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REVIEW

Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials

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Background: Intra-articular injection of hyaluronic acid is a common, yet controversial, therapeutic option for patients with knee osteoarthritis (OA). The purpose of this research was to determine the safety and efficacy of US-approved viscosupplements for symptomatic knee OA.

Methods: We searched MedLine and EMBase for randomized, sham-controlled trials evaluating safety and/or clinical efficacy of US-approved viscosupplements in patients with symptomatic knee OA. Knee pain severity and knee joint function were assessed at 4 to 13 weeks and 14 to 26 weeks. Safety outcomes included serious adverse events, treatment-related serious adverse events, patient withdrawal, and adverse event-related patient withdrawal occurring at any time during follow-up.

Results: A total of 29 studies representing 4,866 unique patients (active: 2,673, control: 2,193) were included. All sham-controlled trials used saline injections as a control. Viscosupplementation resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to preinjection values, with standardized mean difference values ranging from 1.07 to 1.37 (all $P<0.001$). Compared to controls, standardized mean difference with viscosupplementation ranged from 0.38 to 0.43 for knee pain and 0.32 to 0.34 for knee function (all $P<0.001$). There were no statistically significant differences between viscosupplementation and controls for any safety outcome, with absolute risk differences of 0.7% (95% confidence interval [CI]: –0.2 to 1.5%) for serious adverse events, 0% (95% CI: –0.4 to 0.4%) for treatment-related serious adverse events, 0% (95% CI: –1.6 to 1.6%) for patient withdrawal, and 0.2% (95% CI: –0.4 to 0.8%) for adverse event-related patient withdrawal.

Conclusion: Intra-articular injection of US-approved viscosupplements is safe and efficacious through 26 weeks in patients with symptomatic knee OA.

Keywords: hyaluronic acid, intra-articular, viscosupplementation

Introduction

Osteoarthritis (OA) is a common degenerative disease in older adults that is characterized by joint pain and dysfunction due to progressive subchondral bone damage, articular cartilage loss, inflammation/synovitis, and osteophyte formation.[1] Hyaluronic acid (HA) is an integral component of synovial fluid that acts as a joint lubricant during shear stress and a shock absorber during compressive stress. In the setting of knee OA, a marked reduction in concentration and molecular weight of endogenous HA ultimately leads to reduced viscoelastic properties of synovial fluid and induction of proinflammatory pathways.[2] Intra-articular injection of exogenous HA is intended to

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replace this OA-induced deficit and stimulate production of endogenous HA,[3] which may alleviate symptoms of knee OA via multiple pathways including inhibition of chondrodegradative enzymes and inflammatory processes, stimulation of chondrocyte metabolism, and synthesis of articular cartilage matrix components.[4]

Viscosupplements, involving the intra-articular injection of HA, are classified as medical devices in the US, under the regulation of the Food and Drug Administration. Since medical devices are regulated by different regulatory bodies across countries, it is relevant to assess the safety and efficacy profile of such products by country. The purpose of this systematic review and meta-analysis of randomized controlled trials was to determine the safety and efficacy of US-approved viscosupplements for symptomatic knee OA. A secondary rationale for performing the current meta-analysis was that, despite extensive evidence to the contrary,[5–11] the safety of viscosupplementation for knee OA has recently been called into question.[12]

Methods

Data sources

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (File S1).[13] We searched MedLine and EMBase for randomized, sham-controlled trials of intra-articular HA (IAHA) injection for treatment of knee OA using a combination of study design-, treatment-, and disease-specific keywords and Medical Subject Headings terms.

Study selection

No date restrictions were applied to the searches. Main inclusion criteria were injection of a US-approved HA product; randomized, sham-control study design; primary diagnosis of knee OA; identical treatment and follow-up conditions between IAHA and sham-control groups; and at least one extractable efficacy or safety outcome. Trials were excluded if concomitant interventional therapies were uniformly administered; were published in non-English language journals; or data were available only from abstracts, conference proceedings, websites, or personal communication. The details of the MedLine search strategy are listed in File S2. The syntax for EMBase was similar but adapted as necessary. Additionally, reference lists of included papers and relevant meta-analyses were manually searched. The final search was conducted in December 2013.

Data extraction

Data were extracted from eligible peer-reviewed articles by one author (LEM) and verified by a second author (JEB). Data extraction discrepancies between the two coders were determined by discussion and consensus. The following variables were recorded in standardized, pretested data extraction forms: general manuscript information (author, institution name and location, journal, year, volume, page numbers), patient characteristics (sex, age, body mass index [BMI], symptom duration, Kellgren–Lawrence grade), study characteristics (study quality, sample size, blinding assessment, HA trade name, number of injections and cycles, industry funding), efficacy outcomes (knee pain, knee function), and safety outcomes (serious adverse events [SAEs], treatment-related SAEs, patient withdrawals, patient withdrawals due to adverse events [AEs]).

Methodologic quality of studies was assessed using the Jadad score,[14] rated from 0 to 5 according to the presence of three key methodological features: randomization, blinding, and patient accountability. We defined a higher-quality trial as Jadad score ≥ 3. Main outcomes included pain severity, joint function, and safety variables. Pain severity and joint function data were extracted from papers in a nonbiased manner using the knee OA outcome meta-analysis hierarchy of Juhl et al.[15] Briefly, the first variables to be extracted from this prioritized list included the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale, pain during activity, and pain during walking for pain severity effects and WOMAC function subscale, physical composite summary, and physical function domain scores of the short form (SF)-36, SF-12, or SF-8. This hierarchy contains eight potential pain variables and four potential function variables. If none of the variables in this hierarchy were reported, we then used relevant pain and physical function assessments reported in the studies.

