Viscosupplementation for Osteoarthritis of the Knee

A Systematic Review and Meta-analysis

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Background: Viscosupplementation, the intra-articular injection of hyaluronic acid, is widely used for symptomatic knee osteoarthritis.

Purpose: To assess the benefits and risks of viscosupplementation for adults with symptomatic knee osteoarthritis.

Data Sources: MEDLINE (1966 to January 2012), EMBASE (1980 to January 2012), the Cochrane Central Register of Controlled Trials (1970 to January 2012), and other sources.

Study Selection: Randomized trials in any language that compared viscosupplementation with sham or nonintervention control in adults with knee osteoarthritis.

Data Extraction: Primary outcomes were pain intensity and flare-ups. Secondary outcomes included function and serious adverse events. Reviewers used duplicate abstractions, assessed study quality, pooled data by using a random-effects model, examined funnel plots, and explored heterogeneity by using meta-regression.

Data Synthesis: Eighty-nine trials involving 12 667 adults met inclusion criteria. Sixty-eight had a sham control, 40 had a follow-up duration greater than 3 months, and 22 used cross-linked forms of hyaluronic acid. Overall, 71 trials (9617 patients) showed that viscosupplementation moderately reduced pain (effect size, −0.37 [95% CI, −0.46 to −0.28]). There was important between-trial heterogeneity and an asymmetrical funnel plot: Trial size, blinded outcome assessment, and publication status were associated with effect size. Five unpublished trials (1149 patients) showed an effect size of −0.03 (CI, −0.14 to 0.09). Eighteen large trials with blinded outcome assessment (5094 patients) showed a clinically irrelevant effect size of −0.11 (CI, −0.18 to −0.04). Six trials (811 patients) showed that viscosupplementation increased, although not statistically significantly, the risk for flare-ups (relative risk, 1.51 [CI, 0.84 to 2.72]). Fourteen trials (3667 patients) showed that viscosupplementation increased the risk for serious adverse events (relative risk, 1.41 [CI, 1.02 to 1.97]).

Limitations: Trial quality was generally low. Safety data were often not reported.

Conclusion: In patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.

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Osteoarthritis is set to become the 4th-highest impact condition in women and the 8th-most important in men in the developed world (1). Nonsteroidal anti-inflammatory drugs are the most commonly prescribed agents for this condition but a frequent cause of serious adverse gastrointestinal and cardiovascular events (2, 3). Hyaluronic acid is a naturally occurring polysaccharide in the synovial fluid, which acts as a lubricant and shock absorber (4). In patients with osteoarthritis, synovial hyaluronic acid is depolymerized and cleared at higher rates than normal, resulting in a decrease of molecular weight and concentration (5). To improve biomechanical function, different hyaluronic acids were devised for intra-articular injection, commonly called *viscosupplementation* (5).

At least 6 systematic reviews compared the effectiveness of viscosupplementation with sham intervention in patients with knee osteoarthritis (6). Of these, 3 reviews concluded that viscosupplementation was more effective than sham, whereas the remaining 3 reviews did not. Several trials have since been published. In addition, we were aware of unpublished trials, which were never included in any meta-analysis to date. Therefore, we did a comprehensive, up-to-date systematic review to determine whether viscosupplementation is clinically effective and safe to treat symptomatic knee osteoarthritis.

See also:

Print
Summary for Patients I-36

Web-Only
Supplements

Methods

We followed a standard protocol for all review steps.

Literature Search

We searched several electronic databases, without language restrictions, including the Cochrane Central Register of Controlled Trials (from inception), MEDLINE (from 1966), and EMBASE (from 1980) through Ovid. The last update search was done on 31 January 2012 (**Supplement 1**, available at www.annals.org, shows search algorithms). We manually searched conference proceedings; used the Science Citation Index to retrieve reports citing relevant articles; contacted content experts; screened reference lists of all obtained articles, including related reviews; and searched several clinical trial registries (ClinicalTrials.gov, Current Controlled Trials [www.controlled-trials.com], Australian New Zealand Clinical Trials Registry [www.actr.org.au], and University Hospital Medical Information Network Clinical Trials Registry [www.umin.ac.jp/ctr]) to

identify ongoing trials. The last update was done on 31 January 2012.

Trial Selection

We included randomized or quasi-randomized, controlled trials (7) that compared viscosupplementation with sham or nonintervention control in adults with symptomatic knee osteoarthritis. Any type of intra-articular viscosupplementation with hyaluronic acid or a derivative was eligible. No language restrictions were applied. If several reports described the same trial, we chose the most recent report as the main report, which typically was the latest full-text publication in a peer-reviewed journal. Remaining reports were checked for complementary data on clinical outcomes, descriptions of study participants, or design characteristics. If outcome data differed between reports, we extracted the data that most closely adhered to the intention-to-treat principle. Two of 3 reviewers evaluated reports independently for eligibility and extracted data. Disagreements were resolved by consensus or discussion with a third reviewer.

Outcome Measures

Pain intensity was the prespecified primary effectiveness outcome and physical function the secondary effectiveness outcome, as currently recommended for osteoarthritis trials (8, 9). If data on more than 1 scale for pain or function were provided, we referred to previously described hierarchies (7, 10, 11) and extracted data on the scale that was highest on this hierarchy. For example, if both the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscores and pain on standing measured on a visual analogue scale (VAS) were reported for a trial, we extracted data only on Western Ontario and McMaster Universities Arthritis Index pain subscores. If pain and function outcomes were reported at several time points, we extracted the time point closest to 3 months after the end of treatment.

