

# The Role of Viscosupplementation in the Ankle Using Hylan G-F 20

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*The use of intra-articular injections of high molecular weight elastoviscous solutions of hyaluronan or hylans (cross-linked derivatives of hyaluronan) to treat arthritis is termed viscosupplementation. The function of viscosupplementation is to restore the rheologic properties of synovial fluid. Although anecdotal data exist, no long-term studies regarding the use of viscosupplementation in the ankle have been published to date. The goal of this clinical trial was to compare pain reduction following ankle arthroscopy versus that following ankle arthroscopy combined with weekly intra-articular instillation of hylan G-F 20 during the first 3 postoperative weeks. In the series of patients described in this report, we found that both treatment groups experienced statistically significantly decreased pain following the intervention ( $P = .002$  and  $P = .0009$  for the arthroscopy alone and arthroscopy plus hylan groups, respectively), and that those who received 3 intra-articular injections of hylan G-F 20 following ankle arthroscopy improved statistically significantly ( $P = .0014$ ) more than did those who underwent arthroscopy as a sole therapy. These preliminary results suggest that viscosupplementation combined with arthroscopy may be more beneficial than arthroscopy alone, and provide further insight into the role of viscosupplementation in the treatment of ankle osteoarthritis. Level of Clinical Evidence: 4 (The Journal of Foot & Ankle Surgery 47(5):377-384, 2008)*

Key Words: ankle arthroscopy, cartilage, hyaluronan, osteoarthritis, Synvisc, viscosupplementation

The use of intra-articular injections of high molecular weight elastoviscous solutions of hyaluronan (also called hyaluronic acid) or hylans (cross-linked derivatives of hyaluronan) to treat osteoarthritis is termed viscosupplementation (1). The purpose of viscosupplementation is to restore the rheologic properties, namely viscosity and elasticity, of synovial fluid by normalizing the concentration and molecular weight of hyaluronan. Viscosupplementation has been

described in the literature for use in animal and human subjects. The benefits of viscosupplementation are not limited to restoring the mechanical function of the synovial fluid, but further induce the other important roles that hyaluronan plays in a synovial joint. Specifically, hyaluronan is a polysaccharide made of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. In vitro, mononuclear phagocytes termed type A synoviocytes (hyalocytes) are the primary producers of hyaluronan (2). Fibroblasts and chondrocytes also synthesize hyaluronan and secrete it into the joint space (3). Highly purified natural hyaluronan and its derivatives can be used for viscosupplementation. Typically, hyaluronan is extracted from umbilical cord or rooster comb, purified, and separated from any pyogenic, inflammatory, immunogenic or chemotactic fractions, without being structurally and/or functionally degraded.

Balazs (4) developed the first pure high molecular weight hyaluronan in the 1960s, and this specific hyaluronan was identified as the noninflammatory fraction of Na-hyaluronan (NIF-NaHA) and was marketed for ocular surgery. The first therapeutic injections of hyaluronan in animal joints were

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**Financial Disclosure:** None reported.

**Conflict of Interest:** None reported.

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1067-2516/08/4705-0002\$34.00/0

doi:10.1053/j.jfas.2008.06.013

performed in racehorses for traumatic osteoarthritis, and these injections proved to be effective (5, 6). Viscosupplementation was first used for osteoarthritis in the human knee in the early 1970s (7). Since that time, multiple authors have investigated the effectiveness in restoring the synovial joint environment both directly and indirectly using several different hylans of varying molecular weights.

The primary role of synovial fluid is protective, by means of limiting axial forces on the articular surface and decreasing friction between joint surfaces. Specific functions of the synovial fluid include shock absorption, traumatic energy dissipation and storage, lubrication and protective coating of the articular cartilage surface and of the inner lining of the synovial membrane, as well as control of the cell and molecular “traffic” between the synovial fluid and the cartilage by means of an exclusion effect on migrating cells and large molecules. Hyaluronan is entirely responsible for the elastoviscosity of synovial fluid (8). Because of its hyaluronan content, synovial fluid can behave as either a predominantly viscous fluid or a predominantly elastic fluid (8). Hyaluronan is also responsible for protecting the collagen fibrils and cells of articular surfaces, synovial tissue, capsule, and ligaments from mechanical damage (5). Laurent and Fraser (9) found that hyaluronan in both synovial

fluid and articular tissues plays a critical role in contributing to joint homeostasis and maintaining normal function. In addition to restoring the rheologic properties of the joint, hyaluronan has also been found to influence a number of other factors critical to the articular environment (Table 1) (9–20).