Due to the variation in reporting the postinjection pain and function trajectories, we a priori stratified data into two postinjection time windows: 4 to 13 weeks and 14 to 26 weeks. Efficacy data reported outside of these windows were excluded. If multiple pain or function effects within a given window were reported in a specific trial, the final value for each was extracted for analysis purposes. Safety outcomes included SAEs, treatment-related SAEs, withdrawals, and AE-related withdrawals occurring at any time during follow-up.

Data synthesis

A random effects meta-analysis model was selected a priori for all analyses. For each efficacy outcome, we calculated

two separate effect size statistics in each time window: a) pretreatment to posttreatment standardized mean difference (SMD) for IAHA, and b) SMD for IAHA versus control. For reference, SMD values of 0.2, 0.5, 0.8, and 1.0 are defined as small, medium, large, and very large effect sizes, respectively.[16] For each safety outcome, the absolute risk difference (RD) was selected since this statistic considers data from all studies, including zero total event trials.[17] When a single control group was compared with multiple treatment groups within a study, the sample size of the control group entered into the meta-analysis was adjusted based on the number of treatment groups.[18] Forest plots were used to visually assess effect sizes and corresponding 95% confidence intervals (CIs) across studies. We used the I^2 statistic to estimate heterogeneity of treatment effects with values of ≤25%, 50%, and ≥75% representing low, moderate, and high inconsistency, respectively.[19] Publication bias was visually assessed with funnel plots and quantitatively assessed using Egger's regression test.[20] Predefined subgroup analyses were undertaken to quantify the relationship of individual moderators on safety and efficacy outcomes. A priori, we identified the following subgroups as possible moderators of heterogeneity: female sex ≥67% versus <67%, age ≥65 years versus <65 years, BMI ≥30 kg/m^2 versus <30 kg/m^2, symptom duration ≥5 years versus <5 years, Kellgren–Lawrence grade ≥3 versus <3, total sample size ≥100 versus <100, Jadad score ≥3, and presence or absence of industry funding. *P*-values were two-sided with a significance level <0.05. All analyses were performed using Comprehensive Meta-analysis (version 2.2; Biostat, Englewood, NJ, USA).

Results

Study selection

After screening 1,653 records for eligibility, 29 randomized, saline-controlled trials[21–49] reporting 38 treatment effects from 4,866 unique patients (IAHA: 2,673, control: 2,193) were included in the meta-analysis. The most common reasons for study exclusion included lack of a sham control group, nonrandomized design, or use of HA products not approved in the US. All included trials used a saline control vehicle. A flow diagram of study identification and selection is shown in Figure 1.

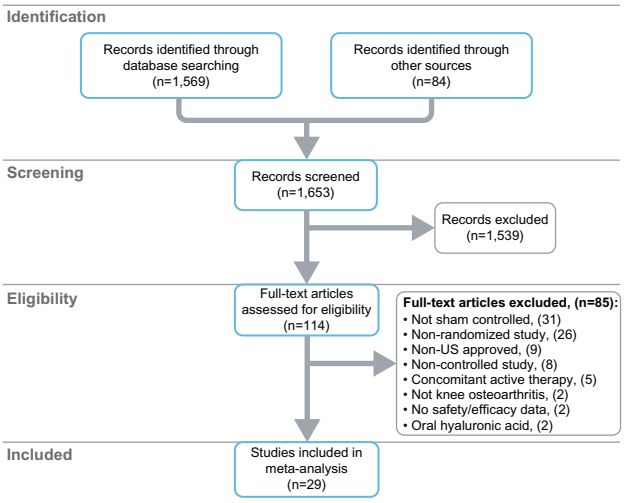

Figure 1 PRISMA flow diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Patient characteristics

Baseline patient characteristics were similar between the IAHA and control groups (Table 1). Approximately two in three patients were female with a mean age of 65 and 62 years in the viscosupplement and control groups, respectively. Patients were typically overweight or obese and presented with OA symptom duration of 4 years on average, with moderate radiographic disease severity.

Study characteristics

Most (28 of 29) studies utilized an unblinded injector, with patients (26 of 29) and outcome assessors (21 of 29) typically fully blinded. The most commonly studied viscosupplements were Hyalgan (18), Synvisc (nine), Supartz/Artzal (six), Orthovisc (three), Gel-One (one), and EUFLEXXA (one). Although Artzal is not marketed in the US, the formulation is identical to that of Supartz and, therefore, was included in the meta-analyses. The total number of injections received by patients ranged from one to five, with the exception of the study of Jubb et al,[36] where patients received three cycles of three injections, each with

Table 1 Baseline patient characteristics

Characteristics	Viscosupplementation	Saline
Patients, n	2,673	2,193
Age, yr, mean (min–max)	65 (53–72)	62 (53–73)
Female, %, median (min–max)	64 (27–92)	65 (22–100)
Body mass index, kg/m^2, mean (min–max)	28 (25–32)	29 (25–33)
Symptom duration, yr, mean (min–max)	4.9 (1.0–9.1)	4.3 (0.8–8.5)
Kellgren–Lawrence grade, mean (min–max)	2.5 (1.9–3.0)	2.5 (1.8–3.5)

Abbreviations: max, maximum; min, minimum; yr, years.

efficacy evaluated after the first cycle. All included studies used phosphate-buffered saline as the control, with the saline volume identical between IAHA and control groups. Only two (7%) studies were clearly independent of industry support (Table 2).

