



Comparison of Pain Relief and Functional Improvement in Landmark vs Ultrasound-Guided Corticosteroid Injections for Adhesive Capsulitis: A Prospective Study

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Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

Date: 1 February 2018

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Scholarly Report Title: Comparison of Pain Relief and Functional Improvement in Landmark vs Ultrasound-Guided Corticosteroid Injections for Adhesive Capsulitis: A Prospective Study

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Comparison of Pain Relief and Functional Improvement in Landmark vs Ultrasound-Guided Corticosteroid Injections for Adhesive Capsulitis: A Prospective Study

Ryan C. Xiao, Arun J. Ramappa

Purpose: Corticosteroid injections are commonly prescribed to treat adhesive capsulitis. It is currently unclear whether an ultrasound-guided injection relieves the symptoms of shoulder pain more effectively than if the injection was delivered landmark-guided or 'blind', i.e., without imaging. This study aims to address these uncertainties, and we propose conducting a randomized study on patients with adhesive capsulitis to determine if there is a significant difference in pain relief, function, and range of motion between patients treated via landmark-guided and ultrasound-guided corticosteroid injections at 12 weeks after injection.

Methods: A total of 23 patients with adhesive capsulitis were randomized to receive either a landmark or ultrasound-guided intra-articular corticosteroid injection. The study was powered for an effect size of 1.0. Patients with pain lasting longer than three months duration that is consistent with adhesive capsulitis were eligible to participate. Patients were randomized to receive an intra-articular corticosteroid injection into the affected shoulder via a landmark-guided injection or an injection delivered via ultrasound guidance. Pain, function, and range of motion were assessed at baseline visits and at 6 week and 12 week follow-up appointments.

Results: A total of 23 patients were randomized (10 landmark and 13 ultrasound) into the study. There were no significant differences in patient demographics. No significant differences between treatment groups were found in mean VAS pain, SANE function scores, forward flexion or external rotation range of motion measurements at 6 or 12 weeks. The ultrasound group demonstrated statistically significant improvement in shoulder abduction at 6 weeks compared to the landmark group but there were no significant differences in abduction at 12 weeks between the groups. Within each group, there were statistically significant improvements in pain and function at 6 weeks and at 12 weeks compared to baseline. The landmark group demonstrated significant improvement in forward flexion and abduction at 12 weeks compared to baseline. The ultrasound group demonstrated significant improvement in forward flexion, external rotation, and abduction at both 6 and 12 weeks.

Conclusions: The study was powered for an effect size of greater than or equal to 1.0 and differences less than such may not be detected. Knowing this caveat, the preliminary data suggests that patient outcomes for pain, function, and range of motion improve with glenohumeral corticosteroid injection but that modality chosen (ultrasound or landmark guidance) does not impact the efficacy of injection.

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GLOSSARY OF ABBREVIATIONS

US - Ultrasound – US

AC - Adhesive Capsulitis

ROM – Range of Motion

FF – forward flexion

ER – external rotation

AB – abduction

VAS - Visual Analog Scale

SANE - Single Assessment Numeric Evaluation

INTRODUCTION

Adhesive capsulitis is a common, painful condition of the shoulder that results in gradual loss of passive and active ranges of motion. Though typically self-limiting, symptoms may persist for years. Pain and limitation can persist over 7 years in extreme cases (1, 2, 3). Up to 10 percent of patients never fully regain range of motion in the afflicted shoulder (4). Though typically self-limiting, the disorder remains poorly understood (4). Reflected in the multitude of names for adhesive capsulitis (periarthritis, frozen shoulder), the body of literature on adhesive capsulitis is often conflicting and uncertain regarding etiology, disease course, and effective treatment options. The variability in duration of and uncertainty of recovery from adhesive capsulitis reveals the need for effective treatment options.

Treatment for adhesive capsulitis includes conservative treatment with NSAIDs and physical therapy as well as corticosteroid injections in the intra-articular space. Prospective studies have shown both short- and long-term improvement in pain, function and range of motion in patients following corticosteroid injections (5, 6, 7). Injecting corticosteroids in the intra-articular space can be performed either blindly, using landmark palpation, or guided by ultrasonography (8, 9).

Our study will build on the existing body of literature concerning ultrasound-guided vs landmark-guided injections in the treatment of shoulder disorders, which remains inconclusive whether ultrasound-guided injections significantly improve patient results, particularly for patients with adhesive capsulitis. As posited by Xiao et al (10), without more research, insufficient evidence exists to validate treating adhesive capsulitis with image-guided injections over blind, landmark-guided injections.

There have been several prospective studies in recent years that have examined the accuracy and efficacy of blind and guided corticosteroid injections for shoulder pain (11, 12, 13, 14, 15, 16). These studies have reported conflicting evidence for the efficacy of blind vs guided injections, with one meta-analysis determining that guided injections provide superior accuracy (16) while other studies reported no significant difference in accuracy between guided and blind injections (12,13). One study determined that accurate injections provided greater pain relief than inaccurate injections (14) while another came to the opposite conclusion, demonstrating that equal pain relief was provided regardless of the accuracy of injection (15).

Given the uncertainties regarding accuracy and efficacy, our study will examine patient outcomes without addressing the question of accuracy of injection. The proposed study examines the impact on pain, function, and range of motion in ultrasound-guided vs landmark-guided corticosteroid injections for the treatment of adhesive capsulitis. The proposed study differs from previous studies in that it will examine the impact of corticosteroids alone in treating adhesive

capsulitis. The few studies that have examined injection approach (image-guided vs blind) in the treatment of adhesive capsulitis have either examined corticosteroids with follow-up injections of hyaluronate (8) or did not examine adhesive capsulitis alone (9).

STUDENT ROLE

My role in this project has been two-fold. First, I undertook a literature synthesis of non-operative treatments for adhesive capsulitis, focusing on corticosteroid injections, and produced two first author publications detailing the rationale for the current randomized trial.

- The first publication provides a systematic review of corticosteroid injections for adhesive capsulitis:
 - o Xiao R, Walley KC, DeAngelis J, Ramappa A. Corticosteroid Injections for Adhesive Capsulitis: A Review. *Clin J Sport Med*. 2017 May;27(3):308-320.
- The second publication discusses non-operative management of adhesive capsulitis:
 - o Xiao R, DeAngelis J, Smith C, Ramappa A. Evaluating non-operative treatments for adhesive capsulitis. *J Surg Orthop Adv*. Accepted. 2016 Jul.

Second, I designed and implemented a prospective, randomized study comparing the efficacies of ultrasound-guided vs landmark-guided corticosteroid injections for adhesive capsulitis. I wrote the IRB, worked with Dr. Ramappa to develop a logistical plan for seeing and enrolling patients, and have been enrolling patients in the orthopedic clinic for the study since 2015. With assistance from Dr. Zurakowski at Boston Children's Hospital, I have performed the data analysis for the study.

METHODS

Study design and methods:

The study was designed as a prospective, randomized trial. Patients with pain lasting longer than three months duration that is consistent with adhesive capsulitis were eligible to participate. For the purposes of this study, adhesive capsulitis was defined by the subject selection criteria below and assessed by an orthopedic surgeon involved with the study.

Patients who give informed consent were randomized into one of two treatment groups. The patient inclusion process and follow-up from the study is illustrated in the consort diagram (Figure 1). The randomization was performed according to a computer-based random number generator:

- Patients in Group 1 received an intra-articular corticosteroid injection into the affected shoulder via blind, landmark injections by Dr. Ramappa and Dr. DeAngelis.
- Patients in Group 2 received an intra-articular corticosteroid injection into the affected shoulder via ultra-sound guided injections in the radiology department by Dr. McMahon and Dr. Wu.

Following injection, all patients followed a standardized program of physical therapy that targeted the following: range of motion with shoulder shrugs, retraction, pendulum exercises, etc; flexibility with stretching exercises targeting the anterior and posterior shoulder and cane stretching to assist with forward elevation and external rotation; and finally strengthening exercises that focus on the rotator cuff and scapular stabilizers. The physical therapy program was based on a previously published evidence-based rehabilitation protocol (17). Local centers were provided a copy of this protocol for use with patients enrolled in the study.

Pain and function were evaluated using the Visual Analog Scale (VAS) and the Single Assessment Numeric Evaluation (SANE) respectively. The VAS asks the patient to rate his or her shoulder pain on a scale of 0 to 10, with 0 being no pain and 10 being the worst pain imaginable. The SANE asks patients to evaluate their shoulder function on a scale of 0 to 10, with 10 being the best outcome (18). Patients were also evaluated based on range of motion (ROM) including forward elevation, external rotation and internal rotation. ROM was assessed at each visit by study staff using a goniometer. VAS, SANE, and ROM were assessed at baseline and at patient follow up visits at 6 and 12 weeks post-injection. The follow up exams at these visits included a physical exam to check for signs of muscle atrophy and local tenderness

Subject Selection:

Patients that present to one of the study physicians and satisfy all of the inclusion and exclusion criteria were invited to enroll in the study. The enrolling physician emphasized that participation is voluntary. The study was described in detail and informed consent obtained. Subjects did not receive remuneration for their participation. All adult patients who satisfied the

inclusion/exclusion criteria were eligible for enrollment in this study regardless of sex, race or ethnicity. Vulnerable populations were not recruited.

Inclusion Criteria:

1. Adhesive capsulitis defined by the inability to passively abduct the shoulder to 90 degrees with scapular stabilization
2. Age over 18 years
3. Self-reported pain and/or stiffness in shoulder for 3 or more months

Exclusion Criteria:

4. Prior corticosteroid injection in the affected shoulder
5. Previous diagnosis of calcific tendonitis or evidence of calcific tendonitis on x-ray
6. A previous diagnosis of cervical radiculopathy or the presence of one or more of the following signs on physical exam: Spurling's sign, neck pain, radiating arm pain or numbness, sensory deficits, motor dysfunction in the neck and upper extremities
7. A reason to suspect a full thickness rotator cuff tear including evidence of a full thickness tear on MRI, weakness of arm elevation, a positive "drop arm sign," or a high-riding humerus visible on the shoulder x-ray
8. Radiographic evidence of Os Acromiale

IRB/ Ethical Considerations:

All data was stored in the Department of Orthopaedic Surgery at BIDMC. Study data was maintained in a locked filing cabinet and on password protected computers. The only identifiers or personal information included were name and medical record number. We obtained IRB approval from the BIDMC Committee on Clinical Investigation.

Data Analysis and Biostatistical Methods:

The primary outcome variable was the VAS. Power calculations indicated that a total sample size of 34 patients will provide 80% power to detect an average difference of 2 points or greater in VAS pain scores between US and Landmark methods in placing the needle for steroid injection at each time point using a Student t-test assuming a pooled standard deviation of 2 points (i.e., effect size: $2/2 = 1.0$). Therefore, we planned to enroll a total of 40 patients (20 randomized to each group) to ensure that we have sufficient power accounting for a possible loss to follow-up of 15%. Sample size requirements were determined using nQuery Advisor version 7.0 (Statistical

Solutions, Saugus, MA). Analysis of the data included Student t-tests to assess US versus Landmark differences in VAS scores at baseline and each assessment point as well as repeated-measures ANOVA to evaluate changes over time in pain scores. Statistical analysis was conducted using IBM SPSS software (version 22.0, IBM, Armonk, NY) with two-tailed values of $p < 0.05$ considered statistically significant.

The secondary outcome variables were the improvement in functional status as assessed by the SANE score and range of motion following corticosteroid injections. Because measurements for ROM do not follow a bell-shaped curve, the US + landmark groups will be compared using a Mann-Whitney U Test at the different time points. These sample sizes will provide 80% power for capturing differences in ROM of 15%.

We used a mixed effects regression model with a generalized estimating equations (GEE) strategy to incorporate the two patient time points for pain and ROM and also allow incorporation and adjustment for the provider effect in the mixed effects modeling. GEE allowed estimation of treatment effects while simultaneously handling patients clustered within a provider thus accommodating two features of the data, treatment effect on pain and ROM and well as correlated data within patients to handle both the multiple time points within the same patient and the provider effect.

David Zurakowski from Boston Children's Hospital was our statistical consultant. A limited data set was sent to David Zurakowski, Ph.D., for statistical analysis.

RESULTS

Demographics

The 23 patients analyzed in the preliminary dataset were randomized into group 1 (landmark) (n=10) and group 2 (ultrasound) (n=13). As demonstrated in Table 1, there were no significant differences in mean age (55.1 vs 56.6), BMI (31.0 vs 29.3), % Caucasian (70 vs 92), % African American (30 vs 8), % Hispanic (0 vs 15), % female (60 vs 39), and % diabetic (0 vs 15) between landmark and ultrasound groups respectively.

