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Should Intra-articular Hyaluronic Acid be Used Routinely for Knee Osteoarthritis Pain?

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Case Scenario

A 53-year-old male presents to your clinic for evaluation of intermittent right knee pain and swelling. His symptoms began about 10 years ago during a basketball game with colleagues at a work social event. At the time of injury, he experienced the sudden onset of pain after landing with a twisting motion; a follow-up MRI demonstrated a radial tear of the medial meniscus. He chose to treat the injury conservatively with a physical therapy and strengthening program. Symptoms slowly improved with a full return to non-impact

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sports after approximately 3 months. Currently, he continues to follow a routine exercise program of cycling and occasional higher-impact sports such as running and basketball. He generally follows a Mediterranean diet, maintains a BMI of 23, and takes a turmeric herbal supplement. About once every month or two, he has an episode of medial knee pain and mild swelling that he treats with a course of ibuprofen that usually resolves after several days. On your initial evaluation, you note mild medial joint line tenderness, no significant varus deformity, no instability, and no evidence of bursitis or tendinopathy. X-ray demonstrates mild (K-L Grade II) OA medial compartment. He expresses the long-term goal continued cycling and occasional running with the avoidance of knee replacement surgery later in life. He asks your opinion on methods to achieve these goals. Drs. Buchheit, Eshraghi and Souza will argue that intra-articular hyaluronic acid should be used for this patient. Drs. Hunt, Provenzano and Mittal will argue since IA-HA is not well supported by evidence for routine treatment of knee OA that this patient should not be offered this therapy to address his primary complaint and instead consider alternative including physical therapy as first line treatment.

Drs. Buchheit, Eshraghi and Souza Reply

In this case, we see the common scenario of a patient with mild/moderate knee osteoarthritis (KOA), who desires to maintain a high level of physical function and avoid surgery. He follows an appropriate diet and exercise program and is asking about other potential treatments to improve joint health. Although there are now multiple non-surgical treatment options such as intra-articular corticosteroids (IA-C), biologic therapies such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs), or genicular nerve radiofrequency lesioning (RFL), they have significant limitations. Intra-articular corticosteroid does not provide long-term benefit and carries the risks of accelerated cartilage loss. Biologic therapies such as PRP and MSCs have limitations due to cost, insurance coverage, and regulatory considerations. Genicular RFL may theoretically reduce joint proprioception and potentially necessitate annual neurodestructive procedures. We therefore propose that the best current treatment option for this patient would be to perform an injection of intra-articular hyaluronic acid (IA-HA).

Intra-articular HA (also known as viscosupplementation, hyaluronan, or sodium hyaluronate) was approved by the FDA in 1997, not as a drug, but as a device to alter the viscosity of the joint for “the treatment of pain in osteoarthritis (OA) of the knee for patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics.” [1] It was known that endogenous hyaluronic acid (HA), composed of repeating units of hydrophilic N-acetyl-D-glucosamine and D-glucuronic acid with sizes from 2,500–7,000 kDa, breaks down with age and OA, altering the rheological properties of synovial fluid; [2] IA-HA was developed as a mechanical solution for this loss of viscosity. Manufacturing sources of IA-HA include avian tissue (rooster combs), and more recently, methods of bacterial biofermentation. (See Table) Several techniques have been employed to maximize particle sizes and mimic the larger molecular weights of healthy endogenous HA; these processes include the chemical crosslinking of hylan (hylan G-F 20) and other manufacturing methods to create higher viscosity products that often extend the intra-articular duration of the molecule. Most IA-HA products have a half-life between 1–9

days, although one biofermented HA molecule appears to extend to approximately 30 days (Durolane®). [3]

There have been multiple randomized controlled trials (RCTs) demonstrating superior analgesia following IA-HA vs IA-C or placebo; when compared with IA-C, the analgesia is often equivalent at one month, but favors IA-HA beyond this point. [4] A 2006 Cochrane review of 76 studies concluded that IA-HA improved pain, function, and patient global assessment during the 5–13 week post-treatment period; [5] the improvements in pain were noted to be 28–54% across the spectrum of products and molecular weights studied. More recent meta-analyses and systematic reviews support the long-term superiority of IA-HA over IA-C with analgesia that often lasts up to 6 months. [6,7] When used in patients over the age of 65, the injection of IA-HA has additionally been shown to delay the need for total knee arthroplasty (TKA) an additional 8.7 months. [8]