The prespecified primary safety outcome was a flare-up in the injected knee (12). Flare-ups were typically defined as a hot, painful, swollen knee within 24 to 72 hours after injection. Secondary safety outcomes were (in hierarchical order) serious adverse events, withdrawals or dropouts because of adverse events, adverse events overall, effusions at the injected knee, any local adverse event in the injected knee, and dropouts and withdrawals overall (regardless of reason). The definition of any local adverse event included flare-ups and any other local adverse event as reported by the authors of individual trials. Effusions were defined as excessive joint fluid inside the treated knee after an injection, typically diagnosed by clinical examination, ultrasonography, or arthrocentesis. Serious adverse events were defined as those resulting in inpatient hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality of offspring, life-threatening events, or death (13). We extracted the number of patients per group who had at least 1 event until the end of the trial.

Context

Viscosupplementation, intra-articular injection of hyaluronic acid, is used to treat symptomatic knee osteoarthritis.

Contribution

This review of 89 randomized trials that compared viscosupplementation with sham or nonintervention control in adults with knee osteoarthritis found that viscosupplementation had minimal effects on pain and function but increased risk for serious adverse events.

Caution

Adverse event data were often poorly reported, and trial quality was generally low.

Implication

Viscosupplementation for knee osteoarthritis has minimal benefits and potential for harm.

—The Editors

Data Collection and Quality Assessment

Data were extracted by using a standardized, piloted extraction form accompanied by a codebook (11). We extracted the type of viscosupplementation, average molecular weight, number of cycles, number of injections, patient characteristics (sex, average age, duration of symptoms, and disease severity), characteristics of pain, function and safety outcomes, trial size, trial design, trial duration (defined as time from randomization until end of follow-up), type and source of financial support, and publication status. We then assessed concealment of allocation, blinding of patients, use of a sham control, blinded outcome assessment, and intention-to-treat analyses (14, 15). Definitions used for methodological characteristics and molecular weight are reported in **Supplement 2** (available at www.annals.org). Whenever possible, we used results from an intention-to-treat analysis approach. When necessary, we approximated means and measures of dispersion from graphs in the reports. If effect sizes could not be calculated, we contacted the authors for additional data.

Data Synthesis and Analysis

Continuous outcomes were expressed as effect sizes, defined a priori as between-group differences in mean values at the end of follow-up divided by the pooled SD. If differences in mean values at the end of follow-up were unavailable, differences in mean changes were used. If some of the required data were unavailable, we used approximations, as previously described (11). We prespecified a minimal clinically important difference of −0.37 effect sizes, corresponding to 0.9 cm on a 10-cm VAS (16). This was based on the median minimal clinically important dif-

ference found in recent studies in patients with osteoarthritis (17–20). Binary outcomes were expressed as relative risks (RRs).

We used standard inverse-variance random-effects meta-analysis to combine the trials (21). We calculated the variance estimate τ^2 as a measure of heterogeneity between trials (21). A τ^2 of 0.04 was prespecified to represent low heterogeneity, 0.09 to represent moderate, and 0.16 to represent high heterogeneity between trials (22). The association between trial size and treatment effects was investigated in funnel plots of effect sizes on the *x*-axis against their SEs on the *y*-axis (23, 24). We enhanced funnel plots by contours, dividing the plot into areas of significance (2-sided *P* value $\leq$0.05) and nonsignificance (25, 26). Then, we added lines of predicted effect sizes derived from univariable random-effects meta-regression by using the SE as the explanatory variable (27, 28) and assessed funnel plot asymmetry with weighted linear regression of the effect sizes on their SEs (23, 29).

Stratified analyses of the primary effectiveness outcome were done, according to the following trial characteristics: concealment of allocation, blinding of patients, use of a sham intervention, blinded outcome assessment, intention-to-treat analysis, trial size, publication status, funding source, duration of follow-up, number of treatment cycles, number of injections, molecular structure (cross-linked vs. non–cross-linked), and average molecular weight. Univariable random-effects meta-regression models (30) were used for tests of interaction between treatment effect and these characteristics. We used cutoffs of 100 or more allocated patients per group for trial size (28); 3 or more and 6 or more months for duration of follow-up; 2 or more for number of cycles; 1 or 2, 3, and 4 or more for number of injections; and 1500 kDa or more and 6000 kDa or more for average molecular weight. Then, we restricted the data set to large trials with 100 or more allocated patients per group and blinded outcome assessment because these 2 methodological characteristics were associated with treatment effects at *P* for interaction of 0.05 or less. We repeated stratified analyses according to clinical characteristics for this restricted data set and did a meta-analysis of multiple time points (**Supplement 3**, available at www.annals.org) (21, 25, 31).

We included data from unpublished trials, which were not subject to the U.S. Freedom of Information Act or to a clearance by funding companies (32–34), in all analyses but omitted the presentation of their individual results in tables and figures. All *P* values are 2-sided. Analyses were done by using STATA, release 11 (StataCorp, College Station, Texas).

