Title: The efficacy of ultrasound guided glenohumeral joint injections of platelet rich plasma (PRP) versus hyaluronic acid (HA) in the treatment of glenohumeral osteoarthritis: A randomized, double-blind control trial

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Condition or Intervention to be studied: Treatment of glenohumeral osteoarthritis (OA) with a single injection of hyaluronic acid (HA) or platelet-rich plasma (PRP).

Research questions/specific aims: This study aimed to determine whether HA or PRP can decrease pain, restore function, and improve disability in patients suffering from chronic glenohumeral OA (both primary and secondary) that is refractory to conservative management (including corticosteroid injections).

Hypothesis: PRP injections are more efficacious than HA injections in patients with chronic glenohumeral OA.

Primary outcome: Shoulder Pain and Disability Index (SPADI) score, assessed at baseline and up to 52 weeks post-injection

Secondary outcomes:

1. American Shoulder and Elbow Surgeons Society Standardized Shoulder Assessment Form (ASES; assessed at baseline and up to 52 weeks post-injection)
2. Current numerical rating scale pain score (assessed at baseline and up to 52 weeks post-injection)
3. Average numerical rating scale pain score (assessed at baseline and up to 52 weeks post-injection)
4. Patient satisfaction (assessed up to 52 weeks post-injection)
5. Side effects (assessed up to 52 weeks post-injection)

Background:

Shoulder pain is common, making up 16% of all musculoskeletal complaints,[1,2,3] with a lifetime prevalence as high as 50%.[4,5,6] It is second only to low back pain in musculoskeletal disorders that present to primary care physicians.[7,8] It has a high societal burden, contributing to decreased productivity and worker related disability,[4-6, 9-11] with direct costs of 7 billion US dollars reported in the year 2000.[3] The management and course of patients who present with shoulder pain to a primary care physician is concerning, with only 50% reporting full resolution in 6 months, increasing to only 60% after 1 year.[11-14] Causes of shoulder pain include glenohumeral osteoarthritis, subacromial bursitis, trauma, rotator cuff tear, instability, adhesive capsulitis, or labral pathology. Risk factors include advanced age, history of trauma or instability, rheumatoid arthritis, female sex, and occupations or sports involving repetitive movements of the upper extremity.

Glenohumeral OA involves degeneration of the glenoid and humeral articular surfaces, associated with osteophyte formation, subchondral bony changes, and synovitis.[15] It accounts for approximately 2-5% of all chronic shoulder pain and has an increased risk among the elderly,

patients with a history of glenohumeral subluxation, and those who participate in sports such as swimming, tennis, baseball, or volleyball.[3] It may be classified into primary and secondary forms. Primary glenohumeral OA causes include degenerative joint disease, inflammatory arthropathies such as rheumatoid arthritis, septic arthritis, rotator cuff tear arthropathy (CTA), and neuropathic arthropathy secondary to syringomyelia or diabetes.[16-18] Secondary causes include trauma, postoperative changes after arthroscopy or capsulography, and osteonecrosis due to underlying systemic problems such as chronic steroid or alcohol exposure.[16]

Hyaluronic acid (HA), or hyaluronate, is a high molecular weight glycosaminoglycan, found in synovial joint fluid, with viscoelastic, chondroprotective, and possible anti-inflammatory properties.[19] The purpose of injecting the substance intrarticularly is to promote endogenous hyaluronic acid growth and production, which in turn increases joint lubrication and thus, decreases mechanical stress of the affected joint.[20] Taken as a whole, a number of studies show that at least a total of 3 weekly HA injections to either the subacromial space or glenohumeral joint, when compared to no control group or placebo improved pain and range of motion for 3 to 6 months.[20-25] However, there continues to be inconsistency in the literature in terms of recruitment, sample size, injection technique, whether or not image guidance was used, and what type of hyaluronate was used.

Platelet rich plasma (PRP) injections involve the use of a patient's own platelets to take advantage of autologous blood growth factors present to promote tissue regeneration. It is more widely used for the treatment of tendinopathies and popular among injured athletes,[26] but is beginning to see potential use in the treatment of osteoarthritis.[27,28] Existing research has suggested benefit in pain related to knee and hip osteoarthritis, but limited to no data is available for its effect on chronic glenohumeral osteoarthritis (both primary and secondary).[29-32]

To our knowledge, no study in the literature has been conducted that compares the efficacy of ultrasound guided PRP and HA injections with ultrasound guidance in the treatment of chronic glenohumeral arthroses.

