Natural history of pain after shoulder arthroplasty conducted with multimodal analgesia

FUNDER: Department of Anesthesiology

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TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Protocol Title:	Natural history of pain after shoulder arthroplasty conducted with multimodal analgesia
Protocol Number:	2016-0779
Protocol Date:	12/21/2016
Sponsor:	Department of Anesthesiology
Principal Investigator:	Jacques YaDeau, MD, PhD
Objective:	This is a pilot study looking at the timeline of pain after total shoulder arthroplasty.
Study Design:	Pilot Study/Prospective Cohort Study
Enrollment:	125
Subject Criteria:	1. Patients undergoing Total Shoulder Arthroplasty (TSA) for osteoarthritis, reverse, anatomic procedures. 2. All patients eligible for the standardized anesthetic for TSA 3. Age 18-80 4. Patients who are capable to provide informed consent and answer questions in English (some questionnaires are only validated in English)
Data Collection:	Sources: EPIC, Medical Records, and Patient Reported. Variables: Name, DOB, Race, Gender, Ethnicity, Age, Education, BMI, ASA, Fibromyalgia Score, Pain Catastrophizing Scale, NRS Pain scores at rest and with movement, opioid and other pain medication consumption, number of analgesia prescribed, ORSDS, surgical outcomes, IMMPACT, OR time, surgery time, use of anti-platelet/anticoagulants, PainOUT, Averse events (if they occur).
Statistical Analysis:	Mean pain with movement 2 weeks post TSA (the primary outcome) will be summarized as a point estimate with 95% confidence interval

1.0 INTRODUCTION

We have developed a pathway for shoulder arthroplasty that in many cases results in excellent analgesia (Goon 2014). Roughly half of the patients have minimal needs for additional opioids. However, some patients have significant pain (Goon 2014, YaDeau 2015), including at the 2-week time point (anecdotal evidence, per Dr. Gulotta). Dr. Gulotta noted that many of the patients with pain appear to have significant bruising, and he hypothesizes that the extravasation of blood into the surgical field causes inflammation, swelling, stiffness and pain. Tranexamic acid may reduce the incidence of this problem, and Dr. Gulotta has considered requesting tranexamic acid for some of his shoulder arthroplasty patients. There is limited literature about pain after total shoulder arthroplasty, and relevant data are not available about patients treated with the following anesthetic/analgesic protocol. This is a pilot study that will help develop a protocol for a tranexamic acid study to help reduce swelling in patients undergoing TSA. The study will also provide much needed clinical data about what patients and physicians can expect regarding postoperative pain and total shoulders, when managed with this protocol and thus serve as a benchmark publication.

2.0 OBJECTIVE(S) OF CLINICAL STUDY

The pain experience for patients after total shoulder arthroplasty has not been well described. We believe that our current protocols provide good pain control for many patients while they are in the hospital, but we do not know about their pain experience at POD 14. Review of the literature failed to provide suitable information about pain trajectories after TSA. Moreover, the innovative analgesic protocol recently developed at HSS is apparently unique and makes it difficult to apply data from other institutions. In addition, another reason to conduct this study is to obtain baseline data for a possible follow-up study involving tranexamic acid. (No tranexamic acid will be administered for patients in the current proposed study). Some patients experience pain after shoulder arthroplasty surgery as well as bruising, which could be due to blood extravasation into the surgical site. To design a possible tranexamic acid study, a preliminary baseline study is needed to determine the timeline of pain following TSA. Moreover, the innovative analgesic protocol recently developed at HSS is apparently unique and makes it difficult to apply data from other institutions.

The pain experience for patients after total shoulder arthroplasty has not been well described in scientific papers. Here at HSS, we have developed a unique pathway for shoulder arthroplasty that in many cases results in excellent analgesia, with roughly half of the patients having minimal needs for additional opioids. However, some patients experience significant pain including at the 2 weeks time point. We believe that our current protocols provide good pain control for many patients while they are in the hospital, but we do not know in detail about their pain experience at 14 days after surgery. Many of the patients with pain appear to have bruising at the surgical site, which may contribute to postoperative pain. We wish to describe the pain trajectory after shoulder arthroplasty with this study, including determining how often bruising occurs after shoulder replacement.

3.0 STUDY HYPOTHESES

Since it is a pilot study there is no formal hypothesis. We believe that using our current protocol many patients have postoperative pain that is no worse than their preoperative pain. Previous HSS anesthesia protocols for total shoulder arthroplasty patients have not formally followed patients past their hospital discharge, and we believe that some patients do experience moderate to severe subacute postoperative pain.

