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REVIEW ARTICLE (META-ANALYSIS)

Effectiveness of 3 Weekly Injections Compared With 5 Weekly Injections of Intra-Articular Sodium Hyaluronate on Pain Relief of Knee Osteoarthritis or 3 Weekly Injections of Other Hyaluronan Products: A Systematic Review and Meta-Analysis

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Abstract

Objective: To investigate whether the number of hyaluronic acid (HA) injections in a sodium hyaluronate (Hyalgan) course of therapy alters effectiveness in reducing knee osteoarthritis (OA) pain.

Data Sources: Electronic databases, including PubMed and Embase, were searched from January 1980 until November 2015.

Study Selection: We included clinical studies that evaluated the effectiveness of a course of 3 or 5 weekly intra-articular injections of Hyalgan to treat knee OA pain. We also included clinical studies evaluating the effectiveness of a 3-week course of other Food and Drug Administration—approved HA treatments of knee OA pain. Twenty-four studies were identified, comprising 2168 study participants in 30 treated cohorts.

Data Extraction: We determined effect sizes for selected studies by extracting knee OA pain scores before and after HA or control treatments. Meta-regressions were implemented to determine whether the number of weekly injections in a course of Hyalgan therapy modified outcomes.

Data Synthesis: The pooled estimate for relief from baseline pain was −31.4 (SE, 5.46; 95% confidence interval [CI], −45.5 to −17.4) with a 3-week course of Hyalgan and −32.2 (SE, 5.25; 95% CI, −45.6 to −18.7) with a 5-week course of Hyalgan. Findings from the meta-analysis indicate relief of knee OA pain with a 3-week course of Hyalgan is similar to that with a 5-week course of Hyalgan ($P=.916$). The pooled estimate for relief from baseline pain with a 3-week course of other HA products was −29.4 (SE, 4.98; 95% CI, −42.2 to −16.6), also indicating pain relief with a 3-week course of Hyalgan is similar to that with a 3-week course of other HA products ($P=.696$).

Conclusions: There was no statistical difference between reduction in knee OA pain with a 3-week course of Hyalgan compared with reduction in knee OA pain with a 5-week course of Hyalgan or a 3-week course of other HA products. These findings demonstrate that comparable knee OA pain relief is achieved with a 3-week course of Hyalgan and the 2 control groups.

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Hyaluronic acid (HA) is a glycosaminoglycan found within the extracellular matrix of various soft connective tissues and epithelial and neural tissues. This polysaccharide is a natural biopolymer consisting of repeating units of the disaccharide N-acetylglucosamine and sodium glucuronate. The rheologic properties of HA, transitioning between viscous and elastic behavior, play an important role in its ability to protect articular joints from the shear forces of rapid motion. An essential component of synovial fluid in the knee joint, HA enables the fluid to act as a lubricant and shock absorber.

Osteoarthritis (OA) is characterized by both a loss of articular cartilage and a reduction in the viscoelastic properties of synovial

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fluid. Studies of knee OA have observed a decrease in HA molecular weight and concentration in synovial fluid as the disease progresses.[1] The molecular weight of HA in the synovial fluid of a young, healthy knee is approximately 6000kDa and approximately 1900kDa in an older, osteoarthritic knee.[2,3] Similarly, the concentration of HA in the synovial fluid of a young, healthy knee is approximately 3mg/mL and approximately 1mg/mL in an older, osteoarthritic knee.[4] A decrease in HA concentration and molecular weight reduces the viscoelasticity of synovial fluid and increases the susceptibility to cartilage degradation.

Intra-articular injections of HA or hylan, a derivative of HA, are used to treat knee OA to minimize mechanical stress within affected joints. In clinical studies, intra-articular injections of HA alleviate the symptoms of OA, including pain, stiffness, and functional impairment. Furthermore, in vivo studies have demonstrated that viscosupplementation normalizes the properties of synovial fluid, suppresses cartilage degeneration, and protects the surface of joints.[5]

There are currently 12 hyaluronan products with similar but distinct compositions approved by the U.S. Food and Drug Administration (FDA) for the treatment of knee OA pain. These products can be differentiated by their source of HA or hylan and method of production, molecular weight of the active ingredient, amount and concentration of active ingredient per dose, and injection volume per dose. These products also have distinct biologic characteristics, rheologic and pharmacodynamic properties, and residence time in the joint.[6] However, there are few head-to-head comparisons of hyaluronan products, and none have established a link between the relative effectiveness of one product over another that was demonstrated to be the consequence of a distinct chemical property.[7,8]

Another distinction between these hyaluronans is the number of injections per course of therapy, which range from 1 to 5 weekly intra-articular injections. The FDA-approved treatment regimens per HA product are listed in table 1.

