SYSTEMATIC REVIEW

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# Hyaluronic Acid in the Treatment of Knee Osteoarthritis

## A Systematic Review and Meta-Analysis with Emphasis on the Efficacy of Different Products

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## Abstract

**Background:** Although accepted as a conservative treatment option for knee osteoarthritis, the debate about the effectiveness of intra-articular treatment with hyaluronic acid (HA) is still ongoing because of contrasting outcomes in different clinical studies. Several well designed clinical studies showed a significant improvement in pain at follow-up compared with baseline but no significant improvement comparing the efficacy of HA with placebo (saline) or with other conservative treatment options. Notwithstanding the effectiveness of different types of intra-articular HA products, the question of whether one HA product is better than another is still unanswered. In this systematic review we compare the effects of intra-articularly administered HA with intra-articularly administered placebo in general and, more specifically, the effects of individual HA products with placebo. We also compare the efficacy of different HA products.

**Methods:** A systematic review of randomized controlled trials (RCTs) was conducted using databases including MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Clinical Trial Register and EMBASE.

**Results:** Seventy-four RCTs were included in this systematic review. HA improves pain by approximately 40–50% compared with baseline levels. However, when compared with saline the difference in efficacy is not that large. Due to a large 'placebo effect' of saline (approximately 30% pain reduction, persisting for at least 3 months) we determined a weighted mean difference between the efficacy of HA and saline of just 10.20 using the visual analog scale for pain. It is debatable whether this difference reaches the minimum clinically important difference. Comparing the different HA products, which vary in the molecular weight, concentration, and volume of HA, we were not able to conclude that one brand has a better efficacy than another due to the heterogeneity of the studies and outcomes.

**Discussion:** In the future it will be important to determine the exact mechanism of action of placebo as this may give us an idea of how to treat osteoarthritis more efficiently. Due to the limitations of this review (follow-up of just 3 months and large heterogeneity of the included studies), it is also important to compare the different HA products to determine which product(s), or which molecular weight range, concentration, or volume of HA is the best option to treat osteoarthritis. Our recommendation is to start large (multicenter) RCTs to give us more evidence about the efficacy of the different HA products.

### 1. Introduction

Knee osteoarthritis (OA) is the most common type of OA. Six percent of people over 30 years of age have radiological signs of OA and this increases to 40% in people aged 70 years or older.[1] OA is characterized by focal areas of damage to articular cartilage at weight-bearing areas associated with changes in subchondral bone, variable degrees of synovitis, osteophyte formation, cyst formation, joint space loss due to cartilage loss and joint capsule thickening.[2] All these intra-articular changes cause pain and disability, mostly in the elderly.

There are non-pharmacologic treatment options which include patient education, self-management programs, weight loss, physiotherapy (aerobic exercise programs, range-of-motion

exercises and muscle-strengthening exercises), assistive devices for ambulation, appropriate footwear, occupational therapy, and assistive devices for activities of daily living.[3]

If necessary, these non-pharmacological options may be combined with pharmacological therapy. First-line drug therapy is mainly symptomatic and includes simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). If the result of this conservative treatment fails, symptomatic slow-acting drugs in OA (SYSADOAs), which include intra-articular hyaluronic acid (HA), may also be used. Intra-articular treatment with corticosteroids is used in OA patients with an acute flare where a more rapid relief of symptoms is required. However, it is well known that corticosteroids have a short-lived effect.[4]

Intra-articular HA appears to be well accepted as a good alternative in the conservative treatment of patients with knee OA. In their meta-analysis comparing the intra-articular treatment of knee OA patients with either corticosteroids or HA, Bannuru et al.[5] showed that corticosteroids had a relatively greater effect on pain in the first 4 weeks after infiltration, but HA showed a greater efficacy beyond 8 weeks. A peak in the effect size of intra-articularly injected HA (effect size of 0.46) was observed at 8 weeks. In contrast, other treatments showed a lower effect size (e.g. 0.29 for NSAIDs, 0.44 for COX-2 inhibitors, and 0.13 for acetaminophen).[6] From a clinical point of view, an effect size of 0.2–0.5 is very small.[7]

Lo et al.[8] published a systematic review on the therapeutic effects of intra-articular HA treatment in patients with knee OA, and made some interesting conclusions. They concluded that intra-articular HA has modest efficacy in the treatment of knee OA compared with placebo.[7] Their main concern was the evidence of a publication bias. Seventeen of the 22 included articles were industry-sponsored, dropout rates of up to 40.3% were reported, and some of the articles reported only a completers' analysis. Another remarkable finding was a positive effect size relatively close to zero, and none of these trials had a negative effect size when comparing the efficacy of intra-articularly administered HA with intra-articularly administered placebo. All these findings support the possibility of a publication bias.

The Cochrane Review by Bellamy et al.[9] compared different intra-articularly administered HA products with other HA products and with intra-articularly administered placebo. They concluded that, in general, HA products appear to be superior to placebo, but with the limitation that some of the products or studies do not show differences in efficacy. After pooling of studies that compared HA with placebo, there were differences in favor of HA at 1 week which persisted up to 26 weeks post-infiltration. However, in their analysis the authors show a considerable heterogeneity in the clinical response, suggesting that different HA products have different therapeutic effects.

In this systematic review we will compare the efficacy of intra-articularly administered HA with intra-articularly administered placebo in randomized controlled trials (RCTs) using the visual analog scale (VAS) for pain as a primary outcome measurement at 3-months follow-up. Using this approach we make some recommendations concerning the efficacy of HA compared with the effects of placebo and discuss the differences in efficacy between the different HA products and the differences between the different HA products and placebo.

