

THERAPEUTIC EFFECTS OF HYALURONIC ACID ON OSTEOARTHRITIS OF THE KNEE

A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: The magnitude of the therapeutic effects of intra-articular injection of hyaluronic acid on osteoarthritis of the knee is still in question. The aim of this meta-analysis was to elucidate the therapeutic efficacy and safety of intra-articular injection of hyaluronic acid for osteoarthritis of the knee.

Methods: We conducted a meta-analysis of twenty blinded randomized controlled trials that compared the therapeutic effect of intra-articular injection of hyaluronic acid with that of intra-articular injection of a placebo to treat osteoarthritis of the knee. The outcome end points were classified into three categories: pain with activities, pain without activities, and function. The outcome measures of the efficacy of hyaluronic acid were the mean differences in the efficacy scores between the hyaluronic acid and placebo groups. The outcome measure of the safety of hyaluronic acid was the relative risk of adverse events.

Results: Intra-articular injection of hyaluronic acid can decrease symptoms of osteoarthritis of the knee. We found significant improvements in pain and functional outcomes with few adverse events. However, there was significant between-study heterogeneity in the estimates of the efficacy of hyaluronic acid. Subgroup analysis and meta-regression analysis showed that lower methodological quality such as a single-blind or single-center design resulted in higher estimates of hyaluronic acid efficacy, that introduction of acetaminophen as an escape analgesic in the trial resulted in lower estimates of hyaluronic acid efficacy, and that patients older than sixty-five years of age and those with the most advanced radiographic stage of osteoarthritis (complete loss of the joint space) were less likely to benefit from intra-articular injection of hyaluronic acid.

Conclusions: This meta-analysis confirmed the therapeutic efficacy and safety of intra-articular injection of hyaluronic acid for the treatment of osteoarthritis of the knee. Additional well-designed randomized controlled trials with high methodological quality are needed to resolve the continued uncertainty about the therapeutic effects of different types of hyaluronic acid products on osteoarthritis of the knee in various clinical situations and patient populations.

Level of Evidence: Therapeutic study, Level II-3b (systematic review; nonhomogeneous Level-I studies). See Instructions to Authors for a complete description of levels of evidence.

Osteoarthritis is the most common joint disorder in the elderly¹. There are several options for treating osteoarthritis of the knee, including simple analgesics, nonsteroidal anti-inflammatory drugs, intra-articular injection of glucocorticoids, exercise, physiotherapy, weight-relieving braces, and total knee arthroplasty. Intra-articular injection of hyaluronic acid, which involves use of a medical device² as

well as a slow-acting drug for the treatment of symptoms of osteoarthritis³, has recently become one of the popular nonoperative options for treating osteoarthritis of the knee. Hyaluronic acid is a critical constituent component of normal synovial fluid and an important contributor to joint homeostasis⁴. In osteoarthritis, both the concentration and the molecular weight of intra-articular endogenous hyaluronic acid are decreased, which reduces the viscoelasticity of synovial fluid⁵. Therefore, the original rationale for intra-articular injection of hyaluronic acid was that it restored the viscoelasticity of synovial fluid⁶. In addition, it has been found that



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injected hyaluronic acid can augment the flow of synovial fluid, normalize the synthesis and inhibit the degradation of endogenous hyaluronic acid, and relieve joint pain⁷.

The therapeutic effects of intra-articular injection of hyaluronic acid have been tested in a number of clinical trials; however, different types of outcome instruments were used in these trials. In addition, although many trials demonstrated that hyaluronic acid injection has beneficial effects on knees with osteoarthritis, some showed that it lacks efficacy⁸. These studies raised the question about the actual magnitude of the therapeutic effects of hyaluronic acid injection. Therefore, our aim was to elucidate the therapeutic efficacy and safety of intra-articular injection of hyaluronic acid in the treatment of osteoarthritis of the knee by conducting a meta-analysis of randomized controlled trials.