Th is a pilot study, with the goals of

a) developing data for a subsequent randomized trial

b) describing the pain trajectory after total shoulder arthroplasty given comprehensive multimodal perioperative analgesia

c) gathering preliminary data about which shoulder arthroplasty patients are at high risk for moderate or severe postoperative pain (NRS with movement, POD14, moderate >= 4 6; Gerbershagen 2011; severe >= 710, Krebs 2007) Potential factors include fibromyalgia score, catastrophizing score, anxiety/depression score, gender, preoperative opioid use

d) gathering preliminary data on the potential association between the predictors listed in (c) and NRS pain score with movement on POD14

e) Estimating incidence, size and severity of postoperative bruising on POD 14 and 3 months

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Endpoint

- NRS pain scores with movement on POD14

4.1.2 Secondary Endpoints

- NRS pain with movement – POD1, POD3, POD7, 3 months
- NRS pain scores at rest – POD1, POD3, POD7, POD14, 3 months
- Opioid consumption (in past 24 hours) – POD1, POD3, POD7, POD14, 3 months
- Number of analgesics prescribed – DC on DOS
- Total number of analgesic pills taken – POD14
- Other analgesic use – POD1, POD3, POD7, POD14, 3 months
  - Number of tablets of other analgesics used in past 24 hours, including acetaminophen, NSAIDs, COX2 inhibitors, gabapentin, pregabalin, muscle relaxers
- ORSDS – POD1

- Surgical outcomes – POD14 and 3 months (routine outcomes, range of motion and incidence, bilateral arm circumference, size and severity of postoperative bruising on POD14 and 3 months)
- Extent of bruising at POD14 (routine post-op visit) → present (yes/no) and longest dimension
- Other pain related outcomes per IMMPACT (Dworkin 2005)
  - Hospital Anxiety and Depression Scale (POD1)
  - PainOUT Questionnaire (POD1, POD14); includes satisfaction questionnaire
- Adverse events (if they occur)
- Pain Catastrophizing Scale (pre-op)
- Fibromyalgia Survey (pre-op)

4.2 Study Sites

This study will take place at the main campus of the Hospital for Special Surgery (HSS).

5.0 STUDY POPULATION

5.1 Number of Subjects

125

5.2 Inclusion Criteria

Subjects of either gender will be included if:

1. Patients undergoing Total Shoulder Arthroplasty (TSA) for Osteoarthritis, Reverse, Anatomic procedures
2. Age 18-80
3. All patients eligible for the standardized anesthetic for TSA
4. Patients who are capable to provide informed consent and answer questions in English (study involves questionnaires validated in English)

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- non-English speaking
- Patients incapable to provide informed consent
- Contraindications for regional anesthesia
- Patients undergoing TSA for trauma or rheumatoid arthritis
- Revision TSA (previous non-TSA surgery is not an exclusion)
- Conversion of hemiarthroplasty to TSA
- Planned use of tranexamic acid

6.0 PROCEDURES

6.1 Intraoperative Protocol

Preoperative Pain Phenotyping (see YaDeau Anesthesiology 2016:125)

1. Demographics (age, sex, race, educational status, BMI, ASA, physical status)
2. Opioid use
3. Other analgesic use
4. NRS pain at rest and with movement
5. Pain Catastrophizing Scale (Sullivan. Psychological Assessment 1995; 4:524-32)
6. Fibromyalgia Survey Scale
7. Hospital Anxiety and Depression Scale (HADS)
8. Life Satisfaction (0-10 Likert scale)
9. Preoperative use of anticoagulants and/or antiplatelet agents

The Research Assistant will collect the data in the holding area from patient reports and will fill in the remaining demographic and clinical information from Epic. This will be the case as well for the intra-op protocol as well as for the follow ups. The RA will call the patient on POD7, POD14 and 3 months, as well as will look in the surgeons notes for the questionnaires and assessments.

Anesthetic and Analgesic Protocol

1. Interscalene block: 0.5% bupivacaine, 25 ml, Clonidine, 100 mcg, Dexamethasone, PF, 2 mg, Buprenorphine, 150 mcg
2. IV sedation or GA, as requested by surgeon or deemed necessary by anesthesiologist
    1. Block procedural intravenous sedation protocol included midazolam (up to 5 mg), propofol as needed, and ketamine (10-20 mg).
    2. Both get 50 mg ketamine IV (total, part used with midazolam for block sedation).
    3. Sedation: Intraoperative sedation will be maintained with propofol infusion and a total of 50mg ketamine.
    4. GA: After induction with propofol and insertion of the LMA, anesthesia will be maintained with titrated propofol infusion and 1% sevoflurane. Additionally, intravenous ketamine 50mg total will be given.
3. Intraoperative ondansetron/famotidine/dexamethasone/ketorolac, dosed by protocol
4. IV acetaminophen, then oral: 1000 mg IV x 4 doses (adjusted for weight, if needed:If patient is < 50 kg; IV acetaminophen dose is 15 mg/kg q 6 hr), 650 mg PO q 6hr for 3 days
5. “low dose” oral opioids (for opioid naïve patients): Mild pain - tramadol 50 mg, Moderate pain - tramadol 100mg, Severe pain - oxycodone 5 mg. Allow escalation as needed (e.g. oxycodone 5/10/15 mg). Patients with previous exposure to opioids may receive alternative opioid analgesics as clinically indicated.
6. Ketorolac, then meloxicam: 15 q 8 IV for total of 4 doses, then 7.5 – 15 mg PO daily for 2 weeks
7. IV PCA (0/1.3/10/8)
8. Continue same oral analgesics at home after discharge.
9. Pain service can adjust pain medications as needed.
10. OR time will be calculated, from coming in to leaving the operating room.