Despite these positive outcomes, in 2013 the American Academy of Orthopedic Surgeons (AAOS) recommended strongly against the use of IA-HA for the treatment of knee OA pain; their meta-analysis found the standardized mean difference (SMD) for improvements in pain after IA-HA did not meet the accepted threshold (SMD = −0.39) for minimal clinically important improvement (MCII). Notably, their calculated effect size (−0.26) was derived from pooled studies of diverse molecular weight products. [9] In 2019, The American College of Rheumatology also “conditionally recommended against” the use of IA-HA in the treatment of knee OA using similar rationale. [10]

Injectable HA products constitute a wide range of sizes (from 600 kDa to over 6,000 kDa) and are often classified as high molecular weight (HMWHA) (≥3,000 kDa), moderate molecular weight (MMWHA) (1,500–3,000 kDa), and low molecular weight (LMWHA) (<1,500 kDa). It is increasingly appreciated that HMWHA may confer advantages over smaller molecules in the treatment of OA pain. [11] However, until recently, there have been few studies that stratify by molecular weight. Fortunately, a 2016 meta-analysis clarified the clinical impact of HA size by separately analyzing trials using HMWHA (11 RCTs, 2,094 patients) and LMWHA (15 trials, 2,639 patients). The investigators found an effect size of −0.52 with the use of HMWHA and only −0.18 with LMWHA. A 2020 molecular weight-stratified meta-analysis further supported those findings, observing an SMD of −0.57 for improvements in pain after HMWHA and only −0.23 after LMWHA. [12] The unfortunate inclusion of trials with various molecular weight products in meta-analyses and systematic reviews has reduced the perceived clinical benefit of this intervention and affected the development of treatment guidelines. It is clear that HMWHA provides significant clinical benefit, surpassing accepted thresholds for minimal clinically important improvement in the treatment of KOA pain.

Drs. Hunt, Provenzano and Mittal Reply

We share the concern of our colleagues for the well-being of patients experiencing the common and disabling condition of symptomatic knee OA and agree there is a need for safe and effective treatment options. Since U.S. Food and Drug Administration approval of intra-articular HA (IA-HA) injections for symptomatic knee OA in 1997, it has been

plagued by criticisms regarding evaluations of its efficacy stemming from flaws in study design including publication bias. [13] We provide the most recent updates with respect to the evidence surrounding the use of IA-HA for symptomatic knee OA and evaluate recommendations regarding its role in the conservative treatment of knee pain.

The basic science studies described by our colleagues generated considerable excitement regarding the potential of HA injections for therapeutic efficacy in degenerative joint disease; however, the clinical data has shown mixed results. A recent 12-month prospective observational study of 77 patients with mild to moderate knee OA found improvement in pain and function WOMAC scores through 6 months (decrease in pain from 27.62 to 13.96, decrease in functional limitation from 77.8 to 46.6, $p<0.05$), Pain improved from 27.62 to 20.11 at 1 month and 17.62 at 3 months, and functional limitation declined from 77.8 to 62.3 at 1 month and 55.9 at 3 months.[7,14] In one systematic review, mean difference in effect size between HA and CS groups based on WOMAC score was 5.51 (95% CI 8.77 to −1.54, $p=0.005$) favoring intra-articular HA.[7] Most recent studies of IA-HA have been prospective open label studies or have compared IA-HA to experimental therapies such as platelet-rich plasma (PRP) and/or mesenchymal stem cells (MSC).[15,16] Multiple systematic reviews and meta-analyses have investigated the efficacy of viscosupplementation in knee OA with variable conclusions. Most of these reviews have commented on the heterogeneity of trials and significant publication bias. Results of these reviews are often confounded by small effect size. When restricting the analysis to well-powered trials with blinded outcome assessment, Rutjes et al reported a clinically insignificant benefit of viscosupplementation on pain and no effect on function. [17] Another “best evidence” systematic review examined clinically significant change in terms of minimal important difference (MID) in WOMAC pain relief and functional improvement to assess the effect of HA on knee OA. Inclusion criteria included high quality randomized controlled trials (RCTs) with a minimum of 30 patients per subgroup. The authors did not find clinically meaningful evidence to support the routine use of intra-articular HA in knee OA, concluding similar benefit of HA as compared to normal saline used as a placebo. [18]