Materials and Methods

Search Strategy

We conducted electronic searches for relevant randomized controlled trials in the MEDLINE and EMBASE databases (from January 1966 to December 2001) and the Cochrane Controlled Trials Register⁹. In combination with a search strategy that has optimal sensitivity in identifying randomized controlled trials¹⁰, “osteoarthritis,” “hyaluronic acid,” and their synonyms were entered as textwords for searches. In addition, supplemental issues of *Arthritis and Rheumatism*, *British Journal of Rheumatology*, *Journal of Rheumatology*, and *Acta Orthopaedica Scandinavica*, published between January 1970 and December 2001, were searched by hand. The references cited in review articles and retrieved articles were also reviewed. Unpublished trials were not searched, and the search was restricted to English-language reports.

Trial Inclusion Criteria

Only single-blind or double-blind randomized controlled trials that compared the therapeutic effect of intra-articular injection of hyaluronic acid with that of intra-articular injection of a placebo to treat osteoarthritis of the knee were included in this meta-analysis. Outcome end points for pain or function and quantitative data on therapeutic effects had to be available. Comparison of the therapeutic effect of intra-articular injection of hyaluronic acid with that of intra-articular injection of a placebo is essential to demonstrate the true efficacy of hyaluronic acid.

Data Collection

All relevant randomized controlled trials were selected, and all relevant data were extracted from the text, tables, and figures, by two investigators working independently using a standardized form. Differences in data interpretation were resolved by discussion between the investigators. We did not calculate the interrater and intrarater agreement regarding trial selection and data extraction. Authorship, time periods of enrollment, details of treatment protocols, demographic data on the patients, and other information in the randomized controlled trials were closely examined to avoid inclusion of data on pa-

tients who had been described in multiple reports and to ensure inclusion of the most complete data. The authors, institutions, journals, and identities of the treatment groups were not masked during trial selection and data extraction by the investigators. Available evidence indicates that, for purposes of meta-analysis, such masking imposes substantial burdens without significantly altering the results of a review ($p = 0.35$)¹¹. Masking also hinders efforts to avoid duplication and ensure completeness of data.

The methodological quality of each trial was scored with use of a 28-point checklist (see Appendix), which had been validated¹² and has been used in the development of evidence-based guidelines for the management of osteoarthritis of the knee by the European League Against Rheumatism³. Pain intensity and patient function at different times, which were measured with validated and reliable outcome instruments¹³ (see Appendix), were recorded for statistical analysis. In addition, adverse events were recorded and were classified as major or minor according to the classification in each trial. Study-level data, but not individual patient data, were used in the statistical analysis.

Outcome Measures of Efficacy and Safety of Hyaluronic Acid

We classified the outcome end points for efficacy evaluation into three categories: pain with activities (walking, climbing, and so on), pain without activities (at rest, at night, and so on), and function (see Appendix). To incorporate efficacy outcomes that were measured with different types of outcome instruments and were evaluated at different times after treatment, we defined efficacy scores with a modification of the method of de Craen et al.¹⁴ and Zhang et al.^{15,16}. First, the extracted data were transformed in the following manner. The pain intensity difference was considered to be the difference in pain intensity between one time-point and the baseline. The sum of the pain intensity differences (SPID) was the sum of the average of two consecutive pain intensity differences multiplied by the time-interval between two time-points—that is, the area under the pain intensity difference-versus-time curve. The standard deviation of the sum of the pain intensity differences was the sum of the average of standard deviations of two consecutive pain intensity differences multiplied by the time-interval between two time-points. For a trial that presented mean values without measures of variability, the standard deviation of the sum of pain intensity differences was calculated by multiplying the mean for the trial arm by the median coefficient of variation from other included trial arms that used the same category of outcome¹⁷. The function index difference, the sum of function index differences (SFID), and the standard deviation of the sum of function index differences were defined in the same manner. Then, we defined the efficacy scores, SPID%, adjusted SPID% (ASPID%), and peak PID%, as follows:

$$\text{SPID\%} = \frac{\text{sum of pain intensity differences}}{(\text{maximum scale of pain intensity} \times \text{trial duration})} \times 100\%$$

SPID%, an integrated score with time as a dimension, represents the overall efficacy in the trial period.

$$\text{ASPID}\% = \frac{\text{sum of pain intensity differences}}{(\text{baseline intensity} \times \text{trial duration})} \times 100\%$$

ASPID%, an integrated score with time as a dimension, represents the overall efficacy in the trial period after adjustment for the baseline pain intensity.

$$\text{Peak PID}\% = \frac{\text{maximum pain intensity difference}}{\text{maximum scale of pain intensity}} \times 100\%$$

Peak PID% represents the maximum efficacy during the trial.

