Viscosupplementation for Knee Osteoarthritis: Current Evidence and Recommendations

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ABSTRACT: Osteoarthritis (OA) is the most common joint disorder worldwide and is a leading cause of pain and disability. Appropriate management of younger patients with milder disease remains a challenging area of intense research. Viscosupplementation attempts to restore the biomechanical and biochemical functions of normal synovial fluid hyaluronic acid. Several preparations with varying characteristics are currently available. The literature suggests a small benefit and relative safety, but several recent large meta-analyses have reported conflicting results. Major clinical guidelines provide inconclusive recommendations. Viscosupplementation may be a viable option in younger patients with milder OA where other non-operative modalities are also only modestly successful, but further investigation is clearly warranted. Limitations due to study heterogeneity, outcome reporting, and bias can each be addressed with improved research methodology.

KEY WORDS: viscosupplementation, osteoarthritis, knee, hyaluronic acid, evidence-based medicine

I. THE GLOBAL BURDEN OF OSTEOARTHRITIS

Osteoarthritis (OA) is the most common joint disorder in the world and is a leading cause of pain and disability.1 Risk factors include obesity, female sex, manual labor, joint injuries, and certain genetic, ethnic, and nutritional factors.2,3 It affects approximately 15% of adults over 45 years old,4 and its incidence increases with age.1 In the United Kingdom, 50% of adults with knee OA report at least some disability,5 and in the United States, OA is second only to back pain as a cause of lost productivity.6 Prevalence rates in India range from 22 to 39%.7 In Asia, approximately 40 million of the 130 million people with OA will have severe disabling disease by 2030.8

The global burden of osteoarthritis will continue to increase as patients live longer and remain active later in life.9 Nearly half of all adults will experience symptomatic OA by age 85.3 Total healthcare expenditures related to OA are already as high as $80 billion per year in the United States,10 and in 2009 more than $40
billion was spent on costs directly related to nearly 1 million joint replacements. The worldwide economic impact of lost productivity is also substantial.

II. NON-ARTHROPLASTY MANAGEMENT OF OSTEOARTHRITIS

Total knee arthroplasty (TKA) achieves excellent pain relief and long-term functional outcomes in older patients with severe OA. In younger patients, however, rates of aseptic loosening and revision surgery are both increased. Revision surgery carries substantially greater risks for infection, fracture, and implant failure. Extended hospitalizations, medical complications, functional disability, and perioperative mortality are also increased, and the financial impact is staggering.

Appropriate non-arthroplasty management of younger patients with milder disease remains a challenging area of intense research.

Weight-loss, aerobic exercise, and muscle-strengthening are each supported by meta-analyses of large randomized trials to provide modest benefits, as are the use of non-steroidal anti-inflammatories (NSAIDs) and acetaminophen. Topical NSAIDs are helpful for patients with gastrointestinal or cardiovascular contraindication to oral agents. Mixed evidence suggests a small benefit from glucosamine and/or chondroitin sulfate. Bracing and orthoses may be useful in certain patients, but studies are small and of poor quality. Several randomized trials report that intra-articular corticosteroid injections are effective at providing short-term pain relief, but they do not provide long-term benefit and they may increase rates of infection after eventual TKA.

Periarticular osteotomies and unicompartmental knee arthroplasties are reasonable options in appropriate patients with specific indications. Arthroscopic surgery can benefit patients with symptomatic meniscal pathology, but arthroscopic lavage and debridement have clearly been shown to be of no benefit in isolated osteoarthritis.

III. VISCOSUPPLEMENTATION

Healthy adult knees contain approximately 2 mL of normal synovial that distributes nutrients to chondrocytes and lubricates articular cartilage. Hyaluronic acid (HA) is one of the main components of normal synovial fluid and it is produced by type-B synoviocytes, fibroblasts, and chondrocytes. HA is a glycosaminoglycan molecule made up of repeating units of N-acetyl-glucosamine and glucuronic acid. In normal joints, the average molecular weight of HA is approximately $5 \times 10^6$ Da and the concentration is 2.5 to 4 mg/mL. Biomechanically, HA acts as a viscoelastic shock-absorber under high shear and as a lubricant during slow movement.

