utmb Health
Orthopaedic Surgery
& Rehabilitation

Subacromial injection of methylprednisolone versus ketorolac to treat shoulder impingement: a multicenter double-blind randomized controlled trial

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Protocol – Version 3 – June 17, 2019

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Study Schema

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:*

Signed: _____ Date: _____

Name Jeremy S. Somerson
Title MD

** The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; i.e., if Investigational New Drug study, the individual who signs the Form FDA 1572.*

1.0 Background

Subacromial impingement syndrome is a commonly encountered shoulder condition that consists of a constellation of symptoms, including pain with overhead activities. As the condition progresses, the pain may manifest at night, associated or not with progressive loss of motion and strength of the shoulder [1-3]. Impingement-related pain is thought to result from subacromial bursitis and tendonitis of the supraspinatus due to repetitive overhead activities impinging the coracoacromial arch [3, 4]. Many non-operative treatments have been advocated for subacromial impingement syndrome, beginning with rest, ice, oral non-steroidal anti-inflammatory drugs (NSAIDs), and physical therapy [5, 6]. If patients fail to improve with conservative therapy, subacromial injections could be utilized to treat this condition [2, 7-11]. Although the exact mechanism(s) of corticosteroids and NSAIDs is/are not completely understood, it is hypothesized that symptom relief post subacromial injections is related to their local anti-inflammatory properties [2, 12].

While studies comparing subacromial injection of NSAIDs to steroids exist, they are low-powered or lack long follow-up. Karthikeyan et al. conducted a randomized controlled trial in 2010 that compared subacromial injections of 40 mg methylprednisolone versus 20 mg of tenoxicam for subacromial impingement [13]. Their outcomes were the Disability of Arm, Shoulder, and Hand (DASH) score and the Oxford Shoulder Score (OSS). They concluded that corticosteroids are significantly better than tenoxicam for improving shoulder function in tendonitis of the rotator cuff, but their follow-up was only six weeks. Min et al., on the other hand, conducted a similar randomized controlled trial in 2013 using 40 mg triamcinolone versus 60 mg ketorolac [3]. Their outcome measures were the visual analog (VAS) and the University of California Los Angeles (UCLA) shoulder rating scales. They showed greater improvements in the UCLA rating scale in the ketorolac arm, but their follow-up was only four weeks. Taheri et al. conducted a randomized controlled trial in 2017 to compare subacromial injections of 60 mg ketorolac and 40 mg methylprednisolone [14]. Their outcome measures were the VAS and Constant's score. While the results did not show any significant difference between the two therapeutic arms at three months' follow-up, the study included only 40 patients and an a priori power analysis was not performed. The lack of long-term follow-up and the inadequate power in the aforementioned studies point to the need for further investigation.

If it can be shown that subacromial NSAIDs are superior or equivalent to steroids, the benefits to society could be multiple. Bellamy et al. studied the economic impact of using ketorolac instead of steroid for the treatment of knee osteoarthritis over a three-year period [15]. They found a total potential cost savings of approximately $12,000 if ketorolac was used in place of steroids at their institution. Furthermore, the local tissue reaction of steroids may be mitigated with the use of ketorolac. Shapiro et al. compared injections of methylprednisolone versus ketorolac in a rabbit model [16]. They found that the rabbits injected with steroids demonstrated greater peri-tendinous adhesions and cartilage necrosis compared to the rabbits injected with ketorolac and normal saline.

2.0 Rationale and Specific Aims

Because of the current conflicting evidence, the lack of long-term follow-up, and the multiple potential benefits to the society, we aim to compare subacromial ketorolac versus steroid for the treatment of shoulder impingement. We hypothesize that patients with external shoulder impingement who are treated with a subacromial injection of 80 mg methylprednisolone in 1% lidocaine versus 60 mg ketorolac in 1% lidocaine have similar outcomes based on the American Shoulder and Elbow Surgeon (ASES) self-assessment score (ranging between 0 and 100) at 2, 4, and 12 weeks post-injection. If the follow-up could not be performed exactly at 2, 4, or 12 weeks post-injection, investigators will allow examination and measurements at ±3 days. The study will be performed in The University of Texas Medical Branch (UTMB, coordinating center). This will help us determine the efficiency of either therapeutic modality in the management of patients with subacromial impingement syndrome.