For function, SFID%, adjusted SFID% (ASFID%), and peak FID% were defined in the same manner.

In this meta-analysis, the outcome measures of the efficacy of hyaluronic acid were the differences in mean efficacy scores between the hyaluronic acid and placebo groups. The outcome measure of the safety of hyaluronic acid was the relative risk of adverse events.

Statistical Analysis

Pooled Efficacy and Safety

For efficacy outcomes, the METAN program with methods of unstandardized mean difference¹⁸ was used to calculate pooled mean differences in the efficacy scores and corresponding 95% confidence intervals. For safety outcomes, the METAN program with the methods of Mantel and Haenszel¹⁹ was used to calculate pooled relative risk and corresponding 95% confidence intervals. The chi-square test for Q statistics was used to test between-study heterogeneity. If there was significant between-study heterogeneity (a p value for chi-square test of ≤ 0.1), the random-effects models of the DerSimonian and Laird methods²⁰ were used to calculate pooled mean differences, pooled relative risk, and corresponding 95% confidence intervals. If there was no significant between-study heterogeneity (a p value for chi-square test of > 0.1), fixed-effects models of the inverse variance method were applied in the calculation.

Subgroup Analysis and Meta-Regression Analysis

Subgroup analysis was planned and conducted to investigate the effects of several categorical attributes on the estimates of hyaluronic acid efficacy and to assess between-study heterogeneity within each subgroup of trials. These categorical attributes included blinding status, single-center or multicenter trial, intention-to-treat analysis (meaning that the data on all study subjects were analyzed according to the groups to which they were initially allocated), use of escape analgesics, mean age of the patients (sixty-five years or less, or more than sixty-five years), inclusion of the most advanced radiographic stage of osteoarthritis (defined as a complete loss of joint space), effusion as an inclusion or exclusion criterion, trial duration (twelve weeks or less, or more than twelve weeks), sample size (100 knees or fewer, or more than 100 knees), and whether the trial was industry-funded.

Meta-regression analysis, performed with use of the METAREG program with the method-of-moments estimator

method²¹, was planned and conducted to investigate the effects of several continuous attributes on the estimates of hyaluronic acid efficacy; these included the year of publication, quality score of the methodology, molecular weight of the hyaluronic acid, mean age of the patients, trial duration, and sample size. We also calculated residual heterogeneity variance², which is the residual between-study variance² after accounting for the heterogeneity resulting from the difference in each attribute. The meta-regression analysis was limited to univariate analysis.

Assessment of Publication Bias

Funnel plots of the mean differences in the efficacy scores for all included trials were constructed to assess the degree of publication bias.

