

Efficacy of Hyaluronate injections in rotator cuff disorders: A Level-I Meta-Analysis

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Abstract

Background: Rotator cuff disease is the most common cause of shoulder pain and weakness. Conservative treatment is the first choice of shoulder pain management. Viscosupplementation of hyaluronic acid (HA) seems to be effective for management of tendon disorders.

The objective of this study was to evaluate the scientific evidence reported in literature according to HA shoulder injection in rotator cuff disorders treatment.

Methods: An English-language systematic literature search was performed by two independent researchers; data sources included the following databases: MEDLINE, Embase, CINAHL, Google scholar web, Ovid database, Physiotherapy Evidence Database (PEDro), and the Cochrane Library. We performed a broad research for relevant study up to February 2017. Articles were included if they reported data on clinical and functional outcomes in patients who had undergone HA injection for management of rotator cuff pathology compared to placebo, corticosteroid injection and/or physical therapies. Methodological quality was assessed with the PEDro rating scale. The outcomes were improvement of symptoms (assessed by VAS scale) and shoulder function (assessed through DASH and ASES Score).

Results: 5 RCTs studies (990 patients) were pooled in the Meta-analysis. The PEDro rating scale ranged from 2 to 8. Two studies compared HA injection with corticosteroid injections, patients were injected once a week for three weeks. Four studies compared HA injection with placebo injection, of which two used 3 weekly injections and two used 5 weekly injections. Significant difference was found in pain reduction between HA and placebo group at 26 weeks follow-up (MD= -0.51, 95% CI -0.96 to -0.07), p=0.02.

Conclusion: HA injections might be a valuable safe alternative to other conservative methods for the treatment of rotator cuff disorders. Nowadays, few and low quality randomized controlled trials have been published. Therefore, to reach an overall conclusion about the effect of HA injection in rotator cuff we need more high quality studies.

Level of evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Study design: Meta-analysis.

Introduction

Rotator cuff tendinopathy is a progressive disorder of the shoulder which begins with an acute tendinitis, progresses to tendinosis with degeneration and partial thickness tears, and results in full thickness rupture [1]. Rotator cuff tendinopathy has multifactorial etiology [2]. According to intrinsic factors, tendon degeneration would result from the combination of natural process of aging, poor vascularity, altered biology, and inferior mechanical properties. Constitutional risk factors have been shown to be associated with rotator cuff tendinopathy, including diabetes mellitus, obesity, smoking, and hyperlipidemia [3-6]. Whereas, extrinsic factors include hooked acromion, mechanical overuse, anterior glenohumeral dislocations and fractures of great tuberosity [7].

Non-steroid anti-inflammatory drugs (NSAIDs) and physical therapy are commonly recommended to restore shoulder function in rotator tendinopathy [8,9]. Diercks *et al.* [10] also recommended home exercises of low intensity and high frequency, combining eccentric training with stabilization training of the scapula and focusing on relaxation and proper posture.

If the results of the conservative treatment fails, corticosteroid or anesthetics injection is often used in the management of persistent

shoulder pain [11]. The potential mechanism of corticosteroids include decreased inflammation, inhibition of cellular proliferation, scarring and adhesion, and anti-nociceptive action [12]. However, their effectiveness is ascertained only in the short term follow-up and occurrence of local degradation of tissues has been reported as a result of repeated corticosteroid injection, as well as tendon tearing and corticosteroid arthropathy [11]. Therefore, their use should be restricted to selected cases.

Currently, intra-articular hyaluronic acid (HA) is well accepted as a good alternative in the conservative treatment in patients with osteoarthritis [13-15]. Furthermore new and effective HA, called mobile reticulum hyaluronic acid, with different molecular characteristics is used

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in recent clinical practice [16-18]. Moreover, HA has been proposed for the treatment of tendinopathies due to its viscoelastic properties on connective tissue [19]. Indeed, some studies showed encouraging results on hyaluronic acid's ability to promote tendon gliding and reduce adhesion as well as to improve tendon architectural organisation [20]. HA is a non-sulfated glycosaminoglycan consisting of alternately repeating D-glucuronic acid and N-acetylglucosamine units. HA could bind to specific receptors expressed in many cells, such as the cluster determinant 44 (CD44), the intracellular adhesion molecule-1 (ICAM-1) and the receptor for hyaluronate-mediated motility (RHAMM). The consequences of these connections are to stimulate cell functional activities such as cell migration and proliferation.

In a previous meta-analysis study, Saito *et al.* provided evidence that HA injections could be a valuable alternative to other conservative methods for the treatment of chronic painful shoulder. Only a few conclusions were drawn from this meta-analysis because of the relatively small number of studies included. The authors emphasized the need for additional investigations on the use of HA injections for the treatment and development of clinical practice guidelines for chronic painful shoulder.

Therefore, the aim of this meta-analysis is to compare the efficacy of HA injection with both placebo and corticosteroid or anaesthetic injections in patients with rotator cuff tendinopathies using pain and shoulder function as primary and secondary outcome measures, respectively.

Methods

Criteria for considering studies

Types of studies

We considered the following inclusion criteria:

- Randomized controlled trials (RCTs) of any design (e.g. parallel, cross-over, factorial);
- English-language studies;
- RCTs in which the other intervention arm used a placebo or intra-articular injections of corticosteroids.
- RCTs that reported the methods used to generate the allocation sequence or that included a statement such as "random allocation was used".