3.0 Inclusion/Exclusion Criteria

The center enrolling patients (UTMB) will obtain approval through its own institution review board (IRB). The study will be posted on clinicaltrials.gov. The subjects in this study will be recruited from the investigators' private clinics. Prior to enrollment, the investigator will obtain informed written consent from the subjects. All of the investigators are CITI trained. They will review the consent form with patients and allow sufficient time for potential subjects to read the consent form and consider the risks and benefits of participation. Investigators will leave the clinic room to allow patients to consult with friends and family. If patients decide to defer the decision to enroll, they will be allowed to return at a later date. It will be emphasized to patients that they need not participate in the study to receive a subacromial injection. If they choose not to participate, they will be offered a subacromial injection that consists of the medication that is mutually agreed upon between their physician and them. No coercion to participate in the study will take place.

Adults at least 18 years of age seen in clinic with a diagnosis of severe or recalcitrant shoulder impingement syndrome and to whom the investigator has offered a subacromial injection will be invited to participate.

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation. Exclusion criteria are: allergy/intolerance to steroids or NSAIDs symptoms less than one month, pregnancy or breastfeeding, pre-existing asthma, uncontrolled psychiatric illness, previous shoulder injection within the past three months, evidence of other confounding shoulder pathology on plain radiographs such as calcific tendonitis, MRI evidence or history of a full-thickness rotator cuff tear, active comorbidities of the ipsilateral extremity such as cervical radiculopathy, moderate to severe glenohumeral arthritis, systemic inflammatory conditions, kidney or liver disease, gastrointestinal (GI) ulcers, bleeding disorders, pending litigation or work-related claims related to the shoulder, previous shoulder surgery on the affected shoulder, evidence of local infection, evidence of adhesive capsulitis, and evidence of shoulder instability.

4.0 Treatment Assignment/Randomization

The following measures will be taken to ensure double-blinded randomization. Prior to the initiation of the study, computer-generated tables will be created in Excel to assign each patient a randomization number. This master list will be kept with a statistician and research coordinators, who do not have any patient contact. Based on his/her corresponding generated number (even or odd), the patient will be assigned to his/her therapeutic arm (methylprednisolone and ketorolac, respectively). The statistician will use an equally weighted random number generator to create these assignments. Therefore subjects will have an equal chance of being assigned to either treatment arm. Separate lists for male and female participants will also be generated to ensure equal gender participation. The statistician will then prepare an opaque envelope for each subject number. The unique subject number will be written on the visible outside surface of each envelope. The corresponding treatment arm assignment will be inside the envelope. The statistician will seal each envelope individually and send all of the envelopes to the research coordinator (Marc El Beaino) prior to patient enrollment. The sealed opaque envelopes will be divided equally among the clinics and kept in locked containers in the research coordinator's office. The study staff will not have access to the envelopes. After ensuring that the patient has completed the ASES questionnaire (to establish a baseline prior to the injection), the study staff will contact Marc El Beaino or Safee Ahmed to provide them with the patient's first and last names as well as the MRN. The research coordinator will open one of the sequentially numbered envelopes to assign each patient the corresponding subject number (written on the outside of the envelope), and a member of the clinic staff will prepare the appropriate injection (see below) for the assigned treatment arm. The syringe will be covered with opaque tape prior to being given to the surgeon for administration. The injection will take place in a private clinic room in compliance with the Health Insurance Portability and Accountability Act (HIPAA) guidelines. The blinded surgeon will administer the injection into the subacromial space using standard bony landmarks from the posterolateral approach. The clinic staff will file the drug accountability log after preparing the injection and they will not disclose the treatment arm assignment to the patient nor the provider. This will maintain the blinding for both the patient and research surgeons. Patients' subject number will be recorded on their consent form and in their electronic medical record. Envelopes will be destroyed at the end of the study by the research coordinators. The statistician will unlock the master list only after patient enrollment and follow-up are complete, or if mandated by any regulatory body. Blinding will also be uncovered in case of a patient developing an adverse event while being followed in the trial.