Study quality assessment

Overall, the methodological quality of studies was medium, with a median Jadad score of 3 (range: 2 to 5). Only four (14%) studies were rated with a Jadad score ≥4. The method of randomization and blinding were adequately reported in three (10%) and four (14%) studies, respectively. Patient accountability was adequately detailed in 27 (93%) studies (Table 3).

Viscosupplementation efficacy versus pretreatment

Intra-articular viscosupplement injection resulted in very large treatment effects for knee pain and knee function compared to pretreatment values. The SMD for knee pain was 1.37 (95% CI: 1.12 to 1.61) at 4 to 13 weeks and 1.14 (95% CI: 0.89 to 1.39) at 14 to 26 weeks (both $P<0.001$) (Files S3 and S4). Treatment effects for knee function remained very large although slighter lower with SMDs of 1.16 (95% CI: 0.99

Table 2 Characteristics of studies included in meta-analysis

Study	Blinding[a]				Viscosupplementation details		
	Patient	Injectors	Outcome assessors	Trade[b] name	Total no injections	Total no cycles	Industry-funded study?
Altman and Moskowitz, 1998[21]	1	0	1	Hyalgan	5	1	Yes
Altman et al, 2009[22]	1	0	1	EUFLEXXA	3	1	Yes
Bragantini et al, 1987[23]	0	0	0	Hyalgan	3	1	Unclear
	1	0	0	Hyalgan	3	1	
Brandt et al, 2001[24]	1	0	1	Orthovisc	3	1	Yes
Bunyaratavej et al, 2001[25]	1	0	1	Hyalgan	4	1	Unclear
Carrabba et al, 1995[26]	1	0	1	Hyalgan	5	1	Unclear
					3		
					1		
Cubukçu et al, 2005[27]	0	0	0	Synvisc	3	1	Unclear
Day et al, 2004[28]	1	0	1	Artzal	5	1	Yes
DeCaria et al, 2012[29]	1	0	0	Hyalgan	3	1	No
Diracoglu et al, 2009[30]	1	0	1	Synvisc	4	1	Unclear
Grecomoro et al, 1987[31]	0	0	0	Hyalgan	3	1	Unclear
Henderson et al, 1994[32]	1	0	1	Hyalgan	5	1	Unclear
Huang et al, 2011[33]	1	0	1	Hyalgan	5	1	Yes
Huskisson and Donnelly, 1999[34]	1	0	1	Hyalgan	5	1	Unclear
Jørgensen et al, 2010[35]	1	0	1	Hyalgan	5	1	Yes
Jubb et al, 2003[36]	1	0	1	Hyalgan	3 (9)[c]	1 (3)[c]	Yes
Karlsson et al, 2002[37]	1	0	1	Artzal	3	1	Yes
				Synvisc	3	1	
Kotevoglu et al, 2006[38]	1	0	1	Orthovisc	3	1	Unclear
				Synvisc			
Kul-Panza and Berker, 2010[39]	1	0	1	Orthovisc	3	1	Unclear
Lohmander et al, 1996[40]	1	0	1	Artzal	5	1	Yes
Lundsgaard et al, 2008[41]	1	0	1	Hyalgan	4	1	No
Petrella et al, 2008[42]	1	0	0	Synvisc	3	1	Unclear
				Hyalgan			
Puhl et al, 1993[43]	1	0	1	Artzal	5	1	Yes
Rolf et al, 2005[44]	1	0	1	Synvisc	3	1	Yes
	1	0	1	Artzal	3	1	Yes
Sala and Miguel, 1995[49]	1	0	0	Hyalgan	5	1	Unclear
Scale et al, 1994[45]	1	0	1	Synvisc	2	1	Yes
	1	0	1	Synvisc	3	1	
Strand et al, 2012[46]	1	0	1	Gel-One	1	1	Yes
Wobig et al, 1998[47]	1	1	1	Synvisc	3	1	Yes
Wu et al, 1997[48]	1	0	0	Artzal	5	1	Unclear

Notes: [a]Assessment of blinding adequacy was independent of text description; [b]Artzal is categorized as a US marketed product; Although Artzal is not marketed in the US, the formulation is identical to Supartz, which is marketed in the US; [c]one cycle of three injections each for safety evaluation.

Table 3 Assessment of study quality using Jadad scale

Study	Randomization	Blinding	Accountablility	Total score
Altman and Moskowitz, 1998[21]	1	1	1	3
Altman et al, 2009[22]	1	1	1	3
Bragantini et al, 1987[23]	1	1	1	3
Brandt et al, 2001[24]	1	2	1	4
Bunyaratavej et al, 2001[25]	1	1	0	2
Carrabba et al, 1995[26]	1	1	1	3
Cubukçu et al, 2005[27]	1	0	1	2
Day et al, 2004[28]	1	1	1	3
DeCaria et al, 2012[29]	1	1	1	3
Diracoglu et al, 2009[30]	1	1	1	3
Grecomoro et al, 1987[31]	1	1	1	3
Henderson et al, 1994[32]	1	1	1	3
Huang et al, 2011[33]	1	1	1	3
Huskisson and Donnelly, 1999[34]	1	1	1	3
Jørgensen et al, 2010[35]	1	1	1	3
Jubb et al, 2003[36]	1	1	1	3
Karlsson et al, 2002[37]	1	1	1	3
Kotevoglu et al, 2006[38]	1	1	1	3
Kul-Panza and Berker, 2010[39]	1	1	1	3
Lohmander et al, 1996[40]	1	1	1	3
Lundsgaard et al, 2008[41]	2	2	1	5
Petrella et al, 2008[42]	1	1	1	3
Puhl et al, 1993[43]	2	2	1	5
Rolf et al, 2005[44]	1	1	1	3
Sala and Miguel, 1995[49]	1	1	1	3
Scale et al, 1994[45]	1	1	0	2
Strand et al, 2012[46]	2	2	1	5
Wobig et al, 1998[47]	1	1	1	3
Wu et al, 1997[48]	1	1	1	3

