Intra-articular Injection of Hyaluronate Versus Corticosteroid in Adhesive Capsulitis

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abstract

The goal of this study was to prospectively compare the early clinical results of intra-articular injection of hyaluronate or corticosteroid in patients with idiopathic adhesive capsulitis. The authors’ hypothesis was that there would be no difference between groups. Sixty-eight patients with idiopathic adhesive capsulitis were equally randomized to receive either corticosteroid or hyaluronate injection. All patients underwent standard physical examination and magnetic resonance imaging. Intra-articular injection was performed through an anterior approach by the same orthopedic surgeon without image guidance. Patients were followed up 2 and 12 weeks after completion of the injection. The primary outcome was the Constant score at week 12. Secondary outcomes included the visual analog scale (VAS) pain score, the American Shoulder and Elbow Surgeons (ASES) score, and range of motion at each time point. No significant differences were noted in preoperative demographic features or baseline shoulder function between groups. After treatment, no significant differences were noted in early clinical outcomes (at weeks 2 and 12) with VAS, ASES, and Constant scores between groups (all \( P > 0.05 \)). Evaluation of range of motion showed no difference in forward elevation or external rotation at each time point. Internal rotation was significantly lower at week 2 in the hyaluronate group compared with the corticosteroid group (\( P = 0.015 \)). Internal rotation improved at week 12, with no significant difference between groups. Patients treated with intra-articular injection of hyaluronate and corticosteroid for idiopathic adhesive capsulitis showed significant improvement in early clinical scores and range of motion without significant differences between groups.
Corticosteroid injection is one of the most commonly used treatment modalities for conservative management of adhesive capsulitis. It reduces synovial inflammation and alleviates pain and inflammation of the glenohumeral joint. Compared with other treatments, corticosteroid injection has been reported to have similar outcomes to physiotherapy alone and to more invasive measures, such as manipulation and hydrolitation.1-3 However, side effects of prolonged use of corticosteroid injection, such as injection flare,4 increase in blood glucose level in diabetes,5 increased tendon fragility,6 and arthropathic change,7 are important concerns.

Hyaluronans are naturally occurring glycosaminoglycans that form the backbone of proteoglycan aggregates in the extracellular matrix and are integral to the structure and function of the articular cartilage.8 Based on its anti-inflammatory effect, treatment with sodium hyaluronate is emerging as an alternative intra-articular regimen for osteoarthritic knee joints.9,10 In the shoulder joint, clinical studies have reported the safety and efficacy of hyaluronate injection in patients with osteoarthritis, periarthritis, rotator cuff tears, and adhesive capsulitis.8,11-17

On the basis of these biologic and clinical features of sodium hyaluronate, the authors postulated that if hyaluronate injection can be as effective as corticosteroid, it could be used to treat some patients for whom corticosteroid injection is inappropriate. The goal of this study was to prospectively compare the early clinical results of intra-articular injection with hyaluronate and corticosteroid in patients with idiopathic adhesive capsulitis. The authors hypothesized that there would be no difference in clinical outcomes between corticosteroid and hyaluronate injection.

**Materials and Methods**

The current study was a prospective, randomized, clinical trial of injection with corticosteroid or hyaluronate in patients with idiopathic adhesive capsulitis. The study was approved by the authors’ institutional review board (IRB No 2009-06-072-002).

**Eligibility Criteria**

The study included patients with idiopathic adhesive capsulitis, which was defined as follows: insidious onset of shoulder pain; global limitation of both active and passive range of motion (forward flexion <100°, external rotation at the side of 0°-20°, and internal rotation below the thoracic vertebral level); and no history of major trauma, infection, or surgery around the affected shoulder. All patients underwent a thorough history, physical examination, and radiographic imaging studies, including standard plain radiographs and magnetic resonance imaging (MRI) scan. Patients were excluded from the study for 5 reasons: (1) if they lived far away from the urban tertiary referral center hospital because difficulty with transportation could preclude adherence to a regular follow-up schedule (patients who would be assigned to 1 treatment arm required at least 6 follow-up visits, including 3 weekly visits during the treatment period); (2) previous surgery or fracture of the affected shoulder; (3) identification of calcific tendinitis or arthritis of the glenohumeral joint or acromioclavicular joint on plain radiographs; (4) the finding of shoulder pathology on MRI scan, such as rotator cuff tendinopathy, rotator cuff tear, or biceps lesion; or (5) MRI scan that was performed at another institution.