Types of participants

We included studies involving participants with rotator cuff tendinopathy for any duration.

We excluded trials that included any participants with a history of significant trauma or systemic inflammatory conditions such as rheumatoid arthritis, hemiplegic shoulders, and pain in the shoulder region as part of a complex myofascial neck. Animal studies were also excluded.

Types of interventions

We included RCTs comparing HA injections to placebo, no treatment, corticosteroid injections, or any other intervention. Because saline solution is accepted as a placebo "treatment", we used the term "placebo" for the administration of saline solution injections.

Types of outcome measures

- a. Overall pain [mean or mean change measured by visual analogue scale (VAS) [21], numerical or categorical rating scale].

- b. Clinical improvement, evaluated by the following shoulder functional scales:

- ✓ Assessment Shoulder and Elbow scale (ASES) [22,23];
- ✓ Constant-Murley Score [24].

Search methods for identification of studies

Electronic searches

Our search strategies included the following databases: MEDLINE, Embase, CINAHL, Google scholar web, Ovid database, Physiotherapy Evidence Database (PEDro), and the Cochrane Library. We performed a broad research for relevant study up to February 2017. Search methods for identification of studies: ["Hyaluronic Acid" OR ("Viscosupplementation") AND ("Shoulder Impingement Syndrome") OR ("Rotator Cuff Injuries") OR ("Rotator Cuff")]

Data collection and analysis

Selection of studies

Two review authors independently screened all search results (title, abstract, and descriptors) to identify studies for possible inclusion in the review. After the initial screening, they assessed all included trials for eligibility based on the full text. Any disagreements were resolved through discussion or, if necessary, through another independent researcher. Where required, we contacted study authors for additional information. When trial results were not normally distributed and so reported as median and range, the trial was not included in the meta-analysis.

Assessment of risk of bias in included studies

Characteristics of extraction data are presented in Table 1. Included studies were evaluated by 2 independent reviewers for their methodological quality using the PEDro rating scale (<http://www.pedro.org.au>). Elements were only scored as "yes" where quality clearly met the specified criteria. Disagreements were settled by a third reviewer. Data were then extracted and cross-checked for accuracy. The reviewers were not blinded to the authors of the articles.

We assessed the following items for each included trial: sequence generation (randomisation), allocation concealment, blinding of participants, therapists who administered the therapy and personnel outcome assessors, intention-to-treat analysis, the numbers of participants lost to follow-up and missing values.

Measures of treatment effect

For each study, mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CIs) were calculated for continuous outcomes using the Cochrane Collaboration's software RevMan version 5.2 [25].

Assessment of heterogeneity

Assessment of heterogeneity between comparable trials was evaluated visually with I^2 statistics. Values of I^2 were interpreted as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity [26].

Results

The literature searches identified 3861 potentially relevant studies, which were assessed by their abstracts. A total of 50 titles were obtained

Table 1. Details of randomized controlled trials of HA (hyaluronate) injections for rotator cuff disorders.

Author, Year	Diagnosis	Treatment Schedule	Subjects (N)	Follow Up
Blaine et al, 2008 [29]	OA RCT, adhesive capsulite	<ul style="list-style-type: none"> ✓ Intra-articular injection ✓ HA (Hyalgan) 5 weekly or 3 weekly +2 saline solution vs 5 weekly saline solution 	660	<ul style="list-style-type: none"> ✓ VAS: 7, 9, 13,17,26 weeks
Chou et al, 2009 [27]	RCT without complete tears	<ul style="list-style-type: none"> ✓ Subacromial injection ✓ HA (Supartz) vs Saline solution 5 weekly 	51	<ul style="list-style-type: none"> ✓ VAS : 1-6 weeks ✓ CMS: 1-6 weeks
Moghtaderi et al, 2013 [28]	SAI syndrome	<ul style="list-style-type: none"> ✓ Subacromial injection ✓ HA (Fermathron™) vs Saline solution 3 weekly 	40	<ul style="list-style-type: none"> ✓ VAS: 1 Week ✓ CMS: 12 weeks
Penning et al, 2014[25]	SAI syndrome	<ul style="list-style-type: none"> ✓ Subacromial injection 3 weekly ✓ Group A:HA (Ostenil) and 8 ml lidocaine 1% ✓ Group B: corticosteroid 10 mg/ml 8 ml lidocaine 1%; ✓ Group C: 2 ml NaCl 0.9% and 8 ml lidocaine 1% 	150	<ul style="list-style-type: none"> ✓ VAS: 3, 4, 12, 26 weeks ✓ CMS: 3, 4, 12, 26 weeks
YS Kim et al, 2012 [26]	SAI syndrome	<ul style="list-style-type: none"> ✓ Subacromial Ultrasound guided ✓ HA (Hyruan plus) vs corticosteroid, 3 weekly 	105 (80)	<ul style="list-style-type: none"> ✓ VAS :3, 6, 12 weeks ✓ ASES: 3, 6, 12 weeks

RCT: Rotator Cuff Tear, **SAI:** Subacromial Impingement; **VAS:** Visual Analogue Scale; **CMS:** Constant Murley Scale; **ASES:** American Shoulder and Elbow Surgeons (ASES) Assessment Form

from electronic databases after removing duplicates, no-intervention study, in vitro study or failed eligibility criteria. Of these, 44 articles were excluded because they were retrospective, experimental, and observational or not controlled study.

