Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders

RAPID COMMUNICATION

US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials

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Abstract: We conducted a systematic review and meta-analysis of randomized saline-controlled trials to determine the safety and efficacy of US-approved intra-articular hyaluronic acid (IAHA) injections for symptomatic knee osteoarthritis. A total of 29 studies representing 4,866 unique subjects (IAHA: 2,673, saline: 2,193) were included. IAHA injection resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to pre-injection values, with standardized mean difference (SMD) values ranging from 1.07–1.37 (all $P < 0.001$). Compared to saline controls, SMDs with IAHA ranged from 0.38–0.43 for knee pain and 0.32–0.34 for knee function (all $P < 0.001$). There were no statistically significant differences between IAHA and saline controls for any safety outcome, including serious adverse events (SAEs) ($P = 0.12$), treatment-related SAEs ($P = 1.0$), study withdrawal ($P = 1.0$), and AE-related study withdrawal ($P = 0.46$). We conclude that intra-articular injection of US-approved HA products is safe and efficacious in patients with symptomatic knee osteoarthritis.

Keywords: hyaluronic acid, knee, meta-analysis, osteoarthritis, systematic review, viscosupplementation

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Introduction

Osteoarthritis (OA) is a common degenerative disease in older adults that is characterized by joint pain and dysfunction due to progressive articular cartilage and subchondral bone damage, inflammation/synovitis, osteophyte formation, and joint space loss.[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 replace this OA-induced deficit and to stimulate production of endogenous HA,[3] which may alleviate symptoms of knee OA via multiple pathways including stimulation of chondrocyte metabolism, synthesis of articular cartilage matrix components, and inhibition of chondrodegradative enzymes and inflammatory processes.[4]

Intra-articular injection of hyaluronic acid (IAHA) is classified as a medical device in the US and is regulated by the Food and Drug Administration. Since medical devices are regulated by different regulatory bodies in different countries, the safety and efficacy profile of such products must be assessed by country. In their recent clinical practice guidelines for treatment of knee OA, the American Academy of Orthopaedic Surgeons stated "We cannot recommend using hyaluronic acid for the treatment of symptomatic knee OA".[5] Methodological issues related to the systematic review supporting this recommendation included only 14 studies, assessment of efficacy outcomes beyond 6 months, inclusion of HA products not commercially available in the US, and confusion in effect size interpretation. Therefore, a re-evaluation of IAHA efficacy is warranted to address these concerns. A separate rationale for performing the current meta-analysis was that, despite extensive evidence to the contrary,[6–12] the safety of IAHA for knee OA has recently been called into question.[13] The purpose of this systematic review and meta-analysis of randomized saline-controlled trials was to determine the safety and efficacy of US-approved IAHA injections for symptomatic knee OA.

Methods

The PRISMA Statement for reporting systematic reviews and meta-analyses served as a template for this report.[14] We searched MEDLINE and EMBASE for randomized, saline-controlled trials of IAHA injection for treatment of knee OA using a combination of study design-, treatment-, and disease-specific keywords and MeSH terms. No date restrictions were applied to the searches. Reference lists of included papers and relevant meta-analyses were manually searched. The final search was conducted in June 2013.

The main inclusion criteria were injection of a US-approved HA product, randomized, saline-control study design, primary diagnosis of knee OA, identical treatment and follow-up conditions between IAHA and saline-control groups, and at least one extractable efficacy or safety outcome. Studies were excluded if concomitant interventional therapies were uniformly administered, the study was published in a non-English language journal, or if data were available only from abstracts, conference proceedings, websites, or personal communication.

Data were extracted from eligible peer-reviewed articles by one author (LM) and were verified by a second author (JB). Data extraction discrepancies between the two coders were determined by discussion and consensus. Methodological quality of studies was assessed using the Jadad score.[15] Main efficacy outcomes included knee pain and knee function. These data were extracted in a non-biased manner using the knee OA outcome meta-analysis hierarchy of Juhl et al.[16] Due to variations in reporting the post-injection knee pain and function trajectory, we stratified data into two post-injection time windows: 4–13 weeks and 14–26 weeks. Efficacy data reported outside of these windows were excluded. If a study reported multiple pain or function treatment effects within a given window, the final value for each was extracted for analysis purposes. Safety outcomes included serious adverse events (SAEs), treatment-related SAEs, subject withdrawals for any reason, and AE-related subject withdrawals occurring at any time during follow-up.

