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ORIGINAL RESEARCH

The Impact of Excluding Patients with End-Stage Knee Disease in Intra-Articular Hyaluronic Acid Trials: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: The Kellgren–Lawrence (K–L) grade is the most commonly used measure of radiographic disease severity in knee osteoarthritis (OA). Studies suggest that intra-articular hyaluronic acid (IA-HA) should only be considered in cases of early stage knee OA. The purpose of this review was to determine if trials administering IA-HA in early-moderate knee OA patients demonstrated greater pain relief than studies that also included patients with end-stage disease.

Methods: We conducted a systematic search of the literature to identify randomized controlled trials (RCT) comparing IA-HA with saline injections and that diagnosed disease severity using the K–L grade criteria. The primary outcome was mean change in pain from baseline at 4–13 weeks and 22–27 weeks. Safety was evaluated on the total number of participants experiencing a treatment-related adverse event (AE).
Results: Twenty RCTs were included. In the early-moderate OA subgroup, the mean change in pain scores was statistically significant favoring IA-HA from baseline to 4–13 weeks [SMD = − 0.30, 95% CI − 0.44 to − 0.15, $p < 0.0001$] and within 22–27 weeks [SMD = − 0.27, 95% CI − 0.39 to − 0.16, $p < 0.00001$]. No significant differences were observed in the late OA subgroup. IA-HA was associated with a significantly greater risk of treatment-related AEs relative to saline in the late OA subgroup [RR = 1.76, 95% CI 1.16–2.67, $p = 0.008$].
Conclusion: IA-HA provides significant pain relief compared to saline for patients with early-moderate knee OA, compared to cohorts including patients with end-stage OA (KL grade 4), with no increase in the risk of treatment-related AEs, up to 6 months. Patients with end-stage disease had lower levels of pain relief and may be diluting study results if included in the treatment cohort.
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INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the USA, estimated to affect over 30 million adults, and the prevalence is expected to increase for the foreseeable future [1, 2]. Joint pain is a common complaint among individuals with OA and a primary reason for them to seek medical care [2, 3]. As the disease is chronic and nonfatal, identifying effective measures to not only prevent but also treat it will have significant impacts at both the clinical and socioeconomic levels [1, 4]. Osteoarthritis may occur in any joint, but knee OA is one of the most common manifestations of this disease and, as the knee takes on a substantial amount of the weight-bearing load, can lead to significant disability if left untreated [1, 4].

While surgical intervention is typically reserved for the most severe OA, more conservative therapies are initiated earlier in the disease process in effort to alleviate symptoms and delay progression. Treatment with intra-articular hyaluronic acid (IA-HA) injections is one of these options, although there is inconsistency in its recommendations across knee OA guidelines [4–7]. HA is a naturally occurring substance present in synovial fluid and the quality and quantity of HA are reduced in arthritic knees [3, 8]. IA-HA injections are typically indicated for patients who are non-responders to nonpharmacological and pharmacological therapies or experience adverse effects from these treatments [3, 8, 9]. In addition to restoring the viscoelasticity of the synovial fluid, IA-HA may also have anti-inflammatory and antinociceptive properties, and stimulate in vivo high molecular weight (HMW) HA synthesis [8]. Both basic science studies and clinical trials have demonstrated the potential benefit of HA injections [4]. While a number of different HA products are available in various injection regimens, literature has demonstrated there are also significant differences in molecular and rheological properties [4, 8, 10, 11].

Radiographs play an important role in the diagnosis of OA [1, 2]. In clinical trials investigating knee OA, disease severity is most commonly assessed by the Kellgren–Lawrence (KL) criteria [1, 2]. This system grades OA into five categories of severity, from 0 to 4, with lower grades representing greater joint space and less disease severity [12]. Most IA-HA studies have focused on its use in patients with early to moderate knee OA (K–L grade ≤ 3), suggesting that HA injections should only be considered earlier in the disease process and that studies that have included patients with end-stage disease (K–L grade 4) have contributed to the current controversy surrounding their use [4, 13]. A number of prior studies have demonstrated a greater response to HA therapy when baseline radiographic presentation was less severe [14–16].

The purpose of this review was to determine if the inclusion of end-stage OA (KL grade 4) participants reduced the measured effectiveness of IA-HA in randomized controlled trials measuring its effect on knee OA pain.

METHODS

Literature Search

A comprehensive literature search for relevant articles was conducted using a detailed search of the MEDLINE, EMBASE, and PubMed databases (Supplementary Material). The inclusion criteria were (1) blinded randomized controlled trial (RCT) comparing IA-HA with intra-articular saline injections; (2) knee pain or treatment-related adverse events (AEs) were a reported outcome; (3) described disease severity using the K–L grade criteria; and (4) articles that were published in English. After the list of eligible studies was finalized, a manual search of relevant reference lists was conducted to ensure that no potentially eligible trials were missed. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Search Results

The literature searched identified 2198 citations (Fig. 1). After titles and abstracts were screened, 166 were included for full-text review. Nineteen studies met the predefined inclusion criteria [14, 17–34] and an additional study was hand-selected [35], for a total of 20 trials; however, one of these studies was only included in the analysis of treatment-related adverse events [29]. The hand-selected study was retrieved from the reference list of previously published articles regarding IA-HA use for knee osteoarthritis.