Following a thorough screening, we identified 7 full-text articles [27-33]. We included 5 trials [28-32] in the quantitative analysis (Figure 1).

Study quality

The results of the PEDro rating are shown in Figure 2. The quality of the studies as determined via the PEDro rating scale ranged from 2 to 8 out of a possible score of 10. All studies reported whether groups were equivalent at baseline. Two of the 5 studies did not use an intention-to-treat analysis. Blinding items were unclear in 2 studies (Table 2).

Sample characteristics

A total of 990 participants with rotator cuff disease were included, of which 464 were male (46.86%) and 526 were female (53.14%). Reported mean ages ranged between 51.16 and 63.6 years old. Mean age values were not available in one RCT [31]. Details regarding participant recruitment are presented in Table 1.

Hyaluronic Acid Intervention vs placebo intervention

Four studies compared HA injection with placebo injection [28, 30-32], of which two used 3 weekly injections [28,31,32] and two used 5 weekly injections [30,32]. Blaine *et al.* [32] used 2 ml of sodium hyaluronate (10 mg/ml) in experimental groups and phosphate buffered saline solution in placebo group; Chou *et al.* [30] used 25 mg of ARTZ Dispo in experimental group and 2.5 ml of saline solution 0.9%; Moghtaderi *et al.* [31] used 20 mg/2ml of HA (Fermathron) in experimental group and 2 ml of saline solution 0.9%.

Hyaluronic Acid vs corticosteroid injection

Two studies compared HA injection with corticosteroid injection [28,29]. In Kim *et al.* [29] study, patients were injected once a week for three weeks with 20 mg/2ml HA (Hyruan plus) and once with 5 mg/1ml dexamethasone disodium phosphate diluted with 4ml lidocaine (2% 20 mg/ml) and 5 ml saline solution.

Whereas, Penning *et al.* [28] randomized subjects as follows: the HA group received 8 ml lidocaine 1% with 2 ml HA (ostenil), the corticosteroid group received 8 ml lidocaine 1% with 2 ml triamcinolone acetonide 10 mg/ml and placebo group received 8 ml lidocaine 1% with 2 ml NaCl 0.9%.

Outcome measures

Hyaluronic Acid Intervention vs. placebo intervention

a. Pain

- According to VAS score, the meta-analysis showed no significant difference between HA group and placebo group at: a) 1 week follow-up (MD= -1.16, 95% CI -3.41 to 1.10), p=0.32; b) from 6 to 8 weeks follow-up (MD= -0.47, 95% CI -1.15 to 0.21), p=0.18; c) from 12 to 13 weeks (MD= -0.02, 95% CI -0.73 to 0.69), p=0.96.
- Significant difference was found at 26 weeks follow-up (MD= -0.51, 95% CI -0.96 to -0.07), p=0.02. The results of meta-analysis are showed in Figure 3.

b. Shoulder function

According to Constant-Murley Score, the meta-analysis showed no significant difference between HA group and placebo group at: a) 1 week follow-up (MD=0.30, 95% CI -5.83 to 6.43), p=0.92; b) from 6 to 12 weeks follow-up (MD= -10.95, 95% CI -25.13 to 3.23), p=0.13. The results of meta-analysis are showed in Figure 4.

Hyaluronic Acid vs. corticosteroid injection

c. Pain

According to VAS score, the meta-analysis showed no significant difference between HA group and corticosteroid group at: a) 3 weeks follow-up (MD= -0.22, 95% CI -3.16 to 2.72), p=0.88; b) 6 weeks follow-up (MD= 0.22, 95% CI -3.02 to 3.47), p=0.89; c) 12 weeks follow-up (MD= -0.20, 95% CI -4.47 to 4.07), p=0.93. The results of meta-analysis are showed in Figure 5.

d. Shoulder function

According to Constant-Murley Score, the meta-analysis showed no significant difference between HA group and corticosteroid injection group at: a) 3 weeks follow-up (SMD= 0.05, 95% CI -0.34 to 0.25), p=0.75; b) 6 weeks follow-up (SMD= 0.16, 95% CI -0.13 to 0.46), p=0.27; c) 12 weeks follow-up (SMD= 0.07, 95% CI -0.22 to 0.36), p=0.65. The results of meta-analysis are showed in Figure 6.