Postoperative Follow Up

At POD14 and POD3 months, we will assess any adverse events that may occurred. Pain assessment will be done using NRS pain scores at rest and with movement. POD1, POD3, POD7, POD14, and 3 months. We will assess for postoperative use of anticoagulants or antiplatelet agents.

6.2 Data Collection

The following data will be collected:

Pre-operative/Baseline

- Demographic data (DOB, race, gender, ethnicity, education, age)
- Patient weight & height, BMI
- ASA status
- Fibromyalgia Score
- Pain Catastrophizing Scale
- NRS pain scores at rest and with movement
- IMMPACT – Hospital Anxiety and Depression Scale
- Use of anti-platelet agents or anticoagulants

Surgical procedure (Intra-operative)

- Date of surgery
- Type of surgery
- OR time
- Surgery time
- Surgical outcomes

Post-Operative Day 1 (POD 1)

- NRS pain scores at rest and with movement
- Opioid, NSAID and other pain medication consumption
- ORSDS
- IMMPACT – Hospital Anxiety and Depression Scale
- Use of anti-platelet agents or anticoagulants
- PainOUT Questionnaire
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Discharge

- Number of analgesia prescribed

Post-Operative Day 3 (POD 3)

- NRS pain scores at rest and with movement
- Opioid, NSAID and other pain medication consumption
- Use of anti-platelet agents or anticoagulants

Post-Operative Day 7 (POD 7)

- NRS pain scores at rest and with movement
- Opioid, NSAID and other pain medication consumption
- Use of anti-platelet agents or anticoagulants

Post-Operative Day 14 (POD 14)

- NRS pain scores at rest and with movement
- Opioid, NSAID and other pain medication consumption
- Use of anti-platelet agents or anticoagulants
- Surgical outcomes

Post-Operative 3 months

- NRS pain scores at rest and with movement
- Opioid, NSAID and other pain medication consumption
- Use of anti-platelet agents or anticoagulants
- Surgical outcomes

7.0 STATISTICAL ANALYSIS

- Proposed analysis: N/A
- Interim analysis planned: N/A
- Alpha level: N/A
- Beta or power level: N/A
- Primary outcome variable estimate: N/A
- Number of groups being compared: N/A
- Effect size or change expected between groups: N/A
- Resulting number per group: 100
- Total sample size required: 100

An extensive literature search found no report of pain intensity two weeks post TSA. Therefore, the standard deviation in mean pain intensity was estimated based on the control group of a prior Total Knee Arthroplasty (TKA) trial (YaDeau 2016). In the prior TKA trial, the maximum standard deviation in mean pain intensity (with ambulation, flexion, rest, and worst in past 24 hours) in the control group was 2.3. The following table and figure show how the halfwidth of the 95% CI (i.e., precision) for the mean pain intensity increases with total sample size, and that the gain in precision per additional patient is less pronounced after enrollment of 100 patients.

Mean pain with movement 2 weeks post TSA (the primary outcome) will be summarized as a point estimate with 95% confidence interval. Continuous variables will be summarized as means with standard deviations or medians with 1 st and 3 rd quartiles, depending upon the distribution of the data. Ordinal variables will be summarized as medians with 1 st and 3 rd quartiles. Categorical variables will be summarized as counts and percentages. Longitudinal measurements of pain, opioid consumption, and nonopioid analgesic consumption will be modeled using the generalized estimating equations method. Differences in means or odds ratios (from cumulative odds model) with 95% confidence intervals will be estimated for each postoperative timepoint vs. POD 1, adjusting for preoperative value where applicable. The association between fibromyalgia score, pain catastrophizing score, anxiety/depression score, gender, and preoperative opioid use and the odds of experiencing moderate or severe postoperative pain (POD 14 NRS pain with movement 46 or 710, respectively) will be assessed on a univariate and multivariable basis using logistic regression. The number of

predictor included in each multivariable model will be determined by the number of events observed (i.e., 10 events per included predictor). The association between fibromyalgia score, pain catastrophizing score, anxiety/depression score, gender, and preoperative opioid use and POD 14 NRS pain with movement will be assessed on a univariate and multivariable basis using linear regression. The incidence of adverse events will be reported as point estimates with 95% Wilson score confidence intervals. No P values will be reported unless requested by peer reviewers.

References:
YaDeau JT, et al. Duloxetine and Subacute Pain after Knee Arthroplasty when Added to a Multimodal Analgesic Regimen: A Randomized, Placebo-controlled, Triple-blinded Trial. Anesthesiology 2016, Vol.125, 454-456

8.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report.