Comparative Effectiveness of Particulate Versus Nonparticulate Corticosteroid Injections for the Treatment of Musculoskeletal Conditions

Study Protocol and Statistical Analysis Plan

NCT04278833

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1) Name of study:

Comparative Effectiveness of Particulate versus Nonparticulate Steroid Injections for Treating Musculoskeletal Conditions

2) PI and other key investigators or key study personnel
PI: Eugene Y. Roh, MD
Investigator: Anita Lowe Taylor, MD
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3) Specific source of institutional funding (account number): None

4) List of sources from whom you are seeking funds (or have sought funding) for this project
AMSSM funding
Stanford internal funding
PM&R foundation
Charity from donors

5) Specific aims and basic hypothesis including an explicit primary hypothesis or goal

Specific Aims:

a. To determine if particulate or non-particulate corticosteroid injections are more effective at treating pain from musculoskeletal pathologies of the intra-articular hip, glenohumeral joint, biceps tendon, and subacromial bursa at 2 weeks, 3 months, or 6 months.
b. To determine if there is a significantly different side effect profile between particulate and non-particulate corticosteroids when used for intra-articular hip, glenohumeral joint, biceps tendon, or subacromial bursa injections.

Hypothesis: There will be no significant difference in pain reduction, number of injections received, conversion to surgery, or side effect profile at 2 weeks, 3 months, or 6 months between particulate and non-particulate corticosteroids in the treatment of musculoskeletal pathologies of the intra-articular hip, glenohumeral joint, biceps tendon, or subacromial bursa.

6) General background

Corticosteroid injections are commonly used for the treatment of painful musculoskeletal pathologies including hip and glenohumeral joint osteoarthritis, adhesive capsulitis, biceps tendinopathy, and impingement syndrome/subacromial bursitis (Lambert et al, 2007; Lee et al, 1997; Yoon et al, 2013; Hong et al, 2011), yet there is no consensus on whether particulate or non-particulate steroids are superior. Particulate steroids include betamethasone, triamcinolone, and methylprednisolone, while non-particulate steroids include dexamethasone (Derby et al, 2008).

While particulate steroids might have theoretical improved efficacy due to possible decreased dispersion from the intra-articular space, there is animal data to suggest that particulate steroids may decrease microvascular perfusion (Laemell et al, 2016). Moreover, during animal studies in which steroids were directly injected into the arterial circulation, particulate but not non-particulate steroids resulted in permanent central nervous system damage (Dawdley et al, 2009; Okubadejo et al, 2008). Yet because there is no meaningful data to support one choice over another, there remains significant clinical equipoise.

This is in contrast to spinal epidural corticosteroid injections, where dexamethasone is generally preferred due to comparable efficacy and improved safety profile of non-particulate steroids compared to particulate steroids (Kennedy et al, 2014; Mehta et al, 2017).

While randomized controlled trials have been completed comparing particulate to non-particulate steroids in the treatment of spinal stenosis (Kennedy et al, 2014; Mehta et al, 2017), knee rheumatoid arthritis (Hajialilo et al, 2016), and idiopathic trigger finger (Ring et al, 2008) with conflicting results, there have been no studies comparing these two steroid types in the hip joint, glenohumeral joint, biceps tendon, or subacromial/subdeltoid bursa.

7) Preliminary unpublished data: None

8) Experimental design and data analysis, including inclusion and exclusion criteria, statistical basis for the number of subjects to be enrolled, the statistical plan for analyzing at least the primary hypothesis, matrix showing procedure plan for each study visit, data safety monitoring plan .

Design

This will be a single center, prospective, single blind, randomized controlled trial of hip, glenohumeral joint, peri-tendinous biceps brachii, and subacromial bursa injections comparing the efficacy of particulate (triamcinolone, betamethasone) versus non-particulate (dexamethasone) corticosteroids.

Participants will be recruited for the study by trained physicians and physician extenders at Stanford orthopedic and PM&R clinics only after they have already opted for corticosteroid injection as a part of their routine medical care. The initial decision to pursue steroid injection will be based entirely on joint decision making between the patient and their medical provider prior to mention of the study.

After consenting, basic demographic data, average numeric pain score (NRS) over the past week, and information on other medical interventions tried for their pain (including medication use, physical therapy, chiropractic care, and massage) will be collected. The participant will then be randomized to receive either a particulate (triamcinolone or betamethasone) or non-particulate (dexamethasone) corticosteroid, both of which are within current standards of care. Ultrasound or fluoroscopic guided injection will then be completed using sterile technique as per current clinic practice.