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) pre-treatment to post-treatment standardized mean difference (SMD) for IAHA and (b) SMD for IAHA vs. saline control. For reference, SMD values of 0.2, 0.5, 0.8, and 1.0 are defined as small, medium, large, and very large, respectively.[17] For each safety outcome, the absolute risk difference (RD) was selected because this statistic considers data from all studies, including zero total event trials.[18] When a single control group served 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.[19] Forest plots were used to visually assess the 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.[20] Publication bias was visually assessed using funnel plots (not shown) and quantitatively assessed using Egger's regression test.[21] *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 and characteristics

After screening 1,653 records for eligibility, 29 randomized, saline-controlled trials[22–50] reporting 38 treatment effects from 4,866 unique subjects (IAHA: 2,673, saline: 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. Baseline subject characteristics were similar between the IAHA and saline groups (Table 1). The most commonly studied viscosupplements were Hyalgan (18), Synvisc (9), Supartz/Artzal (6), Orthovisc (3), Gel-One (1), and Euflexxa (1). The total number of injections received by patients ranged from 1–5. Overall, the methodological quality of studies was medium, with a median Jadad score of 3 (range: 2–5).

IAHA efficacy vs. pre-treatment

IAHA injection resulted in very large treatment effects for knee pain and knee function compared to pre-injection values. The SMD for knee pain was 1.37 at 4–13 weeks and 1.14 at 14–26 weeks (both $P < 0.001$). Treatment effects for knee function were slighter lower with SMDs of 1.16 and 1.07, respectively (both $P < 0.001$) (Fig. 1). There was high heterogeneity (I^2 = 74%–92%, all $P < 0.001$) for all IAHA treatment effects with evidence of publication bias for knee pain, but not knee function, during both analysis windows.

Table 1. Baseline patient characteristics.

Characteristic	IAHA	Saline
Patients, n	2,673	2,193
Age, yr, mean (min–max)	65 (53–72)	62 (53–73)
Female gender, %, median (min–max)	64 (27–92)	65 (22–100)
Body mass index, kg/m², mean (min–max)	28 (25–32)	29 (25–33)
Symptom duration, yr, mean (min–max)	4.5 (1.0–9.1)	4.3 (0.8–8.5)
Kellgren-Lawrence grade, median (min–max)	2.5 (1.9–3.0)	2.5 (1.8–3.5)

Abbreviation: IAHA, intra-articular hyaluronic acid.

IAHA efficacy vs. saline control

Compared to saline controls, the SMD for knee pain was 0.43 at 4–13 weeks and 0.38 at 14–26 weeks (both $P < 0.001$). Knee function SMD was 0.34 and 0.32, respectively, at the same time intervals (both $P < 0.001$) (Fig. 2). Heterogeneity among studies was high for knee pain (I^2 = 73%–75%, both $P < 0.001$) and moderate for knee function (I^2 = 54%–69%, both $P < 0.01$). Publication bias was evident for both knee pain treatment effects and for knee function at 4–13 weeks, but not for knee function at 14–26 weeks.

Safety outcomes

There were no statistically significant differences between IAHA and saline controls for any safety outcome. The SAE risk was similar between IAHA and saline (RD = 0.7% (95% CI: –0.2%–1.5%, $P = 0.12$). No SAEs were determined to be related to injection of IAHA or saline. The risk of subject withdrawal from the study for any reason was identical between groups (RD = 0.0%, 95% CI: –1.6%–1.6%, $P = 1.0$). The risk of subject withdrawals due to an AE was also similar with IAHA vs. saline (RD = 0.2%, 95% CI: –0.4%–0.8%, $P = 0.46$) (Fig. 3). There was minimal heterogeneity

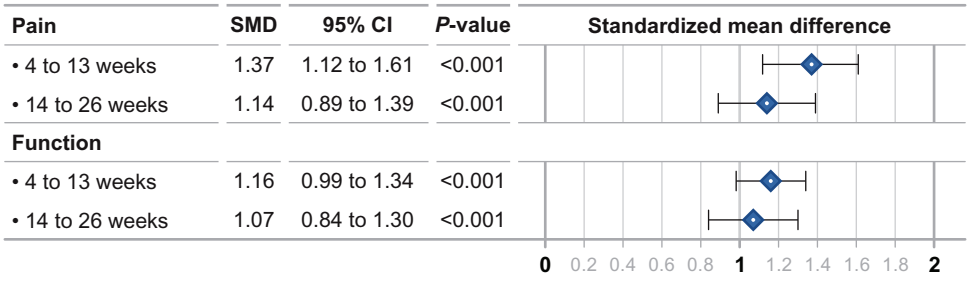

Figure 1. Standardized mean difference in pre-to-post efficacy changes with intra-articular hyaluronic acid injection.
Abbreviation: SMD, standardized mean difference.

among studies (all $I^2 = 0\%$) with no evidence of publication bias for any safety outcome. We conducted two sensitivity analyses for each safety outcome: the first in which the meta-analysis was re-estimated by removing one study at a time and the second in which odds ratios were used as the statistic of interest. The conclusions of the primary analysis were corroborated by both sensitivity analyses.

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 HA products is safe and efficacious in patients with symptomatic knee OA.

