Official title: Effectiveness of Corticosteroid vs. Ketorolac Shoulder Injections: A Prospective Double-Blinded Randomized Trial

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PROTOCOL

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1. Introduction and Purpose
1.1 The purpose of this study is to compare the functional outcomes of patients with shoulder pathology treated with either ketorolac or corticosteroid injections, in a randomized double-blinded study. We will compare the effectiveness of ketorolac compared to corticosteroid.

1.2 Specific Aim 1:
Hypothesis 1: Injection of the shoulder (in the subacromial space) with Ketorolac will be more effective than corticosteroid injection for the treatment of a variety of shoulder pathologies.

1.3 The risks associated with this study primarily concern adverse reactions to the study drugs. The drugs used in this study are not narcotics or habit-forming but can have side effects. The patient's physician will screen for any heart, intestinal, or kidney disease or condition that would increase the chance for the patient to have an unwanted side effect.

2. Background Nonoperative management is the first line of treatment for a variety of painful shoulder pathologies including atraumatic full thickness rotator cuff tears, rotator cuff tendinitis, and rotator cuff tear arthropathy. Conservative management consists of rest/activity modification, ice, physical therapy, nonsteroidal anti-inflammatory (NSAIDs) medications and injections. Frequently, the pain associated with shoulder pathology is secondary to either synovial or bursal inflammation. The goal of injections is to reduce inflammation, decreasing pain and allowing the patient to better tolerate physical therapy in attempts to restore proper shoulder kinematics.

Corticosteroid injections are a commonly used treatment modality in patients who have failed to respond to other less invasive conservative management options such as systemic NSAID medications and physical therapy. Several studies have demonstrated significant improvements with regards to pain relief and range of motion with the use of corticosteroid injections in the subacromial space for the treatment of rotator cuff tendinitis/ full thickness rotator cuff tears,[1-9].

The frequency of corticosteroid injections is limited by associated side effects on connective tissue with numerous reports in the literature of spontaneous tendon rupture following local injections. Additionally, there have been several animal studies that demonstrate corticosteroid exposure can result in tendon and ligament atrophy, fragmentation of collagen bundles, delayed healing, articular cartilage changes, and decreased mechanical properties.[10-14] Furthermore, a study by Wei et al.[14] demonstrated that a single

dose of methylprednisolone to healthy uninjured rotator cuff tendons can have an appreciable effect on biomechanical properties and collagen expression.

Given that it is hypothesized the efficacy of corticosteroid injection is the anti-inflammatory effect, one could extrapolate that injection of NSAID medication may provide similar benefit. Recently Min et al.[5] performed a prospective randomized trial comparing corticosteroid with ketorolac subacromial injection for the treatment of patients with rotator cuff tendinitis. The authors found that ketorolac provided significantly greater improvements in UCLA shoulder rating at 4 weeks as compared to triamcinolone and both medications provided equivalent improvements in VAS pain relief. Ketorolac is a strong nonsteroidal anti-inflammatory agent that can be delivered in an injectable for making it ideal for use in treatment of patients with shoulder pathology. There have been a few studies [15-17] examining the efficacy and safety of NSAIDS intraarticular injections, but no specific studies examining the effects of these medications on rotator cuff tendon. Dogan et al.[15] examined the effects of ketorolac and morphine intraarticular injection in rabbit knees and found synovial membrane inflammatory cell infiltration with minimal histopathologic changes to the synovium. The authors concluded that ketorolac can be used as an intraarticular injection safely. To our knowledge there are no studies examining the effect of ketorolac on rotator cuff tendon.

Adverse Events: Three prior randomized controlled trials have been published using ketorolac in one arm of the trial. In these three studies, no clinically significant adverse event was detected for those getting ketorolac as a post-op intra-articular regional analgesic (Axelsson K et al, Anesth Analg, 2008 and Cho NS et al, Am J Sports Med, 2007) or as an injection therapy (Min KS, J Should Elbow Surg, 2013). While we acknowledge that Ketorolac injections represents “off-label” use The Min article sets specific precedent in the medical literature to support the safe use of this modality. This published study was a double-blind randomized controlled using ketorolac and kenalog with similar dosage and found ketorolac to be equivalent if not superior inefficacy in regards to self-report of function, range of motion, and patient satisfaction. Most importantly, no adverse events were reported for the ketorolac arm of the trial (n = 17). 1 subject who received the kenalog injected experienced a fainting episode secondary to a vasovagal reaction with no long term consequence. We believe these papers provide support for the safety and potential value of a FDA approved intra-articular medication injection and our study aim is to validate the findings of this report in a wider variety of patients with soft-tissue pathologies of the shoulder.