After the injection, patients will follow up in clinic or over the phone at 2 weeks, 3 months, and 6 months and will be asked their average NRS over the past week, functional questionnaires appropriate to pertinent body parts (WOMAC, ASES, QDASH), other treatments they have tried in the interim, and for any side effects they have experienced. In addition to obtaining outcome measures, the treating physicians may order repeat injections, medications, or refer the subject to surgery, at their discretion based upon the patient's pain and functional limitations. Up to a total of three injections to the same musculoskeletal structure are allowed during the 6 month study period. Any injection into a separate space (i.e. glenohumeral joint followed by subdeltoid bursa) will be considered different structures, and follow up for the new anatomical site will begin at the time of that injection. Data collection and follow up on the previous anatomical injection site will continue on the same timeline. Data on number and timing of repeat injections, surgeries, side effects, and medications will be recorded as part of the study.

Data analysis

Patients receiving injections to the intra-articular hip, glenohumeral joint, peri-tendinous biceps, and subdeltoid bursa will be analyzed separately. Depending on normality and cell counts, baseline measures between the particulate and non-particulate injection groups will be compared using two-sample t-tests or Mann-Whitney U-tests for continuous variables and chi-squared tests or Fisher's exact tests for categorical variables.

Within each joint/structure, a mixed-effects model will be used to compare differences in pain (NRS), function (WOMAC, ASES, QDASH), and the number of subsequent injections. These models will include adjustments for repeated measures and potential covariates as determined by the previous univariate tests. A power analysis determined that a sample size of 50 (25/group) will provide at least 80% power to detect 10% differences in pain and 25% differences in function between patients receiving particulate and non-particulate corticosteroids in the subdeltoid bursa and intra-articular hip, while a sample size of 36 (18/group) achieves the same power for patients receiving treatment in the glenohumeral joint, and a sample size of 62 (31/group) achieves this power in the biceps brachii group.

The time until a repeat injection was administered will be analyzed using a Cox proportional hazards survival model and chi-squared tests will be used to analyze repeat injections, repeat surgeries, and side effects between groups. All statistical analyses will be completed using a two-sided level of significance of 0.05.

Inclusion Criteria

-Age greater than or equal to 18
-Ability to provide informed consent
-Capable of complying with the outcome instruments used
-Capable of attending all planned follow up visits
-Patient is deemed appropriate for intra-articular hip, glenohumeral, peri-tendinous biceps, or subdeltoid bursa corticosteroid injection by their treating physician for the treatment of a painful musculoskeletal condition

-Average pain of greater than or equal to 4/10 over the last 7 days

Exclusion Criteria
-Unclear diagnosis
-Pregnancy
-Incarcerated patients
-Prior corticosteroid injection into the anatomical structure within the past 3 months
-Prior prosthetic surgery on the joint
-Any condition that increases injection risk such as bleeding tendencies, uncontrolled diabetes, current active infection, or infection requiring antibiotics within the last 7 days
-Chronic opioid use to control pain
-Workers compensation and litigation.
-BMI > 40

Data safety monitoring
Redcap will be used as a secure database in which to compile and capture all data. All data will be entered directly to the Redcap database. Data will be de- identified and coded through Redcap prior to exportation to spreadsheet form for data analysis. Devices that contain identifiable subject information will be password protected and encrypted. Access to the data will be limited exclusively to members of the research team until after de-identification. Thereafter, files may be shared electronically via encrypted, password protected email.

Participants will be asked to report all adverse events at the time of occurrence to the principal investigator, and information on minor side effects will be elicited via phone or appointment at 2 weeks, 3 months, and 6 months. As the procedures and medications used in this trial are current standard of care, we do not anticipate significant adverse events.

Procedure Plan

Time of Visit	Questionnaires	X-Ray or Ultrasound
Baseline	N/A	Standard care
Injection	Study	Standard care
2 weeks (±1w)	Study	N/A
3months (±4w)	Study	N/A
6 months (±4w)	Study	N/A

9) Significance:

Currently there is no data to support the injection of one type of corticosteroid over another in the treatment of many musculoskeletal conditions. We hope that the results of this study will aide clinicians in selecting the most effective medication for musculoskeletal injections and resolve the clinical equipoise surrounding this question.

10) Key References

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