A double-blinded, prospective, randomized, controlled trial comparing dexamethasone versus ketorolac injection for the treatment of local inflammatory hand and upper extremity disorders: a pilot study

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Study Product: Ketorolac

Protocol Number: S12-00878

IND Number: IND 120923

NCT Number: NCT02266433

Initial version: 7/22/2012
Amended: 07/31/2018

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List of Abbreviations

AE	Adverse Event
AIDS	Acquired immunodeficiency disease syndrome
CNS	Central nervous system
FDA	Food and Drug Administration
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
HJD	Hospital for Joint Diseases
NSAID	Non-steroidal anti-inflammatory drug
NYU	New York University
PHI	Protected Health Information

Study Summary

Title	A double-blinded, prospective, randomized, controlled trial comparing dexamethasone versus ketorolac injection for the treatment of local inflammatory hand and upper extremity disorders: a pilot study
Short Title	Ketorolac in hand and upper extremity soft tissue disorders
Protocol Number	Pending
Phase	Phase 3
Methodology	Randomize, double-blind, prospective active control trial
Study Duration	2 – 3 years
Study Center(s)	Single-center – NYU Langone Medical Center
Objectives	The primary objective of this study is to compare local corticosteroid hand and elbow injections to placebo or ketorolac to determine if there is an equal or better reduction of symptoms for common orthopaedic upper extremity disorders including: De Quervain's tenosynovitis, trigger fingers, and tennis elbow (lateral epicondylitis).
Number of Subjects	Goal of 780 total subjects: • 260 subjects in each of the 3 treatment groups (De Quervain's tenosynovitis, trigger fingers and lateral epicondylitis)
Diagnosis and Main Inclusion Criteria	Subjects 18 years or older, with any of the following diagnoses: De Quervain's tenosynovitis, trigger fingers, or lateral epicondylitis
Study Product, Dose, Route, Regimen	Peritendonous soft tissue injection for De Quervain's tenosynovitis, trigger fingers and lateral epicondylitis: • 1 mL of ketorolac (30mg/mL) and 0.5 mL (5mg) of 1% lidocaine
Duration of administration	Single administration, with a second injection permitted only once as subject desires due to no major clinical response at the 4 or 8-week follow-up.
Reference therapy	Standard of care peritendonous soft tissue injection for De Quervain's tenosynovitis, trigger fingers, and lateral epicondylitis: • 1 mL of dexamethasone sodium phosphate (4mg/mL) and 0.5 mL (5mg) of 1% lidocaine
Statistical Methodology	The sample size as stated above was derived by a power analysis. A power analysis indicated that a total sample size of 200 patients randomized equally (1:1 randomization) to each treatment arm (i.e trigger finger, De Quervain's disease, and tennis elbow) without any blocking or stratification would provide 80% statistical power (alpha=.05, beta=0.20) to detect a 10% difference in mean DASH scores between cohorts assuming a common standard deviation of 25% (effect size = 10/25 = 0.4). To account for an estimated 30% loss to follow-up, we plan to enroll a total of 260 patients per treatment arm (i.e. trigger finger, De Quervain's disease, and tennis elbow). In total, there will be approximately 780 patients enrolled among all treatment arms.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Many orthopaedic hand disorders are comprised of different forms of tendonitis, tenosynovitis, and arthritis. The inflammatory processes of these disorders cause discomfort and functional impairment for patients. Decreasing the inflammatory response by use of splinting, physiotherapy, systemic anti-inflammatory agents, and local anti-inflammatory injections helps to alleviate some or all of the discomfort (2-4). Steroid injections are not entirely benign, and complications include tendon ruptures, subcutaneous fat atrophy, skin pigmentation changes, cartilage damage, and hyperglycemic responses in diabetics (9-11, 22-23). Studies have shown that ketorolac, a non-steroidal anti-inflammatory agent has a potent anti-inflammatory effect comparable to corticosteroids and a strong analgesic effect allowing for reduced opioid consumption postoperatively (7, 8). One could argue that the potent anti-inflammatory properties of ketorolac could be used to substitute for local corticosteroid injections in treating certain hand disorders. Given the side-effect profile for corticosteroids it may be beneficial to treat inflammatory disorders with local ketorolac injections. Nonsteroidal anti-inflammatory agents also have their known systemic adverse effects including gastric ulceration and intestinal bleeding as well as impairment of renal function. Most of these side effects are theoretically avoided with local tissue injections.