Impact on VAS Pain Scores

As seen in Figure 2 and Table 2, mean VAS pain scores at initial visit were not statistically significant between the landmark and ultrasound groups. Statistically significant improvement in VAS pain scores were seen in both landmark-guide and ultrasound-guided injection groups at 6 week and 12 week follow-up visits. The landmark group improved from a mean score of 6.0 at initial visit to a mean of 1.5 at both 6 week and 12 week follow-up visits. The ultrasound group improved from a mean score of 4.7 at initial measurement to 1.5 at the 6 week follow-up and 1.2 at the 12 week follow-up visit. No significant difference between landmark and ultrasound groups was noted at the 6 or 12 week follow-up appointments.

Impact on SANE Function Scores

Mean SANE function scores, demonstrated in Figure 3 and Table 3, did not significantly differ between the treatment groups at initial, 6 week, or 12 week follow-up measurements. Both groups demonstrated statistically significant improvement in mean SANE scores between initial measurement and measurements at both 6 and 12 weeks. The landmark-guided injection group improved from a mean SANE of 34 at initial measurement to 75 at 6 weeks and 85.7 at 12 weeks. The ultrasound-guided injection group improved from a mean SANE of 46.1 at initial measurement to 75.8 at 6 weeks and 81.3 at 12 weeks.

Impact on ROM measurements in forward flexion, external rotation, and abduction

Figure 4 and Table 4 compare ROM between landmark and ultrasound groups. In regards to degree of shoulder forward flexion, no significant difference was noted between groups at initial visit, 6 week follow-up, or 12 week follow-up. The landmark group demonstrated statistically significant improvement at 12 weeks but not at the 6 week visit. The landmark group improved from 128.5 at initial visit to 141.7 at 6 weeks and to 173.3 at 12 weeks. The ultrasound group demonstrated statistically significant improvement at both 6 week and 12 week visits. The ultrasound group improved from 126.5 at initial visit to 168.3 at 6 weeks and 173.5 at 12 weeks.

For shoulder external rotation measurements, there was no significant difference found between groups at initial, 6 week, and 12 week visits. However, the landmark group failed to demonstrate

a statistically significant improvement at either 6 week or 12 week follow-up while the ultrasound group showed statistically significant improvement at both 6 week and 12 week follow-up visits. The landmark group improved from mean shoulder external rotation of 15 degrees to 29.3 at 6 weeks and then decreased to 22.3 at 12 weeks. The ultrasound group improved from mean shoulder external rotation of 8.2 degrees at initial visit to 28.3 degrees at 6 weeks and 36.5 degrees at 12 weeks.

The degree of shoulder abduction did not differ significantly between groups at initial or 12 week visits but did demonstrate a statistically significant difference in favor of the ultrasound group at 6 week measurements. The landmark group did not demonstrate a significant improvement from baseline at the 6 week follow-up but did have statistically significant improvement at 12 weeks. The landmark group improved from a mean of 65 degrees shoulder abduction at initial measurement to 80 degrees at 6 weeks and 97.5 at 12 weeks. The ultrasound group demonstrated statistically significant improvement from baseline at both 6 and 12 week follow-up visits. The ultrasound group improved from a mean of 70.8 degrees at baseline to 93.6 at 6 weeks and 96.0 degrees at 12 weeks.

DISCUSSION

On the whole, our study demonstrated no significant difference in the ability of ultrasound-guided vs landmark-guided corticosteroid injections into the glenohumeral joint to improve patient self-reported pain and function or clinician-measured range of motion in shoulder forward flexion, external rotation, or abduction. The lone time point demonstrating significant difference between the treatment groups, favoring ultrasound over landmark in regards to shoulder abduction at 6 weeks post-injection as seen in Table 4, is more likely due to the difference in sample size between the two groups at that measurement (ultrasound with 12 patients and landmark with 7) rather than a true difference in efficacy between the treatment groups.

As supported by the orthopedic literature (5, 7, 8, 19, 20, 21, 22), our study found that corticosteroid injections into the glenohumeral joint provided significant pain relief, functional improvement, and increased range of motion whether delivered via landmark or ultrasound guidance. Corticosteroid injections into the glenohumeral joint remain a mainstay in non-operative management of adhesive capsulitis and are believed to be most effective in the early inflammatory stages of the disease. Though the exact pathophysiology leading to adhesive capsulitis remains unclear, it has been hypothesized that the process begins with inflammation and later transitions into fibrosis, thereby leading to the symptomatic progression from shoulder pain to shoulder stiffness (23).

Our results are consistent with those of a prior randomized controlled trial by Lee et al examining landmark-guided vs ultrasound-guided intra-articular injections for adhesive capsulitis (8). In their study, Lee et al randomized a total of 43 patients (21 landmark, 22 ultrasound) and examined pain, function, and range of motion (forward flexion, external rotation, abduction, internal rotation) at one week intervals up to 6 weeks. Though the injection protocol by Lee et al included weekly injections of hyaluronate injections (5 total) in addition to a corticosteroid injection and therefore differs significantly from our injection protocol, our study similarly found no significant difference in pain, function, or range of motion between ultrasound-guided and landmark-guided injections past 6 weeks. Lee et al found that the ultrasound-guided injection group had statistically significant improvement in pain scores at weeks 1 and 2, in the functional at weeks 1-3, improved forward flexion at weeks 1 and 3, improved abduction at week 2, and improved internal rotation at week 4. They did not find any statistical difference between the two treatment groups at the 5 or 6 week follow-up visit in any pain, function, or range of motion metrics. Though Lee et al concluded that ultrasound may be beneficial in the first few weeks post-injection, the clinical significance of this early benefit remains unclear, especially since the data at their 5 and 6 week follow-up visits suggests that using ultrasound-guided injections does not shorten the course of disease compared with landmark-guided injections as there was no statistically significant differences in pain, function, or range of motion between treatment groups after the 4 week time point.

In contrast, a study by Ucuncu et al examined ultrasound-guided vs landmark-guided injections for treatment of shoulder pain pathologies and noted that patients injected under ultrasound guidance had significantly improved pain and functional outcomes compared with patients injected via landmark guidance at 6 week follow-up (9). Differences in patient population and injection location may explain the discrepancy between our observed data and that found in the Ucuncu et al study. The Ucuncu patient demographics include a broad category of shoulder pain including rotator cuff tears, impingement, and acromioclavicular degeneration whereas our study examines patients with adhesive capsulitis alone. Secondly, the Ucuncu study utilized injections in the subacromial space whereas our study injected into the glenohumeral joint.

To our knowledge, this is the only study to date that has examined the impact of an intra-articular corticosteroid injection delivered via landmark or ultrasound guidance for treatment of patients with adhesive capsulitis. Continued patient enrollment and follow-up data from the on-going study will provide an increased ability to discern statistically significant differences between treatment groups.

Study Limitations

This study has several limitations. First, given the natural disease history of adhesive capsulitis as averaging 12-15 months, our last patient follow-up at 3 months may not adequately capture patient outcomes for the entire duration of the disease and may not provide enough data points to discern whether injection technique shortens the disease course. Second, variable adherence to physical therapy protocols could confound the effect of the corticosteroid injection. A recent review by Xiao et al suggests that physical therapy protocols that encouraged patients to push past their pain threshold produced worse ROM and functional outcomes compared to protocols that did not, highlighting the impact of physical therapy and inflammation in the resolution of adhesive capsulitis (24). Third, at only 23 patients and only 2 diabetic patients our sample size and demographic distribution may not accurately represent all adhesive capsulitis patients and may therefore limit generalizability of study results. Diabetics are two to four times more likely to experience adhesive capsulitis and tend to experience less improvement following a corticosteroid injection (24). Fourth, the results of our study may not be generalizable to providers with less experience performing corticosteroid injections or ultrasound-guided corticosteroid injections. Fifth, the study is limited in its lack of patient and provider blinding. Patients may have a placebo effect related to use of ultrasound, and physicians who are performing range of motion outcome assessments are the same physicians performing the procedures. Sixth, this study examines the clinical outcomes of ultrasound-guided and landmark guided corticosteroid injections but makes no attempt to characterize the interaction between accuracy of glenohumeral injection and clinical outcomes. Most importantly, the study was powered for an effect size of 1.0 so smaller differences between treatment modalities would likely go undetected. While the clinical significance of changes less than 1 standard deviation remains unclear, at 23 patients in the current data the study remains underpowered and at risk of missing potentially significant differences between landmark-guided and ultrasound-guided injections.

Future Directions

Future work in the field can consider injecting a mix of corticosteroid and contrast dye in order to visualize the accuracy of injection and allow analysis regarding the impact of accuracy of injection on clinical outcomes following injection.

ACKNOWLEDGMENTS

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REFERENCES

- 1) Neviaser AS, Hannafin JA. Adhesive Capsulitis: A Review of Current Treatment. *Am J Sports Med.* 2010; 38(11):2346-56
- 2) Vastamäki H, Kettunen J, Vastamäki M. The Natural History of Idiopathic Frozen Shoulder. *Clin Orthop Relat Res.* 2012; 470(4):1133-43.
- 3) Hand C, et al. Long Term Outcome of Frozen Shoulder. *J Shoulder Elbow Surg.* 2008;17(2):231-6
- 4) Ewald A. Adhesive Capsulitis: A Review. *Am Fam Physician.* 2011; 83(4):417-22
- 5) Shin SJ, Lee SY. Efficacies of corticosteroid injection at different sites of the shoulder for the treatment of adhesive capsulitis. *J Shoulder Elbow Surg.* 2013;22(4):521-7
- 6) Yoon SH, et al. Optimal Dose of Intra-articular Corticosteroids for Adhesive Capsulitis. *Am J Sports Med.* 2013;41(5):1133-9
- 7) Ryans I, et al. A randomized controlled trial of intra-articular triamcinolone and /or physiotherapy in shoulder capsulitis. *Rheumatology (Oxford).* 2005;44(4):529-35
- 8) Lee HJ, et al. Randomized Controlled Trial for Efficacy of Intra-Articular Injection for Adhesive Capsulitis: Ultrasonography-Guided Versus Blind Technique. *Arch Phys Med Rehabil.* 2009;90(12):1997-2002.
- 9) Ucuncu F, et al. A Comparison of the Effectiveness of Landmark-guided Injections and Ultrasonography Guided Injections for Shoulder Pain. *Clin J Pain.* 2009; 25(9):786-9.
- 10) Xiao R, Walley KC, DeAngelis J, Ramappa A. Corticosteroid Injections for Adhesive Capsulitis: A Review. *Clin J Sport Med.* 2017 May;27(3):308-320
- 11) Hseih LF, et al. Is Ultrasound-Guided Injection More Effective in Chronic Subacromial Bursitis?. *Med Sci Sports Exerc.* 2013; 45(12):2205-13
- 12) Dogu B, et al. Blind or Ultrasound-Guided Corticosteroid Injections and Short-Term Response in Subacromial Impingement Syndrome: A Randomized, Double-Blind, Prospective Study. *Am J Phys Med Rehabil.* 2012; 91(8):658-65.
- 13) Rutten MJ, et al. Injection of the subacromial-subdeltoid bursa: blind or ultrasound-guided?. *Acta Orthop.* 2007; 78(2):254-7.
- 14) Eustace Ja, et al. Comparison of the accuracy of steroid placement with clinical outcome in patients with shoulder symptoms. *Ann Rheum Dis.* 1997; 56(1):59-63.
- 15) Kang MN, et al. The accuracy of subacromial corticosteroid injections: A comparison of multiple methods. *J Shoulder Elbow Surg.* 2008; 17(1 Suppl):61S-66S.
- 16) Aly AR, et al. Ultrasound-guided shoulder girdle injections are more accurate and more effective than landmark-guided injections: a systematic review and meta-analysis. *Br J Sports Med.* 2014 [Epub ahead of print]
- 17) Kuhn J E. Exercise in the treatment of rotator cuff impingement: a systematic review and a synthesized evidence-based rehabilitation protocol. *J Shoulder Elbow Surg* 2009; 18(1): 138-160.
- 18) Smith MV, et al. Upper Extremity-Specific Measures of Disability and Outcomes in Orthopaedic Surgery. *J Bone Joint Surg Am.* 2012; 94(3):277-285.
- 19) Bal A, Eksioğlu E, Gulec B, et al. Effectiveness of corticosteroid injection in adhesive capsulitis. *Clinical Rehabilitation.* 2008; 22:503-512
- 20) Bulgen DY, Binder AI, Hazleman BL et al. Frozen shoulder: prospective clinical study with an evaluation of three treatment regimens. *Ann Rheum Dis.* 1984 Jun;43(3):353-60
- 21) Carrette S, Moffet H, Tardif J et al. Intraarticular corticosteroids, supervised physiotherapy, or a combination of the two in the treatment of adhesive capsulitis of the shoulder. *Arthritis Rheum.* 2003 Mar;48(3):829-38

- 22)** Ryans I, Montgomery A, Galway R et al. A randomized controlled trial of intra-articular triamcinolone and/or physiotherapy in shoulder capsulitis. *Rheumatology (Oxford)*. 2005 Apr;44(4):529-35
- 23)** Hand GC, Athanasou NA, Matthews T, Carr AJ. The pathology of frozen shoulder. *J Bone Joint Surg Br*. 2007 Jul;89(7):928-32.
- 24)** Xiao R, DeAngelis J, Smith C, Ramappa A. Evaluating non-operative treatments for adhesive capsulitis. *J Surg Orthop Adv*. Accepted. 2016 Jul.