Sodium hyaluronate (Hyalgan), the first HA product approved by the FDA in 1997, has nearly 20 years of clinical experience in the United States. The indicated regimen for Hyalgan is a course of therapy with 5 injections given at weekly intervals. Hyalgan labeling also states that some patients may achieve therapeutic benefit with a course of therapy with 3 injections given at weekly intervals.[9]

Clinical evidence supporting a regimen of 5 weekly injections of Hyalgan is a randomized controlled trial (RCT) of 495 participants with knee OA pain. At 26 weeks, pain relief was significantly greater in the Hyalgan-treated group than the saline placebo group ($P=.004$).[21] The effectiveness of a 5-week course of Hyalgan was subsequently confirmed in a 6-month RCT of 100 participants with knee OA pain; at 6 months, pain relief was significantly greater in the Hyalgan-treated group than the placebo group ($P=.005$).[22]

Clinical effectiveness supporting a regimen of 3 weekly injections of Hyalgan is based on 3 RCTs of Hyalgan administered as 3 weekly injections in a combined study population of 189 participants with knee OA followed for 60 days posttreatment. At the end of the study, participants treated with a 3-week course of Hyalgan in each study achieved a significantly greater reduction from baseline pain than the saline placebo cohort.[23-25]

The effectiveness of the 2 Hyalgan regimens was compared in a 1-year RCT. In this study of 200 patients with knee OA, pain relief with a 3-week course of Hyalgan administered every 3 months was superior to pain relief with a 5-week course of Hyalgan administered every 6 months.[26] Furthermore, cellular improvements in articular cartilage tissue were observed after a 3-week course of Hyalgan in a separate RCT. In this 6-month study, biopsies of articular cartilage tissue from Hyalgan-treated participants demonstrated an increase in viable chondrocytes to near normative levels observed in control tissues, with a metabolic shift to more anabolic activity.[27]

The effectiveness of different HA treatment regimens is difficult to discern in part because few clinical trials are designed to address this question. The current systematic review and meta-analysis were conducted to determine whether pain relief with a Hyalgan course of 3 weekly injections is comparable with pain relief with a Hyalgan course of 5 weekly injections. The meta-analysis also examined a secondary question, whether pain relief with a 3-week course of Hyalgan is comparable with pain relief with other hyaluronan products similarly administered. The studies included for review and analysis had an observation period of at least 3 months, as required by FDA industry guidelines last reviewed June 1, 2016.[28]

Table 1 HA products approved by the FDA for the treatment of knee OA pain[9-20]

Viscosupplement Product	No. of Weekly Injections Per Course of Therapy
1% sodium hyaluronate (Euflexxa)[13]	3
Cross-linked hyaluronate (Gel One)[14]	1
Sodium hyaluronate for injection (Gel-Syn)[15]	3
Sodium hyaluronate (GenVisc 850)[16]	5*
Sodium hyaluronate (Hyalgan)[9]	5*
High molecular weight viscoelastic hyaluronan (Hymovis)[17]	2
High molecular weight hyaluronan (Monovisc)[18]	1
High molecular weight hyaluronan (Orthovisc)[10]	3–4
Sodium hyaluronate (Supartz FX)[11]	5*
Hylan G-F 20 (Synvisc)[19]	3
Hylan G-F 20 (Synvisc One)[20]	1
Sodium hyaluronate (Visco-3)[12]	3

* Indicated for 5 weekly injections, but some patients may experience benefit with 3 weekly injections.

List of abbreviations:

CI	**confidence interval**
FDA	**Food and Drug Administration**
HA	**hyaluronic acid**
OA	**osteoarthritis**
RCT	**randomized controlled trial**
VAS	**visual analog scale**
WOMAC	**Western Ontario and McMaster Universities Osteoarthritis Index**

Methods

Data sources

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[29]

We performed a systematic literature search of all English-language, peer-reviewed articles reporting RCTs or observational trials of intra-articular HA injections approved for the treatment of knee OA in the United States, using Medical Subject Headings terms and treatment-specific (*hyaluronic acid*, *osteoarthritis*, and *knee*) and study design (*three injections* and *five injections*) keywords. Searches were conducted through the online databases MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials, CINAHL, and Google Scholar from 1980 through November 2015. We also conducted hand searches of abstracts from relevant scientific conferences (American College of Rheumatology and Osteoarthritis Research Society International) and FDA Arthritis Advisory Committee proceedings from 1987 through 2015, published dissertations posted on ProQuest, and bibliographies of relevant systematic reviews and meta-analyses from 1980 through November 2015.