3. Concise Summary of Project

3.1 Study Design: The proposed study is a three arm, double-blinded, prospective randomized controlled clinical trial with follow-up immediately after the injection and at day 2, and weeks 1, 2, 4, 6, and 12. In this study we will compare the effectiveness of ketorolac compared to corticosteroid.

Ketorolac is an injectable solution which should be stored at 15 C to 30 C (59 F to 86 F) and protected from light. Marcaine (Bupivacaine) should be stored at room temperature, between 20 C to 25 C (68 F to 77 F). And Kenalog (triamcinolone) should be stored at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light. Do not refrigerate.[18]

Medications are stored in a locked cabinet at room temperature. The Research Team will prepare the appropriate injection medication according to group assignment at the time of the appointment. Injections will not be prepared beforehand. Injections will be prepared by inserting the syringe into both bottles and drawing the required amount. The syringe contents will be masked from the physician.

Study Groups: Subjects being seen for a rotator cuff injury will be randomized into one of three treatment groups pertaining to their pathology. The intervention will begin once the subject has consented and answered the Baseline Outcome Shoulder Questionnaire. The Baseline Outcome Questionnaire consists of the Visual Analog Score, American Shoulder and Elbow Score, Single Assessment Numeric Evaluation, Pittsburgh Sleep Quality Index, SF-12, range of motion and measure the subjects shoulder strength by using a

dynamometer, and questions pertaining to patient characteristics, injury characteristics, co-morbidities, patient history, medications, and demographics.

A dynamometer is a small, hand-held device which the subject presses against. By pressing against the device, it measures the strength of their shoulder.

Full Thickness Rotator Cuff Tear:

Group 1 (control): will receive an injection of 5 cc 0.25% Marcaine without epinephrine
Group 2 (ketorolac): will receive an injection of 3 cc 0.25% Marcaine without epinephrine and 2 cc ketorolac 30 mg/ml
Group 3 (kenalog): 4 cc 0.25% Marcaine without epinephrine and 1 cc triamcinolone.

Rotator Cuff Tendinitis

Group 1 (control): will receive an injection of 5 cc 0.25% Marcaine without epinephrine
Group 2 (ketorolac): will receive an injection of 3 cc 0.25% Marcaine without epinephrine and 2cc ketorolac 30 mg/ml
Group 3 (kenalog): 4 cc 0.25% Marcaine without epinephrine and 1 cc triamcinolone.

3.3 "**DRUG CLASS AND MECHANISM:**
Ketorolac is a member of a class of drugs called nonsteroidal antinflammatory drugs (NSAIDs) that are used for treating inflammation and pain. Other drugs in this class include ibuprofen (Motrin) and naproxen (Naprosyn, Aleve), but ketorolac is more effective than other NSAIDs in reducing pain from both inflammatory and non-inflammatory causes. Ketorolac reduces the production of prostaglandins, chemicals that cells of the immune system make that cause the redness, fever, and pain of inflammation and that also are believed to be important in the production of non-inflammatory pain. It does this by blocking the enzymes that cells use to make prostaglandins (cyclooxygenase 1 and 2). As a result, pain as well as inflammation and its signs and symptoms - redness, swelling, fever, and pain - are reduced. The FDA approved ketorolac in November 1989."[19]

"Marcaine (Bupivacaine) is a local anesthetic that is similar to lidocaine and mepivacaine (amide type). Bupivacaine, like other local anesthetics reduces the flow of sodium in and out of nerves. This decreases the initiation and transfer of nerve signals in the area in which the drug is applied. This blockage leads first to a loss of sensation of pain, then temperature, touch, deep pressure, and muscle control. The concentration of the drug will determine how quickly it starts working. The FDA approved bupivacaine in October 1972."[20]