TABLES AND FIGURES

Figure 1: CONSORT Diagram illustrating randomization, follow-up, and analysis of study patients

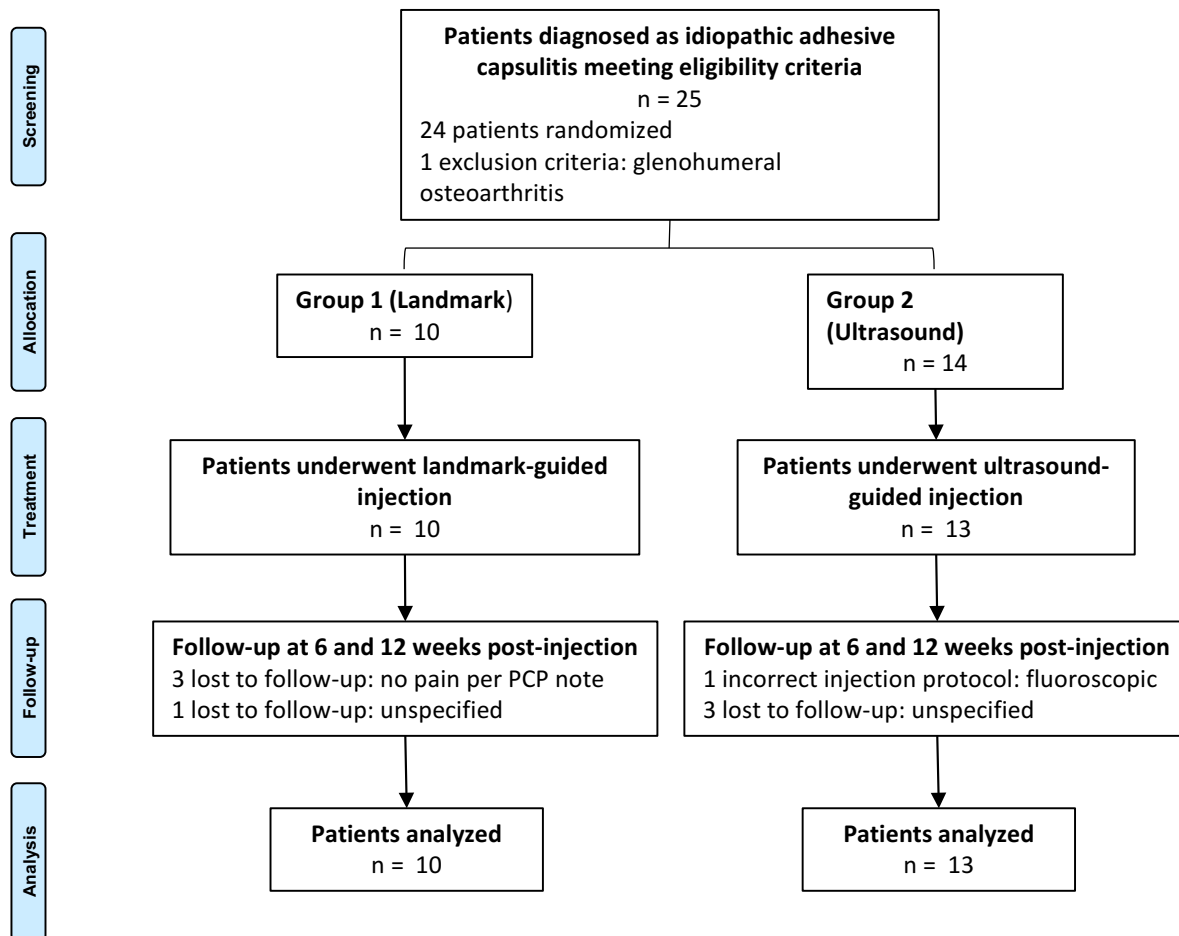


Table 1: Baseline characteristics of patients with adhesive capsulitis in the landmark-guided and ultrasound-guided corticosteroid injection groups.

| Characteristics | Group 1: Landmark | Group 2: Ultrasound | P |
|------------------------|--------------------------|----------------------------|----------|
| | n = 10 | n = 13 | |
| Age | 55.1 (5.5) | 56.6 (7.9) | 0.612 |
| BMI | 31.0 (4.7) | 29.3 (5.7) | 0.449 |
| % Caucasian | 70 | 92 | 0.281 |
| % African American | 30 | 8 | 0.281 |
| % Hispanic | 0 | 15 | 0.486 |
| % Female | 60 | 39 | 0.414 |
| % Diabetic | 0 | 15 | 0.486 |

* Values, except where indicated otherwise, are mean with standard deviation in parenthesis

Table 2: Mean values of change from baseline in VAS pain scores in treatment groups at 6 and 12 weeks after glenohumeral corticosteroid injection.

| <u>Group 1: Landmark</u> | | | <u>Group 2: Ultrasound</u> | | | |
|---------------------------------|-------------|----------------------|-----------------------------------|-------------|----------------------|----------------------|
| Time | Mean | P^a | Time | Mean | P^a | P^b |
| Initial (n=10) | 6.0 (2.8) | — | Initial (n=13) | 4.7 (2.2) | — | 0.243 |
| 6 wk (n=7) | 1.5 (1.4) | 0.002* | 6 wk (n=12) | 1.5 (1.9) | 0.007* | 0.961 |
| 12 wk (n=6) | 1.5 (2.3) | 0.006* | 12 wk (n=10) | 1.2 (1.7) | 0.004* | 0.770 |

- Values, except where indicated otherwise, represent mean with standard deviation in parenthesis
- * indicates P <0.05
- P^a values represent comparison of initial measurements with measurements at time of follow-up within each group
- P^b values represent comparison of measurements at each time point between groups

Figure 2: Mean values of change from baseline in VAS pain scores in treatment groups at 6 and 12 weeks after glenohumeral corticosteroid injection.

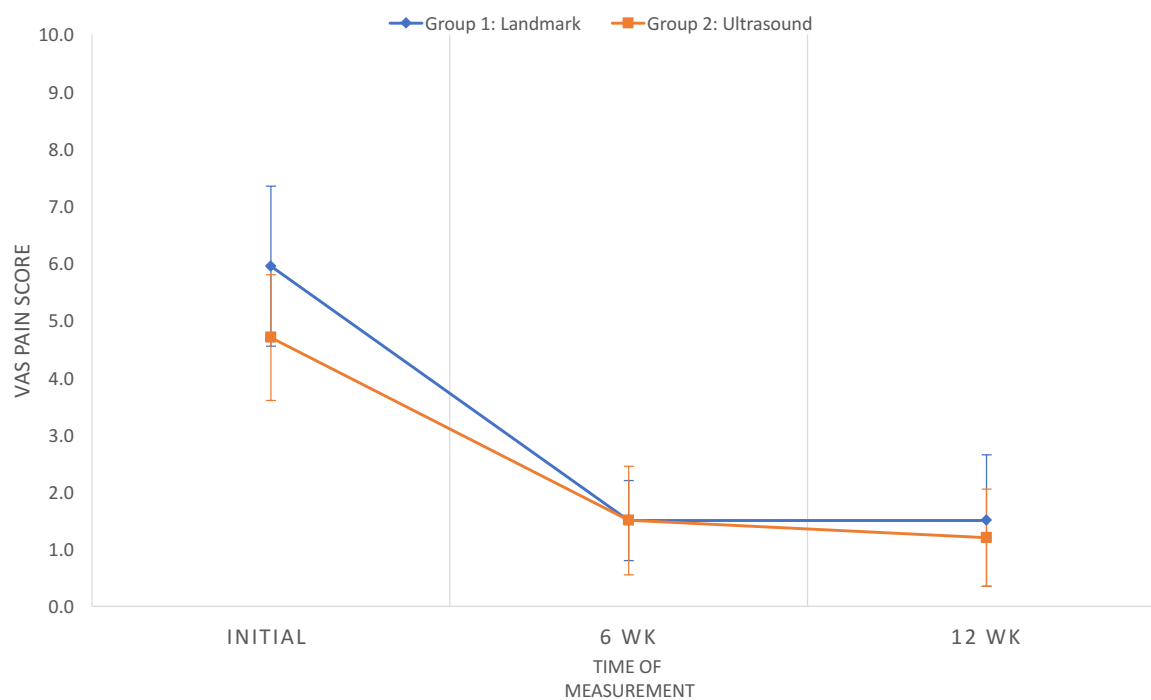


Table 3: Mean values of change from baseline in SANE function scores in treatment groups at 6 and 12 weeks after glenohumeral corticosteroid injection.

| <u>Group 1: Landmark</u> | | | <u>Group 2: Ultrasound</u> | | | p^b |
|--------------------------|-------------|----------------------|----------------------------|-------------|----------------------|----------------------|
| Time | Mean | P^a | Time | Mean | P^a | |
| Initial (n=10) | 34 (16.5) | — | Initial (n=13) | 46.1 (20.1) | — | 0.145 |
| 6 wk (n=7) | 75 (10) | < 0.001* | 6 wk (n=12) | 75.8 (11.7) | <0.001* | 0.618 |
| 12 wk (n=6) | 85.7 (17.8) | <0.001* | 12 wk (n=10) | 81.3 (17.9) | <0.001* | 0.643 |

- Values, except where indicated otherwise, represent mean with standard deviation in parenthesis
- * indicates P < 0.05
- P^a values represent comparison of initial measurements with measurements at time of follow-up within each group
- P^b values represent comparison of measurements at each time point between groups

Figure 3: Mean values of change from baseline in SANE function scores in treatment groups at 6 and 12 weeks after glenohumeral corticosteroid injection.