Study selection

The inclusion criteria were human clinical trials of FDA-approved intra-articular HA products to treat knee OA in adult participants with a course of 3 or 5 weekly injections conducted anywhere in the world that compared relief from baseline pain and between study cohorts at $\geq$3 months posttreatment. Studies were excluded if none of the interventions were HA products approved for use in the United States, if the treatment regimen was not 3 or 5 weekly injections, if the observation of treatment effects was <3 months, or if the results did not report visual analog scale (VAS) or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) measures of reduction in knee OA pain from baseline values. Practice guidelines, editorials, and letters were excluded, as were studies that combined HA treatment with additional treatments (eg, a regimen of glucosamine supplements). The number of RCTs and observational studies included was not large, but it has been reported that meta-analyses of a relatively small number of trials may provide sufficient information to draw conclusions about treatment effects.[30]

Data extraction

Data were extracted from eligible peer-reviewed articles by one author (I.K.) and verified by a second author (T.P.S.). Data were only extracted for cohorts treated with an FDA-approved HA product. The following variables were recorded in a standardized data extraction: general article information (author, year of publication, study location, and citation), participant characteristics (age and severity of knee OA at baseline), study characteristics (population size, study design, HA treatments, and number of injections per course of therapy), and effectiveness outcomes (reduction from baseline knee pain quantified by WOMAC A pain subscale or VAS, and cohort comparisons). The effect of intervention on knee OA pain was estimated from figures in the articles when values were not explicitly reported in text or tables.

Patient-reported assessments of knee pain were extracted from the included articles in a nonbiased manner, using the following knee OA pain outcome hierarchy: (1) WOMAC A pain subscale, item 1; (2) WOMAC A pain subscale (average of all 5 items); (3) VAS pain during activity; and (4) VAS global pain. All extracted data were adjusted to a 0- to 100-mm VAS. The 5 items in the WOMAC A pain subscale are as follows: item 1 (walking on a flat surface), item 2 (going up and down stairs), item 3 (at night in bed), item 4 (sitting or lying), and item 5 (standing upright).

Data synthesis

The studies identified for this meta-analysis contain a number of natural sources of heterogeneity, including differences in HA product composition (source of HA or hylan and method of production, molecular weight of the active ingredient, amount and concentration of active ingredient per dose, and injection volume per dose), differences in observation period posttreatment, and differences in scales used to assess changes in knee pain. Tests for heterogeneity within each HA product across the included studies were conducted using the generic inverse variance method (MedCalc for Windows, version 16.4.3[a]). Because of the high degree of heterogeneity of the studies ($I^2 \geq 75\%$), we used the random effects model to pool the effect sizes.[31]

Treatment differences in the last observation of change from baseline across all studies and HA products were estimated using least-squares means from a random effects model adjusting for independent variables, reference treatment, and observation period (weeks), using an unstructured covariance matrix. This model assumed the intercept and reference to be random effects with an inverse variance weighting (SAS version 9.4 [TS1M3][b]). Effect size was calculated to compare results across studies, and treatment comparisons were conducted using a 5% level of significance.

Our analyses used the basic formula for estimating the difference (Δ) in effect size, developed by Glass et al,[32] which is the mean of the experimental group minus the mean of the control group, divided by the SD of the control group for each comparison of effect sizes:

$$\Delta = \frac{\bar{x}_1 - \bar{x}_2}{s_2}$$

Two overall effect sizes were calculated using the least-squares means SE and the number of references used in the model: (1) 3 injections of Hyalgan versus 5 injections of Hyalgan, and (2) 3 injections of Hyalgan versus 3 injections of other FDA-approved HA formulations. For each treatment group comparison, the control group SD was derived and used in conjunction with the estimated difference in the least-squares means between groups. The parameters for meaningful difference in treatment effects on reduction from baseline pain were set as (1) small effect size (0−.32), (2) medium effect size (.32−.55), and (3) large effect size (>.56).[33]

