**Arvind Modawal, MD, MPH, MRCGP**
Department of Family Medicine, Section of Geriatric Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio

**Montse Ferrer, MD, PhD**
Institut Municipal d'Investigació Mèdica, Barcelona, Spain

**Hyon K. Choi, MD, DrPH**
Arthritis Unit, Massachusetts General Hospital, Boston

**Julia A. Castle, MD, MPH, FACP**
Rheumatology Division, National Naval Medical Center, Bethesda, Md

# Hyaluronic acid injections relieve knee pain

## This meta-analysis shows good therapeutic effect for between 5 and 12 weeks

### Practice recommendations

- Consider injections of hyaluronic acid only after conservative therapy has been tried for at least 3 months or the patient is unable to tolerate NSAIDs.
- Stress to patients that pain relief may not be fully experienced until 5 to 7 weeks following the last injection.

### Abstract

**Objective** To evaluate the efficacy of intra-articular viscosupplementation therapy with hyaluronic acid for pain relief of knee osteoarthritis, we conducted a meta-analysis of randomized, double-blinded, placebo-controlled trials.

**Methods** We searched systematically for randomized, double-blinded, placebo-controlled trials of hyaluronic acid (hyaluronan and hylan G-F20) for pain relief of knee osteoarthritis. Studies reporting pain visual analogue scale (VAS) differences were included in the meta-analysis. Changes in pain were measured by VAS for placebo and treatment, and summary estimates of the differences between the 2 arms were calculated at 1 week, 5 to 7 weeks, 8 to 12, and 15 to 22 weeks after the last intra-articular injection. Sources of heterogeneity were assessed using information on quality score, type of viscosupplementation, and VAS change in pain with activity or rest. Heterogeneity across the studies was significant in all analyses ($P<.01$); therefore a random effect model was used. Pain was measured either on activity or at rest.

**Results** Eleven trials (9 hyaluronan and 2 hylan G-F 20) allowed calculation of the summary estimate of difference in change of VAS pain at 1 week, 6 of the 11 allowed the estimation between 5 to 7 weeks and 8 to 12 weeks, and only 3 at 15 to 22 weeks. The summary estimates of VAS differences between therapy and placebo injection: at 1 week, 4.4 (95% confidence interval [CI], 1.1–7.2); at 5 to 7 weeks, 17.7 (7.5–28.0); at 8 to 12 weeks, 18.1 (6.3–29.9) and at 15 to 22 weeks, 4.4 (–15.3 to 24.1).

**Conclusion** Intra-articular viscosupplementation was moderately effective in relieving knee pain in patients with osteoarthritis at 5 to 7 and 8 to 10 weeks after the last injection but not at 15 to 22 weeks.

Hyaluronic acid injections can help relieve pain for carefully selected patients with knee osteoarthritis. But this option should be reserved for those whose pain has not responded to adequate trials of systemic therapeutic agents (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-2 [COX-2] inhibitors), topical

CORRESPONDING AUTHOR
Arvind Modawal, MD, MPH, MRCGP, University of Cincinnati Department of Family Medicine/Geriatrics, PO Box 670582, Cincinnati, OH 45267-0582. E-mail: modawaa@fammed.uc.edu

## Long time coming

Balazs first proposed hyaluronic acid as a treatment for patients with arthritic diseases in 1942. In the early 1970s, therapeutic studies were begun to test the efficacy of hyaluronic acid on knee osteoarthritis. The results were encouraging and side effects were few.[28] With the FDA's approval in 1998, intra-articular "viscosupplementation" with hyaluronic acid—also called hyaluronan or hyaluronate, and the hylan derivatives of hyaluronic acid—is a welcome option for many of the 16 million older Americans with osteoarthritis of the knee.[1]