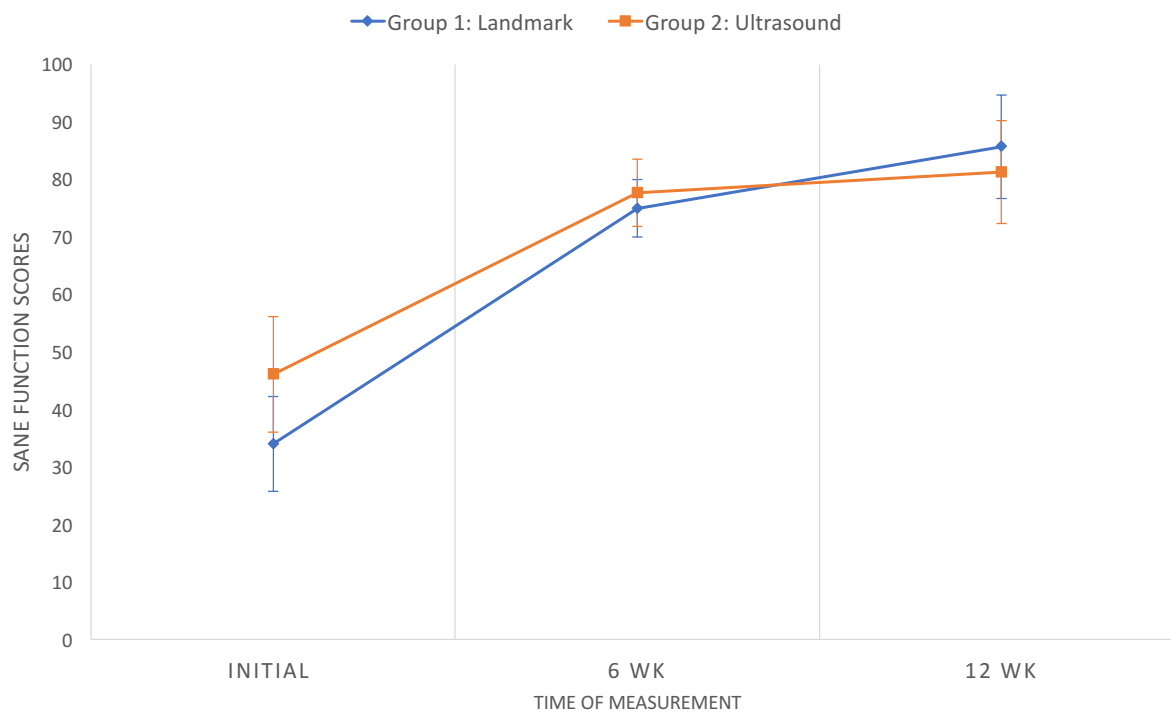


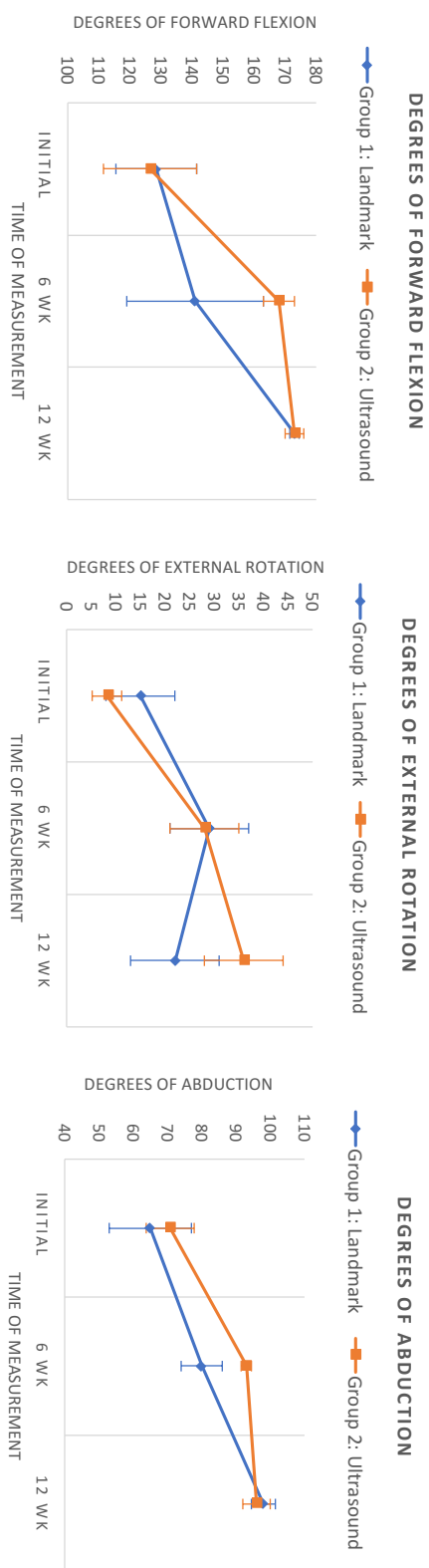
Table 4: Mean values of change from baseline in ROM measurements (forward flexion, external rotation, abduction) in treatment groups at 6 and 12 weeks after glenohumeral corticosteroid injection.

| <u>Group 1: Landmark</u> | | | <u>Group 2: Ultrasound</u> | | | |
|--------------------------|--------------|----------------------|----------------------------|--------------|----------------------|----------------------|
| Degrees of FF | | | | | | |
| Time | Mean | P^a | Time | Mean | P^a | P^b |
| Initial (n=10) | 128.5 (27.4) | — | Initial (n=13) | 126.5 (30.2) | — | 0.976 |
| 6 wk (n=7) | 141.7 (45.4) | 0.211 | 6 wk (n=12) | 168.3 (9.9) | <0.001* | 0.263 |
| 12 wk (n=6) | 173.3 (2.6) | 0.001* | 12 wk (n=10) | 173.5 (5.8) | <0.001* | 0.873 |
| Degrees of ER | | | | | | |
| Time | Mean | P^a | Time | Mean | P^a | P^b |
| Initial (n=10) | 15.0 (15.5) | — | Initial (n=13) | 8.2 (7.2) | — | 0.352 |
| 6 wk (n=7) | 29.3 (16.4) | 0.435 | 6 wk (n=12) | 28.3 (14.8) | 0.001* | 0.764 |
| 12 wk (n=6) | 22.3 (18.1) | 0.159 | 12 wk (n=10) | 36.5 (15.6) | <0.001* | 0.159 |
| Degrees of AB | | | | | | |
| Time | Mean | P^a | Time | Mean | P^a | P^b |
| Initial (n=10) | 65.0 (24.6) | — | Initial (n=13) | 70.8 (13.7) | — | 0.849 |
| 6 wk (n=7) | 80.0 (11.9) | 0.242 | 6 wk (n=12) | 93.6 (3.2) | <0.001* | 0.009* |
| 12 wk (n=6) | 97.5 (6.9) | 0.002* | 12 wk (n=10) | 96 (7.8) | <0.001* | 0.787 |

- Values, except where indicated otherwise, represent mean with standard deviation in parenthesis
- * indicates P <0.05
- P^a values represent comparison of initial measurements with measurements at time of follow-up within each group
- P^b values represent comparison of measurements at each time point between groups

FF = forward flexion
ER = external rotation
AB = abduction

Figure 4: Mean values of change from baseline in ROM measurements (forward flexion, external rotation, abduction) in treatment groups at 6 and 12 weeks after glenohumeral corticosteroid injection.



APPENDIX A**Corticosteroid Injections for Adhesive Capsulitis: A Review**

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Objective:

Adhesive capsulitis is a self-limiting condition in a majority of patients and is often treated non-operatively. However, symptoms may take 2-3 years to resolve fully. A small, but significant, portion of patients requires surgical intervention. The purpose of this systematic review is to evaluate the efficacy of corticosteroid injections for the treatment of adhesive capsulitis.

Data Sources:

A review of articles indexed by the United States National Library of Medicine was conducted by querying the PubMed database for studies involving participants with adhesive capsulitis, frozen shoulder, stiff shoulder, or painful shoulder. Articles that included corticosteroids, glucocorticoids, steroids, and injections were included.

Main Results:

Corticosteroid injections provide significant symptom relief for 2 to 24 weeks. Injections can be performed intra-articularly or into the subacromial space. Evidence suggests that a 20mg dose of triamcinolone may be as effective as a 40mg injection. It remains unclear whether image-guided injections produce a clinically significant difference in outcomes when compared to landmark-guided (blind) injections. Corticosteroids may be less beneficial for diabetic patients. Patients using protease inhibitors (anti-retroviral therapy) should not receive triamcinolone because the drug-drug interaction may result in iatrogenic Cushing's syndrome.

Conclusions:

Corticosteroid injections for adhesive capsulitis demonstrate short-term efficacy, but may not provide a long-term benefit. More high-quality, prospective studies are needed to determine whether corticosteroid injections using ultrasound-guidance significantly improve outcomes.

Key Points:

- Corticosteroid injections provide short-term symptomatic relief for adhesive capsulitis.
- Corticosteroid can be administered intra-articularly or via subacromial injection with equal efficacy.
- It is unclear whether ultrasound-guided injections are more effective than landmark-guided (blind) injections.
- Corticosteroid injections can raise blood glucose levels in diabetic patients.
- Triamcinolone injections can result in Cushing's syndrome in patients on protease inhibitors (ritonavir/norvir)

Keywords: frozen shoulder; adhesive capsulitis; periarthritis; corticosteroid; injection

Disclosures: The authors have nothing to disclose

Corticosteroid Injections for Adhesive Capsulitis: A Review

INTRODUCTION

Adhesive capsulitis is a common condition in which the shoulder loses passive and active range of motion. While the impairment is typically self-limited, the disease remains poorly understood and residual symptoms may persist for years. Conservative treatment of adhesive capsulitis may involve one, or more, injections of corticosteroid. This review aims to evaluate the effectiveness of corticosteroid injections in terms of their effect on the disease's duration and completeness of recovery.

METHODS

A review of articles indexed by the United States National Library of Medicine was conducted by querying the PubMed database for studies involving participants with adhesive capsulitis, frozen shoulder, stiff shoulder, or painful shoulder. Articles that included corticosteroids, glucocorticoids, steroids, and injections were included. Additional references were reviewed from the bibliographies of the retrieved articles. Expert opinion and review articles were excluded. Studies without control or comparison groups were excluded. Studies comparing corticosteroid injections to operative procedures were excluded. Comparisons to physical therapy were included as physical therapy or home exercises often accompanies corticosteroid injections as standard of care. Using this review strategy (Figure 1.), 16 studies met the inclusion criteria.

Data items extracted from each study included: study design, study population, intervention, single or multiple injections, location of injections, injection mixture, control population, follow-up duration, and outcome measurements.

CLINICAL PRESENTATION OF ADHESIVE CAPSULITIS

Adhesive capsulitis (AC), also known as frozen shoulder or periarthrosis, is a painful, debilitating shoulder condition that affects approximately 3% of the U.S. population (1). Adhesive capsulitis can be differentiated from other common shoulder pathologies (*i.e.*, rotator cuff tears, impingement syndrome, and glenohumeral or acromioclavicular joint arthritis) because its painful presentation is accompanied by a gradual loss of both active and passive range of motion (ROM) (abduction and internal/external rotation) in the absence of arthritis and calcific deposition. Though not diagnostic, patients often complain of worsening pain at night and pain at rest.

The natural history of adhesive capsulitis typically progresses through three-phases – freezing (inflammatory), frozen, and thawing stages. The “freezing” stage presents with pain at rest and loss of motion. During the “frozen” state, patients describe shoulder stiffness with a loss

of both active and passive ROM, but no pain at rest. Lastly, there is a gradual improvement in motion as the frozen shoulder completes the “thawing” stage **(2, 3)**

While classification systems exist, patients with adhesive capsulitis may be diagnosed with primary or secondary frozen shoulder. Primary adhesive capsulitis is idiopathic. It lacks radiographic evidence of full or partial thickness rotator cuff tears, calcification, or arthritis. Secondary adhesive capsulitis develops after a trauma or in conjunction with another disease process, such as diabetes and hyperthyroidism **(2, 3, 4)**.

Even though adhesive capsulitis is a self-limited disease, its duration remains ambiguous. In general, it is believed to last between two and three years. However, pain and limitation can persist for more than seven years **(5,6)**.

PATHOPHYSIOLOGY OF ADHESIVE CAPSULITIS

The ball and socket nature of the glenohumeral joint gives the shoulder great mobility but makes it vulnerable to injury. The rotator cuff muscles of the subscapularis, supraspinatus, infraspinatus, and teres minor provide control and stability to the glenohumeral joint in mid-range of motion. The joint’s capsule provides the ligamentous support that affects stability at the end-range of motion **(7)**.

Though the underlying causes of primary adhesive capsulitis remain uncertain, the pathology of adhesive capsulitis is focused on changes in joint capsule and is believed to be inflammatory and/or fibrotic in nature. In 1962, Neviasser described adhesive capsulitis as a “contracture and thickening” of the shoulder capsule due to chronic inflammation **(8)**. Others have argued that adhesive capsulitis arises from fibrosis, not inflammation. Bunker found that the majority of cells present in the glenohumeral joint were fibroblasts and myofibroblasts, with sparse inflammatory cells **(9)**.

Newer studies investigating biomarkers present in the synovial fluid suggest that chronic inflammation is present. Kim *et al.* compared glenohumeral aspirations from patients with adhesive capsulitis and healthy controls. In the adhesive capsulitis patients, they found elevated levels of intercellular adhesion molecule 1 (ICAM-1 or CD54), a cytokine responsible for stimulating leukocyte activation, proliferation, adhesion, and migration in states of inflammation **(10)**. Lending support to the idea that chronic inflammation may lead to adhesive capsulitis, Rodeo *et al.* found an increased presence of TGF-beta and TNF-alpha, other markers of chronic inflammation, in adhesive capsulitis shoulders compared to normal shoulders **(11)**. Lastly, Hand *et al.* found both chronic inflammation and fibrosis in biopsies of periartritic shoulders correlating with the clinical depiction of adhesive capsulitis; the progression from pain to stiffness in frozen shoulders suggests inflammation with subsequent fibrosis **(12)**.

CORTICOSTEROID INJECTIONS

Conservative treatments of adhesive capsulitis may include one or a combination of the therapies, including: corticosteroid injection, ice/watchful waiting, physical therapy, sodium hyaluronate injection, and non-steroidal anti-inflammatory medications (NSAIDs). Corticosteroids participate in numerous physiological pathways, including inflammation and carbohydrate metabolism. They reduce pain and inflammation in frozen shoulder by inhibiting inflammation and prostaglandin production (13).