**Recruitment and Randomization**

Recruitment started in June 2009 and was completed in January 2010. The examining orthopedic surgeon (J.C.Y.) assessed 103 consecutive patients for eligibility, and 68 patients who met the selection criteria were enrolled. Each patient was given full verbal and written information about the trial, and written informed consent was obtained by the treating surgeon. Each patient was randomized into a treatment group, receiving either corticosteroid injection (34 patients) or hyaluronate injection (34 patients). To allocate treatment, a randomization sequence with random permuted blocks was generated by the study statistician. Sequentially numbered opaque sealed envelopes containing treatment allocations were prepared and were opened in sequence by an independent administrator who was not involved in eligibility, treatment, or outcome measurement. Demographic data, including age, sex, dominant arm, history of diabetes, and time from symptom onset to treatment, were also recorded for all patients before injection treatment.

**Treatment Procedure**

All injections were performed by the same shoulder fellowship-trained orthopedic surgeon (T.K.L.), who was skilled in the proper technique for injection into the glenohumeral joint. With the patient in the supine position, a needle was inserted via the anterior approach, just lateral to the coracoid process, without fluoroscopic or ultrasonographic guidance. In the corticosteroid group, patients received a single injection with a mixture of 1 mL 1% lidocaine and 1 mL (40 mg) methylprednisolone acetate (Depo-Medrol; Pfizer, Latina, Italy). In the hyaluronate group, patients received 3-time, 1 week apart, 2-mL injections of sodium hyaluronate at a dosage of 10 mg/mL (Hyruran Plus; LG Life Science Ltd, Osong, Korea; a highly purified and high-molecular-weight hyaluronate with an average molecular weight of 3000 kDa). During the treatment period, analgesics and nonsteroidal anti-inflammatory drugs were prescribed for pain control. All patients were taught to perform home stretching exercises with a rope and pulley.

**Outcome Measures and Follow-up**

A single examiner, an experienced shoulder exercise therapist who was blinded to the treatment group, performed
a standardized assessment of all patients at baseline and again 2 weeks and 12 weeks after the completion of treatment. Patients completed a visual analog scale (VAS) pain score and were assessed with American Shoulder and Elbow Surgeon (ASES) score, Constant score, and range of motion. The primary outcome measure was the Constant score at the 12-week follow-up visit. The Constant score was specifically validated for use in the assessment of adhesive capsulitis20 and has been widely used for overall shoulder condition.11,21,22 It consists of pain (15 points), activities of daily living (20 points), active and painless range of motion (40 points), and strength (25 points). Strength was estimated with a MicroFET2 handheld digital dynamometer (Hoggan Health Industries, Draper, Utah). Secondary outcome measures included VAS pain score, ASES score, and range of motion at each time point. The safety of each injection was also evaluated.

During the study period, all 34 patients in the corticosteroid group received the allocated treatment and completed the follow-up visits, except for 1 patient who did not return for the 12-week follow-up visit. In the hyaluronate group, 3 patients withdrew after the first or second injection and were lost to follow-up, 1 patient refused to return for follow-up because of lack of efficacy at 2 weeks after completion of the trio of injections, and 1 patient dropped out because of a violation of the study protocol that occurred when the patient received another treatment (acupuncture at another institution after the first injection of hyaluronate). Finally, of the 34 patients initially assigned to the hyaluronate group, 29 patients received the allocated treatment and completed the follow-up visits. The authors telephoned the 1 patient in the corticosteroid group and the 5 patients in the hyaluronate group who dropped out at the time of the missed follow-up visits and confirmed that they had no adverse events after treatment.