Kenalog is a corticosteroid; synthetic glucocorticoid analogs with anti-inflammatory effects.[21]

3.4 Independent Variable: One of three injection protocols.

Dependent Variables

- Primary Outcome Variable:
    - Visual Analog Scale
    - American Shoulder and Elbow Score
- Secondary Outcome Variable:
    - Single Assessment Numeric Evaluation (SANE)
    - Pittsburgh Sleep Quality Index
    - SF-12

Functional Outcome: Visual Analog Scale (VAS) is utilized to measure level or intensity of pain. The scale consists of a horizontal (HVAS) or vertical (VHAS) line, usually 10 cm in length [22] with a descriptor at both ends; the left side reading "no pain at all" and the right side reading "worst pain imaginable." While this scale is very subjective, patients have an easier time reporting pain on a continuum rather than jumping from categories of none, mild, moderate [23] or severe.

American Shoulder and Elbow Score (ASES): is a standardized, 17 item [24], patient self-report tool, which can be completed in about 3 minutes. The patient self-reported section consists of three sections: pain, instability, and activities of daily living. The tool also consists of a physician assessment which includes range of motion, signs, strength, and instability.[25]

Single Assessment Numeric Evaluation (SANE): "is an outcome measurement tool used to record the patient's self-reported function [26]. It is implemented on a scale of 0-100 and correlated with a scale of function from 0-100%. The 100% representing full function (or function prior to injury) and 0% representing no function."

Pittsburgh Sleep Quality Index (PSQI): is a standardized measure for quality of sleep. The tool consists of 24 questions which differentiate "good" and "poor" sleepers and is easy to use for both the patient and the researchers.[27]

SF-12: is a standardized general health survey which measures physical and mental health.

Medical Costs / Patient Billing

- Patient's appointment/exam
- Injection – the drug fees are per unit, e.g., 40mg of Kenalog would be billed/charged as 4 units ($4 x 4 = $16).

3.5 Sample Size: Approximately 400 subjects will be enrolled. This will allow approximately 66 subjects per arm of the trial (200 total; approximately 140 subjects will get the ketorolac injection) for both of the diagnostic groups (rotator cuff tears and rotator cuff disease) each of the five diagnostic groups. Subjects will be enrolled at UT Southwestern Ambulatory Outpatient Orthopaedic Surgery Department and John Hopkins clinics: Johns Hopkins Orthopaedics, Johns Hopkins Community Physicians, and Southern Maryland Orthopaedic and Sports Medicine Division of Centers for Advanced Orthopaedics.

3.7 Study Duration: It is anticipated the study will last approximately 5 years.

3.8 Subjects may voluntarily withdraw from study participation at any time, and will continue to receive routine care. Subject withdrawal will not cause any penalty or loss of benefits to which the subject is entitled. No new information will be gathered after the date that permission is withdrawn. Information that has already been gathered may still be used and given to others per the study protocol. Subjects wishing to withdraw should contact their study doctor. If a subject chooses to withdraw from the study before the planned final visit, he/she may be asked by the study doctor to consider completion of a final survey.

The study doctor may stop subject participation in this study at any time without the subject's consent for any of the following reasons:

- The subject withdrawals from the study
- It is in the subject's best interest
- The subject does not complete the follow-up surveys
- The subject does not later consent to any future changes that may be made in the study plan
- Or for any other reason

4. Study Procedures

4.1 Subjects will be identified in clinic following evaluation by the clinician and determination/ diagnosis of the etiology of shoulder pain. During the initial visit, the physician will conduct the standard clinic visit. Female subjects of child-bearing age will not be enrolled into the study. Documentation of female subjects having been permanently sterilized or postmenopausal will be recorded in their medical record.

During the initial visit, the research team will abstract the following information from the subject's medical record

- Demographics
- Medications
- Patient Characteristics
- Injury Characteristics
- Co-morbidities
- Patient History

Subjects identified as meeting inclusion criteria for the study will be asked if they are willing to participate in the study and if agreeable will undergo the informed consent process.