1.2 Study Drugs

Ketorolac

The proposed use of ketorolac in this study is outside of the FDA-approved indication and is the investigational agent in this study

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID). The approved indication for Ketorolac is for the short-term (≤5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. It is highly protein bound (99%) and is largely metabolized by the liver. In it's approved indication it is contraindicated for those with renal impairment, active peptic ulcer disease, pregnant or nursing females, individuals with NSAID hypersensitivity, or individuals at high risk for bleeding/clotting disorders.

Dexamethasone

Dexamethasone is a synthetic corticosteroid and possesses glucocorticoid activity, and will be used within its labeled indication for this study: intra-articular or soft tissue injection for: synovitis of osteoarthritis, epicondylitis, acute nonspecific tenosynovitis. It is the active comparator in this study.

In its approved indication there use limitations for immunocompromised individuals, pregnant females, persons with allergy to steroids, individuals with systemic fungal infections, and individuals with cerebral malaria. It is contra-indicated in systemic fungal infections, and hypersensitivity to any component of this product, including sulfites.

Lidocaine

Lidocaine is a local anesthetic of the amide type, and will be used within its labeled indication for this study: production of local or regional anesthesia by infiltration techniques such as percutaneous injection. It is to be given as concomitant therapy with both the investigational agent, ketorolac injection, and the standard of care therapy, dexamethasone injection.

1.3 Preclinical Data

There are no published studies in the literature that examine local injections of ketorolac in treating orthopaedic hand pathology. Shapiro et al investigated the effects of local injection of corticosteroid and ketorolac on histologic and biomechanical properties of rabbit tendon and cartilage (1). Their goal was to determine the safety and efficacy of local injection of NSAIDs in humans by first testing the histologic and

biomechanical properties of tissues injected with NSAIDs versus corticosteroids in rabbit models. Among the results obtained the study showed that methylprednisolone compared to ketorolac demonstrated a significant increase in cartilage necrosis which was not seen at all in the ketorolac group. The damaging effects of corticosteroids on cartilage has been studied in the literature and it is well known that it is detrimental to cartilage if overused (13, 14). The Shapiro study also showed no notable difference in histologic inflammatory cells when comparing the two groups and no evidence of tendon necrosis despite other studies showing evidence for tendon necrosis/rupture with corticosteroid injections. Case reports exist in the literature that report flexor digitorium superficialis and profundus ruptures following corticosteroid injections for trigger fingers (9, 26). In addition, rabbit model studies show that corticosteroid injection into tendons produce necrosis of collagen resulting in incomplete repair and increased risk for rupture of the tendon (12). The Shapiro study concluded that peri-tendinous injections of either corticosteroid or ketorolac may not be harmful, however cartilage seems to show damage with corticosteroid injections alone (1). The Shapiro study shows that ketorolac does not cause any more harm than corticosteroids when analyzing biomechanical and histologic properties in rabbit models and in some cases causes less damage as demonstrated with cartilage.

1.4 Clinical Data to Date

Investigations comparing local injections of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been conducted. One study by Karthikeyan et al showed that subacromial injections with corticosteroids outperformed injections with tenoxicam at 2 and 4 weeks post injection (24). More recently, a double-blind randomized study between triamcinolone and ketorolac injections into the subacromial space demonstrated that ketorolac showed greater improvements in shoulder functional scores at 4-weeks of follow-up and therefore was found to have equivalent if not superior efficacy compared to steroids without the potential steroid side-effects such as tissue atrophy or cartilage damage (25).