Data Extraction and Outcome Measures

Data extraction consisted of study characteristics, patient demographics, and reported outcome and safety measures. The primary outcome measure was the mean change in knee pain score from baseline at two separate visit windows: (1) 4–13 weeks (earlier visit) and (2) 22–27 weeks (later visit). The Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores were extracted whenever reported. If the WOMAC pain scores were not reported, an a priori hierarchy of outcomes was used to extract the next most relevant pain measure. The hierarchy used was taken from a previous meta-analysis, and was as follows:

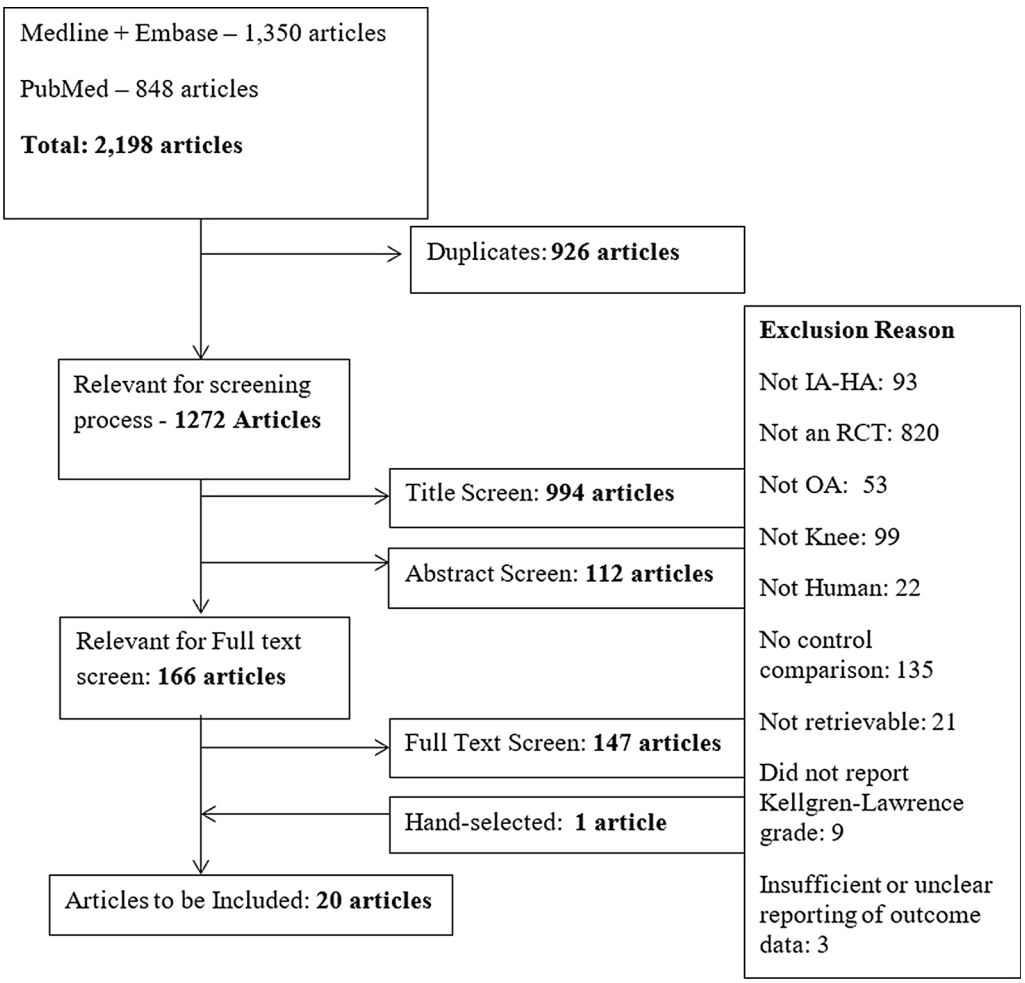

Fig. 1 Flow diagram of search results

WOMAC pain, visual analog scale (VAS) pain on activity/walking, VAS pain on weight-bearing, VAS pain at rest, or other pain outcomes (Knee Injury and Osteoarthritis Outcome Score (KOOS), Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS), Index of Severity for Osteoarthritis for the Knee (ISK) assessment, and WOMAC total score [11]. If data for these outcomes were not reported in a given study, it was not included in the primary outcome. Safety data was also extracted when possible on the total number of participants experiencing a treatment-related AE. If data for these outcomes were not reported in a given study, it was not included in the safety analysis. Data from the intent-to-treat population was used whenever possible. Data extraction was completed in duplicate by two independent reviewers.

Data Analysis

Standardized mean differences (SMD) and relative risks (RRs) were analyzed using the Cochrane Review Manager 5.3 software [36]. For continuous outcomes, a negative SMD represented a result favoring IA-HA, while a positive effect estimate represented a result favoring IA-saline. Missing standard deviations were estimated on the basis of the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [37]. For binary outcomes, an RR less than 1 favored IA-HA, while a value greater than 1 favored IA-saline. Effect size estimates were analyzed using a generic inverse variance statistical method and a random-effects analysis model with a 95% confidence interval (CI). The number of participants who experienced a treatment-related AE was analyzed under a dichotomous outcome assessment using Mantel–Haenzel statistical method and a random-effects analysis model with a 95% CI. Heterogeneity between the included trials was measured using the I^2 statistic.