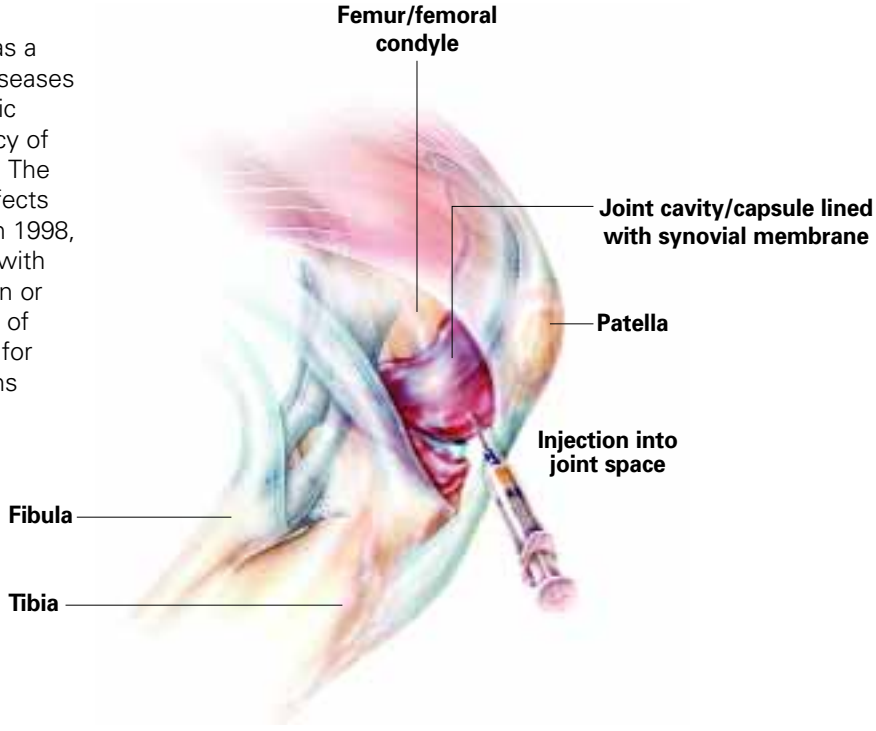


ILLUSTRATION BY: KEVIN SOMERVILLE

agents, or to lifestyle modifications such as weight reduction and exercise.

Hyaluronic acid injections may also be indicated when knee surgery must be delayed for middle-aged persons.[1]

In spite of the Food and Drug Administration's approval of this therapy, uncertainty about its efficacy exists among the medical community. A recent meta-analysis of the effectiveness of intra-articular hyaluronic acid for knee osteoarthritis that included 22 published and unpublished, English and non-English, single or double-blinded, randomized controlled trials in humans showed that hyaluronic acid has only a small effect on pain relief when compared with placebo.[2]

We provide here a stringent test of the efficacy of viscosupplementation for relieving knee pain from osteoarthritis with a meta-analysis that includes only data from randomized, double-blinded, controlled trials of hyaluronic acid that measured pain using a visual analogue scale (VAS), the most widely accepted method for pain evaluation.

## Methods

### Selection of studies

We identified clinical trials of viscosupplementation with hyaluronic acid in humans published in English from 1965 through August 2004 through a computerized literature search of Medline. The keyword used was "hyaluronic acid," which was combined with "trial" or "osteoarthritis knee" or "viscosupplementation." We conducted an additional manual search of the reference lists of included articles and review articles. We also searched the Cochrane Library and websites of the Agency for Healthcare Research and Quality (AHRQ) for information on hyaluronic acid in knee osteoarthritis. We identified 1872 articles with this search process.

Of the 1872 articles, we identified by title and abstract 33 that might be pertinent to this study, including 17 randomized trials. We excluded reviews, meta-analyses, comparison trials, and trials reporting VAS as part of the WOMAC (Western Ontario McMaster Universities Index) scale. We attempted to contact authors of the studies

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**Pain decreased significantly at 5 to 7 weeks and at 8 to 12 weeks after the last injection, as measured by VAS**