to 1.34) and 1.07 (95% CI: 0.84 to 1.30), respectively (both $P<0.001$) (Files S5 and S6). There was high heterogeneity (I^2=74% to 92%, all $P<0.001$) for all treatment effects, with evidence of publication bias for knee pain (Files S7 and S8), but not knee function (Files S9 and S10), in both analysis windows.

Viscosupplementation efficacy versus saline control

Compared to controls, the SMD for knee pain was 0.43 (95% CI: 0.26 to 0.60) at 4 to 13 weeks (File S11) and 0.38 (95% CI: 0.21 to 0.55) at 14 to 26 weeks (Figure 2) (both $P<0.001$). Knee function SMD was 0.34 (95% CI: 0.16 to 0.51) and 0.32 (95% CI: 0.18 to 0.45), respectively, at the same time intervals (both $P<0.001$) (File S12; Figure 3). Heterogeneity among studies was high for knee pain (I^2=73% to 75%, both $P<0.001$) and moderate for knee function (I^2=54% to 69%, both $P<0.01$). Publication bias was evident for both knee pain treatment effects (Files S13 and S14) and for knee function at 4 to 13 weeks (File S15), but not for knee function at 14 to 26 weeks (File S16).

Viscosupplementation safety versus saline control

There were no statistically significant RDs between viscosupplementation and controls for any safety outcome. The risk of SAEs was similar between viscosupplementation and saline (RD =0.7%, 95% CI: −0.2% to 1.5%, P=0.12) (Figure 4). No SAE in any trial was related to injection of viscosupplement or saline. The risk of patient withdrawal from the study for any reason was identical between treatment groups (RD =0.0%, 95% CI: −1.6% to 1.6%, P=1.0) (File S17). The risk of patient withdrawal due to an AE was also similar with viscosupplementation versus control (RD =0.2%, 95% CI: −0.4% to 0.8%, P=0.46) (Figure 5). There was minimal heterogeneity in safety outcomes among studies (all I^2=0%) with no evidence of publication bias for any safety outcome (Files S18–S20).

Subgroup analyses

We performed predefined subgroup analyses to observe the influence of study- and patient-related characteristics on knee pain, knee function, and SAEs. Study-design factors,

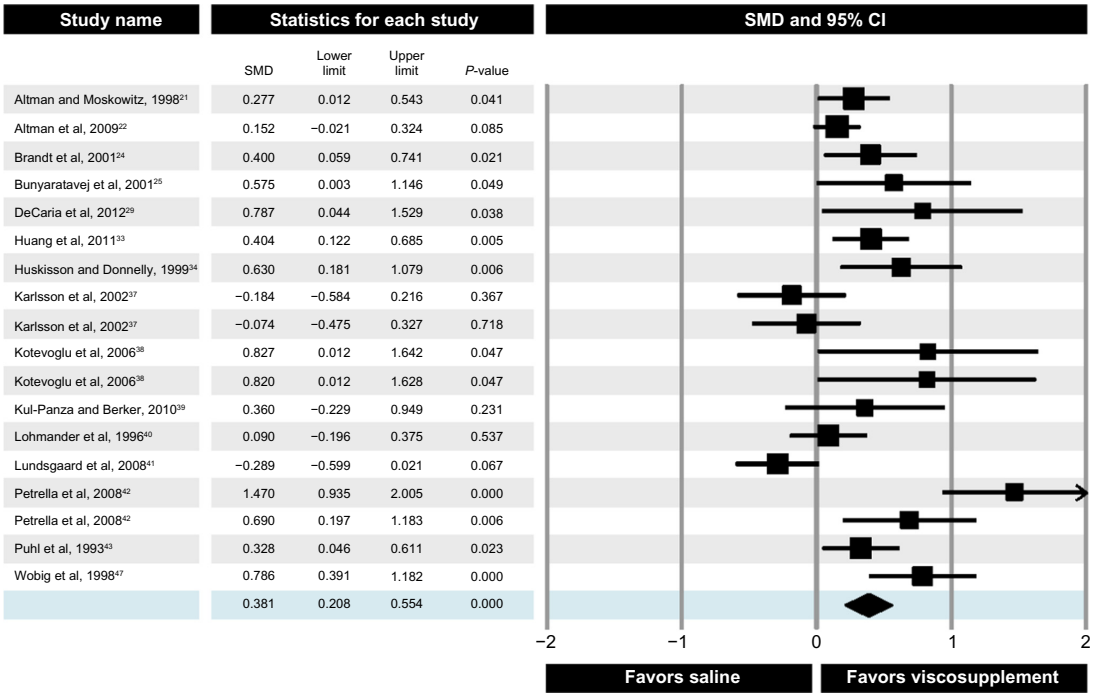

Figure 2 Forest plot of viscosupplementation versus saline controls on knee pain at 14 to 26 weeks.
Abbreviations: CI, confidence interval; SMD, standardized mean difference.

specifically smaller sample size and lower study quality, were associated with greater knee pain (Table 4) and function (Table 5) treatment effects. Studies with higher proportions of female patients yielded better knee function outcomes. No other factors including age, BMI, symptom duration, Kellgren–Lawrence grade, or industry funding were associated with knee pain or function outcomes. No factors influenced the risk of SAEs (Table 6).