HA also functions through anti-inflammatory, anabolic, analgesic, and chondroprotective mechanisms. HA reduces prostaglandin, fibronectin, and cyclic adenosine monophosphate levels, inhibits arachidonic acid release by synovial fibroblasts, and impairs leukocyte phagocytosis, adherence, and stimulation. HA injections stimulate synovial fibroblasts to synthesize endogenous HA, and they reduce pain by inhibiting nociceptors, decreasing bradykinin synthesis, and sequestering the signaling peptide substance P. HA was associated with an increase in cartilage matrix production by chondrocytes in some models, but others found conflicting results. The long-term chondroprotective function of HA remains debated.

The synovial fluid in OA knees contains elevated levels of free radicals, inflammatory cytokines, and cleavage enzymes. These substances contribute to reduced HA production, reduced HA half-life, molecular fragmentation of HA, and water-rich effusions that dilute HA.
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concentrations.\textsuperscript{34,35} Effectively, OA knees are deficient in HA function, and this leads to articular cartilage damage and OA progression.\textsuperscript{25} Fragmented HA molecules also induce proinflammatory signaling cascades, which further accelerate OA progression.\textsuperscript{35,36}

Peyron and Balazs first reported on intraarticular HA for osteoarthritis in 1974.\textsuperscript{37} HA was approved for use as a biological device in humans in Canada in 1992 and in the United States in 1997.\textsuperscript{24,27} Modern commercial HA is either harvested and purified from rooster combs or produced by bacterial fermentation \textit{in vitro}.\textsuperscript{36} The former is more easily manipulated through molecular cross-linking to increase weight, while the latter is particularly useful in patients with poultry allergies.\textsuperscript{36} Higher molecular weight HA is suggested to have greater efficacy, but clinical studies are inconclusive.\textsuperscript{38}

Several preparations are currently available in North America: Hyalgan (Sanofi-Synthelabo Inc., New York, NY), Synvisc (Genzyme Corp., Cambridge, MA), Supartz (Seikagaku Corp., Tokyo, Japan), and Orthovisc (DePuy-Mitek Inc., Woburn, MA) are each avian-derived, and Euflexxa (Ferring Pharmaceuticals Inc., Suffern, NY) is non-avian derived.\textsuperscript{6} Molecular weights vary between manufacturers and range from 0.5 to 6.0 $\times$ $10^6$ Da.$^6$ In 2012, Synvisc (Hylan G-F 20) was reformulated to a single-dose regimen, but the other products require varying regimens of 3 to 5 weekly injections.$^6$ Pharmacodynamics, half-lives, and cost all vary between products.$^6$

IV. CURRENT EVIDENCE

Evidence-based medicine is the integration of the best available research, clinical expertise, and patient values to facilitate decision-making.\textsuperscript{39} New technologies have the potential to markedly improve patients’ lives, but early adoption of unproven interventions can lead to wasted resources, patient morbidity, and even mortality.\textsuperscript{40} The implementation of novel devices or drugs should involve thorough safety and efficacy assessments, and healthcare systems should consider patient tolerability and economic impact.\textsuperscript{40,41}

Meta-analyses are a form of evidence synthesis that utilize statistical methods to combine the results of multiple clinical trials.\textsuperscript{42} They are usually performed as part of a comprehensive systematic review of the literature.\textsuperscript{42} By pooling data, they improve the power otherwise lacking in small individual studies.\textsuperscript{43} Meta-analyses of high-quality randomized trials with homogeneous results sit atop the hierarchy of medical evidence, but only if they are performed with robust methodology.$^4^4$ Common pitfalls in meta-analyses are the inclusion of low-quality primary studies and failure to perform quality assessment.$^4^4$ Poorly executed meta-analyses risk overestimating or distorting pooled treatment effects.$^4^4$

