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BRIEF REPORT

Towards reaching consensus on hyaluronic acid efficacy in knee osteoarthritis

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Abstract

Intra-articular injection of hyaluronic acid (HA) is a controversial treatment for knee osteoarthritis (OA). While clinical efficacy of HA relative to saline injections has been demonstrated in many studies, these results are of limited value in real-world clinical practice since saline injection is not a knee OA treatment. Instead, rigorous postmarket comparative studies of HA versus approved knee OA treatments are encouraged. The conduct of such studies is particularly important given the paucity and heterogeneous nature of current evidence regarding nonsurgical knee OA treatment.

Key Points

- *Societal guidelines recommend nonsteroidal anti-inflammatory drugs and corticosteroid injections, but not hyaluronic acid injections, for knee osteoarthritis (OA) despite inconsistent supportive data.*
- *This article encourages rigorous comparative post-approval studies to clarify the role of nonsurgical treatments used in clinical practice for knee OA.*

Keywords Corticosteroid · Injection · Nonsteroidal anti-inflammatory drugs · Viscosupplementation

Intra-articular hyaluronic acid (HA) injection is a controversial treatment for knee osteoarthritis (OA). Proponents of HA argue that efficacy has been established based on superior clinical outcomes compared to saline injections in numerous randomized trials [1, 2]. Critics of HA argue that the incremental efficacy benefit derived from meta-analyses is not clinically meaningful to patients when accounting for the placebo effect [3, 4]. Ultimately, evidence exists to support either position, thereby fueling the debate.

The primary efficacy endpoint of many HA clinical trials involves an assessment of patient-reported knee pain or function. Patient-reported outcomes are highly susceptible to bias when patients are aware of their treatment assignment [5]. Knowledge of treatment assignment may subconsciously or consciously influence patients to alter their reporting of symptom severity and may affect rates of co-intervention and attrition [6]. Consequently, placebo controls with patient blinding are integral elements of HA studies intended for regulatory approval to minimize the risk of these biases. To date, over a dozen HA products have been approved by the Food and Drug Administration (FDA) and are currently marketed for sale in the USA [7].

Commercialization of drugs and medical devices involves two key milestones—FDA approval to sell the product and a positive coverage decision from healthcare payers so healthcare providers may receive reimbursement. Yet the designs of clinical trials intended to support regulatory approval of HA are often insufficient to draw conclusions about the relative efficacy of that product compared to other treatments currently available on the market. For example, trials of HA versus saline injections designed for regulatory approval are not applicable to real-world clinical practice since saline injection is not a treatment for knee OA. Therefore, it could be argued that once an HA product receives marketing approval by demonstrating superior efficacy over saline injections, the more appropriate comparison in subsequent trials would be against approved alternative treatments that are routinely used in clinical practice for the same condition.

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In the clinical practice guidelines for knee OA treatment released by the American Academy of Orthopaedic Surgeons (AAOS) [4], the only recommended nonsurgical treatment appropriate for all patients was nonsteroidal anti-inflammatory drugs. In the Osteoarthritis Research Society International guidelines [8], corticosteroid injections were the only recommended nonsurgical treatment appropriate for all patients. Therefore, the efficacy of commercially available HA products would be best demonstrated by direct comparisons to nonsteroidal anti-inflammatory drugs and corticosteroid injections to further clarify their clinical utility in real-world settings.

A few direct-comparison meta-analyses have attempted to answer these questions. Bannuru and colleagues reported that the efficacy of HA was superior to corticosteroids and nonsteroidal anti-inflammatory drugs [1]. He and colleagues reported that corticosteroids were more efficacious than HA at 1 month, but HA was more efficacious at 6 months [9]. In a network meta-analysis of indirect evidence sponsored by the AAOS, improvements in knee pain were similar when HA was compared to ibuprofen, naproxen, celecoxib, diclofenac, or corticosteroid. Further, treatment effects between nonsteroidal anti-inflammatory drugs and corticosteroid injections were comparable. Lastly, despite the recommendation in favor of corticosteroid injections, pain and function outcomes with corticosteroid injections were no different than with intra-articular saline injection [10]. The number of relevant trials that informed these comparisons was limited, which lowers the confidence in these results. These findings highlight the inconsistency between study results and societal treatment recommendations for knee OA. Additionally, societal treatment recommendations should consider studies of combination HA products, several of which have reported improvements in efficacy versus HA alone [11, 12]. Based on this paucity of heterogeneous evidence, some of which is inconsistent with societal recommendations, rigorous comparative post-approval research is encouraged to further clarify the role of HA and other nonsurgical treatments in relation to knee OA therapies commonly used in real-world clinical practice.

Certainly, the design of a randomized trial intended to compare HA to knee OA treatments such as nonsteroidal anti-inflammatory drugs or corticosteroid injections must be carefully considered in order to provide meaningful results. For example, to the author's knowledge, only 6 randomized trials of HA vs. NSAIDs have been performed [13–18]. Among these trials, 4 trials enrolled less than 100 patients per group [14–16, 18], 4 trials followed patients for 12 weeks or less [13, 15–17], and 3 trials utilized inadequate patient blinding [13, 17, 18]. Further, no study enrolled patients with advanced disease (Kellgren-Lawrence stage IV). Ultimately, this suggests that the current evidence of the utility of HA vs. NSAIDs is of relatively low quality since sample sizes are often inadequate to detect clinically important group differences or uncommon adverse events, study duration and study quality may be inadequate, and the patients under study may not be representative of those treated in clinical practice. Sample sizes should be derived from power analyses that allow detection of the minimal clinically important difference for the primary efficacy endpoint as well as for a co-primary safety endpoint. Further, clinical trial results derived from no more than 12 weeks of follow-up offers little value since most patients are unwilling to undergo total knee arthroplasty and, therefore, must manage knee OA symptoms for many years following the initial diagnosis [19]. Patient treatment and follow-up of at least 6 to 12 months is recommended to understand the unique risks and benefits of each therapy, which should include patient-reported efficacy outcomes, health-related quality of life, treatment compliance, rates of study withdrawal with associated reasons, and adverse event rates. Finally, patient blinding remains crucial in postmarket trials in order to minimize bias and can be effectively implemented by specifying additional sham injections or oral placebo pills, depending on the comparison group.

Clearly, there is no consensus on the efficacy of HA injections in the treatment of knee OA. Additional high-quality randomized trials that compare HA to knee OA treatments used in clinical practice are needed. Manufacturers of HA are therefore encouraged to plan their clinical trial programs to not only conduct randomized trials to support regulatory approval, but to also plan equally rigorous postmarket trials with active controls used in clinical practice. Until such data become available, the impasse towards reaching consensus regarding HA efficacy for knee OA will likely remain.

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Compliance with ethical standards

Conflict of interest The author has previously received personal fees from DePuy Synthes, OrthogenRx, and OsteoArthritis Centers of America and has previously published manuscripts related to hyaluronic acid efficacy in knee osteoarthritis.

Ethical standards The manuscript does not contain clinical studies or patient data.

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