## 2. Material and Methods

### 2.1 Search Strategy

The goal of the search was to include all RCTs concerning intra-articular HA treatment of knee OA in humans. Diagnosis of OA was made based on history, physical examination, and radiology. All degrees or severities of OA were included. All HA products and all types of intra-articular administration (fluoroscopic and ultrasound guided) were included.

The following databases were searched: MEDLINE (1966 to 27 June 2011), Cochrane Database of Systematic Reviews (1988 to 27 June 2011), Cochrane Clinical Trial Register (1988 to 27 June 2011) and EMBASE (January 1988 to 27 June 2011). The search was independently performed by two reviewers (SC and DH). The references of retrieved publications were also manually checked for studies potentially meeting the inclusion criteria which could have been missed by the electronic search. Papers that were not written in English were considered if translation was possible.

Using the search term ('hyaluronic acid/administration and dosage' [Mesh] OR 'hyaluronic acid/adverse effects' [Mesh] OR 'hyaluronic acid/diagnostic use' [Mesh] OR 'hyaluronic acid-/therapeutic use' [Mesh] OR 'hyaluronic acid/therapy' [Mesh]) AND ('knee') [figure 1], we initially found 516 papers. We did not use the search term 'osteoarthritis' because of the risk of missing some articles.

### 2.2 Selection of Trials

Trial selection was done by reviewing the title and abstract to identify potentially relevant articles for our review. The full manuscript was retrieved when the title, keywords, or abstract revealed insufficient information to determine appropriateness for inclusion. All identified studies were independently assessed according to the MOOSE guidelines by two reviewers (SC and

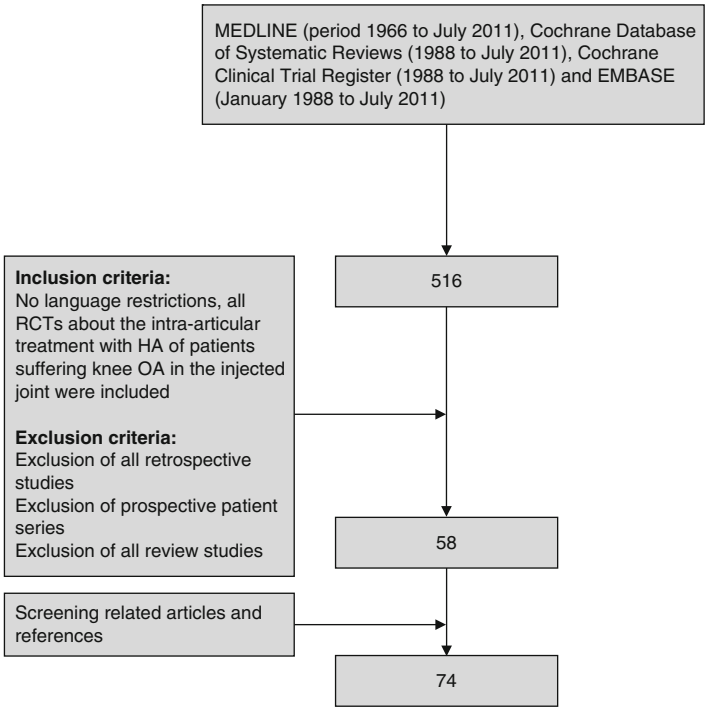



**Fig. 1.** Flowchart summarizing the selection of relevant articles. **HA** = hyaluronic acid; **OA** = osteoarthritis; **RCTs** = randomized controlled trials.

DH) for inclusion using the previously mentioned criteria.[10] Disagreement was resolved by discussion, with arbitration by a third reviewer (MB) when differences remained.

### 2.3 Data Collection

From the included studies, data for the meta-analysis were extracted by one reviewer (SC) using a data extraction form. Extraction was verified by the second reviewer (DH). Disagreements were resolved in a consensus meeting or, if necessary, by third-party adjudication (MB). Articles were not blinded for author, affiliation, or source.[11-13] If necessary, authors were contacted for additional information.

A review manager computer program (Review Manager [RevMan], version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to attempt to pool the results of the different studies.

### 2.4 Analysis

Our primary research objective was to compare intra-articularly administered HA with intra-articularly administered placebo (saline) in RCTs using a VAS for pain as an outcome measurement at 3-months follow-up. We used this therapeutic outcome parameter because it is the most frequently used outcome measure in clinical studies comparing the effect of intra-articularly administered HA with intra-articularly administered placebo. Because saline is accepted as a placebo 'treatment', we use the term 'placebo' for the intra-articular administration of saline. Studies eligible according to the pre-defined criteria were used for data extraction and data were pooled using fixed or random effects models where appropriate. In the presence of heterogeneity, a random-effect meta-analysis weights the studies relatively more equally than a fixed effect analysis.[14] For these combined trials, weighted mean differences with a 95% confidence interval were calculated.

Additionally, the effect size was calculated for this comparison since it allows outcome measurements other than VAS pain (e.g. Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain, Knee injury and Osteoarthritis Outcome Score [KOOS] pain, Lequesne Algofunctional Index) to be included. Effect sizes were also calculated for individual HA products versus placebo and for trials comparing different HA products.

As a secondary outcome measure we calculated the treatment effect for all studies by dividing the outcome (VAS pain, WOMAC pain or Lequesne Algofunctional Index) at 3 months by their pre-first injection (i.e. baseline) value for each included group. We combined these expressions of effect for the following groups: treatment with HA, treatment with physical therapy, and no specific treatment.

To judge whether the different molecular weight distributions of HA had different effects on the outcome we divided the calculated effects per brand of HA.