Though corticosteroid injections remain one of the most commonly prescribed treatments for adhesive capsulitis, their effect on the disease's natural history is unclear. Our literature review revealed twelve controlled studies that examined corticosteroid injections with no treatment, placebo injection, home exercise/physical therapy and/or NSAIDs (Table 1). Three studies (14, 15, 16) did not find a significant benefit for corticosteroid injection over the control group(s). The other nine studies found significant short-term pain reduction and restoration of mobility (from a minimum of 2 weeks to a maximum of 24 weeks) but failed to find benefit for corticosteroid injections beyond 24 weeks compared with the control group(s) (17, 18, 19, 20, 21, 22, 23, 24, 25). Whether the diminished impact of corticosteroids is a result of the natural course of the disease or because the corticosteroid effect had dissipated remains uncertain.

The variability in outcomes between studies could relate to the heterogeneity of the disease or control groups. In the three studies that found no benefit for corticosteroid injections, the comparison group received formal physical therapy (14, 15, 16). In fact, Calis *et al.* demonstrated that corticosteroid injections and formal physical therapy both provided significant benefit compared to a home exercise and stretching program, with no difference between the corticosteroid injection group and the physical therapy group (19).

While the literature does not describe a definitive benefit of corticosteroid injections, most studies recognize a positive effect for six to sixteen weeks, after which the benefits begin to diminish. Corticosteroid injections may not provide better outcomes than physical therapy. However, an injection may be palliative, relieving a patient's pain and improving their quality of life temporarily.

Dosage

Three studies examined the efficacy of a high-dose injection of corticosteroid against a low-dose injection (Table 2). Two of the studies investigated intra-articular injections (25, 26) while the other study looked at subacromial injections for adhesive capsulitis (21). In two studies, a high dose injection of triamcinolone (40 mg) did not improve pain relief or function restoration significantly better than a lower dose injection (20 mg) (25, 21). However, a separate investigation reported that high dose (40mg) was significantly more effective than a lower dose (10 mg) injection (26).

One possible explanation of these contradictory findings is that the increased dose of triamcinolone provides a diminished return above a certain threshold, but this claim has not been investigated. Additionally, the study that found significant improvement with a higher dose injection used three injections, spaced one week apart, for both the high dose and low dose injection whereas the other two studies used a single injection. It is possible that the effect of the corticosteroid was cumulative so that the total effect (120mg vs 30 mg) demonstrated a significant improvement in outcomes whereas the other studies, in which the comparison was 40mg versus 20 mg, did not.

Despite the discrepancy in methodology and results, the evidence suggests that a 20mg dose of triamcinolone is as effective as a 40mg dose.

Glenohumeral vs Subacromial Injections

Three studies examined whether the injection location (glenohumeral or subacromial) impacted the efficacy of the corticosteroid injection (**Table 3**). Though most physicians recommend glenohumeral (intra-articular) injections over subacromial injections for adhesive capsulitis, evidence suggests that these two approaches are equally effective in reducing pain and restoring shoulder function (**16, 24, 27**). One study compared subacromial injections, glenohumeral injections, both subacromial and glenohumeral injections, and NSAIDS (**24**). While they concluded that corticosteroid injections provided better pain relief and restoration of motion than NSAIDS, there were no significant differences among the various injection locations. Two additional studies compared subacromial and glenohumeral corticosteroid injections and found no significant differences in pain or ROM (**16, 27**).

Image-guided vs Landmark-guided (Blind) Injections

To improve injection accuracy, many physicians utilize ultrasound to place the needle into the articular joint space. Several papers examining glenohumeral injections have reported a wide range of accuracies for landmark-guided (blind) injections (45 to 98 percent) (**28, 29**) and image-guided (ultrasound) injections (63 to 100 percent) (**30, 31**). Interestingly, several papers also report blind injection accuracies of over 90 percent (**29, 32, 33**).

There is some evidence to suggest that the injection's accuracy may not matter in the treatment of shoulder pathologies. An older study comparing subacromial corticosteroid injections, intramuscular (gluteal) corticosteroid injections, and intramuscular (gluteal) placebo injections for treatment of supraspinatus tendonitis found a significant difference in pain and ROM between corticosteroid and placebo injections but, curiously, did not find a significant difference between the intramuscular gluteal and subacromial injections. The authors concluded that the corticosteroid injection worked via systemic rather than local effect, making the accuracy of the injection irrelevant to the treatment (**34**). A more recent study looking at pain and function between

patients with accurate and inaccurate intra-articular corticosteroid injections found no significant differences in outcomes. Though the study included other shoulder pathologies in addition to adhesive capsulitis, the results suggest that accuracy of injection may not impact its efficacy (35).

It remains unclear whether image-guided injection alleviates the symptoms of adhesive capsulitis more effectively than blind injections delivered without guidance. This literature review found only one study that examined image-guided versus landmark-guided injections for adhesive capsulitis (Table 4). The study showed that US-guided injections delivered better pain relief and restoration of ROM than blind injections for the first two weeks post-injection, after which time there was no significant difference in outcomes (36). However, the study included follow-up injections of hyaluronate, obscuring the relative value of the corticosteroid injection alone. Without more research, insufficient evidence exists to justify the increased costs for treating adhesive capsulitis with image-guided injections over landmark-guided (blind) injections.

Treatment of Diabetic Patients

Diabetics are two to four times more likely to develop adhesive capsulitis than non-diabetics, making them a significant subgroup of adhesive capsulitis patients (1, 37, 38).

Despite the increased incidence of adhesive capsulitis in diabetic patients, our literature review found only two studies examining the impact of corticosteroid injections for treatment of adhesive capsulitis in diabetic patients (Table 5). Though other confounding factors could explain the discrepancy between the results for diabetic patients and patients with primary adhesive capsulitis, the evidence suggests that corticosteroid injections may have less benefit for diabetic patients than for non-diabetic patients. One study found no difference in pain or function between intra-articular corticosteroid injection and the control group (39) while another study found that a corticosteroid injection provided increased pain relief up to, but not beyond, four weeks compared to control (40). The control groups in both studies were provided NSAIDs and a home exercise program.

Adverse Effects

It is believed that injecting corticosteroids mitigates the systemic effects associated with oral administration. However increased blood glucose levels can still occur in diabetic patients following the intra-articular injection of corticosteroids. One study showed a short-term increase in blood glucose levels in diabetic patients following a knee injection (41). Another study demonstrated no mean increase in blood glucose following intra-articular injection of corticosteroids into the shoulder, though there were rare instances when blood glucose was significantly increased post-injection (42).

For patients on antiretroviral therapy, injected corticosteroids can interact with protease inhibitors (i.e., ritonavir and norvir) leading to an iatrogenic Cushing's syndrome (43, 44, 45). Ritonavir is often used to boost the effect of other antiretroviral drugs by inhibiting the P450 CYP(3A4) and thereby prolonging the half-life of the antiretroviral. As triamcinolone is metabolized by the P450 CYP(3A4) pathway, ritonavir can similarly delay the metabolism of the corticosteroid, leading to prolonged exposure to elevated cortisol (44). Physicians should consider this drug-drug interaction carefully when treating patients receiving antiretroviral therapy.

The most common adverse events are injection-related pain and skin discoloration at the injection site (46). Repeated, or misplaced, corticosteroid injections may weaken tendons in the shoulder (47). While tendon ruptures have been reported following corticosteroid administration (48, 49), a review examining 744 patients treated with corticosteroid injections for shoulder and elbow tendonitis found no tendon ruptures, suggesting that the risk of tendon damage may be small, especially if injections are given infrequently (46).

CONCLUSIONS AND RECOMMENDATIONS

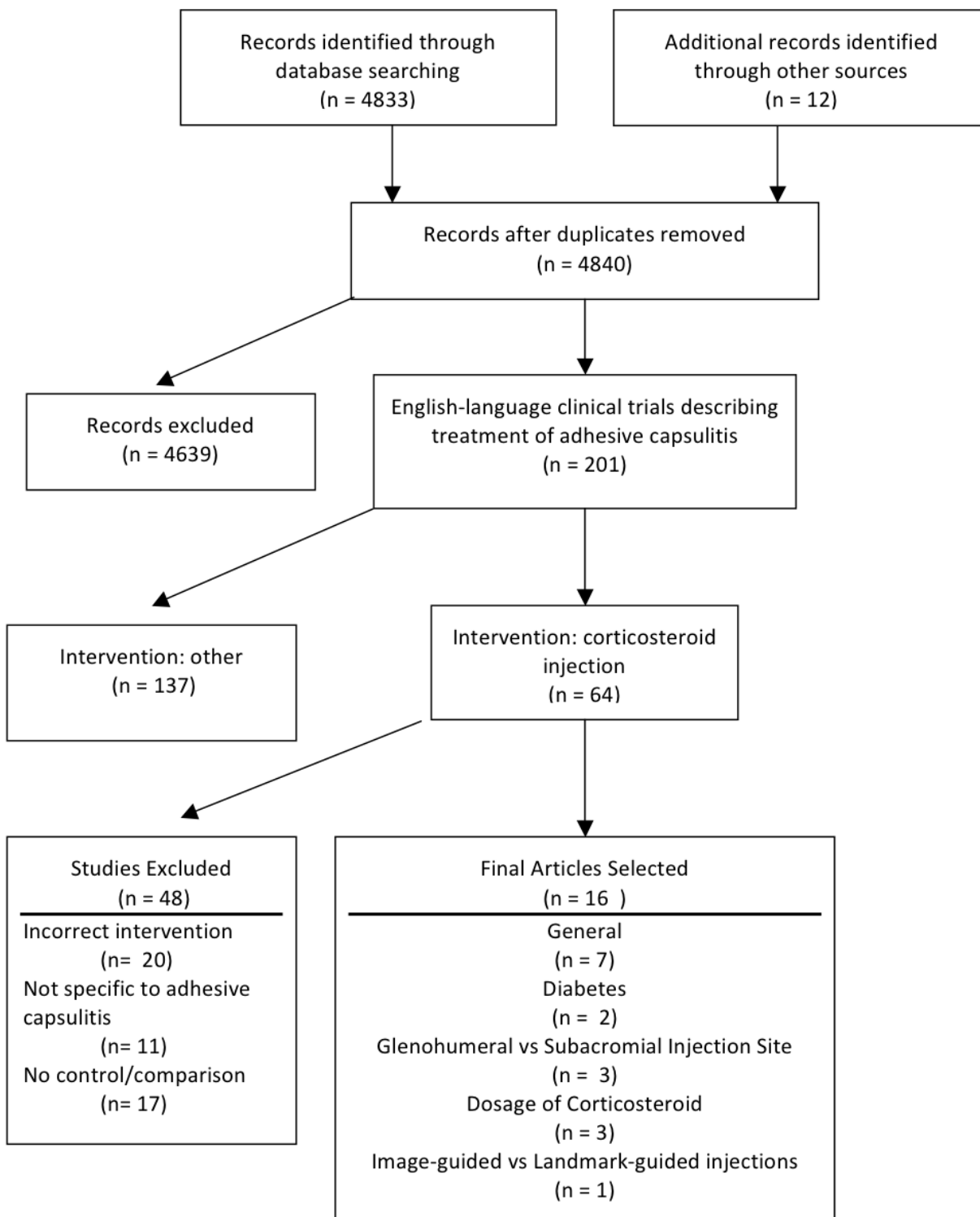
The results of this literature review suggest that corticosteroid injections may have a role in the treatment of adhesive capsulitis. They provide a significant short-term reduction in pain, but may not provide any long-term benefit because the natural history of the condition is self-limited. Nine of twelve studies comparing corticosteroid injections to a control group reported a significant improvement in outcomes for corticosteroid injections for at least two, and up to 24 weeks, after the injection. Beyond 24 weeks, there was no difference between injection and control groups.

Patient outcomes with corticosteroid injection can vary significantly. Diabetic patients may find less relief from corticosteroid injection than non-diabetic patients. Corticosteroid injections and physical therapy may be equally effective in relieving the symptoms of adhesive capsulitis. Corticosteroids can be administered in the joint or the subacromial space with equal efficacy. Compared to a 40mg dose of triamcinolone, a 20mg injection provides similar benefits. It is currently unclear whether image-guided injections relieve shoulder pain more effectively than landmark-guided injections. More high quality prospective studies are needed to define the role of ultrasound-guidance.

Corticosteroid injections should be administered with caution when treating adhesive capsulitis in patients with diabetes or on antiretroviral therapy. Corticosteroid injections can transiently increase blood glucose levels. In patients on protease inhibitors, metabolic changes may result in an iatrogenic Cushing's syndrome after a corticosteroid injection.

