthroplasty)
    l. Concomitant Procedures
    m. Date of Surgery
    n. Intraoperative Complications
    o. Date of Discharge
    p. Post-Operative opioid use

4. **Confounding Variables**
    a. Patients will demonstrate some degree of recall bias when asked about perioperative pain control at their two week, 6-8 wk, and 1 year follow-up

D. **Methods**

1. Patient Enrollment and Identification:
Patients will be identified in clinic by the surgeon performing the shoulder arthroplasty. The surgeon will introduce the concept of opioid-free arthroplasty with the patients, who will then choose whether to follow the traditional or opioid-free pathway. The surgeon will notify the study coordinator of the patient's decision. Patients participating in the intervention arm will have a blood draw (approximately 10 milliliters, or about 2 teaspoons) to determine eligibility based on creatinine clearance. One tube of blood will be collected in a gold serum top vaccutainer tube (approximately 2 teaspoons) by the research staff in the clinic during the screening visit. It will be sent to the local lab for processing. Creatinine clearance will be calculated with the Cockcroft-Gault Formula:

$$CC = [(140 - age_{years}) * weight_{kg}]/(72 * Creatinine_{Serum}\left(\frac{mg}{dl}\right))$$

For females, the calculated value is multiplied by 0.85 (i.e., 85% of the calculated value). For males, there is no additional conversion necessary. For convenience, an online creatinine clearance calculator will be used (http://www.mcw.edu/calculators/creatinine.htm) for the calculation. The

resulting creatinine clearance will be recorded. Patients with a creatinine clearance of less than 30 mL/min will be excluded from the interventional arm of the study, as NSAIDs are contraindicated. Patients with creatinine clearance between 30 and 60 mL/min will receive a half-dose of all NSAIDs if enrolled in the intervention arm of the study. Patients with creatinine clearance greater than 60 mL/min will be eligible to receive full doses of NSAIDs in the intervention arm of the study.

The study consent will be scanned in the clinic and hospital chart to identify them as a study patient. During the screening visit, patients will be registered in the OrthoCarolina OBERD platform that is used to collect and manage patient reported outcome (PRO) data, specifically the ASES, Simple Shoulder Test, and VR-12 measures.

Additionally, color-coded case report forms (CRFs), indicating the patient pathway, will be provided to the unit nurses.

Online surveys containing patient reported outcomes of the ASES, Simple Shoulder Test, and VR-12 will be automatically sent to patients at the 1 year post-operative interval via the OrthoCarolina OBERD platform. OBERD is a software platform that OrthoCarolina uses to collect clinical outcomes data and provide patient education. This platform is interfaced with OrthoCarolina's electronic medical records and administrative claims system.

All patients having a total shoulder replacement or reverse total shoulder replacement at OrthoCarolina complete these questionnaires through the OBERD software platform as part of the OrthoCarolina quality improvement process. If a patient is unable to attend the standard-of-care 1 year postoperative clinic visit, then online and/or phone data collection of patient reported outcomes of the ASES, Simple Shoulder Test, VR-12, and questions of constipation, nausea, pain, or other complications will occur. Patient compliance with PRO online survey completion will be monitored and patients will be contacted via phone to ensure that the surveys are completed if they are unable to attend the standard-of-care 1 year follow up visit. If patients are able to attend the 1 year follow up visit and they have not completed the questionnaires via the OrthoCarolina OBERD platform, those questionnaires will be collected at the 1 year follow up office visit.

2. Randomization: N/A

3. Treatment Administration/Intervention:

Observation arm: No changes from baseline surgeon's management pathway. Anesthesia should be utilized in a routine fashion with all

routine perioperative medications. Patients will be discharged on routine postoperative medications including opioids, NSAIDS, and any other modalities typically used by the treating surgeon. All data collection points will mirror the intervention arm.