Individual and pooled statistics were reported as relative risks with 95% confidence intervals for dichotomous outcomes and weighted mean differences or, where different scales were used, standardized mean differences and 95% confidence intervals for continuous outcome measurements. Heterogeneity between trials was tested using an $I^2$ test. To assess the heterogeneity of a meta-analysis is a crucial issue because the presence versus the absence of true heterogeneity (between-studies variability) can affect the statistical model that should be used. The use of $I^2$ statistics gives the percentage of heterogeneity between the included studies, in which an $I^2$ of 0% can be considered as no heterogeneity, 25% as low, 50% as moderate heterogeneity and 75% as high heterogeneity. Where $I^2$ is 50% or less, it is correct to use a fixed effects model when pooling the data, in case of a higher heterogeneity, a random effects model should be used. When possible, sensitivity analyses were conducted to assess the effects of exclusion of trials in which the quasi-randomization method was used.

Because we focus on the therapeutic effects of intra-articularly administered HA, parameters such as joint replacement delay, slow-down of disease progression, or histological changes induced by the use of intra-articularly administered HA are not reported in this review.

## 3. Results

Seventy-four RCTs were included after applying the predetermined inclusion and exclusion criteria. Some of these articles made more than one comparison. Thirty-seven compared HA with placebo, six compared HA with no treatment, 13 compared different types of HA or different HA doses with placebo, 13 compared HA with corticosteroid infiltration, five compared HA with physical therapy, and five compared HA with regular treatment (home exercises, NSAIDs, etc.).

Only 18 studies with 20 groups of patients comparing different HA products with placebo could be pooled. A total of 1180 patients were included, showing a weighted mean difference of −10.20 (95% CI −15.97, −4.42) with an $I^2$ of 92% between VAS pain at baseline and at 3 months follow-up (figure 2).[15-32]

Comparing the effect of intra-articularly administered HA versus intra-articularly administered placebo, physical therapy,[33-36] or other conservative treatments, we observed that all treatments showed a good result, defined by a 30–40% pain reduction compared with baseline, which is still measurable at 3 months follow-up (figure 3).[15-88] None of the placebo-controlled studies provide a good explanation for this large treatment effect in the placebo group or an explanation as to why this 'placebo effect' continues and is still measurable at 3 months.

As shown in figure 3, there are differences in mean pain improvement between the different HA products. Hyalgan®, as the lowest molecular weight HA product, Artz® and Orthovisc®, as medium molecular weight HA products, and Synvisc®, as the highest molecular weight HA product, are the most studied products and all showed (compared with baseline) an improvement of 40–50% reduction in pain scores at 3 months. Other less frequently studied products also showed a significant improvement in pain scores at 3 months, compared with baseline values. However, studies that report the effects of placebo injections, physiotherapy,[33-36] and 'no treatment'[46,47,58,59,63,68] also show an improvement of pain between 20 and 64% (figure 3).

Twenty-five RCTs with 1095 patients compared Hyalgan® treatment with other HA products, other conservative therapies, or with placebo. As shown in figure 3, Hyalgan® in patients with knee OA caused a pain reduction of 43% compared with baseline. Similar results are observed in the effects of intra-articularly administered Synvisc® compared with baseline (figure 3). In 35 studies, which included 2117 patients, the treatment with Synvisc® showed a mean pain improvement of 41% compared with baseline. Artz®, with 612 patients in 10 studies, and Orthovisc®, with 1370 patients in 13 studies, are also well studied and also showed similar effects.

By reporting the improvement per therapy in this way, we can observe and compare the effect of intra-articularly administered

