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 compare 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 arises 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 activity[1]. Classically, the diagnosis is clinical, characterized by pain, mostly during the night, severe disability and functional impairment[2,3]. MRI and US may usefully this diagnosis[4,5]. The first management is conservative, including oral anti-inflammatory drugs, topic agents, cortisone injections, physical therapies, and joint rehabilitation exercises[6-8]. 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 ligaments[9-14]. 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-term[15].
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 collagen[16]. After hand surgery, it improves the motion of fingers lubricating the tendon surface and reducing friction and adhesions[17,18].
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 score[25-28], 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 Assessment[29], Shoulder Rating Questionnaires[27], 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[27] to 602[24], for a total number of 1102 patients. Specifically, 701 patients underwent intra-articular injections of HA, 236 underwent intra-articular injections of saline solution[21,24,26], 53 underwent intra-articular injections of methylprednisolone acetate[20,23], 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 20[22], Fermathron™[26], Hyruan Plus®[23], SportVis™[29], Jointex[27], Artz[25] were used in one study each, a not specified high weight HA[19,20,28] and Hyalgan[21,24] in 3 and 2 studies, respectively.

The mean age of patients managed was 59.2 years. The numbers of injections varied: 2 in 1 studies[29], 1 a week for five weeks in 5 studies[19-21,24,25], one[23,28] in 2

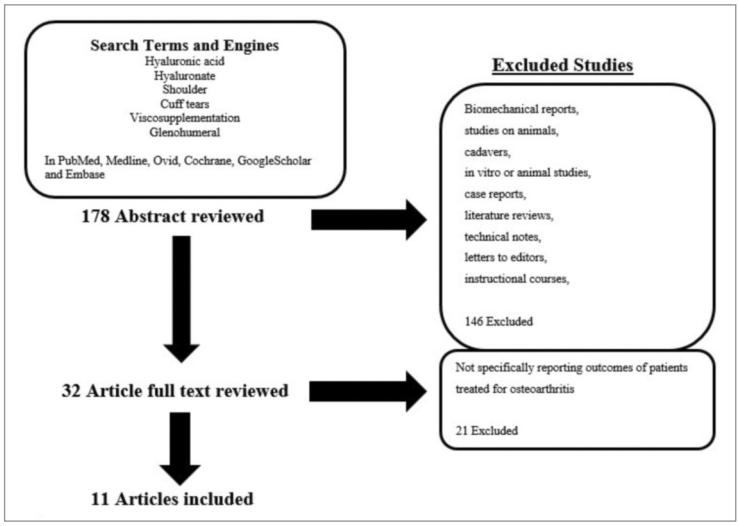

Figure 1. Flow-chart showing the process and results for systematic review and article exclusion.

Table 1. Studies features.

