

**The efficacy/effectiveness of  
viscosupplementation in treating ankle,  
including talocalcaneal joint,  
osteoarthritis of primary or  
secondary origin**

**A rapid review**

By

WorkSafeBC Evidence-Based Practice Group

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# The efficacy/effectiveness of viscosupplementation in treating ankle, including talocalcaneal joint, osteoarthritis of primary or secondary origin

## A rapid review

### Background

Hyaluronic acid (HA), a glycosaminoglycan, is a principal component of synovial fluid joints. In osteoarthritis (OA), both the concentration and the molecular size of hyaluronic acid are reduced, as well as the interaction between the hyaluronic molecules. This results in much lower dynamic viscous and elastic properties of the synovial fluid. The loss of lubrication also causes increasing stress forces that disrupt the collagen network surrounding the joints.<sup>(19,24)</sup> It is thought that “replenishing” the lost hyaluronic acid, through injection of synthetic HA (*a.k.a. a viscosupplementation process*), would help treat osteoarthritic joints. Viscosupplementation began in the late 1960s and was initially developed for ophthalmic use as well as being injected into race horses after traumatic injuries.<sup>(19,31)</sup> Since then, several HA preparations have been developed by different companies worldwide.<sup>(19,24)</sup>

In Canada, the first HA products for osteoarthritis were licensed in 1999, and, at present, several are available.<sup>(1)</sup> Some are licensed for use only in specific joints, such as the knee. Other HA products have broader Health Canada licensing that covers use in the knee and other synovial joints, such as the hip. These agents include Durolane® (Q-Med AB), Hyalgan® (Fidia Farmaceutici SpA), NeoVisc® (Stellar Pharmaceuticals), Orthovisc® (Anika Therapeutics, Inc.), Ostenil® (TRB Chemedica), Suplasyn® (Bioniche Teoranta), and Synvisc® (also known as Hylan G-F 20, Genzyme Corporation).<sup>(1)</sup> Interestingly, these products are regulated by Health Canada as class III or class IV medical devices since it is thought that their mode of action originates from the mechanical effects of high elastoviscosity in the synovium.<sup>(24)</sup> HA products in Canada are sold as pre-filled single-use 2 mL (3 mL for Durolane) syringes.<sup>(1)</sup> HA products are divided into low [0.5 to 2 megadaltons (MDa)] and high (6 to 7 MDa) molecular weights; Durolane, Orthovisc, and Synvisc are generally considered to be of higher molecular weights.<sup>(2)</sup>

Many randomized/controlled studies, including corresponding systematic reviews and meta-analyses,<sup>(2-13)</sup> have investigated the efficacy/effectiveness of HA in treating knee and hip OA. With regard to the efficacy/effectiveness of HA in treating knee or hip OA, these systematic reviews and meta-analyses provide conflicting conclusions that need to be investigated further.<sup>(14)</sup>

Recently, the WorkSafeBC Evidence Based Practice Group (EBPG) received a question regarding the effectiveness of HA injection in treating post-traumatic osteoarthritis (OA) of the subtalar (talocalcaneal) joint. As such, the purpose of this rapid review is to investigate the efficacy/effectiveness of HA in treating OA of the ankle, including the talocalcaneal joint.

## Methods

- a systematic literature search was conducted on February 9, 2009
- the search was done on commercial medical literature databases, including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ACP Journal Club, York University Database of Abstracts of Reviews of Effects, UK NHS Health Technology Assessment Database, UK NHS Economic Evaluation Database, Medline, Medline Daily Update, EMBASE and BIOSIS Previews. These databases are available through the Ovid SP<sup>®</sup> interface
- the search employed the following keyword combinations: (hyaluronic acid or synvisc or viscosupplementation) and ((ankle or subtalar or talo calcaneal) and joint and osteoarthritis)
- there were no limitations implemented in these searches. A manual search was also conducted on review articles in order to identify studies that may provide data in answer to the objectives of this rapid review
- the search yielded 24<sup>(15-38)</sup> published articles. Upon examination of the titles and abstracts of these articles, 14<sup>(15,16,19,21,22,23,24,26,28,29,31,32,36,38)</sup> articles were retrieved in full. One additional article<sup>(39)</sup> was retrieved as the result of a manual search through the references of these articles
- of these 15 articles, 6<sup>(19,22,23,24,26,31,)</sup> were excluded since they were expert review articles that did not provide any relevant data. Further, 2 articles by Salk et al.<sup>(28,29)</sup> that were published in two different journals were exactly the same; as such, only one of these articles is critically appraised and presented below
- overall, the results of 8 studies<sup>(15,16,21,28,32,36,38,39)</sup> were critically appraised and are presented below
- a level of evidence (Appendix 1) was assigned for each article according to the levels of evidence adopted by the EBPB

## Results

Of the eight studies<sup>(15,16,21,28,32,36,38,39)</sup> critically appraised, four<sup>(15,16,21,28)</sup> were randomized/controlled trials (R/CT) (level of evidence 1) and four<sup>(32,36,38,39)</sup> were case series (level of evidence 4).