Results

Study search

All reports published since 1980 that evaluated the effectiveness of HA in relieving knee OA pain and satisfied study inclusion criteria were evaluated. Of 1575 potentially eligible studies identified, 528 were included based on title and abstract screening. Forty-one additional studies were identified after a hand search of reviews and meta-analyses, increasing the total number of reviewed articles to 569. From these study reports, 24 articles were identified as eligible for inclusion in our meta-analysis. The studies identified were 5 studies of 3 weekly injections of Hyalgan,[34-38] 8 studies of 5 weekly injections of Hyalgan,[21,22,37,39-43] and 12 studies of 3 weekly injections of other HA products.[44-55] One of the 24 articles compared the ability of Hyalgan to reduce knee OA pain with a course of 3 weekly injections and 5 weekly injections.[37] Figure 1 shows the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study identification and selection.

Characteristics of included studies and participants

As a result of this systematic literature review, 24 studies were included in this meta-analysis. Seventeen of the studies were RCTs,[21,22,34-36,39-42,44,45,47,48,51-54] 6 were observational,[37,38,43,49,50,55] and 1 was retrospective.[46] Among the 17 RCTs, 8 included a placebo cohort with an intra-articular injection of physiologically buffered saline,[21,22,35,41,45,47,51,52] and 7 included either another HA product or a nonsteroidal anti-inflammatory drug as an active comparator.[34,40,42,44,48,53,54] One RCT compared Hyalgan treatment with arthroscopic lavage,[39] and another RCT compared Hyalgan treatment with platelet-rich plasma.[36]

The data extracted from the 24 studies included in the analyses represent 2168 study participants who were adults with knee OA pain: 511 participants in the 5 studies of 3 weekly injections of Hyalgan; 457 participants in the 8 studies of 5 weekly injections of Hyalgan; and 1200 participants in the 12 studies of 3 weekly injections of other HA products. Table 2 provides a summary of study characteristics.

In 6 of the 24 studies, results were reported for the intent-to-treat population,[34,39,41,42,45,46] and in 18 studies, results were