Results

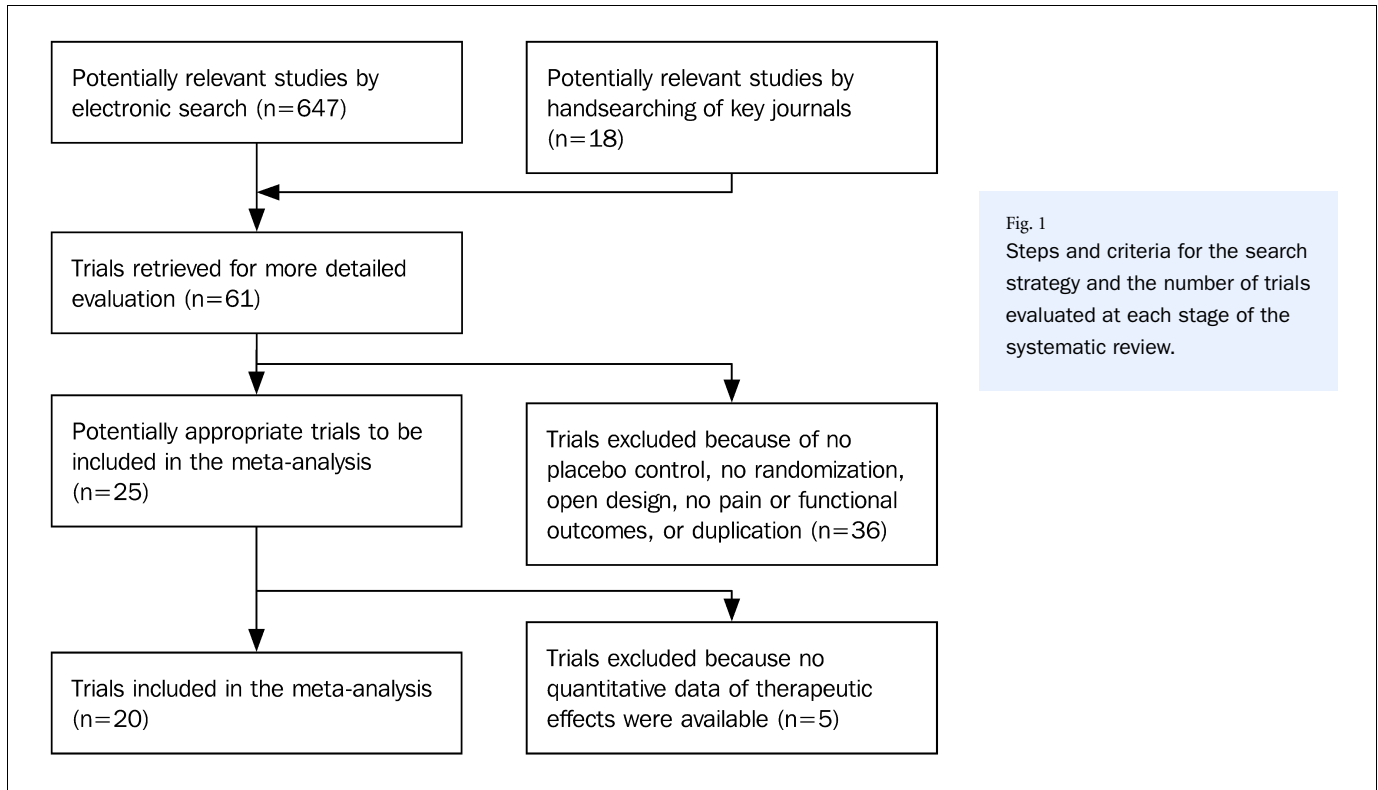
Included Trials

Figure 1 shows the steps and criteria for the search strategy and the number of trials evaluated at each stage of the systematic review. A total of 665 potentially relevant studies were identified and screened for retrieval: 647 were identified by electronic searches and eighteen, by hand-searching of key journals. After the exclusion of non-trial studies, sixty-one relevant trials were retrieved for more detailed evaluation. Of these trials, thirty-six were excluded because of no placebo control, no randomization, an open design, no pain or functional outcomes, or duplication. Of the remaining twenty-five potentially appropriate randomized controlled trials^{8,22-45}, only twenty provided quantitative data on therapeutic effects. These twenty trials were included in the meta-analysis (see Appendix)^{8,22-34,39,41-45}.

The twenty included trials provided data on therapeutic effects for a total of 1647 randomly assigned knees (818 knees treated with hyaluronic acid injection and 829 treated with placebo injection) and data on safety for a total of 2252 knees (1141 knees treated with hyaluronic acid injection and 1111 treated with placebo injection). The twenty included trials differed in many dimensions, including study design, characteristics of the patients, inclusion and exclusion criteria, type of hyaluronic acid product, evaluated outcome end points, outcome instruments, and status with respect to industry funding. Of the hyaluronic acid products, only Synvisc (hylan G-F 20; Genzyme, Cambridge, Massachusetts) is a cross-linked hyaluronic acid. Each type of hyaluronic acid product has its own recommended dose schedule, including the amount and number of doses. All of the included trials used validated and reliable outcome instruments¹³ (see Appendix). Allocation concealment was unclear in all included trials.

