Viscosupplementation (Hyaluronans) in the Treatment of Ankle Osteoarthritis


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Osteoarthritis (OA) is second only to cardiovascular diseases in producing chronic disability that directly impacts quality of life [1]. The nature of its initial morphologic event is still unclear; however, in the intermediate and late stages of disease, there is progressive destruction of articular cartilage. The progression of this disease leads to exposure of subchondral bone at a weight bearing site, where the bone is then subjected to abrasion and further damage.

Pain management usually involves the use of oral analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular (IA) corticosteroid injections, and surgical intervention. Analgesics may relieve symptoms when used in the short-term but have no significant impact on the underlying disease. Furthermore, the use of NSAIDs and cyclooxygenase-2 inhibitors for chronic pain management of patients who have OA of the knee has recently been questioned based on their modest effect and potential adverse reactions [2]. The potential to develop adverse reactions is present especially in the elderly who characterize the OA population. In addition, the elderly tend to be on multiple medications for concurrent medical conditions, which also raises the possibility of drug interactions. Irrespective of the pros and cons of these oral medications for symptomatic relief, clinical management of chronic OA patients should also consider the im-
pact of any therapy on the disease process. For example, some NSAIDs in pre-
clinical studies have a deleterious effect on cartilage metabolism [3,4], and the
chronic use of IA corticosteroid injections may be disruptive to the extracellular
matrix of the cartilage [5–7].

Hyaluronan (HA) is a high-molecular-weight polysaccharide and a major
natural component of the synovial fluid and the extracellular matrix of the
cartilage [8]. It is a glycosaminoglycan consisting of repeating units of glucuronic
acid and N-acetylglucosamine, bound together by a glycoside bond beta. HA is
synthesized by chondrocytes in the cartilage and by fibroblasts of the synovial
lining known as synoviocytes. The HA synthesized by the former becomes
integrated in the cartilage matrix, whereas the synoviocyte HA is released in the
synovial cavity. In degenerative joint diseases, the average molecular weight and
centration of HA in the synovial fluid is reduced, as is the HA and
proteoglycan content of the extracellular matrix of the cartilage. The rationale for
use of HA is based not only on the concept of “fluid replacement” or visco-
supplementation, but also on the mounting evidence that HA plays a major role
in biologic activation or “biosupplementation” that may decrease the symp-
toms and the disease progression [8]. The fact that all injected HAs are gone
within days [9] but the clinical benefit lasts for months [1] suggests that bio-
logic activation is the dominant mechanism by which HAs mediate their clini-
cal benefit.

The treatment of OA by IA HAs (Hyalgan and Synvisc) has been approved
by the Food and Drug Administration (FDA) for OA knee pain since 1997.
Recently, two additional HAs have also been approved: Supartz (sodium hyal-
uronate) and Orthovisc (high-molecular-weight HA). A recent meta-analysis
of controlled clinical studies confirmed the clinical benefit of IA HAs in the
treatment of OA knee pain [10]. These products differ in approved treatment
regimens, dosing, and average molecular weight; however, no well-controlled
clinical study has demonstrated a superiority of one approved product over
another. There are numerous published reports using IA HAs to treat the pain of
OA of various joints; however, no well-controlled, double-blind studies have
been conducted for OA of the ankle. The purpose of this pilot study was to
investigate the possible efficacy and safety of IA injections of sodium hyaluro-
nate (500–730 kd).

Materials and methods

Study group

Subjects were drawn from private practice patient populations of the Northern
California Foot and Ankle Center in San Francisco and Santa Rosa, California.
All patients were administered an informed consent fully disclosing the risks and
benefits of study participation. The experimental design and protocol was de-
veloped by physicians of the Northern California Foot and Ankle Center and reviewed and approved by the Western Institutional Review Board and the FDA. The procedures were performed in accordance with the approved protocol.

Twenty consecutive subjects with clinically diagnosed OA were screened for this study. A detailed history and physical was obtained from patients who complained of ankle pain. If clinical examination and radiographic procedures confirmed OA of the ankle, patients were then included in the study and the level of OA was confirmed using Kellgren-Lawrence [11] classification (grade II–IV). In addition, all patients (1) were 18 years of age or older, had chronic ankle pain for 3 months or longer but less than 5 years, and had a current total Ankle Osteoarthritis Scale (AOS) score of greater than 30 and less than 90 (range, 0–100); (2) were normally active, not bedridden or confined to a wheelchair, and able to walk 50 m without help of a walker, crutches, or cane; (3) signed and understood the informed consent; (4) were willing to discontinue all NSAIDs or other analgesic medication for the duration of the study (except for rescue medication); (5) were able to complete efficacy measurements questionnaires; (6) were not on any research protocol for 30 days; and (7) if a woman, were postmenopausal or using effective contraception.

