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REVIEW ARTICLE

Outcomes of hyaluronic acid injections for glenohumeral osteoarthritis: a systematic review and meta-analysis

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Background: Hyaluronic acid (HA) is an analgesic and chondroprotective agent often used for the nonoperative treatment of osteoarthritis (OA). The effects of HA injections are well studied in the treatment of knee OA, but the effects in glenohumeral OA remain unclear. This study evaluated the efficacy of HA to reduce pain in patients with glenohumeral OA.

Methods: PubMed, MEDLINE, CENTRAL, and Embase were searched from the database inception date through January 16, 2018. Two reviewers independently screened articles for eligibility and extracted data for analysis. A methodological quality assessment was completed for all included studies, including assessment of risk of bias. The primary outcome was change in visual analog scale for pain. The secondary outcomes were functional outcome and adverse events.

Results: In the HA arm, the reduction of visual analog scale pain score at 3 months was 26.2 mm (95% confidence interval, 22.0-30.3 mm; $I^2 = 31\%$) and at 6 months was 29.5 mm (95% confidence interval, 25.5-33.4 mm; $I^2 = 19\%$). All studies reported an improvement in functional outcome. Similar clinical improvements were reported in the intervention and control groups, suggesting that these improvements may not be directly related to HA. Commonly reported adverse events were rare and included swelling and mild pain at the injection site, local effusion, lethargy, and face rash.

Conclusion: Intra-articular HA injection is safe and improves pain for patients with glenohumeral OA. Pain improvements also reported in the control group suggest that a significant placebo effect may be present with respect to intra-articular shoulder injection. Further randomized controlled trials are necessary to evaluate the efficacy of HA and identify optimal dosing and route of administration.

Level of evidence: Level IV; Systematic Review

Keywords: Shoulder; osteoarthritis; hyaluronic acid; pain management; shoulder arthroplasty; intra-articular injection

This review did not require Institutional Review Board approval.

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Osteoarthritis (OA) is the leading cause of disability in elderly individuals.[27] With a forecasted prevalence of 18.2% in the American population by 2020, OA is a significant socioeconomic burden for patients and the health care system.[27]

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OA involves the degeneration of articular cartilage, resulting in pain, functional limitations, and disability.[11] Definitive surgical treatment for glenohumeral OA is shoulder arthroplasty, which is effective but is associated with significant cost and morbidity. Arthroplasty is avoided in young patients due to longevity concerns and is not indicated in early OA.[8]

Current forms of nonoperative management of glenohumeral OA include nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injections.[8] Evidence supporting these treatments has been inconclusive, and may be associated with a significant adverse effect profile.[3,38] NSAIDs, for instance, have the potential to cause gastrointestinal, renal, and cardiac effects.[21,43]

During the past 2 decades, hyaluronic acid (HA) has emerged as an alternative treatment for the conservative management of OA.[8] HA has both analgesic and chondroprotective properties.[8] In an arthritic glenohumeral joint, inflammatory effusion, abnormal synoviocytes, and molecular fragmentation can decrease the HA concentration by 33% to 50%.[15] Decreased lubrication places further stress on diseased cartilage, thereby damaging the integrity of the chondral surface and resulting in further pain.[15] HA therapies can be broadly classified as high-molecular-weight (HMW) preparations, 620 to 3200 kDa, and low molecular weight (LMW) preparations, 500 to 730 kDa.[1] Comparatively, natural human HA is a single-chain product with a molecular weight of 5000 kDa.[36] The efficacy of HMW compared with LMW is unclear in the setting of glenohumeral OA.

Evidence in animal models suggests that HA may have immunologic properties by reducing the concentration of inflammatory mediators such as prostaglandins, fibronectin, and cyclic adenosine monophosphate.[15] This is supported by the observation that although HA has a relative short half-life to provide lubrication, the pain relief associated with HA can be maintained up to 6 months after the injection.[1,3,6,7,22,34,37,47] These findings have sparked growing interest in the expanded use of HA as a conservative treatment for OA.

Several reviews have been published on the effect of viscosupplementation for OA involving joints other than the knee. Strauss et al[45] reported that HA injection is well tolerated to treat shoulder pain of various pathologies and may present as an alternative to physical therapy and steroid injections. A systematic review by Colen et al[13] in 2012 identified a sample of 6 studies, of which only 3 included a homogenous population of patients with OA. Due to the diversity of shoulder pathologies, no quantitative synthesis could be performed. In 2014, Colen et al[12] published a systematic review of 8 studies on the effect of intra-articular HA injections for glenohumeral OA.

Since then, 4 additional studies have been published,[3,18,22,38] of which 2 studies are large randomized controlled trials (RCTs).[3,18] Given that experts recommend limiting viscosupplementation to primary glenohumeral OA after excluding other shoulder pathologies,[24] we wanted to conduct a systematic review on the use of viscosupplementation in a homogenous cohort of patients with glenohumeral OA.

Currently, viscosupplementation is primarily indicated for patients with OA of the knee[24] but is frequently prescribed off-label for the hip, ankle, and shoulder. The purpose of this systematic review and meta-analysis was to comprehensively review the literature evaluating the efficacy of HA with respect to pain relief and safety in patients with glenohumeral OA. We hypothesized that HA would result in a significant reduction in shoulder pain but that a significant therapeutic placebo effect also may be present.