Intervention arm:

a) In the preoperative area, patients will receive an oral dose of both gabapentin and celecoxib (toradol if patient has sulfa allergy). Communication with the anesthesia team will take place the day before surgery to identify the patient as an opioid-free participant, and a reminder will be provided while patient meets with the anesthesiologist in pre-op. The patient will be identified as a research patient on the hospital chart. Patients will receive an ultrasound-guided interscalene regional block by a board certified anesthesiologist in standard fashion without the aid of opioid co-medication.
b) Intra-operative management by anesthesia will be done with non-opioid modalities but should include one dose of intravenous acetaminophen during the procedure. Anesthetic modalities will include, but are not limited to, regional block, propofol, IV lidocaine, rocuronium/vecuronium, and sevoflurane/desflurane. If the attending anesthesiologist deems it necessary to dose with opioids during the procedure, this will be recorded and reported. Liposomal bupivacaine will be injected into the peri-articular soft tissues as an adjunct to the block performed by the anesthesia team.
c) Post-operative hospital care:
   An in-service will be performed with both the recovery room staff and the orthopaedic care floor to the pathway.
   The presence of both the block and the liposomal bupivacaine should obviate the concern for pain control in the anesthesia recovery area.

   Every opioid-free patient will have:
   - Cryotherapy
   - Scheduled gabapentin (300mg q8hr)
   - Toradol (15mg IV q6hr for four doses). Toradol will transition to celecoxib for the duration of the hospitalization (or meloxicam for patients with sulfa allergy).
   - PRN medications will include both oral and intravenous acetaminophen, as well as up to an additional 15mg of toradol per 6hr period (noting that the scheduled dose was limited to 15mg and not 30mg). Creatinine clearance will

be checked upon admission to confirm no underlying chronic renal dysfunction.

- The designed order set includes scheduled medications targeting multiple pain receptor targets. Additionally, there are instructions to notify either the principal investigator (NH), or resident investigator (DL) directly if the patient's pain continues to be inadequately controlled despite the above pathway. After exhausting all non-opioid modalities, either NH or DL will approve the administration of an opioid at the patient's request and notate this patient for the record.

d) Discharge medications: Upon discharge, patients will continue gabapentin 300mg q8hr for an additional 14 days, as well as celecoxib (or meloxicam for those with sulfa allergies) for an additional 14 days. They will additionally be allowed to continue utilizing acetaminophen in a PRN fashion.

- NOTE: Patients with creatinine clearance between 30 and 60 mL/min will receive a half-dose of all NSAIDs if enrolled in the intervention arm of the study. Patients with creatinine clearance greater than 60 mL/min will be eligible to receive full doses of NSAIDs in the intervention arm of the study.

4. Data Collection
   i. Preoperative patient data:
      1. Baseline (current and average) pain score (NRS), baseline opioid use, baseline creatinine clearance
      2. Patient demographics: Age, Gender, Height, Weight, BMI, Tobacco Use, Comorbidities, and Primary Diagnosis
      3. ASES
      4. Simple Shoulder Test (SST)
      5. VR-12
   ii. Operative chart data:
      1. Surgeon
      2. Surgical approach
      3. Concomitant procedures
      4. Date of surgery
      5. Morphine milli-equivalents (MMI) utilized during procedure
      6. Intraoperative complications
   iii. Postoperative chart data:
      1. Date of discharge
      2. Postoperative patient data: Pain score at 6hr, 12hr, and 24hr
      3. Nursing calculated delirium score at 6, 12, and 24hr: Confusion Assessment Method (CAM) [25]

4. Number of doses of anti-emetic/nausea
5. Falls
6. MMI during hospitalization
7. Treatment failure (Y/N)

iv. Postoperative patient diaries
1. Pain NRS: Pain score every 8 hours for three days after discharge, then once per day until 2 week visit
2. Opioid medications taken

v. 2 week postoperative visit:
1. Current pain NRS and average pain NRS
2. Constipation (Y/N)
3. Nausea (Y/N)
4. Were you satisfied with your overall pain control? (Y/N)
5. Have you fallen at home? (Y/N)
6. Observational Arm: Still using opioids? (Y/N)
7. ASES
8. Simple Shoulder Test (SST)
9. VR-12

vi. 2 month postoperative visit:
1. Current pain NRS and average pain NRS
2. Constipation (Y/N)
3. Nausea (Y/N)
4. Were you satisfied with your overall pain control? (Y/N)
5. Have you fallen at home? (Y/N)
6. Observational Arm: Still using opioids? (Y/N)
7. ASES
8. Simple Shoulder Test (SST)
9. VR-12

vii. 1 year postoperative visit:
1. Current pain NRS and average pain NRS
2. Constipation (Y/N)
3. Nausea (Y/N)
4. Were you satisfied with your overall pain control? (Y/N)
5. Have you fallen at home? (Y/N)
6. Observational Arm: Still using opioids? (Y/N)
7. ASES
8. Simple Shoulder Test (SST)
9. VR-12