Bvii pst	Inclusion Criteria	Exclusion Criteria	Location	Case	Control	Age	N. patients	Outcomes
Jqlbf[v-2:: 6~	Subacromial bursitis, tendinitis and capsulitis.	Osteoarthritis, local corticosteroid preparation within 2 weeks before the study; severe complications (impairment of hepatic, renal, or hematopoietic function); history of drug allergy; pregnancy or lactation; difficulty in obtaining information from the patient; and unsuitability of the patient	glenoid cavity(20) or the subacromial bursa(42).	25 mg HMW HA in 1% solution, 1 injections once weekly for 5 weeks (If periarthritis resolved during this period, treatment was stopped)		Total=65.4(39-86)	Total=62	Pain(at rest, on motion, on pressure),ROM, ADL, The global severity rating, Global improvement
Ti jcbtb-[3112ù	Full-thickness rotatorcuff tear diagnosed by arthrography or magnetic resonance imaging	Undergone intra-articular injection of any drugs, abnormal hepatic or renal function, pregnant, severe osteoarthritic changes of the affected, shoulder joint were excluded, symptoms resulting from cervical lesions.	intra-articular glenohumeral joint	25 mg sodium hyaluronate(molecular weight: 80 × 10) + 3mL of 1% lidocaine once weekly for 5 weeks	2 mg of dexamethasone + 3mL of 1% lidocaine once weekly for 5 weeks	HI=59.5±9.1 DI=62.4±8.6	Total=78 HI=38 DI=40	UCLA,ROM
Nfqpoj-[3118iù	Clinical, echographic and magnetic resonance diagnosis of supraspinatus tendinosis unresponsive to physical and medical therapy	Cervical lesions, undergone intra or periarticular injection of any drugs	subacromial injections under US guidance	Hyalgan®, Fidia SpA once a week for 5 weeks (SH)	sodium chloride solution injections once a week for 5 weeks(SC)	Total=31–71	Total=56	VAS, ROM, echographic controls
ö]hfo-[3123ù	Supraspinatus tendinitis through manifestation and MRI	Younger than 18 years, dislocation or fracture, of the shoulder joint, rotator cuff laceration, cervical radiculopathy, inflammatory joint disease (rheumatoid arthritis and ankylosing spondylitis), malignity, pregnancy, oacgulation disease, received any therapy for the same problem for the last 3 months	Intra-articular glenohumeral joint	2 ml (16 mg) of G–F 20 once a week for 3 weeks	physical therapy agents (transcutaneous electrical nerve stimulation, ultrasound and hot pack)	HI=58.67 PTA=52.50	Total=24 HI=12 PTA=12	VAS, ROM and functional evaluation (function part of the "Society of the American Shoulder and Elbow Surgeons Rating Scale")
Czvo-[3122dZ	Clinically painful arc and Hawkin's sign, positive Neer's impingement sign, partial tear or full thickness tear, subacromial bursitis among periarticular soft tissue disorders of the shoulder in a sonogram	Adhesive capsulitis, history of previous shoulder surgery, steroid or hyaluronate injection in the shoulder for the same cause, hemiplegic shoulder pain syndrome.	subacromial injections under US guidance	40 mg triamcinolone acetonide + 0.5% lidocaine (5 ml) + hyaluronate Hyruan Plus®	40 mg triamcinolone acetonide (1 ml) and 0.5% lidocaine (5 ml)	G1=55.5±12.1 G2=55.4±10.0	Total=26 G1=13 G2=13	VAS, SFA, SDQ, ROM (Flexion,Abduction,IR,ER)
Cthjof-[3119ù	Persistent shoulder pain associated with limitation of ROM, refractory to standard treatments, joint osteoarthritis, rotator cuff tear (partial or complete), and/or primary or secondary adhesive capsulitis	Major injury within the past year, chronic pain lasting for more than five years, cervical spine disease, surgery involving the shoulder within the previous twelve months, inflammatory arthropathy, severe frozen shoulder involving either shoulder (with retention of <20% range of motion), gout or calcium pyrophosphate diseases involving the upper extremities within the previous twelve months, intraarticular corticosteroid injections of any other joint within the previous month, intrarticular hyaluronan therapy within the previous twelve months, radiographic findings indicative of acute fracture of the shoulder, severe loss of bone density, osteonecrosis, severe deformity, osteoarthritis glenohumeral joint equivalent to Kellgren-Lawrence stage IV.	intra-articular glenohumeral joint	(Hyalgan; molecular weight, 500 to 730 kDa) 1 group: Three-Injection Sodium Hyaluronate + phosphate-buffered saline 1 weekly for two weeks 2 group: Five-Injection Sodium Hyaluronate	phosphate-buffered saline 1 weekly for five weeks	1 group=62.3 [SD:12.7] 2 group=63.4 [SD:12.4] PBS=63.6 [SD:12.3]	Total=602 1 group=197 2 group=201 PBS=204	VAS, ROM, night pain, Short-Form Health Survey-12 general health questionnaire, use of rescue medication.