Materials and methods

This study was conducted following the methods of the *Cochrane Handbook for Systematic Review of Interventions*[25] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[35]

Eligibility criteria

We included studies that (1) enrolled patients aged older than 18 with (2) primary glenohumeral OA who received (3) intra-articular injections of HA. Studies that recruited patients with adhesive capsulitis, rheumatic arthritis, or tendonitis were excluded. There were no restrictions regarding the use LMW or HMW HA, comorbidities, previous treatment for shoulder OA, length of follow-up, publication date, or language of publication. We excluded editorials, reviews, expert opinions, and basic science articles.

Identification of studies

A systematic search was conducted using MEDLINE, CENTRAL, and Embase from the database inception date through January 16, 2018. The search was adapted to PubMed by including articles published online ahead of print. Investigators with methodological and content expertise developed and performed the search. Medical Subject Headings and Emtree headings and subheadings were used to increase sensitivity (see Supplementary Appendices S1-S4). A hand search of related references and cited articles was also performed.

Screening and assessment of eligibility

Two reviewers (B.Z. and A.T.) used piloted screening forms to independently screen the titles and abstracts of all studies for eligibility. Duplicate articles were manually excluded. The full-text review of all potentially eligible studies was completed independently and in duplicate. Discrepancies were discussed by the 2 reviewers until agreement was reached. Remaining discrepancies were resolved in a consensus decision with a third reviewer (M.K.).

Data extraction and assessment of risk of bias

Data were extracted independently by both reviewers (B.Z. and A.T.) using a piloted electronic Excel data extraction form (Microsoft, Redmond, WA, USA). The primary outcome was change in the visual analog scale (VAS) pain score (mm), and the secondary outcomes were function outcome and adverse events. Extracted data included year, study location, journal of publication, number of patients, sex, age at time of surgery, dose and route of administration of HA,

severity of OA, comorbidities, comorbid shoulder conditions, adverse events, and length of follow-up.

Two reviewers (B.Z. and A.T.) independently assessed the methodological quality using the Methodological Index for Non-Randomized Studies (MINORS)[44] tool for all nonrandomized studies and the Cochrane Risk-of-Bias Tool for all Randomized Controlled Trials.[26] Level of evidence was graded according to the criteria of Wright et al.[48] The quality of evidence and across outcomes was assessed by the Grading of Recommendations Assessment, Development and Education (GRADE) approach.[41]

Statistical analysis

Interobserver agreement for the title and abstract screening and full-text screening were calculated with the Cohen unweighted κ statistic.[30] Interobserver agreement for risk of bias was calculated using the intraclass correlation coefficient (ICC). The κ and ICC values were calculated using Excel. Mean differences (MDs) were used to summarize identical continuous outcome measures. The MDs were weighted by sample size using the random effects model based on the inverse variance method.[25] Standard deviations (SDs) were calculated from confidence intervals (CIs) or standard errors, whenever possible. Imputation of standard deviations for changes from baseline was conducted in accordance to the *Cochrane Handbook*.[25] Adverse events, and functional outcomes are presented descriptively. Publication bias was assessed using forest plots. The forest and funnel plots were created with RevMan 5.2 software (Cochrane Collaboration, London, United Kingdom).[46]

Evaluation of heterogeneity and sensitivity analysis

Heterogeneity was quantified using the χ^2 test for heterogeneity and the I^2 statistic, which estimates the proportion of total variability among studies due to heterogeneity rather than chance alone.[25] I^2 values were interpreted according to the *Cochrane Handbook:* 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, and 50% to 90% substantial heterogeneity.[25] A priori hypotheses were developed to evaluate study design as a potential source of heterogeneity.

Results

Search results and study characteristics

The literature search generated 1658 relevant citations. After removal of duplicates and application of eligibility criteria, 1392 articles were identified from the electronic search and 2 from the manual search and underwent title and abstract screening. Of the 31 articles eligible for full-text review, 15 met all inclusion criteria, which enrolled 1,594 patients in total.[2,3,7,8,10,19,20,23,30,32,35,38,39,44,49] Seven studies were available for quantitative synthesis enrolling a total of 1,001 study participants (Fig. 1).[3,6,7,22,34,37,47] The remaining 8 articles did not report a mean change in the VAS pain score from baseline or did not contain a descriptor of deviation from the mean necessary to estimate the CI. The κ for overall agreement between reviewers for final eligibility was 0.86.

Of the 15 included studies, 7 were conducted in the United States,[3,6,7,29,34,42,47] 1 in China,[22] 4 in Italy,[8,18,31,38] 1 in Germany,[37] 1 in Turkey,[19] and 1 in Spain.[2] There were 10 single-center studies,[2,7,9,18,19,22,31,34,42,47] and 5 multicenter studies.[3,6,29,37,38] Demographics were tabulated by treatment group (Table I). Dosage, administration schedule, and type of HA administered was also tabulated by treatment group (Table II). Length of follow-up ranged from 12 weeks to 36 weeks.