Discussion

Hyaluronic acid has been hypothesized to have an anti-inflammatory effect in patients with subacromial synovitis associated with rotator cuff disease. Histologically, subacromial synovitis consists of non-specific inflammation accompanied by proliferation of subacromial synovial fibroblasts (SSF) with less infiltration of inflammatory cells. Pro-

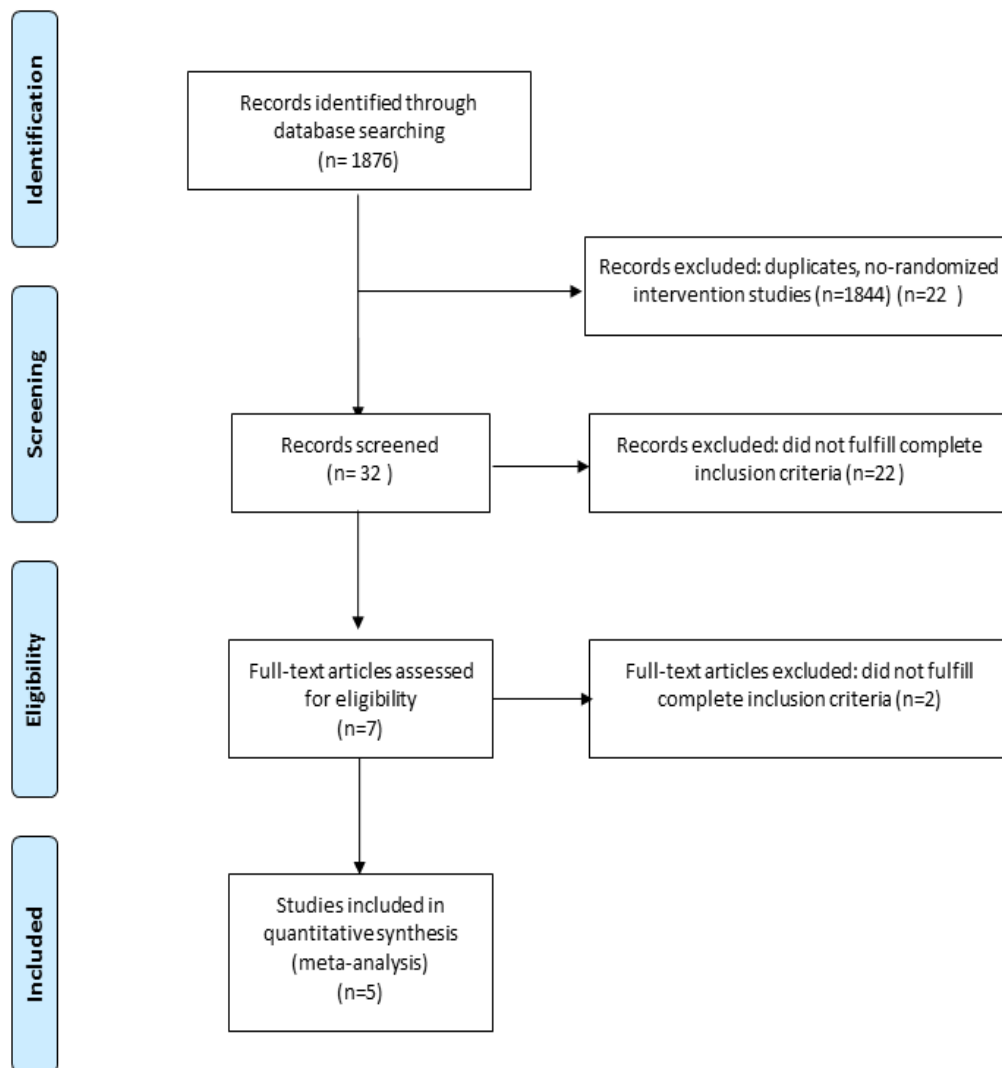
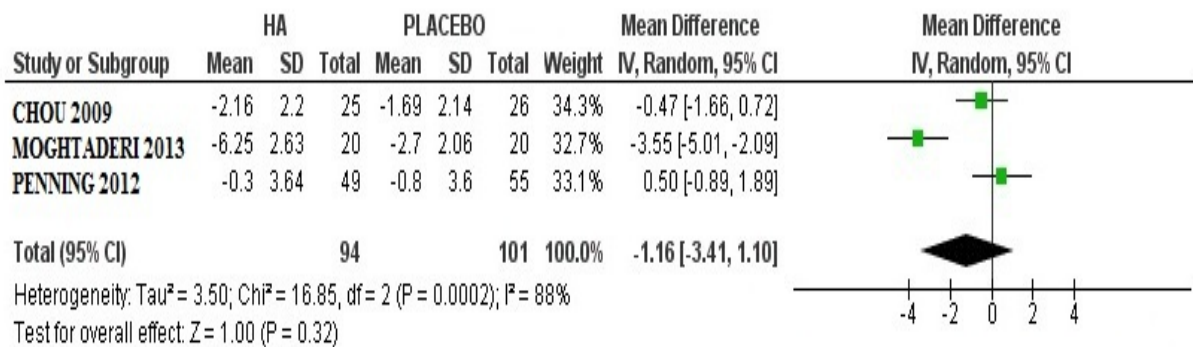


Figure 1. Literature searches identified 7 full-text articles.