In osteoarthritis, the synovial fluid is more abundant and less viscous (21). Hyaluronan becomes depolymerized, its concentration and molecular weight are decreased, resulting in a decrease in elastoviscosity. These changes increase the susceptibility of cartilage to injury (22–25). Dahl et al (25) found this breakdown of hyaluronan produced dialyzable hyaluronan fragments and disaccharide monomers. Reactive oxygen-derived metabolites are involved in hyaluronan depolymerization (26, 27), which reduces the viscosity of the synovial fluid and hence its lubricating and antioxidant capacities. Osteoarthritic synovial fluid functions primarily as a viscous rather than elastic fluid through the entire range of joint movement, which reduces its protective effect on cartilaginous, fibrous, and cellular structures (14). As articular cartilage is progressively damaged, the net rate of proteoglycan synthesis ultimately falls and the cartilage thins, resulting in a decrease in the load-bearing capacity (28).

**TABLE 1 Publications reporting beneficial effects of hyaluronan therapy**

Author (Reference No.)	Year	Findings
Darzynkiewics and Balazs (10)	1971	Inhibition of lymphocyte transformation
Forrester and Balazs (11)	1980	Inhibits phagocytic activity of macrophages and leukocytes and the release of prostaglandins, may promote normalization of native hyaluronan synthesis
Forrester and Wilkinson (12)	1981	
Smith and Ghosh (13)	1987	
Larsen et al (14)	1992	Hylan and hyaluronan protect chondrocytes or cartilage explants from degradation by enzymes, IL-1, and oxygen-derived free radicals (molecular weight dependent)
Yasui et al (15)	1992	Stimulates the production to tissue inhibitor of metalloprotease-1 (bovine model)
Al-Assaf et al (16)	1995	Free radical scavenging, especially with hylans
Corrado et al (17)	1995	Hyaluronan in chondrocyte culture increases proteoglycan synthesis. In animal models, intra-articular hyaluronan injections showed slowing progression of joint damage. Pain intensity was reduced by 50% in the active treatment group but by only 29% in placebo group.
Pozo et al (18)	1997	Anti-nocioceptive effects
Marshall (19)	1997	Hyaluronan based therapy may be chondroprotective
Ronchetti et al (20)	2001	Sodium hyaluronate modified structural organization of the human osteoarthritic knee synovium towards the appearance of normal synovium when compared to methylprednisolone acetate. Examined via biopsy.

Hylans are polymers of hyaluronan that have been cross-linked through their hydroxyl groups (8, 29). They are highly hydrated (30), are very powerful scavengers of hydroxyl radicals, and are more stable to the action of these agents than are non-cross-linked hyaluronan (16). Hylan G-F 20 (Synvisc, Genzyme Corporation, Cambridge, MA) is a mixture of two hylan polymers, 80% by volume hylan A fluid and 20% hylan B gel. The average molecular weight of hylan G-F 20 is  $6 \times 10^6$  daltons. This molecular weight is the closest commercially available of any hylans to the native hyaluronan molecular weight of  $3.5 - 5.0 \times 10^6$  daltons (24, 31). Hylan B is a viscoelastic gel that is also derived from hyaluronan. It is hydrated but not water soluble, and it is suspended with hylan A in the vehicle. The advantage of hylan G-F 20 over other viscosupplements may be related to its high molecular weight. The elastic modulus of hylan G-F 20 is greater than that of normal synovial fluid. The residence time of hylan G-F 20 in the articular cavity is longer than that of natural hyaluronan (32, 33). Residence time is about 23 hours for a 1% solution of hyaluronan and about 20 to 30 days for a 0.4% solution of hylan B. The unit dose of hylan G-F 20 is 2 mL (16 mg of hylan), and the recommended dose is 1 injection per week for 3 consecutive weeks in the knee. To date, hylan G-F 20 (Synvisc) is approved by the US Food and Drug Administration only for the treatment of osteoarthritis in the knee, although its off-label use in other synovial joints is widely known. To the best of our knowledge, there have been no long-term ankle viscosupplementation studies published in the peer-reviewed biomedical literature, although anecdotal evidence does exist (33). In an effort to gain insight into the difference between pain reduction in patients who underwent ankle arthroscopy versus patients who underwent ankle arthroscopy followed by 3 postoperative intra-articular injections of hylan G-F 20 at weekly intervals, we undertook a prospective study of a series of patients who had failed to satisfactorily respond to nonsurgical treatment of their ankle arthritis.