Pooled Efficacy and Safety

With regard to pain with activities in all included trials, the pooled mean difference for SPID%, which represents the overall hyaluronic acid efficacy in the trial period, was 7.9% (95% confidence interval, 4.1% to 11.7%). The pooled mean difference for ASPID%, which represents the overall hyal-



uronic acid efficacy in the trial period after adjustment for the baseline pain intensity, was 13.4% (95% confidence interval, 5.5% to 21.3%). The pooled mean difference for peak PID%, which represents the maximum hyaluronic acid efficacy during the trial, was 9.9% (95% confidence interval, 4.8% to 15.0%) (see Appendix).

Both the trials involving cross-linked hyaluronic acid and those involving non-cross-linked hyaluronic acid had significantly positive pooled mean differences in the efficacy scores at each outcome end point (see Appendix). The trials involving cross-linked hyaluronic acid had much greater pooled mean differences than did those involving non-cross-linked hyaluronic acid (pain with activities: 23.6% compared with 5.4% for SPID%, 34.8% compared with 8.7% for ASPID%, and 27.1% compared with 7.4% for peak PID%; function: 21.9% compared with 5.3% for SFID%, 38.3% compared with 11.7% for ASFID%, and 26.8% compared with 8.2% for peak FID%). However, there was significant between-study heterogeneity in the estimates of hyaluronic acid efficacy among the trials involving non-cross-linked hyaluronic acid ($p \leq 0.1$, chi-square test) (see Appendix).

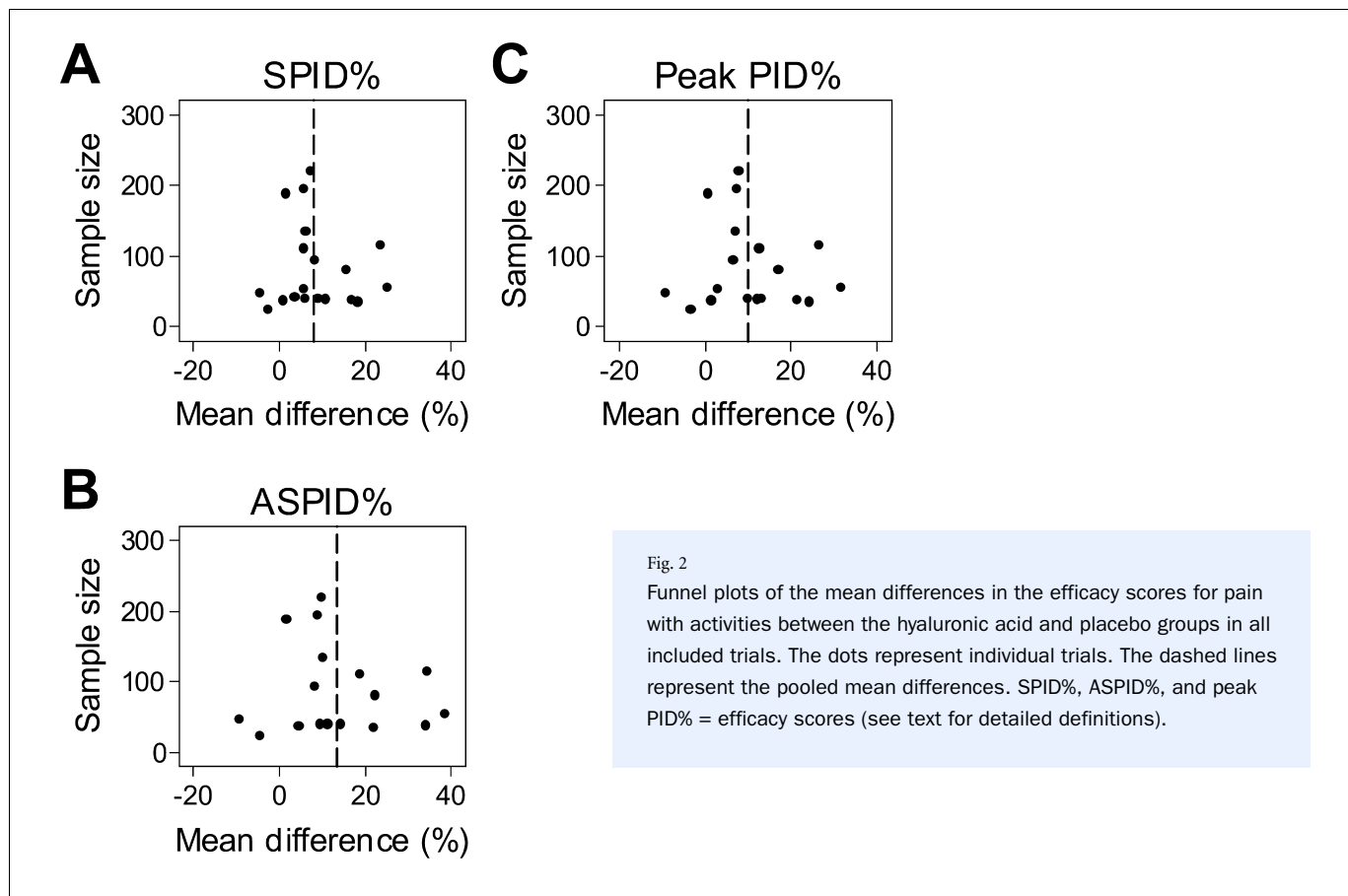
No mortality was associated with hyaluronic acid injection. Major adverse events were noted in three of 1002 knees treated with injection of non-cross-linked hyaluronic acid (severe swelling in one, vasculitis in one, and hypersensitivity reaction in one) and in one of 139 knees treated with injection of cross-linked hyaluronic acid (Synvisc) (a painful acute local reaction)^{22,34,42}. Minor adverse events consisted of a transient mild increase in local pain or swelling. The pooled relative risk