Correspondingly, patient exclusion criteria required the response to be “no” to all of the following items:

1. Bilateral ankle OA requiring treatment for both ankles other than simple analgesics such as acetaminophen
2. IA injection of corticosteroids within the last 3 months
3. Use of systemic steroids (excluding inhalation or topical steroids) within the last 3 months
4. Any IA injection within the last month
5. Surgery to signal joint in the prior 6 months
6. Dosage of glucosamine or chondroitin sulfate that has been stable over the preceding 3 months, with the dosage remaining constant during the study
7. Planned arthroscopy or any other surgical procedure to the study ankle during the study period
8. Diagnosis of rheumatoid arthritis
9. Systemic active inflammatory condition or infection, such as inflammatory arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, septic arthritis, gout/acute pseudogout, or any other connective tissue disease
10. Active skin disease or infection in the area of the injection site
11. Significant venous or lymphatic stasis present in the legs
12. Any medical condition that in the opinion of the investigator makes the patient unsuitable for inclusion (eg, severe progressive chronic disease, malignancy, bleeding disorder, clinically significant pain from part of the musculoskeletal system other than the ankle, fibromyalgia)
13. Treatment with anticoagulant (except for acetylsalicylic acid up to 325 mg/d)
14. Pregnant or breastfeeding woman or woman of child-bearing potential not practicing adequate contraception
15. Conditions that can confound pain and function assessments in the ankle, such as plantar fasciitis, tendonitis of foot and ankle, sciatica, OA of other joints, sprains of foot, and so forth

Among subjects meeting all inclusion criteria, the most important factor for subject selection was accurate diagnosis of the underlying disorder without other underlying pathology. In distinguishing OA of the ankle, standard clinical diagnostic criteria were based on symptoms, clinical signs, and radiographic findings. Symptoms included history of pain during ROM and rest and history of stiffness. Clinical signs included limited range of ankle movement or crepitus, tenderness over ankle joint, and ankle edema. Radiographic findings included narrowing of joint anterior tibial lipping and erosions, osteophytes, eburnation, and osteolytic lesions.

Study design and blinding

Patients who qualified for inclusion were randomly divided into two treatment groups: IA HA and IA phosphate-buffered [PB]-saline (control). Injection technique followed standard clinical procedures, with strict adherence to aseptic technique [12]. Patients first received a subcutaneous lidocaine injection as a local anesthetic, followed by five weekly IA injections of HA (1 mL of sodium hyaluronate, 10 mg/mL) or PB-saline (1 mL). Patients were clinically assessed before each injection (on days 0 [baseline], 7, 14, 21, and 28) and on follow-up visits (weeks 2, 6, 12, and 26) by a blinded observer (R. Salk). All patients were supplied 500-mg acetaminophen tablets and were permitted up to 4000 mg/d for escape analgesia as needed for ankle pain. Patients were instructed to not take other NSAIDs, narcotic analgesics, non-narcotic analgesics, or corticosteroids. Tablet counts of acetaminophen were performed at each visit.

The study required a blinded observer and an unblinded injector (T. Chang) of the study product. This protocol was necessitated because of the distinct viscosity properties between the treatment and control. The blinded observer performed and recorded efficacy assessments and progress notes and was not present during the injection. The unblinded injector performed all injections. As well as could be determined, the patient and the blinded observer could not determine to which therapeutic group the patient was assigned.

Efficacy and safety measures

Efficacy and safety was assessed at each visit. Measurements were obtained at time of screening, at baseline, and after the series of injections at weeks 2, 6, 12, and 26. The primary efficacy measure was the assessment of total Ankle Osteoarthritis Scale (AOS) [13] recorded at each visit. The AOS is a globally recognized assessment tool that is reliable and a valid self-assessment instrument.
that specifically measures patient symptoms and disabilities related to ankle arthritis. Secondary efficacy variables included the following:

1. Western Ontario McMasters (WOMAC) Osteoarthritis Index pain domain [14]
2. Patient’s global assessment of ankle pain (complete recovery, much better, somewhat better, no change, somewhat worse, much worse)
3. Categoric scale of pain by a 5-point scale (none, mild, moderate, marked, severe)
4. Ankle girth
5. Total range of motion (ROM)
6. EuroQoL (EQ-5D)
7. Short form 12 (SF-12)
8. Rescue medication tablet count

Evaluations were performed in the morning before the patient received injections and ingested acetaminophen; acetaminophen was not taken from the previous midnight until testing had been completed.