## Patients and Methods

### Patient Population

Patients were enrolled in this investigation from the clinical practice of the principal investigator (B.C.), between September 2002 and June 2004. To be included in the investigation, patients had to have a diagnosis of ankle osteoarthritis; display radiographic evidence of joint space narrowing with or without subchondral sclerosis, osteophytosis, or subchondral cyst formation; failed to satisfactorily respond to a course of conservative therapy consisting of exercise and at least 6 weeks of nonsteroidal anti-inflammatory drug (NSAID) administration and 3 or fewer intra-

articular corticosteroid injections at bi-weekly intervals; and be suitable candidates for, and consent to, either ankle arthroscopy alone or in combination with intra-articular hylan instillation. Our institutional review board approved the protocol for this clinical trial. Participants in the investigation were consecutively enrolled in the study as they consented for ankle arthroscopy, and they were allowed to decide if they would consent to the hylan therapy in addition to arthroscopy. Baseline outcomes included the age, gender, side of ankle involvement, and the subjective measurement of pain using a 10-point categorical pain scale that is commonly used in the clinical setting. Specifically, each patient was asked to rate their ankle pain from 0 to 10, with 0 representing no pain and 10 representing the worst pain that the patient could imagine.

### Interventions

The interventions of interest in this investigation included ankle arthroscopy alone (AAA), and ankle arthroscopy plus hylan (AA+H) instillation. After obtaining consent to surgery, and to participation in the investigation, all of the patients underwent ankle arthroscopy. For every patient in the series, cartilage defects were smoothed with a micro-abrader, and subchondral drilling was used if cartilage defects less than  $1 \text{ cm}^2$  were encountered. All of the joint debris, including meniscoid and osseous bodies, was removed. Hypertrophic synovitis was also debrided. All of the patients in the series underwent a similar level of arthroscopic ankle intervention in regard to the degree of talar dome osteochondral and synovial debridement, and every arthroscopic procedure was performed by the same surgeon (B.C.). At the end of the procedure, the ankle was lavaged with approximately 200 mL of normal sterile saline. For the patients in the AA+H intervention group, beginning 1 week post arthroscopy, a 2-mL (unit dose) intra-articular injection of hylan G-F 20 (Synvisc) was instilled into the same ankle. Before the articular injection, joint fluid was aspirated from the ankle as recommended by Adams et al (34). This process of aspiration followed by instillation of hylan G-F 20 was repeated again at 2 and 3 weeks post arthroscopy, for a total of 3 intra-articular instillations of hylan following the arthroscopic procedure.

In every case in this series, the patient was allowed to ambulate in a removable cast-walker, partial weight bearing with crutches, during the first postoperative week, and then full weight bearing by the end of the first postoperative week. Ankle range of motion exercises were initiated on the second or third postoperative day, and the cast-walker was discontinued by 3 weeks in all of the cases. Postoperative pain score data were obtained at approximately 3 months following the intervention in all of the patients in the series.

The patients were followed for at least 12 months to determine whether or not any adverse events developed.

### Statistical Plan

The data were analyzed with a particular emphasis being paid to data type and distribution. Descriptive and inferential analyses were undertaken, and nonparametric methods were used to test the null hypothesis when comparisons were made between the intervention groups. Statistical significance was defined at the 5% ( $P \leq .05$ ) level.