**TABLE 1**

## Trials of viscosupplementation with hyaluronic acid in knee osteoarthritis

| Author (year) | Grecomoro[11] (1987) | Puhl[12] (1993) | Henderson 1[13] (1994) | Henderson 2[13] (1994) | Scale[14] (1994) | Lohmander[15] (1996) | Altman[16] (1998) | Wobig[17] (1998) | Huskisson[18] (1999) | Petrella 1[19] (2002) | Petrella 2[19] (2002) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No. subj*** | 40 knees | 209 | 37 | 47 | 80 | 240 | 333 | 117 knees | 100 | 120 | 120 |
| **Treatment** | 20 [20] | 102 [95] | 20 [18] | 25 [22] | 40 [20] | 120 [96] | 105 | 57 | 50 | 25 | 29 |
| **Control** | 20 [18] | 107 [100] | 20 [19] | 26 [25] | 40 [11] | 120 [93] | 115 | 60 | 50 | 28 | 28 |
| **SUBJECTS** | | | | | | | | | | | |
| **Inclusion criteria** | Knee OA | Knee OA Clinical | Knee OA Bilateral | Knee OA Bilateral | Knee OA | Knee OA Unilateral Clinical | Knee OA ACR crit. | Knee OA Clinical | Knee OA ARA crit. Pain prev. 3 mos | Knee OA ACR crit. | Knee OA ACR crit. |
| **RSI** | K&L II | N.S. | K&L I-II | K&L III-IV | Larsen II-IV | Ahlbäck I-II | K&L II-III | Larsen I-IV | K&L II-III | K&L I-III | K&L I-III |
| **Age, mean** | 65 years | 61 years | 62 years | 70 years | 60 years | 58 years | 62 years | 62 years | 66 years | 66 years | 66 years |
| **TREATMENT** | | | | | | | | | | | |
| **Name** | HA | Sodium hyaluronate | Hyaluronan | Hyaluronan | Hylan G-F20 | Hyaluronan | HA | Hylan G-F20 | HA | Sodium hyaluronate | Sodium hyaluronate |
| **MW (kDa)** | 500–750 | 600–1200 | 750 | 750 | | 1000 | 500–750 | | 500–750 | | |
| **Dose** | 20 mg | 25 mg | 20 mg | 20 mg | 2–3 inj. | 25 mg | | | 20 mg/2 mL | 10 mg/mL 2 mL | 10 mg/mL |
| **Frequency** | 2x wk | Weekly | Weekly | Weekly | | Weekly | 2x wk | | Weekly | Weekly | Weekly |
| **Weeks** | 5 | 5 | 5 | 5 | | 5 | 5 | | 5 | 1 | 1 |
| **Other treatment** | | Aceta. | Aceta. | Aceta. | | | Aceta. | Rescue TX | Analg. or anti-inflam. | Aceta. Resistance exercise | Aceta. NSAIDs + resistance exercise |
| **Placebo** | Saline | Saline + 0.25 mg HA | Saline | Saline | Saline | Saline | Saline | Saline | Saline + | Saline + + lactose tablet | + Saline + lactose tablet |
| **EVALUATION WEEKS** | 5, 8 | 5,9 | 1, 5, 22 | 1, 5, 22 | 1, 2, 3, 8, 12, 26 | 1, 5, 9, 20 | 1, 5, 9, 12 16, 21, 26 | 1, 2, 3, 8 12, 26 | 0, 5, 8, 16, 26 | 1, 10 | 1, 10 |
| **QUALITY SCORE†** | **0.439** | **0.80** | **0.777** | **0.777** | **0.570** | **0.798** | **0.788** | **0.731** | **0.708** | **0.798** | **0.798** |

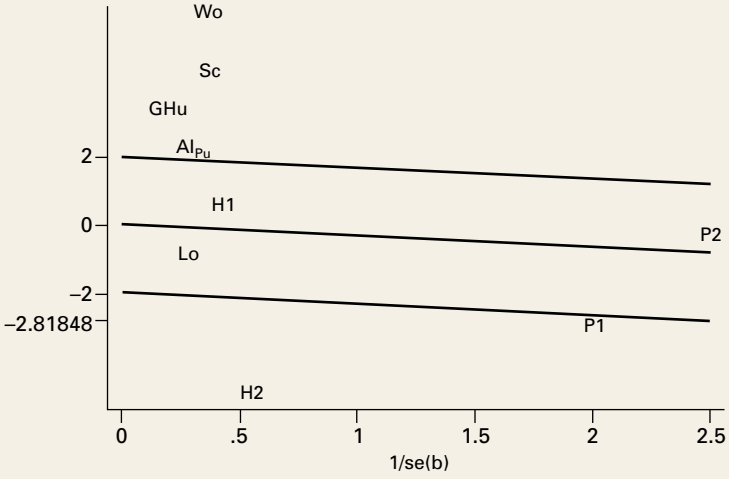
*Number of subjects included in the study [number of subjects with completed follow-up].
†Chalmers et al method.[14]

Aceta., acetaminophen; ACR, American College of Rheumatology; ARA, American Rheumatology Association; HA, hyaluronic acid; K&L, Kellgren & Lawrence; MW, molecular weight; NS, not specified; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; RSI, radiological severity index

that used a double-blind, randomized controlled design, to obtain any data that may not have been included in the publications. Three authors provided the details requested; the others did not respond or stated that additional data were not available. Of the 17 randomized trials we identified, 8 were excluded because they were open, single-blinded, or did not use the VAS to measure pain outcomes.[3–10] The remaining 9 double-blinded, placebo controlled, randomized clinical trials of viscosupplementation with hyaluronic acid for knee osteoarthritis that did use a VAS to measure pain were included in this meta-analysis (**TABLE 1**). Because one of the studies (by Henderson) included 2 subgroups of pain severity, these were considered as 2 separate trials. The trial by Petrella had 2 treatment groups, one with only hyaluronic acid and the other with hyaluronic acid and NSAIDs. We considered them separately in the analysis, resulting in a total of 11 clinical trials for the meta-analysis.[19] Henceforth in this report, we will refer to 11 rather than 9 clinical trials.

