Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review of the Evidence

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Viscosupplementation for Osteoarthritis of the Knee

A SYSTEMATIC REVIEW OF THE EVIDENCE

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Abstract

Background: The purpose of this analysis was to determine the clinical significance of injectable hyaluronic acid (HA) in the treatment of knee osteoarthritis, and to assess which trial-level factors influence the overall treatment effect of HA on pain (as measured by a VAS [visual analog scale] or the WOMAC [Western Ontario and McMaster Universities Osteoarthritis Index]) and the WOMAC function and WOMAC stiffness subscales.

Methods: A comprehensive literature search of PubMed, EMBASE, the Physiotherapy Evidence Database, and the Cochrane Central Register of Controlled Trials was done to locate randomized controlled trials that compared HA with control treatment and had a minimum of thirty patients per subgroup. To be considered for inclusion, each article had to include VAS or WOMAC pain, WOMAC function, and/or WOMAC stiffness as outcomes because the minimal important difference (MID) has been established for these instruments. A “best-evidence” systematic review and meta-analysis of

nineteen trials was performed; because of high heterogeneity among the trials, meta-regression analyses were conducted to determine the influence of trial characteristics on overall HA treatment effects for pain, function, and stiffness.

Results: The most consistent finding was that double-blinded, sham-controlled trials had much smaller treatment effects than trials that were not sufficiently blinded ($p < 0.05$). For double-blinded trials, the overall treatment effect was less than half of the MID for pain, function, and stiffness. Other significant associations were found for cross-linked HAs and follow-up duration. However, the effect sizes among double-blinded trials of cross-linked HAs were still less than half of the MIDs for pain and stiffness. The statistically significant effect of follow-up duration disappeared when the open-label trials were removed from the analysis.

Conclusions: Meta-analysis of only the double-blinded, sham-controlled trials with at least sixty patients did not show clinically important differences of HA treatment over placebo. When all literature was added to the analysis, the overall effect was greater but was biased toward stronger treatment effects because of the influence of nonblinded or improperly blinded trials.

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

Knee osteoarthritis is responsible for a large burden of care and cost within health care. Osteoarthritis results from an imbalance between the breakdown and repair of articular cartilage in any joint and occurs as a result of multiple risk factors including mechanical overload (obesity, heavy lifting), trauma, overuse (repetitive knee bending), and genetic predisposition. The CDC (U.S. Centers for Disease Control and Prevention) reports that one in two individuals may develop symptoms of osteoarthritis in at least one knee by eighty-five years of age[1]. The incidence of new knee osteoarthritis in the U.S. is estimated at 240 persons per 100,000 per year[2]. The prevalence of the condition increases with age, especially in women. In adults over fifty years of age, it is estimated that the incidence of knee osteoarthritis in women is 45% higher than in men[3]. The prevalence of symptomatic knee osteoarthritis in patients at least forty-five years of age has been estimated to be 5.9% to 13.5% in men and 7.2% to 18.7% in women. Physician visits for knee pain in patients over the age of sixty-one years in the U.S. increased from 4.48 million in 2002 to 6.11 million in 2006[4]. The economic impact of the treatment of osteoarthritis in the U.S. was estimated to be $185.5 billion in a 2009 study, with a large portion of those dollars being spent for knee osteoarthritis[5].

A number of systematic reviews addressing intra-articular administration of hyaluronic acid (HA) have been performed and reported[6-10]. Those reviews have shown significance with respect to symptom relief,

but not all have taken into account the magnitude of the effect. Three systematic reviews utilizing clinical significance were unable to demonstrate efficacy with respect to pain relief[6,7,10]. The authors of all reviews commented on the substantial publication bias and heterogeneity of the clinical trials of intra-articular HA. In an attempt to minimize heterogeneity, we assessed the effect of intra-articular HA for knee osteoarthritis using a "best-evidence" systematic review as described by Slavin[11].

Rutjes et al.[6] provided an excellent analysis of the influence of trial-level characteristics on the statistical heterogeneity of HA treatment effects across trials, and they evaluated the clinical significance of HA in the treatment of knee osteoarthritis. However, some argue that their method of determining clinical significance on the basis of a difference of at least the minimal important difference (MID) was too conservative, as an appreciable number of patients may still benefit from an average effect of >50% of the MID even if the confidence interval does not overlap with the MID[12]. The present analysis uses this less conservative approach to measure the clinical significance of viscosupplementation in the treatment of osteoarthritis of the knee, while exploring causes of heterogeneous treatment effects in the HA literature.

Methods

Literature Search

The systematic review started with a comprehensive literature search of articles published prior to February 16, 2015, in four electronic databases: PubMed, EMBASE, the Physiotherapy Evidence Database, and the Cochrane Central Register of Controlled Trials. The search utilized key terms shown in the Appendix.

The electronic search was supplemented with a manual search of the bibliographies of all retrieved systematic reviews and other review articles for potentially relevant citations. Retrieved articles were evaluated for possible inclusion on the basis of the trial selection criteria; an attrition flowchart is shown in the Appendix.

Search Inclusion Criteria

A trial was eligible for inclusion in the systematic review if it (1) was a randomized clinical trial, (2) had a minimum of four weeks of follow-up, (3) had a minimum of thirty patients per treatment subgroup, (4) used the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) and/or a VAS (visual analog scale) for pain (outcomes for which the MID is available), (5) involved patients with knee osteoarthritis, and (6) was reported in English.