Studies were stratified into two groups: (1) studies with early to moderate (early-moderate) knee OA participants (i.e., K–L grade $\leq$ 3 only), and (2) studies with early to late (late) knee OA patients (i.e., the authors enrolled patients with K–L grade 1–4 knee OA) based on the trial's demographic characteristics. If a trial had less than 5% of the patients with a baseline K–L grade of 4, the trial was included in the early-moderate OA subgroup.

Sensitivity Analysis

A sensitivity analysis was conducted to determine if single-blinded studies and the non-blinded study had a significant impact on the total treatment effect of IA-HA on knee pain vs IA-saline at 13-week and 26-week follow-up periods. To accomplish this, single-blinded studies were removed from analyses to determine if they had a significant impact on treatment efficacy. Additionally, we conducted a sensitivity analysis to determine if the hand-selected study had a significant impact on the total treatment effect of IA-HA on knee pain vs IA-saline. To accomplish this, the hand-selected study was removed from analyses to determine if it had a significant impact on treatment efficacy.

RESULTS

Study Characteristics and Demographics

The sample sizes of the included trials ranged from 12 to 588 patients (Table 1). Sixteen studies (80.0%) were double-blinded RCTs and four (20.0%) were single-blinded. The IA-HA formulations used across these trials were Adant, Durolane, Euflexxa, Fermathron Plus, Gel-One, Hyalgan, Orthovisc, Monovisc, and Synvisc; the specific brand was not reported in two studies.

The average ages and BMIs ranged from 53 to 73 years and 25 to 33 kg/m [2], respectively, (Table 2). Of 19 studies, 16 were included in the early-moderate OA subgroup and the other three were included in the late OA subgroup. The other study, Henderson et al. presented their results for patients with K–L grade 2 and those with K–L grade 3–4; therefore this study was represented in both subgroups as Henderson 1994a (early-moderate OA subgroup) and Henderson 1994b (late OA subgroup) [25].

Table 1 Study characteristics of the included trials

Study	Sample size	Countries	Study design	IA-HA formulation	Outcome measure for pain
Altman et al. (2004)	346	USA, Canada, Sweden	Double-blinded RCT	Durolane	WOMAC pain, 0–20 Likert
Altman et al. (2009)	588	USA	Double-blinded RCT	Euflexxa	VAS pain, 100 mm
Arden et al. (2014)	218	Sweden, German, UK	Double-blinded RCT	Durolane	WOMAC pain, 0–20 Likert
Brandt et al. (2001)	226	USA	Double-blinded RCT	Orthovisc	WOMAC pain, 5–25 Likert
Chevalier et al. (2010)	253	UK, France, Czech Republic, Germany, Belgium, the Netherlands	Double-blinded RCT	Synvisc	WOMAC pain, 0–4 Likert
Creamer et al. (1994)	12	UK	Single-blinded RCT	Hyalgan	VAS pain, 100 mm
Cubukcu et al. (2005)	40	Turkey	Single-blinded RCT	Synvisc	WOMAC pain, 5–25 Likert
DeCaria et al. (2012)	30	Canada	Double-blinded RCT	Hyalgan	WOMAC pain, 0–20 Likert
Diracoglu et al. (2009)	63	Turkey	Double-blinded RCT	Synvisc	WOMAC pain, 0–20 Likert
Hangody et al. (2017)	368	Europe, Canada	Double-blinded RCT	Monovisc	WOMAC pain, 100 mm
Henderson et al. (1994)	91	UK	Double-blinded RCT	Hyalgan	VAS pain, 100 mm
Huang et al. (2011)	200	Taiwan	Double-blinded RCT	Hyalgan	WOMAC pain, 100 mm
Huskisson et al. (1999)	100	UK	Single-blinded RCT	Hyalgan	VAS pain, 100 mm
Lundsgaard et al. (2008)	308	UK, the Netherlands	Double-blinded RCT	Hyalgan	VAS pain, 100 mm
Navarro-Sarabia et al. (2011)	306	Spain	Double-blinded RCT	Adant	WOMAC pain, 100 mm
Neustadt et al. (2005)	229	USA, Canada	Double-blinded RCT	Orthovisc	WOMAC pain, 0–500
Petrella et al. (2006)	106	Canada	Double-blinded RCT	Suplasyn	WOMAC pain, 5–25 Likert

Table 1 continued

Study	Sample size	Countries	Study design	IA-HA formulation	Outcome measure for pain
Sezgin et al. (2005)	41	Turkey	Single-blinded RCT	Orthovisc	WOMAC pain, 5–25 Likert
Strand et al. (2012)	379	Japan	Double-blinded RCT	Gel-ONE	WOMAC pain, 100 mm
Van der Weegen et al. (2015)	196	The Netherlands	Double-blinded RCT	Fermathron plus	VAS pain, 100 mm

Pain at 4–13 Weeks (Earlier Visit)

In the early-moderate OA subgroup (16 trials; $n = 1578$ for IA-HA, $n = 1341$ for saline), the mean change in pain scores from baseline within this visit window was statistically significant in favor of IA-HA [SMD = − 0.30, 95% CI − 0.44 to − 0.15, $p < 0.0001$; $I^2 = 68\%$] (Fig. 2). In the late OA subgroup (4 trials; $n = 288$ for IAHA, $n = 278$ for saline), there was no significant effect between IA-HA and saline [SMD = 0.28, 95% CI − 0.12 to 0.68, $p = 0.17$; $I^2 = 72\%$].