**FIGURE 1**

**Evidence of heterogeneity for the studies evaluated at outcome measurement time** (week 1)




This Galbraith plot shows standardized effects (b/se=mean difference/standard error) as a function of study precision (1/standard error), slope of the line shows average effect over all the studies with upper and lower lines denoting an approximate 95% confidence interval for this common effect. Under the hypothesis of study heterogeneity, the common slope intersect zero at 1/se=0, and 95% of all study estimates (authors initials) will fall within the confidence interval of the regression line. Gr: Grecomoro; Pu: Puhl; H1: Henderson 1; H2: Henderson 2; Sc: Scale; Lo: Lohmander; Al: Altman; Wo: Wobig; Hu: Huskisson; P1: Petrella 1; P2: Petrella 2.

## Extraction of data

Two investigators independently extracted the following data for each study: year of publication, study design, mean age, number of patients enrolled in each treatment group, number of doses of treatment used, and outcomes measured. When disagreements between investigators occurred, the point of disagreement was discussed until a consensus was reached. Since the treatment duration and the time post-treatment when pain was assessed varied among the trials, we grouped outcomes into four time intervals: at 1 week, 5 to 7 weeks, 8 to 12 weeks, and 15 to 22 weeks after the last hyaluronic acid injection.

## Statistical analysis

The outcome was knee pain reported by patients on activity or at rest, measured using a VAS of 100 mm. The results of the clinical trials were recorded as the mean differences of change from baseline between the treatment and placebo groups. If not reported in the publication or provided by the authors, standard error was imputed using the method of Follman et al.[20] We used the method of Chalmers for measuring the quality of randomized trials, with 2 of the authors rating the studies independently.[21]

This clinical trial grading system takes into account the following aspects of the trial to determine a quality score: evaluation of recruitment of subjects, rejection log, therapeutic regimen definition, randomization, blinding, prior estimates of numbers, testing compliance, statistical inference, use of appropriate statistical analysis, handling of withdrawal and side effects, dates of starting and ending, timing and tabulation of events. Because 4 of the trials had poor quality scores, an additional analysis excluding these 4 was performed. The DerSimonian and Laird random-effects model was used to obtain the summary estimates.[22,23]

An important element of meta-analysis is exploration of the heterogeneity of the outcomes and the possible causes of hetero-

TABLE 2

**Knee pain on activity or rest, and changes for each group after treatment with hyaluronic acid** (weeks 1, 5–7, 8–12, and 15–22)

| | BASAL, MEAN (SD) | | CHANGE AT 1 WEEK | | | CHANGE AT 5–7 WEEKS | | |
|---|---|---|---|---|---|---|---|---|
| | Hyalgan, mean (SD) | Placebo, mean (SD) | Hyalgan mean | Placebo mean | Difference* mean (SE) | Hyalgan mean | Placebo mean | Difference* mean (SE) |
| Grecomoro | 47 (22.4) | 44 (21.2) | 35 | 13 | 22 (6.7) | 27 | 12 | 15 (6.5) |
| Puhl | 54.1 (22.6) | 51.4 (22.4) | 25.5 | 20 | 5.5 (3.2) | 26.3 | 18.3 | 8 (3.2) |
| Henderson 1 | 43.7 (7.8) | 53.3 (7.2) | 15.6 | 14.5 | 1.1 (2.4) | | | |
| Henderson 2 | 48.5 (5.5) | 49.3 (6.2) | 8.7 | 18 | –9.3 (1.8) | | | |
| Scale | 67 (8) | 71 (6) | 33 | 21 | 12 (2.7) | 51 | 21 | 30 (2.7) |
| Lohmander | 44.4 (25.3) | 42.31 (24.8) | 12.5 | 16 | –3.5 (3.6) | | | |
| Altman | 53 (29) | 49 (29) | 34 | 26.5 | 7.5 (3.9) | 33 | 27 | 6 (3.8) |
| Wobig | 71 (15) | 75 (15.5) | 40 | 22 | 18 (2.8) | 47 | 15 | 32 (2.8) |
| Huskisson | 65.8 (18) | 61.9 (22.9) | 38.3 | 21.3 | 17 (5.2) | 33.5 | 19.8 | 13.7 (5.4) |
| Petrella 1 | 3.3 (1.8) | 3.3 (1.4) | 2.6 (1.6) | 1.8 (1.3) | –1.4 (0.5) | | | |
| Petrella 2 | 3.6 (1.9) | 3.3 (1.4) | 1.6 (1.3) | 1.6 (1.3) | –0.2 (0.4) | | | |