| Study or subgroup | Reference | Dosage regimen infiltrations (n) | Hyaluronic acid Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean difference IV, random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| Altman and Moskowitz, 1998 | 15 | 5 | 23.0 | 25.0 | 115 | 24.0 | 26.0 | 129 | 5.4% | −1.00 [−7.40, 5.40] |
| Baltzer et al., 2009 | 16 | 3 | 52.1 | 23.0 | 135 | 48.8 | 22.5 | 107 | 5.5% | 3.30 [−2.46, 9.06] |
| Bragantini et al., 1987 | 17 | 3 | 13.0 | 8.0 | 39 | 40.0 | 8.0 | 18 | 5.6% | −27.00 [−31.47, −22.53] |
| Carrabba et al., 1995* | 18 | 1 | 33.0 | 15.8 | 20 | 39.9 | 14.6 | 20 | 5.0% | −6.90 [−16.33, 2,53] |
| Carrabba et al., 1995* | 18 | 3 | 29.3 | 9.3 | 20 | 39.9 | 14.6 | 20 | 5.3% | −10.60 [−18.19, −3.01] |
| Carrabba et al., 1995* | 18 | 5 | 29.7 | 22.9 | 20 | 39.9 | 14.6 | 20 | 4.7% | −10.20 [−22.10, 1.70] |
| Corrado et al., 1995 | 19 | 2 or 3 | 29.7 | 22.9 | 20 | 43.2 | 22.3 | 20 | 4.3% | −13.50 [−27.51, 0.51] |
| Creamer et al., 1994 | 20 | 5 | 41.0 | 10.0 | 12 | 41.0 | 40.0 | 12 | 3.0% | 0.00 [−23.33, 23.33] |
| Grecomoro et al., 1987 | 21 | 3 | 19.0 | 5.0 | 20 | 41.0 | 7.0 | 20 | 5.7% | −22.00 [−25.77, −18.23] |
| Huskisson and Donnelly, 1999 | 22 | 3 | 33.0 | 29.2 | 39 | 48.3 | 31.6 | 39 | 4.4% | −15.30 [−28.80, −1.80] |
| Jorgensen et al., 2010 | 23 | 5 | 30.0 | 20.0 | 165 | 29.0 | 20.0 | 170 | 5.7% | 1.00 [−3.28, 5.28] |
| Jubb et al., 2003 | 24 | 3 | 46.0 | 25.3 | 160 | 51.0 | 25.3 | 159 | 5.5% | −5.00 [−10.55, 0.55] |
| Karlsson et al., 2002 | 25 | 3 | 42.0 | 29.0 | 180 | 46.0 | 32.0 | 66 | 5.1% | −4.00 [−12.81, −4.81] |
| Kul-Panza and Berker, 2010 | 26 | 3 | 31.0 | 31.0 | 24 | 33.0 | 31.0 | 24 | 3.8% | −2.00 [−19.54, 15.54] |
| Lohmander et al., 1996 | 27 | 5 | 28.4 | 25.0 | 120 | 28.3 | 25.0 | 120 | 5.5% | 0.10 [−6.23, 6.43] |
| Lundsgaard et al., 2008 | 28 | 4 | 43.0 | 25.2 | 84 | 47.0 | 25.2 | 84 | 5.3% | −4.00 [−11.62, 3.62] |
| Petrella et al., 2008 | 29 | 3 | 42.0 | 20.0 | 150 | 58.0 | 20.0 | 50 | 5.4% | −16.00 [−22.40, −9.60] |
| Scale et al., 1994 | 30 | 5 | 29.7 | 22.9 | 21 | 43.2 | 22.3 | 19 | 4.3% | −13.50 [−27.52, 0.52] |
| Westrich et al., 2009 | 31 | 3 | 7.6 | 14.9 | 20 | 23.3 | 23.1 | 23 | 4.7% | −15.70 [−27.18, −4.22] |
| Wobig et al., 2008 | 32 | 3 | 24.0 | 15.5 | 57 | 60.0 | 15.5 | 60 | 5.5% | −36.00 [−41.62, −30.38] |
| Total (95% CI) | | | | | 1421 | | | 1180 | 100% | −10.20 [−15.97, −4.42] |

Heterogeneity: $I^2 = 92\%$

* Comparing different dose regimens of hyaluronic acid with placebo.

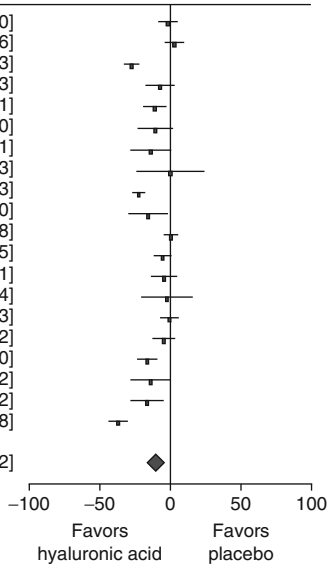



**Fig. 2.** Different hyaluronic acid products versus placebo.

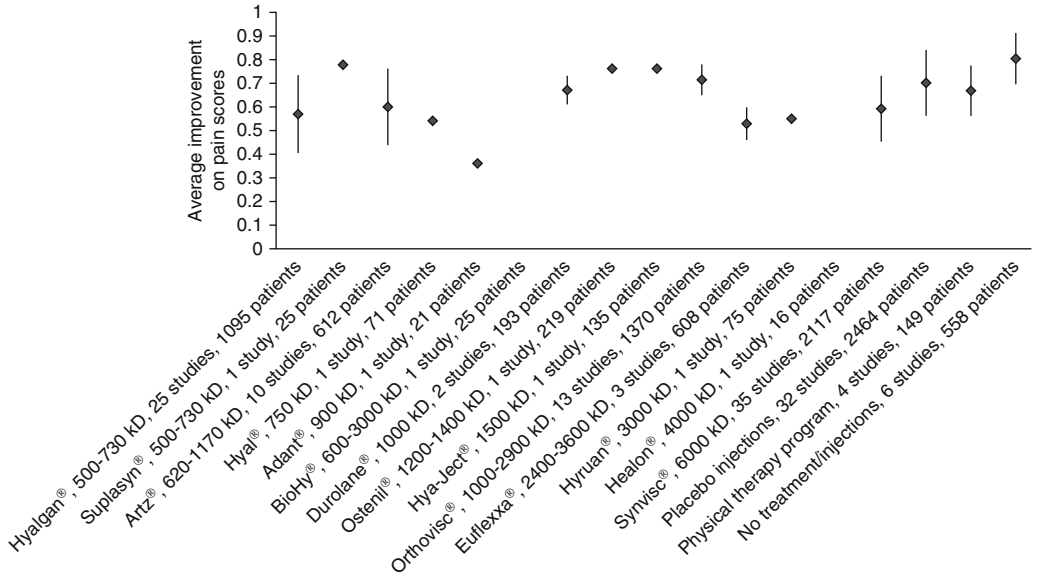



**Fig. 3.** Efficacy of different treatment options.

placebo and other treatment options. Intra-articularly administered placebo provides a mean pain reduction of 30% at 3 months follow-up compared with baseline, while for physiotherapy this value is 33% and for 'no treatment' there is a 20% pain reduction (figure 3).