5.0 Study Procedures

Shoulder impingement is a syndrome characterized by shoulder pain that is exacerbated by passive and/or active elevation, with positive provocative testing for impingement such as Neer and Hawkins tests, and/or the diagnosis of subacromial bursitis based on tenderness to palpation of the acromion. Generally, patients who present with shoulder impingement will be treated initially with non-invasive measures such as activity modification, ice, physical therapy, and a trial of oral NSAIDs. If those measures do not provide adequate relief, then patients will be offered a therapeutic subacromial injection. The investigators will follow these principles of conservative management except when the patients' pain is

severely limiting their activities of daily living and their ability to work and provide for themselves or when patients are having pain at night that interferes with sleep. In those situations, a subacromial injection may be offered prior to attempting less invasive measures. Ultimately, the decision to offer a subacromial injection will be made in clinic by the investigators based on their clinical judgment. All of the investigators are fellowship-trained orthopedic surgeons who subspecialize in shoulder diseases. Their decision to offer patients a subacromial injection will be independent of whether the patients wish to participate in the study. Patients will be given the opportunity to participate in the study only after the decision to offer an injection is made by the clinician. Patients will not be solicited outside of a regularly scheduled clinic visit to participate in this study.

Investigational Drug Service (IDS) staff will not be directly involved with the handling of the study drugs; however, a plan has been documented and agreed upon by both parties regarding study drug supply, storage, randomization, preparation, administration, and accountability (Study Drug Management Form). Therefore, the clinic staff will maintain the blinding of the surgeons, who are licensed by the medical board of Texas to perform the injection.

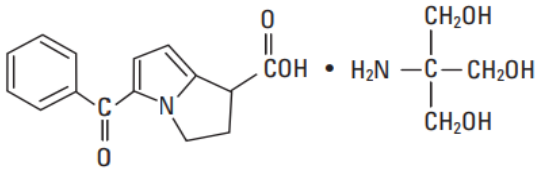
Drugs that will be injected will be dispended to medically-licensed research personnel by the clinic staff to be delivered to the treating surgeon. For the methylprednisolone treatment arm, the injection will consist of 9 mL of lidocaine HCl (1% without epinephrine) and 1 mL of methylprednisolone acetate (80 mg/mL). For the ketorolac treatment arm, the injection will consist of 8 mL of lidocaine HCl (1% without epinephrine) and 2 mL of injectable ketorolac tromethamine (30 mg/mL). The total injection volume in each treatment arm will be 10 mL. After the clinic encounter, a blinded member of the research staff will call or email the patient to complete the ASES questionnaire at 2, 4, and 12 weeks post-injection. If the follow-up could not be performed exactly at 2, 4, or 12 weeks post-injection, investigators will allow examination and measurements at ±3 days.

6.0 Study Product Description

The following information has all been retrieved from the methylprednisolone acetate and the ketorolac tromethamine package inserts.

Formulation, Packaging, and Labeling

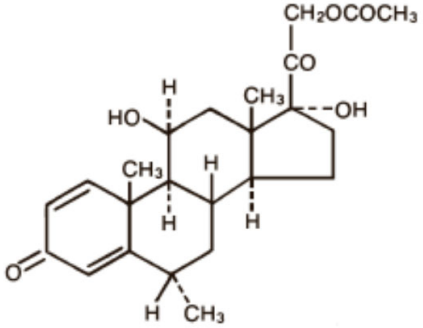
Ketorolac tromethamine is a member of the NSAIDs. The chemical name for the drug is: (±)-5-benzoyl2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). Its structural formula is presented below.



$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$

Ketorolac tromethamine is a racemic mixture of [-]S and [+]R ketorolac tromethamine. It is soluble in water. Injectable ketorolac tromethamine is available for intravenous (IV) administration as 15 mg in 1 mL and 30 mg in 1 mL in sterile solution. For intramuscular (IM) administration, ketorolac tromethamine is available only as 60 mg in 2 mL (30 mg/mL) in sterile solution. In this case, the latter contains 10% alcohol and 8.70 mg of sodium chloride in sterile water. The pH range is 6.9 to 7.9 and is adjusted with sodium hydroxide and/or hydrochloric acid. The sterile solutions are clear and slightly yellow in color.