- Carpenter et al.<sup>(15)</sup> conducted a non-randomized, unblinded controlled trial investigating the effectiveness of Hylan G-F 20 in reducing pain following ankle arthroscopy among patients diagnosed with ankle OA. Fourteen patients received three injections of Hylan G-F 20 at one, two, and three weeks post ankle arthroscopy, while 12 patients received only ankle arthroscopy. These patients were then followed up for three months and subjective visual analog scale (VAS) pain was measured. At three months, the mean pain score of the Hylan+arthroscopy group was 1, while the score for the arthroscopy alone group was 3 (p value 0.0002) on a 10 point VAS scale. *It should be noted that this is a small, non-randomized, unblinded clinical trial. The authors did not provide any information on the number of potential participants seen at the study site during the study period. It is not clear whether a 2 (out of 10) point difference in VAS pain is clinically significant. The authors did not provide any data on objective measurements such as functional improvement. With limited*

*information on the baseline characteristics of the two intervention groups, it is likely that there were some imbalances between these two groups that may have affected pain outcomes at three months – for example, the amount of oral analgesics consumed. Of note, the authors stated that none of the patients in this study suffered from any adverse events.*

- Cohen et al.<sup>(16)</sup> conducted a pilot (small) double blind, randomized controlled trial comparing the efficacy and safety of five weekly injections of Hyalgan® against phosphate buffered saline. Thirty consecutive patients (*the authors did not provide any information on the actual number of potential participants seen during the study period*) diagnosed with x-ray documented ankle OA were randomly (*it is not clear how the randomization was done*) assigned to an intervention (16 patients) or control (14 patients) group and were followed up for six months after the completion of five weekly injections. There were many outcomes assessed in this study, however, the authors stated that the primary outcome was pain on movement and weight bearing, assessed by employing the Ankle Osteoarthritis Scale (AOS) at three months after the completion of the interventions. The analysis was done according to intention to treat principles. The authors stated that at three months the intervention group demonstrated a statistically significantly greater improvement from baseline in AOS total score than the control group (*this is not the primary outcome, which was AOS pain*). *It should be noted that even though patients were assigned randomly, there was an imbalance in baseline characteristics between the intervention and control groups. The data presented showed imbalances in AOS pain, AOS disability, and AOS total scores, as well as in WOMAC scores.*
- Karatosun et al.<sup>(21)</sup> randomized 30 patients diagnosed with ankle OA, of whom 15 patients received progressive ankle exercise therapy and 15 patients received three weekly injections of HA. These patients were then followed for 12 months. Outcomes, including the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hind Foot score, gait, pain at rest, and pain on activities, were evaluated and analyzed at 1, 2, and 3 weeks and 2, 3, 6, and 12 months. (*The authors did not provide any information on what the primary outcome was. As such, this study suffered from multiple comparisons, due to the number of outcomes and frequencies of the statistical tests conducted without making necessary adjustments in the statistical tests used.*) At 12 months, the authors did not find any statistical difference in the outcomes between the exercise and HA injection groups, including pain during activity, pain at rest, activity limitation, walking distance, walking surface, gait abnormality, sagittal motion, and total AOFAS Ankle-Hind Foot score.
- Salk et al. conducted a pilot single blind randomized controlled trial investigating the efficacy and safety of HA among patients diagnosed with ankle OA. Their study results were presented in two different journals.<sup>(28,29)</sup> Briefly, twenty consecutive patients diagnosed with ankle OA were randomly assigned to receiving five weekly intra articular HA injections or phosphate buffered saline (*it is not clear how many exactly were assigned to each group as well as how the randomization was done*). Outcomes, including Ankle Osteoarthritis Scale (AOS) as the primary outcome, WOMAC Osteoarthritis Index pain domain, patient's global assessment of ankle pain, pain as a categorical variable, ankle girth, total range of motion, EuroQoL (EQ-5D), SF-12, and rescue medication tablet counts, were collected and analyzed at weeks 2, 6, 12, and 26 as well as at 6 months (*even though*

*the authors stated AOS as the primary outcome in this study, this one variable was analyzed many times during the course of the study without the authors taking into account the effect of multiple testing in their statistical tests). At the end of 6 months only 17 patients (9 in the HA group and 8 in the phosphate saline group) were available for analysis (it should be noted that the analysis presented was not done in an intention to treat manner). The difference in AOS scale results between the HA and phosphate groups was not statistically significantly different at 6 months. It should be noted that 29% of patients reported pain at the injection site that lasted less than 3 days.*