Intra-articularly administered Hyalgan® (molecular weight 500–730 kDa) was compared with intra-articularly administered placebo in 11 studies (734 patients treated with Hyalgan® and 732 with placebo) [figure 4].[15,17-24,28,31] With the exception of two studies, all studies showed a favorable effect of Hyalgan® compared with placebo.[19,20] With effect sizes of –0.61 and –0.89 respectively, both Hyalgan® and Synvisc® have a modest improvement in pain compared with placebo.[7] Two studies comparing the effects of Hyalgan® with placebo show a much larger improvement than the other studies. In 1987, Bragantini et al.[17] were among the first to study the efficacy of HA compared with placebo. Their study compared two different dosages (20 and 40 mg) of Hyalgan®, administered once a week for 3 weeks, with intra-articularly administered placebo. According to their results, there were no differences between the 20 mg and 40 mg groups for pain improvement. However, there was a large difference between these two treatment groups and

| Study or subgroup | Reference | Dosage regimen infiltrations (n) | Hyalgan® Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. mean difference IV, random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| Altman and Moskowitz, 1998 | 15 | 5 | 23 | 25 | 115 | 24 | 26 | 129 | 9.4% | –0.04 [–0.29, 0.21] |
| Bragantini et al., 1987 | 17 | 3 | 13 | 8 | 39 | 40 | 8 | 18 | 5.9% | –3.33 [–4.17, –2.48] |
| Carrabba et al., 1995 | 18 | 1 | 34.1 | 15.2 | 20 | 39.9 | 14.6 | 20 | 7.2% | –0.38 [–1.01, 0.24] |
| Carrabba et al., 1995 | 18 | 3 | 29.3 | 9.3 | 20 | 39.9 | 14.6 | 20 | 7.0% | –0.85 [–1.50, –0.20] |
| Carrabba et al., 1995 | 18 | 5 | 33 | 15.8 | 20 | 39.9 | 14.6 | 20 | 7.2% | –0.44 [–1.07, 0.18] |
| Corrado et al., 1995 | 19 | 2 or 3 | 29.7 | 22.9 | 20 | 43.2 | 22.3 | 20 | 7.1% | –0.59 [–1.22, 0.05] |
| Creamer et al., 1994 | 20 | 5 | 41 | 10 | 12 | 41 | 10 | 12 | 6.1% | 0.00 [–0.80, 0.80] |
| Grecomoro et al., 1987 | 21 | 3 | 19 | 5 | 20 | 32 | 8 | 18 | 6.2% | –1.93 [–2.72, –1.15] |
| Huskisson and Donnelly, 1999 | 22 | 3 | 33 | 29.2 | 39 | 48.3 | 31.6 | 39 | 8.3% | –0.50 [–0.95, –0.05] |
| Jorgensen et al., 2010 | 23 | 5 | 30 | 20 | 165 | 29 | 20 | 170 | 9.6% | 0.05 [–0.16, 0.26] |
| Jubb et al., 2003 | 24 | 3 | 46 | 25.3 | 160 | 51 | 25.3 | 159 | 9.6% | –0.20 [–0.42, 0.02] |
| Lundsgaard et al., 2008 | 28 | 4 | 43 | 25.2 | 84 | 47 | 25.2 | 84 | 9.2% | –0.16 [–0.46, 0.14] |
| Westrich et al., 2009 | 31 | 3 | 7.6 | 14.9 | 20 | 23.3 | 23.1 | 23 | 7.2% | –0.78 [–1.40, –0.16] |
| Total (95% CI) | | | | | 734 | | | 732 | 100.0% | –0.61 [–0.92, –0.29] |

Heterogeneity: Tau² = 0.26; Chi² = 88.70, df = 12 (p < 0.00001); I² = 86%
Test for overall effect: Z = 3.75 (p = 0.0002)

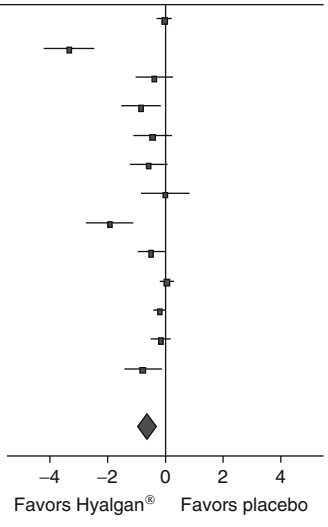



**Fig. 4.** Hyalgan® versus placebo.

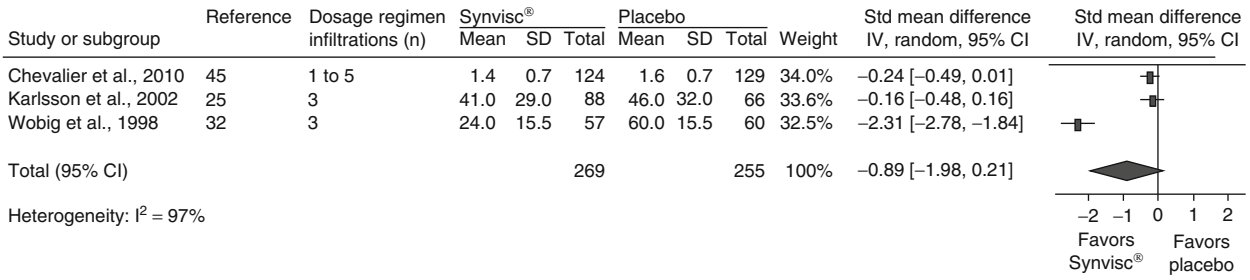



**Fig. 5.** Synvisc® versus placebo.

placebo, with a mean VAS for pain of 13 ± 8 mm in the HA group and a mean score of 40 ± 8 mm in the placebo group at the end of the study (day 60). The other study, also performed in 1987, by Grecomoro et al.,[21] compared 20 osteoarthritic knees infiltrated with Hyalgan® with 18 osteoarthritic knees infiltrated with placebo. The mean VAS pain after the treatment was 19 ± 5 mm in the Hyalgan® group and 32 ± 8 mm in the placebo group. Comparing the remaining studies, there are standardized mean differences ranging between 0.05 and –0.85, with a negative effect outcome of Hyalgan® compared with placebo only in the study of Jorgensen et al.[23]