Sensitivity analyses

In order to explore the impact of single studies on the main outcomes, we performed a "one study removed" analysis by

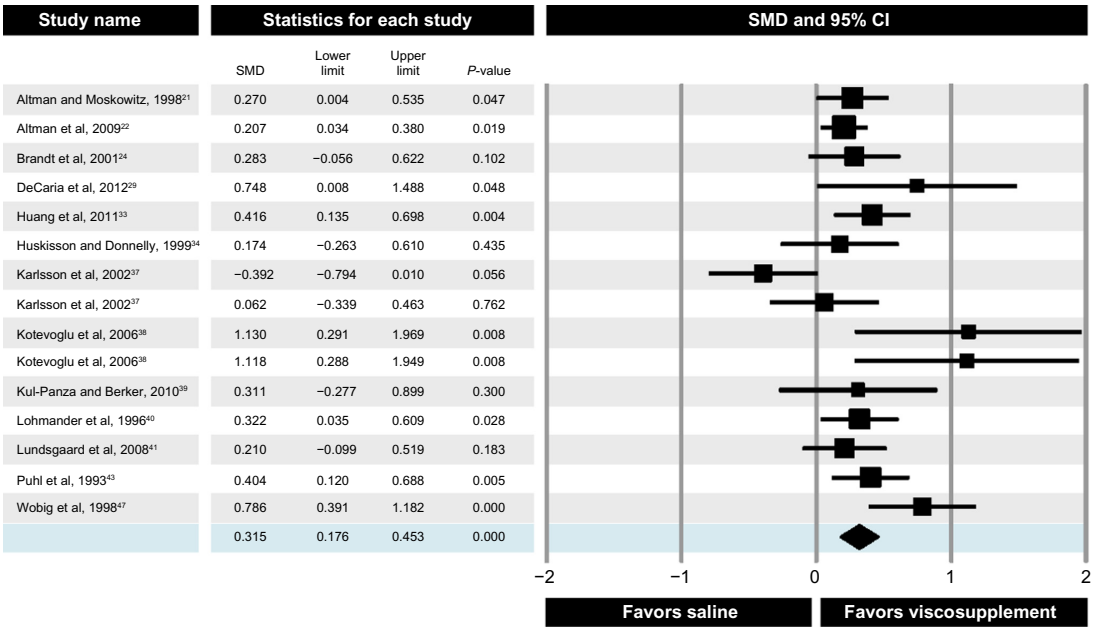

Figure 3 Forest plot of viscosupplementation versus saline controls on knee function at 14 to 26 weeks.
Abbreviations: CI, confidence interval; SMD, standardized mean difference.