Role of the Funding Source

The study was funded by the Arco Foundation. The funding source did not play a role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

We identified 1882 references and considered 410 to be potentially eligible (**Supplement 4**, available at www.annals.org). One hundred seventy-seven reports describing 89 trials in 12 667 patients met our inclusion criteria (32–117). Fifty-seven trials were published as full journal articles and 23 as conference proceedings, and 2 were published in a pamphlet and 1 in a book chapter. Six trials in 1357 patients were unpublished, 2 of which were funded by Anika Therapeutics (Bedford, Massachusetts), 2 by Seikagaku (Tokyo, Japan), 1 by Genzyme (Cambridge, Massachusetts), and 1 by Sanofi-Aventis (Paris, France). Reports on the trials funded by Anika were provided by the company. For one of these, results for a subgroup were published, for which a statistically significant benefit of hyaluronic acid was detected, as compared with placebo (118). Results from the trials funded by Seikagaku were found at the U.S. Food and Drug Administration Web site (74). The report of the trial funded by Genzyme was sent to us by a confidential source unrelated to the manufacturer and primary investigator—we subsequently attempted to obtain the report directly from Genzyme, but the company declined (Murray C. Personal communication). Safety results of the trial by Sanofi-Aventis were found at ClinicalTrials.gov.

The average age of participants ranged from 50 to 72 years (median of 63 years, reported in 69 trials), and the average percentage of women ranged from 27% to 100% (median of 67%, reported in 71 trials). Twenty-seven trials reported on Kellgren–Lawrence grades of radiographic severity (119); grade 2 was found in a median of 44% of participants, and grade 3 in a median of 39% (27 trials). The average length of follow-up ranged from 0 to 104 weeks (median of 16 weeks, reported in 78 trials), and the average completeness of follow-up ranged from 50% to 100% (median of 92%, reported in 44 trials). **Supplement 5** (available at www.annals.org) presents further clinical characteristics of trials. Cross-linked preparations were evaluated in 18 trials (20%) and non–cross-linked in 67 trials (75%), and 4 trials evaluated both (5%). Low, moderate, and high molecular weight were used in 38 (43%), 17 (19%), and 17 (19%) trials, respectively, and 5 trials (6%) evaluated several preparations of different molecular weights. **Supplement 6** (available at www.annals.org) presents the methodological characteristics of trials. All trials used a parallel group design. Thirteen trials reported adequate concealment of allocation (15%), 68 trials used a sham intervention in the control group (76%), 16 were judged to have adequately blinded patients (18%), and 48 had blinded outcome assessment (54%). Seventeen trials had analyzed all patients according to the intention-to-treat principle (19%), and 23 trials had sample sizes of 100 patients or more per trial group (26%).

Figure 1. **Forest plot of differences in pain intensity expressed as effect size comparing the effects of any type of viscosupplementation and control (sham or no intervention) on knee pain in 71 trials.**