### Results

A total of 26 patients were treated in this case series, and the median follow-up duration was 13 months (interquartile range: 2 months) for the patients receiving hylan G-F 20, 14 months (interquartile range: 1.5 months) for the patients that did not receive hylan G-F 20, and 13 months (interquartile range: 2 months) for both treatment groups. The complete dataset for these patients is depicted in Table 2. The median

and interquartile range for the overall age of the patients was 57 (44, 62) years. Overall, there were 14 (53.85%) females and 12 (46.15%) males, and 16 (61.54%) left and 10 (38.46%) right ankles, involved in the series. Overall, the median and interquartile range for the pre-intervention and post-intervention pain scores was 8.5 (8, 9) and 2 (1, 3), respectively, and this difference was statistically significant ( $P < .0001$ ). Overall, the median and interquartile range for the reduction in pain (the difference between the pre- and post-intervention pain scores) was 6 (5, 8). In regard to intervention, 12 (46.15%) of the patients underwent ankle arthroscopy alone (AAA), whereas 14 (53.85%) underwent ankle arthroscopy plus hylan (AA+H) therapy. Table 3 depicts the comparisons of age, gender, involved side, pre-intervention pain score, post-intervention pain score, and the difference between the pre- and post-intervention pain scores, stratified by intervention group, for the case series. The median and interquartile range for the age of the patients in the AAA group was 55 (44, 61.5) years, whereas that for the patients who underwent AA+H therapy was 59 (51, 56) years, and this difference was not statistically significant ( $P = .4396$ ). For the group of patients who

**TABLE 2 The dataset (N = 26 patients)**

Patient	Age	Gender	Side	Treatment	Pain*		
					Pretreatment	Posttreatment	Difference†
1	57	Female	Left	AAA	7	4	3
2	67	Male	Right	AA + H	9	0	9
3	42	Male	Left	AAA	10	3	7
4	59	Male	Right	AA + H	8	1	7
5	33	Female	Right	AA + H	10	2	8
6	66	Female	Left	AA + H	7	1	6
7	44	Female	Right	AAA	6	3	3
8	34	Female	Left	AA + H	9	0	9
9	62	Female	Left	AA + H	8	0	8
10	41	Male	Left	AA + H	10	3	7
11	72	Male	Right	AA + H	10	1	9
12	66	Female	Left	AAA	9	4	5
13	59	Male	Left	AA + H	9	0	9
14	41	Male	Left	AAA	7	2	5
15	57	Female	Right	AA + H	9	1	8
16	56	Male	Left	AAA	8	2	6
17	50	Male	Right	AAA	8	2	6
18	44	Male	Right	AAA	8	3	5
19	56	Female	Right	AA + H	8	2	6
20	61	Female	Left	AAA	8	2	6
21	51	Female	Left	AA + H	7	2	5
22	68	Female	Left	AA + H	9	2	7
23	69	Female	Left	AAA	9	3	6
24	62	Female	Left	AAA	10	5	5
25	54	Male	Left	AAA	10	3	7
26	62	Male	Right	AA + H	7	1	6

AAA, ankle arthroscopy alone; AA + H, ankle arthroscopy plus hylan G-H 20.

\*Pain = patient's subjective categorical pain score, ranked 0–10, with 0 representing no pain, and 10 representing the worst pain that the patient can imagine.

†Difference = (pre-intervention – post-intervention) categorical pain score.

**TABLE 3 Comparison of different clinical variables by treatment group**

Variable	AAA, median (interquartile range) or count (%)	AA+H, median (interquartile range) or count (%)	<i>P</i> value*
Age, y	55.0 (44.0, 61.5)	59.0 (51.0, 66.0)	.4396
Male gender	6 (50%)	6 (42.86%)	.7211
Right ankle	3 (25%)	7 (50%)	.2002
Pre-intervention pain <sup>†</sup>	8.0 (7.5, 9.5)	9.0 (8.0, 9.0)	.6525
Post-intervention pain <sup>†</sup>	3.0 (2.0, 3.5)	1.0 (0, 2.0)	.0002
Pain reduction <sup>‡</sup>	5.5 (5.0, 6.0)	7.5 (6.0, 9.0)	.0014

AAA, ankle arthroscopy alone (n = 12); AA+H, ankle arthroscopy plus hylan (n = 14).

\*Wilcoxon rank-sum (Mann-Whitney) test.

<sup>†</sup>10-point categorical pain scale (0 = no pain, 10 = the most severe pain the patient can imagine).