In addition there are several studies that examine the potent anti-inflammatory effects of ketorolac when compared to corticosteroids in other fields of research. The ophthalmology literature has examined the effect of ketorolac for postoperative inflammatory control following cataract surgery. When comparing it to corticosteroids, ketorolac topical ophthalmic formulations were as effective as corticosteroids in controlling inflammation and pain following cataract surgery without the known complications associated with corticosteroids including infection, increased intra-ocular pressure, and inhibition of cellular wound-healing (6, 8).

1.5 Dose Rationale

Dose rationale for the study was determined based on available concentrations and clinical data. Ketorolac is readily available at very low costs in vials of 15mg/mL and 30mg/mL. The Shapiro study that examined ketorolac injection into rabbit tendon and cartilage showed favorable safe results using 15mg/mL concentrations and the Min study comparing ketorolac to triamcinolone in the shoulder used 60mg of ketorolac (1,25). We chose 30mg/mL concentrations simply because for small injections in the hand and upper extremity this should prove sufficient if any outcome were to be recorded. A lower concentration puts the study at risk for showing no clinical response. Because the side-effect profile is essentially equivalent between the two we chose to proceed using the higher of the two readily available concentrations.

The dose of dexamethasone used in this study is based on the standard of care used on patients for hand and upper extremity pathology which consists 4mg/mL of dexamethasone sodium phosphate per injection.

Lastly, 1% lidocaine is used in this study to provide simple analgesia from the injections for immediate relief for patients as these injections can be painful at times. This is a standard of care dose of local analgesia.

1.6 Research Risks & Benefits

1.6.1 Risk of Study Drug

All patients will be monitored closely as per the data and safety monitoring plan established for this project for any side-effects that may arise from using these medications for local soft tissue infections. Patients will be checked for common side effects at the time of their follow-up visits. In addition, the patient will be given instructions to contact the private office/HJD hand clinic to report any potential side effects that they may be experiencing.

Risks associated with dexamethasone injections include (9-11, 22-23):

- Pain/discomfort at the site of injection
- Tendon ruptures
- Subcutaneous fat atrophy
- Skin pigmentation changes
- Cartilage damage
- Hyperglycemic responses in diabetic patients

Risks associated with Ketorolac in the literature refer mainly to systemic or intramuscular administration and no risks are noted for local soft tissue injections. Ketorolac has been shown to cause (28-29):

- Pain/discomfort at the site of injection
- Increased risk for bleeding
- Skin rashes
- Pruritis
- Allergic reactions such as face/throat swelling
- Abdominal pain/GI upset
- Gastrointestinal ulcers/GI bleeding
- Renal impairment

Risks associated with lidocaine mainly involve side-effects from systemic administration which include (30,31):

- CNS depression or excitation (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, vomiting, twitching, convulsions, unconsciousness, respiratory depression and arrest)
- Bradycardia
- Hypotension
- Cardiovascular collapse
- Allergic reactions

Protection against risks

Patients will be injected using sterile technique to avoid any infectious risk with the medication. Patient will be informed that some discomfort will be experienced with needle injection however small gauge needles will be used to minimize the pain felt by the patient. Any patient that experiences an adverse event will be withdrawn from the study and will follow-up with their primary care provider promptly.

Payment for the office visit and any procedures performed will be billed to the insurance company of the patient and the patient is responsible for any copayments needed.

1.6.2 Potential benefits

This research study may change how patients are treated with simple hand/upper extremity inflammatory disorders.

2 Study Objectives

The primary objective of this study is to compare local corticosteroid hand and elbow injections to ketorolac to determine if there is an equal or better reduction of symptoms for common orthopaedic upper extremity disorders including: De Quervain's tenosynovitis, trigger fingers, and tennis elbow (lateral epicondylitis).

3 Study Design

3.1 General Design

This study will be a double-blinded prospective randomized controlled trial comparing the effects of dexamethasone (standard of care) and ketorolac in hand and upper extremity soft tissue disorders.