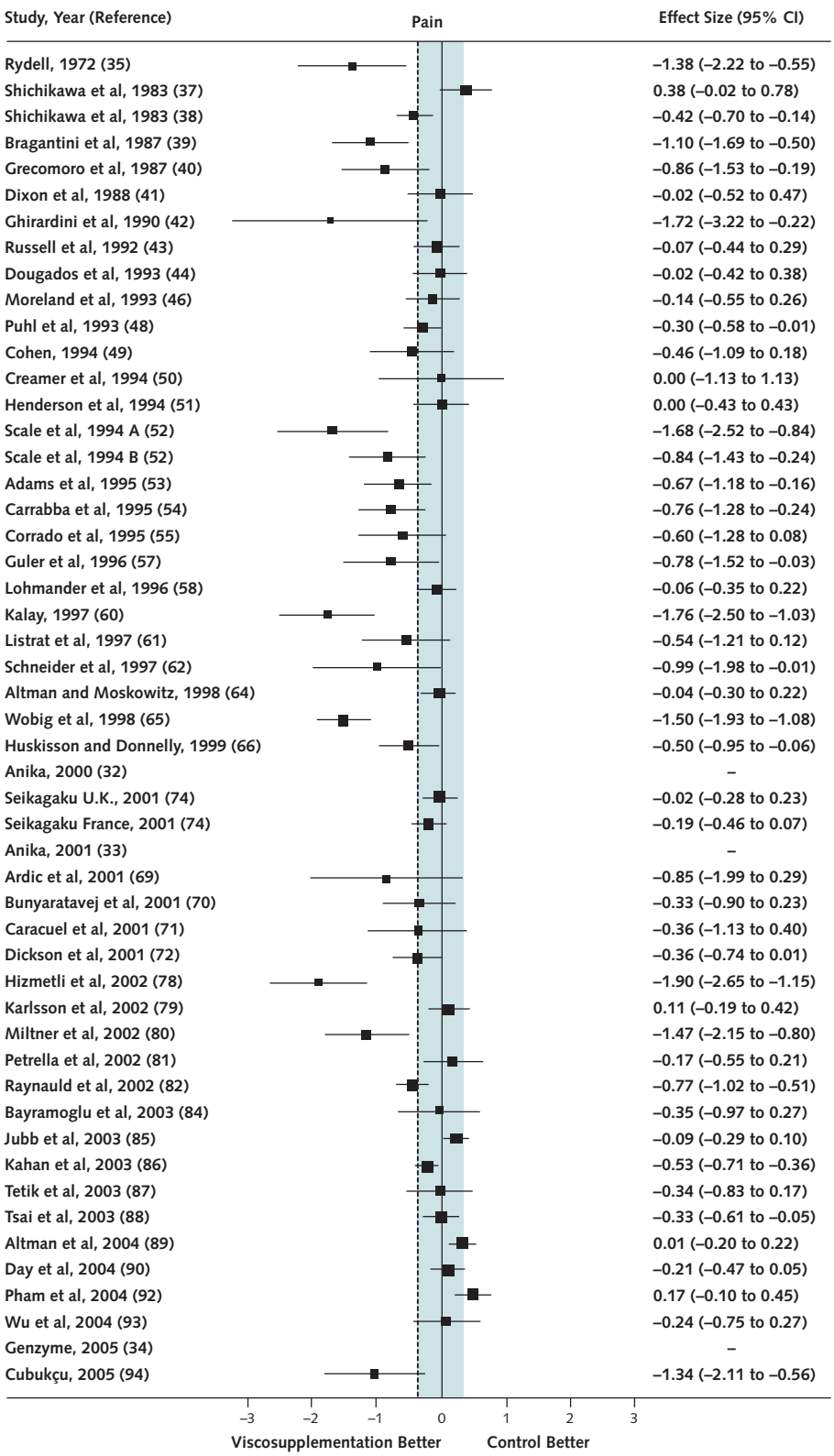

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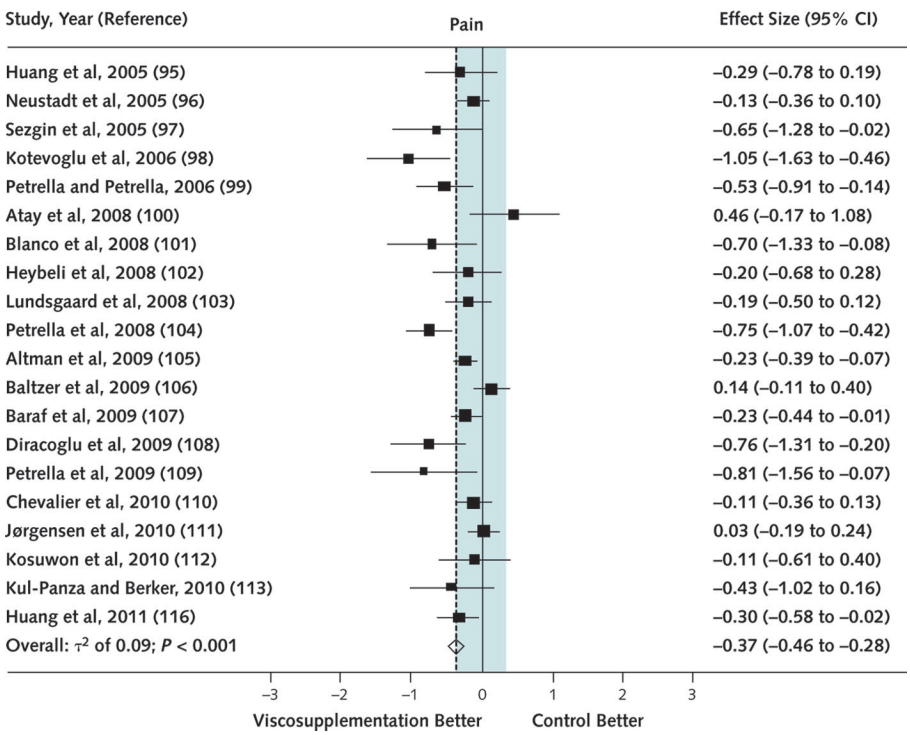
Figure 1—**Continued**



Shading represents area of clinical equivalence smaller than minimal clinically important difference. Weights are from random-effects analysis.

Knee Pain

Seventy-one trials in 9617 patients contributed to the meta-analysis of pain outcomes (**Figure 1** and **Supplement 7** [available at www.annals.org]). The overall analysis suggested that viscosupplementation had a moderate effect size of −0.37 (95% CI, −0.46 to −0.28), which met the prespecified minimal clinically important difference of −0.37. A τ^2 of 0.09 indicated a moderate degree of between-trial heterogeneity (P for heterogeneity <0.001 [**Figure 1**]), and the funnel plot was asymmetrical ($P < 0.001$ [**Figure 2**]). **Figure 3** shows results from stratified analyses. Estimates varied to some extent, according to concealment of allocation, blinding of patients, follow-up duration, number of injections, structure, and molecular weight, but CIs overlapped considerably between strata and P values for interaction were all negative. Conversely, there was an interaction between trial size and treatment effect (P for interaction was 0.002). The effect size for large trials of −0.16 (CI, −0.26 to −0.07) did not reach the minimal clinically important difference, despite being statistically significant at the conventional 5% level. The 5 unpublished trials contributing to the meta-analysis showed a null result (effect size, −0.03 [CI, −0.14 to 0.09]), whereas effect sizes derived from published trials showed moderate to large effects (P for interaction was 0.040). There was an interaction between blinding of outcome assessment and treatment effect (P for interaction was 0.003), with a smaller effect size in trials with blinding, but the CI overlapped the line of minimal clinically important difference (effect size, −0.25 [CI, −0.34 to −0.16]).