Injectable methylprednisolone acetate is an anti-inflammatory glucocorticoid. The chemical name for the drug is: pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-,(6α,11ß)-. Its structural formula is presented below.



Injectable methylprednisolone acetate is used for intramuscular, intra-articular, soft-tissue or intralesional injection. It is available in three strengths: 20 mg/mL, 40 mg/mL, and 80 mg/mL. In this study, the latter (80 mg/mL) will be used as indicated for large joints in the FDA brochure of this medication. Each mL of this preparation contains 80 mg of methylprednisolone acetate, 28.2 mg of polyethylene glycol 3350, 1.88 mg of polysorbate 80, 6.59 mg of monobasic sodium phosphate, 1.37 mg of dibasic sodium phosphate, and 8.88 mg of benzyl alcohol (as a preservative). The pH range is 3.5 to 7.0 and is adjusted with sodium hydroxide and/or hydrochloric acid.

Product Storage and Stability

Injectable ketorolac tromethamine must be stored between 15ºC (59ºF) and 30ºC (86ºF). Injectable methylprednisolone acetate must be stored between 20ºC (68ºF) and 25ºC (77ºF). They both should be kept at controlled room temperature while being protected from light.

Dosage, Preparation and Administration of Study Intervention/Investigational Product

The sealed envelopes that contain each patient's therapeutic arm assignment will be equally distributed to the study staff prior to the enrollment. They will be kept in locked containers in each investigator's clinic. Only study staff will have access to the envelopes. After patient enrollment and informed consent completion, the study staff will open one of the sequentially numbered envelopes and the patient assigned the corresponding subject number written on the outside of the envelope. The study staff will prepare the appropriate injection (see below) for the assigned treatment arm. The syringe will be covered with opaque tape prior to being given to the surgeon for administration. The injection will take place in a private clinic room in compliance with HIPAA guidelines. The surgeon will administer the injection into the subacromial space using standard bony landmarks from the posterolateral approach. After the injection is given by the research MD, the clinic staff will then dispose of the syringe without disclosing the treatment arm assignment to the patient nor the provider. Patients' subject number will be recorded on their consent form and in their electronic medical record. The statistician will unlock the master list only after patient enrollment and follow-up are complete, or if mandated by any regulatory bodies. Blinding will also be uncovered in case of a patient developing an adverse event while being followed in the trial.

Both drugs will be intra-articularly delivered through a single subacromial injection within 30 to 45 minutes. For the methylprednisolone treatment arm, the injection will consist of 9 mL of lidocaine HCl (1% without epinephrine) and 1 mL of methylprednisolone acetate (80 mg/mL). For the ketorolac treatment arm, the injection will consist of 8 mL of lidocaine HCl (1% without epinephrine) and 2 mL of injectable ketorolac tromethamine (30 mg/mL). The total injection volume in each treatment arm will be 10 mL. These drugs are not suitable for multi-dose use. Following administration of the desired dose, any remaining suspension will be returned to IDS.

Modification of Study Intervention/Investigational Product for a Participant

The study consists of a subacromial single dose injection of either methylprednisolone acetate (80 mg) or ketorolac tromethamine (60 mg). Patients will then be followed-up for 12 weeks and ASES data will be recorded at 2, 4, and 12 weeks post-injection. If the follow-up could not be performed exactly at 2, 4, or 12 weeks post-injection, investigators will allow examination and measurements at ±3 days. No additional injections will be needed, and therefore, no dose modification will be required. Patients meeting any of the exclusion criteria will not be initially enrolled in the study.

Accountability Procedures for the Study Intervention/Investigational Product(s)

Drugs that will be injected will be prepared by clinic staff and will then be delivered to the treating surgeon. The clinic staff will be responsible of maintaining the drug accountability at each enrollment site. There will be an inventory accountability log kept by the clinic staff at each location. For the methylprednisolone treatment arm, the injection will consist

of 9 mL of lidocaine HCl (1% without epinephrine) and 1 mL of methylprednisolone acetate (80 mg/mL). For the ketorolac treatment arm, the injection will consist of 8 mL of lidocaine HCl (1% without epinephrine) and 2 mL of injectable ketorolac tromethamine (30 mg/mL). The total injection volume in each treatment arm will be 10 mL. Treatment will be administered once and patients will be evaluated afterwards at 2, 4, and 12 weeks post-injection. Injectable drugs administered in this study are not suitable for multi-dose use.