Di pv-[3121ù	Pain around the shoulder, positive impingement sign, positive imaging diagnosis of rotator cuff pathology without a complete tear, not respond to conservative therapy or rehabilitation for at least 3 months; aged between 35 and 80 years	Rheumatic diseases, glenohumeral osteoarthritis, full-thickness cuff tears, fractures, infections or tumors, hypersensitivity to hyaluronate	subacromial space under US guidance	ARTZ once weekly for consecutive 5 weeks	Placebo	HI=51.16±7.84 Placebo=52.38±8.95	Total=54 HI=25 Placebo=26	Constant scores,VAS
N phi tbefsj-[3124ù	Patients between 30 and 80 years old with shoulder pain, a positive Neer, Hawkins sign, ultrasonographic diagnosis of rotator cuff pathology without a complete tear, not respond to conservative treatments or rehabilitation for at least 6 months, signed the informed consent form.	Rheumatic disease, glenohumeral osteoarthritis, full thickness rotator cuff tears, fractures, diabetes mellitus, infections, tumors, had hypersensitivity to hyaluronate, had participated in any other study within 6 months, subacromial injection within 8 weeks, pregnant or planned to become pregnant, risk of complications of intra articular injections such as patients who received anti coagulant drugs.	subacromial injections under US guidance	3 weekly injections of Fermathron™, 20 mg/2 ml of sodium hyaluronate.	3 weekly injections of 0.9% normal saline solution, at 2 mL/syringe.	No significant differences between two in demographic data gender and age	Total:40 HI=20 Control=20	Constant scores,VAS
Dpubojop-[311: ù	Non-traumatic etiology of the rupture of the tendons, documented with the echographic or with the MRI imaging		Intra-articular with anterior access	Jointex starter once a week for 3 weeks followed by a targeted rehabilitative intervention (passive and active assisted kinesitherapy)		Age=78.1	Total=22	VAS,Costant Murley, Shoulder Rating Questionnaires
Ubhjbjdp-[3121ù	Massive rotator cuff tear (physical examination, x-ray,ultrasound or MRI) shoulder OA scored as equal or above grade III Hamada classification	History of shoulder trauma, previous surgery, tumors in the shoulder area, painful conditions in the cervical spine, chronic regional pain syndrome, and active workers' compensation claim or other active litigation involving the affected shoulder. Poultry allergies or allergic reactions to previous viscosupplementation treatments	subacromial injections under US guidance	1 injection of high weight sodium hyaluronate	Not treated	HI=72±6.2 Control=71±6.1	Total:90 HI=30 Control=60	Constant scores,VAS
Nfspmb-[3124ù	Persistent shoulder pain for at least 4 months, clinical diagnosis of RC tendinopathy detected with MRI (high tendon signal intensity that was anatomically intact), no previous treatment with articular or subacromial steroid injections within the last 4 months,	History of shoulder trauma, partial or complete RC tears, calcifying tendinitis, previous arthroscopic or open shoulder surgery, shoulder instability, infections or neoplasm, symptomatic cervical spine disease, rheumatoid arthritis or immune diseases, gout and uric acid diseases, severe medical conditions, pregnant	subacromial injections under US guidance	SportVis™ 1 injections once weekly for 2 weeks	Physical therapy	HA=49±2.35 PT=51±2.64	Total=48 HI=25 PT=23	VAS, Constant–Murley scale, Oxford Shoulder Score, Patient Global Assessment