Supplement 8 (available at www.annals.org) presents results after restriction to the 18 large trials with blinded outcome assessment (5094 patients). The overall effect size was −0.11, the 95% CI did not overlap the line of a minimal clinically important difference (CI, −0.18 to −0.04), and there was low heterogeneity between trials ($\tau^2 = 0.01$). In stratified analyses, we found little evidence for interactions between treatment effect and trial characteristics; in all subgroups, estimates failed to reach minimal clinical importance, although CIs were frequently wide. Estimates for τ^2 varied across strata from 0.00 to 0.03. **Supplement 9** (available at www.annals.org) presents results of a meta-analysis of multiple time points after restriction to large trials with blinded outcome assessment. Estimates or CIs did not reach the minimal clinically important difference for any of the time points, although estimates reached conventional levels of statistical significance at 3 and 6 months.

Physical Function

Fifty-two trials (7904 patients) contributed to the meta-analysis of function. The analysis suggested that viscosupplementation had a moderate effect size of −0.33 (CI, −0.43 to −0.22) (**Supplements 10** and **11**, available

at www.annals.org). Again, we saw a moderate degree of between-trial heterogeneity ($\tau^2 = 0.11$; P for heterogeneity <0.001) and the funnel plot seemed to be asymmetrical (P for asymmetry <0.001) (**Supplement 12**, available at www.annals.org). The pooled estimate for large trials with blinded outcome assessment (15 trials including 4296 patients) resulted in an overall effect size of −0.09 (CI, −0.17 to 0.00) and showed no heterogeneity between trials ($\tau^2 = 0.01$).

Supplement 13 (available at www.annals.org) presents results of a meta-analysis of multiple time points after restriction to large trials with blinded outcome assessment. Estimates or CIs did not reach the minimal clinically important difference for any of the time points.

Safety

Figure 4 presents results from meta-analyses of all safety outcomes on the basis of an analysis of all trials and of large trials with blinded outcome assessment. Six trials (811 patients) contributed to the meta-analysis of flare-ups as the primary safety outcome. Viscosupplementation was associated with increased risk for flare-ups (RR, 1.51 [CI, 0.84 to 2.72]) that was not statistically significant. There was low statistical heterogeneity ($\tau^2 = 0.00$). When restricting the analysis to large trials with blinded outcome assessment, we found that the RR increased to 2.39, but again with a wide CI that overlapped the line of no difference at 1.00. For secondary safety outcomes, we found that viscosupplementation was associated with an increased risk for serious adverse events (RR, 1.41 [CI, 1.02 to 1.97]), dropouts due to adverse events (RR, 1.33 [CI, 1.01 to 1.74), and local adverse events (RR, 1.34 [CI, 1.13 to 1.60]), which were all statistically significant. **Supplement 14** (available at www.annals.org) presents a forest plot of the meta-analysis of serious adverse events with large trials with blinded outcome assessment. For any adverse events (RR, 1.04 [CI, 0.99 to 1.09]), effusions (RR, 1.15 [CI, 0.38 to 3.54]), and overall number of withdrawals (RR, 0.97 [CI, 0.87 to 1.09]), estimates were close to 1.00 and CIs overlapped the line of no difference. When restricting our analysis to large trials with blinded outcome assessment, we found similar results.

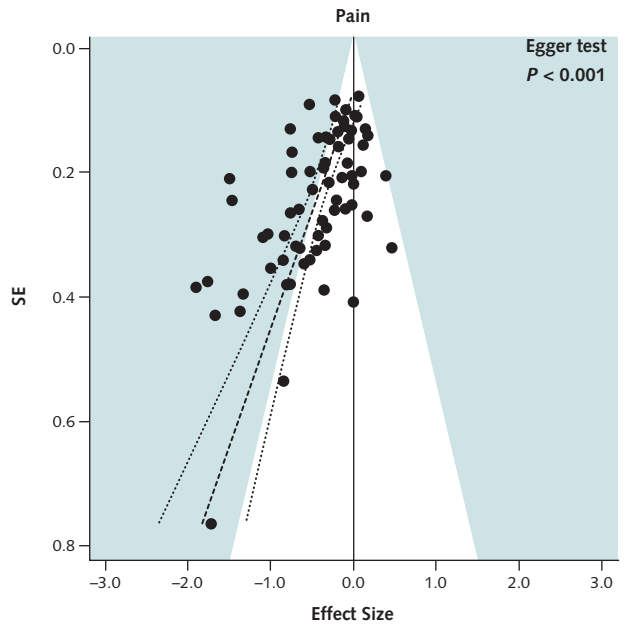
Eight of 14 trials that contributed to the analysis of serious adverse events reported some or all of the conditions that led to serious adverse events. Among these 8 trials, 27 events that occurred in 26 viscosupplementation patients and 21 events that occurred in 14 control patients were described. Most frequent disorders were related to the gastrointestinal system (2 events among viscosupplementation patients vs. 8 events among control patients), cardiovascular system (5 vs. 2 events), cancer (6 vs. 0 events), and musculoskeletal system (4 vs. 2 events).

DISCUSSION

In our meta-analysis of large trials with blinded outcome assessment, we found a small, clinically irrelevant effect of viscosupplementation on pain. For function, no effect remained. Conversely, we found clinically important increases in the risk for serious adverse events, dropouts because of adverse events, and local adverse events of 30% to 50%. We saw pronounced small study effects, which may be because of a combination of methodological flaws of study conduct and analysis and publication and other reporting biases, predominantly in small trials (120, 121). We identified 6 unpublished trials, of which 5 contributed to the analysis of pain, with 1149 patients, or 12% of the total number of patients included in the meta-analysis of pain outcomes. We could not disclose detailed results of 3 of them, but could report summary estimates after pooling all 5 unpublished trials, which yielded an effect size of −0.03 and a τ^2 of 0.00. Such publication bias is disconcerting and unacceptable from an ethical and scientific point of view.