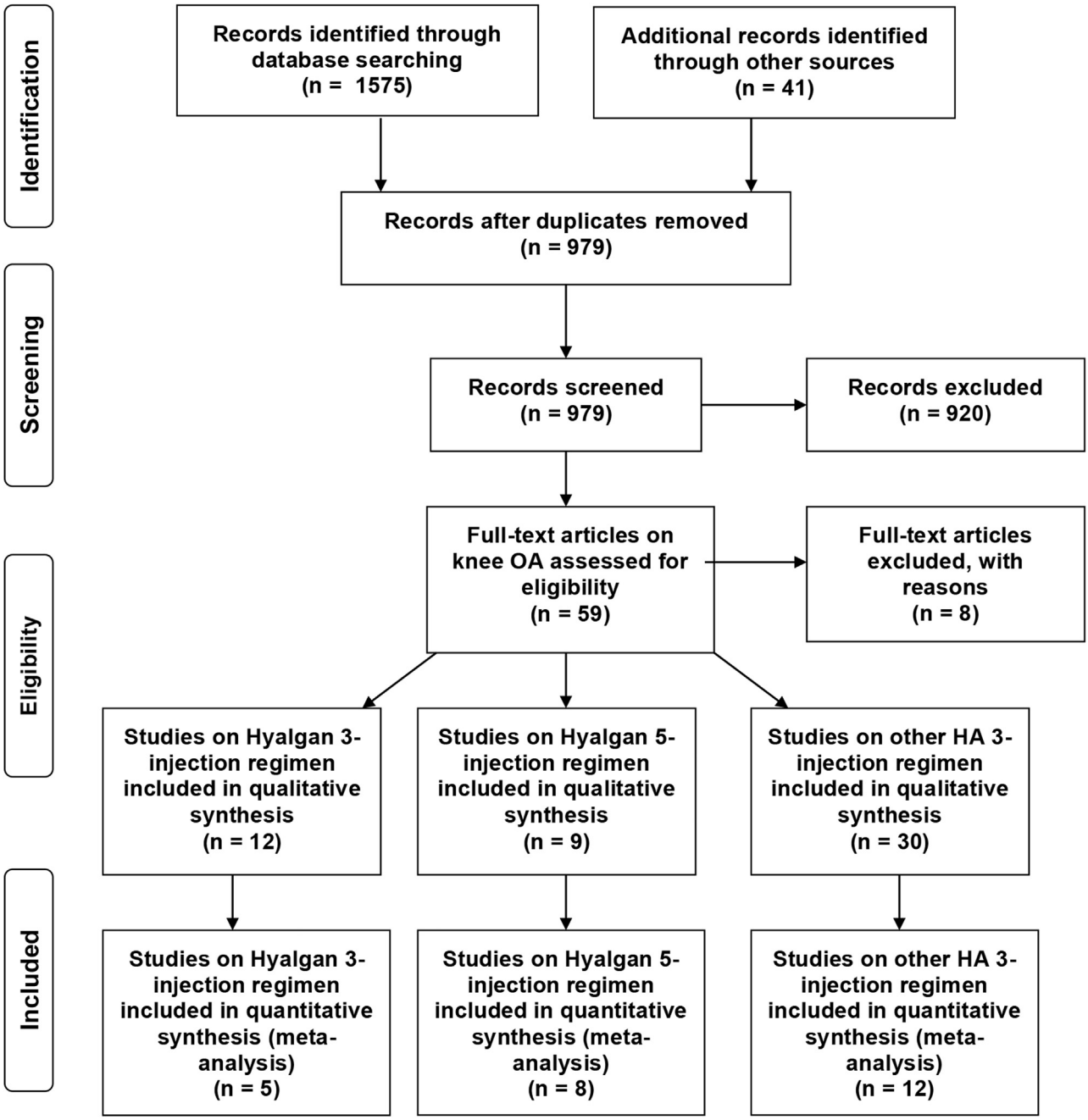

Fig 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the search process for identification of eligible studies.

Table 2 Summary of characteristics of studies included in the meta-analysis

Study	Study Population (n)	Treatment Cohorts	Last Observation Posttreatment (wk)	Measurement Scale
Summary of studies of a 3-week course of Hyalgan				
Berenbaum et al[34]	209	Hyalgan	26	WOMAC A pain subscale*
Dougados et al[35]	47	Hyalgan, saline	52	VAS pain with exercise†
Raeissadat et al[36]	62	Hyalgan, platelet-rich plasma	52	WOMAC A pain subscale†
Stitik et al[38]	9	Hyalgan 5 weekly injections, 3 weekly injections	52	VAS pain with exercise†
Turajane et al[38]		Hyalgan, cohorts grouped by severity of baseline pain	52	VAS pain†
Group 1	46			
Group 2	70			
Group 3	67			
Summary of studies of a 5-week course of Hyalgan				
Altman et al[21]	105	Hyalgan, naproxen, saline	26	VAS pain†
Forster and Straw[39]	19	Hyalgan, arthroscopic lavage	52	VAS pain*
Frizziero and Pasquali Ronchetti[40]	38	Hyalgan, methylprednisolone	26	VAS pain†
Huskisson and Donnelly[22]	39	Hyalgan, saline	26	VAS pain with exercise†
Jones et al[42]	32	Hyalgan, triamcinolone	26	VAS pain†
Jørgensen et al[41]	139	Hyalgan, saline	52	VAS pain with exercise†
Scali[43]		Hyalgan‡	12	VAS pain with exercise†
Females	40			
Males	35			
Stitik et al[37]	10	Hyalgan 5 weekly injections, 3 weekly injections	52	VAS pain with exercise†
Summary of studies of a 3-week course of other HA products				
Adams et al[44]	25	Synvisc, NSAID ± Synvisc	12	VAS pain†
Altman et al[45]	291	Euflexxa, saline	26	VAS pain with exercise*
Bostan et al[46]	11	Orthovisc, mud packs	26	WOMAC A pain subscale*
Brandt et al[47]	66	Orthovisc, saline	26	WOMAC A pain subscale†
Caborn et al[48]	113	Synvisc, triamcinolone	26	VAS pain†
Chou et al[49]	37 (contralateral knee treated with comparator)	Synvisc, Supartz (5 weekly injections)	26	VAS pain†
Clarke et al[50]	25	Synvisc	52	VAS pain†
Hizmetli et al[51]	20	Saline	26	WOMAC A pain subscale†
Karlsson et al[52]		Supartz, Synvisc, saline	26	VAS weight-bearing pain†
Supartz Fx	76			
Synvisc	77			
Kirchner and Marshall[53]		Euflexxa, Synvisc	12	WOMAC A pain subscale†
Euflexxa	156			
Synvisc	158			
Maheu et al[54]	117	Synvisc	26	VAS pain†
Tascioglu and Öner[55]	28	Orthovisc, methylprednisolone	26	VAS pain with exercise†

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

* Intent-to-treat population.