studies and 3[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 rotaror 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).

Table 2. Clinical results, follows up and complication.

Authors	Pre-treatment scores	Follow-Up	Post-treatment scores	Complication
Jupl b[v-!2: : 6−	ROM= Extension 33.4 ± 14.7 Flexion 118.2 ± 37.8 Adduction 14.6 ± 16.0 Abduction 100.2 ± 36.8 Internal rotation 63.8 ± 26.8 External rotation 39.3 ± 32.1	8.16±0.88 w	Pain at rest=39 Improved, 13 Unchanged, 0 Aggravated, 52 Total Assessed, 75.0 Improvement Rate (%) Pain on motion= 42, 15, 0, 57, 73.7 Pain on pressure= 26, 7, 0, 33, 78.8 ADL: Face washing 15, 16, 0, 31, 48.4 Hair grooming 30, 16, 0, 46, 65.2 Tying a sash behind the back 32, 16, 0, 48, 66.7 Placing hand on opposite shoulder 20, 12, 0, 32, 62.5 Removing upper garments 23, 13, 1, 37, 62.2 ROM: Extension 35.7 ± 14.5 <O.Ol (35 patient) Flexion 130.0 ± 35.8 <O.OOl (55) Adduction 17.9 ± 18.8 <0.05 (35) Abduction 116.0 ± 35.6 <O.OOl (58) Internal rotation 68.9 ± 22.2 <O.Ol (37) External rotation 47.9 ± 31.9 <O.OOl (38) Global improvement rating: 32 (51.6%) of 62 patients=moderately improved or better 51 (82.3%) of 62 patients=slightly improved or better.	none
Ti jcbib-!3112ù	Patient background and ROM=NS between two groups UCLA score(satisfaction patient)= HI:13.6 ± 2.6 DI:11.9 ± 3.6 (NS)	4,24 w	UCLA score(satisfaction patient=16): HI (16p): 27.6 ± 3.1(4w), 26.2 ± 3.1(24w) P < .0001 DI (15p):26.5 ± 2.0(4w), 25.3 ± 2.5(24w) P < .0001 ROM in abduction (24w): significantly different	none
Nfmoj-!3118ù−	VAS=SH=8.7 SC=8.5	4 w,3 SH+SC 6,12 m SH only	VAS=SH=2.8 (4w),3.1(12w),3.8(6m),5.1(1y) SC=8.0 (4w),8.1(12w), ROM=unchanged echographic controls= no no substantial differences in aspects regarding betwen two groups	none
ö !hfo-!3123ùà	Pain at rest: HI: 0.5 (0–3.5) PTA: 3 (0–6.5) P value >0.05 Pain on motion:HI:6 (4–9.5) PTA: 5 (4.5–8.5) P value >0.05 Pain at night:HI: 5 (3.5–8.5) PTA: 8.5 (6.5–10) P value >0.05 Functional evaluation: HI:37 (29.5–44.5) PTA: 24 (16.5–39) P value >0.05 ROM HI/PTA: P value >0.05	3w,3m,4y	Pain at rest: HI: 0 (0–2.5), 0 (0–1.5), 0 (0–0) PTA: 0 (0–0), 0 (0–0), 0 (0–0) P value >0.05 >0.05 >0.05 Pain on motion: HI: 0.5 (0–4), 0 (0–0), 0 (0–0) PTA: 0 (0–3), 2.5 (0–4), 0 (0–0) P value >0.05 <0.05 >0.05 Pain at night:HI: 2 (0–4.5), 0 (0–3), 0 (0–0) PTA: 0 (0–1), 1 (0–4), 0 (0–0) P value >0.05 >0.05 >0.05 Functional evaluation: HI:56.5 (52–60), 60 (59,5–60), 60 (60–60) PTA:56.5 (40–59), 56 (46–59), 60 (60–60) P value >0.05 <0.05 >0.05 ROM: P value >0.05 HI/PTA at 3e,6m,4y. P value <0.05 in active abduction at 3m	none