Outcomes with MIDs

A recent clinical practice guideline cited MIDs for VAS pain and for the WOMAC scale and its subscales[7]. The MIDs for the WOMAC pain, function, and stiffness subscales are 8.3, 8.0, and 10.1, respectively, on a 100-point scale[13]. The MID for VAS pain is 19.9 mm on a 100-mm scale[14]. WOMAC and VAS pain outcomes in the included trials were extracted and analyzed. The follow-up durations in the included trials ranged from six to fifty-two weeks, with the most common end point being at approximately twenty-six weeks.

Data Abstraction

Because all of the outcomes considered in this analysis were continuous, their means and measures of dispersion were extracted from each trial. Data on the trial quality characteristics and on the treatment (HA cross-linking, HA molecular weight, and the number of injections) were also extracted from each trial (**Tables I** and **II**).

TABLE I View inline

Trial Quality Information

TABLE II View inline

Trial Treatment Information

Statistical Methods

Meta-analyses used the random-effects method of DerSimonian and Laird[15]. Heterogeneity was assessed with the I^2 statistic, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Meta-regression analyses were performed to assess the influence of trial characteristics on the treatment effects for VAS or WOMAC pain, WOMAC function, and WOMAC stiffness. Regression analyses were performed using the permutation method of Higgins and Thompson[16] with 10,000 iterations. All analyses were performed with STATA software (version 12.1; StataCorp).

The mean difference and standard error (SE) of each trial were converted into MID units, using the method described by Johnston et al.[12]: standardized MID = (mean difference)/MID, and standardized SE = (SE of mean difference)/MID. Estimated treatment effects of 0.5 to 1.0 MID units according to this method may be beneficial to an appreciable number of patients even if the upper confidence limit does not include 1 MID. It is unlikely that an appreciable number of patients will show a clinically important benefit as the treatment effect falls below 0.5 MID units[12].

Source of Funding

This study received no external funding.

Results

Of the 628 abstracts identified by the literature search, 545 did not meet the inclusion criteria. The remaining eighty-three articles were retrieved for full text review; of these, six were systematic reviews and an additional sixty-four articles did not meet the inclusion criteria. Nineteen articles thus remained for data abstraction, with a total of 4485 patients included in the analysis.

Fourteen (74%) of the trials compared HA with placebo (sham treatment), two (11%) compared HA with conventional (usual) care, and three (16%) paired HA with an additional active treatment and compared the results with those in a control group that received that active treatment alone. Nine (47%) of the trials confirmed that the randomization sequence was adequately concealed to prevent selection bias. Fourteen (74%) of the trials (the sham-controlled trials) were double-blinded. An intent-to-treat analysis was used in nine (47%) of the trials. Twelve (63%) of the trials were stated to be industry-funded. Seven (37%) of the trials confirmed that groups were demographically similar with a hypothesis test, and six (32%) of the trials confirmed that outcome measures were similar at baseline.

Pain

Initial meta-regression analyses for pain revealed that significant causes of heterogeneity ($p < 0.05$) were (1) use of a double-blinded sham-controlled design, (2) HA cross-linking, (3) follow-up duration, and (4) confirmation of baseline outcome measure equivalency (**Table III**).

TABLE III View inline

Meta-Regression P Values

The meta-analysis for pain was thus repeated with stratification: HA alone compared with sham, HA plus additional active treatment compared with active treatment alone, and HA compared with usual (appropriate) care (**Fig. 1**). In the sham-controlled trials, the HA group had significantly better pain scores. However, the average treatment effect was only 29% of the MID. It is unlikely that an appreciable number of patients received a clinically important benefit, as the average treatment effect was <50% of the MID[12]. In the trials that compared HA plus an additional active treatment with that active treatment alone, the effect size was still only about one-half (51%) of the MID. The treatment assignment in these trials was not blinded, as the treatment group received two interventions (HA plus additional treatment)

whereas the control group received only one intervention (the same additional treatment as in the treatment group, with no HA). However, the fact that the control group received an active treatment instead of a placebo may have tempered some of the placebo effect. The final group of trials that compared HA with usual (appropriate) care provided no control for the placebo effect. The treatment effect was far greater in these trials than in the previous two groups of trials, with the overall effect size of 1.52 MID units being 5.2 times greater than the effect size of 0.29 MID units in the double-blinded trials.