**Sample Size Calculation**

For the Constant score, the minimal clinically important difference has not been reported,23 although a difference of 10 to 12 points is accepted as a clinically meaningful change.21,22 In the current study, it was postulated that the expected difference in mean values for the Constant score between the 2 groups would be 10 points and the common standard deviation would be 12 points, with a 2-sided significance level of $P=.05$ and a power of 80%. Assuming that the $t$ test was used, the sample size for each treatment arm was determined to be 29 patients. Allowing for possible dropout of participants, the authors recruited 34 patients in each group.

**Statistical Analyses**

Missing data for 1 patient in the corticosteroid group at the 12-week follow-up visit were imputed by the worst outcome and included in the analysis, according to the intention-to-treat principle.24 However, missing data for the 5 patients in the hyaluronate group were not appropriate for evaluation because their results after injection were not available. Therefore, the full analysis set was performed for the 34 patients in the corticosteroid group and the 29 patients in the hyaluronate group.25 Demographic data were compared with Student’s $t$ test for age and time from symptom onset to treatment and with the chi-square test for sex and dominant arm. Comparisons between baseline and each follow-up period were performed with the paired $t$ test or Wilcoxon signed rank test according to the normality of the difference. Comparisons between groups at baseline and at each follow-up period were performed with the 2-sample $t$ test or Mann-Whitney U test according to the normality of the variable being compared. Bonferroni correction was used for multiple comparisons. Statistical analyses were performed with SPSS version 12.0 software (SPSS, Chicago, Illinois). Significance was set at $P=.05$.

**RESULTS**

**Subjects**

The study included 68 patients (19 men, 49 women), with a mean age of 53.8 years (range, 37-77 years). The right shoulder was involved in 36 patients (53%), and the dominant side was involved in 39 patients (57%). Mean interval from symptom onset to treatment was 7.3 months (range, 6-13 months), and mean duration of follow-up was 12.5 weeks (range, 11.4-13.2 weeks). Six patients had a history of diabetes (3 in the corticosteroid group and 3 in the hyaluronate group). No statistical differences were found between the 2 groups in preoperative demographic data and functional status, including age, sex, symptom duration, clinical scores, and range of motion.

**Corticosteroid Injection**

The VAS pain score improved from 7.2 ($\pm1.8$) at baseline to 4.1 ($\pm1.8$) at week 2 ($P=.000$) and 3.6 ($\pm2.0$) at week 12 ($P=.000$). The ASES score increased from 13.2 ($\pm7.7$) at baseline to 23.4 ($\pm11.1$) at week 2 ($P=.000$) and 30.7 ($\pm13.5$) at baseline to 45.2 ($\pm13.8$) at week 12 ($P=.000$). The Constant score at the 12-week follow-up visit was imputed by the worst outcome and included in the analysis, according to the intention-to-treat principle.24 However, missing data for the 5 patients in the hyaluronate group were not appropriate for evaluation because their results after injection were not available. Therefore, the full analysis set was performed for the 34 patients in the corticosteroid group and the 29 patients in the hyaluronate group.25 Demographic data were compared with Student’s $t$ test for age and time from symptom onset to treatment and with the chi-square test for sex and dominant arm. Comparisons between baseline and each follow-up period were performed with the paired $t$ test or Wilcoxon signed rank test according to the normality of the difference. Comparisons between groups at baseline and at each follow-up period were performed with the 2-sample $t$ test or Mann-Whitney U test according to the normality of the variable being compared. Bonferroni correction was used for multiple comparisons. Statistical analyses were performed with SPSS version 12.0 software (SPSS, Chicago, Illinois). Significance was set at $P=.05$.
week 2 ($P=.000$) and 53.8 (±19.4) at week 12 ($P=.000$). The Constant score also improved from 35.8 (±12.2) to baseline to 42.0 (±14.6) at week 2 ($P=.005$) and 52.3 (±18.7) at week 12 ($P=.000$). For range of motion, forward elevation increased from 98.6 (±5.1) at baseline to 114.5 (±18.8) at week 2 ($P=.000$) and 119.0 (±17.6) at week 12 ($P=.000$). External rotation increased from 8.6 (±11.2) at baseline to 17.0 (±13.4) at week 2 ($P=.006$) and 26.6 (±16.1) at week 12 ($P=.000$). Internal rotation showed no significant change at week 2 (L3-L4, 15.2±3.5) vs baseline (L3-L4, 15.5±4.0; $P=.691$), but was significantly increased at week 12 (L1-L2, 13.6±3.3; $P=.032$).

