

Unraveling the confusion behind hyaluronic acid efficacy in the treatment of symptomatic knee osteoarthritis

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Abstract: Hyaluronic acid (HA) is a commonly prescribed treatment for knee pain resulting from osteoarthritis (OA). Although numerous HA products have been approved for use by the US Food and Drug Administration, the efficacy of HA injections for knee OA remains disputed with meta-analyses and societal clinical guidelines drawing disparate conclusions. The American Academy of Orthopaedic Surgeons (AAOS) recently published a best-evidence systematic review and concluded that available data did not support the routine use of HA for knee OA. The purpose of the current article is to highlight issues that confound interpretation of meta-analyses on HA for knee OA, to provide realistic estimates of the true efficacy of HA injections in knee OA, and to provide commentary on the methods and conclusions from the AAOS systematic review. In general, the clinical benefit of HA is underestimated using conventional meta-analytic techniques. When accounting for differential control group effects in HA studies, it can be reasonably concluded that HA injections may be beneficial to an appreciable number of patients with knee OA. In addition, the systematic review methodology used by AAOS was questionable due to exclusion of numerous relevant studies and inclusion of studies that used HAs not approved for use in the US, both of which underestimated the true efficacy of HA injections. Overall, the efficacy of HA injections for knee OA is likely better than previously reported. Future clinical trials and meta-analyses should account for differential control group effects in order to avoid the continued confusion surrounding HA injection efficacy.

Keywords: effect size, hyaluronic acid, injection, knee, minimal important difference, osteoarthritis

Osteoarthritis (OA) of the knee is the leading cause of disability in adults¹⁻³ and is characterized by progressive joint pain and dysfunction due to subchondral bone damage, articular cartilage loss, inflammation/synovitis, and osteophyte formation.⁴ Hyaluronic acid (HA) is a component of synovial fluid that acts as a joint lubricant during shear stress and a shock absorber during compressive stress. Patients with knee OA exhibit reductions in the concentration and molecular weight of endogenous HA.⁵ Intra-articular injection of exogenous HA replaces this deficit and stimulates production of endogenous HA,⁶ which may alleviate symptoms of knee OA via inhibition of chondrodegradative enzymes and inflammatory processes, stimulation of chondrocyte metabolism, and synthesis of articular cartilage matrix components.⁷

A number of meta-analyses on the safety and efficacy of HA for knee OA have been recently published, each using different methodology leading to different conclusions.⁸⁻¹⁶ Meta-analysis is a useful tool that involves systematic evaluation and analysis of published

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data on a specific topic to derive conclusions about that body of research. A benefit of conducting a meta-analysis is that pooling data from multiple studies allows calculation of a more precise treatment effect compared to those reported in individual studies. However, valid conclusions can only be drawn from a meta-analysis when the methodology is thorough and unbiased.

The American Academy of Orthopaedic Surgeons (AAOS) recently published a best-evidence systematic review with meta-analysis and concluded that available data did not support the routine use of HA injections for knee OA.¹⁷ In their review, the therapeutic effect of HA was expressed in “minimal important difference (MID) units”, which is defined as the treatment effect observed in patients treated with HA relative to that of patients who received saline injections and then divided by the MID. However, reporting HA injection treatment effects after correcting for changes in the saline control group does not accurately reflect the treatment effect attributable to HA injections as a therapy. Unfortunately, there is no ideal control group with which to evaluate HA injections in knee OA. The clinical benefit of HA injections versus usual care would likely be overestimated and confounded by expectation bias. In addition, the clinical benefit of HA versus saline injections is likely underestimated since the therapeutic efficacy of active treatments is consistently lower when considerable treatment effects are observed in the control group,^{18,19} such as those observed in HA studies.

The standardized effect size (ES) is a commonly reported statistic in meta-analyses, where values of 0.2, 0.5, 0.8, and 1.0 are taken to represent small, moderate, large, and very large treatment effects, respectively.²⁰ Given that the ES associated with HA injections is ~0.38 relative to saline injections^{15,16,21} and that the ES for saline injections is ~0.30 relative to oral placebo,²² it is reasonable to conclude that the true ES of HA injections may be closer to 0.68. This is considered a moderate-to-large treatment effect and is comparable to the ES of 0.60 reported for HA in patients with knee OA after adjusting for differential control group effects.²² By reasonably assuming that the true treatment effect of HA injections is closer to 0.68 (not 0.38), then the outcomes and conclusions from the AAOS systematic review can be adjusted accordingly. That is, for the highest quality trials, the more realistic treatment effect attributable to HA injections is 0.5 MID units for visual analog scale (VAS) pain, 0.9 MID units for Western Ontario and McMaster Universities Arthritis Index function, and 0.7 MID units for Western Ontario and McMaster Universities Arthritis Index stiffness, all of which are treatment effects that “may be beneficial to an appreciable number of patients”.²³

In addition to these issues related to their meta-analysis, the systematic review methodology and recommendations in the AAOS report warrant further evaluation. First, eight randomized controlled trials of HA versus saline injections that met the AAOS criteria (ie, reported at least one main efficacy outcome [VAS or Western Ontario and McMaster Universities Arthritis Index subscore] and sample size ≥ 30 per group) were not included in this systematic review.^{24–31} It would be helpful to understand if these studies were considered for inclusion and, if so, the reason for their exclusion. In a previous meta-analysis,¹⁶ the treatment effect reported in these eight studies was 2.5-fold greater compared to the remaining studies, suggesting that exclusion of these studies may have significantly underestimated the clinical benefit of HA injections. Second, given that HAs approved for use in the US are considerably more efficacious than non-approved HAs¹⁶ and since the systematic review in question was commissioned by the AAOS, the inclusion of studies using HAs that are not available in the US is questionable. Finally, it is perplexing that the AAOS does not recommend HA injections for symptomatic knee OA citing lack of efficacy, but it does recommend nonsteroidal anti-inflammatory drugs.³² This is despite numerous reports that HA injections are safe and that efficacy of HA is at least comparable, if not superior, to that of nonsteroidal anti-inflammatory drugs.^{16,33–35}

In summary, mounting evidence suggests that HA injections for knee OA are more efficacious than previously reported. Future clinical trials and meta-analyses should be designed to account for differential control group effects in order to avoid the continued confusion surrounding HA injection efficacy.

Disclosure

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