Pain measured on a visual analog scale of 100 mm at baseline. Scale and Wobig trials used hylan G-F20.
*Differences between groups of treatment were calculated by resting change in placebo group from change in hyalgan group. Standard error of this difference was imputed using the method of Follman et al.[13]

geneity if it exists. Heterogeneity is the degree to which results vary from study to study. If a test for heterogeneity is statistically significant, there is significant variability among the treatment effects observed in the trials. We explored heterogeneity using Galbraith plots (**FIGURE 1**).[24] In the absence of heterogeneity, all points fall within the confidence limits. Because we did find heterogeneity among these trials, we developed random-effect regression models to explore 3 possible sources of heterogeneity in the efficacy of hyaluronic acid; pain (measured at rest or on activity), the form used (hyaluronan or hylan G-F20), and the quality of the study method (good or poor).

Publication bias was assessed by the Egger et al regression asymmetry test.[25] Analyses were performed using the meta-analytic software program of STATA, Inc (College Station, Tex; available at www.stata.com).

## Results

The 11 randomized, placebo-controlled, double-blinded clinical trials that met our inclusion criteria are summarized in **TABLE 1**. Nine trials used hyaluronic acid, hyaluronan, or hyaluronate (all types will be referred to as hyaluronan in the text), and 2 studies used hylan GF-20. Only 3 hyaluronan trials have published outcome data at 15 to 22 weeks follow-up. Treatment was administered to patients as 3 to 5 weekly injections, with the exception of the Grecomoro study in which treatment was administered twice weekly. The control group in 10 trials received intra-articular saline injections as placebo. In the Puhl study the investigators added 0.25 mg of hyaluronic acid to the saline injections to impart viscosity to the solution. The mean age of the subjects for the 11 trials was 63 years.

| | CHANGE AT 8–12 WEEKS | | | CHANGE AT 15–22 WEEKS | | |
|---|---|---|---|---|---|---|
| | Hyalgan mean | Placebo mean | Difference* mean (SE) | Hyalgan mean | Placebo mean | Difference* mean (SE) |
| | | | | | | |
| | 27.6 | 17.4 | 10.2 (3.2) | | | |
| | | | | | | |
| | | | | | | |
| | 54 | 20 | 34 (2.7) | | | |
| | 15 | 12 | 3 (3.6) | 31.9 (25.5) | 15.4 (24.8) | 14.4 (3.6) |
| | 34 | 26.5 | 7.5 (3.8) | 16.4 (29) | 23.1 (29) | 10.2 (3.9) |
| | 48 | 14 | 34 (2.8) | | | |
| | 32.8 | 13.6 | 19.2 (5.7) | 39.4 (27.8) | 53.7 (29.9) | 18.2 (5.5) |
| | | | | | | |
| | | | | | | |

Eight trials received support from pharmaceutical companies and 3 (the 2 by Henderson and the Grecomoro study) did not disclose any pharmaceutical support. One study was conducted in the United States, 3 in the UK, 3 in Germany, 1 in Sweden, 1 in Italy, and 2 in Canada. Five of the studies had scores over a cutoff quality score of >0.75,[12,13,15,16,19] indicating they were good-quality randomized controlled trials; the remaining 4 had scores below 0.75.[11,14,16,17]

The outcomes of the 11 trials are summarized in **TABLE 2**. Patients' pain ratings in both the active treatment and placebo groups improved in all the trials. Mean difference between improvements in treatment and placebo groups are shown in **FIGURES 2A–2D** for pain assessed at weeks 1, 5 to 7, 8 to 12 and 15 to 22, respectively. In each figure, we show the summary estimate of effect size with all the trials included and after excluding the 4 trials considered of poor quality, shown as "good quality studies."

The mean difference in pain scores between treatment and placebo at week 1 was 4.4 (95% CI, +1.1, +7.2) and –1.0 (95% CI, -3.2, +1.2) for analysis restricted to the 7 good quality trials. The mean difference in pain scores at 5 to 7 weeks was 17.6 (95% CI, +7.5, +28.0) and 7.2 (95% CI, +2.4, +12.0) for the analysis restricted to the 2 good quality studies. At weeks 8 to 12 the mean difference in VAS between treatment and control was 18.1 (95% CI, +6.3, +29.9), and 7.1 (95% CI, +3.0, +11.3) in the analysis restricted to good quality trials. At weeks 15 to 22, the mean difference was 4.4 (95% CI, –15.3, +24.1). The Egger test was not statistically significant (2.3; *P*=.096; 95% CI, –0.5, +5.2) suggesting that there is no publication bias.