<sup>‡</sup>Decrease in pain scores between the pre-intervention and post-intervention periods.

underwent AAA, 6 (50%) were female, and 6 (50%) were male; whereas for the group of patients who underwent AA+H therapy, 8 (57.14%) were females and 6 (42.86%) were male, and this distribution of males and females was not statistically significant ( $P = .7210$ ). Moreover, for the group of patients who underwent AAA, the left ankle was involved in 9 (75%) of the patients, and the right ankle was involved in 3 (25%) of the patients; whereas for the group of patients who underwent AA+H therapy, the left ankle was involved in 7 (50%) of the patients, and the right ankle was involved in 7 (50%) of the patients. For the AAA group, the median and interquartile range for the pre-intervention pain score was 8 (7.5, 9.5), whereas that for the post-intervention score was 3 (2, 3.5), and this difference was statistically significant ( $P = .002$ ). For the AA+H group, the median and interquartile range for the pre-intervention pain score was 9 (8, 9), and that for the post-intervention pain score was 1 (0, 2), and this difference was highly statistically significant ( $P = .0009$ ). The median and interquartile range for the pre-intervention pain score for the AAA group was 8 (7.5, 9.5); whereas that for the AA+H group was 9 (8, 9), and this difference was not statistically significant ( $P = .6525$ ). The median and interquartile range for the post-intervention pain score for the AAA group was 3 (2, 3.5); whereas that for the AA+H group was 1 (0, 2), and this difference was statistically significant ( $P = .0002$ ). The median and interquartile range for the reduction in pain for the AAA group was 5.5 (5, 6); whereas that for the AA+H group was 7.5 (6, 9), and this difference was statistically significant ( $P = .0014$ ). None of the patients in this series suffered with any type of postoperative complication, and none of those receiving hylan G-F 20 injections displayed any type of local or systemic adverse reaction to the agent.

## Discussion

While our study is currently limited to a small number of patients, our preliminary data provide insight into the role

and benefit of viscosupplementation in the ankle. In a thorough review by Weiss and Band (33), it was suggested that the physician treating the injured, deformed, dysvascular, metabolically abnormal, arthritic, and neurogenic foot and ankle should consider viscosupplementation as a treatment modality. They also state that this form of treatment is an ideal, safe, nonimmunogenic, biocompatible way to restore joint homeostasis, reduce arthritic pain, diminish surgical trauma and postsurgical scarring, and to augment articular soft tissues. Our experience has led us to agree with their view, and we have found viscosupplementation with hylan G-F 20 to be a safe way to decrease post-intervention pain, and to restore the intra-articular milieu of the ankle directly by restoring the rheologic properties and indirectly by functioning as a buffer via its exclusion effect on migrating cells and large molecules such as pro-inflammatory mediators.

Because use of hylan G-F 20 in the ankle is an "off label" application of this agent, patient safety is a key issue when considering this form of treatment. In general, viscosupplementation with hylan G-F 20 is safe and there have been no reports of adverse systemic reactions to the use of intra-articular hyaluronan therapy; however, cases of local adverse reactions do exist. Local inflammatory flares secondary to injection of the hyaluronan occur in 2% to 4% of hylan G-F 20 injections when treating osteoarthritis of the knee, and these typically occur within 24 to 48 hours of the injection, and are usually mild in nature and self-limited (35–39). However, in a small series by Puttick et al (40), clinically significant local inflammatory reactions occurred in 27% of their patients. It is also interesting to note that similar local flare reactions occur with intra-articular corticosteroid injections in approximately 3% of patients (41, 42). Cases of post injection-induced pseudogout with hylan G-F 20 have also been reported (36, 43). Zardawi and Chan (44) observed granulomatous inflammation with hylan G-F 20 in the perisynovial adipose tissue and described the histological findings associated with the condition. Martens (45) described symmetrical knee inflammation after hyaluronan injection and suggested that some individuals may be

