Hyaluronic Acid Injections in Knee Osteoarthritis: What Do the Updated Recommendations Say?

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The session 'ESCEO Symposium: Update of the 2017 recommendations for the use of hyaluronic acid injections in patients with knee osteoarthritis: a patient-centered experts' consensus' at the World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (WCO-IOF-ESCEO) 2026 brought together leading rheumatologists to explore the evidence for intra-articular hyaluronic acid injections in osteoarthritis (OA) care.

UMBRELLA REVIEW SUPPORTS IAHA EFFICACY

Olivier Bruyère, University of Liège, Belgium, opened the conversation on the efficacy of intra-articular hyaluronic acid (IAHA) injections, showcasing the lack of universal consensus in regard to their benefits in knee OA.

Guidelines significantly differ for this treatment. USA guidelines generally do not recommend IAHA injections, whereas guidelines from international bodies, including the Osteoarthritis Research Society International (OARSI) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), support their use in selected patients.[1,2]

Bruyère outlined an umbrella analysis that he and his team published,[3] in which the principal objectives were to clarify the effectiveness of IAHA in knee osteoarthritis using evidence from previously conducted systematic reviews (SR) and meta analyses, identify the characteristics of SRs and meta-analyses that may explain discrepancies in reported conclusions, and describe the outcomes that were consistent across studies.

This umbrella analysis adhered to the Cochrane guidelines for Overviews of Reviews and the Preferred Reporting Items for Overviews of Reviews (PRIOR) checklist, as well as being recorded in the Prospective Register of Systematic Reviews (PROSPERO). Inclusion criteria consisted of SRs of RCTs with or without meta-analyses, assessing pain or functional efficacy outcomes compared with placebo, including saline or any alternatives. SRs including both randomised and non-RCTs were excluded from the analysis, alongside scoping reviews and abstract, commentaries, and narrative reviews of SRs.

He also outlined A Measurement Tool to Assess Systematic Review version 2 (AMSTAR-2) checklist, which was used to assess the quality of meta-analyses and mitigate bias. The tool categorises them into critically low, low, moderate, and high-quality analyses.

Out of more than 1,500 papers identified, 22 SRs or meta-analyses were included. Twenty of these 22 reported significant benefits of IAHA for improving patient symptoms. Collective significant results from these studies displayed 15 as having positive conclusions, three mixed, and four negative. The AMSTAR-2 checklist demonstrated that the five analyses

categorised as 'high-quality' demonstrated statistically significant benefits to the patients following IAHA treatment. However, author conclusions remained mixed, with three positive and two negative interpretations. Bruyère and his team explored this discrepancy and concluded that negative interpretations often arose when there were restrictions in the inclusion criteria, such as the number of patients in the RCT, or when the clinical relevance of the results was challenged.

Overall, the umbrella study demonstrated that high-quality SRs and meta-analyses consistently support a significant effect of IAHA on pain and function in knee osteoarthritis. However, Bruyère argued that, because responses to treatment vary, patient selection remains important.

SAFETY PROFILE OF IAHA INJECTIONS

Ali Mobasheri, University of Oulu, Finland, speaking on behalf of Emmanuel Maheu, Hôpital Saint-Antoine, Paris, France, then discussed the efficacy and safety of IAHA treatment. He highlighted the substantial placebo effect associated with IAHA, noting that injections of saline, or even a single puncture without injection, may improve OA pain.[4] He argued that saline itself may act as an active treatment rather than a true placebo.

An SR by Bannuru RR et al.[5] studied 74 trials and 13,032 patients aged 45–75 years. Global incidence of local adverse events was shown to be 8.5%, with the most common being transcient local reactions, pain at injection site, effusion, and arthralgia, all of which resolved spontaneously. Overall safety was therefore excellent and was comparable to the placebo. This was supported by a Cochrane collaboration, which concluded that IAHA treatment led to more local reactions, but fewer systemic adverse effects, than systemic treatments.[6]

Maheu et al.[7] also reported an 8.5% rate of local post-injection reactions, consisting of pain, redness, and short flares. Clinical trials and post-marketing surveys have demonstrated similar rates, while repeated cycles of injections do not increase the frequency of these reactions.

