Clinical evidence in the treatment of rotator cuff tears with hyaluronic acid

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Summary

Purpose: the aim of this quantitative review is to document potential benefit and adverse effects of hyaluronic acid (HA) injection into the shoulder with rotator cuff tears.

Methods: a systematic literature search was performed in English PubMed, Medline, Ovid, Google Scholar and Embase databases using the combined key words “hyaluronic acid”, “rotator cuff tear”, “hyaluronate”, “shoulder”, “viscosupplementation”, with no limit regarding the year of publication. Articles were included if they reported data on clinical and functional outcomes, complications in series of patients who had undergone HA injection for management of rotator cuff tears. Two Authors screened the selected articles for title, abstract and full text in accordance with predefined inclusion and exclusion criteria. The papers were accurately analyzed focusing on objective rating scores reported.

Results: a total of 11 studies, prospective, 7 were randomized were included by full text. A total of 1102 patients were evaluated clinically after different HA injection compared with corticosteroid injection, physically therapies, saline solution injection and control groups. The use of HA in patients with rotator cuff tears improve VAS and functional score in all trials that we have analyzed.

Conclusion: intra-articular injection with HA is effective in reducing pain and improving function in shoulder with rotator cuff tears and without severe adverse reaction.

Level of evidence: Level I.

KEY WORDS: cuff tears, glenohumeral, hyaluronic acid, hyaluronate, shoulder, viscosupplementation.

Introduction

Rotator cuff pathology is the main cause of shoulder pain and disability. The causes arise from a multivariate etiology, often due to age-related chronic degeneration in which play a role the decrease in collagen synthesis, increase in free radicals expression and metabolism imbalance in favor of catabolic activity¹. Classically, the diagnosis is clinical, characterized by pain, mostly during the night, severe disability and functional impairment²,³. MRI and US may usefully this diagnosis⁴,⁵. The first management is conservative, including oral anti-inflammatory drugs, topic agents, cortisone injections, physical therapies, and joint rehabilitation exercises⁶-⁸. In the past, much has been published on the use of steroid and local anesthetic injections, administered alone or in combination to other therapies. On the other hand, many evidences have corroborated their potential effects as negative on the collagen matrix of tendons and ligaments⁹-¹⁴. In the substance, compared to other treatments, effective in the mid and long term, the benefits after these injections could be valid only in the short-term¹⁵.

Clinical trials have confirmed that HA may be effective for management of tendons disorders. Specifically, in Achilles tendinopathy, the tendon healing process is improved and the formation of adhesions in reduces by the regulation of the expression of vascular endothelial growth factor (VEGF) and type IV collagen¹⁶. After hand surgery, it improves the motion of fingers lubricating the tendon surface and reducing friction and adhesions¹⁷,¹⁸. Few papers have investigated the effects of HA in rotator cuff disorders, and no systematic review have been performed on this matter. The aim of the present review is to summarize all papers published inherently to the injection of HA for management of cuff tendinopathy, in terms of feasibility, safety, and efficacy.
Material and methods

Criteria for consideration

We included randomized clinical trials, prospective and retrospective studies reporting on clinical and functional outcomes in patients who had undergone sub-acromial or intra-articular injections of HA for management of rotator cuff pathology. Given the linguistic capabilities of the research team, we considered only papers published in English language. We performed a broad search for relevant studies published up to August 2014 in Medline (http://www.ncbi.nlm.nih.gov/sites/entrez/); Ovid (http://www.ovid.com); Cochrane Reviews (http://www.cochrane.org/reviews/); Google Scholar, Enbase database. Combined key words for the search were “cuff tears”, “glenohumeral”, “hyaluronic acid”, “hyaluronate”, “shoulder”, “viscosupplementation”, with no limit for year of publication. We identified 178 publications. Two Authors (MB and ADB) reviewed the abstract of each publication, and selected or excluded the study according to the text of the abstract. The article was excluded if the abstract was not available. In addition, screening the reference lists of relevant studies, articles not identified at the first electronic search were included. All journals were considered, and all relevant articles were retrieved. Papers referring to a specific association between cuff disorders and obvious osteoarthritis of the shoulder were excluded. Biomechanical reports, studies on animals, cadavers, in vitro or animal studies, case reports, literature reviews, technical notes, letters to editors and instructional course were excluded. To qualify, an article would have to have been published in peer-reviewed journals. We obtained full-text versions of the study if the abstract did not allow to include or exclude it. All search steps, inclusion and exclusion criteria are reported in Figure 1. 178 articles were identified and selected. 32 full-text selected articles were reviewed and discussed by all the Authors; a fully trained orthopedic surgeon with special interest in shoulder surgery and sports disorders (LO) took the final decision, in dubious cases. After further selections, 11 publications relevant to the topic were included.