Enrollment
Once a patient is identified as meeting inclusion criteria they will be informed of the study and asked if they are willing to participate. They will be informed that enrollment is completely voluntary and will not impact treatment of the underlying shoulder pathology. Additionally, potential subjects will be informed that both corticosteroid and ketorolac are safe and effective modalities for injection that would be used as part of routine treatment of shoulder pain. These medications are commonly mixed with an anesthetic such as Marcaine for both diagnostic and therapeutic means.

The anesthetic allows both patient and clinician almost immediate feedback with resolution of pain once the anesthetic takes effect-providing information that the injection was properly delivered into the subacromial space.

The subjects will be informed that they will be randomized into one of 3 treatment groups and will be asked to complete a questionnaire about the status of the shoulder as well as follow-up questions at predetermined intervals for a total of 12 weeks. They will also be informed that all other treatment of the shoulder will proceed as is standard based on the pathology (i.e. physical therapy, oral medications) and eligibility for surgical intervention should these conservative measures fail to provide relief of symptoms. If a patient agrees to participate in the study they will undergo the informed consent process by the research staff. Research staff will determine if the patient continues to be eligible according to inclusion/exclusion criteria and if the patient is willing to participate in the follow-up.

Once consented into this study, baseline data regarding patient characteristics, injury characteristics, and medical history and co-morbidities, including current use of pain medication, will be collected and entered in to the data collection system. Some of this information will be obtained via the Outcome Shoulder Questionnaire with the patient.

Randomization
Subjects will be randomized to one of three injection groups: Group 1 will receive the control injection (Marcaine), Group 2 will receive a NSAID injection (Ketorolac & Marcaine), and Group 3 will receive a steroid injection (Kenalog & Marcaine).

Five to 10 minutes following injection, subjects will be asked how the injection changed shoulder symptoms by utilizing the Visual Analog Scale (VAS) and Single Assessment Numeric Evaluation (SANE).

Patients will be contacted by phone to complete a follow-up questionnaire 2 days after the injection as well as at 1, 2, and 4 weeks. The subjects will be followed up in clinic at 6 and 12 weeks, after the shoulder injection, which is standard clinical practice with completion of the outcomes questionnaire. Subjects will reach study completion at 12 weeks following injection.

Subject Baseline Outcome Shoulder Questionnaire
All data collected as part of this study will be through the use of standardized instruments. Once enrolled, subjects will be randomized, complete the baseline Outcome Shoulder Questionnaire, and then receive a shoulder injection in standard fashion under sterile conditions. Five minutes following the injection the subjects will again be asked questions as to the % improvement of their symptoms and VAS score will be obtained. At this time, baseline demographic information will be collected, in addition to measures of pain.

Injection Procedure Description:
The posterior aspect of the shoulder will be prepped in a sterile fashion with clorohexadine scrub. The anatomic shoulder landmarks will be palpated under sterile conditions and using a standard posterior shoulder portal a subacromial injection will be given. For those subjects in which subacromial injection would be appropriate (i.e. rotator cuff disease) a 20 gauge needle is inserted posteriorly along the posterior border of the acromion, once contact is made with the underlying bone the needle is slid beneath the acromion and directed to the anterolateral aspect of the subacromial space then injection medication delivered. Dosages for each of the three group assignments will be as follows: Group 1 (control): 5 cc 0.25% Marcaine without epinephrine; Group 2 (ketorolac): 3 cc 0.25% Marcaine without epinephrine and 2 cc Ketorolac 30 mg/ml; Group 3 (kenalog): 4 cc 0.25% Marcaine without epinephrine and 1 cc kenalog.

The Research Team will prepare the appropriate injection medication according to group assignment and the syringe contents will be masked from the physician. Each injection will contain a total of 5 cc.

Follow-up Interviews
Subjects will be contacted by phone to obtain VAS score at day 2, and weeks, 1, 2, and 4 after the injection. They will be instructed to return to clinic at routine follow-up intervals at 6 and 12 weeks after the injection and will again be asked to complete the Outcome Shoulder Questionnaire containing VAS, ASES, SF-12, PSQI scores. Subjects range of motion and shoulder strength will also be collected. All data collected with regards to this study will be kept in a password-protected database, which will only be accessible, by study investigators and the research team.