3.2 Primary Study Endpoints

The primary endpoint will be functional outcome scores at various follow-up time points using the quickDASH and EQ-5D questionnaire as well as a pain visual analog scale. The primary endpoint for the study would be resolution of symptoms or surgical intervention.

Primary endpoints will depend on the diagnosis of the patient. The following details what will be assessed at each follow-up visit after the initial injection:

1) Trigger finger group primary endpoint measures include the resolution of objective triggering and resolution of tenderness at the A1 pulley at subsequent follow-up visits. In addition, patients will be graded based on the Quinnell system to monitor for improvement: 0-normal movement of finger; 1-uneven movement; 2-active correctible locking of digit; 3-passively correctible locking; 4-fixed deformity (15). Patients will complete the quickDASH and EQ-5D questionnaires as well as a pain visual analog scale at each follow-up visit (27).
2) De Quervain's tenosynovitis group primary endpoint measures will include objective physical exam findings for the resolution of pain/tenderness over the 1st dorsal extensor compartment and the resolution of pain elicited during the Finkelstein test. In addition, patients will complete the quickDASH and EQ-5D questionnaires as well as a pain visual analog scale at each follow-up visit.
3) Lateral epicondylitis of the elbow group primary endpoint measures include the resolution of lateral elbow pain/tenderness over the extensor origin and the resolution of pain at the lateral epicondyle with resisted wrist extension during follow-up examinations. Patient grip strength will also be measured in this cohort using a hand dynamometer. Grip strength will be measured at each follow-up and the average of three tests with 20 second rests in between will be recorded. The contralateral side will also be measured for comparison. Lastly, patients will complete the quickDASH and EQ-5D questionnaires as well as a pain visual analog scale at each follow-up visit.

3.3 Secondary Study Endpoints

Secondary outcome measures include objective physical exam findings (clinical grading/classification systems), and grip/pinch strength using dynamometers.

3.4 Primary Safety Endpoints

Patients will follow-up after the first injection at 4-weeks, 8-weeks, 12-weeks, and 6 months post injection. During follow-up appointments patients in this study will be monitored based on history and physical exam for any side-effects associated with the administration of local soft tissue injections of dexamethasone or ketorolac.

Patients can withdraw from the study at any time if they wish. Patients whose symptoms do not improve and are candidates for surgery can withdraw from the study and have surgery to correct their specific pathology (secondary endpoint). Patients enrolled in the study will be counseled regarding the likelihood of

the injections working and will be given the opportunity for a second injection at 4 weeks from the time of the first injection if no significant symptoms have resolved. Ultimately it will be up to the patient whether they chose another injection or if they want to resort to a surgical intervention.

Patients who receive ketorolac by randomization as the therapeutic option will have an expected failure rate of approximately 30-50% based on clinical experience and literature review that shows the failure rate of dexamethasone (standard of care) on trigger fingers. The study population will be statistically analyzed biannually to determine if there is a significant difference in the rate of failures between the two groups, however a sizeable study population needs to be established before these conclusions can be drawn. If the rate of failure proves to be statistically significant between the ketorolac and dexamethasone group then the study will have to be ethically abandoned. This determination needs to take into consideration the pre-treatment symptoms of the patient since patients who begin treatment with a severe trigger finger (quinnell score=4) have a different prognosis compared to patients who begin with a mild trigger finger (quinnell score=1).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Patients must be diagnosed with at least one of the following: trigger finger, de quervain's tenosynovitis, or tennis elbow (lateral epicondylitis)
- Subjects may be treated for multiple sites of pathology simultaneously or sequentially and up to three sites of pathology can receive an injection during an office visit
- Subjects may have a maximum total of two injections at each site of pathology during the study
- Age 18 years of age or older from all racial/ethnic types
- Both males and females
- Study participants will not receive splinting as a therapeutic addition to their treatment.
- Study participants will include any NYU employee or students as these individuals also can get hand and upper extremity pathology. It will be specifically reiterated to them that their academic status or grades, or employment will not be affected by their decision to participate in this study. Record of the participation cannot be linked to an academic record.