of minor adverse events for all included trials was 1.19 (95% confidence interval, 1.01 to 1.41). There was no significant between-study heterogeneity in the relative risk of minor adverse events ($p = 0.585$, chi-square test).

Subgroup Analysis and Meta-Regression Analysis

Considering a potential so-called drug-class difference between non-cross-linked and cross-linked hyaluronic acid products, we conducted a subgroup analysis and a meta-regression analysis of only the trials involving non-cross-linked hyaluronic acid. Subgroup analysis of pain with activities showed no significant between-study heterogeneity ($p > 0.1$, chi-square test) in the mean difference for at least one efficacy score within most subgroups of trials. It indicated that the data from the different trials within each of these subgroups can be meaningfully combined and thus the pooled estimates of these efficacy outcomes may be more realistic (see Appendix). Similar results were found in the subgroup analysis of the mean differences in the efficacy scores for pain without activities and function (see Appendix).

Subgroup analysis of the efficacy scores for the three outcome end points showed that all of the single-blind trials, double-blind trials, single-center trials, and multicenter trials had significantly positive pooled mean differences in pain with activities. Moreover, the single-blind trials had greater pooled mean differences than did the double-blind trials, and the single-center trials had greater pooled mean differences than did the multicenter trials, indicating that the single-blind trials and the single-center trials provided higher estimates of



hyaluronic acid efficacy. The trials with acetaminophen as an escape analgesic had smaller pooled mean differences than did those without escape analgesics, indicating that introduction of acetaminophen as an escape analgesic in trials results in lower estimates of hyaluronic acid efficacy.

The trials with a mean patient age of sixty-five years or less had significantly positive pooled mean differences, whereas those with a mean patient age of more than sixty-five years did not. Moreover, the trials with a mean patient age of more than sixty-five years had smaller pooled mean differences than did those with a mean patient age of sixty-five years or less, indicating that hyaluronic acid may be less effective for patients over sixty-five years of age. The trials that included patients with the most advanced radiographic stage of osteoarthritis had smaller pooled mean differences than did those in which no patient had the most advanced radiographic stage of osteoarthritis, indicating that hyaluronic acid may be less effective for the most advanced radiographic stage of osteoarthritis. In addition, while both the trials with a sample size of 100 or fewer and those with a sample size of more than 100 had significantly positive pooled mean differences, the trials with a sample size of 100 or fewer had greater pooled mean differences than did those with the larger sample size. This indicated that there may be a small-trial bias favoring the estimation of hyaluronic acid efficacy. The industry-funded trials were found to

have smaller pooled mean differences in the scores for pain with activities and function than did the non-industry-funded trials. However, the industry-funded trials had greater pooled mean differences in the scores for pain without activities than did the non-industry-funded trials (see Appendix).