As shown in figure 5, there is a modest difference in efficacy in favor of intra-articularly administered Synvisc® (molecular weight 6000 kDa) compared with placebo.[7,25,32,45] As shown, the results of Wobig and colleagues are different from those of the other two studies.[32] This study included a small group of patients with, however, a difference between the two groups for disease characteristics at baseline. In the Synvisc® group, more knees had a duration of pain of less than 1 year ($p < 0.025$) and the severity of OA (according to the Larsen classification) was also different in favor of the Synvisc® group. Although the VAS at baseline was not different, it is thought that patients with a shorter period of pain and a lower grade of OA respond better to an intra-articular treatment with HA.

A comparison with more uniform results is shown in figure 6, comparing the efficacy of intra-articularly administered Orthovisc® (molecular weight of 1000–2900 kDa) with intra-articularly administered placebo.[26,85] The effect sizes are between –0.20 and 0.03. The randomized, controlled, multicenter trial by Neustadt and colleagues[85] compared four weekly injections with Orthovisc® (O4), three weekly injections with Orthovisc® followed by one arthrocentesis (O3A1), and four weekly arthocentheses without injection (A4). A total of 372 patients were included and there was no difference between the O4 and A4 groups throughout the study, although both showed an improvement in pain compared with baseline. At 12 weeks' follow-up there was a decrease of –146.2 ± 119.3 in the WOMAC scores in the O4 group compared with baseline. The decreases in the WOMAC scores at 12 weeks were –121.0 ± 120.5 and –129.5 ± 121.7 in the O3A1 and A4 groups, respectively. Comparing these outcome measurements, there were no differences between the treatment groups, although the O4 group seemed to have the best efficacy. However, due to the fact that the standard deviation was that large, we can also conclude that a large group of patients did not receive any benefit from the treatment.

Kul-Panza and Berker[26] compared Orthovisc® with placebo and concluded that there was no difference between the groups ($p > 0.05$). However, as shown in all studies discussed in this section, there was an improvement in both groups compared with baseline.

Only three studies compared intra-articularly administered Artz® (molecular weight 620–1170 kDa) with intra-articularly administered placebo (figure 7).[25,27,86] In their multicenter