A systematic review and meta-analysis of 12 RCTs (a total of 1,794 subjects) comparing IA-C to IA-HA reported statistically significant superior pain relief in Visual Analog Scale (VAS) scores for IA-CS at 1 month (mean difference 0.67, 95% CI 0.07 – 1.27, $p = 0.03$, I^2 66%), no difference in efficacy at 3 months ($p = 0.29$, I^2 85%) and superior relief with IA-HA at 6 months (mean difference –0.73, 95% CI –1.25 – –0.21, $p = 0.006$, I^2 56%).[7] Overall heterogeneity was high at I^2=85%. (The I^2 statistic is a measure of overall study (most commonly treatment effect) heterogeneity commonly reported in systematic reviews and meta analyses, with generally levels of 5%–20% implying a low level of study heterogeneity, 60%–75% a moderate level, and 80% or greater a high level of study heterogeneity. [19] Study heterogeneity may be high due to several factors including differences in patient characteristics or settings across studies. The overall marginal degree of pain relief, despite its statistical significance, calls into question its clinical relevance. Differences in the WOMAC score were statistically significant only at 6 months, with IA-HA demonstrating superior efficacy (mean difference −5.15, 95% CI −8.77 – −1.54, $p = 0.005$, I^2 70%). Treatment-related adverse events (most commonly knee pain, swelling, stiffness) were higher among the IA-HA groups (risk ratio 1.66, 95% CI 1.34 – 2.06, I^2

40%). Although all studies reported randomization, they varied in terms of blinding and allocation concealment and only 4 studies used an intention-to-treat analysis. A second systematic review and meta-analysis comparing IA-HA and methylprednisolone identified 5 RCTs with 1,004 patients and found no difference in terms of pain, function or knee stiffness at time points through 26 weeks between the two groups. [20] Overall, the treatment effect size barely meets the threshold of clinically meaningful difference or falls short of statistical significance, with high heterogeneity plaguing the more positive meta-analyses.

Multiple national society guidelines have argued against the routine use of IA-HA for the treatment of symptomatic knee OA. The American Academy of Orthopedic Surgeons (AAOS) in 2013 made a strong recommendation against the use of IA-HA for systematic knee OA based on an overall treatment effect of less than 0.5 meaningfully important difference (MID) units for both pain and function found among 14 studies that they identified. [21] More recently, the 2019 American College of Rheumatology (ACR)/Arthritis Foundation guidelines conditionally recommended against the use of IA-HA in knee OA given the fact that the studies publishing favorable results demonstrated high risk of bias, and considering with the meta-analysis of low risk of bias trials, the treatment effect size of HA compared to saline is nearly zero. [10] These guidelines acknowledge that some patients may have failed other conservative management including IA-CS and/or may not be candidates for IA-CS injection, thus shared decision-making between patients and providers is essential.

In terms of the distinction drawn between HMW-HA and LMW-HA, our colleagues point to the systematic review published by Hummer et al suggesting that not all HA preparations are created equal, and that HMW-HA meets the threshold for meaningful clinical significance. [12] Although the fact that authors of the study are all employees or consultants of a company with vested financial interest in IA-HA may in and of itself not discredit their work, the fact that indeed there were no statistically significant differences in pain scores between HMW-HA and LMW-HA or IA corticosteroids should give patients and providers pause. Certainly, this review warrants further study stratifying differences between HMW-HA and LMW-HA in terms of treatment effect, but it should not be interpreted as definitive evidence supporting the routine use of HMW-HA for painful knee OA.

Since the publication of these guidelines multiple articles have argued in favor of preserving IA-HA as an option for therapy, suggesting that HMW preparations have better efficacy compared to LMW HA meeting the standard for clinically significant improvement [12]. However, no subsequent studies, editorials or other publications have addressed the issue of bias among studies reporting more favorable results, particularly given the higher costs associated with HA treatment among patients who may or may not proceed to knee arthroplasty. Only 3 of 48 studies examining IA-HA for knee OA declare no conflicts of interest, and no studies with authors reporting at least one conflict of interest report unfavorable conclusions of this therapy. [22] The numerous FDA-approved IA-HA formulations vary in terms of their administration. Several require a series of three or even five injections typically spaced one week apart, incurring further burden on the patient as well as cost. [23] There is general concern regarding the cost effectiveness of IA-HA injections. Two retrospective studies of Medicare data samples found that although patients

undergoing IA-HA injections experienced delayed time to surgery by several months, these cohorts were associated with higher healthcare costs without clear evidence that the delayed time to surgery resulted in any meaningful improvement in long-term patient outcomes. [24,25] While knee replacement is certainly the greatest contributor to healthcare costs in patients undergoing knee surgery, HA treatment costs still exceeded other non-operative management including medications, physical therapy, bracing and CS injections. Without clear evidence that IA-HA provides clinically significant benefit to patients, it is difficult to justify such a costly treatment.