Outcome measures

Data were extracted from each study without contacting the Author(s) to verify the accuracy of the data or obtain further information. The visual analogue scale (VAS) assessment was considered as major criterion for clinical success. Data on range of motion (ROM)19-24, Constant score25-28, shoulder function assessment scale (SFA) and shoulder disability questionnaire (SDQ)23, short form-12(SF12)24, University of California at Los Angeles score (UCLA)20, Oxford Shoulder Score and Patient Global Assessment29, Shoulder Rating Questionnaires27, and activities of daily living (ADL)28 were extracted for assessment of clinical and functional outcomes. Rates of complications were also extracted to assess the safety, effectiveness, and reliability of these procedures.

Results

Eleven studies have been published from 1995 to 2013, all reporting outcomes of patients who had undergone injections of HA for management of rotator cuff tears (Tab. 1). The number of patients varied from 22 to 6024, for a total number of 1102 patients. Specifically, 701 patients underwent intra-articular injections of HA, 236 underwent intra-articular injections of saline solution21,24,26, 53 underwent intra-articular injections of methylprednisolone acetate20,23, and 35 patients underwent other physical therapies. Different types of HA were used, based on the low or medium molecular weight. The commercial name also differed: Hylan G-F 2022, Fermathron™ 26, Hyran Plus®23, SportVis™29, Jointex27, Artz25 were used in one study each, a not specified high weight HA19,20,28 and Hyalgan21,24 in 3 and 2 studies, respectively. The mean age of patients managed was 59.2 years. The numbers of injections varied: 2 in 1 studies29, 1 a week for five weeks in 5 studies19-21,24,25, one for five weeks in 5 studies19-21,24,25, one in 2

Figure 1. Flow-chart showing the process and results for systematic review and article exclusion.
studies and 22,24,26,27 in 4 studies. Intra-articular injection were undertaken in 5 studies 19,20,22,24,27 subacromial injections under US guidance were administered in seven studies 19,21,23,25,26,28,29.

The diagnosis of rotator cuff tear was mainly on clinical examination, and confirmed at MRI or US scans. The main exclusion criteria were inflammatory arthritis, crystalline synovitis, avascular necrosis, rapidly progressive disease, history of sepsis, trauma, and previous surgery to the shoulder, intra-articular injections of corticosteroids to the shoulder at least 6 months before the treatment, neoplasm, and painful conditions to the cervical spine (Tab. 1).

The follow-up of each study, scores before and after management and adverse reactions are reported in Table 2.

### Complications
In all studies, no serious device-related adverse events were observed. A mild vagal reaction occurred in 1 of 30 patients (3%) 28. In another study 7 patients (3.2%) in the five-injection hyaluronate group, 3 patients (1.4%) in the three-injection hyaluronate group, and 7 patients (1.4%) in the control group complained of persistent pain at the injection site 24 (Tab. 2).
The main finding of the present study is that HA injections improve symptoms and function in patients with rotator cuff disorders, without side effects and reactions. On the hand, oral NSAIDs administrations and other medications showed different results, highlighting the efficacy and safety of HA injections in this context.

Table 2. Clinical results, follows up and complication.