**FAST** TRACK

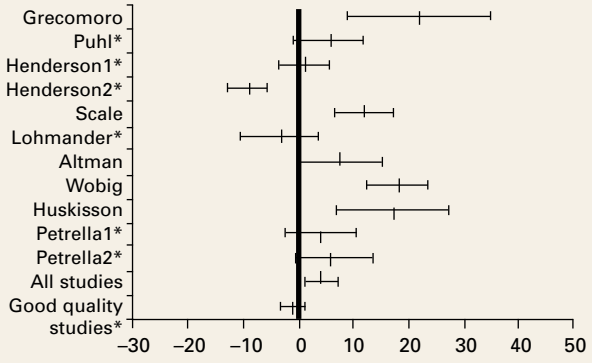
**Weigh cost-benefit: 3 to 5 weekly knee injections may cost $1000 or more per knee treated**

FIGURE 2

**Mean differences between treatment and placebo groups of change from baseline on pain** (measured with a 100-mm visual analog scale)

2A

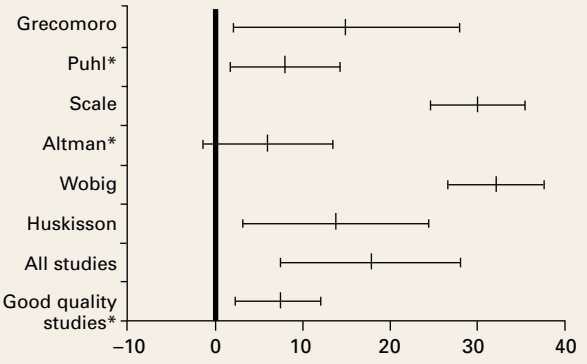
**Mean differences between treatment and placebo groups** (week 1)




Test for heterogeneity: all studies, Q=121.7 on 10 degrees of freedom (*P*<.001); good-quality studies, Q=34.7 on 6 degrees of freedom (*P*<.001).

2B

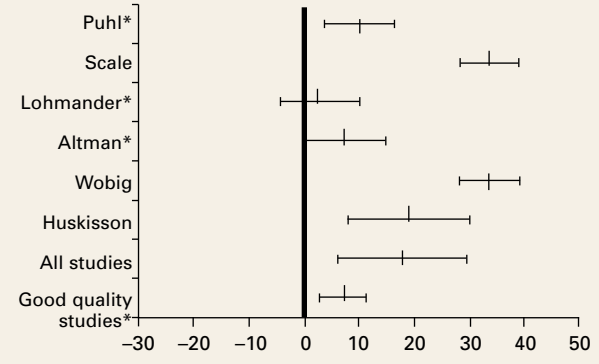
**Mean differences between treatment and placebo groups** (weeks 5–7)




Test for heterogeneity: all studies, Q=60.6 on 5 degrees of freedom (*P*<.001); good-quality studies, Q=0.2 on 1 degrees of freedom (*P*=.688).

2C

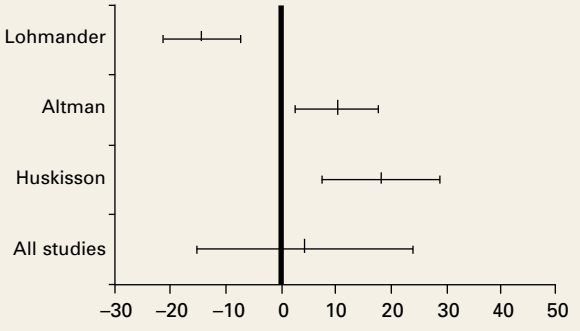
**Mean differences between treatment and placebo groups** (weeks 8–12)




Test for heterogeneity: all studies, Q=92.3 on 5 degrees of freedom (*P*<.001); good-quality studies, Q=2.2 on 2 degrees of freedom (*P*=.332).

2D

**Mean differences between treatment and placebo groups** (weeks 15–22)




Test for heterogeneity: all studies, Q=33.6 on 2 degrees of freedom (*P*<.001). All studies of good quality.

Short vertical lines indicate the point estimates; horizontal lines depict the 95% confidence intervals. Summary 1 was calculated with all the trials, and summary 2 was calculated only with trials considered of good quality (marked with an asterisk*). Mean differences between groups of treatment equal to 0 indicate no change, higher than 0 indicate a beneficial effect of viscosupplementation therapy on pain relief on VAS and lower than 0 indicate a prejudicial effect of viscosupplementation therapy on pain relief on VAS. Summary estimates of the mean difference between groups of treatment was calculated using DerSimonian and Laird random-effects model.