† Per-protocol population.

‡ Hyalgan is referred to as Hyalart in Scali.[43] Hyalgan is commercially sold as Hyalart in certain countries outside the United States.

reported for the per-protocol population who completed the study.[21,22,35-38,40,43,44,47-55] Effectiveness in knee pain relief was measured as a primary or secondary end point using the WOMAC A pain subscale item 1 in 5 studies,[34,36,46,47,51] and in 1 study, outcomes were reported as an average of all 5 items in the WOMAC A pain subscale.[53] In the remaining 18 studies, outcomes were reported as a VAS score. In 7 of these studies, a VAS pain score was obtained after walking 50 feet,[22,35,37,41,43,45,55] 10 were reported as a VAS global pain score,[21,38-40,42,44,48-50,54] and 1 was reported as a VAS score for weight-bearing pain.[52] Outcomes

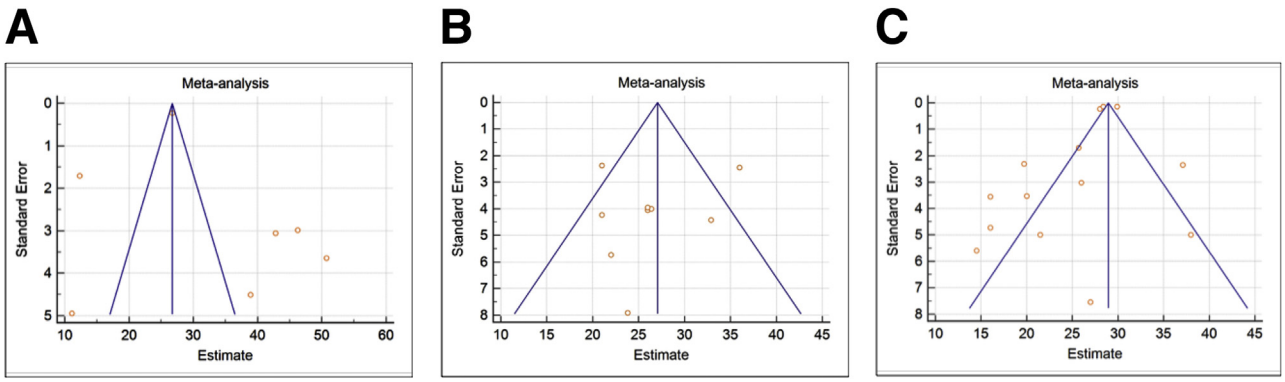

Fig 2 Funnel plots of studies of (A) 3-week course of Hyalgan; (B) 5-week course of Hyalgan; and (C) 3-week course of other HA products.

were recorded for the last observation of treatment effect, which was 12 weeks posttreatment in 3 studies,[43,44,53] 26 weeks posttreatment in 14 studies,[21,22,34,40,42,45-49,51,52,54,55] and 52 weeks posttreatment in 7 studies.[35-39,41,53]

Heterogeneity of treatment references was calculated for each of the 3 groups of studies. The I^2 statistic was 97.0% for the 5 studies of 3 weekly injections of Hyalgan and 91.6% for the 12 studies of 3 weekly injections of other HA products ($P<.001$ for both groups). The I^2 statistic was 67.8% for the 8 studies of 5 weekly injections of Hyalgan. Although the I^2 statistic for this group of studies evaluating 5 weekly injections with Hyalgan is <75% traditional threshold, the level of statistical significance is $P=.002$; therefore, reporting results from the random effects model was deemed appropriate. Funnel plots are shown in figure 2.

Relation between effect sizes for improvement in knee OA pain

The primary outcome of this meta-analysis is comparison of the mean effect of a 3-week treatment regimen of Hyalgan on patient-reported improvement from baseline knee OA pain with the mean effect of a 5-week treatment regimen of Hyalgan. The secondary outcome is the mean effect of a 3-week treatment regimen of Hyalgan on patient-reported improvement from baseline knee OA pain compared with the mean effect of a 3-week treatment regimen of other HA products. The effect size for each group was determined by the estimated mean change from baseline in 100-mm VAS scores across all outcomes used.