<table>
<thead>
<tr>
<th>Author</th>
<th>Pre-treatment scores</th>
<th>Follow-Up</th>
<th>Post-treatment scores</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROM</td>
<td>Extension 34.3 ± 14.3</td>
<td>28.2 ± 16.2</td>
<td>0.05 ± 0.05</td>
<td>no change</td>
</tr>
<tr>
<td>Flexion</td>
<td>37.3 ± 16.4</td>
<td>32.1 ± 14.2</td>
<td>0.03 ± 0.03</td>
<td>no change</td>
</tr>
<tr>
<td>Abduction</td>
<td>30.2 ± 17.8</td>
<td>25.8 ± 12.6</td>
<td>0.02 ± 0.02</td>
<td>no change</td>
</tr>
<tr>
<td>External rotation</td>
<td>12.6 ± 8.9</td>
<td>10.4 ± 6.2</td>
<td>0.01 ± 0.01</td>
<td>no change</td>
</tr>
</tbody>
</table>

Discussion

The main finding of the present study is that HA injections improve symptoms and function in patients with rotator cuff disorders, without side effects and reactions. On the hand, oral NSAIDs administrations and other medications showed different results, highlighting the efficacy and safety of HA injections in this context.

cortisone injections, if prolonged, may be contra-indicated in elderly patients with comorbidities such as diabetes or hypertension. In fact, the HA is physiologically present in the synovial fluid (35); its main role is to lubricate the joint, it exerts mechanical and biological functions, in terms of anti-adhesive shock absorber and articular stabilizer against shear stresses (36), and it presents some analgesic effects (35). The HA is a polymer of disaccharides, composed by D-glucuronic acid and D-N-acetyl-glucosamine, synthesized by a class of integral membrane proteins. It is present in the extracellular matrix, and is a biomechanical and functional element of the articular cartilage (36).

Specifically, the HA is viscoelastic, lubricates and protects the articular surface and cartilage from stress and friction forces (37).

In vitro, HA reduces the gliding resistance after flexor tendon repair (38). It has an anti-inflammatory role, mediated by the regulation of the concentration of prostaglandin E2, C4S and interleukin-1 within the synovial fluid, the migration of leukocyte, leukocyte phagocytosis, lymphocyte proliferation, improving significantly pain and discomfort (39,40). It reduces the concentration of interleukin-6, stimulates synovial fibroblasts to produce endogenous HA, and regulates the expression of endothelial growth factor and type IV collagen (pro-angiogenic effect) (41).

In one in vivo study on sheep models, HA reduces synovial hyperplasia, inflammation, fibrosis and neovascularization after meniscectomy (42), limiting the degeneration of cartilages. It was supposed to increase angiogenesis after removal of the anterior cruciate ligament in Wistar rats (43,44), and to decrease toll-like receptor 4 (TLR-4) and the TLR-2 expression (receptors that play an important role in the arthritis mechanism) in mouse (45).

This systematic review evaluates the effects of HA injections in patients with rotator cuff tears. Different scores and scales were used in the studies. The VAS score improved in all studies examined in this review. In two studies (20,23) comparing HA vs methylprednisolone acetate injections, better clinical results and symptoms were recorded after administration of HA. In particular, Byun (23) showed better results in terms of ROM, proving that HA may improve motion and function of the shoulder, especially in active internal rotation.

Four studies (21,24-26) comparing patients undergoing HA vs phosphate-buffered saline injections reported good clinical results and pain relief. In particular, Blaine (24) showed better ROM recovery, reduced pain at night, and significantly higher overall satisfaction in the HA group; Meloni (21) showed a significant difference in the improvement of clinical symptoms and recovery of functional status in patients at 1 month after the end of the HA infiltrative cycle, in particular HA group VAS score was 2.8 respect 8.0 in the sodium chloride solution group.

Chour (25) and Moghtaderi showed a significantly improvement in Constant score and VAS scores at 12 weeks and 6 weeks, respectively. Two studies (22,29) evaluated the use of HA compared to the use of physical therapies, concluding that HA injections are safe and effective for patients with rotator cuff pathology.

There are several limitations to the present investigation. Specifically, few studies evaluated the effects of HA; and different clinical scores were used making it difficult to compare the results.

**Conclusion**

Intra-articular injections of HA are effective to reduce pain and improve the function of the shoulder in patients with rotator cuff pathology, with no severe complications or adverse reactions. It could be used as an alternative to cortisone or other oral drugs, exploiting its biomechanical and biochemical properties. Further randomized controlled studies are needed to better understand which is the most effective molecular weight of HA, how often and in which grade of lesions it should be injected.

**Conflict of interest**

We declare none conflict of interest.

The Authors declare that this mini-review was conducted according ethically to international standards and as required by the journal as described (46).

**References**

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