Study quality and risk of bias

The 15 studies included in the review consisted of 5 RCTs (Level I Evidence),[2,3,6,18,29] 6 prospective cohort studies (Level II Evidence),[7,9,22,31,37,47] 1 retrospective cohort study (Level III Evidence),[34] and 3 case series (Level IV Evidence).[19,38,43] Of the 7 studies included in the meta-analysis, 2 were double-blind RCTs (Level I Evidence),[3,6] 4 were prospective cohort studies (Level II Evidence),[7,22,37,47] and 1 was a retrospective cohort study (Level III Evidence).[34] The MINORS score for nonrandomized studies and the Cochrane risk of bias assessment for randomized studies are summarized in Table I and Fig. 2, respectively. Interobserver agreement in the assessment of risk of bias was excellent (ICC, 0.993; 95% CI, 0.975-0.998). Reviewers rated the quality of evidence for all comparisons of VAS pain as moderate given the potential risk of bias from inclusion of non-RCTs in the analysis (Table III).

HA administration

The dose and type of HA varied among studies. The dose of HA varied between 2 mL and 8 mL.[3,6,7,9,18,37,42,47] The frequency of injections is listed in Table II. Of the 10 studies that described the injection technique, 2 studies used image-guided technique,[6,38] 7 used blind technique,[6,9,18,34,37,43,47] and 1 used a combination of both.[29] The injection approach was described in 8 studies, of which 4 studies used a posterior approach,[7,18,34,38] 2 used an anterior approach,[9,43] and 2 left the approach up to the discretion of the clinician.[5,47] Five studies examined the use of HMW HA (620-3200 kDa),[3,9,18,29,47] 7 studies examined the use of LMW HA (500-730 kDa),[6,7,22,34,37,38,42] and 3 studies did not specify the molecular weight of HA used.[2,19,31] Single-chained HA preparations were administered in 7 studies,[3,6,9,18,22,29,47] branched HA preparations were administered in 5 studies,[7,34,36-38,42] and the remaining 3 studies did not describe HA structure.[2,19,31]

VAS pain

Administration of HA resulted in a significant decrease in VAS pain. The MD improvement in VAS pain score was 26.2 mm

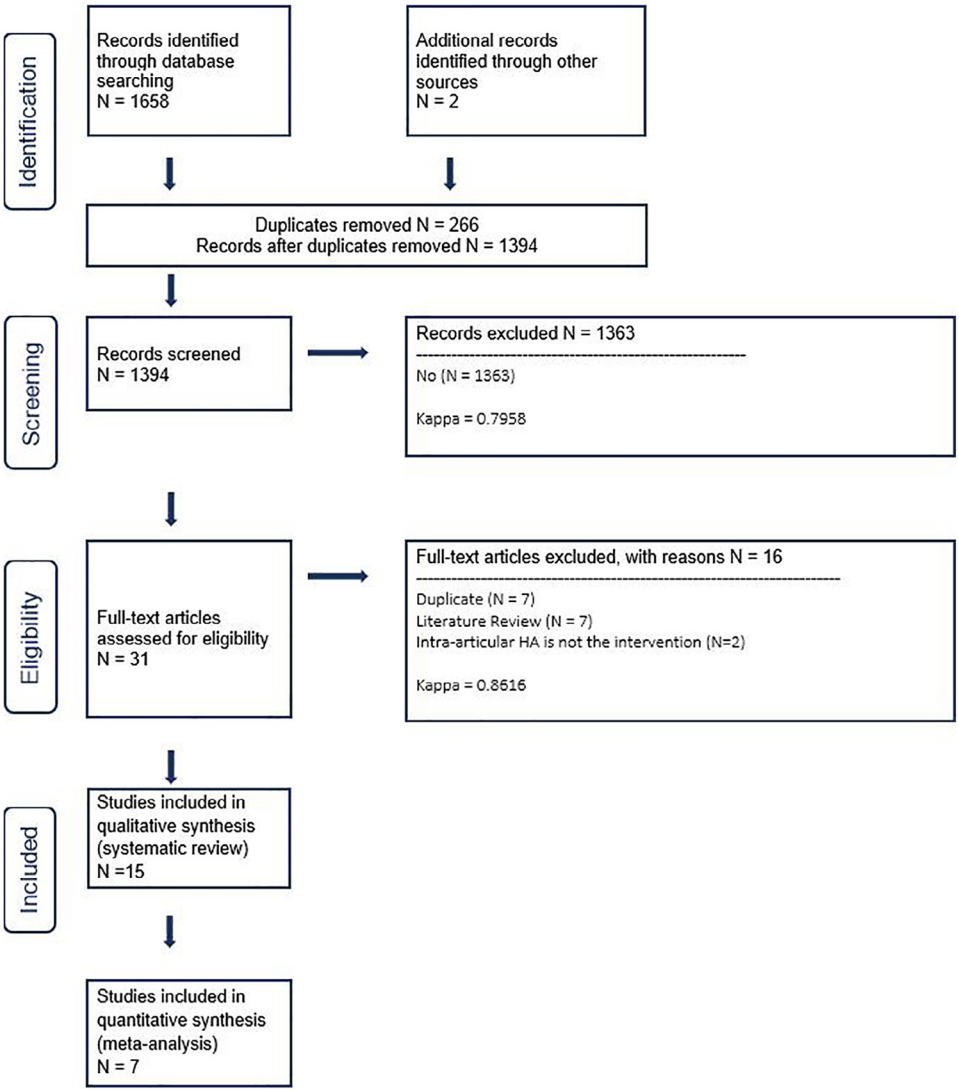

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram describing the inclusion of studies.