These adjusted estimates demonstrate that treatment with 3 weekly injections of Hyalgan provides a reduction in knee OA pain that is comparable with that achieved in the 2 other groups, 5 weekly injections of Hyalgan and 3 weekly injections of other intra-articular HA products. Between the 2 Hyalgan study groups, the pooled estimate (SE) was −31.4 (5.46) with 3 weekly injections of Hyalgan and −32.2 (5.25) with 5 weekly injections of Hyalgan. Similarly, among the 2 groups of studies of 3 weekly injections (Hyalgan vs other HA products), the pooled estimate (SE) for reduction in knee OA pain was −31.4 (5.46) with 3 weekly injections of Hyalgan and −29.4 (4.98) with 3 weekly injections of other HA products (table 3).

The adjusted least-squares estimates of change from baseline in VAS scores and its corresponding 95% confidence interval (CI) estimated the differences in pain resolution between the participants in the studies of 3 injections of Hyalgan treatment and each of the 2 control groups. Based on the values and corresponding 95% CIs, the calculated difference (Δ) in effect size (difference between 2 means divided by a SD for the control data) and the *P* value for treatment differences are provided in table 3. The calculated estimates of 3 injections of Hyalgan versus 5 injections of Hyalgan show no difference between the groups, with a small effect of .05 in favor of the 5 injections of Hyalgan treatment group ($P=.916$). Similarly, the calculated estimates of 3 injections of Hyalgan versus 3 injections of other FDA-approved HA products show no difference between the groups, with a small effect of −.12 in favor of the 3 injections of Hyalgan ($P=.696$). Unadjusted estimates for each treatment group are provided in figures 3A–C.

Table 3 Least-squares estimates and calculated effect size

Treatment Group	LS-Mean (SE) of Change From BL VAS Score	95% CI of LS-Mean	Estimated Difference Between Groups (SE)	95% CI of Treatment Difference	*P* Value for Treatment Difference	Estimated Effect Size*
3 injections of Hyalgan	−31.4 (5.46)	−45.5 to −17.4				
5 injections of Hyalgan	−32.2 (5.25)	−45.6 to −18.7	0.7 (6.62)	−16.3 to −17.8	.916	.05
3 injections of other HA products	−29.4 (4.98)	−42.2 to −16.6	−2.0 (5.91)	−17.2 to −13.2	.696	−.12

Abbreviations: BL, baseline; LS-Mean, least-squares mean.

* Effect size is calculated as the difference in LS-Means between 3 weekly injections of Hyalgan versus each of the other 2 groups, divided by the SD of the respective group.

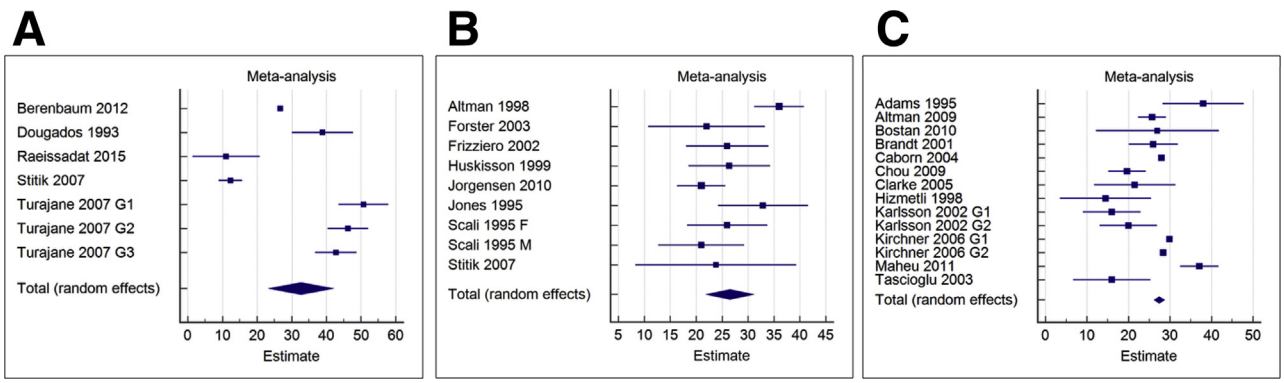

Fig 3 Forest plots of the effect sizes of VAS scores of improvement in baseline pain from studies of (A) 3-week course of Hyalgan, (B) 5-week course of Hyalgan, and (C) 3-week course of other HA products. Abbreviation: G, group.

Sensitivity analysis

The previously described random effects model demonstrated that the effect of the period of observation was nonsignificant ($P = .678$). In a sensitivity analysis, a second random effects model was conducted without the effect of the period of observation. Table 4 displays the results of this sensitivity analysis, which supports the results from this model. The effect sizes in the sensitivity analysis demonstrate no significant differences in outcomes between the 3 groups.