**Corticosteroid vs Hyaluronate Injection**

When the corticosteroid and hyaluronate groups were compared, the Constant score was not significantly different at week 2 (48.6 and 42.0, respectively; $P=.137$) and week 12 (58.7 and 52.3, respectively; $P=.194$), as the primary outcome of the study. Similarly, no significant difference was seen between the 2 groups at week 2 or week 12 in other clinical scores with regard to VAS pain score and ASES score. Range of motion was also comparable between the 2 groups, with no significant difference seen after 12 weeks. The exception was mean internal rotation at week 2, which was significantly lower at week 2 in the hyaluronate group, but had recovered at week 12, without a significant difference between the groups. Both groups achieved significant improvement of clinical outcomes, with no serious adverse events. Based on the current findings, in terms of early clinical results, intra-articular injection of sodium hyaluronate was as effective as corticosteroid injection. Therefore, sodium hyaluronate is an alternative option when corticosteroid injection is relatively or absolutely contraindicated.

The primary goal of the study was to evaluate the efficacy of intra-articular injection in patients with idiopathic adhesive capsulitis. To address this question adequately, the authors deliberately selected patients with idiopathic adhesive capsulitis based on the findings of MRI scan and physical examination. Yoo et al recently showed that magnetic resonance arthrography showed a partial- or full-thickness tear of the supraspinatus tendon in approximately one-third of patients with clinically diagnosed stage 2 adhesive capsulitis. MRI scans allowed the authors to successfully exclude patients with other causes of secondary adhesive capsulitis, such as rotator cuff tendinopathy or partial tear, which could be missed by other imaging tools, such as ultrasonography. Because of this process of patient selection, the current patient groups provided the most appropriate study cohort to evaluate the efficacy of treatment for idiopathic adhesive capsulitis.

Although the safety and efficacy of sodium hyaluronate injection for adhesive capsulitis has been reported, the authors are aware of only 1 published study that compared the outcome of this treatment with corticosteroid injection. Calis et al compared the efficacy of sodium hyaluronate injection with corticosteroid injection, physical therapy, and a control group. They reported no difference in the Constant score at 3 months between the hyaluronate and corticosteroid groups in a subgroup analysis, and the current findings concur with these results. However, a limitation of the study of Calis et al was that the diagnosis of idiopathic adhesive capsulitis was determined only on a clinical basis, without use of an imaging modality. In addition, the study design was neither a randomized clinical trial nor sufficiently powered for the Constant score.

Study of the mechanism of action of hyaluronate in joints has led to several theories: reduced friction via increased viscoelasticity with injection of hyaluronate into the joint, coating and protection of the damaged cartilage, anti-inflammation, and improved synovial fluid concentrations and synovium abnormalities. In adhesive capsulitis of the shoulder, gadolinium-enhanced MRI scan shows significant signal enhancement in the synovium and subsequent attenuation of this hyperintensity with treatment. This enhancement in synovium decreased after intra-articular injection of sodium hyaluronate, indicating that hyaluronate has an anti-inflammatory effect. Clinical studies of the efficacy of intra-articular injection of sodium hyaluronate for adhesive capsulitis as well as the current study supported this anti-inflammatory effect by showing improvement in pain.
For improvement in range of motion in adhesive capsulitis, Calis et al reported no significant difference in abduction or external rotation between the hyaluronate and corticosteroid groups, similar to the current findings. In patients with subacromial impingement syndrome, Kim et al reported no significant difference between the hyaluronate and corticosteroid groups in shoulder range of motion at 12 weeks.