(95% CI, 22.0-30.3 mm; Fig. 3) at 3 months' follow-up and 29.5 mm (95% CI, 25.5-33.4 mm; Fig. 4) at 6 months' follow-up compared to baseline. Kwon et al[29] and Blaine et al[6] compared the effect of HA injection vs. phosphate-buffered saline; however, their findings did not reach statistical significance. Kwon et al[29] reported a MD of 2.8 mm in favor of the HA group, but this was not reach statistical significance ($P = .112$). Blaine et al[6] reported a between-group difference in reduction of VAS pain of -1.2 ± 3.4 mm ($P = .720$) between a 3-injection HA group vs. control.

Merolla et al[34] and Aileen et al[3] compared HA to corticosteroid therapy and reported nonsignificant differences between groups with respect to pain relief between the 2 therapies. At 6 months' follow-up, the improvement in VAS pain for the HA group vs. corticosteroid group was 36.0 ± 7.4 mm vs. 68.0 ± 12.7 mm for the Merolla et al[34] study and 28.92 ± 2.23 mm vs. 30.39 ± 3.04 mm for the Aileen et al[3] study.

We performed a subgroup analysis of change in VAS pain by the type of control, which included corticosteroids, phosphate-buffered saline, and no control. At 3 months, the MD improvement in VAS pain was 27.0 mm (95% CI, 21.2-32.8 mm; $I^2 = 86\%$) for the corticosteroid group, 24.7 mm (95% CI, 21.3-28.1 mm; $I^2 = 10\%$) for the phosphate-buffered saline group, and 28.0 mm (95% CI, 15.3-40.7 mm; $I^2 = 0\%$) for the no control group. These subgroups were unable to explain the source of heterogeneity.

Functional outcome

Reporting for functional outcome was highly variable across studies. The most common scales used to measure functional outcome included the Constant-Murley Shoulder score, Short-Form Health Survey questionnaire, Western Ontario Rotator Cuff Index score, Simple Shoulder Test, Western

Table I Characteristics of all included studies

Study	Publication year	Location	Study design	Level of evidence	Patients, No. (% male)		Patients	Mean MINORS score
					Intervention	Control	No. (% male)	
Aileen et al[3]	—	USA	Double-blind RCT	I	87 (76.0)	183 (75.9)	270 (75.9)	—
Blaine et al[6]	2008	USA	Double-blind RCT	I	265 (—)	133 (—)	398 (—)	NA
Brander et al[7]	2010	USA	Prospective cohort	II	34 (40.0)	—	34	15/16
Busilacchi et al[9]	2011	Italy	Prospective cohort	II	25 (—)	75 (—)	100 (—)	—
Di Giacomo et al[17]	2017	Italy	Open-label RCT	I	39 (43.6)	39 (38.5)	78 (41.0)	NA
Eyigor et al[15]	2009	Turkey	Prospective case series	IV	15 (—)	—	15	12/16
Guo et al[20]	2015	China	Prospective cohort	II	129 (52.7)	—	129	12.5/16
Kwon et al[26]	2013	USA	Double-blind RCT	I	150 (59.3)	150 (50.0)	300 (54.7)	NA
Leardini et al[28]	1998	Italy	Prospective cohort	II	17 (—)	12 (—)	29 (—)	—
Merolla et al[30]	2011	USA	Retrospective cohort	III	51 (25.5)	33 (30.3)	84 (27.4)	20/24
Noël et al[33]	2009	France, Germany	Prospective cohort	II	33 (54.5)	—	33	14/16
Pereira et al[2]	2008	Spain	RCT	I	15 (—)	15 (—)	30 (—)	—
Porcellini et al[34]	2015	Italy	Prospective case series	IV	41 (73.2)	—	41	14/16
Silverstein et al[39]	2007	USA	Prospective case series	IV	27 (63.0)	—	27	12/16
Weil et al[44]	2011	USA	Prospective cohort	II	27 (51.9)	—	27	14.5/16

MINORS, Methodological Index for Non-Randomized Studies; *RCT*, randomized controlled trials.

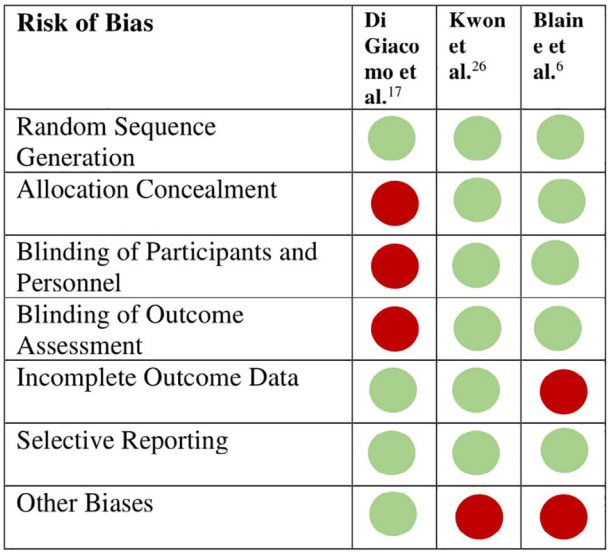

Figure 2 Cochrane Risk of Bias Assessment for Randomized Controlled Trials included in the meta-analysis. *Red* represents a high risk of bias in a given assessment category, while *green* represents a low risk of bias.