Study subjects who do not respond to the follow-up phone calls in a timely manner, will be mailed a paper copy of the Follow-up Outcome Shoulder Questionnaire and/or emailed a website link to the same questionnaire on www.surveymonkey.com

	Baseline Shoulder Questionnaire			Follow-up					
	Med Record Review	Pre-Injection	5 Minutes Post Injection	Day 2	Week 1	Week 2	Week 4	Week 6	Week 12
Visual Analog Score (VAS)		X	X	X	X	X	X	X	X
American Shoulder and Elbow Score (ASES)		X						X	X
Single Assessment Numeric Evaluation (SANE)		X	X					X	X

Pittsburgh Sleep Quality Index		X						X	X
SF-12		X						X	X
Range of Motion		X	X					X	X
Dynamometer measurements		X	X					X	X
Pt Characteristics	X								
Injury Characteristics	X								
Co-Morbidities	X								
Pt Hx	X								
Meds	X								
Demographics	X								

4.3 Each phone follow-up should take approximately 10 minutes each and the standard follow-up visits should each take approximately 30 to 45 minutes.

4.4 At each time frame, the subjects will be asked to complete a questionnaire. Blood and tissue samples will not be collected for this study.

4.5 Subjects will be billed for the services received whether they participate in the study or not.

4.6 The only change in clinic practice of shoulder disorders as part of this study protocol will be the randomization of injection medication they will be receiving. Subjects will be prescribed physical therapy as is standard for the treatment of shoulder disorders.

We believe the ketorolac injection will be equivalent with regards to pain relief as the corticosteroid injection. Additionally, with the results of this study we can provide an alternative pain relief modality that is safe and effective for patients with shoulder disorders. Furthermore, with the results obtained from this study we can provide patients who may have medical comorbidities such as uncontrolled diabetes mellitus that are contraindicated for corticosteroid injections, an effective treatment option.

5. Sub Study Procedures N/A

6. Inclusion Criteria

- Age: > or = 18 years old
- Rotator Cuff Tendinitis
- Atraumatic Rotator Cuff Tear
- Rotator Cuff Tear Arthropathy
- Subjects who speak English

7. Exclusion Criteria

- Age: < 18 years old
- Prior Shoulder Surgery
- Fracture
- Acute Traumatic Rotator Cuff Tear
- Infection
- Uncontrolled Diabetes Mellitus (HbA1c >8)
- Recent Prior Shoulder Injection in either the Subacromial space
- Workers Compensation

- History of Gastric Ulcers
- Tumor Involving the Shoulder Region
- Prior history of gastrointestinal bleeding, allergic reactions, impaired renal function, seizures or cardiac arrhythmias
- Subject unable to provide informed consent
- Subjects who don't speak English
- Patients who are pregnant or lactating at time of screening or are of child bearing age
- Patients currently receiving an aspirin, NSAID regimen or any other anti-inflammatory agents that could affect inflammation response.
- Patients with any bleeding disorders.
- Patients with severe renal failure.
- Patients likely to have severe problems maintaining follow-up, including patients diagnosed with severe psychiatric conditions, patients who live too far outside the hospital's catchment area, patients who are incarcerated and patients who have unstable housing situations.
- Patients who are allergic to aspirin, ketorolac tromethamine and other NSAIDs

Spanish-speaking patients will not be enrolled at this time as the study does not have the resource and it could increase risk to participants from communication barrier. No washout period. The use of oral NSAIDS will not have any influence on the injection response. Female subjects of child-bearing age will not be enrolled into the study. Documentation of female subjects having been permanently sterilized or postmenopausal will be recorded in their medical record.

8. Sources of Research Material

8.1 Information will be obtained from the subjects medical records as well as patient surveys.

8.2. Information will be obtained specifically for research purposes.

9. RECRUITMENT METHODS and CONSENTING PROCESS:

9.1 *Screening*

The treating physicians will identify potentially eligible subjects from the UT Southwestern Ambulatory Outpatient Orthopaedic Surgery clinic and John Hopkins clinics: Johns Hopkins Orthopaedics, Johns Hopkins Community Physicians, and Southern Maryland Orthopaedic and Sports Medicine Division of Centers for Advanced Orthopaedics. Study Investigators and their research teams will assess subjects for the study and include a review of the medical record to ensure none of the study exclusion criteria are met. The study will be discussed with potentially eligible subjects.