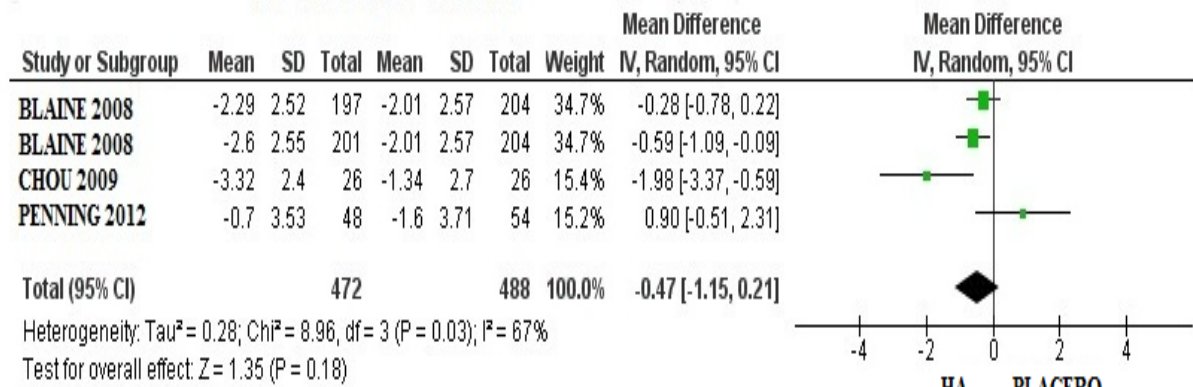
Table 2. The PEDro Scale.

The PEDro Scale	BLAINE, 2008	CHOU, 2009	KIM, 2012	MOGHADDERI, 2016	PENNING, 2014
1. Eligibility criteria were specified	YES	YES	YES	YES	YES
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	YES	YES	YES	YES	YES
3. Allocation was concealed	NO	YES	NO	NO	YES
4. The groups were similar at baseline regarding the most important prognostic indicators	YES	YES	YES	YES	YES
5. There was blinding of all subjects	NO	YES	UNCLEAR	UNCLEAR	YES
6. There was blinding of all therapists who administered the therapy	NO	YES	UNCLEAR	UNCLEAR	YES
7. There was blinding of all assessors who measured at least one key outcome	YES	YES	UNCLEAR	UNCLEAR	YES
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	YES	YES	YES	YES	YES
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	YES	YES	NO	NO	YES
10. The results of between-group statistical comparisons are reported for at least one key outcome	YES	YES	YES	YES	YES
11. The study provides both point measures and measures of variability for at least one key outcome	YES	YES	YES	YES	YES
Total Score	7	10	5	5	10

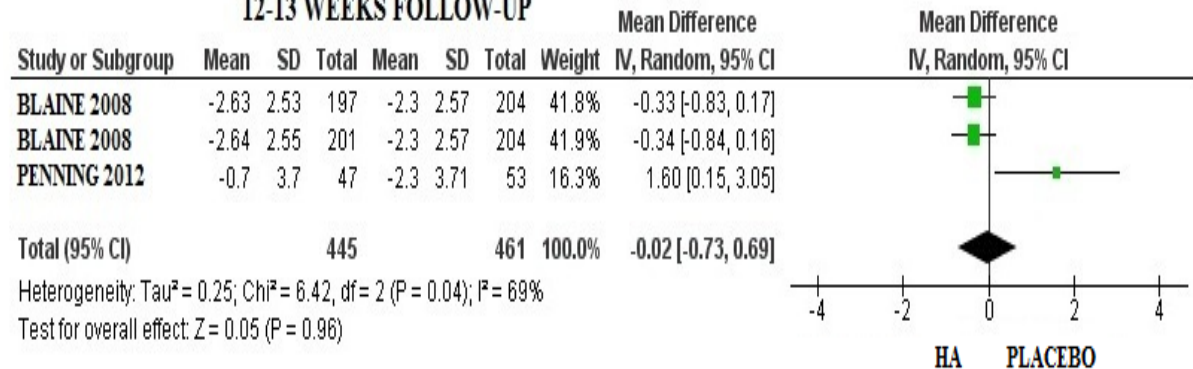
1 WEEK FOLLOW-UP



6-8 WEEKS FOLLOW-UP



12-13 WEEKS FOLLOW-UP



26 WEEKS FOLLOW-UP

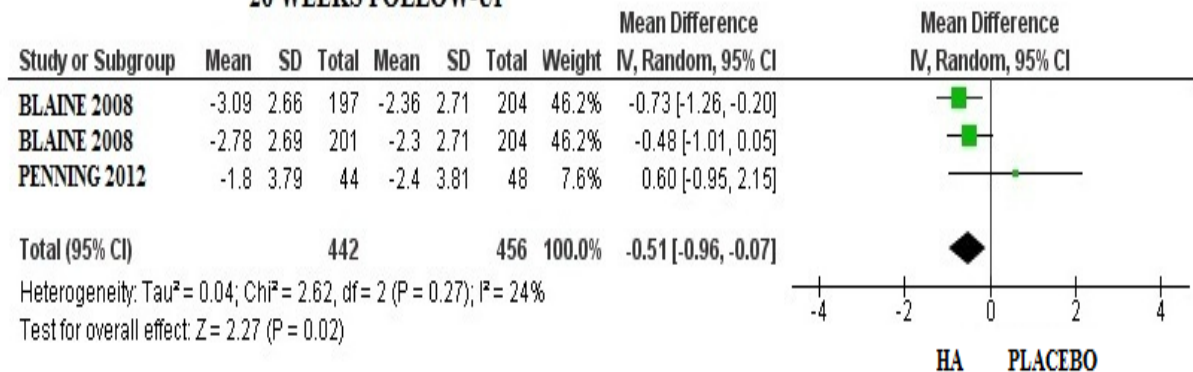


Figure 2. Results of the PEDro rating.