Assessment of Subject Compliance with Study Intervention/Investigational Product

The responsible investigator will administer the treatment in a double-blinded fashion to the patient, who will be examined and followed at 2, 4, and 12 weeks by the same investigator. At enrollment and at 12 weeks, the follow-ups will be performed in the clinic, whereas at 2 and 4 weeks, this will be performed by phone contact/email. The ASES questionnaire will be completed prior to the injection, and then at those time points (2, 4, and 12 weeks). If the follow-up could not be performed exactly at 2, 4, or 12 weeks post-injection, investigators will allow examination and measurements at ±3 days.

Risks

The risks associated with this study include the risks of randomization, loss of confidentiality, and the burden associated with answering a questionnaire. Also, administration of methylprednisolone or ketorolac into the subacromial space is associated with certain risks; however, eligible subjects of this study would receive one of these medications regardless of their participation in this research. The ASES questionnaire at follow up will take approximately four minutes to fill out at each of the three follow-up time points (2, 4, and 12 weeks post-injection). The risk of loss of confidentiality will be minimized by storing all protected health information in locked filing cabinets in the orthopedic offices of UTMB, accessible only to those study staff that have a need to access. All digital health information will be de-identified with research-specific subject numbers and it will be stored on password protected and encrypted computers on the secure institution' network. Only serious and unanticipated problems associated with the injectable product will be reported to the IRB.

Minor side effects of steroid injections include post-injection flare, uterine bleeding, and facial erythema; major toxicities include Cushing syndrome and radiologic deterioration of joints and osteonecrosis [12, 17]. Local adverse effect of steroid injection includes permanent skin depigmentation, infection, tendon rupture, and fat necrosis or calcification. Systemic side effects of ketorolac include increased risk for cardiovascular thrombotic events including myocardial infarction and stroke, GI bleeding, ulceration and perforation, renal failure, and risk of bleeding.

Benefits

There are no foreseeable benefits to the subjects for participation in this study. If ketorolac is shown to be equivalent or superior to methylprednisolone, then the potential benefits to

the society are multiple. These include health care cost savings, standardization of care, and the furthering of orthopedic knowledge.

Concomitant Medications/Treatments

The information below report mainly drug interactions with other medications on the package insert of the agent of interest. This also included the current literature pertaining to each medication. In either arm, the drug is delivered intra-articularly (locally), which mitigates its systemic absorption and therefore its potential side effects.

Modern evidence do not indicate a significant interaction between ketorolac tromethamine and warfarin, heparin, aspirin, digoxin, diuretics, probenecid, lithium, methotrexate, ACE inhibitors, and angiotensin II receptor antagonists. Sporadic cases of epilepsy and hallucinations have been reported when combining ketorolac with antiepileptic or psychoactive drugs, respectively. When administered with SSRI, an increased risk of bleeding was noted. However, all of these adverse events occurred with IV (systemic) rather than intra-articular (local) administration of the drug. No teratogenicity or tumorigenicity were reported to date.

Recent evidence indicates an interaction between corticosteroids and either antifungals or antibiotics. However, patients with any sign or symptom of infection will be screened, and therefore excluded, prior to the injection in case an infection is suspected. Corticosteroids have been shown to interact with anticoagulants. Nonetheless, bleeding problems are also screened for prior to the injection, and if present, patients will be excluded from the trial. Corticosteroids may also intervene with hepatic enzyme inducers/inhibitors, and patients with liver diseases will be excluded. No adequate studies have been conducted to evaluate the tumorigenic effect of corticosteroids. These agents may exhibit teratogenic effects, which is the reason why pregnant women will be take part of the study.