4.2 Exclusion Criteria

- Patients had previous steroid injection at the site in question within 90 days of enrollment
- Patients with a history of gastric ulcers, renal impairment, allergy/hypersensitivity to non-steroidal anti-inflammatory (NSAID) or lidocaine derivative medications, immunocompromised patients (HIV/AIDs) and pregnant females

4.3 Subject Recruitment and Screening

This study comprises several arms each of which is a specific disease involving the hand and upper extremity: trigger finger, De Quervain's disease, and tennis elbow. Subjects will be identified in the office visit for their hand and upper extremity complaints.

Equal gender distributions are expected in this study. Subjects will be 18 years of age or older. The hand and upper extremity disorders involved in the study are rarely if ever seen in patient population younger than 18 years of age. There will be no restriction to racial/ethnic background in terms of enrollment nor will any one particular racial/ethnic background will be sought out for enrollment over another. The diversity of the research subjects will be dependent on the diversity of patients seen in the hand offices of the investigators which is very broad as is the New York City Metropolitan area.

Patients will be enrolled from the private office of orthopaedic hand surgeons (Dr. Paksima and Dr. Sapienza) and the resident hand clinic at NYU Hospital for Joint Diseases held at the 23rd street clinic.

There are no vulnerable subjects included in this study.

4.4 Subject Withdrawal

Patients can withdraw from the study at any time if they wish. Patients whose symptoms do not improve and are candidates for surgery can withdraw from the study and have surgery to correct their specific pathology (secondary endpoint). Patients enrolled in the study will be counseled regarding the likelihood of the injections working and will be given the opportunity for a second injection at 4 weeks from the time of the first injection if no significant symptoms have resolved. Ultimately it will be up to the patient whether they chose another injection or if they want to resort to a surgical intervention.

If patients experience adverse events they will be counseled regarding treatment alternatives for their pathology and any complications from the injection/medications will be treated appropriately. Because the study consists of a single injection at time point zero followed by serial examinations and completion of functional outcome surveys there is no need to stop treatment and withdraw patients from the study despite having an adverse event. The patient will simply not receive any more injections.

5 Study Drugs

5.1 ***Ketorolac*** *(Investigational Agent)*

5.1.1 Description

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID). The approved indication for Ketorolac is for the short-term (≤5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. It is highly protein bound (99%) and is largely metabolized by the liver. It is indicated for short-term management of severe acute pain as intravenous or intramuscular injections.

In its approved indication it is contraindicated for those with renal impairment, active peptic ulcer disease, pregnant or nursing females, individuals with NSAID hypersensitivity, or individuals at high risk for bleeding/clotting disorders.

5.1.2 Treatment regimen

The proposed use of ketorolac in this study is outside of the FDA-approved indication and is the investigational agent in this study. Ketorolac will be administered as a peritendonous soft tissue injection of 1 mL of ketorolac (30mg/mL) and 0.5 mL (5mg) of 1% lidocaine.

Patients will be followed at the initial office visit, 4-weeks, 8-weeks, 12-weeks, and 6 months post injection to determine clinical response. A second injection can be given only once at each site of pathology if the patient desires due to no clinical response at the 4 or 8-week follow-up.

Patients will be divided into two groups. Group 1: 1 mL of dexamethasone sodium phosphate (4mg/mL) and 0.5 mL (5mg) of 1% lidocaine ***(standard of care)***. Group 2: 1 mL of ketorolac (30mg/mL) and 0.5 mL (5mg) of 1% lidocaine ***(experimental group)***. Patients will be followed at the initial visit, 4-weeks, 8-weeks, 12-weeks, and 6 months post injection to determine clinical response. A second injection can be given only once if the patient desires at the 4 or 8-week follow-up. These injections will be offered if the patient reports some improvement since the prior injection but still some persistent symptoms that have not completely resolved or if they had no response but would like another attempt to avoid surgery by receiving a second injection. The injection administered for the second time will correspond to the randomized group for the patient. Patients will not be compared separately if they receive one or two injections. However, with enough enrollment subgroup analysis can be performed to determine if receiving two injections significantly alters the outcome of the patient in regards to functional score improvement, surgery endpoint, or resolution of symptoms. The primary endpoint for the study would be resolution of symptoms or surgical intervention.