TABLES AND FIGURES

Figure 5: Flow Diagram for Literature Review



REFERENCES

- 1) Bridgman JF. Periarthritis of the shoulder and diabetes mellitus. *Ann Rheum Dis.* 1972 Jan;31(1):69-71.
- 2) Lewis J. Frozen shoulder contracture syndrome: aetiology, diagnosis, and management. *Man Ther.* 2014;20(1): 2-9
- 3) Nagy M, MacFarlane R, Khan Y et al. The frozen shoulder: myths and realities. *Open Orthop J.* 2013 Sep 6; 7:352-5
- 4) Neviasser AS, Hannafin JA. Adhesive capsulitis: a review of current treatment. *Am J Sports Med.* 2010; 38(11):2346-56
- 5) Vastamäki H, Kettunen J, Vastamäki M. The natural history of idiopathic frozen shoulder. *Clin Orthop Relat Res.* 2012; 470(4):1133-43.
- 6) Hand C, Clipsham K, Rees J et al. Long term outcome of frozen shoulder. *J Shoulder Elbow Surg.* 2008;17(2):231-6
- 7) Neviasser JS. Adhesive capsulitis of the shoulder. *J Bone Joint Surg Am.* 1945;27(2):211-222
- 8) Neviasser JS. Arthrography of the shoulder joint: study of the findings in adhesive capsulitis of the shoulder. Study of the findings in adhesive capsulitis of the shoulder. *J Bone Joint Surg Am.* 1962 Oct;44-A:1321-59.
- 9) Bunker TD, Anthony PP. The pathology of frozen shoulder. A Dupuytren-like disease. *J Bone Joint Surg Br.* 1995 Sep;77(5):677-83.
- 10) Kim YS, Kim JM, Lee YG et al. Intercellular adhesion molecule-1 (ICAM-1, CD54) is increased in adhesive capsulitis. *J Bone Joint Surg Am.* 2013;95:e18(1-8)
- 11) Rodeo SA, Hannafin JA, Tom J, et al. Immunolocalization of cytokines and their receptors in adhesive capsulitis of the shoulder. *J Orthop Res.* 1997 May;15(3):427-36.
- 12) Hand GC, Athanasou NA, Matthews T, Carr AJ. The pathology of frozen shoulder. *J Bone Joint Surg Br.* 2007 Jul;89(7):928-32.
- 13) Greaves MW. Anti-inflammatory action of corticosteroids. *Postgraduate Medical Journal* 1976;52(612):631-633
- 14) Arslan S, Çeliker R. Comparison of the efficacy of local corticosteroid injection and physical therapy for the treatment of adhesive capsulitis. *Rheumatol Int.* 2001;21:20-23.
- 15) Dacre JE, Beeney N, Scott DL. Injections and physiotherapy for the painful stiff shoulder. *Annals of the Rheumatic Diseases.* 1989; 48: 322-325
- 16) Rizk TE, Pinals RS, Talaiver A. Corticosteroid injections in adhesive capsulitis: investigation of their value and site. [Arch Phys Med Rehabil.](#) 1991 Jan;72(1):20-2

- 17) Bal A, Eksioglu E, Gulec B, et al. Effectiveness of corticosteroid injection in adhesive capsulitis. *Clinical Rehabilitation*. 2008; 22:503-512
- 18) Bulgen DY, Binder AI, Hazleman BL et al. Frozen shoulder: prospective clinical study with an evaluation of three treatment regimens. *Ann Rheum Dis*. 1984 Jun;43(3):353-60
- 19) Calis M, Demir H, Ulker S, et al. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? *Rheumatol Int*. 2006 Apr; 26(6): 536-50
- 20) Carette S, Moffet H, Tardif J et al. Intraarticular corticosteroids, supervised physiotherapy, or a combination of the two in the treatment of adhesive capsulitis of the shoulder. *Arthritis Rheum*. 2003 Mar;48(3):829-38
- 21) Hong JY, Yoon SH, Moon DJ et al. Comparison of high- and low-dose corticosteroid in subacromial injection for periarticular shoulder disorder: a randomized, triple-blind, placebo-controlled trial. *Arch Phys Med Rehabil*. 2011 Dec;92(12):1951-60
- 22) Prestgaard T, Wormgoor M, Haugen S, et al. Ultrasound guided intra-articular and rotator interval corticosteroid injections in adhesive capsulitis of the shoulder. A double blind, sham controlled randomized study. *Pain*. 2015 Apr [epub ahead of print]
- 23) Ryans I, Montgomery A, Galway R et al. A randomized controlled trial of intra-articular triamcinolone and/or physiotherapy in shoulder capsulitis. *Rheumatology (Oxford)*. 2005 Apr;44(4):529-35
- 24) Shin SJ, Lee SY. Efficacies of corticosteroid injection at different sites of the shoulder for the treatment of adhesive capsulitis. *J Shoulder Elbow Surg*. 2013 Apr;22(4):521-7
- 25) Yoon SH, Lee Y, Jung H et al. Optimal dose of intra-articular corticosteroids for adhesive capsulitis. *Am J Sports Med*. 2013 May;41(5):1133-9
- 26) de Jong BA, Dahmen R, Hogeweg JA. Intra-articular triamcinolone acetonide injection in patients with capsulitis of the shoulders: a comparative study of two dose regimens. *Clin Rehabil*. 1998 Jun;12(3):211-5
- 27) Oh JH, Oh CH, Choi JA et al. Comparison of glenohumeral and subacromial steroid injection in primary frozen shoulder: a prospective, randomized short-term comparison study. *J Shoulder Elbow Surg*. 2011 Oct;20(7):1034-40
- 28) Tobola A, Cook C, Cassas K et al. Accuracy of glenohumeral joint injections: comparing approach and experience of provider. *J Shoulder Elbow Surg*. 2011 Oct;20(7):1147-54
- 29) Sidon E, Velkes S, Shemesh S et al. Accuracy of non assisted glenohumeral joint injection in the office setting. *Eur J Radiol*. 2013 Dec;82(12):e829-31
- 30) Amber KT, Landy DC, Amber I et al. Comparing the accuracy of ultrasound versus fluoroscopy in glenohumeral injections: a systematic review and meta-analysis. *J Clin Ultrasound*. 2014 Sep;42(7):411-6
- 31) Aly AR, Rajasekaran S, Ashworth N. Ultrasound-guided shoulder girdle injections are more accurate and more effective than landmark-guided injections: a

- systematic review and meta-analysis. *Br J Sports Med*. 2014 [Epub ahead of print]
- 32) Jo CH, Shin YH, Shin JS. Accuracy of intra-articular injection of the glenohumeral joint: a modified anterior approach. *Arthroscopy*. 2011 Oct;27(10):1329-34
 - 33) Johnson TS, Mesfin A, Farmer KW et al. Accuracy of intra-articular glenohumeral injections: the anterosuperior technique with arthroscopic documentation. *Arthroscopy*. 2011 Jun;27(6):745-9
 - 34) Valtonen EJ. Double acting betamethasone (celestone chronodose) in the treatment of supraspinatus tendinitis: a comparison of subacromial and gluteal single injections with placebo. *J Int Med Res*. 1978;6(6):463-7
 - 35) Hegedus EJ, Zavala J, Kissenberth M et al. Positive outcomes with intra-articular glenohumeral injections are independent of accuracy. *J Shoulder Elbow Surg*. 2010 Sep;19(6):795-801
 - 36) Lee HJ, Lim KB, Kim DY et al. Randomized controlled trial for efficacy of intra-articular injection for adhesive capsulitis: ultrasonography-guided versus blind technique. *Arch Phys Med Rehabil*. 2009 Dec;90(12):1997-2002
 - 37) Arkkila PE, Kantola IM, Viikari JS, et al. Shoulder capsulitis in type I and II diabetic patients: association with diabetic complications and related diseases. *Ann Rheum Dis*. 1996 Dec;55(12):907-14.
 - 38) Lo SF, Chu SW, Muo CH, et al. Diabetes mellitus and accompanying hyperlipidemia are independent risk factors for adhesive capsulitis: a nationwide population-based cohort study. *Rheumatol Int*. 2014 Jan; 34(1):67–74.
 - 39) Dehghan A, Pishgooei N, Salami MA, et al. Comparison between NSAID and intra-articular corticosteroid injection in frozen shoulder of diabetic patients; a randomized clinical trial. *Exp Clin Endocrinol Diabetes*. 2013 Feb; 121(2): 75-9.
 - 40) Roh YH, Yi SR, Noh JH et al. Intra-articular corticosteroid injection in diabetic patients with adhesive capsulitis: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2012 Oct;20(10):1947-52
 - 41) Habib GS. Systemic effects of intra-articular corticosteroids. *Clin Rheumatol*. 2009 Jul;28(7):749-56
 - 42) Habib GS, Abu-Ahmad R. Lack of effect of corticosteroid injection at the shoulder joint on blood glucose levels in diabetic patients. *Clin Rheumatol*. 2007;26(4):566–568
 - 43) Maviki M, Cowley P, Marmery H. Injecting epidural and intra-articular triamcinolone in HIV-positive patients on ritonavir: beware of iatrogenic Cushing's syndrome. *Skeletal Radiol*. 2013 Feb;42 (2):313–315.
 - 44) Albert NE, Kazi S, Santoro J, et al. Ritonavir and Epidural Triamcinolone as a Cause of Iatrogenic Cushing's Syndrome. *Am J Med Sci*. 2012 Jul;344(1):72-4.
 - 45) Stepan JG, London DA, Boyer MI, et al. Blood glucose levels in diabetic patients following corticosteroid injections into the hand and wrist. *J Hand Surg Am*. 2014 Apr;39(4):706-12

- 46) Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomized controlled trials. *Ann Rheum Dis.* 2009;68:1843-1849
- 47) Wiggins ME, Fadale PD, Ehrlich MG, et al. Effects of local injection of corticosteroids on the healing of ligaments. a follow-up report. *J Bone Joint Surg Am.* 1995 Nov;77(11): 1682-91.
- 48) Halpern AA, Horowitz BG, Nagel DA. Tendon ruptures associated with corticosteroid therapy. *Western Journal of Medicine.* 1977;127(5):378-382.
- 49) Nichols AW. Complications associated with the use of corticosteroids in the treatment of athletic injuries. *Clin J Sport Med.* 2005;15(5): 370-5

APPENDIX B**EVALUATING NON-OPERATIVE TREATMENTS FOR ADHESIVE CAPSULITIS**

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ABSTRACT

Patients commonly present with shoulder complaints to the primary care and orthopaedic setting. The differential includes rotator cuff tears, subacromial impingement, osteoarthritis, and adhesive capsulitis also known as frozen shoulder. Despite the prevalence of adhesive capsulitis, it is commonly misdiagnosed and management remains unclear. This article reviews the presentation of adhesive capsulitis, presents an overview of the pathophysiology of this poorly understood disease, and evaluates non-operative treatment options for adhesive capsulitis.

KEYWORDS

Frozen Shoulder; Adhesive Capsulitis; Periarthritis; Corticosteroid; Injection; Physical Therapy

INTRODUCTION

Adhesive capsulitis (AC) is a debilitating shoulder condition in which the shoulder loses both passive and active range of motion. While adhesive capsulitis is a self-limiting condition in a majority of patients, the disease remains poorly understood and symptoms may persist for years. Treatment is often managed non-operatively and can include oral non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy and soft tissue modalities, hyaluronate injections, oral corticosteroids, and corticosteroid injections.

Prevalence

Commonly known as frozen shoulder, AC is the second most common cause of non-traumatic shoulder injury in the primary care setting, affecting approximately 3% of the U.S. population, with onset at approximately 50 years of age (1, 2). While frozen shoulder can be idiopathic, it is commonly associated with periods of relative immobility of the shoulder or with endocrine conditions such as diabetes or hypothyroidism. Shoulder immobility is frequently due to other shoulder injuries such as impingement syndrome or a post-surgical state. Tighe et al report that up to 70% of patients with AC have either diabetes or prediabetes and recommend that physicians screen newly diagnosed AC patients for diabetes (3).

Pathophysiology of Adhesive Capsulitis

The rotator cuff muscles provide dynamic stability to the shoulder, holding the humeral head in the glenoid fossa, while thickenings of the glenohumeral joint capsule provide stability at the end range of motion. AC results from an abnormal thickening of the shoulder capsule, limiting the shoulder's range of motion (ROM)

and decreasing the joint space capacity (4). While the exact cause of adhesive capsulitis remains unclear, studies have demonstrated that it arises from inflammatory changes in the shoulder joint followed by fibrosis. The transition from inflammation to fibrosis mirrors its clinical presentation of pain (inflammation) followed by stiffness (fibrosis) (5).

Natural History of the Disease

As a self-limiting disorder, AC tends to resolve without intervention, with an average duration of 30 months from onset to resolution of symptoms (2). However, the duration can vary significantly as some patients have reported symptoms persisting over 7 years (6, 7). Even with treatment, the course of recovery from AC remains slow. The duration of symptoms and variability in its natural history illustrate our limited understanding of the condition and the need for better treatment.