7.0 Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Most of these contra-indications are retrieved from the medications package inserts. Due to the randomization and blinding design of the study, a contra-indication to either drug (methylprednisolone acetate or ketorolac tromethamine) is considered an absolute contra-indication for the patient to be enrolled in the study. Subjects meeting any of these conditions at baseline will be excluded from study participation. These conditions include: allergy/intolerance to steroids or NSAIDs symptoms less than one month, pregnancy or breastfeeding, pre-existing asthma, psychiatric illness, previous shoulder injection within the past three months, evidence of other confounding shoulder pathology on plain radiographs such as calcific tendonitis, MRI evidence or history of rotator cuff tear, active comorbidities of the ipsilateral extremity such as lateral epicondylitis and cervical radiculopathy, moderate to severe glenohumeral arthritis, systemic inflammatory conditions, kidney or liver disease, gastrointestinal (GI) ulcers, bleeding disorders, pending litigation or work-related claims related to the shoulder, previous shoulder surgery on the

affected shoulder, evidence of local infection, evidence of adhesive capsulitis, evidence of shoulder instability, and bilateral shoulder pain.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) defines an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of medicinal product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product. In such cases, the statistician will uncovering the patient blinding and randomization process to reveal the medication that was administered to the patient.

Severity of Event

All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, than the following guidelines will be used to quantify intensity.

Mild – Events require minimal or no treatment and do not interfere with the patient's daily activities; **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures; **Moderate** – Events may cause some interference with functioning; **Severe** – Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating; and **Life threatening** – Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products

The clinician's assessment of an AE's relationship to test article is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: associated or not associated. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used: **Associated** – Event temporally related to the administration of the study product and no other etiology explains the event; and **Not Associated** – Event temporally independent of study product and/or the event appears to be explained by another etiology.

Serious Adverse Event (SAE)

An SAE is defined as an AE that meets one of the following conditions: (1) Death during the period of protocol defined surveillance; (2) Life threatening event (defined as a subject at immediate risk of death at the time of the event); (3) An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance, results in congenital anomaly or birth defect, results in a persistent or significant disability/incapacity; or (4) Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs will be recorded on the appropriate SAE case report form, followed through resolution by a study clinician, and reviewed and evaluated by a study clinician.

Reporting Procedures for Serious Adverse Events

Any AE considered serious by the principal investigator or co-investigators or which meets the aforementioned criteria must be submitted on the SAE form to the IRB in accordance with IRB policies and procedures.

In addition, SAE's should be de-identified and anonymously reported to all investigators to emphasize on the possibility of other patients exhibiting a similar problem. The investigators are responsible of transmitting this information to their respective IRBs, who will then report the events that are serious, unexpected, and associated with the study product(s) to the Food and Drug Administration (FDA) within the required timelines as specified in 21 CFR Part 312.32: fatal and life-threatening events within 7 calendar days (by phone or fax) and all other SAEs in writing within 15 calendar days. All serious events designed as "not associated" to study product(s), will be reported to the FDA at least annually in a summary format.

The study clinician will complete a sponsor provided Serious Adverse Event Form within the following timelines: (1) All deaths and immediately life-threatening events, whether

related or unrelated, will be recorded on the Serious Adverse Event Form and sent by fax within 24 hours of site awareness; and (2) Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported via fax by the site within 72 hours of becoming aware of the event.

All SAEs will be followed until satisfactory resolution or until the principal investigator or co-investigator deems the event to be chronic or the patient to be stable.

8.0 Study Withdrawal/Discontinuation

Reasons for Withdrawal

A study subject will be discontinued from participation in the study if any of the following occur: (1) Unacceptable AE; (2) Development of any exclusion criteria; and (3) Subject withdrawals consent to continue in the research for any reason. The development of an inter-current illness, or other medical condition or situation would not risk the continued participation in the study since the injection occurs once, after the patient has been entirely screened based upon the inclusion and exclusion criteria.

Handling of Withdrawals

Subjects who withdraw from the study will still be followed-up since they are receiving the same therapeutic modality whether they were enrolled in the trial or not. Safety data on any subject discontinued because of an AE or SAE will be collected and reported to the investigators, who will then communicate it to their corresponding IRBs. If voluntary withdrawal occurs, the subject should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

Termination of Study

The study will be terminated if: (1) the patients target number has been achieved and a complete follow-up has been accomplished; or (2) similar SAE patterns occur (5 consistent events in patients receiving the same therapy). In the first case, statistical analysis will be performed, whereas in the second, recruitment will be halted and AEs/SAEs reported to all investigators, IRBs, and if unexpected and deemed associated with the drug injected, to the FDA (via the IRB).