Spontaneous adverse events reported by the patient were recorded at each visit. The Institutional Review Board and the FDA Center for Devices and Radiologic Health (CDRH) approved the protocol and received periodic reports of progress and patient safety.

**Statistical methods**

Univariate analysis was performed to obtain mean distribution for demographic characteristics among the 17 patients completing the study. The primary outcome measure was change in the AOS from baseline and between treatment groups for those patients who completed the study. The analysis for this variable was measured by the mean and the mean differences in pain at 0.5 months, 3 months, and 6 months for the HA treatment group versus the PB-saline control group using an analysis of variance (ANOVA) and the procedural general linear model, with the main effects for treatment (HA and PB-saline) and baseline VAS assessment as a variant. Analysis was also performed to obtain ratio of mean square (F value) and $P$ values using repeated-measures ANOVA between- and within-subject effects and related interactions between HA and PB-saline in time.

Secondary efficacy variables that were continuous, such as ankle girth and total ROM, were analyzed by using pairwise $t$ tests to compare means and standard deviations. Categoric variables were analyzed using the $\chi^2$ test for trend and the Fisher exact test. Other categoric data such as EuroQoL (EQ-5D) was presented, using frequency, percentage, and $P$ values from the Fisher exact tests. The SF-12 Health Survey was scored using scoring algorithms described by Hays and colleagues [15] and Ware and coworkers [16], whereby the mean scores between groups were compared using Student’s $t$ test. All statistical tests with
P values were two-sided, and the selected level of significance for all variables was $\alpha = 0.05$. The SAS statistical software version 8.2 (SAS, Cary, North Carolina) was used to analyze all continuous and categoric data.

Previous studies on long-term randomized clinical trials have estimated dropout rate to be 15% to 25% [1,17]. Because the effect and variation of saline control or sodium hyaluronate injections has not been reported in the literature, the authors were unable to calculate an effect size for this pilot study. Previous reports in the knee, however, were able to achieve statistically significant differences with as few as 20 patients per group, and their effect size can be calculated to estimate a sample size (80% powering) of between 11 and 17 patients per group depending on the variability, robustness of the saline control and sodium hyaluronate response, and the time point selected. Accordingly, for this pilot study, a sample size of 10 patients per group was selected to provide preliminary safety and efficacy data for a future larger controlled study.

Results

Patient population

One hundred twenty-eight potential subjects were screened, with 20 meeting the entrance criteria. The 108 patients who did not meet the entrance criteria had other medical conditions (85 patients) such as incompatible radiographic criteria (10 patients), on anticoagulant therapy (10 patients), and inadequate pain by VAS (3 patients).

Seventeen of the 20 enrolled patients completed the study through the 6-month follow-up and were evaluated for statistical analysis as completers. The patient demographic characteristics of the 9 patients in the HA treatment group and the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics of completed patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HA (n = 9)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Mean (SD) 57.8 (14.7)</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
</tr>
<tr>
<td>Sex (n)</td>
<td>women/men 5/4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean (SD) 171 (11.9)</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD) 85.5 (24.0)</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Affected side</td>
<td>Left 6</td>
</tr>
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<td></td>
<td>Right 2</td>
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</table>
8 patients in the PB-saline control group are summarized in Table 1. The mean age was comparable between the HA and PB-saline groups. Other descriptive characteristics were similar between groups, such as female-to-male ratio, height, and weight. The OA-affected side was similarly distributed between the groups, with the right ankle being more commonly treated than the left ankle (not significant; see Table 1).

