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Cochrane in *CORR*®: Viscosupplementation for the Treatment of Osteoarthritis of the Knee

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Importance of the Topic

Osteoarthritis is the most common joint disorder in the world [1]. It affects approximately 15% of adults older than 45 years of age [19], and nearly half of all adults will experience symptomatic osteoarthritis by age 85 [20]. Osteoarthritis is more common than Type 2 diabetes and most forms of cancer [22, 24]. In the United States, osteoarthritis is second only to back pain as a cause of lost productivity [25], and annual total healthcare expenditures related to osteoarthritis are as high as USD 80 billion. This figure is expected to increase during the next decade [27]. The appropriate management of younger patients with mild or moderate osteoarthritis remains a challenging area in the day-by-day clinic and intense research is being conducted [5, 11, 15].

Hyaluronic acid is a glycosaminoglycan molecule made of repeating units of N-acetyl-glucosamine and glucoronic acid [3]. It is one of the main components of normal synovial fluid. Hyaluronic acid functions through antiinflammatory, anabolic, analagesic, and chondroprotective mechanisms [2]. Biomechanically, it may act as a viscoelastic shock absorber, and perhaps as a lubricant in the joint [6]. The synovial fluid in knees with osteoarthritis contains elevated levels of free radicals, inflammatory cytokines, and cleavage enzymes [13], which impair hyaluronic acid function and contribute to the progression of osteoarthritis [3]. Viscosupplementation attempts to restore the biomechanical and biochemical functions of normal synovial fluid through intraarticular injections of hyaluronic acid. This systematic review and meta-analysis examined the effects of

A Note from the Editor-in-Chief: I am pleased to announce the partnership between CORR®, The Cochrane Collaboration®, *and McMaster University's Evidence-Based Orthopaedics Group for a new column, called* Cochrane in CORR®. *In the column, we will identify an abstract originally published in* The Cochrane Library *that we think is especially important, and colleagues from McMaster University will provide expert perspective on it.*
(Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005321. DOI: 10.1002/14651858.CD005321.pub2.)

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Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library (http://www.thecochranelibrary.com) should be consulted for the most recent version of the review.

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viscosupplementation in the treatment of osteoarthritis of the knee.

Upon Closer Inspection

Several preparations of modern commercial hyaluronic acid are currently globally available. They differ mostly by molecular weight, method of production, half-lives, and cost [25]. They are produced either from harvested rooster combs or via bacterial fermentation in vitro [18]. Some can be administered in single-dose regimens, but most require three to five weekly injections [25]. Higher molecular weight hyaluronic acid is suggested to have greater clinical efficacy, but the current literature is inconclusive [17]. This meta-analysis included only randomized controlled trials, and compared 19 different formulations of hyaluronic acid across 76 studies (9847 patients). However, there were few head-to-head trials and firm conclusions about the relative value of each formulation were not possible. Additionally, a diversity of control interventions were utilized, including placebo, intraarticular corticosteroids, nonsteroidal antiinflammatory drugs, physiotherapy, and arthroscopy, which meant that most analyses were based on only a few small trials.

The authors reported no major safety issues for viscosupplementation, but cautioned that the included trials were underpowered to detect rare adverse events [4]. Self-limited (and benign) soft-tissue reactions at viscosupplementation injection sites have been reported in up to 3% of injections [25, 26], and several reports have also described a rare but much more severe acute local reaction known as "pseudosepsis." Severe acute local reactions typically require arthrocentesis, nonsteroidal antiinflammatories, and intra-articular corticosteroid injections [12]. One study [16] reported a 21% incidence of severe acute local reactions in patients receiving more than one course of treatment, suggesting that patients who desire additional courses should be counseled of their possible increased risk. Future studies should investigate if certain patients are at risk for these reactions, and whether they could safely receive specific formulations [25]. Long-term safety could best be observed in large observational studies modeled after current total joint arthroplasty device registries or pharmaceutical postmarketing "phase-IV" surveillance studies [10, 14, 23].

Take-Home Messages

This Cochrane review found overall benefits to viscosupplementation in comparison to placebo for pain, function, and patient global assessment scores. Several other recent meta-analyses have produced conflicting results [9, 20, 28]. Rutjes et al. [21] found overall no clinically important benefit for pain intensity or frequency of osteoarthritis flares in 89 trials involving 12,667 patients, but high-molecular-weight and cross-linked preparations had greater effects, according to the Rutjes and colleagues study. Campbell et al. [9] reviewed six meta-analyses, and highlighted differences in search strategies, selection criteria, choices of pooled outcome measures and time-points, assessments of study quality, and selection of statistical model. Current clinical guidelines mention poor study quality, publication bias, conflicting results, industry-sponsorship, and unclear clinical significance for their inconclusive recommendations [7, 11, 29].