Patients receiving a second injection should be allowed to continue in the study. It is common practice for patients as part of the standard of care to receive multiple injections for hand and upper extremity pathology until these injections have been deemed non-therapeutic by the treating physician and surgical intervention is indicated.

5.2 Dexamethasone (Standard of care comparator)

5.2.1 Description

Dexamethasone is a synthetic corticosteroid and possesses glucocorticoid activity. It is indicated for intra-articular or soft tissue injection for: synovitis of osteoarthritis, epicondylitis, acute nonspecific tenosynovitis.

In its approved indication there use limitations for immunocompromised individuals, pregnant females, persons with allergy to steroids, individuals with systemic fungal infections, and individuals with cerebral malaria. It is contra-indicated in systemic fungal infections, and hypersensitivity to any component of this product, including sulfites.

5.2.2 Treatment regimen

Dexamethasone will be used within its labeled indication for this study: intra-articular or soft tissue injection for: synovitis of osteoarthritis, epicondylitis, acute nonspecific tenosynovitis. It is the active comparator in this study.

Dexamethasone will be administered as a peritendonous soft tissue injection of 1 mL of dexamethasone sodium phosphate (4mg/mL) and 0.5 mL (5mg) of 1% lidocaine

Patients will be followed at the initial office visit, 4-weeks, 8-weeks, 12-weeks, and 6 months post injection to determine clinical response. A second injection can be given only once if the patient desires due to no clinical response at the 4 or 8-week follow-up.

5.3 Lidocaine (Standard of care co-administered anesthetic)

Lidocaine is a local anesthetic of the amide type, and will be used within its labeled indication for this study: production of local or regional anesthesia by infiltration techniques such as percutaneous injection. It will be administered as 0.5 mL (5mg) of 1% lidocaine in combination with both the investigational agent, ketorolac injection, and the standard of care therapy, dexamethasone injection.

5.4 Supply of study drugs

Medications will be provided by the NYUHJD pharmacy for the 23rd street clinic. For the faculty private offices, the medications will be provided by their own office and stored at those sites as well. The primary endpoint for the study would be resolution of symptoms or surgical intervention. They will be stored in their pre-packaged containers at room temperature which is within the storage temperature parameters for the medication of 20 to 25°C (68 to 77°F).

5.5 Method for Assigning Subjects to Treatment Groups

When a patient is enrolled and consented into the study a random envelope (labeled with an identification number) will be opened and in it will contain the group that the patient is randomized to: steroid or ketorolac. Envelopes are made using a randomization software that chooses one of the two drugs at random. When a patient is being enrolled in the study for an additional site of pathology, they will receive the same drug to which they were initially randomized at each site of pathology and a separate identifier number will be used to track the progress of each site.

5.6 Preparation and Administration of Study Drug

On the date of the planned injection a nurse, resident, fellow or research assistant present at the site and not directly involved in the patient's care will draw up the medication appropriate to the randomized treatment assignment and hand it to the physician who will administer the drug. Both the patient and the treating physician are blinded to the identity of the medication. Patient data will be recorded and kept in

the envelope and only the hand department research assistant or the resident in charge of this project (who will not be directly involved in patient care) will know the identity of the treatment given to the enrolled patients. Because both liquids are clear the contents of the syringes do not need to be covered.