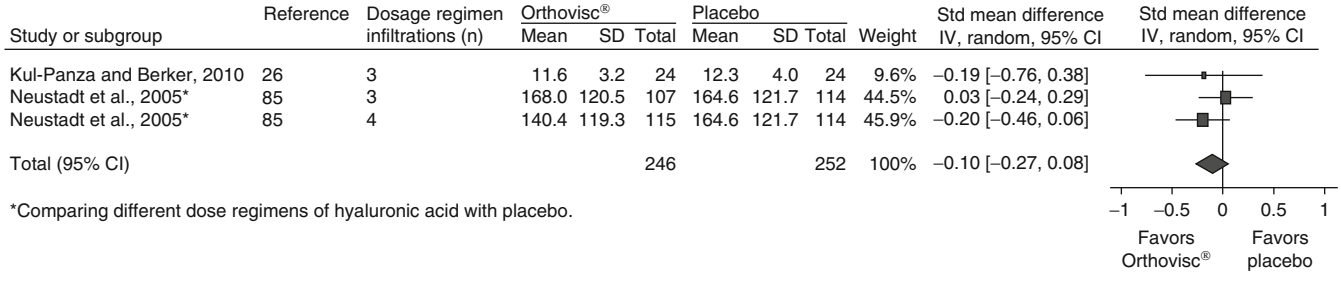



**Fig. 6.** Orthovisc® versus placebo.

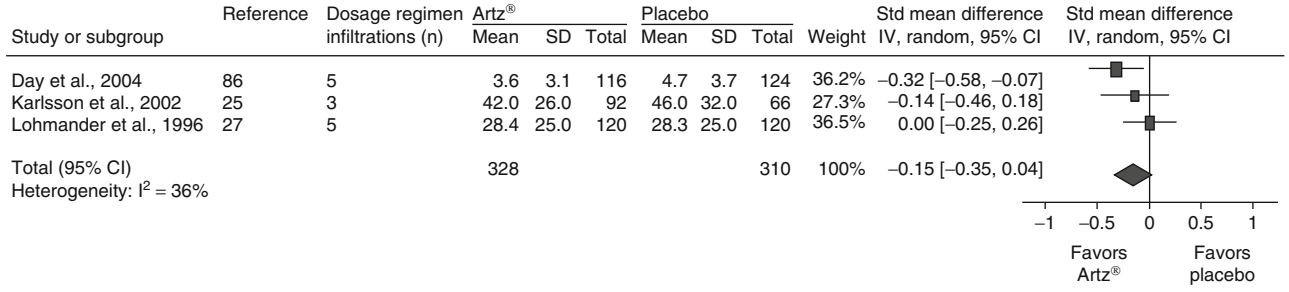
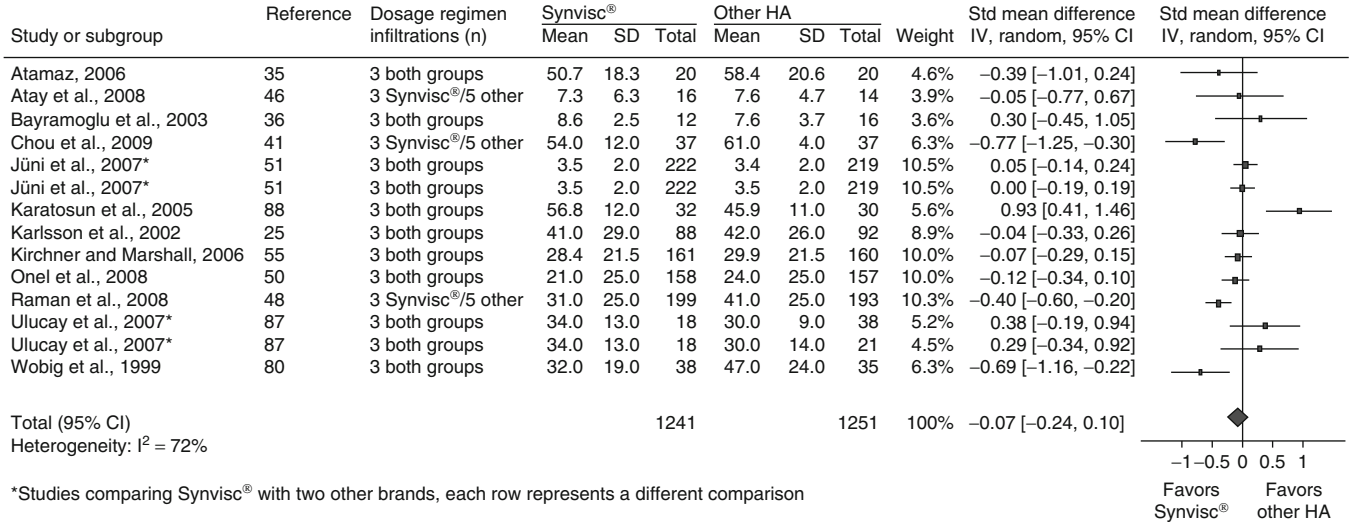



**Fig. 7.** Artz® versus placebo.

RCT, Day et al.[86] showed a difference between both groups at 13 weeks' follow-up using the WOMAC pain. However, the clinical difference between the groups is just small (an effect size of –0.32 in favor of Artz®).[7] Karlsson et al.[25] compared the efficacy of both Artz® and Synvisc® with intra-articularly administered placebo and they showed no differences between the different HA groups and placebo at 3 months' follow-up. Lohmander and colleagues[27] included 240 patients in their randomized, double-blind, placebo controlled, multicenter trial comparing Artz® with placebo and showed an improvement in pain in both groups at 13 weeks' follow-up, compared with baseline, but no difference between the groups ($p = 0.608$). However, after stratifying the groups by age they showed a significant difference between the groups for patients older than 60 years using the VAS for pain ($p = 0.014$). No other interactions such as gender or inclusion centre were found. They concluded that young patients with moderate symptoms or only early-stage radiographic signs of OA do not seem to have benefit from intra-articular treatment with HA. To our knowledge, no other published study made this stratification.

We identified 12 studies (1241 patients) comparing Synvisc® with other HA products (figure 8).[25,35,36,41,46,48,50,51,55,80,87,88] Atamaz et al.[35] showed a favorable effect of Synvisc® compared with Orthovisc® while other authors showed the opposite.[36,87,88] There is conflicting evidence regarding the comparison of Synvisc® with other HA products. Pooling the outcome of similar studies, Synvisc® has a modest pain improvement compared with Hyalgan®, Artz®, or Euflexxa®[7] (table I).[25,41,46,48,50,55,80] Conversely, Orthovisc® has a favorable efficacy on pain compared with Synvisc®.[35,36,51,87,88] Other comparisons between different products were only done in single studies and these showed no differences. As discussed before, only Hyalgan® and Synvisc® showed an improvement in VAS for pain compared with placebo. However, in table I we show that Synvisc® has a better efficacy than Hyalgan®, but less efficacy than intra-articularly administered Orthovisc®, which has only a favorable effect size of –0.10 compared with placebo. These different findings illustrate the difficulty comparing different studies carried out with different products. Due to this conflicting evidence, we are not able to conclude that one brand of HA has a better efficacy than another.




*Studies comparing Synvisc® with two other brands, each row represents a different comparison

**Fig. 8.** Synvisc® versus other hyaluronic acid (HA) products.

**Table I.** Synvisc® versus other hyaluronic acid products

| Comparison | No. of studies | No. of patients | $I^2$ (%) | SMD (95% CI) |
|---|---|---|---|---|
| Synvisc® vs Orthovisc®[35,36,51,87,88] | 5 | 627 | 70 | 0.25 (–0.15, 0.64) |
| Synvisc® vs Hyalgan®[46,48] | 2 | 422 | 0 | –0.37 (–0.57, –0.18) |
| Synvisc® vs Artz®[25,41,80] | 3 | 327 | 79 | –0.47 (–0,99, –0.04) |
| Synvisc® vs Euflexxa®[50,55] | 2 | 636 | 0 | –0.09 (–0.25, 0.06) |

**SMD** = standardized mean difference.

## 4. Discussion

We are aware of the fact that, in this systematic review, pooling of different studies (single- and double-blind) with different treatment strategies and different grades of OA is not ideal. However, we only included RCTs with similar treatment groups at baseline and with the same treatment strategy (besides the intra-articularly administered products). Another limit of this systematic review is the fact that we only compared the efficacy of intra-articularly administered HA at 3 months' follow-up and not longer. This was for two main reasons. First, the number of studies reporting the efficacy of intra-articularly administered HA compared with another product of intra-articularly administered HA, placebo, or other kind of conservative treatment at a longer follow-up is very small and the follow-up durations varied (6 months, 1 year, 2 years, etc.). Second, the systematic review of Bannuru et al.[5] showed that at 3 months or longer the efficacy of intra-articularly administered HA is better than intra-articularly administered corticosteroids. The efficacy of other pharmacological treatment options is also not that good at 3 months' follow-up compared with HA.[6] Because we focus on the therapeutic effects of intra-articularly administered HA, parameters such as joint replacement delay, slow-down of disease progression, or histological changes induced by the use of HA are not reported in this review.