The test for subgroup differences (early-moderate OA versus late OA) was statistically significant ($p = 0.008$). The funnel plot revealed no evidence of publication bias (Fig. 3).

Pain at 22–27 Weeks (Later Visit)

In the early-moderate OA subgroup (9 trials; $n = 1058$ for IA-HA, $n = 981$ for saline), the mean change in pain scores from baseline within this visit window was statistically significant in favor of IA-HA [SMD = − 0.27, 95% CI − 0.39 to − 0.16, $p < 0.00001$; $I^2 = 38\%$] (Fig. 4). In the late OA subgroup (2 trials; $n = 254$ for IAHA, $n = 254$ for saline), there was no significant effect between IA-HA and saline [SMD = 0.03, 95% CI − 0.14 to 0.21, $p = 0.72$; $I^2 = 3\%$].

The test for subgroup differences (early-moderate OA versus late OA) was statistically significant ($p = 0.005$). The funnel plot revealed no evidence of publication bias (Fig. 5).

Treatment-Related AEs

In the early-moderate OA subgroup (9 trials; $n = 1304$ for IA-HA, $n = 1104$ for saline), there was no significant difference in the risk of treatment-related AEs between IA-HA and saline injections [RR = 1.03, 95% CI 0.89–1.20, $p = 0.68$; $I^2 = 36\%$] (Fig. 6). In the late OA subgroup (3 trials; $n = 230$ for IAHA, $n = 232$ for saline), IA-HA was associated with a significantly greater risk of treatment-related AEs relative to saline [RR = 1.76, 95% CI 1.16–2.67, $p = 0.008$; $I^2 = 0\%$].

The test for subgroup differences (early-moderate OA versus late OA) was statistically significant ($p = 0.02$).

Sensitivity Analysis

Three single-blinded studies and one non-blinded were removed in the sensitivity analysis [23, 24, 29, 34]. The pooled effect size remained statistically significant with little change in total effect size at 13-week (SMD = − 0.16 [− 0.32, − 0.01], $P = 0.004$) and 26-week (SMD = − 0.19 [− 0.30, − 0.07], $P = 0.001$) follow-up periods.

At 13-week and 26-week follow-up periods, the pooled effect size remained statistically significant with little change in total effect size when the hand-selected study was removed from the analysis. Similar results were observed when single-blinded studies were removed from analyses; total treatment efficacy and subgroup differences remained statistically significant at 13 weeks and 26 weeks.

Table 2 Demographic characteristics of the included trials

Study	IA-HA arm					Control arm				
	n	Mean age	Mean BMI	% male	K–L grade, (%)	*n*	Mean age	Mean BMI	% male	K–L grade, *n* (%)
Altman (2004)	172	62.9	M: 29.5 F: 31.3	54.1	1–3: 76.7 4: 23.3	174	63.3	M: 29.0 F: 29.8	36.2	1–3: 74.1 4: 25.9
Altman (2009)	291	62.5	32.4	37.0	1–3: 100.0 4: 0.0	295	60.8	33.0	37.0	1–3:100.0 4: 0.0
Arden (2014)	108	64.5	M: 28.2 F: 26.4	45.0	1–3: 100.0 4: 0.0	110	60.9	M: 28.1 F: 26.9	54.0	1–3: 100.0 4: 0.0
Brandt (2001)	114	65.0	32.0	37.0	1–3: 100.0 4: 0.0	112	67.0	30.1	37.0	1–3: 100.0 4: 0.0
Chevalier (2010)	124	63.6	29.1	25.8	1–3: 100.0 4: 0.0	129	62.5	29.8	31.8	1–3: 99.2 4: 0.8
Creamer (1994)	12	NR	NR	0.0	1–3: 66.7 4: 33.3	12	NR	NR	0.0	1–3: 66.7 4: 33.3
Cubukcu (2005)	30	52.6	NR	30.0	1–3: 100.0 4: 0.0	10	57.6	NR	0.0	1–3: 100.0 4: 0.0
DeCaria (2012)	15	71.9	30.5	53.0	1–3: 100.0 4: 0.0	15	72.9	29.4	53.0	1–3: 100.0 4: 0.0
Diracoglu (2009)	42	59.4	31.1	10.0	1–3: 100.0 4: 0.0	21	56.2	31.3	0.0	1–3: 100.0 4: 0.0
Hangody (2017)	150	59.2	28.4	34.0	1–3: 99.3 4: 0.7	69	58.0	29.1	26.1	1–3: 100.0 4: 0.0
Henderson (1994)	40	NR	NR	NR	1–3: 82.2 4: 17.8	44	NR	NR	NR	1–3: 71.7 4: 28.3
Huang (2011)	100	65.9	25.7	26.0	1–3: 100.0 4: 0.0	100	64.2	25.4	22.0	1–3: 100.0 4: 0.0
Huskisson (1999)	50	65.8	NR	24.0	1–3: 100.0 4: 0.0	50	64.8	NR	42.0	1–3: 100.0 4: 0.0
Lundsgaard (2008)	82	68.8	29.6	42.9	1–3: 63.1 4: 36.9	80	69.6	29.3	47.6	1–3: 61.2 4: 38.8
Navarro-Sarabia (2011)	153	63.0	28.4	16.3	1–3: 100.0 4: 0.0	153	63.9	28.7	16.3	1–3: 100.0 4: 0.0