E. **Risks**

- Surgical risks; patients will sign a separate surgical consent form. The shoulder replacement surgery risks are the same if patients choose to be in this study or not.
- Loss of confidentiality
- Risks associated with blood draws include pain, discomfort, bruising and infection. Rarely, a person may faint.

- As with all medications, side effects may include allergic reaction. Allergic reactions may range from minor itching or rash to major reactions which can result in death. All of the medications being used in this study are FDA-approved and are medications that are routinely given after total shoulder replacement surgery.

F. **Benefits**

This study may or may not improve the condition of the study subjects. The information gained from subjects' cases may benefit others with the same condition.

Proposed timeline:

Procedure	Preop/Screen	Op	6 hour	12 hour	24 hour	2 week	2 month	1 year
ICF	X							
Demographic	X							
Comorbidities	X							
Creatinine Clearance (Intervention Arm Only)	X							
Complications (nausea, constipation, falls)			X	X	X	X	X	X
Delirium Score (CAM25)		X	X	X	X			
ConMeds (specifically anti-emetic/nausea and pain medication)	X	X	X	X	X	X	X	X
Surgical Information		X						
Pain Score (NRS), current	X		X	X	X	X	X	X
Pain Score (NRS), average	X					X	X	X
ASES	X					X	X	X
Simple Shoulder Test	X					X	X	X
VR-12	X					X	X	X
Patient Pain (NRS) Diary±						X		
Patient Pain Medication Diary±						X		

± The diaries will be completed daily from day of discharge until the 2 week visit. They will be collected at the 2 week visit.

8. **Use of Data:** Investigators may use the data for regional and national presentation or peer review journal publication.

9. **Estimation of Sample Size:** The calculation of the sample size estimate is based on the primary outcomes of patient reported post-operative pain (VAS). Statistical analysis will be two-sided with an alpha level of 0.05. Statistical power will be 80% for the primary outcome. Assuming a 2-point mean difference in pain VAS between the control and intervention groups with a 2.5-point standard deviation in each group [26, 27], 27 patients per group are required. Assuming a 30% loss to follow-up, 35 completed patients per group for a total sample size of 70 patients will be necessary to ensure statistical significance.

10. **Statistical Procedures:** Standard descriptive statistics will be reported including measures of central tendency, variance as well as frequencies and proportions. For bivariate analyses, chi-square or Fishers Exact tests will be used for categorical data to determine statistical differences. For normally distributed interval or continuous variables a student's T-test will be used. For non-normally distributed data a Wilcoxon rank sum test will be used.

11. **Data Management:** Data should be entered on at least a weekly basis, via REDCap (http://project-redcap.org/). REDCap is a secure web application designed exclusively to

support data capture for research studies. It allows users to build and manage online surveys and databases quickly and securely with site and personnel specific usernames and passwords. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages like SPSS, SAS, and Stata.

12. **Data Safety Monitoring Plan:** Serious adverse events (SAEs) that are "related," "probably related" or have an "unknown" relatedness to the study procedure, will be reported to the data safety monitoring board (DSMD) via email as they occur. Robert Anderson, M.D., Chairman, Research Advisory Committee will serve as the safety monitor. A data safety monitoring board (DSMB) will review data on a bi-monthly basis or as needed. The DSMB are members of the OrthoCarolina Research Institute (OCRI) Research Advisory Committee. At each meeting the study will be reviewed for adverse events, serious adverse events, and overall feasibility issues.

13. **Funding:** This is an investigator initiated study with funding provided by OrthoCarolina Research Institute.

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