Mobasheri also highlighted flaws in studies presenting evidence against the use of IAHA injections, warning of misleading data where there is a lack of analysis of the plausibility of these serious adverse effects. He reiterated Bruyère's statement that certain patient groups may derive greater benefit from treatment.

He then likened criticism of IAHA safety data to COVID-19 anti-vaccination movements, stating that an epidemiological, contextual perspective should be considered when looking at adverse events associated with IAHA.

He concluded by highlighting the extensive safety record of IAHA, demonstrating local adverse events comparable to placebo injections, and very few systemic effects.

NEXT-GENERATION COMBINATION THERAPIES

Finally, Nicholas Fuggle, University of Southampton, UK, discussed the newest developments in hyaluronic acid (HA) therapy for OA, specifically combination therapy. These included combinations with mannitol, sorbitol, chondroitin, polynucleotides, and tranexamic acid (TXA).

Mannitol acts as a scavenger of reactive oxygen species, reducing degradation of HA and thereby increasing its residence time within the joint, potentially prolonging the therapeutic effect. Rheological models have shown that, in chondrocytes from patients with OA, HA alone loses both its elastic and storage modulus over time, whereas with the addition of mannitol, both these properties are maintained over 30 minutes.[8]

Fuggle then presented a study by Maheu et al.,[9] which demonstrated non-inferiority of combined HA–mannitol therapy compared with HA alone in a two-arm, single-injection study.

He then went on to outline the differential yet similar chemical structure of mannitol and sorbitol as diastereomers. Although both are six-carbon sugar alcohols, mannitol is derived from mannose, whereas sorbitol is derived from glucose. Their distinct chemical structure provides them with different medical applications, as mannitol is excreted in the urine and sorbitol is metabolised by the liver.

Similar to mannitol, sorbitol scavenges hydroxyl radical species. Mongkhon et al.[10] demonstrated that sorbitol abrogated IL-1β-induced catabolism, inflammation, and reactive oxygen species production in the joint. Furthermore, baseline functional status has been shown to predict response to HA–sorbitol, with the bottom 10th percentile for baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function as the strongest predictor (odds ratio: 13.81).[11]

He then moved on to discuss chondroitin sulphate as a combination therapy with HA. Chondroitin sulphate is known to exert anti-inflammatory effects through reduction of nuclear factor kappa-light-chain-enhancer of activated B cell (NF-kB) activation. Given its role as a component of the cartilage matrix, it can also contribute to hydration and elasticity.[12] Chondroitin combination therapy may therefore increase the viscosity of synovial fluid, improve HA tissue adherence, and enhance rheological properties of elastic and storage modulus. Combination therapy with chondroitin sulphate and HA significantly reduced IL-1β, IL-6, and TNF-α levels more than either treatment individually, while increasing levels of aggrecan and collagen-II.[12]

Fuggle next discussed polynucleotide combination therapy. Polynucleotides are highly-purified, high molecular weight polymers that act as a substrate for nucleases within the joint, and therefore potentially have a synergistic effect with HA. Stagni et al.[13] reported a significantly greater difference in WOMAC pain scores versus baseline after 2, 6, and 12 months for polynucleotides and HA combination therapy.

Finally, similar to mannitol combination therapy, TXA modifies HA and protects it against degradation. It may also serve as an anti-inflammatory factor through reduction of IL-6 and C-reactive protein (CRP) via plasminogen-dependent and plasminogen-independent pathways.[14] Potential cartilage benefits have also been suggested. The murine study by Brochard et al.[14] found symptomatic benefits of TXA-modified HA. Structural benefits were also observed, however they were seen in both HA alone and TXA/HA combination therapy, suggesting no additional benefit of TXA combination therapy.

Fuggle concluded by summarising the range of emerging combination therapies for HA. Mannitol and sorbitol combinations have demonstrated non-inferiority, likely paving the way for superiority studies as the next steps. Chondroitin combinations, however, have been demonstrated to be effective in single-arm studies, but would require controlled studies to validate these findings. Looking ahead, polynucleotides and TXA combination therapies represent novel areas of development that may prove beneficial in osteoarthritis management.

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