We were recently criticized for being too stringent in our choice of cutoff to delineate minimal clinically important differences in a network meta-analysis of food supplements (122). Our cutoff is based on the median minimal clinically important difference found in recent studies in patients with osteoarthritis and corresponds to 9 mm on a 10-cm VAS (16). Ruyssen-Witrand and colleagues (123) investigated the pain decrease considered clinically relevant when designing a trial and reporting its results in a systematic review of randomized trials with pain as the primary

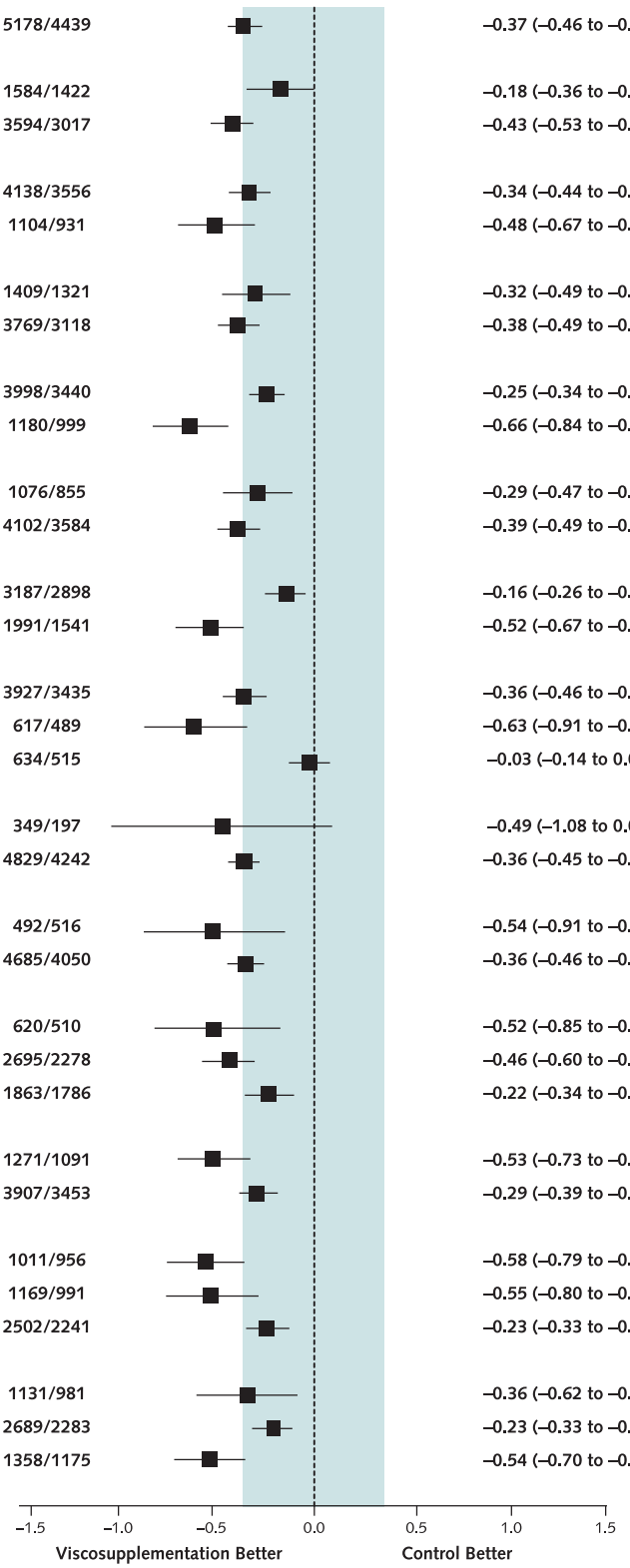
Figure 2. **Contour-enhanced funnel plot for effects on knee pain.**



Includes prediction lines with 95% confidence lines from univariable meta-regression models with SE as explanatory variable (*dashed and dotted lines*). Contour areas to display areas of significance at $P \leq 0.05$ (*green*) and nonsignificance (*white*). Lines for predicted effects should be interpreted independently of contours delineated by shaded areas.