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Study design: Randomized controlled trial

Enrollment target: 70

Inclusion criteria:

1. English speaking/literate
2. Age 18-100 years
3. ≥5/10 visual analog scale pain as a direct result of primary or secondary glenohumeral OA
4. At least 3 months of pain after onset of symptoms that has failed conservative treatments, including corticosteroid steroid injection (must be 3 months after corticosteroid injection)
5. Pre-procedure imaging of the affected glenohumeral joint
6. Transient relief of symptoms after diagnostic intra-articular injection into the glenohumeral joint

Exclusion criteria:

1. Painful active, concurrent cervical spine conditions
2. Current NSAID use (can be held for study)
3. History of taking Coumadin or similar anticoagulant, have a known coagulopathy, bleeding dyscrasia, or platelet count <150,000/mm^3
4. Allergic reaction to poultry or previous viscosupplementation
5. Involved in workers' compensation or active litigation involving affected shoulder
6. Inability to refrain from NSAID use for 5 days prior to and 6 weeks after injection
7. History of corticosteroid injection to affected shoulder within the last 3 months
8. History of viscosupplementation or PRP to affected shoulder within the last 6 months
9. Presence of acute fracture
10. History of shoulder tumor
11. Known uncontrolled systematic illness (uncontrolled diabetes, HIV, vasculitis, autoimmune/inflammatory disease)
12. Psychiatric and somatoform disorders

Study procedures:

1. Patients will be randomized in a 1:1 fashion to the ultrasound-guided glenohumeral HA alone or PRP injection treatment group. Prior to injection, patients will be asked to discontinue any anti-inflammatory medications for 5 days prior to treatment.
    a. HA group will receive one 6 mL injection of low molecular weight (average 500,000-730,000 dalton) HA preparation, Hyalgan (Fidia Farmaceutici S.p.A., Abano Terme, Italy). Needle guidance and injection will be performed under ultrasound to the affected glenohumeral joint, posterior approach, by a fellowship-trained physician. The syringe will be covered with an opaque shield to blind both the patient and treating physician.
    b. PRP group will undergo the same above procedure as the HA group in respect to ultrasound guidance, anatomic approach, and double blinding. The Harvest Technologies Corporation (Plymouth, MA) SmartPReP Clear PRP preparation kit and machine will be used to prepare the samples in accordance with manufacturer

instructions. Venipuncture and blood collection, PRP centrifuge, final PRP preparation, and covering of the syringe with an opaque shield will be performed in a sterile manner by a trained study team member not involved in the direct care and management of the study subjects. Final PRP samples will aim to be leukocyte reduced. Prior to injection, each sample in the PRP group will be sent to the laboratory for hemoglobin / hematocrit, WBC, and platelet counts. 6 mL PRP will be injected.

2. In order to ensure that the treating physician is blinded to the treatment study subjects receive, the treating physician will perform ultrasound guidance and needle placement, but an Interventional Spine and Sports Medicine fellow or a Physiatry attending not involved in the study will prepare and perform the actual injection.
3. Post procedure:
    a. Patients will be instructed to take acetaminophen 500 mg every 6 hours (maximum of 3 gms) for pain relief as needed.
    b. Ice applied over the affected joint will not be allowed for 3 days and NSAIDs are to be avoided for at least 6 weeks after the intervention is performed due to their anti-inflammatory properties.
    c. Patients will be instructed to avoid taking baths and swimming in order to minimize risk of infection. Showers are allowed. Patients can continue their usual activities of daily living, as tolerated.
    d. Follow-up questionnaires will be administered at 1, 2, 3, 6, and 12 months post-injection.

Sample size analysis and statistical analysis plan:

Proposed analysis: Two-way repeated measures ANOVA
Alpha level: 0.05
Beta or power level: 0.861
Primary outcome variable estimate: SPADI
Number of groups being compared: 2
Effect size or change expected between groups: 10-point change (±15)
Resulting number per group: 30
Total sample size required: 70

Descriptive analyses of the patient population will include reporting means (with standard deviations) for continuous variables and frequencies (with percentages) for discrete variables. Prior to initiation of inferential analyses, data will be evaluated for completeness and, for continuous measures, normality. Comparative differences between the study groups will be evaluated using independent samples t-test for continuous variables and chi-square/Fisher's exact test for categorical variables. This will include comparisons of patient characteristics as well as baseline patient reported outcomes and all range of motion measures. Factors that do not meet the assumption of normality will be analyzed using the non-parametric equivalents.

The primary outcome in this study is the total SPADI score and the longitudinal assessment of that score over four follow-up time points after baseline. A systematic review by Roy et al

(Arthritis Rheum, 2009) found that the minimal clinical important difference (MCID) for patients with general shoulder pain ranged between 8 and 13 points. Williams et al. (J Rheumatol, 1995) found that changes in the SPADI score between +10 and -10 points were not able to distinguish between shoulder patients whose condition improved, remained the same, or worsened. In a similarly designed study looking at the effect of intra-articular corticosteroids and supervised physiotherapy, Carette et al. (Arthritis & Rheumatism, 2003) used a 10-point change as their MCID. Given those estimates, we calculated our sample size based on the ability to detect a similar 10-point change between treatment groups in the total SPADI scores.

Group sample sizes of 25 patients in each treatment group of the study will achieve 86% power to detect an MCID of 10 points in the total SPADI score between groups with an estimated standard deviation of ±15 points in a two-way repeated measures ANOVA design with statistical significance set to alpha equal to 0.05. To adjust for any loss of patients due to early withdrawal, we will increase our sample size by 20% for group sample sizes of 30 and a total sample size of 70 patients. All analyses will be based on an intent-to-treat model, and any missing data will be imputed using a last observation carried forward methodology. Mixed models will also be generated to adjust for any effects of potential confounding from age, sex, and other factors. Longitudinal assessment of the other patient reported outcomes will also be evaluated using similar statistical models.