Having performed a systematic review using a robust methodology with the objective of pooling and comparing the outcome data of numerous studies, we can conclude that intra-articular treatment with HA has good therapeutic efficacy in patients with knee OA compared with baseline. After pooling the efficacy of different products of HA compared with the efficacy of placebo we showed a weighted mean difference of –10.20 (95% CI –15.97, –4.42) with an $I^2$ of 92% between VAS for pain at baseline and at 3 months' follow-up. This is a statistical difference, but since the VAS for pain has a range of 0–100, it is debatable whether this difference is clinically relevant. Using the VAS, the minimal clinically important difference (MCID) is reported to be between 10 and 30. Most studies report a MCID of around 14, while other studies report a value of 10 or even 30.[89-92]

Despite the fact that there are several HA products, there is only evidence that Hyalgan® and Synvisc® have a modest efficacy compared with placebo. Other products have at least equal efficacy compared with placebo without significant differences between these 'treatments'. This is probably a sample size problem due to the smaller number of patients included in these studies.

Based on the results of the RCTs comparing HA with placebo we observed an improvement in the placebo group which showed a mean reduction of approximately 30% (range 16–44%) in baseline VAS for pain and which persists for at least 3 months. It is this placebo effect which makes the results of single-arm prospective documentation less relevant in interpreting the results of HA. However, it also has implications in analyzing these RCTs, since an interesting question is why this placebo effect is so clearly present. In 1964, Wright had already reported a significant placebo effect after intra-articular injections of saline solutions.[93] This effect was also observed in studies comparing intra-articular corticosteroid injections with placebo.[94] One of the reasons of this placebo effect may be the non-pharmacological recommendations including patient education, weight loss, physiotherapy, assistive devices for ambulation, appropriate footwear, and occupational therapy. In addition, patients might undergo arthrocentesis before intra-articular administration of HA or placebo. Arthrocentesis alone can be considered as a form of short-term symptomatic treatment *per se* as the altered inflammatory synovial fluid is removed.[18] Joint irrigation after arthrocentesis would increase the benefits by diluting inflammatory cytokines and cartilage degrading enzymes, while the intra-articular injection of any solution (saline, etc.) would also have a short-term beneficial effect because the procedure would favorably alter the abnormal joint environment.[95]

There are studies reporting that saline injection diminishes the symptoms of knee OA.[96-98] Egsmose et al.[99] reported significant pain relief in half of their patients for at least 3 months. Although this could also be a placebo effect, one wonders if the

saline injection itself is not also a treatment option.[99] However, Lundsgaard et al.[28] compared HA infiltration in the knee with the intra-articular infiltration of both 2 mL and 20 mL saline and showed no difference between these three groups.[28] They showed that a saline injection may be a suitable placebo and that it is just the placebo effect we are looking at. If this holds true, it must be said that the difference between HA and placebo is rather disappointing (10 mm on a 100 mm VAS pain). However, if saline may have an effect on the symptoms we might be making the wrong comparison, causing the difference to seem smaller than it in fact is.

In their meta-analysis, Zhang et al.[100] determined the placebo effect of different treatment options in patients with OA. They had two main conclusions. First, the placebo effect was greater in pharmacologically treated patients than in non-pharmacologically treated patients and this effect was even larger when the drugs were injected. Second, placebo is effective for OA, especially for subjective outcomes like pain, stiffness, self-reported function and doctor's global assessment. Most of the outcomes used in the studies included for this review were subjective, which could also explain the high placebo effect.

When comparing different HA products (and hence molecular weights, concentration and volumes of HA), it is still impossible to make recommendations based on the publications we have reviewed. Synvisc® is the only brand of HA that has been extensively compared with other products. One of the reasons for this could be the hypothesis that higher molecular weight HAs have the best efficacy; however, recent studies show no differences between high and low molecular weight HAs.[46,50,51,55,87] Another reason could be the fact that the company producing Synvisc® (Genzyme, Cambridge, MA, USA) is one of the market leaders and new agents are often compared with the products of the market leader. Another reason could be that Genzyme (but also other market leaders in producing HA) are sponsoring studies with their product. Of the studies using HA as an intra-articular treatment of knee OA, 59.5% were industry sponsored (in 27.4% of the studies it is not known if these were industry sponsored or not). A total of 12 studies compared Synvisc® with other HA products, but due to the heterogeneity of the studies and outcomes we are not able to conclude that one brand has a better efficacy than another.

For future studies, it is relevant to determine the exact mechanism of action of saline infiltrations used as placebo, because this may give us an idea of how to treat OA more efficiently. It is also important to compare different intra-articularly administered HA products to determine if one product or specific molecular weight range, concentration and volume of HA is superior for the treatment of OA. Large (multicenter), well designed (double-blind) RCTs comparing different products (and molecular weights, concentrations and volumes) of intra-articularly administered HA are required to give us more evidence about the efficacy of the different products of HA.

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