9.2 *Recruitment:* Only those presenting for a shoulder evaluation at the UT Southwestern Ambulatory Outpatient Orthopaedic Surgery clinic and John Hopkins clinics: Johns Hopkins Orthopaedics, Johns Hopkins Community Physicians, and Southern Maryland Orthopaedic and Sports Medicine Division of Centers for Advanced Orthopaedics, who meet inclusion criteria will be recruited for potential participation in the study.

Informed consent will be obtained prior to initiation of the study. The physician will be involved in the consent conversation. The conversation will be initiated by the research team and physician together. The consent process will involve a dialogue. Specifically, patients and their families will be provided with a pamphlet describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate.

Consent must be obtained from the patient in this study; no legally authorized representatives or surrogates may consent on behalf of the patient. This is due to the subjective nature of assessing pain. All recruitment materials will be provided in English.

9.3 Screening, enrollment, and informed consent process will take place in a private treatment area.

9.4 If a patient decides to withdraw from the study, he/she may do so at any point by informing the Principal Investigator in writing. A 'Note to File' must be inserted into the patient's chart and research file stating the patient formally withdrew from the study with the reason (if given). The patient will be assured that the medical care which they receive will not be affected should they elect to discontinue participation in the study.

Undue Influence: Patients will be told they are not required to participate in research to be treated at UT Southwestern Medical Center and its affiliates or at John Hopkins clinics.

9.5 Waiver of Informed Consent: N/A

9.6 Inclusion of Vulnerable Populations: N/A

10. Potential Risks

10.1 The risks associated with this study primarily concern adverse reactions to the study drugs. The drugs used in this study are not narcotics or habit-forming but can have side effects. The treating physician will screen for any heart, intestinal, or kidney disease or condition that would increase the chance for the patient to have an unwanted side effect. However, there is a small possibility that an injection of these medicines can be painful and cause bleeding or infection. The patient should seek medical assistance if any of the following occur:

- chest pain, weakness, shortness of breath, slurred speech, problems with vision or balance;
- black, bloody, or tarry stools;
- coughing up blood or vomit that looks like coffee grounds;
- swelling or rapid weight gain;
- urinating less than usual or not at all;
- nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
- fever, sore throat, and headache with a severe blistering, peeling, and red skin rash;
- the first sign of any mouth sores or skin rash, no matter how mild;
- pale skin, easy bruising, severe tingling, numbness, pain, muscle weakness; or
- fever, headache, neck stiffness, chills, increased sensitivity to light, purple spots on the skin, and/or seizure (convulsions).
- gastritis or gastric ulceration, intestinal bleeding, impaired renal function seizures, or irregular heartbeat.

The patient will be told to seek immediate medical help if there is any sign of an allergic reaction such as hives; difficulty breathing; or swelling to their face, lips, tongue, or throat

Side Effects of Ketorolac. Concerns about renal impairment, gastrointestinal irritation, and platelet inhibition constrain usage and limit the dose and duration of ketorolac administration. More directly relevant to orthopaedics, in animal models, NSAIDs in general and ketorolac in particular are known to impair osteogenesis.[28-30] The effects for these drugs, however, are reversible after short-term treatment.[28] Similarly, animal studies with chronic ketorolac administration raise concern with respect to the strength of healed wounds, with variable results for muscle and ligamentous injury.[31-33] In human studies of spinal fusion, 48 hours of ketorolac therapy for a total dose of 240 mg appears not to affect the fusion rate,[34, 35] but longer duration therapy, even at lower doses may be problematic.[36, 37] However, in a fracture model with young mice, a variety of COX antagonists did not affect long-term tibial healing,[38] consistent with a similar observation in young patients undergoing scoliosis surgery.[34]

10.3 The possibility of risks are low and will be minimized by information the patient provided from the initial questionnaire. In addition, any medicine the patient is currently taking will be evaluated by the physician to

screen for any unwanted side effects. Patients in the study will be actively monitored for any adverse reactions. The risks associated with this study primarily concern adverse reactions to the study drugs. The drugs used in this study are not narcotics or habit-forming but can have side effects. The patient's physician will screen for any heart, intestinal, or kidney disease or condition that would increase the chance for the patient to have an unwanted side effect.