Figure 3. **Results of stratified analyses of pain outcomes.**

Variable	Trials, *n*	Patients in Experimental Group/Control Group, *n/N*	Effect Size (95% CI)	τ^2	*P* for Interaction
All trials	71	5178/4439	–0.37 (–0.46 to –0.28)	0.09	
Concealment of allocation					0.053
Adequate	13	1584/1422	–0.18 (–0.36 to –0.01)	0.08	
Inadequate or unclear	58	3594/3017	–0.43 (–0.53 to –0.32)	0.10	
Type of control intervention					0.33
Sham intervention	54	4138/3556	–0.34 (–0.44 to –0.24)	0.09	
Nonsham intervention	18	1104/931	–0.48 (–0.67 to –0.29)	0.10	
Blinding of patients					0.53
Adequate	16	1409/1321	–0.32 (–0.49 to –0.14)	0.09	
Inadequate or unclear	55	3769/3118	–0.38 (–0.49 to –0.28)	0.10	
Blinded outcome assessment					0.003
Adequate	46	3998/3440	–0.25 (–0.34 to –0.16)	0.06	
Inadequate or unclear	25	1180/999	–0.66 (–0.84 to –0.44)	0.16	
Intention-to-treat					0.46
Yes	15	1076/855	–0.29 (–0.47 to –0.10)	0.08	
No or unclear	56	4102/3584	–0.39 (–0.49 to –0.28)	0.10	
Trial size					0.002
≥100 per trial group	21	3187/2898	–0.16 (–0.26 to –0.07)	0.04	
<100 per trial group	50	1991/1541	–0.52 (–0.67 to –0.39)	0.17	
Publication status					0.040
Full journal articles	52	3927/3435	–0.36 (–0.46 to –0.26)	0.09	
Other publications*	14	617/489	–0.63 (–0.91 to –0.36)	0.17	
Unpublished	5	634/515	–0.03 (–0.14 to 0.09)	0.00	
Funding independent of industry					0.70
Yes	4	349/197	–0.49 (–1.08 to 0.09)	0.30	
No or unclear	67	4829/4242	–0.36 (–0.45 to –0.27)	0.09	
Number of cycles					0.50
>1	8	492/516	–0.54 (–0.91 to –0.16)	0.22	
1	64	4685/4050	–0.36 (–0.46 to –0.27)	0.09	
Number of injections					0.058
1–2	7	620/510	–0.52 (–0.85 to –0.18)	0.14	
3	38	2695/2278	–0.46 (–0.60 to –0.32)	0.13	
>3	30	1863/1786	–0.22 (–0.34 to –0.10)	0.06	
Structure					0.099
Cross-linked	19	1271/1091	–0.53 (–0.73 to –0.34)	0.13	
Not cross-linked or unclear	56	3907/3453	–0.29 (–0.39 to –0.20)	0.08	
Molecular weight					0.110
Very high	18	1011/956	–0.58 (–0.79 to –0.36)	0.14	
High	15	1169/991	–0.55 (–0.80 to –0.30)	0.17	
Low	34	2502/2241	–0.23 (–0.33 to –0.13)	0.04	
Follow-up duration					0.078
>6 mo	12	1131/981	–0.36 (–0.62 to –0.09)	0.17	
3–6 mo	28	2689/2283	–0.23 (–0.33 to –0.12)	0.04	
<3 mo	31	1358/1175	–0.54 (–0.70 to –0.37)	0.13	



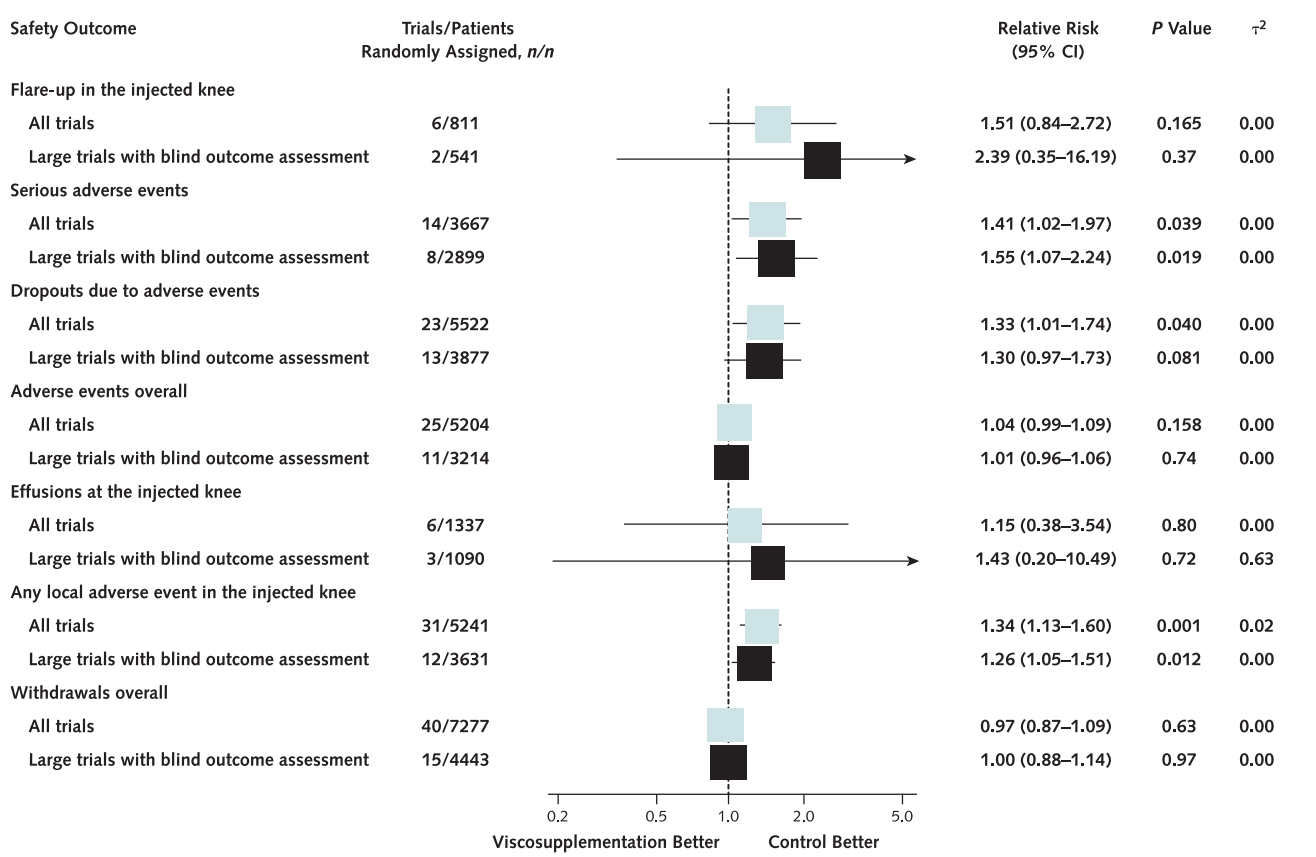
Shading represents the area of clinical equivalence smaller than minimal clinically important difference.
* *P* values from test for trend.