As a nonoperative treatment option for idiopathic adhesive capsulitis, corticosteroid injection in the intra-articular or subacromial space has been popular and has provided fast relief of pain and improvement in function. However, disadvantages of corticosteroid injection include periarticular calcification, cutaneous atrophy, cutaneous depigmentation, tendon rupture, avascular necrosis, and joint infection as local effects. Systemic effects include a transient increase in blood glucose levels over a few days in diabetic patients and a decrease in serum cortisol level after 1 to 4 weeks. Although these adverse effects are neither specific to the shoulder nor more common in the shoulder, they are cause for concern when corticosteroid injection is planned for patients with adhesive capsulitis, especially those with diabetes or a history of multiple corticosteroid injections over a short period. Based on the current findings, intra-articular injection of sodium hyaluronate may be a good alternative when corticosteroid injection is not considered appropriate. In the current study, this treatment provided favorable relief of pain and improvement in function similar to corticosteroid injection.

This study had several limitations. A major limitation was that the treatment regimen was different in the 2 groups in that the authors tested the efficacy of 3 weekly injections of hyaluronate vs 1-time injection of corticosteroid. This discrepancy in treatment regimens had several drawbacks. First, the hyaluronate group was more subject to technical error because the patients needed 3 injections vs 1 injection in the other group. Furthermore, because all injections were done freehand, without sonographic or fluoroscopic guidance, there is important concern whether the injections were truly inserted into the glenohumeral joint. However, all injections were done by a single experienced shoulder surgeon who was familiar with the intra-articular injection technique. Therefore, the authors believe that this uniformity in injection procedure may have minimized performance bias. Further, the accuracy (90.6%-100%) of anterior injection into the glenohumeral joint without radiographic assistance was recently confirmed. In addition, the allocated treatment could not be blinded to either patient or treating surgeon because of the discrepancy between the treatment regimens. However, outcome assessment was performed by an independent observer who was completely blinded to the treatment group. Further, at the completion of the trial, sample sizes available for analysis showed the discrepancy between groups, although treatments were allocated to equal numbers of patients in each treatment arm. Study dropout was more common in the hyaluronate group, indicating that patients receiving hyaluronate treatment were less compliant than the corticosteroid group. The authors believe that the difference in compliance between groups can be attributed to the study design. To avoid these drawbacks, a study design comparing 3 weekly injections of sodium hyaluronate vs injection of corticosteroid in the first week and injection of placebo (ie, normal saline) at the next 2 sessions might be more appropriate. However, this kind of study could not be approved by the authors’ institutional review board. A 3-week injection protocol in which sodium hyaluronate is given once a week is generally recommended, whereas corticosteroid is injected once. The current authors thought that their treatment protocols might be more clinically relevant in a general office setting. Notably, because a 1-time injection of sodium hyaluronate is being introduced on the market, a study comparing its effect with corticosteroid injection may reach a more valid conclusion. This project is being planned as part of the authors’ ongoing research. Finally, this study did not evaluate the cost-effectiveness of hyaluronate injection compared with corticosteroid. Considering the direct and indirect costs of hyaluronate and corticosteroid injection, further study is needed to determine the cost-effectiveness of these interventions.

CONCLUSION

In patients with idiopathic adhesive capsulitis, intra-articular injection of hyaluronate and corticosteroid showed clinical improvement in pain and function. Hyaluronate injection can be an alternative treatment option, and its efficacy is predicted to be as favorable as that of corticosteroid injection.

REFERENCES