11 Subject Safety and Data Monitoring

The DSMB will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head.

11.1 We have set up a Data and Safety Monitoring Board (DSMB) with three committee members to ensure the patient's safety, one of which is not from the Department of Orthopaedic surgery. The DSMB committee will meet at least every six months or every 20 subjects to ensure that there is not more than a 5% increase in adverse events in the experimental group (ketorolac). The exhaustive list of exclusion criteria that have been put in place greatly reduce the risk of any kind of adverse or unintended consequence of the injection

11.2 Generally the DSMB would be involved in the decision of unblinding to limit potential bias. However, if a subject has a life threatening reaction to the injection, the physician is allowed to unblind the subject, without DSMB approval, to provide proper care. Immediately afterwards, the physician must report the unblinding to the study statistician and submit a detailed report explaining the unblinding event. "If unblinding occurs, the statistician should record and maintain the following in a confidential log:[39]

- ID number of the participant whose treatment assignment was unblinded
- Date
- Reason for unblinding study staff
- Person responsible for unblinding study staff
- List of persons who are unblinded.

Adverse event

Any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject's participation in the study, whether or not considered related to the subject's participation.

Unanticipated problem

Any incident, experience, or outcome that meets all of the following criteria:
(1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the study.
(2) is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments.
(3) suggests that the participation in the study may place subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Please note that not all adverse events are unanticipated problems and only some unanticipated problems are in fact adverse events. For instance, if a laptop containing study data is stolen, this is an unanticipated problem but it is not an adverse event since it is not an untoward or unfavorable medical occurrence in a human subject

Serious Adverse Event
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject 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.

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Intervention to Prevent Permanent Impairment
- Other Serious (Important Medical Events)

Methods and Timing of Assessment
Adverse events and complications will be assessed during the initial study visit and at follow-up phone calls and visits, as well as during any unscheduled visits to the clinic. The events will be recorded on study data forms, with a determination of whether or not they are thought to be associated with the study or with one of the study treatments.

Management of Adverse Events
Adverse Events and Serious Adverse Events will be managed according to protocol guidelines. If specific guidelines do not exist, AEs/SAEs will be managed according to the medical judgment of the treating physician.

Non-Reportable Adverse Events
Adverse events collected as study outcomes such as, somnolence, dizziness, headaches, and other central nervous system effects, peripheral edema, visual changes, dry mouth, excessive bleeding and thrombocytopenia will be recorded on study data forms whether or not they are thought to be associated with the study or with one of the treatments.

All SAEs related to use of study medications will be reported to the individual manufacturers to contribute safety data for these drugs, as well as to the FDA via the Med Watch voluntary reporting mechanism using form FDA 3500.

Type and Duration of the Follow-up of Participants After Adverse Events
Study patients who experience a SAE will be followed until resolution of the event, and a final report will be submitted to the IRB, DSMB, and FDA.

Modifications of Study Agent(s)/Intervention(s) for a Participant
Stopping Rules for an Individual Participant/Cohort
The DSMB will review the overall progress of the trial in terms of recruitment and data quality and make a formal recommendation to the IRB at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications or be stopped.

Premature Withdrawal of a Participant

A participant may be withdrawn from the study without consent if the investigator decides to end the study. Other reasons for removing a participant without consent may include but are not limited to non-adherence with the protocol and/or therapy, inappropriate behavior towards study personnel, etc.

12 Procedures to Maintain Confidentiality:

12.1 Collected data will be maintained by an authorized member of the Orthopaedic Research Staff, Research Coordinator, or Research Nurse. All data will be kept in locked files and/or password protected electronic files, and will be used for research purposes only. No patient information will be disclosed outside the study team.