Ontario and McMaster Universities Osteoarthritis Index, Western Ontario Osteoarthritis of the Shoulder, and University of California, Los Angeles Shoulder Rating Scale. Of the 9 studies reporting functional outcome, all reported improvement after HA administration[3,7,18,22,34,37,38,42,47] (Table IV). Of the 7 studies with qualitative data included in Table IV, 4 studies found statistically significant improvements in functional outcome between the baseline and 26-week follow-up.[6,18,34,47] Assuming a minimally clinically important difference of +10.4 points for the Constant-Murley score,[28] Porcellini et al,[38] Merolla et al,[34] and Di Giacomo et al[18] reported a clinically significant improvement in functional outcome. Two studies only provided qualitative descriptions of functional outcome. Blaine et al[6] compared improvements in range of motion between intervention and placebo and found a statistically significant but clinically insignificant increase in range of motion in favor of HA injections. Kwon et al[29] also compared functional outcome for intervention and placebo, but found no statistical difference between the 2 groups. In studies comparing HA injections to corticosteroid injections, a similar trend of nonsignificance with respect to between-group comparisons of functional outcome was observed.[3,34]

Adverse events

Thirteen studies recorded adverse events after intra-articular administration of HA[2,3,7,8,19,20,23,30,35,38,39,44,49] and found a pooled adverse event rate of 33.92% (406 of 1197) and a serious adverse event rate of 5.35% (64 of 1197). Almost all of these events were deemed by the study investigators to be not related to the study product. Common adverse events include musculoskeletal pain, headache, pain at injection site, diarrhea, and flu symptoms.[3,6,7,19,29,34,37,38,42,47] Serious adverse events include severe musculoskeletal pain, abscess, chest pain, and cancer. Similar findings were present in control groups receiving intra-articular injection of corticosteroids or

Table II Classification of osteoarthritis and characteristics of study drug

Study	Stage of osteoarthritis					Intervention	Control
	I	II	III	IV	Not specified	Hyaluronic acid administration	Type of control
Aileen et al[3]	—	—	—	—	270	One-time injection of 8 mL of Orthovisc	One-time injection of 6 mL of anesthetic (Marcaine) with 2 mL of corticosteroid (Celestone)
Blaine et al[6]	—	—	—	—	398	Two groups: (1) received 3 weekly 2 mL injections of sodium hyaluronate at a dosage of 10 mg/mL; and (2) 5 weekly 2 mL injections of sodium hyaluronate at a dosage of 10 mg/mL	Five weekly 2 mL injection of phosphate-buffered saline solution
Brander et al[7]*	0	1	8	25	—	Two injections of 2 mL hylan G-F 20, under fluoroscopic guidance, 2 weeks apart	—
Guo et al[20]	—	—	—	—	129	All patients received NSAIDs, corticosteroid injection, and sodium hyaluronate on an unspecified schedule over 3 years	—
Merolla et al[30†]	21	51	12	0	—	Three weekly injections of hylan G-F 20	Three weekly injections of 6-methylprednisolone 40 mg/mL
Noël et al[33]	—	—	—	—	33	One-time injection of 2 mL of hylan G-F 20 under fluoroscopic guidance with a second injection given at 1, 2, or 3 months if patients had inadequate pain relief	—
Silverstein et al[39‡]	2	11	14	0	—	Three weekly injections of 2 mL of hylan G-F 20	—
Weil et al[44]	—	—	—	—	27	Three weekly injections of 2.5 mL of Euflexxa	—

NSAIDs, nonsteroidal anti-inflammatory drug.
Orthovisc, Anika Therapeutics, Bedford, MA, USA. *Marcaine,* Hospira, Inc., Lake Forest, IL, USA. *Celestone*, Schering, Kenilworth, NJ, USA. *Hylan G-F 20*, Sanofi, Paris, France. *Euflexxa*, Ferring Pharmaceuticals, Parsippany, NJ, USA.
* Kellgren-Lawrence criteria[25] used for grading of osteoarthritis.
† Samilson and Prieto criteria[38] used for grading of osteoarthritis.
‡ Guyette et al criteria[18] used for grading of osteoarthritis.

Table III GRADE summary of findings

Quality assessment							Quality
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Pain							
7	2 RCTs, 5 observational studies	Not serious	Not serious	Not serious	Serious	Wide confidence intervals with nonrandomized studies. Larger effect size with retrospective studies	⊕⊕⊕◯ Moderate
Functional outcome							
9	2 RCTs, 7 observational studies	Not serious	Serious	Not serious	Serious	Diverse population based measure by different scales	⊕⊕◯◯ Low

GRADE, Grading of Recommendations Assessment, Development and Education; *RCT*, randomized controlled trial.

phosphate-buffered saline, with a reported pooled adverse event rate of 48.88% (240 of 491) and a serious adverse event rate of 2.24% (11 of 491).[3,6,29,34] Common adverse events in the control group include rash, local effusion, pain at injection site, and musculoskeletal pain.[3,6,34] Infectious complications were not reported in either treatment group.