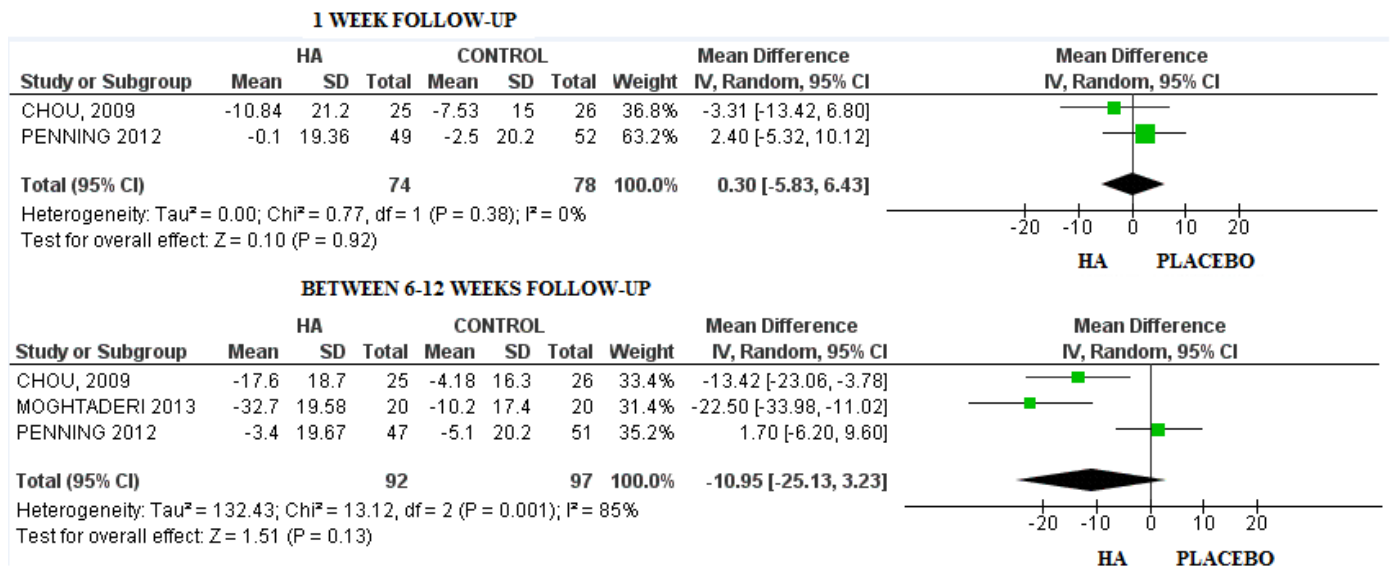


Figure 3. Results of meta-analysis in Pain (Hyaluronic Acid Intervention vs placebo intervention).

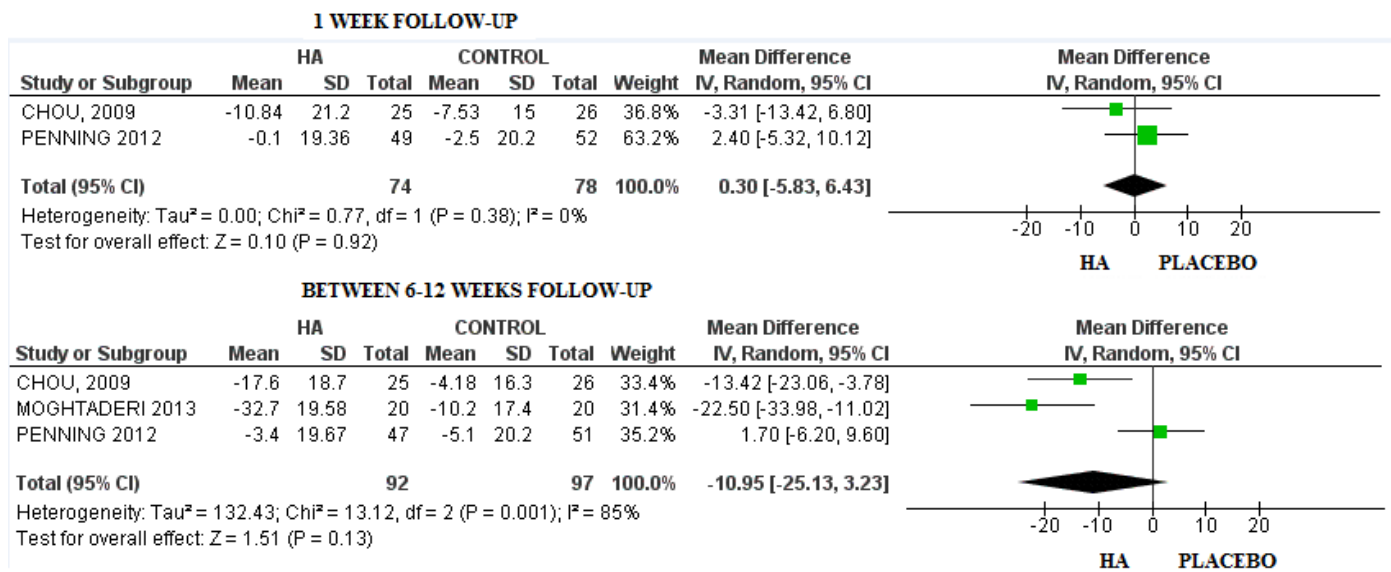


Figure 4. Results of meta-analysis in Shoulder function (Hyaluronic Acid Intervention vs placebo intervention).