Effective treatments for symptomatic knee OA include physical therapy, incorporation of a regular exercise program, weight loss for patients with obesity, topical anti-inflammatories (and oral NSAIDs in patients for whom they are safe for chronic use), IA-C injections particularly in the short term, and emerging advanced interventions such as genicular nerve RFA. One study of 158 participants demonstrated superiority of internally cooled RFA compared to IA-HA in terms of pain and function in knee OA, with 71% of patients receiving RFA experiencing >50% pain relief at 6 months compared to 38% of participants who received IA-HA (4.1 ± 2.2 versus 2.5 ± 2.5, $p<0.0001$) and mean WOMAC score improvement 48.2% in patients receiving cooled RFA versus 22.6% in patients receiving IA-HA at 6 months ($p<0.0001$). [26] We argue that comprehensive management for knee OA supported by national society guidelines and sound evidence basis does not include the routine use of IA-HA injections. In the case of this particular patient, the frequency of his symptoms, the relative lack of their impact on his daily activities given his ongoing active lifestyle, and the fact that several of the treatments with more robust evidence basis as described have not yet been trialed all suggest that IA-HA is not the most appropriate next step in treatment. We recommend that the patient be advised that while no treatment has been definitely proven to prevent need for surgery for painful knee OA, referral to physical therapy is the most appropriate next step.

Drs. Buchheit, Souza and Eshraghi Rebut

While we certainly understand the hesitation to contradict guidance from AAOS and ACR, we respectively disagree with the omission of this valuable therapy in treatment guidelines for non-surgical KOA. Drs. Hunt, Provenzano and Mittal bring forth the concern of potential commercial bias in a publication that supports the advantages of HMWHA. We completely agree on the importance of equipoise in the analysis and reporting of data; we also note that these observed advantages of HMWHA are not isolated and there are now several meta-analyses and systematic reviews that have drawn similar conclusions. Three recent studies of HMWHA reveal SMDs of − 0.52, − 0.57, and − 0.76, all exceeding the accepted thresholds for clinically meaningful improvement by the AAOS. [11,12,27] In response to questions regarding the cost of therapy, we agree that IA-HA should not be primarily used to delay surgery for patients with advanced KOA; this indication would not constitute conscientious use of medical resources. We propose that the ideal use of IA-HA is part of a multi-modal strategy to improve pain, function, and joint health, with the ultimate goal of reducing the need for TKA and associated expenses.

Drs. Hunt, Provenzano and Mittal also highlight the increased incidence of adverse events such as joint swelling and arthralgia with the use of IA-HA.[7] This finding is not surprising. Within the context of a clinical trial, temporary joint pain after injection is clearly an adverse event; however, in the context of disease-modifying therapies for OA, temporary joint discomfort may be merely a sign of a therapeutic immune response. IA-HA provides biochemically beneficial and potential disease-modifying effects within the knee. The health (and molecular size) of hyaluronic acid (HA) regulates the inflammatory signature of synovial fluid: smaller particles, especially those < 400 kDa, not only reduce viscosity and joint lubrication, but also act as ligands at CD44 transmembrane receptors and immunologically active Toll-like receptors (TLR-2, TLR-4) in chrondrocytes and synovial tissue. Collectively, these small HA breakdown products upregulate NF-kB pathways and increase the expression of pro-inflammatory cytokines such as IL-1β and TNFα, peripheral drivers of joint damage in OA, especially in early disease; [28] this pro-inflammatory state further reduces the production of beneficial growth factors for cartilage such as TGF-β. [29] These small HA fragments augment the concentrations of catabolic enzymes such as matrix-metalloproteinases (MMP-1 and -3), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS 4 and 5). MMP cleaves type II collagen, the most abundant articular cartilage in healthy joints; ADAMTS breaks down aggrecan – a critical component of cartilage proteoglycan. The over-expression of these enzymes directly contributes to the progression of OA, often proceeding radiographic damage. Conversely, their suppression is likely the key to reducing the severity and burden of radiographic and symptomatic OA. [30]

IA-HA with molecular weight > 500 kDa has the opposite effect, inhibiting activities at TLR and CD44 receptors, suppressing MMP and ADAMTS production, and protecting cartilage from inflammatory and enzymatic damage. It has been shown that incubation of joint tissue from OA patients with synthetic HA products reduces, in a dose-dependent manner, IL-1β, TNFα, and IL-6. [30] HA of various molecular weights have also been shown to increase the synthesis of extracellular matrix proteins, cartilage proteoglycan, and the production of the protective TIMPs (tissue inhibitors of metalloproteinases). [30] These benefits appear to be magnified with the use of HMWHA that demonstrates a more profound suppression of inflammatory cytokines and catabolic enzymes than LMWHA. High molecular weight HA is able to additionally blunt the impact of a wide spectrum of pronociceptive factors including prostaglandin E_2, and even the chemotherapeutic agent, paclitaxel. [31] The biochemical functions of HA explain how an HA molecule with a short intra-articular half-life (days) can potentially provide prolonged analgesia (months). [3]