Discussion

We found a significant reduction in pain at 3 months (MD, 26.2 mm; 95% CI, 22.0-30.3 mm) and 6 months (MD, 29.5 mm; 95% CI, 25.5-33.4 mm) for patients receiving intra-articular HA injections for glenohumeral OA. Also noted were

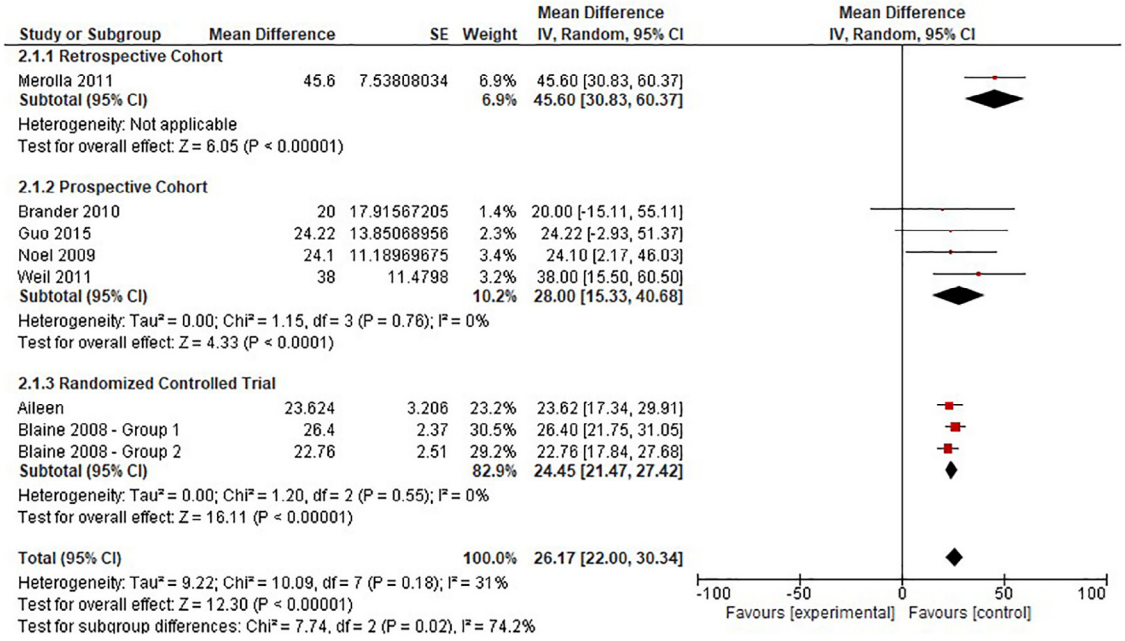

Figure 3 Forest plot of change in visual analog scale for pain at 3 months (intervention) with subgroups by study design. *SE*, standard error; *IV*, inverse variance; *CI*, confidence interval. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *diamonds* indicates the weighted mean difference, and the lateral tips of the diamonds indicate the associated CIs The *horizontal lines* represent the 95% CI.