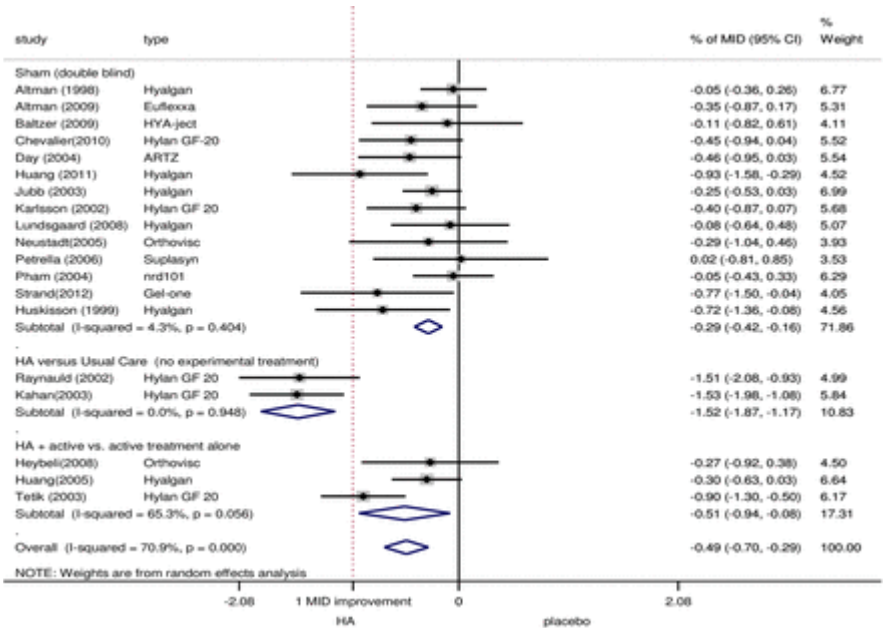

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Fig. 1

Meta-analysis for pain stratified by control type and blinding. CI = confidence interval.

Cross-linked HAs had significantly greater treatment effects than their non-cross-linked counterparts (p = 0.003). The meta-analysis for pain was therefore repeated with stratification by cross-linking (**Fig. 2**). The treatment effect for cross-linked HAs was 0.68 units closer to the MID than that for the non-cross-linked versions (93% of the MID for cross-linked and 25% of the MID for non-cross-linked). The average treatment effect for cross-linked HAs in the double-blinded sham-controlled trials was less than one-half

of the MID (49%) (Fig. 3). Conversely, the average treatment effect for cross-linked HAs in the trials with insufficient patient blinding was 29% greater than the MID.

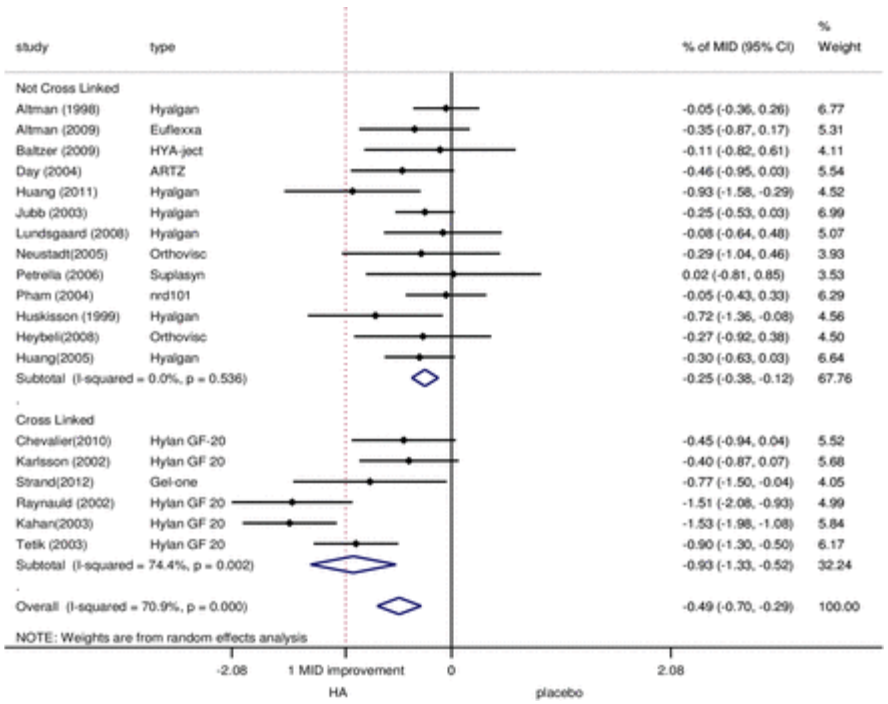

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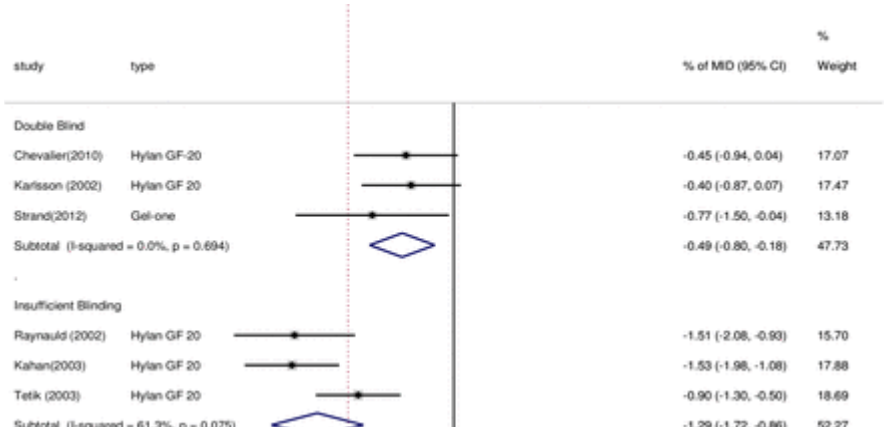
Fig. 2

Meta-analysis for pain stratified by cross-linking. CI = confidence interval.