5.7 Prior and Concomitant Therapy

There are no restrictions to concomitant oral medical therapy for subjects enrolled in this study

5.8 Blinding of Study Drug

The study will be a double-blinded prospective randomized controlled trial. Drugs will be stored in the local clinic/office medication storage room. When a patient is enrolled and consented into the study a random envelop (labeled with an identification number) will be opened and in it will contain the group that the patient is randomized to: steroid or ketorolac. On the date of the planned injection a nurse, resident, fellow or research assistant present at the site and not directly involved in the patient's care will draw up the medication and hand it to the physician who will administer the drug. Both the patient and the treating physician are blinded to the identity of the medication. Patient data will be recorded and kept in the envelope and only the hand department research assistant or the resident in charge of this project (who will not be directly involved in patient care) will know the identity of the treatment given to the enrolled patients. Because both liquids are clear the contents of the syringes do not need to be covered

6 Study Procedures

A specific patient population with hand and upper extremity pathologies will be studied including trigger finger, De Quervain's tenosynovitis, and lateral elbow epicondylitis. Patients with trigger finger will be diagnosed clinically by observing symptoms of catching or triggering of the digit with range of motion and tenderness localized to the A1 pulley. Patients with De Quervain's tenosynovitis will be identified clinically as having pain/tenderness at the first dorsal extensor compartment combined with a positive Finkelstein test (pain during full thumb adduction with ulnar deviation of the wrist). Patients with tennis elbow (lateral epicondylitis) will be defined as having lateral elbow pain/tenderness over the extensor origin and/or pain at the lateral epicondyle with resisted wrist extension.

Patients will be consented at the time of their visit with the hand surgeon. Based on inclusion/exclusion criteria it will be determined whether or not to enroll the patient in the study. Consent will be performed by discussing the study with the patient in the privacy of the exam room and having them sign the written consent form that will be IRB approved. There is no payment to the patient for participation and they will be charged for their normal office visit for treatment rendered.

7 Statistical Plan

7.1 Sample Size Determination

The sample size as stated above was derived by a power analysis. A power analysis indicated that a total sample size of 200 patients randomized equally (1:1 randomization) to each treatment arm (i.e trigger finger, De Quervain's disease, and tennis elbow) without any blocking or stratification would provide 80% statistical power (alpha=.05, beta=0.20) to detect a 10% difference in mean DASH scores between cohorts assuming a common standard deviation of 25% (effect size = 10/25 = 0.4). To account for an estimated 30% loss to follow-up, we plan to enroll a total of 260 patients per treatment arm (i.e. trigger finger, De Quervain's disease, and tennis elbow). In total, there will be approximately 780 patients enrolled among all treatment arms, however we expect the trigger finger group to be the treatment arm that most rapidly enrolls patients.

7.2 Statistical Methods

Statistics will be conducted by the statistician on faculty with the NYU Hospital for Joint Diseases. Primary analysis will consist of comparisons of the baseline functional scores (quickDASH and EQ5D). These scores will be analyzed and compared to subsequent scores at the various follow-ups (4-weeks, 8-weeks,

12-weeks, 6 months). In addition, changes in scores will also be analyzed between the baseline scores and the subsequent follow-ups. Statistical significance will be determined by p-values less than 0.05.

Secondary analysis will consist of physical exam findings and resolution of symptoms following injections as well as grip or pinch strength using pressure dynamometers to gage improved function following injections as well. In addition, observation of side effects will also be included in the secondary analysis.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Recording of Adverse Events
At each contact with the subject, information will be sought from each subject on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.2 Reporting of Serious Adverse Events and Unanticipated Problems

8.2.1 Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements,

though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3 Unblinding Procedures

Because of the low side-effect profile for this study it will not be necessary to unblind subjects for any particular reason unless they want to be withdrawn from the study and informed of what drug was given to them. If this were to occur the investigator must inform the sponsor-investigator of all subjects whose treatment was unblinded immediately within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator and Study Regulatory Sponsor to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events. A full Data and Safety Monitoring Plan is attached.