Each patient's identity and information will be collected and analyzed and will be treated with professional standards as defined by the HIPAA Compliance mandate. In addition, all requirements for HIPAA compliance concerning patient confidentiality will be adhered to. All funding agencies, Institutional Review Boards of involved centers and the U.S. Department of Health and Human Services will have the right to inspect all medical records related to this study for the purpose of verifying data and patient confidentiality. The information obtained in this study may be published in medical journals in a deidentified manner.

All hard copies of questionnaires or case report forms will be stored in the Department of Orthopaedic Surgery research office which is a key-accessed suite. Electronic records (computer files, electronic databases, etc.) is also secured and backed-up at this location.

12.2 Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB, FDA, or DSMB. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with IRB requirements for compliance with The Health Insurance Portability and Accountability Act (HIPPA).

12.3 A Certificate of Confidentiality will not be requested for this study.

13. Potential Benefits

This clinical investigation will evaluate the effectiveness of different injectable medications in controlling shoulder pain. All subjects will receive a short-term pain relief medication. This study presents possible benefits of improved pain management for subjects who are randomized to one of the treatment arms of the study. While, the researchers cannot guarantee that subjects will benefit from participation in this research directly, the subjects may benefit altruistically. The feedback provided by the subjects will assist the medical community in providing the right type of medicine for shoulder pain. Our hope is that the information learned from this study will benefit others with shoulder pain in the future. Information gained from this research could lead to better treatment for a variety of shoulder injuries.

Therapeutic Alternatives

There are medical and therapeutic alternative to this study including oral medications, usual medical advice, and prescription of physical therapist. All subjects of this study will be offered these interventions at the discretion of the physician.

14. Biostatistics

14.1 Statistical Analysis: The specific purpose of this study is to provide descriptive statistics for both the primary and secondary outcomes. Unpaired t or chi-square tests on all pre-op demographic data. The dependent variables will be analyzed by repeated measure of variance to determine if statistically significant differences exist at follow-up assessment. To protect against Type I error, Tukey tests will be used to ensure the alpha levels ($p < 0.05$) will not be falsely declared significant. This is a prospective double-blinded randomized trial. The investigator of the study and examiner who provides the injection will be blind to which group assignment has been provided. Patients will not be told of the injection type. The billing department will create a study account which will allow billing subjects, for the ketorolac or kenalog, without their knowing which injection they received.

14.2 Sample Size: We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. In a previous study the response within each subject group was normally distributed with standard deviation 23. If the true difference in the experimental and control means is 12, we will need to study 59 experimental subjects and 59 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8 for each diagnostic category of rotator cuff tendinopathy, small to medium rotator cuff tears, and large rotator cuff tear arthropathies. The Type I error probability associated with this test of this null hypothesis is 0.05.To account for a 15% drop out rate we will recruit 66 subjects for each of the 3 arms of the trial in each of the 2 diagnostic categories for a total of 400 patients.

Randomization: Subjects will be recruited from the UT Southwestern Orthopaedic Surgery Clinic and John Hopkins clinics: Johns Hopkins Orthopaedics, Johns Hopkins Community Physicians, and Southern Maryland Orthopaedic and Sports Medicine Division of Centers for Advanced Orthopaedics, from patients who meet the inclusion criteria. As this study design will be prospective randomized double-blinded, we will utilize computer generated block randomization technique. After identifying a patient who meets the inclusion criteria by history, physical examination, and obtaining informed consent, HIPPA, health screen, and baseline measurements, subjects will be randomized into one of three cohorts: 1) Control (Marcaine injection), 2) NSAID injection (ketorolac & Marcaine injection), or 3) Steroid injection (kenalog & Marcaine injection). To ensure that the number of subjects is about the same in the three arms of the study, the randomization scheme will assign patients in a 1:1:1 ratio in randomly permuted blocks of assignments stratified by clinical center. Block size will be determined randomly and the patient will be the unit of randomization.

Enrollment and randomization results will be documented in the patient's chart according to protocol. The randomization allocation will be blinded to both the patient (initially) as well as the physician performing the injection and the investigator conducting statistical analysis of the results. Given the nature of this study looking at the effects of this intervention on multiple shoulder pathologies we anticipate approximately 200 subjects per diagnostic category would be needed for enrollment and complete follow-up.

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