Czvo-!3122ùŽ	VAS: G1:7.7±1.7 G2: 6.9±1.9 SFA: G1:67.4±18.6 G2:67.2±7.7 SDQ: G1:10.5±6.4 G2:8.9±4.5 ROM: Flexion 170.0±17.3 (G1)166.2±15.0 (G2) Abduction 151.5±25.4(G1) 159.2±19.8(G2) IR 56.9±23.6 (G1)83.9±17.1(G2) ER 73.1±25.0(G1) 83.9±11.2(G2)	1w after 1 inj, 1w after 2inj, 2w after 3 inj	VAS G1=4.7±2.2 (p<0.05) 2.8±1.2 (p<0.05) 1.7±1.1 (p<0.05) G2=3.5±1.8 (p<0.05) 2.5±1.5, 2.4±1.9 (p<0.05) SFA G1 =79.3±11.8 (p<0.05) 86.3±9.9 (p<0.05) 91.0±8.0v G2=80.9±10.5, 86.0±8.2, 86.0±8.3 (p<0.05) SDQ G1=6.6±6.0 (p<0.05) 5.1±4.8 (p<0.05) 3.5±3.8 (p<0.05) G2=4.9±3.8 (p<0.05) 3.5±2.8, 3.1±2.6 (p<0.05) ROM: Flexion G1=176.2±11.2 (p<0.05)177.7±8.32 178.5±5.6 (p<0.05) G2=175.4±8.8, 178.5±3.8, 177.6±6.0 (p<0.05) Abduction G1=163.9±19.4 (p<0.05) 170.8±14.4 (p<0.05) 174.6±10.5 (p<0.05) G2=172.3±9.3 (p<0.05) 176.2±5.1, 176.2±8.7 (p<0.05) Internal rotation G1=70.4±23.3 (p<0.05) 76.2±20.6 (p<0.05) 80.1±17.1 (p<0.05) G2=65.4±14.5, 66.2±15.6, 69.2±17.1 (p<0.05) External rotation G1=83.9±17.1 (p<0.05) 84.6±14.5 86.2±9.6 (p<0.05) G2=83.85±11.2, 89.2±2.8, 89.2±2.8 (p<0.05)	none
Chjof-!3119ù		7,9,13,17,26 w	Mean Reduction from Baseline VAS 1 group=22.9 ± 1.8 (7w), 25.0 ± 1.8(9w),26.3 ± 1.8(13w),27.4 ± 1.9(17w), 30.9 ± 1.9(26w) 2group=26.0 ± 1.8 (7w), 26.4 ± 1.8(9w),26.4 ± 1.8(13w),29.8 ± 1.8(17w), 27.8 ± 1.9(26w) PBS=20.1 ± 1.8(7w),22.6 ± 1.8(9w),23.0 ± 1.8(13w),21.9 ± 1.9(17w),23.6 ± 1.9(26w) p 1g/PBS=0.228(7w),0.320(9w),0.173(13w),0.025(17w),0.005(26w) p2g/PBS=0.011(7w),0.116(9w),0.155(13w),0.001(17w),0.100(26w) treatment effect through 26 weeks was significant in patients with osteoarthritis in the three-injection (p = 0.003) and five-injection (p = 0.002) groups ROM HI/PBS=p < 0.05 PAIN NIGHT: 1g/PBS at 17w p=0.009, at 26w p=0.003 2g/PBS at 7w p<0.001, at 17w p=0.003 PATIENT GLOBAL ASSESSMENT: 1g/PBS at 26w p= 0.019 2g/PBS at 7 w p= 0.012	The most frequently adverse event: injection-site pain (1g:3,2%, 2g:1,4%, PBS:1,4%)
Di pv-!3121ù	Constant score: HI=61.64±13.37 Placebo=64.89±9.46 VAS: HI=6.36±1.35 Placebo= 6.46±1.27	1 w, 6 w, 2 y after 5 injections	Constant score: HI=72.48±16.46(1w), 79.24±13.09(6w) Placebo=72.42±11.75(1w), 69.07±13.29(6w) VAS: HI=4.20±1.76(1w), 3.04±2.03(6w) Placebo= 4.77±1.75(1w), 5.12±2.42(6w)	none
Nphi tbefsj-!3124ù	Constant score: HI=37.7+9.9 Control=40.5±11.3 VAS: HI=9.35±1.1 Control=9.5±0.8	1,2,3,12 w	Constant score: HI=70.4±16.9(12w) Control=50.7±13.2(12w) P=0.00 VAS: HI=6.8±1.5(1w) 4.9±1.8(2w) 3.1±2.4(3w) Control=8.2±1.2(1w) 7.3±1.4(2w)(p=0.001) 6.8±1.9(3w)(p=0.001)	none