In many cases, AC progresses through three phases: a painful inflammatory phase, a frozen (or stiff) phase, and a thawing phase. Initially, during the inflammatory stage, the shoulder becomes painful, with the hallmark symptom of pain at rest. During the frozen stage, the shoulder remains stiff but the pain resolves. Lastly, the stiffness resolves during the thawing stage (8).

Diagnosis

Russell et al. found that only 17 percent of patients diagnosed with frozen shoulder met their criteria for an idiopathic AC (9). AC can be easily misdiagnosed given its nonspecific findings of pain and stiffness. These symptoms are common in other shoulder conditions, including rotator cuff tears, tendonitis, impingement, and osteoarthritis. Depending on the stage, a patient with adhesive capsulitis may or may not have pain in the shoulder.

For this reason, shoulder stiffness, rather than pain, is the key finding in diagnosing AC. Though AC can be bilateral, the disorder tends to present unilaterally with a loss in both active and passive motion (due to the articular rather than soft tissue nature of the condition), allowing for a side-to-side comparison. While there is no clear consensus for how much ROM deficit denotes AC, in general, a loss of passive ROM in multiple planes (external rotation, abduction, forward elevation, internal rotation) is suggestive of the diagnosis.

In particular, the loss of passive external rotation combined with passive shoulder abduction less than 90 degrees makes AC very likely. There are only two other disorders that can cause a loss of both active and passive external rotation, glenohumeral osteoarthritis and a posterior shoulder dislocation; however, both of these conditions can be excluded with the correct radiographs.

Non-operative Treatment for Adhesive Capsulitis

Conservative treatment for AC should be continued for 6 months before operative measures, such as capsular release or manipulation under anesthesia, are pursued. Up to 90% of cases of AC resolve with non-operative treatment (10). Non-operative treatments include oral non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy (PT) and soft tissue modalities, hyaluronate injections, oral corticosteroids, and corticosteroid injections (CSI). Though a number of proposed treatments exist, the literature remains ambiguous regarding the effectiveness of non-operative approaches at shortening the natural history of AC.

RESULTS

Physical Therapy

Rationale

PT is believed to benefit patients with AC by facilitating restoration of ROM and function. Because AC limits shoulder mobility, it may also produce a contraction of the shoulder's muscles and ligaments, further reducing shoulder ROM. PT may achieve symptomatic relief of frozen shoulder by stretching the tight, contracted capsule tissue, promoting more favorable redistribution of collagen, and increasing synovial fluid. It is hypothesized that joint mobilization may also inhibit nociceptors and thereby support pain relief. **(11, 12).**

Efficacy

Though the heterogeneity of PT protocols and intensity makes an accurate assessment of efficacy difficult, studies show that PT produces significant reductions in pain and improvements in ROM in patients with AC. When PT alone was compared to CSI alone, one study showed that corticosteroids provide more immediate benefit than PT, with greater relief of pain and restoration of shoulder function during the first 7 weeks of treatment **(13)**, while another study demonstrated no difference between CSI and PT **(14)**. In both cases, PT demonstrated a significant improvement from baseline.

One study compared intra-articular hyaluronate injection, intra-articular corticosteroid injection, PT, and a control group (home exercise). All three experimental groups demonstrated significant ROM and Constant score improvements over control at the 12-week follow up. Though not statistically significant, the PT

group demonstrated the greatest improvements in ROM, validating a role for PT in the treatment of AC (15).

Combined Physical Therapy and Corticosteroid Injection

Though the literature suggests that a combined PT and corticosteroid injection approach may provide better clinical outcomes than PT or CSI alone, the evidence is not definitive. Dacre et al demonstrated no differences in pain or ROM at six weeks or six months between combined PT and injection, PT alone, and intra-articular CSI alone (14). However, a meta-analysis by Maund et al. indicates combining PT with steroid injection provides significant pain reduction compared to PT or steroid injection alone (16). In two additional studies, patients were segregated into four groups – combined CSI and PT; CSI alone; saline injection and PT; and PT alone. In both studies the combined CSI and PT group had superior outcomes at 6 weeks in pain and ROM of at least 10% compared to either CSI or PT alone but these differences were not statistically significant. Both studies also demonstrated significantly greater improvement in CSI groups compared with non-CSI groups (17, 18).

Intensity of Physical Therapy

The intensity of PT may influence its efficacy. One study compared mild PT and intense PT. In the mild groups patients were encouraged to perform exercises up to, but not exceeding, the onset of pain, while the intense PT group exceeded a patient's pain threshold. The study determined that patients engaged in mild, pain-free, PT had significantly better clinical outcomes than patients engaged in intense, potentially painful PT (2). Another study compared high-grade mobilization techniques (HMGT) and low-grade mobilization techniques (LMGT) (12). It found that HMGT delivered better mobility and functional recovery than LMGT. Though the HMGT was a more intense mobilization procedure than the LMGT, the HMGT sought

to minimize pain when it occurred and decreased the intensity of therapy if pain occurred. From these two studies, we conclude that PT should be done to encourage mobilization without causing pain.

Adjuvants to Physical Therapy

Given that the primary complaint is stiffness in patients with AC, the addition of a static stretching device (a Dyna-splint for example) to a PT regime may yield additional benefit in restoring mobility and function. These devices are used at home several times per day and allow the patient to set the device angle and slowly increase the angle of stretch to improve ROM. In a study of 60 patients, Ibrahim et al compared PT and PT plus static progressive stretch device. **(11)** They demonstrated increased ROM and lower disability when a static progressive stretch device was used in conjunction with PT. At each follow up appointment (4, 12, 24, 52 weeks), the combined PT and static stretch device demonstrated improved ROM compared to PT alone

Corticosteroid Injections

Rationale

CSI may provide the same, if not better, anti-inflammatory effects as oral corticosteroids by delivering a concentrated dose to the area of pain, while mitigating some of the systemic side effects seen in oral administration.

Efficacy

CSI remain one of the most commonly prescribed treatments for adhesive capsulitis. Compared to placebo (saline injection) and control (no injection), CSI significantly reduces pain and increase shoulder ROM for six to sixteen weeks before the benefit begins to diminish (**15, 18, 19, 20, 21, 22**). The diminished long-term impact of CSI may result from the natural resolution of the disease or because the CSI's effect dissipates.

Dosage

In two studies, a high dose injection of triamcinolone (40 mg) did not improve pain or function significantly better than a lower dose injection (20 mg) (**19, 22**). However, a separate investigation reported that high dose (40mg) was significantly more effective than a lower dose (10 mg) injection (**23**).

Glenohumeral vs Subacromial Injections

Though most physicians recommend glenohumeral (intra-articular) injections over subacromial injections for adhesive capsulitis, evidence suggests that these two approaches are equally effective in reducing pain and restoring shoulder function (**21, 24, 25**). One study compared subacromial injections, glenohumeral injections, combined subacromial and glenohumeral injections, and oral NSAIDS (**21**). While they concluded that CSI provided better pain relief and restoration of motion than NSAIDS, there were no significant differences among the different injection groups. Two additional studies have compared subacromial and glenohumeral CSI and found no significant differences in pain or ROM (**24, 25**).

Image-guided vs Landmark-guided Intra-articular Injections

It remains unclear whether image-guided intra-articular injections are more effective than injections guided by anatomical landmarks. One study examined ultrasound-guided versus landmark-guided intra-articular injections for AC. The study showed that US-guided injections delivered better pain relief and greater restoration of ROM than landmark-guided injections for the first two weeks post-injection, after which time there was no significant difference in outcomes **(26)**. However, the study included follow-up injections of hyaluronate, obscuring the relative value of the CSI alone. Without more research, insufficient evidence exists to justify the increased costs for treating AC with image-guided injections over landmark-guided injections.

Frequency of Injection

We recommend one injection (with a maximum of two injections, spaced at least 3 months apart) when using CSI to treat adhesive capsulitis **(50)**. One injection provides symptomatic relief in many patients **(15, 18, 19, 20, 21, 22)**. There is clinical evidence demonstrating a correlation between increasing the number of “local injections” of corticosteroids into the shoulder and poorer rotator cuff repair outcomes as well as weaker tendon integrity. One to four total injections correlated with a minor increase in rate of poor outcomes (4/68) while 5 or more injections were associated with a large increase in poor outcomes (8/20) **(28)**.

Adverse Effects

Increased blood glucose levels can still occur in diabetic patients following the intra-articular injection of corticosteroids. One study showed a short-term increase in blood glucose levels in diabetic patients following a knee injection **(29)**. Another study demonstrated no mean increase in blood glucose following

intra-articular injection of corticosteroids into the shoulder, though there were rare instances when blood glucose was significantly increased post-injection (30).

Repeated or misplaced CSI may also weaken tendons in the shoulder. While tendon ruptures have been reported following corticosteroid administration (31, 32), a review examining 744 patients treated with CSI for shoulder and elbow tendonitis found no tendon ruptures, suggesting that the risk of tendon damage may be small for a single injection in the setting of an intact tendon (33).

The most common adverse events are temporary pain and permanent skin discoloration (associated with subcutaneous injections) around the injection site, though this finding is rare in and around the shoulder (33).

A rare but serious interaction occurs between corticosteroids and protease inhibitors (i.e., ritonavir and norvir), leading to an iatrogenic Cushing's syndrome (34, 35, 36). Ritonavir is often used to boost the effect of other antiretroviral drugs by inhibiting the P450 CYP(3A) and thereby prolonging the half-life of the antiretroviral. As triamcinolone is metabolized by the same P450 enzyme, ritonavir can impede the metabolism of the corticosteroid, leading to prolonged exposure to elevated cortisol (35). Physicians should consider this drug-drug interaction carefully when treating patients receiving antiretroviral therapy.

NSAIDS

Rationale

Non-steroidal anti-inflammatory drugs (NSAIDs) act by reducing pain and inflammation, and are used as a primary treatment for a variety of joint and muscle disorders, as well as a supplement to other treatments like PT and CSI in the treatment of adhesive capsulitis (37). Because pain can trigger inflammation and exacerbate the cycle of pain and stiffness in AC, NSAIDs may help prevent further stiffness and allow PT to be more effective.

Efficacy

NSAIDs provide short-term pain relief for shoulder disorders such as rotator cuff tendinopathies and calcific tendonitis. No studies have examined the impact of NSAIDs vs. placebo on AC. Some studies have compared the efficacy of different NSAIDs in treating AC (38, 39). These trials found statistically significant reductions in pain compared to baseline over the course of four weeks, but not stiffness. Because they did not compare NSAIDs to placebo, the pain reduction may be attributed to the gradual resolution of the disease, not just the effectiveness of NSAIDs alone.

Adverse Effects

Prolonged use of NSAIDs may result in gastrointestinal, renal, or cardiovascular problems (40, 41). Gastrointestinal complaints are common given NSAIDs role in inhibiting the prostaglandin production necessary for mucosal protection. In one study, 30 patients reported 88 minor side effects including indigestion and nausea after four weeks of high-dose NSAIDs for treatment of AC (38). The risk of GI bleeding is increased in patients who use NSAIDs concurrent with corticosteroids or aspirin, those who take NSAIDs chronically, elderly patients, and patients with a history of GI ulceration.

Hyaluronate Injections

Rationale

Hyaluronate is a large glycosaminoglycan present in connective tissue, including cartilage. The anionic nature of hyaluronate attracts water, giving hyaluronate its viscous, lubricating properties. Hyaluronate is hypothesized to treat adhesive capsulitis by lubricating the inflamed joint and suppressing inflammatory elements in the cartilage matrix (42, 43). Hyaluronate may provide an anti-inflammatory benefit similar to a corticosteroid, without the systemic side effects.

Efficacy

Evidence supporting the use of hyaluronate for adhesive capsulitis remains inconclusive. A recent study comparing intra-articular hyaluronate injections and CSI showed no significant differences in pain or ROM. (44). Calis et al demonstrated no significant difference in outcome between intra-articular injections of corticosteroid and hyaluronate after 12 weeks. Hyaluronate injections provided a significant improvement in ROM and Constant score over control (home exercise) (15). A recent study compared a combined benefit of intra-articular hyaluronate injection plus PT to PT alone (45). While both groups demonstrated significant improvement in ROM, there was no additional benefit derived from the addition of hyaluronate injections.

Adverse Effects

In rare cases, hyaluronate injections can result in an acute inflammatory reaction characterized by pain and swelling, mimicking pseudogout or pseudosepsis. The literature remains unclear whether repeat hyaluronate injections increase the risk of adverse events (43).

Oral Corticosteroids

Rationale

Corticosteroids participate in numerous physiological pathways, including inflammation and carbohydrate metabolism. They reduce pain and inflammation in frozen shoulder by inhibiting inflammation and prostaglandin synthesis (46).