A. Efficacy

Several meta-analyses have examined the efficacy of viscosupplementation for knee OA. In 2007, Campbell et al. published a review of six meta-analyses with conflicting results.$^4^5$ They found that all six meta-analyses asked similar clinical questions, but differences in the search strategies and selection criteria led to inclusion of different primary trials. There were also differences in the choices of pooled outcome measures and outcome time-points, assessments of study quality, and selection of statistical models. Overall, they concluded, based on the GRADE (Grades of Recommendation Assessment, Development and Evaluation) approach, that viscosupplementation provides a probable therapeutic benefit for pain reduction and physical function improvement with a low risk for harm. They suggested that further research would be unlikely to change the confidence in their estimate of effect.
Bellamy et al. published an updated industry-sponsored Cochrane review in 2006 that included 76 primary trials of 18 different HA products or derivatives. The median quality score of the included studies was 3 of 5, and sample sizes ranged from 12 to 495. They found statistically significant benefits compared to placebo for pain, function, and patient global assessment scores that were most pronounced at 5 and 13 weeks post-injection. They attempted to examine differences between individual HA preparations, but heterogeneity of the included studies precluded meaningful comparisons.

More recently, Rutjes et al. published a meta-analysis in *Annals of Internal Medicine* in 2012. They compared the primary outcomes of pain intensity and frequency of OA flares across 89 trials involving 12,667 patients. In their analysis, trial size, use of blinded outcome assessment, and publication status were each associated with treatment effect size. An asymmetrical funnel plot suggested the presence of publication bias, that trial quality was generally low, and that safety data were infrequently reported. Using validated minimum important differences (MIDs), they determined that viscosupplementation provided only an irrelevant small benefit, and they noted a significant increase in the risk for serious adverse effects. Overall, they recommended against the use of viscosupplementation for patients with knee OA.

**B. Safety**

Recognized contraindications to HA injection include active joint infections, bacteremia, overlying skin disease, avian allergies, pregnancy or nursing, and pediatric patients. Adverse events are uncommon, but a self-limited soft-tissue reaction at the injection site has been recognized. These reactions are characterized by localized pain and a knee effusion, and they typically resolve without treatment in 1–3 days. These adverse effects may be related to improper injection techniques (such as injection into the subcutaneous tissues or infra-patellar fat pad in an obese patient) or inappropriate mixture of corticosteroids or local anesthetic with the HA products, but their etiology remains poorly understood. Rutjes et al. reported no significant increase in risk for this event compared to controls. Bellamy et al. cautioned that their included studies were too underpowered to detect uncommon adverse events.

Case reports describe a rare but much more severe reaction known as “pseudosepsis.” It is suggested to be an immune-mediated response triggered by sensitization to HA cross-links, but the exact pathogenesis remains unclear. Five diagnostic criteria were described by Goldberg and Coupts: (1) marked inflammation of the joint, typically with significant effusion and pain and normally occurring within 24–72 hours after injection; (2) occurring more often after exposure to more than one injection; (3) sepsis or pseudogout are ruled out by the absence of infectious organisms and calcium pyrophosphate crystals in the synovial fluid; (4) synovial fluid may include high numbers of mononuclear cells; (5) pseudosepsis is generally not self-limited and requires clinical intervention, usually NSAIDs, arthrocentesis, and intra-articular steroid injection. Future studies should identify patients at risk for this reaction and indicate whether they may safely receive certain formulations of viscosupplementation.

**C. Guidelines**

In 2007, the Osteoarthritis Research Society International (OARSI) performed a detailed systematic review and critical appraisal of all research and existing treatment guidelines for the management of hip and knee OA. This work was followed by a set of evidence-based consensus guidelines in 2008, which was updated to accommodate cumulative changes...
in the literature in 2010.\textsuperscript{17,52} They identified that 8 of 9 major clinical practice guidelines recommended HA as a useful therapeutic modality, despite significant controversy about its efficacy, safety, and cost-effectiveness.\textsuperscript{17} Based on their interpretation of 17 meta-analyses, they recommended that viscosupplementation may be useful in patients with knee OA, but cautioned that significant study heterogeneity, likely publication bias, and industry-sponsoredship limited the strength of their conclusions.\textsuperscript{17} The American Academy of Orthopaedic Surgeons (AAOS) published an evidence-based Clinical Practice Guidelines Summary of non-arthroplasty treatment for knee OA in 2009.\textsuperscript{18} Their recommendations were based primarily on a systematic review of 42 published studies and the consensus opinion of an expert work group. Although they determined that viscosupplementation had generally positive therapeutic effects, the results were limited by poor study quality, publication bias, conflicting results, and unclear clinical significance. They cautiously concluded, “We cannot make a recommendation for or against the use of intra-articular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee”.\textsuperscript{18}