**TABLE 3**

**Regression models to assess the sources of heterogeneity in the meta-analysis**

| | WEEK 1 | | WEEKS 5–7 | | WEEKS 8–12 | |
|---|---|---|---|---|---|---|
| | Coef. (SE) [95% CI] | *P* value | Coef. (SE) [95% CI] | *P* value | Coef. (SE) [95% CI] | *P* value |
| **Pain** | | | | | | |
| With activity<br>At rest | 1.7 (3.8)<br>[–5.8, +9.2] | 0.657 | 1.8 (4.3)<br>[–6.6, +10.2] | 0.671 | –0.5 (4.6)<br>[–9.5, +8.6] | 0.916 |
| **Medication** | | | | | | |
| Hyaluronan**<br>Hylan G-F 20 | –3.4 (6.8)<br>[–16.7, +9.9] | 0.614 | 17.5 (4.9)<br>[+7.8, +27.1] | <0.001 | 14.8 (6.1)<br>[+2.8, +26.8] | 0.016 |
| **Quality*** | | | | | | |
| Poor (<0.75)<br>Good (≥0.75) | –19.9 (5.7)<br>[–31.1, –8.7] | 0.001 | –7.4 (4.9)<br>[–17.0, +2.2] | 0.131 | –11.7 (7.0)<br>[–25.3, +1.9] | 0.092 |
| **Constant** | 18.4 (5.6)<br>[+7.5, +29.3] | 0.001 | 13.5 (4.5)<br>[+4.6, +22.3] | 0.003 | 19.2 (5.8)<br>[+7.9, +30.5] | 0.001 |

*<.75 quality score: Grecomoro .439, Scale .570, Wobig .731, Huskisson .718.
** 9 trials for hyaluronan (3 for Hyalgan®) and 2 trials for hylan G-F20 (Synvisc®).

High heterogeneity was observed at all time intervals except 1 week (**FIGURE 1**). Of the 5 trials outside the confidence bounds (positioned 2 units above and below the regression line), 4 were poor-quality studies.

**TABLE 3** shows the random-effect regression models we used to test the influence on the outcome of type of pain measured (pain with activity or pain at rest), type of medication (hyaluronan or hylan G-F 20), and study quality (good or poor). No significant association between treatment efficacy and type of pain used as outcome variable was observed. Clinical trials using hylan GF-20 showed statistically significant better results than those using hyaluronan at weeks 5 to 7 and 8 to 12. Poor-quality studies showed a larger treatment effect, but the difference was statistically significant only at week 1.

## Discussion

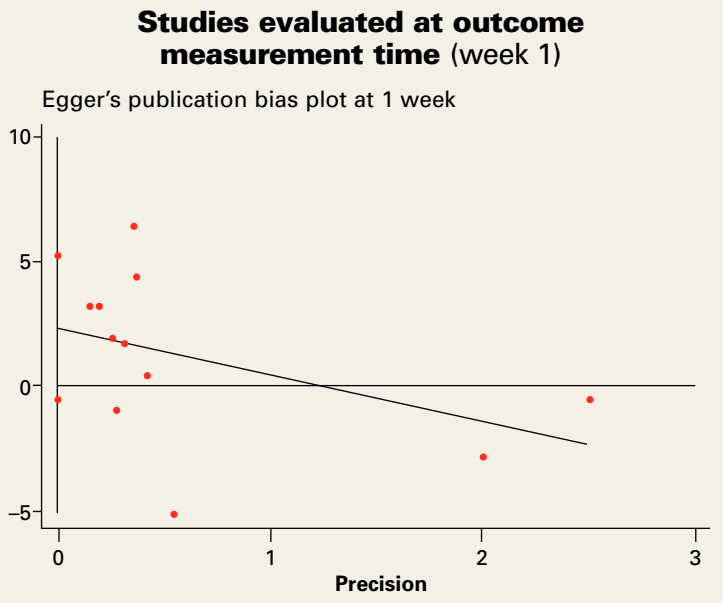
This meta-analysis synthesized data from 9 randomized, double-blinded, placebo-controlled trials that evaluated the efficacy of intra-articular hyaluronic acid. Our findings show significantly decreased pain as measured by VAS at 5 to 7 weeks and at 8 to 12 weeks after the last injection. Intra-articular hyaluronic acid was not more effective than placebo in relieving pain at 1 week or at 15 to 22 weeks after the last injection. Because only 3 of the trials assessed patients after 12 weeks, however, the sample size is too small to definitively rule out a significant therapeutic effect after 12 weeks.