Efficacy

Tested against placebo and control (no treatment), oral corticosteroids produce statistically significant pain relief but the benefit wears off when it is discontinued. In one study, patients were given either prednisolone (30 mg) or placebo for three weeks. Patients receiving prednisolone demonstrated a significant benefit in both pain and ROM during the three weeks of treatment compared to placebo. However, the benefits decreased once the medication was discontinued (47). A reduced benefit was seen at six weeks for the prednisolone group and no benefit was seen at twelve weeks. Another study similarly compared six weeks of oral prednisolone to control (no treatment). Over the course of eight months, both prednisolone and control groups showed a similar improvement in ROM. Though both groups demonstrated similar pain reduction after eight months, prednisolone produced more rapid pain relief, primarily during the six weeks of treatment. (48).

Adverse Effects

Corticosteroids are associated with a significant long-term (immunosuppression, adrenal dysfunction, loss of bone density) and short-term (hyperglycemia) risks and side-effects (49, 50). Further, the sudden discontinuation of oral corticosteroid administration may cause a recurrence of pain coincident to the steroid withdrawal (47).

DISCUSSION

Adhesive capsulitis (AC) is a common and often debilitating shoulder condition which is often manifest by pain and a marked reduction in range of motion.

PT can significantly improve ROM and reduce pain in frozen shoulders. PT should be performed with an emphasis on joint mobilization while seeking to minimize pain associated with PT as painful PT can limit its efficacy. A static progressive stretching device (i.e. Dyna-splint) for home-use may provide additional benefit when combined with PT.

CSI may offer the single greatest opportunity to reduce pain and restore mobility. CSI can provide significant short-term symptom relief for up to 16 weeks. Corticosteroids may be administered into the glenohumeral joint or the subacromial space with equal efficacy. In regards to intra-articular injections, it is currently unclear whether image-guided injections relieve shoulder pain more effectively than a blind (landmark-guided) injection. When combined with PT, CSI may lead to a better outcome than either CSI or PT alone.

Despite the widespread use of NSAIDs for AC, the efficacy for NSAIDs alone remains unclear. No study has directly compared NSAIDs to placebo. Hyaluronate injections might be useful in patients unable to undergo CSI, but more research is required to validate its effectiveness as a substitute. Oral corticosteroid treatment for AC provides short-term pain relief but the benefits diminish rapidly following termination of treatment. The many potential negative consequences of oral corticosteroids further complicate their use.

Conservative treatment can offer patients symptomatic relief of pain and enhance range of motion. However, it is not known if CSI or other measures shorten the natural history of AC. The variability that occurs in response to treatment and the disease's long duration of symptoms highlight the need for continued research into primary idiopathic adhesive capsulitis.

REFERENCES

- 50) Bridgman JF. Periarthritis of the shoulder and diabetes mellitus. *Ann Rheum Dis*. 1972 Jan;31(1):69-71.
- 51) Diercks R, Stevens M. Gentle thawing of the frozen shoulder: A prospective study of supervised neglect versus intensive physical therapy in seventy-seven patients with frozen shoulder syndrome followed up for two years. *J Shoulder Elbow Surg*. 2004 Sep-Oct;13(5):499-502
- 52) Tighe CB, Oakley WS. The prevalence of a diabetic condition and adhesive capsulitis of the shoulder. *Southern Medical Journal*. 2008; 101(6): 591-5

- 53) Neviaser JS. Arthrography of the shoulder joint: study of the findings in adhesive capsulitis of the shoulder. Study of the findings in adhesive capsulitis of the shoulder. *J Bone Joint Surg Am.* 1962 Oct;44-A:1321-59.
- 54) Hand GC, Athanasou NA, Matthews T, Carr AJ. The pathology of frozen shoulder. *J Bone Joint Surg Br.* 2007 Jul;89(7):928-32.
- 55) Hand C, Clipsham K, Rees J et al. Long term outcome of frozen shoulder. *J Shoulder Elbow Surg.* 2008;17(2):231-6
- 56) Vastamäki H, Kettunen J, Vastamäki M. The natural history of idiopathic frozen shoulder. *Clin Orthop Relat Res.* 2012; 470(4):1133-43.
- 57) Reeves B. The natural history of the frozen shoulder syndrome. *Scand J Rheumatol.* 1975;4:193e6
- 58) Russell S, Jariwala A, Conlon R, et al. A blinded, randomized, controlled trial assessing conservative management strategies for frozen shoulder. *J Shoulder Elbow Surg.* 2014 (23): 500-7
- 59) Levine W, Kashyap C, Bak S et al. Nonoperative management of idiopathic adhesive capsulitis. *J Shoulder Elbow Surg.* 2007 Sep-Oct;16(5):569-73.
- 60) Ibrahim M, Donatelli R, Hellman M, et al. Efficacy of a static progressive stretch device as an adjunct to physical therapy in treating adhesive capsulitis of the shoulder: a prospective, randomized study. *Physiotherapy.* 2014; 100: 224 – 234
- 61) Vermeulen HM, Rozing PM, Obermann WR, et al. Comparison of high-grade and low-grade mobilization techniques in the management of adhesive capsulitis of the shoulder: randomized controlled trial. *Phys Ther.* 2006; 86:355-368

- 62) van der Windt DA, Koes BW, Deville W et al. Effectiveness of corticosteroid injections versus physiotherapy for treatment of painful stiff shoulder in primary care: randomised trial. [*BMJ*](#). 1998 Nov 7;317(7168):1292-6
- 63) Dacre JE, Beeney N, Scott DL. Injections and physiotherapy for the painful stiff shoulder. *Annals of the Rheumatic Diseases*. 1989; 48: 322-325
- 64) Calis M, Demir H, Ulker S, et al. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? *Rheumatol Int*. 2006 Apr; 26(6): 536-50
- 65) Maund E, Craig D, Suekarran S et al. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. [*Health Technol Assess*](#). 2012;16(11):1-264
- 66) Ryans I, Montgomery A, Galway R et al. A randomized controlled trial of intra-articular triamcinolone and/or physiotherapy in shoulder capsulitis. [*Rheumatology \(Oxford\)*](#). 2005 Apr;44(4):529-35
- 67) Carette S, Moffet H, Tardif J et al. Intraarticular corticosteroids, supervised physiotherapy, or a combination of the two in the treatment of adhesive capsulitis of the shoulder. [*Arthritis Rheum*](#). 2003 Mar;48(3):829-38
- 68) Hong JY, Yoon SH, Moon DJ et al. Comparison of high- and low-dose corticosteroid in subacromial injection for periarticular shoulder disorder: a randomized, triple-blind, placebo-controlled trial. [*Arch Phys Med Rehabil*](#). 2011 Dec;92(12):1951-60
- 69) Prestgaard T, Wormgoor M, Haugen S, et al. Ultrasound guided intra-articular and rotator interval corticosteroid injections in adhesive capsulitis of the shoulder. A double blind, sham controlled randomized study. *Pain*. 2015 Apr [epub ahead of print]
- 70) Shin SJ, Lee SY. Efficacies of corticosteroid injection at different sites of the shoulder for the treatment of adhesive capsulitis. [*J Shoulder Elbow Surg*](#). 2013 Apr;22(4):521-7

- 71) Yoon SH, Lee Y, Jung H et al. Optimal dose of intra-articular corticosteroids for adhesive capsulitis. [*Am J Sports Med.*](#) 2013 May;41(5):1133-9
- 72) de Jong BA, Dahmen R, Hogeweg JA. Intra-articular triamcinolone acetonide injection in patients with capsulitis of the shoulders: a comparative study of two dose regimens. [*Clin Rehabil.*](#) 1998 Jun;12(3):211-5
- 73) Oh JH, Oh CH, Choi JA et al. Comparison of glenohumeral and subacromial steroid injection in primary frozen shoulder: a prospective, randomized short-term comparison study. [*J Shoulder Elbow Surg.*](#) 2011 Oct;20(7):1034-40
- 74) Rizk TE, Pinals RS, Talaiver A. Corticosteroid injections in adhesive capsulitis: investigation of their value and site. *Arch Phys Med Rehabil.* 1991Jan;72(1):20-2
- 75) Lee HJ, Lim KB, Kim DY et al. Randomized controlled trial for efficacy of intra-articular injection for adhesive capsulitis: ultrasonography-guided versus blind technique. *Arch Phys Med Rehabil.* 2009 Dec;90(12):1997-2002
- 76) Blair B, Rokito AS, Cuomo F, et al. Efficacy of injections of corticosteroids for subacromial impingement syndrome. *J Bone Joint Surg Am.* 1996 Nov;78(11):1685-9
- 77) Watson M. Major ruptures of the rotator cuff. The results of surgical repair in 89 patients. *J Bone Joint Surg Br.* 1985 Aug; 67 (4): 618-24
- 78) Habib GS. Systemic effects of intra-articular corticosteroids. *Clin Rheumatol.* 2009 Jul;28(7):749-56
- 79) Habib GS, Abu-Ahmad R. Lack of effect of corticosteroid injection at the shoulder joint on blood glucose levels in diabetic patients. *Clin Rheumatol.* 2007;26(4):566–568
- 80) Halpern AA, Horowitz BG, Nagel DA. Tendon ruptures associated with corticosteroid therapy. *Western Journal of Medicine.* 1977;127(5):378-382.

- 81) Nichols AW. Complications associated with the use of corticosteroids in the treatment of athletic injuries. *Clin J Sport Med.* 2005;15(5): 370-5
- 82) Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomized controlled trials. *Ann Rheum Dis.* 2009;68:1843-1849
- 83) Maviki M, Cowley P, Marmery H. Injecting epidural and intra-articular triamcinolone in HIV-positive patients on ritonavir: beware of iatrogenic Cushing's syndrome. *Skeletal Radiol.* 2013 Feb;42 (2):313–315.
- 84) Albert NE, Kazi S, Santoro J, et al. Ritonavir and Epidural Triamcinolone as a Cause of Iatrogenic Cushing's Syndrome. *Am J Med Sci.* 2012 Jul;344(1):72-4.
- 85) Stepan JG, London DA, Boyer MI, et al. Blood glucose levels in diabetic patients following corticosteroid injections into the hand and wrist. *J Hand Surg Am.* 2014 Apr;39(4):706-12
- 86) Van der Windt D, Van der Heijden G, Scholten R et al. The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) for shoulder complaints. A systematic review. *J Clin Epidemiol.* 1995 May;48(5):691-704
- 87) Rhind V, Downe WW, Bird HA et al. Naproxen and indomethacin in periartthritis of the shoulder. *Rheumatology.* 1982; 21(1): 51-53
- 88) Duke O, Zecler E, and Grahame R. Anti-Inflammatory drugs in periartthritis of the shoulder: a double-blind, between-patient, study of naproxen versus indomethacin. *Rheumatology.* 1981;20 (1): 54-59
- 89) Andres B, Murrell G. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res.* 2008 Jul;466(7):1539-54

- 90) Sostres C, Gargallo C, Arroyo M et al. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract Res Clin Gastroenterol.* 2010 Apr;24(2):121-32
- 91) Masuko K, Murata M, Yudoh K et al. Anti-inflammatory effects of hyaluronan in arthritis therapy: Not just for viscosity. *International Journal of General Medicine* 2009;2:77-81
- 92) Gross C, Dhawan A, Harwood D et al. Glenohumeral joint injections: a review. *Sports Health.* Mar 2013; 5(2): 153–159
- 93) Lim TK, Koh KH, Shon MS et al. Intra-articular injection of hyaluronate versus corticosteroid in adhesive capsulitis. [*Orthopedics.*](#) 2014 Oct;37(10):e860-5
- 94) Hsieh LF, Hsu WC, Lin YJ et al. Addition of intra-articular hyaluronate injection to physical therapy program produces no extra benefits in patients with adhesive capsulitis of the shoulder: a randomized controlled trial. [*Arch Phys Med Rehabil.*](#) 2012 Jun;93(6):957-64
- 95) Greaves MW. Anti-inflammatory action of corticosteroids. *Postgraduate Medical Journal* 1976;52(612):631-633
- 96) Buchbinder et al. Short course prednisolone for adhesive capsulitis (frozen shoulder or stiff painful shoulder): a randomised, double blind, placebo controlled trial. [*Ann Rheum Dis.*](#) 2004 Nov;63(11):1460-9
- 97) Binder A, Hazleman BL, Parr G, Roberts S. A controlled study of oral prednisolone in frozen shoulder. *Br J Rheumatol* 1986;25:288–92.
- 98) Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009;15:469-74
- 99) Keenan GF. Management of complications of glucocorticoid therapy. *Clin Chest Med* 1997;18:507-20.