In summary, IA-HA, especially with high molecular weight products, is an underutilized intervention that provides both clinically important benefits and favorable biological activities in the treatment of KOA. Multiple randomized, controlled trials and a Cochrane Review support its benefits and its clinical impact has been underestimated because of the pooling of multiple molecular weight products in meta-analyses; when HMWHA is separately evaluated, the analgesic and functional benefits are clearIA-HA is a biologically active treatment, providing suppression of inflammatory cytokines such as IL-1β, IL-6, TNFα and catabolic enzymes such as MMP and ADAMTS. IA-HA is a safe, time-tested, and easily administered intervention that has the potential to improve symptoms and joint

health in thousands of individuals in the US who experience functional limitations from mild-moderate OA and are not candidates for joint arthroplasty. Both the clinical and basic science studies support that the use of high-molecular weight IA-HA as the optimal next treatment option for this patient. It is time to revisit the treatment guidelines for mild to moderate KOA to include these safe and effective therapies.

Drs. Hunt, Provenzano and Mittal Rebut

Our colleagues make a sound argument in favor of IA-HA based on proposed molecular mechanisms, albeit with limited clinical data available to support their conclusion that this therapy should be routinely offered as first-line interventional therapy for knee OA. Although there are many chronic pain conditions for which we do not have clear evidence-based management recommendations, there are comprehensive guidelines available supporting non-surgical management of knee OA. High quality clinical trials fail to demonstrate clear efficacy of IA-HA for improvement of pain and function in knee OA, particularly given IA-HA's increased costs compared to other conservative treatment measures. There are more adverse effects (AEs) associated with IA-HA compared to IA-CS, [7] with the most commonly cited AEs including arthralgia (2.8–7.2%), joint swelling (1.2–5.6%), peripheral edema (0.7%), and injection site pain (0.5%). [32] Indeed, a systematic review of RCTs studying IA-HA observed that viscosupplementation did significantly increase the risk for serious AEs (relative risk, 1.41 [CI 1.02–1.97]) without clinically significant benefit in terms of pain or function. [17] Nevertheless, individual patients may experience relief with these injections and practitioners continue to use viscosupplementation despite AAOS and ACR guidelines.

Physicians and patients should engage in shared decision-making regarding the mixed evidence supporting IA-HA for symptomatic knee OA. When considering appropriate treatment for painful knee OA we advocate for a critical review of the evidence. Considering the high risk of bias present in clinical studies evaluating IA-HA for knee OA, considerable degree of statistical heterogeneity even in recent meta-analyses, and clinically very little difference between IA-HA and placebo or IA-CS with IA-HA associated with higher cost and risk for AEs, pain practitioners should not offer IA-HA routinely for patients with painful knee OA. Instead, providers should consider physical therapy with maintenance of home exercise program, weight loss in obese patients, and from an interventional standpoint intra-articular corticosteroid injection or genicular nerve radiofrequency ablation.

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Table 1:

Approximate molecular weights and sources of commonly used IA-HA products

Product	Compound	Approximate Molecular Weight	Source	Injection Number
Durolane®	Sodium Hyaluronate	Modified High Molecular Weight	Bacterial Fermentation	Single
Gel-One®	Sodium Hyaluronate	Modified High Molecular Weight	Avian	Single
Hymovis®	Sodium Hyaluronate	Modified High Molecular Weight	Bacterial Fermentation	Multiple
Synvisc-One®	Crosslinked Hylan G-F 20	6,000 kDa	Avian	Single
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Euflexxa®	Sodium Hyaluronate	2,400–3,600 kDa	Bacterial Fermentation	Multiple
Monovisc®	Sodium Hyaluronate	1,000–2,900 kDa	Bacterial Fermentation	Single
Orthovisc®	Sodium Hyaluronate	1,000–2,900 kDA	Bacterial Fermentation	Multiple
Gelsyn-3®	Sodium Hyaluronate	1,100 kDa	Bacterial Fermentation	Multiple
Tri-Visc™	Sodium Hyaluronate	620–1,170 kDA	Bacterial Fermentation	Multiple
GenVisc® 850	Sodium Hyaluronate	620–1,170 kDA	Bacterial Fermentation	Multiple
Supartz®	Sodium Hyaluronate	620–1,170 kDA	Avian	Multiple
Visco-3™	Sodium Hyaluronate	620–1,170 kDA	Avian	Multiple
Hyalgan®	Sodium Hyaluronate	500–730 kDA	Avian	Multiple