Reasons for the differences in efficacy among trials of hyaluronic acid in the treatment of knee osteoarthritis include dose, type, and frequency of administration, genetic or age differences among the study subjects, severity of osteoarthritis, time of follow-up, and quality of the studies. We confirmed that the treatment effect is time dependent. Although our meta-regression analysis (**TABLE 2**) suggests that hylan GF-20 is more effective than hyaluronan at 5 to 12 weeks, the number of clinical trials is relatively small and both of the hylan G-F20 studies were of poor quality. Therefore, we cannot say with confidence that one form is better

**FAST TRACK**

**We cannot say with confidence that one form of hyaluronic acid is better than another**

FIGURE 3




Egger's publication bias plot for the studies evaluated at outcome measurement time (week 1) not significant (+2.3, *P*=0.096, 95% CI: –0.5, +5.2).

**FAST** TRACK

**Patients should have 3 months' conservative therapy or be unable to tolerate NSAIDs before a course of hyaluronic acid injections**

than the other. Data in these trials were insufficient to assess the impact of body mass index, genetics, or severity of osteoarthritis.

We did not evaluate functional improvement in this meta-analysis because functional status was not measured in some trials and the assessment methods were too variable in the trials that did assess functional status. Publication bias, or the possibility that unpublished data would contradict the results of published studies, is always a potential source of bias in meta-analysis. However, the Egger test was not statistically significant (6.5; 95% CI, –0.5, +13.5) suggesting that there is no publication bias.[25]

Finally, the presence of heterogeneity of results indicates there were important differences among the studies. Exclusion of clinical trials considered of poor quality diminished this heterogeneity substantially. Subanalysis restricted to good-quality studies supports the efficacy of intra-articular hyaluronic acid in the treatment of knee osteoarthritis pain, although the effect size is smaller when one considers only the good quality studies.

There are 2 other potential limitations of this meta-analysis. Five studies allowed pain to be treated with analgesics such as acetaminophen or NSAIDs,[12,13,16–18] and use of acetaminophen or NSAIDs may have altered the response to hyaluronic acid treatment. An intention-to-treat analysis was performed in only 2 studies (by Altman and Huskisson),[16,18] wherein a post-hoc and "last observation carried forward" analysis showed a trend favoring hyaluronic acid. The treatment effects may have been smaller had the other trials used an intention to treat analysis.

This meta-analysis confirms that viscosupplementation with hyaluronic acid is modestly effective in short term relief of pain in knee osteoarthritis. Our meta-analysis included only double-blinded, randomized trials published in English language in humans using VAS as the pain outcome measure, and our conclusions are very similar to those of Lo.[2]

**Indications for use.** Hyaluronic acid is helpful in relieving pain for carefully selected patients with knee osteoarthritis who have not responded to adequate use of systemic therapeutic agents, including acetaminophen, NSAIDs and COX-2 inhibitors and topical agents, along with lifestyle modification such as weight reduction and exercise.

Patients should have a trial for at least three months of conservative therapy or be unable to tolerate NSAIDs before a decision to give 3- to 5-injection course with hyaluronic acid is made.

Hyaluronic acid may be an option when there is a need to delay knee surgery in middle-aged persons[1] or for patients who have failed other treatments.

**Time to pain relief.** To improve adherence to treatment, tell patients receiving intra-articular hyaluronic acid that the benefits in pain reduction may not be noticeable until 5 to 10 weeks after the last injection.

**Cost.** Although the cost of hyaluronic acid treatment is covered by Medicare and most insurance plans for symptomatic osteoarthritis of knee, documentation in

patient medical records should indicate the signs and symptoms supporting the diagnosis and functional impairment. Objective data to support a diagnosis of osteoarthritis such as x-ray, arthroscopy report, computed tomography scan, or magnetic resonance imaging should be available in the event of a review.

The cost of 1 hyaluronic acid (30 mg/mL) injection is approximately $230. Considering a course of 3 to 5 weekly knee injections, and adding other pharmacy, hospital, or clinic charges, the cost per treatment may exceed $1000 per knee.[26,27] The cost-benefit of pain control with viscosupplementation must be carefully compared with other therapeutic agents and regimens currently available for knee osteoarthritis management. ■

**ACKNOWLEDGMENTS**

Jeff Welge, PhD, University of Cincinnati Medical Center, Center for Bio-statistical Services, for comments on final data analysis and presentation, Marie Marley, PhD for editing the manuscript, and Charity Noble for help in preparation of this manuscript.

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