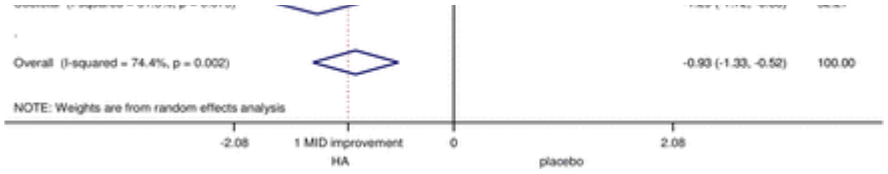


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Fig. 3

Meta-analysis for pain among the subgroup of trials that used cross-linked HAs, stratified by blinding. CI = confidence interval.

As the follow-up duration significantly influenced pain (p = 0.01), the meta-analysis for pain was stratified by follow-up durations of six to thirteen weeks or greater than thirteen weeks (**Fig. 4**). Although the effect size was larger in the trials with follow-up of at least thirteen weeks, visual inspection of the forest plot indicates that this resulted from two trials, by Raynauld et al.[17] and Kahan et al.[18]. These were unblinded trials that compared HA with usual care. When these trials were removed from the analysis, follow-up duration was no longer a significant predictor of HA treatment effect (p = 0.938).

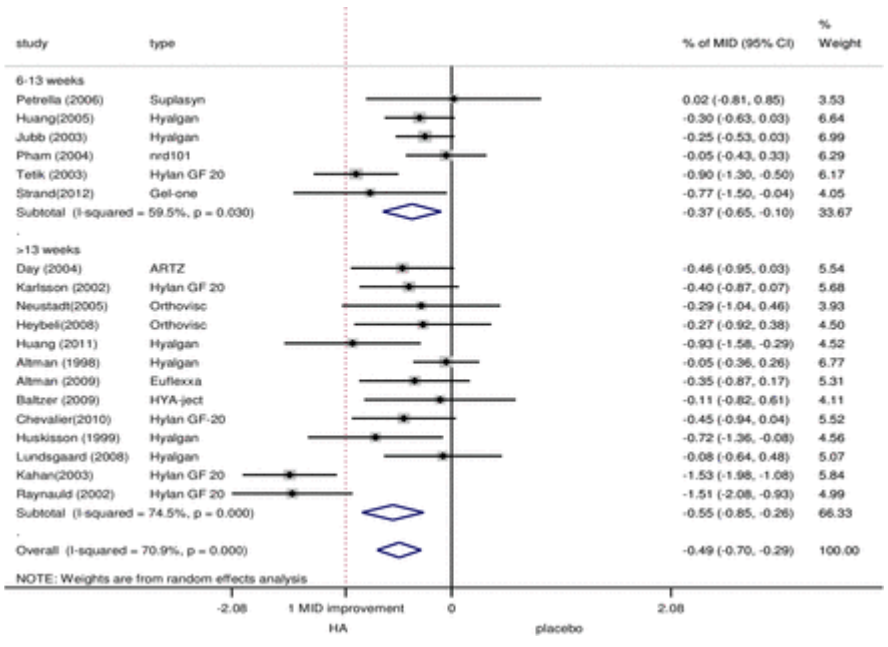

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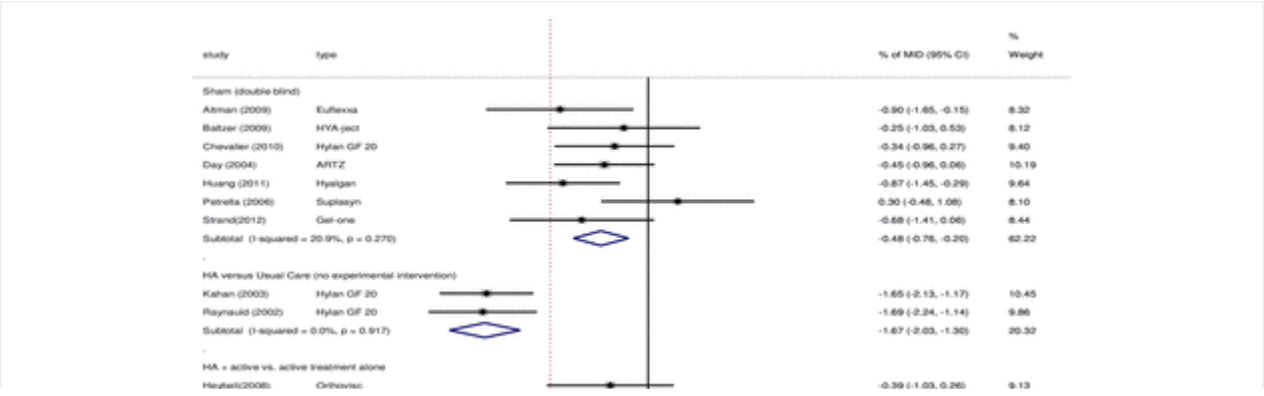
Fig. 4

Meta-analysis for pain stratified by follow-up of six to thirteen and greater than thirteen weeks. CI = confidence interval.