Table 2 continued

Study	IA-HA arm					Control arm				
	n	Mean age	Mean BMI	% male	K–L grade, (%)	*n*	Mean age	Mean BMI	% male	K–L grade, *n* (%)
Neustadt (2005)	115	58.4	28.9	54.8	1–3: 100.0 4: 0.0	114	59.1	29.4	50.0	1–3: 100.0 4: 0.0
Petrella (2006)	53	63.9	NR	56.9	1–3: 100.0 4: 0.0	53	62.4	NR	53.7	1–3: 100.0 4: 0.0
Sezgin (2005)	22	59.9	30.2	18.2	1–3: 100.0 4: 0.0	19	59.4	29.3	31.6	1–3: 100.0 4: 0.0
Strand (2012)	247	60.9	28.3	40.5	1–3: 100.0 4: 0.0	128	60.3	28.7	39.8	1–3: 100.0 4: 0.0
Van der Weegen (2015)	99	58.7	28.6	49	1–3: 100.0 4: 0.0	97	60.1	29.3	50	1–3: 100.0 4: 0.0

NR not reported

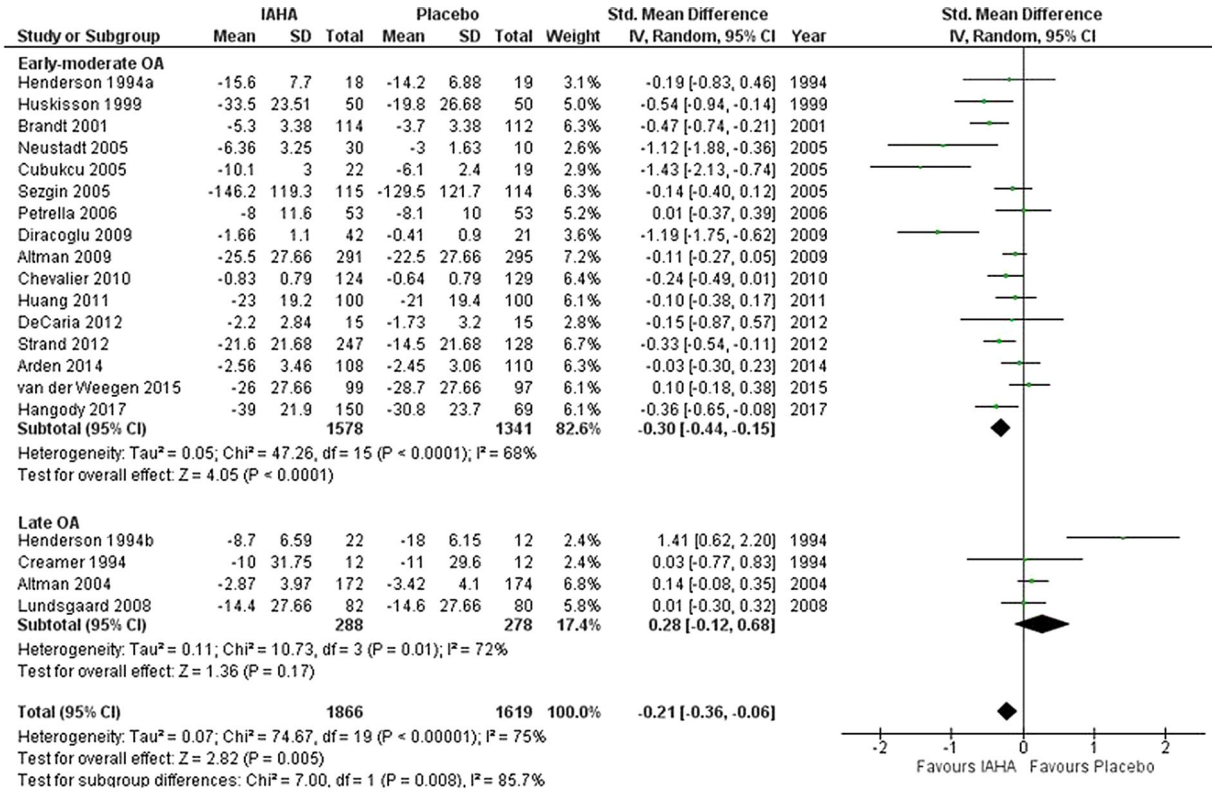

Fig. 2 Pain at 4–13 weeks

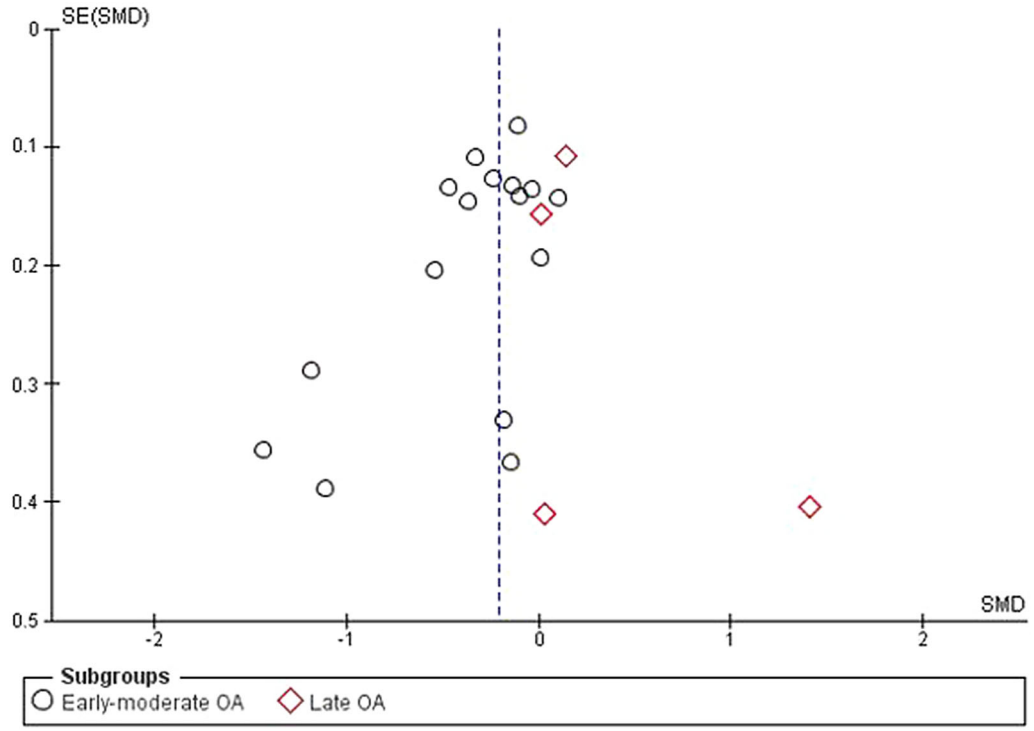

Fig. 3 Funnel plot for pain at 4–13 weeks

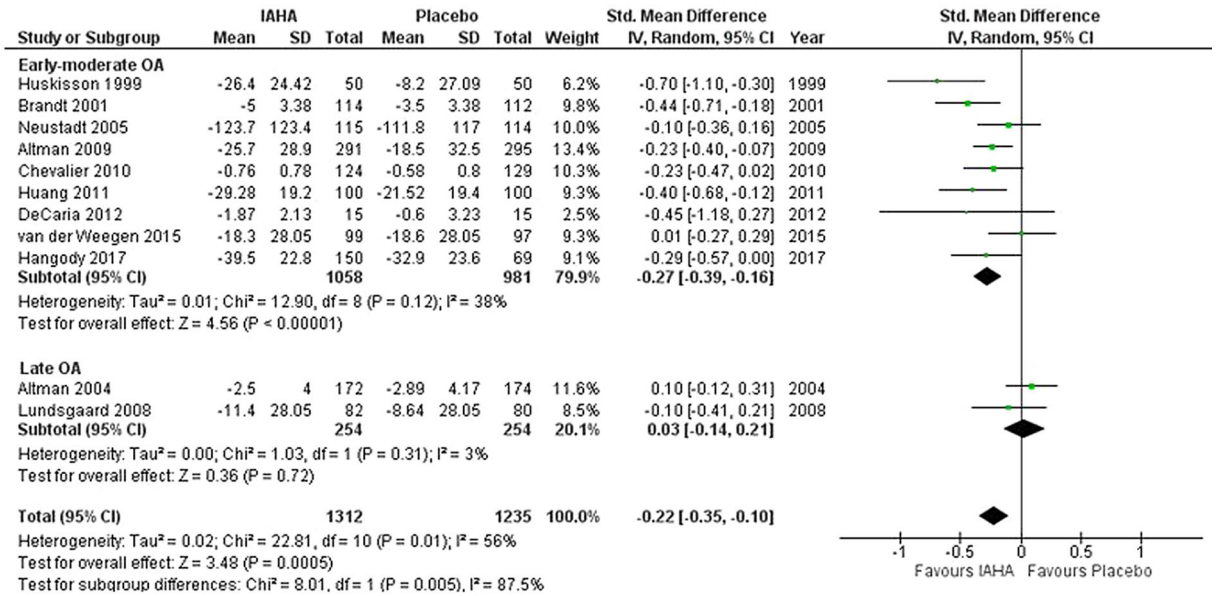

Fig. 4 Pain at 22–27 weeks

DISCUSSION

The results of this meta-analysis suggest that IA-HA therapy is most efficacious in reducing pain in patients with early-moderate knee OA, but not in the late OA subgroup. This analysis also revealed that significant pain relief with HA injections can occur within 4–13 weeks (earlier