Discussion

The findings of this research support the thesis that there is no significant difference in the relief of knee OA pain with a regimen of 3 or 5 weekly intra-articular injections of Hyalgan or 3 weekly injections of other HA products. The clinical effect of these regimens on knee OA pain is comparable in all 3 groups.

To our knowledge, the studies of Karras,[26] Stitik,[37] and colleagues are the only reports in the literature of a clinical trial that conducted a head-to-head investigation of the effect of different regimens of weekly injections of Hyalgan on effectiveness in reducing knee OA pain. Both studies reported findings similar to this study. However, the Karras study also compared the effect of differences in the time period between repeat courses of therapy with Hyalgan. In the Stitik study, relief of knee OA pain at 3 months was similar with 3 or 5 weekly injections of Hyalgan.

Also in support of our findings, the FDA has issued labeling decisions that acknowledge the number of intra-articular injections in a course of HA treatment of knee OA may not alter its effectiveness. For example, in pivotal clinical studies for the approval of high molecular weight hyaluronan (Orthovisc), effectiveness superiority was demonstrated for a regimen of 4 weekly injections compared with a regimen of 3 weekly injections; however, Orthovisc is approved for administration with either a 3- or 4-injection regimen.[10,47]

Another HA product, sodium hyaluronate (Supartz FX), is indicated for administration with 5 weekly injections, including the potential of deriving therapeutic benefit with 3 weekly injections in some patients with knee OA.[11] A recent study of 3 weekly injections of the Supartz FX formulation demonstrated noninferiority in knee OA pain relief compared with that of 3 weekly injections of 1% sodium hyaluronate (Euflexxa).[56] Based on outcomes from this study, the 3-injection regimen of Supartz Fx was approved by the FDA under the brand name Visco-3, via the premarket approval supplement number P980044/S027.[12,57]

The significance of the findings of this research demonstrates that Hyalgan treatment of knee OA pain with a course of 3 weekly intra-articular injections may deliver pain relief comparable with a course of 5 weekly injections of Hyalgan or a course of 3 weekly injections with other HA products. The study itself did not factor in cost analysis, but future studies examining this could be beneficial.

Study limitations

A limitation of this meta-analysis is the limited number of studies eligible for analysis in each treatment regimen group, which led to significant heterogeneity and wide CIs. In addition, variation in study populations (intent-to-treat or per-protocol) used for efficacy analyses may have inserted a slight bias in favor of outcomes for the study treatment. Furthermore, other than the studies of

Table 4 Sensitivity analysis of least-squares estimates and calculated effect size without the period of observation independent variable

Treatment Group	LS-Mean (SE) of Change From BL VAS Score	95% CI of LS-Mean	Estimated Difference Between Groups (SE)	95% CI of Treatment Difference	*P* Value for Treatment Difference	Estimated Effect Size*
3 injections of Hyalgan	−26.8 (1.04)	−29.4 to −24.1				
5 injections of Hyalgan	−27.1 (4.46)	−38.5 to −15.6	0.3 (4.58)	−11.4 to −12.1	.947	.02
3 injections of other HA products	−28.7 (0.62)	−30.2 to −27.1	1.9 (1.22)	−1.2 to 5.0	.180	.88

Abbreviations: BL, baseline; LS-Mean, least-squares mean.

* Effect size is calculated as the difference in LS-Means between 3 weekly injections of Hyalgan versus each of the other 2 groups, divided by the SD of the respective group.

Karras,[26] Stitik,[37] and colleagues, there was an absence of any head-to-head comparison studies investigating the effect of different regimens of weekly injections of Hyalgan on effectiveness in reducing knee OA pain. Publication bias is also a study limitation in this analysis as evidenced by the funnel plots provided for each treatment group (see fig 2). In light of this, some of the estimates used were taken from articles where the treatment did not achieve a statistical significance versus its comparator within its article.

Conclusions

The findings from this study infer that Hyalgan treatment of knee OA pain with a course of 3 weekly intra-articular injections may be expected to provide similar relief, comparable with that achieved with a course of 5 weekly injections of Hyalgan or a course of 3 weekly injections with other HA products approved for use in the United States.

Suppliers

a. MedCalc for Windows, version 16.4.3; MedCalc.
b. SAS version 9.4 [TS1M3]; SAS Institute.

Keywords

Clinical protocols; Hyaluronic acid; Meta-analysis [publication type]; Osteoarthritis, knee; Rehabilitation

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