Primary effectiveness assessments

AOS pain and disability assessment

Over the 6-month follow-up period of the study, both groups showed a decrease in AOS pain and disability (Fig. 1). Table 2 demonstrates variation in the mean difference between the HA and PB-saline groups and within-subject effects, the time effect, and interaction using the repeated-measures ANOVA test. The within-subject effect for HA and PB-saline was statistically significant (F value = 17.62; \( P < 0.0001 \)). Between-groups analysis was not statistically significant (F value = 1.05; \( P = 0.3210 \)). Although it was not statistically significant, there was a greater overall reduction trend in the HA group compared with the

\[ \text{Table 2} \]

Repeated-measures analysis of variance between-and within-subject effects and time

<table>
<thead>
<tr>
<th>Repeated-measures ANOVA</th>
<th>df</th>
<th>MS (Mean square)</th>
<th>F (Ratio of mean squares)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between-subject effects (HA and PB-saline) (Error ( df = 15 ) and MS = 521.14)(^a)</td>
<td>1</td>
<td>548.96</td>
<td>1.05</td>
<td>0.3210</td>
</tr>
<tr>
<td>Within-subject effects (HA and PB-saline) (Error ( df = 45 ) MS = 150.90)(^a)</td>
<td>3</td>
<td>2658.96</td>
<td>17.62</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\) Error is residual variation in the means that cannot be attribute to a specific variable.
PB-saline group. The improvement began at 0.5 months, with difference in means of AOS between groups (7.13 mm; \( P = 0.2399 \)). The greatest difference in means of AOS between groups occurred at 6 months but was not statistically significant (11.48 mm; \( P = 0.1640 \)). At 3 months, however, there was an increase in means in both groups and a decrease in mean differences between groups, which was not statistically significant (4.66 mm; \( P = 0.5964 \)).

At 6 months, there were more HA patients compared with PB-saline patients who had an improvement from baseline that was greater than 30 mm on the AOS. Five of the nine patients in the HA treatment group had an improvement difference greater than 30 mm from baseline to 6 months (55.56%) compared with only one of eight patients in the PB-saline group (12.50%; \( P = 0.1312 \), two-tailed Fisher exact test).

**Responder analysis**

A responder analysis using the AOS score was also performed. Clinical responsiveness was considered at three levels of discrimination (\( \geq 20\% \), \( \geq 50\% \), and \( \geq 70\% \)) based on improvement in the conglomerate score (AOS) or improvement in the continuous measure of VAS pain. Percentages of patients showing 20\%, 50\%, or 70\% improvement from baseline in VAS at 3 and 6 months were higher for the HA group than for the PB-saline group (Fig. 2). The difference between the HA and PB-saline groups approached statistical significance for 50\% improvement in VAS at 6 months (\( P = 0.088 \)).

**Secondary effectiveness assessments**

Overall, differences in patients’ global assessment and the WOMAC Osteoarthritis Index at 3 and 6 months were not statistically significant between the HA and PB-saline groups. Five of the nine patients in the HA group (55.56%), however, were in the “much better” category after the 6-month follow-up compared with three of the eight patients in the PB-saline group (37.50%).

![Fig. 2. Percentages of patients showing 20%, 50%, or 70% improvement from baseline in AOS at 3 and 6 months. BL70 after 3 months follow-up had 0% responders (saline).](image-url)
Similarly, ankle girth and total ROM was not statistically different between groups; however, there was a trend in favor of the HA group over the PB-saline group (ankle girth, \(-0.033\) versus \(0.212\) cm; ROM, \(3.666\) versus \(2.000\)) (Table 3). There were no significant differences between groups in the five dimensions assessed in the EuroQoL (EQ-5D; mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) (see Table 3); however, there was greater improvement in the HA group (83%) after 6 months compared with the PB-saline group (33%) in reporting “no problems performing usual activities,” which approached statistical significance in favor of HA treatment \((P = 0.056)\). It is interesting that the SF-12 summary scores (Fig. 3) demonstrated a statistically significant difference in mean scores for the vitality domain (47.22 versus 25.00; \(P = 0.029\)).

**Safety**

Among the 20 randomly selected patients, 3 did not complete the study, leaving 9 in the treatment arm and 8 in the control arm. The basis for premature discontinuation was lack of efficacy (2 patients) and lost to follow-up (1 patient). Before completing the full injection regimen, 1 patient reported a lack of efficacy and underwent an ankle fusion at week 6 of the follow-up. The second patient was found to have significant cystic lesions throughout the talus and tibia and moderate osteoarthritic changes of the subtalar joint based on a subsequent MRI and was consequently removed from study analysis.
No serious adverse events were observed during the course of this study. Injections were well tolerated. One patient who received HA experienced an anxiety attack in week 2, but this event was deemed unrelated to the study medication and associated with the stress of anticipating an injection. This patient subsequently completed the study criteria without other adverse events. Pain at the injection site was described by 29% (5/17) of the patients, with no significant difference between study groups. This injection site pain typically lasted no more than 3 days. No soft tissue or IA infections were reported.