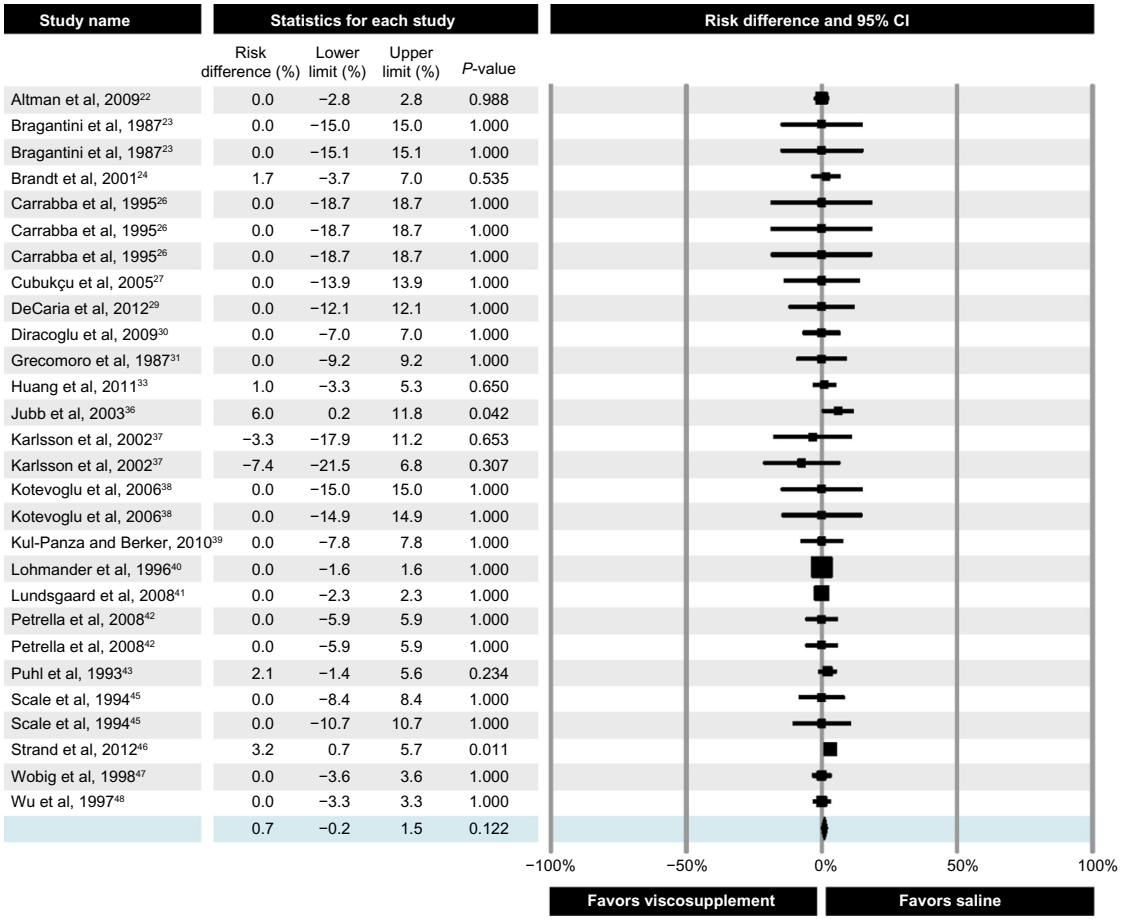

Figure 4 Forest plot of viscosupplementation versus saline controls on risk of serious adverse events.
Abbreviation: CI, confidence interval.

reestimating the meta-analysis after removing one study at a time for each main outcome. No single study had a major influence on any outcome (File S21). Additionally, we performed an analysis of safety outcomes using the odds ratio with no correction for zero total event trials as the statistic of interest, the method used in the meta-analysis of Rutjes et al.[12] This analysis demonstrated no differences in risk between groups for any outcome (File S22). Overall, the results of the sensitivity analyses corroborated those of the main meta-analysis.

Comparison of US- versus non-US-approved viscosupplements

We extended the original literature search using the same methodology to include saline-controlled studies of non-US-approved viscosupplements and compared outcomes to those of US-approved viscosupplements. Nine studies of non-US-approved viscosupplements were included in this analysis.[42,50–57] All knee pain and function treatment effects with non-US-approved viscosupplements were negligible to small (SMD range: −0.02 to 0.26) and were statistically inferior to US-approved products at the 4 to 13 week window, but not at 14 to 26 weeks. There were no statistically significant RDs in any safety outcome between US- and non-US-approved viscosupplements (File S23).

Discussion

We conducted the first systematic review and meta-analysis of US-approved HA products on knee OA symptoms. Overall, we conclude that intra-articular injection of US-approved viscosupplements is safe and efficacious in patients with symptomatic knee OA. Several systematic reviews and meta-analyses have been published on this topic, with the SMD of viscosupplementation versus a control group for efficacy outcomes ranging from 0.0 to 0.46.[5,6,9,12,58] For comparison, the saline-adjusted SMD in the current meta-analysis ranged from 0.32 to 0.43, depending on outcome and time window. Another notable finding was that, while safe, the efficacy of non-US-approved viscosupplements was poor. The reason for the differences in treatment effect with US- versus