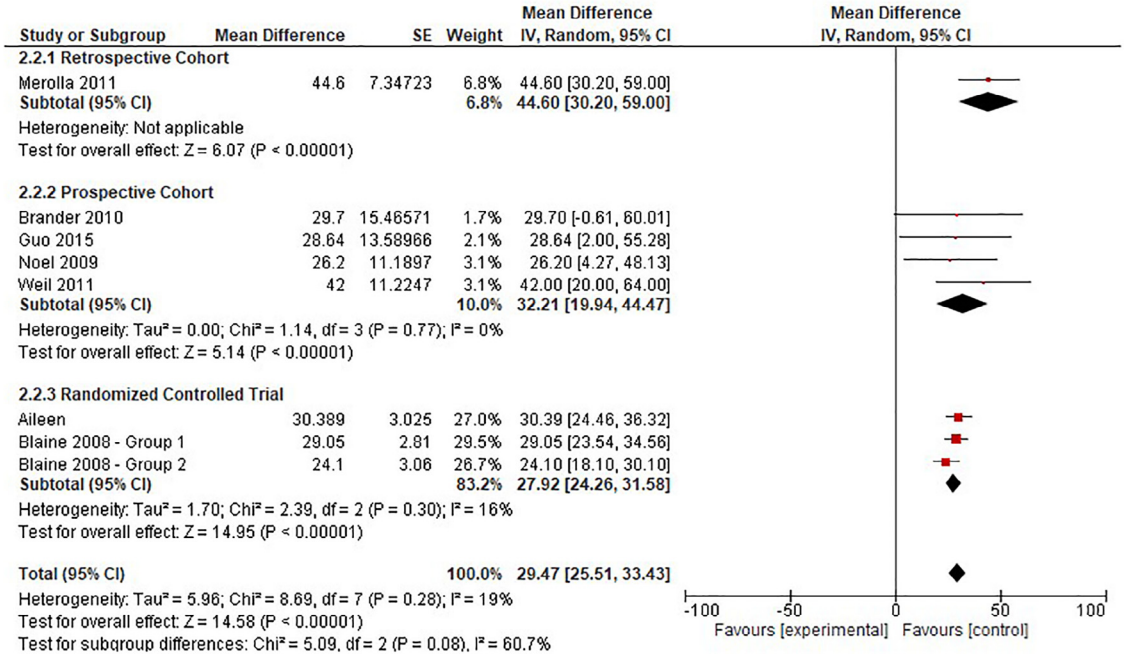

Figure 4 Forest plot of change in visual analog scale for pain at 6 months (intervention) with subgroups by study design. *SE*, standard error; *IV*, inverse variance; *CI*, confidence interval. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *diamonds* indicates the weighted mean difference, and the lateral tips of the diamonds indicate the associated CIs The *horizontal lines* represent the 95% CI.

improved functional outcomes at every follow-up time point across all included studies. Although the intervention groups experienced clinical improvements, many of the control groups experienced smaller but comparable effects. We identified a strong placebo effect of intra-articular shoulder injection. Included comparative studies demonstrated similar outcomes with respect to pain reduction associated with HA injections when compared with placebo, saline, or corticosteroid

Table IV Functional outcome at 3 months and 6 months of follow-up

Study	Change in shoulder function compared with baseline		Functional outcome measure
	At 3 months (%)	At 6 months (%)	
Scores measuring improvement in function			
Di Giacomo et al[17]	—	22.5	Constant-Murley Score
Guo et al[20]	20.6	6.4	Simple Shoulder Test
Porcellini et al[34]	—	26.7	Constant-Murley Score
Silverstein et al[39]	32.5	30.6	UCLA Shoulder Score
Scores measuring decrease in disability			
Merolla et al[30]	−65.1	−59.3	Shoulder Pain and Disability Index
Weil et al[44]	−62.4	−66.6	Western Ontario Rotator Cuff Score
Brander et al[7]	−23.4	−30.0	Western Ontario Rotator Cuff Score

UCLA, University of California, Los Angeles.

injections. The incidence of attributable adverse events was low.

The results of this study are similar to findings in the literature regarding the effects of HA injections.[13,20,24] A 2012 systematic review of 56 trials, including 18 RCTs on the use of viscosupplementation for the hip, shoulder, ankle, carpometacarpal, facet, sacroiliac, and metatarsophalangeal joint, found evidence of decreased pain compared with baseline.[13] The significant placebo effect of intra-articular injection has recently become an area of focus in the literature. Bannuru et al[5] found the placebo effect of intra-articular injection in the knee may exceed the therapeutic effect of oral NSAIDs. This may partly explain the similar findings in comparative studies when evaluating HA injections and various intra-articular placebo interventions.[3,6,29,34]

Improvements in functional outcome and range of motion is variably reported in the literature with respect to intra-articular HA injections.[4,10,20] Systematic reviews have found limited functional outcome improvement with HA for knee and ankle OA compared with placebo.[4,17] This potentially may be attributable to the placebo effect of intra-articular injection.

This systematic review similarly identified functional outcome improvement compared with baseline but was not significantly different when compared with placebo or corticosteroid therapy.

There is uncertainty in the literature regarding the efficacy of LMW HA compared with HMW HA. Although research suggests HMW may be more efficacious with respect to the knee,[39] our study was unable to comment on the association between the molecular weight of HA and effectiveness.

Common adverse effects of intra-articular HA injections include pain at the injection site, effusion, and painful flares,[3,15,39] which is consistent with the findings in our study. Compared with findings in the literature reporting a low rate of local reaction to HA,[8] the incidence of adverse events in this systematic review was high due to the inclusion of events