Discussion

The primary objective of this pilot study was to perform a preliminary assessment of the efficacy and safety of HA (sodium hyaluronate [Hyalgan], 500–730 kd) compared with PB-saline in treating pain associated with OA of the ankle. A randomized, double-blinded, saline-controlled clinical trial was used to determine whether decrease in ankle joint pain and improvement in function occurred subsequent to IA injections of sodium hyaluronate compared with saline control. Until now, no well-designed, carefully controlled studies have been performed to assess efficacy of HA for ankle OA.

Clearly, a larger patient population and additional clinical studies are warranted to confirm the authors’ results; however, this pilot study is consistent
with the results of previous multiple trials in a variety of articular joints demonstrating a benefit of IA HA in the treatment of OA of the knee, hip, shoulder, temperomandibular, and sacroiliac joints. Maheu and colleagues [18] reviewed 24 clinical trials with IA HA treatments of OA of the knee and concluded that Hyalgan significantly improved the pain and functional status of patients. In addition to the therapeutic effects of HAs before surgical treatment, there have been studies that have shown its positive effects with perioperative and postoperative use [19,20].

This study demonstrates that IA administration of HA (Hyalgan) in patients who have ankle OA is safe, improves joint function, and ameliorates pain. It is also interesting to note that the saline-control patients also demonstrated a significant clinical benefit, albeit to a lesser degree than the HA-treated patients. This reduction of pain in the saline-control group may not be a “pure placebo effect” but possibly related to the result of the saline (1) breaking apart scar tissue and adhesions classically found with OA, (2) perhaps providing a minimal affect as a lubricant due to a decrease in synovial fluid associated with OA, and (3) diluting the lytic enzymes and proinflammatory cytokines associated with OA. This study was characterized by having a positive treatment result in both treatment arms, which is consistent with other studies of HA. Other studies have shown benefit with saline-controlled injections [1,10,17]. It is worthy to note that the average improvement from baseline was about 34% for the saline-control group; not only is this response clinically significant but it also exceeds that reported for most studies of OA knee pain using standard-of-care oral NSAIDs or cyclooxygenase-2 inhibitors [10].

IA HA has been documented to provide alleviation of pain, improvement in joint ROM, prevention of adhesions, and protection of cartilage. The widely reported efficacy of IA HA in the treatment of OA may be related to a number of different effects of the molecule. The beneficial effect of HA is even more interesting when one considers that exogenous HA is rapidly eliminated from the joint. The initial effect of HA injection is related to the introduction of a viscoelastic material into the arthritic joint, whereby it augments the lubricating potential of the synovial fluid. It is widely accepted, however, that this phenomenon alone cannot account for the observed long-term benefits of HA in OA. In vitro studies have indicated that HA has a wide range of effects on synoviocytes, chondrocytes, and inflammatory cells, which invade the synovial cavity during OA. In vivo studies in animal models and preliminary pharmacologic studies in humans have indicated that HA may protect cartilage structure, exert an effect on the inflammatory process, and reduce pain. Of particular interest is the recent report that Hyalgan when administered in three weekly injections every 4 months can slow down the progression of OA. An earlier pilot study using blinded arthroscopic examination reported similar findings [21].

In regard to other joints of the lower extremity affected with OA, we must look at the first metatarsal phalangeal joint. Hallux limitus/rigidus is clearly the most common form of degenerative joint disease in the human foot. Currently, a study is being performed on the use of HAs for hallux limitus. A recent poster
[22] was presented at the 2005 American College of Foot and Ankle Surgeons conference showing promise for the treatment of OA of the first metatarsal phalangeal joint. These investigators are also planning a clinical trial on the efficacy and safety of HAs for hallux limitus.

OA is a devastating disease, which leads to a sedentary lifestyle and exacerbates other medical conditions. The authors believe that in the future, HAs will be a standard of care in the treatment and prevention of OA. As advancements are made with HAs, the authors anticipate that some form of HAs will be used even before the onset of OA occurs.

Summary

Nonsurgical alternatives for symptomatic OA remain limited to NSAIDs, analgesics (including opioids), weight loss, physical and occupational therapy, assistive devices for walking, aerobic exercise programs, and corticosteroid injections. Although much pathology can be successfully treated with surgical intervention, many patients are not good surgical candidates or prefer to not have surgery. A safe and effective nonsurgical therapeutic modality would be a welcomed addition to the therapeutic repertoire we can offer our patients. In the present pilot study, the authors found sodium hyaluronate, (500–730 kd) to be safe and effective in the treatment of pain associated with OA of the ankle.

References