Numerous systematic reviews and meta-analyses have been published on this topic over the last decade, with the SMD of IAHA versus a control group for efficacy outcomes ranging from 0.0–0.46.[6,7,10,13,51] For comparison, the saline-adjusted SMD in the current meta-analysis ranged from 0.32–0.43, depending on outcome and time window. However, this statistic may underestimate the overall treatment effect of IAHA since control group improvements in pain and function are substantial in OA clinical trials, particularly when control treatments, such as saline, are administered via injections.[52] There is a distinct difference between a pre-to-post treatment effect and a placebo-adjusted treatment effect; the former assesses the overall patient experience in the IAHA group while the latter teases out the independent effect of IAHA above and beyond that of saline, a statistic that is arguably irrelevant from the perspective of the patient. Thus, the efficacy results of the current meta-analysis can be best characterized by a very large treatment effect of US-approved IAHA injections on knee pain and function between 4 and 26 weeks and, after statistically adjusting for saline-control improvements, a medium treatment effect with US-approved IAHA during this same period.

Perhaps the most notable finding from this meta-analysis is that US-approved HA products are not associated with increased safety risks. This is in sharp contrast to Rutjes et al[13] who concluded that IAHA injections increased the risk of SAEs and AE-related subject withdrawals. However, there were several important subtleties associated with their analysis. Although the calculated risk of SAEs was marginally higher with IAHA vs. controls, the association between SAE and treatment was not considered. In fact, in our analysis, 100% of reported SAEs were unrelated to treatment. Second, the safety analysis in the Rutjes paper was heavily influenced by inclusion

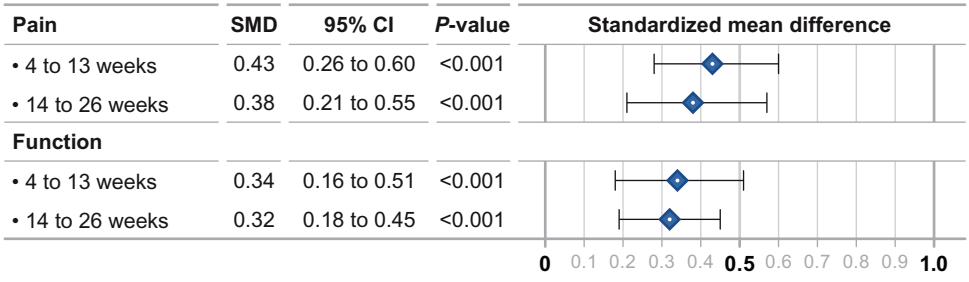

Figure 2. Standardized mean difference in intra-articular hyaluronic acid injection vs. saline controls.
Abbreviation: SMD, standardized mean difference.

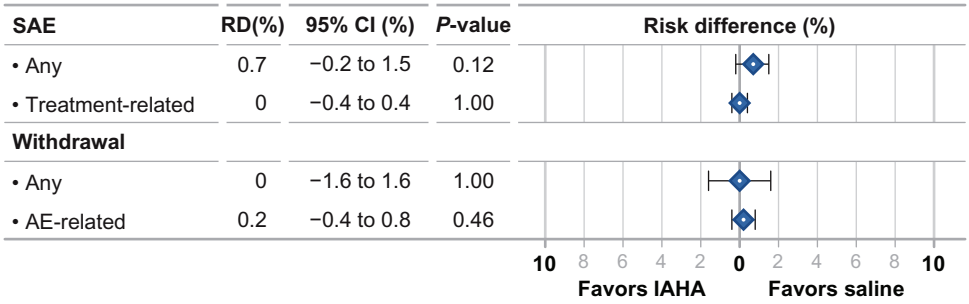

Figure 3. Risk difference in safety outcomes for intra-articular hyaluronic acid injection vs. saline controls.
Abbreviations: AE, adverse event; IAHA, intra-articular hyaluronic acid; RD, risk difference; SAE, serious adverse event.

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, a statistic that excludes zero total event trials.[18] Considering that 30 of 38 SAE treatment effects in the current meta-analysis reported zero total events, the odds ratio is arguably an inappropriate statistic for this type of analysis since most data are disregarded.

Our meta-analysis has several limitations that may influence interpretation. Most, but not all, studies excluded subjects with end-stage (Kellgren-Lawrence grade IV or equivalent) knee OA and, therefore, the efficacy of IAHA in these patients cannot be determined. Next, we did not consider HA products without US approval and, therefore, implied comparisons of safety and efficacy between US approved vs. non-US approved products should be performed with caution. Due to sample size considerations, we did not attempt to analyze treatment effects by HA brand. Lastly, efficacy outcomes were inconsistent across studies and publication bias was evident for knee pain outcomes. 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.

Overall, this systematic review and meta-analysis of randomized, saline-controlled trials confirms that intra-articular injection of US-approved HA products is safe and efficacious in patients with symptomatic knee OA.

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Author Contributions

Conceived and designed the experiments: LM, JB. Analyzed the data: LM. Wrote the first draft of the manuscript: LM. Contributed to the writing of the manuscript: JB. Agree with manuscript results and conclusions: LM, JB. Jointly developed the structure and arguments for the paper: LM, JB. Made critical revisions and approved final version: LM, JB. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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