outcome. Twenty-nine of 31 trials (94%) specified minimal clinically important differences larger than 9 mm on a 10-cm VAS (123). Criticisms of the present meta-analysis are likely to include that some estimates reached conventional levels of statistical significance. The high number of patients and the low heterogeneity between trials meant that comparisons between viscosupplementation and placebo were overpowered. For example, for the time window of 2 to 6 weeks after randomization, set up to depict early effects occurring immediately at completion of treatment cycles, more than 4000 patients were included in the analysis and there was no heterogeneity between trials ($\tau^2 = 0.00$). This meta-analysis may be roughly equal to a trial including 4000 patients, which would have nearly 100% power to detect a clinically irrelevant difference in mean pain intensity of only 5 mm on a 10-cm VAS and 89% power to detect a minute difference in mean pain intensity of 2.5 mm. In addition, viscosupplementation requires the involvement of a health professional, which increases cost and patient burden in a way that differs from what would be the case for food supplements, where the critique of our choice of the minimal clinically important difference originated.

A major limitation is the poor methodological quality and reporting quality of many of the included trials, as previously described for a larger body of osteoarthritis trials (28, 124, 125). Some trials (78, 80) showed unrealistically large effect sizes—2 to 3 times that of what would be expected for total joint replacement (10). Reasons for these unrealistic effect sizes include methodological deficiencies or chance. Many reports did not provide adequate data on adverse events, which is concerning in light of the observed safety signals. The low quality of reporting of safety data means that we could not understand the probable causes of serious adverse events. Several trials did not provide sufficient details to allow exact calculations of effect sizes, and we had to use approximations to derive effect sizes. Although these approximations are established for meta-analyses of continuous outcomes, their validity has not been evaluated systematically in osteoarthritis research.

In 2007, Campbell and colleagues (6) discussed 6 systematic reviews, which determined the effectiveness of

Figure 4. **Results from meta-analyses of all safety outcomes based on an analysis of all trials (*green squares*) and of large trials with blinded outcome assessment (*black squares*).**



Note that comparisons with 0 events in both groups did not contribute to the analysis: 19 trials (1349 patients) for flare-ups, 24 trials (1947 patients) for serious adverse events, 19 trials (1659 patients) for dropouts because of adverse events, 10 trials (579 patients) for any adverse events, 15 trials (1109 patients) for effusions, 8 trials (1191 patients) for local adverse events, and 7 trials (427 patients) for withdrawals.

viscosupplementation. Of these, 3 reviews concluded that viscosupplementation was more effective than sham (126–128). The remaining 3 reviews were more cautious, suggesting that viscosupplementation had no proven clinical effectiveness (129), suggesting that the presence of publication bias may have led to an overestimation of the observed small effects (130), or stating that viscosupplementation may have short-term effects on pain and physical function but that these effects do not last beyond 6 months (131). Differences in review methods could at least partially explain discordant conclusions. None of the systematic reviews included all evidence available at the time they were done. Reviews differed in the choice of pain and function scales, the use of statistical methods, and the handling of trial quality. Campbell and colleagues concluded that "in the balance of benefit to harm, the trade-off is probable benefit with respect to pain reduction and physical function improvement with low risk of harm" (6). Our conclusions are diametrically opposed. Not only did we not find clinically relevant benefits of viscosupplementation, we also saw concerning safety signals compared with placebo. The increased risk in serious adverse events associated with viscosupplementation is particularly concerning, but causal mechanisms are unclear. Only an individual-patient data meta-analysis of all relevant large trials done after independent readjudication and classification of serious adverse events could clarify this issue.

Recently, Bannuru and colleagues (132) described potential therapeutic trajectories of viscosupplementation over time, suggesting that the intervention was effective by 4 weeks, reached peak effectiveness at 8 weeks, and showed residual effectiveness up to 24 weeks. Although we found a similar pattern across time, the effects we saw were considerably smaller (and sometimes nonexistent) in our study. The most important reason for this discrepancy is our more stringent trial selection based on trial size and methodological quality. Bannuru and colleagues used a cutoff of 100 patients who were randomly assigned overall for their definition of large-scale trials, which is probably too small (28). The other reason is that we analyzed considerably more trials, including 3 more unpublished trials that contributed an additional 713 patients to the overall analysis.

We conclude that the benefit of viscosupplementation on pain and function in patients with symptomatic osteoarthritis of the knee is minimal or nonexistent. Because of increased risks for serious adverse events and local adverse events, the administration of these preparations should be discouraged.

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