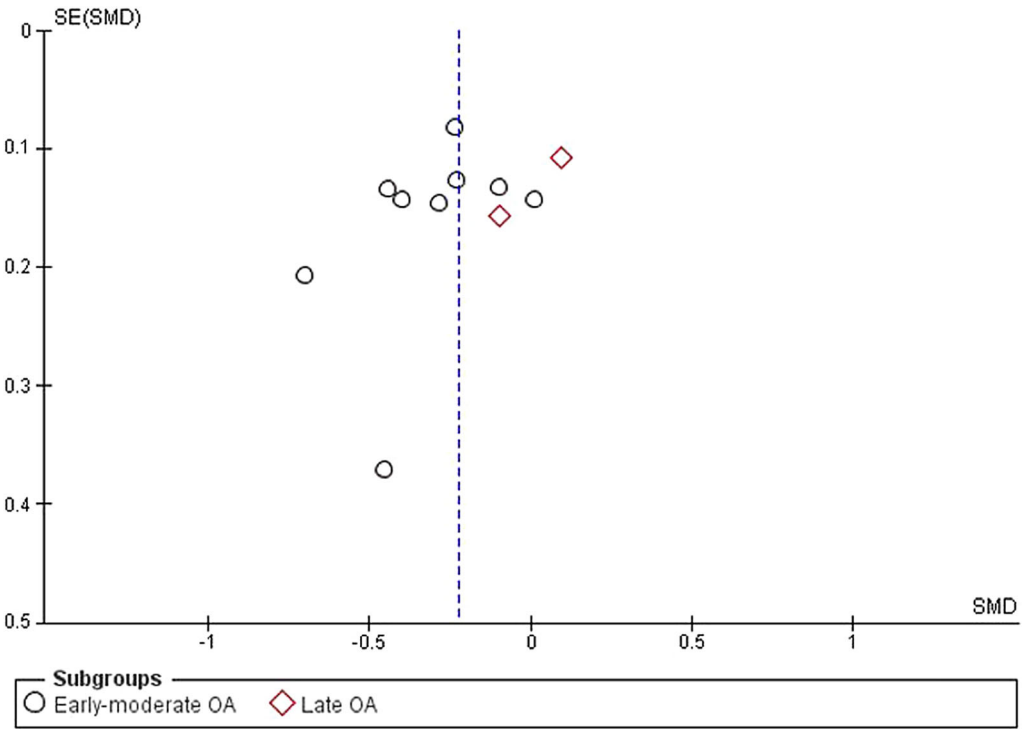

Fig. 5 Funnel plot for pain at 22–27 weeks

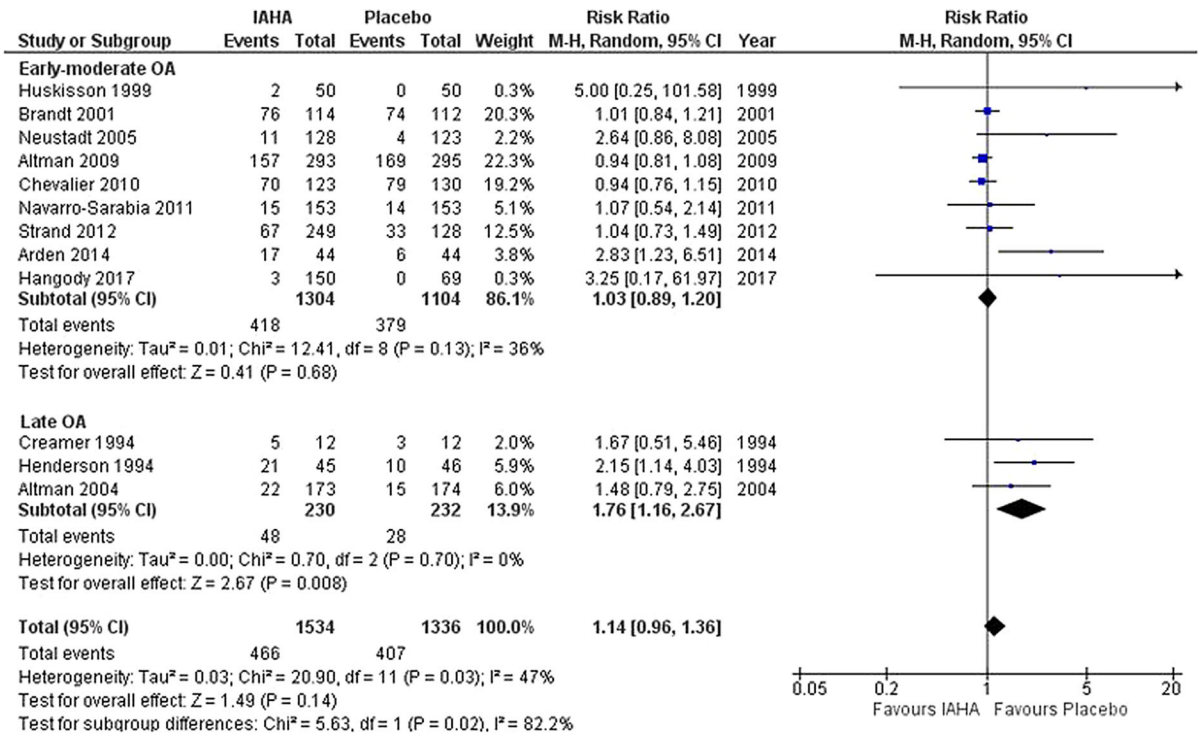

Fig. 6 Treatment-related AE

visit) post-injection and remain beneficial up to approximately 6 months (later visit); the effect estimates were similar between these two time points (SMD = − 0.30, 95% CI − 0.44 to − 0.15 at the earlier visit and SMD = − 0.27, 95% CI − 0.39 to − 0.16 at the later visit). This suggests that the effect seen with HA plateaus and is maintained up to 6 months post-injection.