Finally, the effect of HA treatment on pain was significantly affected by whether or not the trial reported tests of significance to confirm that baseline pain was similar between treatment groups ($p = 0.032$). However, there was still substantial heterogeneity in the outcome when meta-analyses were stratified according to confirmation of baseline equivalence in pain level between the groups (59.5% in the trial with no or unclear confirmation and 74.5% in the trials with confirmed equivalence). The stratified meta-analysis is not included here because of the difficulty in reaching a definitive conclusion in the presence of the remaining large variations among trials within the two subgroups.

WOMAC Function

Meta-regression analyses revealed that trials using a double-blinded sham-controlled design had significantly lower treatment effects for WOMAC function compared with insufficiently blinded trials. The function meta-analysis was therefore repeated with stratification by blinding and the type of control group used (**Fig. 5**). Double-blinded trials with a sham control group had a significant treatment effect that was not clinically important (48% of the MID). The trials that compared HA plus another active treatment with the additional treatment alone had an effect that was 50% of the MID. The trials by Raynauld et al.[17] and Kahan et al.[18], which compared HA with usual care (no active experimental treatment) and were of open-label design, had a pooled treatment effect that was significantly higher than the MID. However, the large difference between these open-label trials and the double-blinded trials indicates that they had a substantial placebo effect.



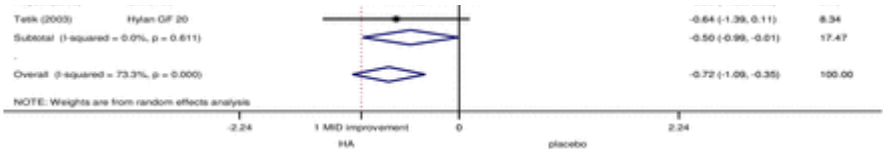


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Fig. 5

Meta-analysis for WOMAC function stratified by control type and blinding. CI = confidence interval.

The meta-regression analyses did not reveal cross-linking to be a significant cause of heterogeneity (p = 0.110) in the WOMAC function results. However, a subgroup analysis according to cross-linking was undertaken because the two unblinded trials with the strongest treatment effect both used the cross-linked Hylan G-F 20 (**Fig. 5**). A function meta-analysis of cross-linked HAs further stratified by blinding was also performed (**Fig. 6**). The pooled effect from the two double-blinded trials was 48% of the MID, meaning that it is unlikely that an appreciable number of the patients would have benefitted from cross-linked HA over placebo.

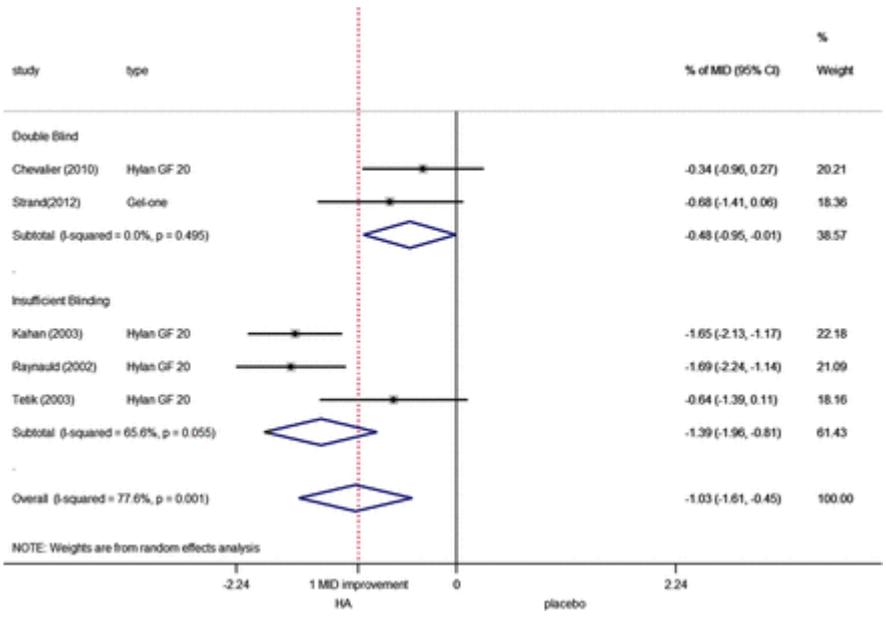

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Fig. 6

Meta-analysis for WOMAC function among the subgroup of trials that used cross-linked HAs, stratified by blinding. CI = confidence interval.

Follow-up duration was also a significant cause of heterogeneity in WOMAC function results (p = 0.003). However, the effect of duration was no longer significant when the two open-label trials were removed from the analysis (p = 0.212).

WOMAC Stiffness

Meta-regression analyses for WOMAC stiffness revealed that, again, sham-controlled blinding was a significant source of heterogeneity (p = 0.03). A stiffness meta-analysis stratified by blinding and type of control was therefore performed (Fig. 7). The sham-controlled trials had a pooled treatment effect that was only 39% of the MID. The inadequately blinded trials had much stronger treatment effects. Again, the large difference between the two blinding subgroups was likely due to the placebo effect.

