Systematic Review

Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses

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Purpose: To conduct a systematic review of overlapping meta-analyses comparing treatment of knee osteoarthritis (OA) with intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA]) versus oral nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids (IA-corticosteroids), intra-articular platelet-rich plasma (IA-PRP), or intra-articular placebo (IA-placebo) to determine which meta-analyses provide the best current evidence and identify potential causes of discordance. **Methods:** Literature searches were performed for meta-analyses examining use of IA-HA versus NSAIDs, IA-corticosteroids, IA-PRP, or IA-placebo. Clinical data were extracted, and meta-analysis quality was assessed. The Jadad algorithm was applied to determine which meta-analyses provided the highest level of evidence. **Results:** Fourteen meta-analyses met the eligibility criteria and ranged in quality from Level I to IV evidence. In studies reporting patient numbers, there were a total of 20,049 patients: 13,698 receiving IA-HA, 355 receiving NSAIDs, 294 receiving IA-corticosteroids, and 5,702 receiving IA-placebo. Ten studies examined the effects of IA-HA versus IA-placebo; of these, 5 found that IA-HA improved pain and 4 found that IA-HA improved function. No clinically relevant differences in the efficacy of IA-HA versus NSAIDs regarding pain and function were found. Regarding IA-HA versus IA-PRP, IA-HA improved knee function at 2 and 6 months after injection but the effects were less robust than those of IA-PRP. Regarding IA-HA versus IA-corticosteroids, the positive effects of IA-HA were greater at 5 to 13 weeks and persisted for up to 26 weeks. After application of the Jadad algorithm, 2 concordant high-quality meta-analyses were selected and both showed that IA-HA provided clinically relevant improvements in pain and function compared with IA-placebo. **Conclusions:** This systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA shows that the current highest level of evidence suggests that IA-HA is a viable option for knee OA. Its use results in improvements in knee pain and function that can persist for up to 26 weeks. IA-HA has a good safety profile, and its use should be considered in patients with early knee OA. **Level of Evidence:** Level IV, systematic review of Level I to IV studies.

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Knee pain due to osteoarthritis (OA) is one of the most common complaints in patients presenting to orthopaedic clinics, resulting in significant societal costs including cost of treatment and lost time from work or activities.[1,2] Several nonoperative and operative treatment options exist to mitigate this pain and the resulting limitations in function occurring in patients with arthritis. The goal of nonoperative treatment modalities is to minimize pain and restore function in a noninvasive manner while prolonging the need for a total knee arthroplasty (TKA).

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The authors report the following potential conflict of interest or source of funding: B.R.B. receives support from Arthrex, Ossur, Linvatec, and Smith & Nephew. B.J.C. receives support from Arthrex, DJ Orthopaedics, Johnson & Johnson, Regentis, Zimmer, and Smith & Nephew. N.N.V. receives support from Minivasive, Smith & Nephew, Arthrosurface, Omeros, Arthrex, Athletico, ConMed Linvatec, Miomed, and Mitek.

Received December 10, 2014; accepted March 19, 2015.

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0749-8063/141037/$36.00

http://dx.doi.org/10.1016/j.arthro.2015.03.030

These options include intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA]), intra-articular corticosteroids (IA-corticosteroids), oral nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular platelet-rich plasma (IA-PRP).

Viscosupplementation is the injection of an intra-articular compound made of high-molecular-weight fluid containing hylan products (derivative of hyaluronan) that essentially functions as a viscoelastic glycosaminoglycan. Hyaluronic acid (HA) is naturally present in joint fluid and serves multiple purposes including shock absorption, joint lubrication, and energy dissipation; in addition, it coats the articular cartilage surfaces of the femur, tibia, and patella to protect them.[3]

The desire to delay the treatment of knee OA with TKA lies in the desire to reduce the possibility of the need for early revision TKA. Although the failure rate varies on an individual basis, it is generally accepted that the revision rate for knee arthroplasty is slightly less than 1% per year with a 10-year survivorship rate of approximately 95% and a 20-year survivorship rate of approximately 85%.[4-8] Recent evidence has shown that approximately 4 million persons in the United States are living with a TKA and that over half of the adults in the United States diagnosed with knee OA will eventually undergo TKA.[9]

Despite the plethora of studies examining the array of less invasive treatment options that exist for knee OA prior to performing a TKA, there has been no definitive consensus as to which treatments are the most effective at improving pain and function.[10,11] Arrich et al.[10] performed a meta-analysis to determine if IA-HA improved pain or function in patients with knee OA and found that it did improve activity-related knee pain. Conversely, Bannuru et al.[11] conducted a meta-analysis comparing IA-HA with oral anti-inflammatory medications, and although both treatments showed improvements in function and stiffness, there were no differences between the groups.

Therefore the purpose of this study was to conduct a systematic review of overlapping meta-analyses comparing treatment of knee OA with IA-HA versus oral NSAIDs, IA-corticosteroids, IA-PRP, or intra-articular placebo (IA-placebo) to determine which meta-analyses provide the best current evidence and identify potential causes of discordance. The main objectives of this study were (1) to conduct a systematic review of meta-analyses comparing the aforementioned treatment options for knee OA, (2) to provide an analytical framework for interpreting the presently discordant best available evidence to develop treatment recommendations, and (3) to identify gaps in the literature that require continued investigation. We hypothesized that intra-articular injections of HA would provide significant improvement in pain and function with minimal side effects compared with IA-corticosteroids, IA-PRP, IA-placebo, or oral anti-inflammatory medications.

Methods

A systematic review of the literature was performed using the PubMed database, CINAHL (Cumulative Index to Nursing and Allied Health Literature) Complete database, Cochrane Database of Systematic Reviews, Scopus database, and Embase database. The following search terms were used: meta-analysis AND hyaluronic acid AND (knee [arthritis OR osteoarthritis]) AND (corticosteroid OR NSAID OR placebo OR [platelet rich plasma OR PRP]). The search was performed on August 24, 2014, and was limited to articles written in English. Broad search query terms were used to include all possibly applicable studies. All reviewed articles were then manually cross-referenced to ensure that all potential studies were included.

The abstracts that resulted from these searches were reviewed by 2 of the authors (K.A.C. and R.M.). The inclusion criteria were meta-analyses that compared the use of IA-HA in knee OA with the use of IA-placebo, IA-PRP, IA-corticosteroids, or oral NSAIDs. Cadaveric, animal, and biomechanical studies were excluded. The exclusion criteria included narrative reviews, reviews without an organized and reported search algorithm, reviews that did not directly compare IA-HA versus another treatment modality, studies without clinical outcome data, and non−English-language studies. Systematic reviews that did not pool data or perform a meta-analysis were also excluded. Full-text articles were then obtained for those studies that met both the inclusion and exclusion criteria. The references for each of these citations were manually screened to ensure that no studies were missed. The tables of contents for the past 2 years of *Arthroscopy*, *The Journal of Bone and Joint Surgery*, *The American Journal of Sports Medicine*, *Clinical Orthopaedics and Related Research*, *Osteoarthritis and Cartilage*, and *The New England Journal of Medicine* were manually searched for any additional studies that were not identified in our prior search. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram shows our study selection algorithm (Fig 1).

Data were extracted from the studies that met the inclusion criteria and included information about levels of evidence included in the studies, length of follow-up, duration of symptomatic relief, adverse events, knee function, knee pain outcomes, and pooled effect size. Standardized outcome scores that were collected included Lequesne scores, visual analog scale (VAS) pain scores, and Western Ontario and McMaster Universities Osteoarthritis Index pain subscores. Data specific to the methodology of the included meta-analyses were extracted and included the rationale for repeating