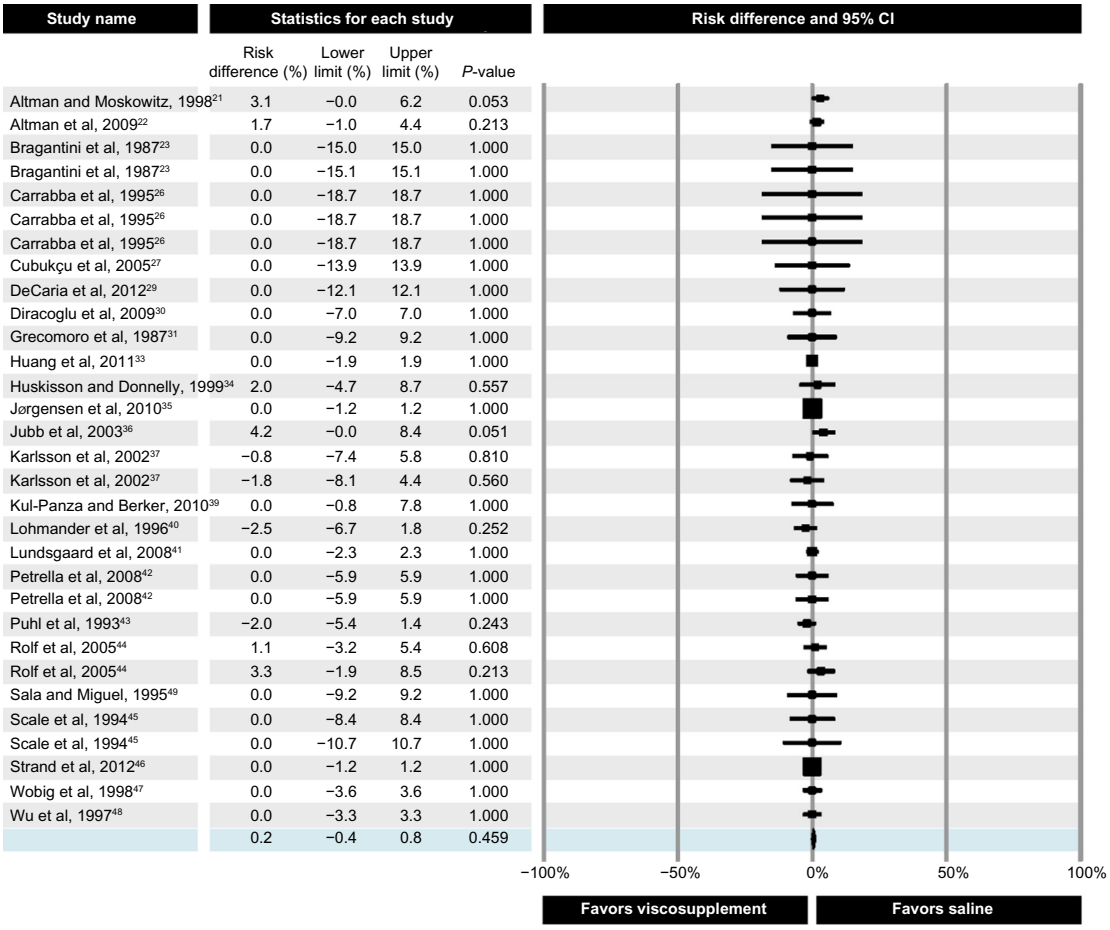

Figure 5 Forest plot of viscosupplementation versus saline controls on risk of adverse event-related patient withdrawals.
Abbreviation: CI, confidence interval.

non-US-approved viscosupplements is unknown, but may be related to the stringency of regulatory and clinical trial requirements among countries. Additional research in this area is warranted.

The use of the effect size statistic to infer clinically meaningful changes in efficacy outcomes is frequently misinterpreted. For example, the control group-corrected treatment effect of viscosupplementation is frequently cited in meta-analyses. However, it would be erroneous to estimate clinical relevance or responder rates from this statistic. In order to estimate the clinical benefit to a patient, the pretreatment to posttreatment effect size in the viscosupplement group, not the control group-corrected effect size, is the most appropriate statistic. Rutjes et al[12] report an effect size of 0.37 (corrected for control changes) and then erroneously state that this is equivalent to an improvement in knee pain of 0.9 cm on a 10 cm scale. In fact, Rutjes et al's[12] reference for this statement[59] was derived from other papers,[60–63] which clearly state that pretreatment to posttreatment treatment effects, not control group-corrected treatment effects, should be used to make this calculation.

The current meta-analysis is the only known report to cite the pretreatment to posttreatment SMD. Injection of US-approved viscosupplements resulted in an SMD for knee pain of 1.37 at 4 to 13 weeks and 1.14 at 14 to 26 weeks. SMDs for knee function were 1.16 and 1.07, respectively. These values represent very large treatment effects for viscosupplementation and are independent of changes reported in saline control groups. Using the assumption that a standardized effect size of 0.37 equates to a 0.9 cm improvement (on a 10 cm scale) in knee pain or function, the pretreatment to posttreatment treatment effects for US-approved viscosupplements would be equal to improvements of 2.8 to 3.3 cm for knee pain and 2.6 to 2.8 cm for knee function (on a 10 cm scale). Importantly, the lower-bound confidence limits for all efficacy outcomes (ranging from 0.84 to 1.12) are substantially higher than the minimum threshold for clinical importance (0.37).

Table 4 Subgroup analysis of study- and patient-related factors on saline-corrected knee pain

Factor	SMD	95% CI	*P*-value
Age			
≥65 years (n=11)	0.27	0.03 to 0.51	0.20
<65 years (n=23)	0.46	0.29 to 0.64	
Body mass index			
≥30 kg/m^2 (n=5)	0.28	0.00 to 0.56	0.72
<30 kg/m^2 (n=18)	0.34	0.17 to 0.51	
Female proportion			
≥67% (n=15)	0.54	0.30 to 0.77	0.15
<67% (n=19)	0.32	0.14 to 0.49	
Symptom duration			
≥5 years (n=9)	0.35	0.10 to 0.60	0.07
<5 years (n=15)	0.66	0.43 to 0.89	
Kellgren–Lawrence grade			
≥3 (n=6)	0.07	−0.28 to 0.42	0.06
<3 (n=12)	0.47	0.24 to 0.70	
Kellgren–Lawrence grade IV			
≥ any (n=6)	0.11	−0.24 to 0.46	0.25
< none (n=11)	0.35	0.14 to 0.57	
Total sample size			
≥100 (n=14)	0.17	0.01 to 0.33	<0.001
<100 (n=20)	0.67	0.47 to 0.86	
Jadad score			
≥3 (n=30)	0.34	0.20 to 0.48	0.03
<3 (n=4)	0.87	0.42 to 1.33	
Industry funding			
Yes or unclear (n=32)	0.41	0.27 to 0.56	0.21
No (n=2)	0.04	−0.52 to 0.61	

Abbreviations: CI, confidence interval; SMD, standardized mean difference.