Based on the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach [8], viscosupplementation for knee osteoarthritis provides a probable pain reduction and improvement of physical function with a low-risk of harm [4, 9, 29]. It is a viable option in younger patients with less severe disease, but further investigations are still required. Future studies should examine whether high molecular weight and cross-linked preparations have superior efficacy, determine long-term outcomes and safety, and include economic analyses [4, 25]. Recurrent methodological limitations related to study heterogeneity, outcome reporting, and bias must be overcome [9, 11, 20, 29].

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Appendix

Viscosupplementation for the treatment of osteoarthritis of the knee (Review)

Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

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[Intervention Review]

Viscosupplementation for the treatment of osteoarthritis of the knee

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ABSTRACT

Background

Osteoarthritis (OA) is the most prevalent chronic joint disorder worldwide and is associated with significant pain and disability.

Objectives

To assess the effects of viscosupplementation in the treatment of OA of the knee. The products were hyaluronan and hylan derivatives (Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease, Euflexxa, Nuflexxa), Durolane, Fermathron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), Hyruan, NRD-101 (Suvenyl), Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject and Zeel compositum).

Search methods

MEDLINE (up to January (week 1) 2006 for update), EMBASE, PREMEDLINE, Current Contents up to July 2003, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Specialised journals and reference lists of identified randomised controlled trials (RCTs) and pertinent review articles up to December 2005 were handsearched.

Selection criteria

RCTs of viscosupplementation for the treatment of people with a diagnosis of OA of the knee were eligible. Single and double-blinded studies, placebo-based and comparative studies were eligible. At least one of the four OMERACT III core set outcome measures had to be reported (Bellamy 1997).

Data collection and analysis

Each trial was assessed independently by two reviewers for its methodological quality using a validated tool. All data were extracted by one reviewer and verified by a second reviewer . Continuous outcome measures were analysed as weighted mean differences (WMD) with 95% confidence intervals (CI). However, where different scales were used to measure the same outcome, standardized mean differences (SMD) were used. Dichotomous outcomes were analyzed by relative risk (RR).

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Main results

Seventy-six trials with a median quality score of 3 (range 1 to 5) were identified. Follow-up periods varied between day of last injection and eighteen months. Forty trials included comparisons of hyaluronan/hylan and placebo (saline or arthrocentesis), ten trials included comparisons of intra-articular (IA) corticosteroids, six trials included comparisons of nonsteroidal anti-inflammatory drugs (NSAIDs), three trials included comparisons of physical therapy, two trials included comparisons of exercise, two trials included comparisons of arthroscopy, two trials included comparisons of conventional treatment, and fifteen trials included comparisons of other hyaluronans/hylan. The pooled analyses of the effects of viscosupplements against 'placebo' controls generally supported the efficacy of this class of intervention. In these same analyses, differential efficacy effects were observed for different products on different variables and at different timepoints. Of note is the 5 to 13 week post injection period which showed a percent improvement from baseline of 28 to 54% for pain and 9 to 32% for function. In general, comparable efficacy was noted against NSAIDs and longer-term benefits were noted in comparisons against IA corticosteroids. In general, few adverse events were reported in the hyaluronan/hylan trials included in these analyses.

Authors' conclusions

Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment; and at different post injection periods but especially at the 5 to 13 week post injection period. It is of note that the magnitude of the clinical effect, as expressed by the WMD and standardised mean difference (SMD) from the RevMan 4.2 output, is different for different products, comparisons, timepoints, variables and trial designs. However, there are few randomised head-to-head comparisons of different viscosupplements and readers should be cautious, therefore, in drawing conclusions regarding the relative value of different products. The clinical effect for some products, against placebo, on some variables at some timepoints is in the moderate to large effect-size range. Readers should refer to relevant tables to review specific detail given the heterogeneity in effects across the product class and some discrepancies observed between the RevMan 4.2 analyses and the original publications. Overall, the analyses performed are positive for the HA class and particularly positive for some products with respect to certain variables and timepoints, such as pain on weight bearing at 5 to 13 weeks postinjection.

In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events.

In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

PLAIN LANGUAGE SUMMARY

Viscosupplementation for the treatment of osteoarthritis of the knee

Osteoarthritis (OA) is the most common form of chronic arthritis worldwide. Hyaluronan and hylan (HA) products provide opportunity to treat OA in individual knee joints. To evaluate the efficacy, effectiveness and safety of HA products, in knee OA, we have conducted a systematic review using Cochrane methodology. The analyses support the contention that the HA class of products is superior to placebo. There is considerable between-product, between-variable and time-dependent variability in the clinical response. The clinical effect for some products against placebo on some variables at some time points is in the moderate to large effect size range. In general, sample size restrictions preclude any definitive comment on the safety of the HA class of products, however, within the constraints of the trial designs employed, no major safety issues were detected. The analyses suggest that viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events, and that HA products have more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

Viscosupplementation for the treatment of osteoarthritis of the knee (Review)

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