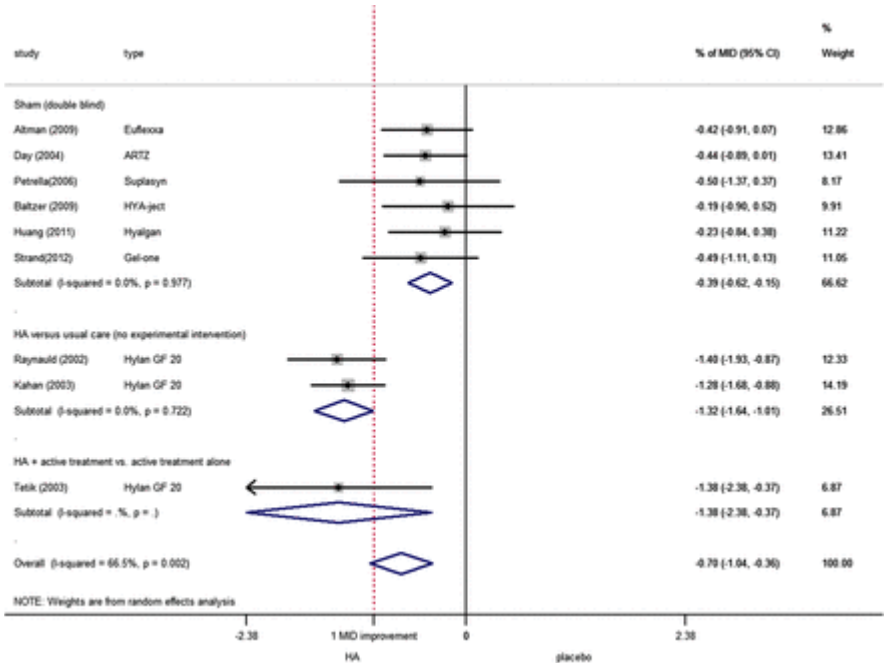

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Fig. 7

Meta-analysis for WOMAC stiffness stratified by control type and blinding. CI = confidence interval.

As for pain and function, trials that used cross-linked HAs had lower WOMAC stiffness scores (p = 0.014) (Fig. 8). However, a subgroup analysis of cross-linked HAs by blinding status was not undertaken because there was only one double-blinded sham-controlled trial. Therefore, it is unclear whether the cross-linked HAs actually resulted in better stiffness scores or the observed difference was caused by lack of blinding. On visual inspection of the forest plot (Fig. 8), the difference between cross-linked HA and sham treatment was not significant in the trial that was double-blinded (Strand et al.[19]).

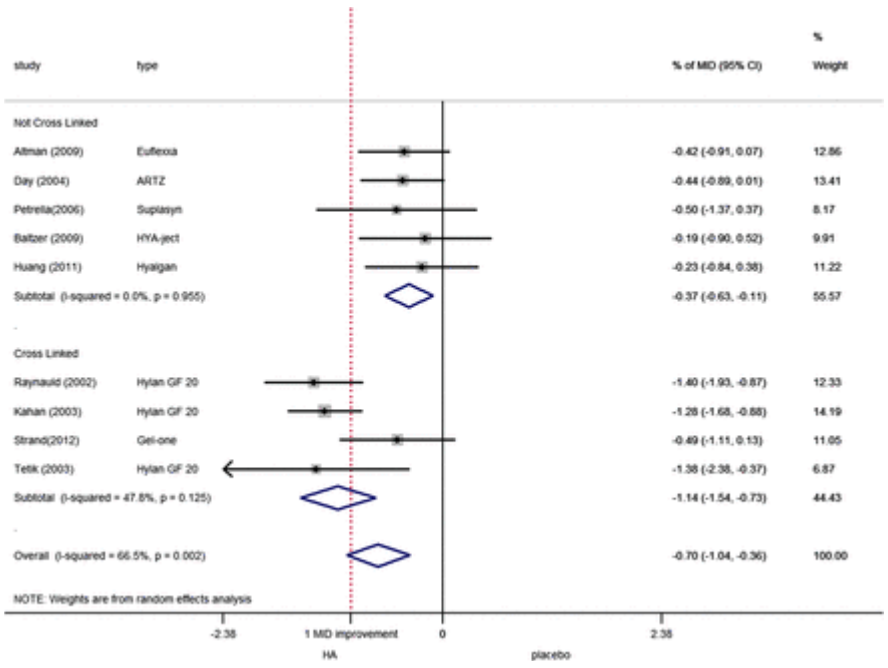

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Fig. 8

Meta-analysis for WOMAC stiffness stratified by cross-linking. CI = confidence interval.

Publication Bias

Previous meta-analyses have consistently documented the presence of publication bias in the viscosupplementation literature[6,8,9]. Consequently, an Egger[20] test was used to determine whether the effect sizes in this analysis have been inflated by publication bias. The p value of the Egger test was 0.796 for pain, 0.628 for WOMAC function, and 0.907 for WOMAC stiffness, indicating statistically insignificant inflation of effect sizes due to selective publication (see Appendix for funnel plots).

Discussion

Our analysis showed a difference in treatment effect when adequacy of blinding was considered. Trials that employed a double-blinded methodology showed a smaller effect than trials comparing HA with no treatment (29% compared with 152% of the MID for pain, 48% compared with 167% of the MID for function, and 39% compared with 132% of the MID for stiffness). Lumping the lower-quality evidence with the high-quality (double-blinded sham-controlled) evidence thus skewed the overall effect (49% rather than 29% of the MID for pain, 72% rather than 48% of the MID for function, and 70% rather than 39% of the MID for stiffness), demonstrating why the use of best evidence is preferable to the use of all available trials. The effect in trials involving cross-linked HAs was also decreased with appropriate blinding.