V. RECOMMENDATIONS

Much of the heterogeneity in the primary trials can be attributed to inadequate sample sizes.\textsuperscript{53} In the review by Bellamy et al., the majority of included trials randomized less than 100 patients each and were grossly underpowered to detect small differences in outcomes important to patients.\textsuperscript{54} Randomized trials with insufficient power risk missing true effects or giving misleading results.\textsuperscript{54} In doing so, they waste resources and potentially cause harm.\textsuperscript{55,56} Future trials should justify and recruit appropriately large sample sizes based on conservative estimates of potential effect.\textsuperscript{54} Rare adverse events and long-term safety should be best observed in large cohort studies or registry-type databases rather than randomized studies.\textsuperscript{57} Study heterogeneity also results from the inclusion of heterogeneous patient populations, such as a diversity of advanced OA, limb malalignment, knee effusions, pseudogout, and inflammatory arthropathy.\textsuperscript{42}

“Minimal important differences” (MIDs) are the smallest treatment effects that individual patients perceive as beneficial enough to justify a change in their management.\textsuperscript{58} In clinical trials or in meta-analyses, small effects may often be statistically significant without demonstrating real-world patient benefits.\textsuperscript{58} MIDs are critically important because they determine whether the magnitudes of treatment effects are trivial, small but important, moderate, or large. MIDs also rationally inform the sample size calculations for subsequent studies.\textsuperscript{59} In their industry-sponsored Cochrane review, Bellamy et al. did not include an MID but concluded that viscosupplementation was an effective treatment based on statistically significant differences in weighted means between groups.\textsuperscript{46} In contrast, Rutjes et al. used a validated MID for pain relief in knee OA and determined that viscosupplementation provided a statistically significant but clinically irrelevant benefit.\textsuperscript{47} Future investigations should evaluate patient outcomes based on validated MIDs to truly inform clinicians and patients about the desirable and undesirable outcomes of proposed therapies.\textsuperscript{60}

Finally, clinicians must note that most of the trials for viscosupplementation have been industry sponsored, if not industry designed and industry executed.\textsuperscript{17} Industry sponsorship of clinical research is known to bias investigators towards statistically significant pro-industry findings.\textsuperscript{61} The discretionary publication of trials with positive results further accentuates this bias and may seriously distort estimates of treatment effect.\textsuperscript{62} Rutjes et al. revealed an asymmetrical funnel plot and demonstrated a significant risk of publication bias among their
89 included trials, and the Cochrane review by Bellamy et al. included multiple disclosures of industry support. Although large studies of new devices have inherent economic and logistic challenges, researchers must emphasize strategies to minimize the influence of industry. Study funding, design, and management should be transparent, and the processes of manuscript preparation and authorship should be reported clearly. Ideally, these aspects should be completely independent from the sponsoring organization. Additional strategies to limit bias include registration of all clinical trials prior to enrollment, and blinding of patients, caregivers, and outcome assessors.

VI. CONCLUSION

In conclusion, the role of viscosupplementation for OA of the knee remains unclear. The literature suggests a small benefit and relative safety, but several recent large meta-analyses have reported conflicting results. Major clinical guidelines report inconclusive recommendations. Viscosupplementation may be a viable option in younger patients with milder OA where other non-operative modalities are also only modestly successful, but further investigation is clearly warranted. Limitations due to study heterogeneity, outcome reporting, and bias can each be addressed with improved research methodology.

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