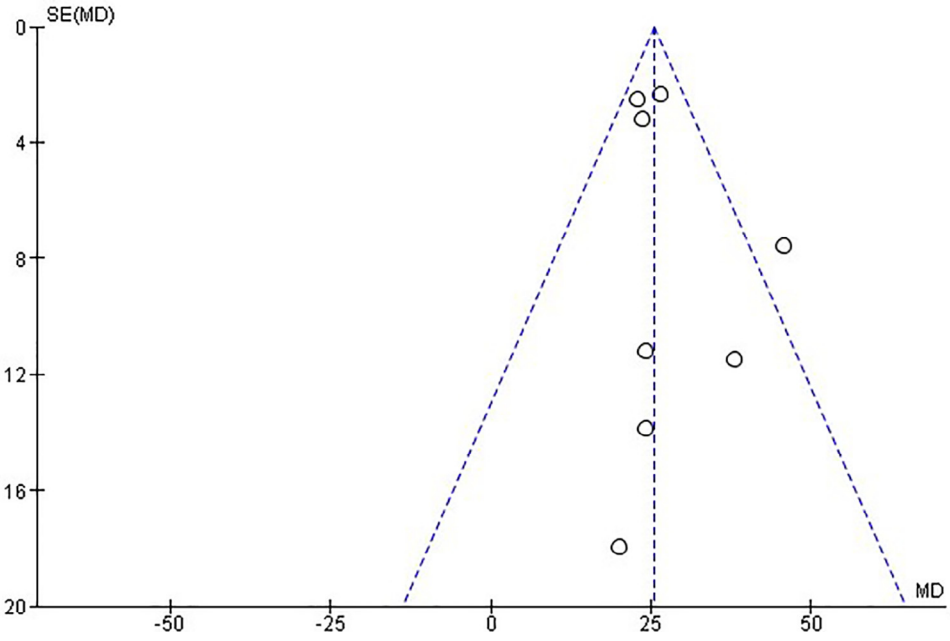

Figure 5 Funnel plot for publication bias for change in visual analog scale for pain at 3 months (intervention). *SE*, standard error; *MD*, mean difference.

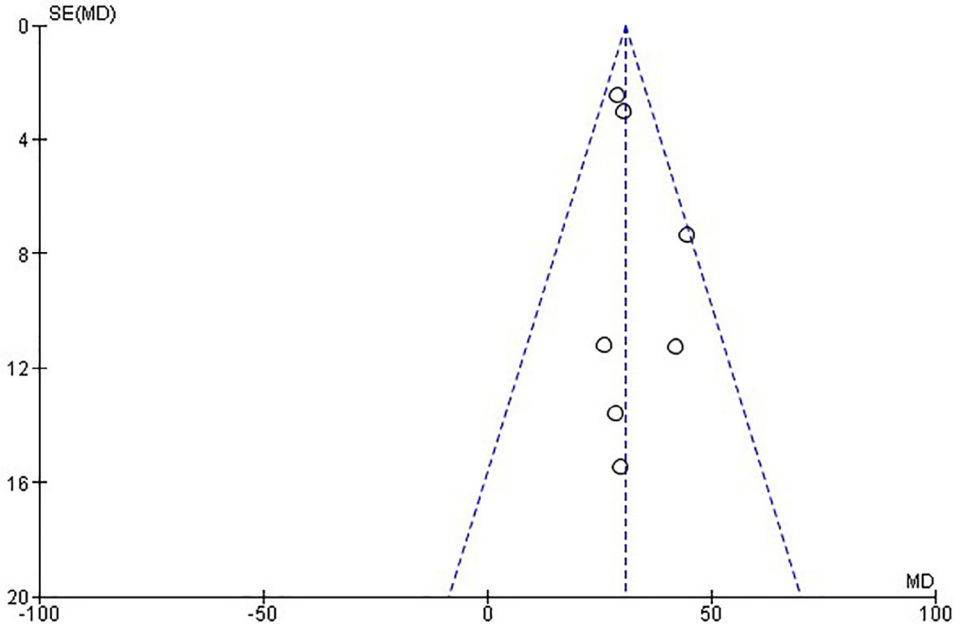

Figure 6 Funnel plot for publication bias for change in visual analog scale for pain at 6 months (intervention). *SE*, standard error; *MD*, mean difference.

not directly related to HA injection (ie, bypass surgery, breast cancer, etc.).

This review used broad search terms, duplicate assessment of study eligibility, and a methodological quality assessment of included studies. The agreement between reviewers regarding study eligibility and methodological assessment was high. Although the small sample size limits the robustness of our conclusions, the funnel plot analysis shows a low risk of publication bias (Figs. 5 and 6).

This study has some limitations. Primarily, the administration of HA varied in the type of HA administered, the number of injections, and dosage. Ultrasound-guided or fluoroscopy technique may offer improved accuracy compared with the blind technique. A RCT validates the clinical significance of improved injection accuracy.[32] However, other researchers have questioned whether improved injection accuracy translates directly into better clinical outcomes.[16,23] There is a similar divide in expert opinion regarding the administration of HMW HA vs. LMW HA. Although some laboratory studies have found that HMW HA has a longer residence time within the joint. However, a *JAMA* review of intra-articular HA injections in the setting of knee OA found "little evidence to support these theories."[33]

In terms of an optimal dosing regimen, 1 meta-analysis of 89 trials examining the dose-dependent efficacy of HA for knee OA found a larger effect size for studies that administered 1 to 3 injections compared with more than 3 injections.[40] However, another meta-analysis on the efficacy of multiple vs. single HA injections found that injections at 2-week to 5-week intervals provided superior pain relief compared with single injections.[14] Because dosing regimens for HA in the setting of glenohumeral OA have not been clearly established, pooling the different regimens reflects current clinical practice.

Baseline demographic of patients with respect to degree of shoulder OA and other shoulder comorbidities resulted in a heterogenous but pragmatic study population. The results of this review are applicable across patient populations. Although the use of HA to treat shoulder pain has been investigated in the literature, this review focuses on the effects of HA specific to shoulder OA and provides a quantitative synthesis of the available data.

Conclusion

Intra-articular HA injection is safe and improves pain for patients with glenohumeral OA. Pain improvements also reported in the control group suggest that a significant placebo effect may be present with respect to intra-articular shoulder injection. Further randomized controlled trials are necessary to evaluate the efficacy of HA and identify optimal dosing and route of administration.

Disclaimer

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jse.2018.09.011.

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