- Hanson<sup>(39)</sup> and Valiveti et al.<sup>(36)</sup> reported the application of HA injection in two and five ankle OA patients, respectively. These studies will not be discussed further due to the small number of cases reported.
- In a relatively large case series, Sun et al.<sup>(32)</sup> reported six month follow up outcomes of 75 patients diagnosed with ankle OA who had been treated with five weekly injections of sodium HA. In the beginning of the study, 93 patients were treated (*it is not clear how many patients were eligible to participate in this study*) and 75 patients remained and reported at the six month follow up (*the authors did not provide any information regarding the differences, if any, between patients who dropped out and those who remained for the six month follow up report*). Outcomes assessed in this study included total Ankle Osteoarthritis Scale (AOS), AOS pain subscale, AOS disability scale, total AOFAS Ankle-Hind Foot score, ankle sagittal ROM, patient's global satisfaction with ankle pain relief, and rescue medication taken. Assessments, and corresponding statistical analyses against their baseline values, were conducted at one, two, three, four, and five weeks as well as at one, three and six months post injection. The authors reported that at each assessment period, with the exception of ankle sagittal ROM, patients showed statistically significant differences compared to their baseline values. (*It should be noted that for each outcome measure, there were at least eight statistical tests conducted. This statistical testing represents major multiple comparisons. This was not adjusted for by the authors in stating their statistical significance level.*)
- In a multi centre case series, Witteveen et al.<sup>(38)</sup> reported the outcomes of one or two times Hylan G-F 20 injections in 55 patients diagnosed with ankle OA (*it is not clear how many patients were eligible to participate during the 27 months recruitment period of this multi centre study*). Patients were enrolled from five centres: one in the Netherlands, two in Germany and two in Italy. The primary outcome measurement in this study was change from baseline (c.q. baseline was defined as immediately prior to the last injection) to 3 months after the last injection using the patient's own assessment of "Study Ankle OA Pain" within the past 48 hours (*it is not clear whether this so-called "Study Ankle OA Pain" is the same as the Ankle Osteoarthritis Scale (AOS) pain section, which is validated and widely used. Most likely this "Study Ankle OA Pain" is a subjective VAS pain measurement which had a 100 mm scale*). Fifty-five patients participated in this study (*it is not clear how many patients were recruited in this study*) and 51 completed the 3 month follow up (*the authors stated that the analysis was done according to the intention to treat principle—i.e. on 55 patients; however, it is not clear whether the outcomes presented originated from 51 or 55 patients*). At 3 months follow up, for all patients, the mean Study Ankle OA Pain VAS score was 33.8 mm

(baseline mean was 68.0 mm) and the difference was statistically significant (*this difference in a subjective VAS pain score of 35 mm, out of 100 mm, may not be clinically significant*). It should be noted that among patients who received two injections the difference in the Study Ankle OA Pain VAS score was not statistically significant. *In this study patients were allowed to take acetaminophen, NSAIDs or other analgesics and this fact was not taken into account in presenting the results of this study.* Thirty-five patients (63.6%) experienced a total of 89 adverse events. The majority of adverse events were arthralgia, injection site pain, and joint swelling, which were reported to be mild or moderate in intensity and transient in nature.

## Summary

- Hyaluronic acid (HA) products to treat osteoarthritis have been approved by Health Canada since 1999. These products have been approved for treating osteoarthritis of large joints such as the knee and hip. Many randomized controlled trials investigating the efficacy of HA in treating knee and hip joints have been performed; however, systematic reviews and meta analyses published to date have shown conflicting conclusions with regard to its efficacy.
- This rapid systematic review identified four randomized/controlled trials (level of evidence 1) investigating the efficacy of HA in reducing pain among patients diagnosed with ankle OA. The outcomes of these low quality randomized/controlled trials did not provide enough evidence on the efficacy of HA in reducing pain among patients with ankle OA. Further, these studies did not provide any evidence on the improvement of function among ankle OA patients.
- While the results of four case series (level of evidence 4) reported in this rapid systematic review may provide some evidence of the reduction of pain among ankle OA patients, this reduction in pain may not be clinically significant. Further, the lack of controls in these case series mean they cannot provide definitive conclusions on the efficacy of HA in reducing pain among ankle OA patients.

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## Appendix 1

### WorkSafeBC - Evidence-Based Practice Group Levels of Evidence <sup>(adapted from 1,2,3,4)</sup>

<b>1</b>	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
<b>2</b>	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
<b>3</b>	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
<b>4</b>	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
<b>5</b>	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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