Dptuboojop-!311: ù		1,3,6 m	Friedman test V.A.S. p<0.0005 Costant Murley p<0.0005 ShoulderRating Questionnaire p<0.0005 Flexion p<0.0005 Abduction p<0.0005	none
Ublujbgjdp-!3121ù	Constant score (p:NS): HI=35±6.6 Control=37±3.2 VAS (p:NS): HI=7.7±2.3 Control= 7.6±1.2	1,2,3,4,5,6 m	Constant score: HI=66±3.1(1m),65±3.2(2m),66±3.4(3m),62±3.0(4m),42±3.8(5m),46±3.3(6m) Control=37±6.9(1m),35±7.2(2m),33±6.1(3m),34±6.5(4m),34±6.5(5m),32±7.2(6m) p HI/Control=<0.001(1m),<0.001(2m),<0.001(3m),<0.001(4m),NS(5m),NS(6m) VAS: HI=1.9±1.2(1m)1.7±1.2(2m),2.3±1.2(3m),3.3±1.4(4m),5.8±1.9(5m),7.2±2.3(6m) Control=6.9±2.2(1m),6.8±2.5(2m),6.6±1.9(3m),7.8±3.1(4m),7.4±2.2(5m),7.6±1.2(6m) p HI/Control=<0.001(1m),<0.001(2m),<0.001(3m),<0.001(4m),NS(5m),NS(6m)	mild vagal reaction in 1/30 patients (3%)
Nfspnb-!3124ù	VAS HI=7.48 ± 1.61 PT=7.17 ± 1.23 (p:0.9671) CS= HI=53.08 ± 1.04 PT=52.91 ± 2.10(p:0.9539) OSS= HI=23.28 ± 0.98 PT=26.21 ± 1.08(p:0.7841)	2,4,12,24 w	VAS= HI=4.22 ± 0.96 (2w), 4.12 ± 1.12 (4w), 4.01 ± 1.04 (12w), 6.04 ± 1.21 (24w) PT=4.43 ± 1.26 (2w)(p:0.7281), 6.34 ± 1.18(4w)(p:0.0149), 6.17 ± 1.16 (12w)(p:0.0168),6.26 ± 1.32(24w)(p:0.8725) CS= HI=70.12 ± 1.09 (2w), 69.72 ± 1.16(4w), 67.44 ± 1.09 (12w), 59.04 ± 1.13(24w) PT=66.82 ± 1.92(2w)(p:0.8782), 59.21 ± 1.88 (4w)(p:0.0492), 59.30 ± 1.21(12w)(p:0.0593), 57 ± 1.89(24w)(p:0.2891) OSS= HI=38.68 ± 1.12(2w), 38.12 ± 1.21 (4w), 38.21 ± 1.16(12w), 29.36 ± 1.07(24w) PT=37.21 ± 1.04(2w)(p:0.9614),29.13 ± 1.09(4w)(p:0.0395),29.34 ± 1.03(12w)(p:0.0485),28.82 ± 1.15(24w)(p:0.9238)	none

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

cortisone injections, if prolonged, may be contra-indicated in elderly patients with comorbidities[30-32] such as diabetes or hypertension. In fact, the HA is physiologically present in the synovial fluid[33]: its main role is to lubrificate the joint, it exerts mechanical and biological functions, in terms of anti-adhesive shock absorber and articular stabilizer against shear stresses[34], 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, lubrificates 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[16] (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 examinated 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.
Chou[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 conduct according ethically to international standards and as required by the journal as described[46].

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