Table 5 Subgroup analysis of study- and patient-related factors on saline-corrected knee function

Factor	SMD	95% CI	*P*-value
Age			
≥65 years (n=7)	0.17	−0.07 to 0.40	0.07
<65 years (n=17)	0.42	0.26 to 0.59	
Body mass index			
≥30 kg/m^2 (n=4)	0.28	−0.01 to 0.56	0.91
<30 kg/m^2 (n=15)	0.30	0.13 to 0.46	
Female proportion			
≥67% (n=9)	0.63	0.36 to 0.89	0.01
<67% (n=15)	0.25	0.10 to 0.39	
Symptom duration			
≥5 years (n=6)	0.30	0.02 to 0.59	0.15
<5 years (n=11)	0.58	0.33 to 0.83	
Kellgren–Lawrence grade			
≥3 (n=4)	0.45	0.09 to 0.81	0.86
<3 (n=8)	0.41	0.16 to 0.66	
Kellgren–Lawrence grade IV			
≥ any (n=2)	0.25	−0.17 to 0.67	0.78
< none (n=9)	0.31	0.13 to 0.50	
Total sample size			
≥100 (n=13)	0.22	0.08 to 0.35	0.001
<100 (n=11)	0.69	0.44 to 0.93	
Jadad score			
≥3 (n=21)	0.28	0.15 to 0.40	0.002
<3 (n=3)	1.05	0.57 to 1.52	
Industry funding			
Yes or unclear (n=22)	0.35	0.21 to 0.49	0.86
No (n=2)	0.30	−0.18 to 0.78	

Abbreviations: CI, confidence interval; SMD, standardized mean difference.

We found that neither US-approved nor non-US-approved viscosupplements were associated with increased safety risks. These findings are in contrast to those of Rutjes et al[12] who concluded that viscosupplementation increased the risk of SAEs and AE-related patient withdrawals. However, there are several important distinctions between the two meta-analyses that are worth mentioning. First, although the calculated risk of SAEs was marginally higher with viscosupplementation versus controls in the Rutjes study, the treatment association of the reported SAE was not considered. In our analysis, no SAE was related to treatment. Second, the safety analysis and conclusions in the Rutjes paper were heavily influenced by inclusion of unpublished, unverifiable data. In contrast, we only included data from full-text manuscripts published in peer-reviewed journals. Lastly, Rutjes et al analyzed all safety data using an odds ratio without a correction factor for zero total event trials, a statistic that excludes zero total event trials. Considering that 30 of 38 SAE treatment effects in the current meta-analysis reported zero total events, use of such an analysis is inadvisable since most data are disregarded.

Our meta-analysis is associated with several issues that may influence interpretation. Most, but not all, studies excluded patients with end-stage (Kellgren–Lawrence grade IV or equivalent) knee OA and, therefore, the efficacy of viscosupplements in these patients cannot be determined. Due to sample size considerations, we did not attempt to analyze treatment effects by viscosupplement type or molecular weight. Lastly, efficacy outcomes were inconsistent across studies and influenced by study design factors and publication bias. Strengths of this meta-analysis are inclusion of only randomized, saline-controlled trials, structured data extraction methodology, inclusion of all zero total event trials in safety analyses, and sensitivity analyses that accounted for choice of statistical test and potentially influential studies. Finally, it should be noted that our group previously published a brief summary of main findings from this meta-analysis.[64] The current paper extends that initial work by providing a comprehensive and detailed accounting of additional aspects of the meta-analysis not previously reported, including the detailed search strategy, PRISMA flow diagram, characteristics and quality assessment of included studies, detailed forest

Table 6 Subgroup analysis of study- and patient-related factors on serious adverse events

Factor	RD (%)	95% CI (%)	*P*-value
Age			
≥65 years (n=10)	0.1	−1.4 to 1.6	0.39
<65 years (n=18)	0.9	−0.1 to 1.9	
Body mass index			
≥30 kg/m^2 (n=5)	1.0	−1.0 to 3.1	0.75
<30 kg/m^2 (n=15)	0.7	−0.3 to 1.7	
Female proportion			
≥67% (n=12)	1.5	−1.0 to 4.1	0.48
<67% (n=16)	0.6	−0.3 to 1.5	
Symptom duration			
≥5 years (n=7)	0.5	−1.1 to 2.1	0.26
<5 years (n=13)	1.7	0.2 to 3.3	
Kellgren–Lawrence grade			
≥3 (n=5)	0.0	−1.7 to 1.7	0.053
<3 (n=9)	2.4	0.7 to 4.2	
Kellgren–Lawrence grade IV			
≥ any (n=4)	0.0	−2.2 to 2.2	0.15
< none (n=7)	2.0	0.4 to 3.6	
Total sample size			
≥100 (n=12)	0.8	−0.1 to 1.7	0.57
<100 (n=16)	0.0	−2.4 to 2.4	
Jadad score			
≥3 (n=25)	0.7	−2.0 to 1.5	0.83
<3 (n=3)	0.0	−0.6 to 0.6	
Industry funding			
Yes or unclear (n=26)	0.8	−0.1 to 1.7	0.53
No (n=2)	0.0	−2.3 to 2.3	

Abbreviations: CI, confidence interval; RD, risk difference.

plots and bias plots for all safety and efficacy outcomes, and results of subgroup and sensitivity analyses.

Conclusion

Intra-articular injection of US-approved viscosupplements is safe and efficacious through 26 weeks in patients with symptomatic knee OA. Limitations of this meta-analysis were significant heterogeneity in efficacy outcomes among included studies and smaller treatment effects in higher quality trials.

Author contributions

LEM contributed to study design and conception, literature search, data extraction, data analysis, data interpretation, drafting of the manuscript, and provided critical revision of the manuscript for intellectual content. JEB contributed to study design and conception, data extraction, data interpretation, drafting of the manuscript, and provided critical revision of the manuscript for intellectual content. VS, LFM, and WRB contributed to study design and conception, drafting of the manuscript and provided critical revision of the manuscript for intellectual content. All authors read and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

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