Meta-regression analysis of the efficacy scores for the three outcome end points showed that nearly all three estimated regression coefficients of three covariates (quality score of the methodology, mean age of the patients, and sample size) were negative, indicating that these three attributes were negatively correlated with the estimates of hyaluronic acid efficacy. The analysis suggested that the trials with lower methodological quality provided higher estimates of hyaluronic acid efficacy, that hyaluronic acid may be less effective for older patients with osteoarthritis, and that there may be a small-trial bias favoring the estimation of hyaluronic acid efficacy (see Appendix).

Publication Bias

The funnel plots of the mean differences in the efficacy scores for pain with activities in all included trials showed that the data are clustered symmetrically around the vertical dashed line (Fig. 2). This indicated that publication bias was unlikely to have had an important influence on the overall analysis of hyaluronic acid efficacy.

Discussion

This meta-analysis of randomized controlled trials confirmed that intra-articular injection of cross-linked hyaluronic acid (Synvisc) and of non-cross-linked hyaluronic acid (Hyalgan [FIDIA, Padua, Italy], Orthovisc [Anika Therapeutics, Woburn, Massachusetts], Artz [Seikagaku, Tokyo, Japan], and BioHy [Savient, East Brunswick, New Jersey]) can decrease symptoms of osteoarthritis of the knee. We found significant improvements in pain and functional outcomes with few adverse events. The trials involving cross-linked hyaluronic acid had much greater pooled estimates of hyaluronic acid efficacy than did the trials involving non-cross-linked hyaluronic acid. However, there was significant between-study heterogeneity in the estimates of hyaluronic acid efficacy. In addition, whether cross-linked hyaluronic acid has greater therapeutic efficacy than non-cross-linked hyaluronic acid is controversial^{38,46}. Therefore, more randomized controlled trials comparing different types of hyaluronic acid products are needed to clarify the effects of cross-linked status on hyaluronic acid efficacy.

In the subgroup analysis and meta-regression analysis of the trials involving non-cross-linked hyaluronic acid, we found that all of the single-blind trials, double-blind trials, single-center trials, and multicenter trials showed a significant decrease in pain with activities. Moreover, lower methodological quality such as a single-blind or single-center design resulted in higher estimates of hyaluronic acid efficacy. In addition, we found that introduction of acetaminophen as an escape analgesic in trials resulted in lower estimates of hyaluronic acid efficacy. This may be due to the additional therapeutic effect of acetaminophen in the placebo groups.

We found that the patients who were older than sixty-five years of age and those with the most advanced radiographic stage of osteoarthritis (complete loss of joint space) were less likely to benefit from intra-articular injection of hyaluronic acid. Understanding the differences in hyaluronic acid efficacy among different patient populations is important when selecting patients for this therapy.

Both the small trials and the large trials showed significant improvements in pain and functional outcomes. However, there may be a small-trial bias favoring the estimation of hyaluronic acid efficacy, suggesting that some small trials that did not show a positive therapeutic effect of hyaluronic acid may not have been published. This may introduce the likelihood that the effect is skewed in the positive direction. Furthermore, we found that the study's status with regard to industry funding did not have a consistent effect on the estimates of hyaluronic acid efficacy based on the three outcome end points, although there is now reasonable evidence that the funding source is strongly associated with published outcomes and publication bias in biomedical research^{47,48}.

This meta-analysis showed that intra-articular injection of hyaluronic acid was associated with few adverse events. Despite the low rate of complications, injection of cross-linked hyaluronic acid may be associated with a painful acute local reaction, which should be considered a major adverse

event⁴⁹⁻⁵². However, the rate of painful acute local reactions to Synvisc injection in this meta-analysis (one of 139 knees) was lower than those in some other reports⁴⁹⁻⁵², in which the rates have ranged between 2% and 8%. One possible reason for this is that all of the three Synvisc trials in this meta-analysis were industry-funded. There is now reasonable evidence that adverse events may be minimally reported in industry-funded trials^{47,48}.