inflammatory cytokines and enzymes (IL-1, TNF- α , IL-6, and COX-2) produced by SSF play a major role in shoulder pain. The level of IL-1 β mRNA expression in SSF correlates well with the degree of rotator cuff disease [34]. Mitsui *et al.* [35] examined the anti-inflammatory effect of HA in vitro using IL-1-stimulated SSF derived from patients with rotator cuff disease. The results demonstrated that HA inhibits not only expression of mRNA for proinflammatory cytokines (IL-1 β , IL-6, and TNF- α), but also COX-2/PGE2 production via CD44 in IL-1-stimulated SSF. The CD44, a transmembrane glycoprotein widely distributed on T cells, granulocytes, monocytes, fibroblasts, keratinocytes, and epithelial cells, is a major cell surface receptor for HA.

This meta-analysis compared the efficacy of HA injections with both placebo and corticosteroid injections in patients with rotator cuff tendinopathies according to pain and shoulder function as outcome measures.

Although no significant differences were found in VAS score between HA injections and both placebo and corticosteroid injections until 13 weeks and 12 weeks respectively, a significant difference in relief of pain was shown between HA injections and saline solution at 26 weeks follow-up. No significant differences exist between groups in shoulder function at follow-up.

We found a substantial clinical heterogeneity with respect to the interventions tested and only few trials were combined in meta-analysis to reach an overall conclusion about the effect of HA injection in rotator cuff tendinopathy. According to methodological quality, the results generated by our meta-analysis are, as a whole, based on trials of small participants that may be biased by Type II error (the failure to demonstrate a difference which is in truth present or false negatives). A few studies analyzed results using intention to treat principles and clearly specified blind allocation. Moreover, the meta-analysis showed

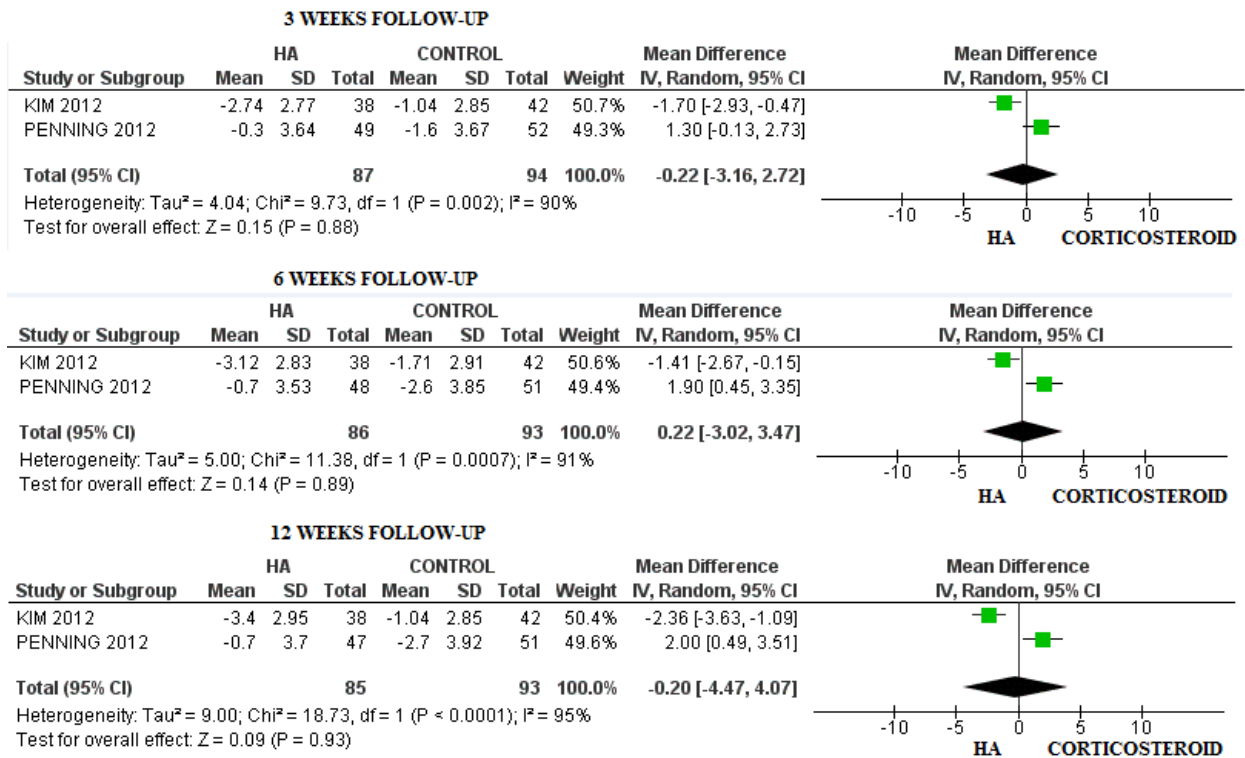


Figure 5. Results of meta-analysis in Pain (Hyaluronic Acid Intervention vs corticosteroid injection).