9.0 Statistical Considerations

This study is a non-inferiority multicenter randomized controlled double-blinded trial that evaluates the efficacy of injectable methylprednisolone acetate monotherapy and ketorolac monotherapy in the treatment of patients with subacromial impingement syndrome in the outpatient setting. Therapeutic arms consist of two groups (groups 1 and 2 receiving injectable methylprednisolone acetate and ketorolac, respectively). Patients will be evaluated and compared based on the ASES self-assessment score (ranging between 0 and

100). Our main outcome is ASES score at the 12-week time-point, with details of analysis provided in the next paragraph. We will also, as exploratory analysis, compare the functional outcome at 2 and 4 weeks post-injection. We will report summary statistics containing means and standard deviations of ASES scores for each treatment arm at each time point. We will determine whether there is non-inferiority of ketorolac at each time point.

Based on historical data (at 12 weeks post injection), the mean ASES score in the control (steroid) group is expected to be about 68.7, and the standard deviation about 12.3 [18]. The ASES patient self-assessment is a validated questionnaire that can quantify pain and decreased function of the affected shoulder, and it is usually filled out by patients as part of routine care for shoulder pain [19, 20]. Based on a review of the literature, the minimum clinically relevant effect size was determined to be ranged between 12 and 17 [21]. We therefore chose to use the lower value as reference. We calculated the minimum sample size (n) that would be required in order to ensure that the study has an 80% power with an enrollment ratio of 1, using the following formula:

$$2\mathrm{n} = \frac{4\left(z_{1-\alpha} + z_{1-\beta}\right)^2 \sigma^2}{\Delta^2} = \frac{4(1.64 + 0.84)^2 . 12.3^2}{12^2} = 25.8 \approx 26$$

In this formula, Δ represents the absolute difference between the means (μ) of groups 1 and 2 ($\Delta = |\mu_2 - \mu_1|$); σ, the variance of the mean; n, the sample size per arm; α, the probability of type 1 error (0.05); β, the probability of type II error (0.2); and z, the critical z value for a given α or β. To this end, 13 individuals per arm (26 in total) should have been enrolled and completed the trial. Assuming that 20% of patients will be lost to follow-up [3], we will attempt to enroll 26/0.8 = 33 patients. For this end, we would aim at including a total of 40 patients in the study, which correspond to 20 patients per therapeutic arm. We will also assess whether there are differences in baseline scores between the 2 groups. In the case that the ASES scores differ, we will control for baseline value for each patient by including it as a covariate in a linear regression analysis, with covariates being baseline value and treatment group.

10.0 Ethics and the Protection of Human Subjects

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The investigator must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate (UTMB).

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Privacy/Confidentiality Issues

A confidentiality breach is a risk associated with chart review research. To this end, only personnel from UTMB designated by the Principal Investigator(s) will have access to study records. These personnel will be fully trained to maintain confidential nature of patient health information. Each research member will have taken the institutional human subjects protection and confidentiality training courses. Patient information and relevant data will be stored on password-protected institutional computers behind the institution firewall. Data will not be transferred to laptop computers that are removed from the institution. Paper records will be stored in locked files inside a locked office. External storage, if used, will be password-protected and encrypted. Study data will not be shared with any individual or entity that are not involved in the study. These data will be used only for research purposes and for this research study. Patients will be reassured that no personal identifiable or identity information will be published once the results of the study are available.

In accordance with the FDA Amendment Act of 2007 (FDAAA) and The International Committee of Medical Journal Editors (ICMJE) member journals trials-registration policy as a condition for publication, this study will be registered in the public trials registry ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Results will be published to clinicalTrial.gov when available but will not identify individual subjects.

11.0 Record Retention

Study data will not be shared with any individual or entity that are not involved in the study. These data will be used only for research purposes and for this research study. Study data and paper records will be destroyed within 5 years after publication of the findings.

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