Although this systematic review on the use of intra-articular HA pooled the highest-quality trials, as described above, a number of limitations are still present in our analysis. First, the trials in our meta-analyses used different protocols for the treatment of knee osteoarthritis with intra-articular HA. The dosages, formulations, and timing of injections were not uniform and varied across trials. Differences also exist between HA preparations used in the U.S. and those approved for use in other countries[8]. Trial populations, although similar in most demographic criteria, addressed a range of grades of knee osteoarthritis. Another limitation is the lack of uniformity in the timing of patient assessment after the therapeutic injections. Finally, we decided not to include industry funding in the meta-regression model, as the funding source was unclear in some trials. We elected to analyze the effect of treatment at four weeks post-injection and later because of the large volume of reporting at this time interval.

With the exception of the systematic reviews performed by Rutjes et al.[6] and Colen et al.[10], most systematic reviews have relied on statistical significance for evaluating the efficacy of intra-articular HA injections. Since many of the trials reporting on patient-reported outcomes used the WOMAC score, for which MIDs are available, we opted to rely on clinical significance as determined by comparison of significant effects with the MID, which is the smallest improvement that is considered clinically important.

The MID value has been described and validated for the WOMAC and VAS pain in patients with knee osteoarthritis[13,14,21,22].

We believe that the MID is the best available tool for defining clinically important improvement in this patient population. The use of the MID in a post hoc analysis when it was not measured individually within the trial populations has been criticized, but it still represents a better-validated tool than significance or arbitrary percentage improvements. The use of differences between group means may limit the ability to determine improvement at the individual patient level, but all data were reported in this manner. However, in randomized controlled trials, it is a reasonable assumption that changes from baseline in the individual patients measure exactly the same intervention effects as differences in final raw scores between groups[23,24]. We also argue that this criticism is inconsistent with real clinical practice, where orthopaedic surgeons routinely predict patient outcomes such as time to fracture-healing, surgical prognosis, surgical recovery, or return to activities using similar post hoc analysis of the available literature. When available, an a priori measure of clinical significance is desirable both in trial design and reporting as well as in systematic reviews.

To our knowledge, this systematic review is the first to report results using best-evidence techniques. Slavin[11] expressed concerns about the use of all available data and trials in performing a meta-analysis. When all data are used, the data parameters from poorly performed, and on occasion non-peer-reviewed, studies attain equivalency to those from peer-reviewed studies performed with greater internal validity and patient numbers. Slavin argued further that higher-quality studies merit greater weighting, since those studies likely reflect higher-quality, more believable, and more reproducible results. This methodology also addressed the “small-study effect,” in which studies with inadequate sample size or statistical precision can lead to distortion of meta-analysis results in osteoarthritis[25].

When compared with the two most recent systematic reviews by Rutjes et al.[6] and Miller and Block[8], the results of our meta-analyses are consistent with Slavin’s argument. For function, the standardized mean difference (SMD) of 0.29 derived in our study (**Fig. 9**) was similar to those in the reviews by Miller and Block (0.32) and Rutjes et al. (0.33). For pain, our SMD of 0.26 (**Fig. 10**) was considerably smaller than those reported by Miller and Block (0.43) and Rutjes et al. (0.37). Rutjes et al. reported that trial size, blinding, and publication bias were associated with the effect size. We did not detect any significant associations for publication bias, probably because we included trials with a minimum of thirty patients per group. This is not to say that publication bias does not exist in the viscosupplementation literature, but rather that the results of our analysis were less influenced by small-study effects because smaller trials were excluded. Larger trials are not as susceptible to publication bias because they have smaller standard errors and are thus less likely to yield extreme effect sizes. Rutjes et al.[6] and the AHRQ

(Agency for Healthcare Research and Quality) Technology Assessment[9] stratified studies by sample sizes of ≤100 and >100 to control for publication bias. Rutjes et al. found that the effect size in trials with ≤100 subjects was 3.3 times that in larger trials. The AHRQ found that the effect size in trials with ≤100 patients was up to twice as great as that in larger trials. The majority of trials in our meta-analysis had a sample size of >100. Fifteen of nineteen, nine of eleven, and eight of nine trials had sample sizes of >100 for pain, function, and stiffness, respectively, which would explain why the effect sizes were not significantly affected by selective publication of smaller trials with larger positive effects. We believe that the nearly twofold difference in mean effect size for pain between our study and that by Miller and Block was due to publication bias in the latter review.