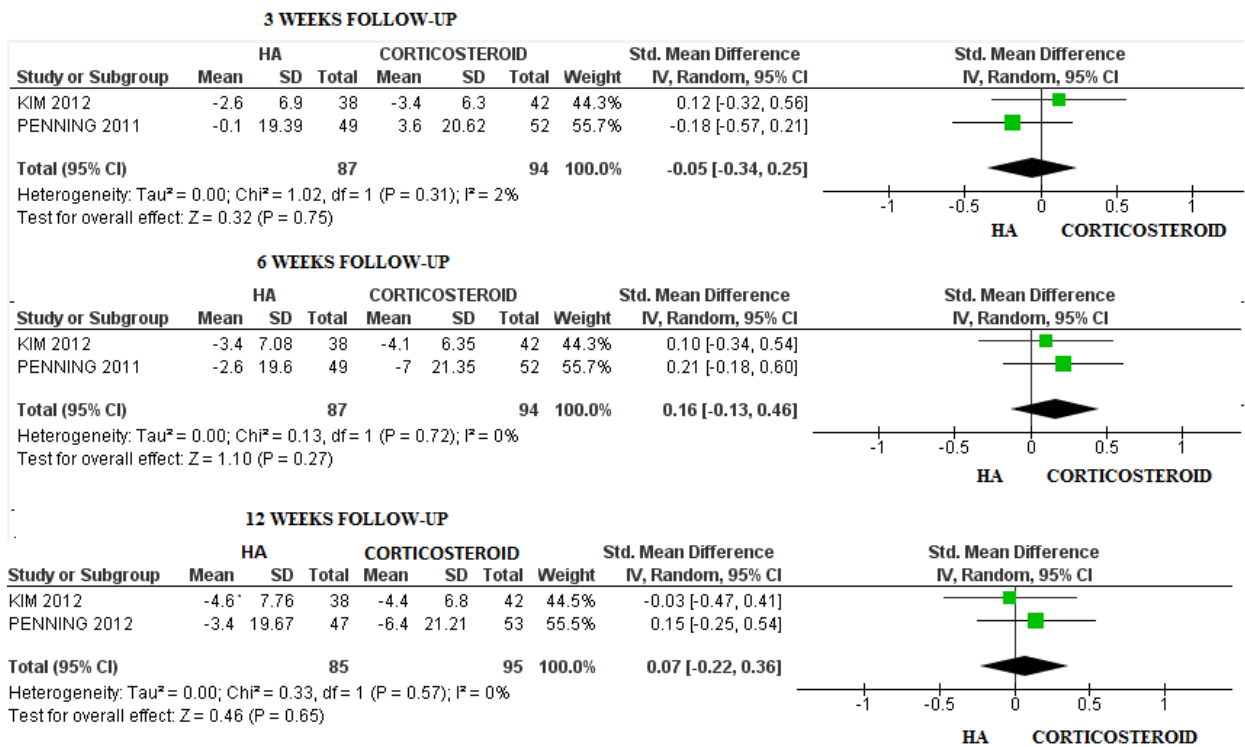


Figure 6. Results of meta-analysis in Shoulder function (Hyaluronic Acid Intervention vs corticosteroid injection).

different weights to the different studies that are related with the inverse of the standard error reported in the studies. Therefore, findings of no significant benefit are consistent with no evidence to support or refute the use of the HA intervention.

In an interesting in vitro study conducted by Osti et al. [36], has been found that HA enhanced viability, proliferation and expression of collagen type I in tendon derived cells. In a systematic review, Osti et al. [31] evaluated the potential benefit and adverse effects of HA injection in patients with rotator cuff tears. The authors included 11 studies (1102 subjects) comparing HA injections with corticosteroid injections, physical therapies and control groups. The use of HA was found to be effective in reducing pain and improving function in shoulder with rotator cuff tears without showing severe adverse reactions.

Currently, Mohamadi et al. [11], performed a meta-analysis including eleven prospective randomized controlled trials comparing corticosteroid and placebo injections. The authors found that corticosteroid injections provide minimal transient pain relief in a small number of patients with rotator cuff tendinosis and cannot modify the natural course of the disease. Moreover, multiple injections were not found to be more effective than a single injection at any time.

Conclusion

Despite complex study design, on HA injection there is insufficient evidence to either support or disprove this therapy for treatment of patients with rotator cuff disorder. In completing this study we had some problems: 1) there have not been many randomized controlled trials (RCT), 2) the quality of the studies that were found was not high; 3) the homogeneity of the papers that were found was low (in particular for diagnosis, inclusion criteria, HA dose and type, site of injection). For these reasons only few trials were combined in meta-analysis and to reach an overall conclusion about the effect of HA injection in rotator cuff we need more high quality data. So future studies aiming to investigate HA injection should aim to minimize bias by presenting homogeneity, with respect to dose, HA type and injection site.

Considering the increased use of HA in the treatment of tendinopathies and the evidence in recent research study regarding the effect of HA on the enhanced of viability, proliferation and expression of collagen type I in tendon derived cells.

Future studies aiming to investigate HA injection in the treatment of tendinopathies should aim to minimize bias by presenting a homogeneity, with respect to dose, HA type and injection site.

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