9 Data Handling and Record Keeping

9.1 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In addition to the data security standards noted below, we will also required a signed subject authorization (incorporated into the study consent form) informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Study Records

The study records will collect the primary data collection instrument for the study. All data required by the protocol must be recorded. All missing data must be explained. Study records will be maintained in a secure area accessible to the Principal Investigator and study staff.

9.4 Study Electronic Data

Data will be maintained on a database on a computer which the investigators of this study as well as research assistants have access (however not everyone will see the data due to blinding of the physicians involved in the study). The data will be kept on an NYU research network drive that is password protected. If the data is shared among the investigators it will also be emailed within the NYU email system which is also password protected and encrypted.

All data will be stored for future use. It will take approximately 1-2 years to obtain the number of patients required for the trigger finger arm of the study due to the multitude of patients requiring trigger finger injections in everyday practice. However, it can take longer for the other arms of the study to collect the required amount of patients. The following list explains how this long term data will be handled:

- Data will contain patient names abbreviated with initials of first and last names as well as medical record numbers attached in order to easily obtain more information on the patient in the hospital electronic medical record (EMR)

- Data will be stored indefinitely until it is determined that enough data has been obtained to publish results.
- Data will be kept on an NYU research network drive that the department of hand surgery maintains and is password protected. The resident investigator of this study along with hand department research assistants will have access to the data however any physicians involved in the treatment of these patients will not be able to see the data for blinding purposes.
- Data stored for future use will continue to be maintained in the event a retrospective review of the data is conducted (pending an IRB approval for this as well). At this time it is unknown what this data can also be used for aside from the primary purpose of the study.
- Once the study is complete the results will be shared among physicians. A subject's research data will be provided to subjects upon request. Patient will only be told their personal data outcomes and the general outcomes of the study as a whole however other patient information will be kept from them as per patient confidentiality rules.
- Storage for future use is not optional. This data needs to be stored because it can be used for other research in the future (retrospective reviews, etc).

9.5 Records Retention

Study source information collected in the EPIC system will be maintained according to institutional standards (and a least 6 years) and other study essential documents will be maintained for a minimum of 6 years after completion of the study and analysis of the study data.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring

For full details on study data and safety monitoring, see the accompanying Data and Safety Monitoring Plan for this study. The responsibility for gathering the data will rest with the individual investigators/health care providers that are directly treating the patients (either at the NYU HJD hand clinic on 23rd street or in the private office of hand attending). Individuals treating patients will be informed to relay any unanticipated problems/concerns/adverse events to the resident research coordinator (Sergio Glait, MD). Data will be consolidated and sent to the resident researcher for further evaluation and for monitoring during the course of each patient's length of treatment.

The resident research coordinator (Sergio Glait, MD) will ensure data accuracy by monthly asking how the data was collected and ensuring individuals are following proper protocol. In addition, data accuracy will also be maintained with quick training sessions on the study to be conducted at the study site once every 2 month basis. This will be done by the hand research coordinators/assistants, the resident researchers, or the principal investigators/attending involved. Monitoring work will be reviewed at regular intervals with the study Principal Investigator.

Patients that ultimately drop out of the study will be monitored for the course of their regularly scheduled follow-up appointments until there are discharged from the clinic or the care of the attending orthopaedic hand surgeon.

Primary and secondary efficacy endpoints will be monitored. Either patients will have resolution of their symptoms (primary endpoint) with improvement in hand function to their desired satisfaction or they must undergo surgery (secondary endpoint) for correction due to failure of the local soft tissue injection in relieving their symptoms.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is funded by the Department of Orthopaedic Surgery.

12.2 Conflict of Interest

The NYULMC Investigator, Sub-investigators, and study staff will follow the applicable University conflict of interest policies.

12.3 Subject Stipends or Payments

There are no subject stipends or payments for participation in this study.

13 Publication Plan

Once data is complete and analyzed by our institution's statisticians we will plan to submit the study for publication within approximately 3 months of the completion of the study. The primary responsibility for the publication of the results of the study lies with the principal investigator Dr. Anthony Sapienza.

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