The outcome measures of hyaluronic acid efficacy used in this meta-analysis have several advantages. First, they can incorporate efficacy outcomes that are measured by different types of outcome instruments and are evaluated at different times after treatment. Second, the mean differences in the efficacy scores used in this meta-analysis have more comprehensive clinical meanings than does the so-called effect size used in other meta-analyses. With use of the mean differences in the efficacy scores, we provided easily understandable evidence regarding the magnitude of therapeutic effects, which can facilitate evidence-based decisions in clinical practice. Third, in this meta-analysis, different types of outcome measures had different clinical meanings: the mean difference for SPID% (or SFID%) represents the overall hyaluronic acid efficacy in the trial period, the mean difference for ASPID% (or ASFID%) represents the overall hyaluronic acid efficacy in the trial period after adjustment for the baseline pain intensity (or function index), and the mean difference for peak PID% (or peak FID%) represents the maximum hyaluronic acid efficacy during the trial. All three types of outcome measures are important for efficacy evaluation of slow-acting drugs used to treat the symptoms of osteoarthritis because the therapeutic effects of these drugs usually last several months. Among these efficacy scores, SPID% and peak PID% have been previously described¹⁴⁻¹⁶. Fourth, we placed the outcome end points for efficacy evaluation into three categories: pain with activities, pain without activities, and function. Because these end points are different, it is not suitable to pool them together. Clarifying the therapeutic effect of hyaluronic acid on different symptoms of osteoarthritis of the knee may help clinicians to more appropriately prescribe intra-articular injection of hyaluronic acid to relieve specific symptoms.

This meta-analysis has several limitations. First, unpublished trials were not searched. Since trials with "negative" results tend to be unpublished^{53,54}, exclusion of unpublished trials may introduce the likelihood that the effect is skewed in the positive direction because of publication bias. However, the funnel plots in this meta-analysis showed the data to be clustered symmetrically around a vertical line. This indicated that publication bias was unlikely to have had an important influence on the overall analysis of hyaluronic acid efficacy. Second, interrater and intrarater agreement was not calculated, and this limits the confidence that the reader can have in some of the assessments. Third, not all validated outcome instruments fit neatly into categories like "pain with activities," "pain without activities," and "function." This classification might be somewhat arbitrary and might affect results, depending on how it was performed. However, the classifica-

tion was done independently by two investigators and the differences in classification were resolved by discussion between the investigators, which could minimize the likelihood of misclassification. Fourth, the twenty included trials differed in many dimensions, including study design, characteristics of the patients, inclusion and exclusion criteria, type of hyaluronic acid product, evaluated outcome end points, outcome instruments, and status with regard to industry funding. Meanwhile, there was significant between-study heterogeneity in the estimates of hyaluronic acid efficacy. The heterogeneity of included trials is a common limitation of this and other meta-analyses summarizing treatment effects. Therefore, we conducted a subgroup analysis, in which we found the studies within the same subgroup to be similar enough to allow combination. Fifth, the results of subgroup analysis, which were calculated from study-level data but not from individual patient data and thus were hypothesis-generating only, should be applied cautiously when substantiating any inference.

In conclusion, this meta-analysis of randomized controlled trials confirmed that intra-articular injection of cross-linked hyaluronic acid and non-cross-linked hyaluronic acid can decrease symptoms of osteoarthritis of the knee. We found significant improvements in pain and functional outcomes with few adverse events. However, the patients over sixty-five years of age and those with the most advanced radiographic stage of osteoarthritis (complete loss of joint space) were less likely to benefit from intra-articular injection of hyaluronic acid. More well-designed randomized controlled trials with high methodological quality are needed to resolve the continued uncertainty about the therapeutic effects of different types of hyaluronic acid products on osteoarthritis of the knee in various clinical situations and patient populations.

Appendix

 A figure demonstrating the mean differences in the efficacy scores for pain with activities between the hyaluronic acid and placebo groups in all of the individual trials as well as tables showing (1) the checklist for the assessment of the methodological quality, (2) characteristics of the randomized controlled trials included in the meta-analysis, (3) subgroup analysis of the mean differences in the efficacy scores for pain with activities, pain without activities, and function, and (4) a meta-regression analysis of the mean differences in the efficacy scores for different outcome end points are available with the electronic versions of this article, on our web site at www.jbjs.org (go to the article citation and click on "Supplementary Material"), and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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