In 2015, Strand et al. published a meta-analysis evaluating the effects of IA-HA within subcategories of disease severity [16]. Similar to the current study, Strand et al. found that the effect size for pain between IA-HA and saline injections in the early-moderate OA subgroup (K–L grade ≤ 3) was statistically significant (SMD = − 0.35, 95% CI − 0.57 to − 0.14), but this outcome was not significant in the subgroup that also included K–L grade 4 patients (SMD = − 0.11, 95% CI − 0.46 to 0.24). Other SMDs reported in previous meta-analyses, without considering OA grade, have ranged from − 0.19 to − 0.43 [10, 16, 38–42]. The estimates that were calculated in the current analysis for the early-moderate OA subgroup (− 0.30 at 4–13 weeks and − 0.27 at 22–-27 weeks) were within this range, but those for the late OA subgroup (0.28 at 4–13 weeks and 0.03 at 22–27 weeks) were not. Such an observation may be explained by the fact that most IA-HA studies have only included patients with early to moderate knee OA [4]. The current study provides further quantitative evidence that including patients with K–L grade 4 knee OA dilutes the benefit of HA injections when averaging treatment effects within a sample. These results also demonstrated the potential for HA to provide greater benefit to patients if it is provided earlier in the course of their disease, as opposed to being provided as a later treatment option once disease severity has already progressed to late stages. These results also demonstrate that the late OA subgroup experienced significantly more treatment-related AEs, suggesting that patients with KL grade 4 may be more susceptible to adverse events. These results may have been influenced by the inclusion of avian-derived HA and non-animal stabilized HA formulations, as well as the use of low molecular HA. Further insight into the product differences of IA-HA in KL grade 4 participants is required.

Several knee OA guidelines are available to practicing physicians; however, there is clearly inconsistency in the recommendations for IA-HA injections [4, 5, 43]. What many of these guidelines fail to address is how the efficacy of IA-HA may vary by select patient characteristics. The results of this systematic review suggest that future clinical practice guidelines base their treatment recommendations on the individual patient's disease state and focus on the potential for greater benefit when IA-HA is provided in earlier stage knee OA.

A limitation of the current study is the heterogeneity within subgroups, suggesting that there may be other factors contributing to the difference in results between the subgroups. It has been previously established that IA-HA trials are variable in terms of patient eligibility criteria, HA molecular characteristics, injection schedules, and outcomes assessment [3], which must also be further investigated. Additionally, there is a small proportion of included patients who were in advanced stages of their knee OA. Although this proportion is small, the results of this study still provide valuable information regarding the potential effects seen in these late stage patients. Studies included in this analysis varied in terms of blinding, HA product (with different injection regimens and molecular weights), and used either the VAS for pain or WOMAC pain subscale, though there is even variability in the subscale for WOMAC pain (e.g., the 0–100 mm, 0–20 or 5–25 Likert, or 0–500 scale). The K–L grade is the most widely used OA severity scale; however, other measures exist, with their own definitions and scoring systems [1], and studies that reported relevant outcomes were excluded from this analysis for this reason. There is also controversy as to whether or not radiographic criteria always correlate with clinical symptoms [1]. It cannot be said, definitely, that patients with more severe OA based on radiographs are also more symptomatic at baseline. Non-English trials were excluded, which may limit the generalizability of these findings and confidence in the effect estimates. The included studies were predominantly representative of sites in North

America and Europe, though two trials were conducted in Asia [26, 33] and demonstrated comparable treatment effects for HA. Lastly, the number of studied including participants with KL grade 4 knee OA was limited, suggesting that this cohort may not be actively recruited in IA-HA clinical trials.

A strength of this analysis was that only data from randomized, saline-controlled trials were included, ensuring that pooled effects estimates were from evidence of high-quality studies with a common comparator. There was also a large number patients in the analysis (n = 3485 in the assessment of pain at the earlier visit window), though a substantial proportion of this sample represented patients in the early-moderate OA subgroup. The outcome scales used to assess pain (i.e., the VAS and WOMAC) are validated measures and commonly evaluated in the knee OA literature. The funnel plots also revealed that publication bias is unlikely.

CONCLUSIONS

Treatment with IA-HA provides statistically significant pain relief compared to saline injections for patients with early-moderate knee OA, with no increase in the risk of treatment-related adverse effects, up to 6 months post-injection. IA-HA demonstrated no benefit over controls in the late OA subgroup and was associated with significantly greater treatment-related AEs. In this regard, some of the prior studies that demonstrated no significant benefit with HA injections may have confounded their results with the inclusion of a considerable proportion of patients with end-stage knee disease. Future investigations on the topic should take caution in completely rejecting the potential benefit of IA-HA when it may indeed be efficacious for a subset of the knee OA population.

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