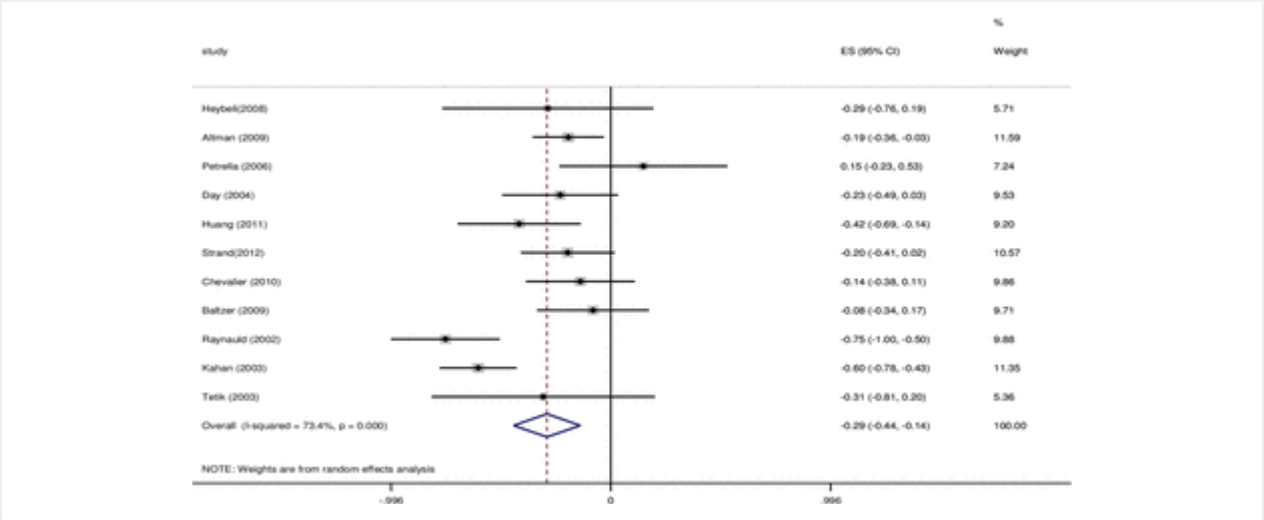

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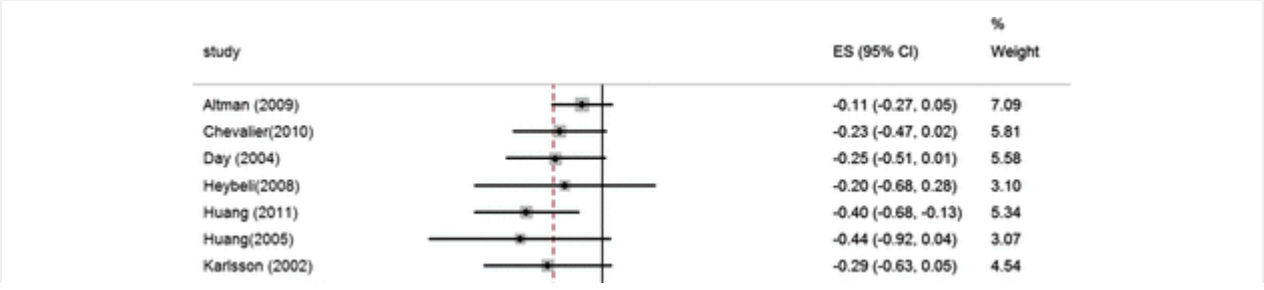
Fig. 9

Meta-analysis of SMDs in WOMAC function. CI = confidence interval, and ES = effect size.



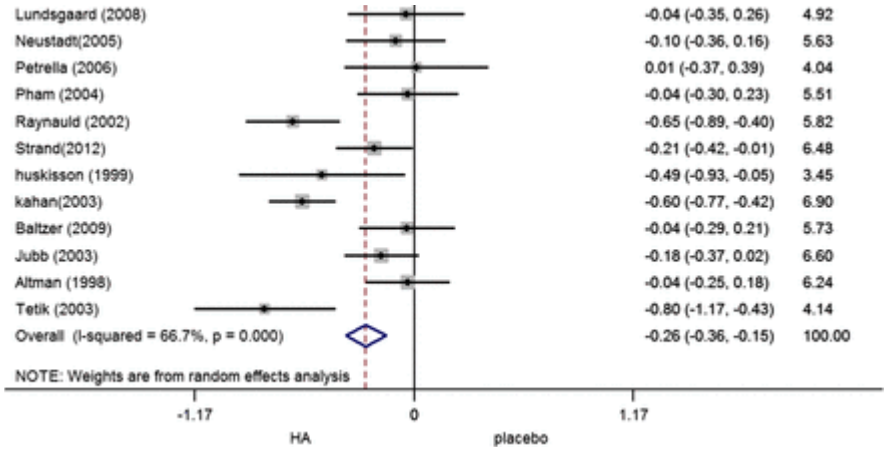


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Fig. 10

Meta-analysis of SMDs in pain. CI = confidence interval, and ES = effect size.

In conclusion, this best-evidence systematic review assessing the clinical significance of outcomes involving pain relief and functional improvement does not support the routine use of intra-articular HA. In contrast to previous reviews, we found no significant evidence of publication bias in the studies that we selected for analysis. The patient benefit of intra-articular HA was not clinically important when compared with intra-articular saline solution injections used as a placebo. Subdividing HA preparations by molecular weight did not change the results of the analyses. Selecting the best evidence resulted in significantly reduced heterogeneity but did not change the outcome; no clinically important improvement in pain and other outcomes from a patient's perspective was found.

Appendix

The literature search strategy and figures showing a flowchart of the trial identification process and funnel plots for pain, function, and stiffness are available with the online version of this article as a data supplement at jbjs.org.

Acknowledgments

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Footnotes

- Investigation performed at the American Academy of Orthopaedic Surgeons, Rosemont, Illinois
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