uniquely susceptible to inflammatory responses. Although the specific etiopathogenesis of these reactions is unclear, interest has focused on the role of small hyaluronan fragments as pro-inflammatory mediators. These pro-inflammatory fragments might arise from degradation of hylan G-F 20, as well as other hylans, after these agents are administered via injection (46). When planning the use of hylan G-F 20 in ankles, we believe the benefits of viscosupplementation outweigh the risks of a possible local reaction. In the series of patients described in this report, we did not observe any evidence of adverse local or systemic reactions to hylan G-F 20. Several authors have compared the safety of hylan G-F 20 to NSAID therapy, which is a common method of treatment of osteoarthritis, and have noted that the risk of gastrointestinal bleed secondary to NSAID use is more common than experiencing an adverse event following hylan injection therapy (47). One study suggested that as many as 16,500 patients per year in the United States die from NSAID-induced bleeding (48). Altman and Moskowitz (49) suggested that therapy with hylans was as effective for patients with knee osteoarthritis as naproxen therapy, with fewer side effects. Adams et al (35) found that 3 hylan G-F 20 injections were as good or better than continuous nonsteroidal therapy, and could be used to replace continuous use of NSAIDs for periods up to 6 months at a time.

For the purposes of this investigation, hylan G-F 20 was chosen over other commercially available hylans because its high molecular weight is closest to that of native hyaluronan. Sripada et al (50) found that hylan G-F 20 demonstrated greater efficacy than did lower molecular weight hylans for the relief of pain and improved mobility in the treatment of osteoarthritis of the knee. Their findings also supported the claim that higher molecular weight products convey a therapeutic advantage in the treatment of osteoarthritis of the knee. A number of other authors also agree with this claim, and suggest that the cytoprotective activities of high molecular weight hylans are dependent on both the concentration and the molecular weight of hyaluronan in the joint (10–15). Still further, it has been shown that synovial cells obtained from patients with osteoarthritis show an increased amount of hyaluronan synthesized in culture when exposed to exogenous high molecular weight hyaluronan ( $5$  to  $6 \times 10^6$  daltons) (13), whereas hyaluronan of low molecular weight ( $5$  to  $7 \times 10^5$  daltons) does not induce the same beneficial response (28).

Viscosupplementation conveys a number of direct and indirect effects that are associated with normalization of the rheological properties of synovial fluid. In vitro studies of human synoviocytes from osteoarthritic joints revealed that exogenous hyaluronan stimulated de novo synthesis of hyaluronan (13), inhibited arachidonic acid and interleukin-1-alpha activity, and induced prostaglandin E2 synthesis by human synoviocytes (15, 51). Exogenous hyaluronan has also been found to influence leukocyte adherence, prolifer-

ation, migration, and phagocytosis (52), and to protect against cellular damage by enzymatic free radicals (53). Interleukin-1 is released in association with cartilage degradation in osteoarthritis, and this process is known to stimulate hyaluronan synthesis in cultured fibroblasts. However, this newly synthesized hyaluronan has a very low molecular weight and may account for the smaller size of hyaluronan found in the joint fluid of osteoarthritic joints (34, 54). The high molecular weight of native hyaluronan in healthy synovial tissue also serves to insulate pain fibers (18). However, with progression of osteoarthritis, the capacity of the hyaluronan to insulate pain fibers decreases because of disease-related alteration of its molecular weight and, finally, as the concentration of hyaluronan falls, less hyaluronan is available to function as an insulator. Based on our accumulated data, we agree with Marshall (55), that it is reasonable to consider viscosupplementation early in cartilage injury or disease before the establishment of symptomatic osteoarthritis.

Studies with viscosupplementation have shown that non-permanent relief can be expected to last from 3 to 12 months. This temporary relief is understandable when one considers the ongoing degradation of cartilage, and the associated release of inflammatory products and other cell signals that induce phagocytosis, that occurs in osteoarthritic joints. However, if relief can be experienced for up to 6 to 12 months following instillation of hylan into an arthritic joint, periodic viscosupplementation therapy could provide patients an alternative to joint reconstruction or replacement surgery. In a subset of the series of patients described in this article, we used hylan G-F 20 after ankle arthroscopy to help restore a more native joint environment. We have not used viscosupplementation in patients without a previous arthroscopy, and therefore are unable to comment on the effects that could be expected with isolated viscosupplementation therapy, or the use of such therapies in joints other than the ankle. We believe that ankle arthroscopy also provides the physician the opportunity to make an appropriate joint evaluation. Furthermore, we also believe that arthroscopic lavage of the joint removes or significantly dilutes inflammatory mediators that are present with osteoarthritis.

In our series, a 3-injection regimen of hylan G-F 20 was used beginning 1 week post-intervention, and carried out at weekly intervals for a total of 3 articular injections. We based our decision to use a series of 3 post-arthroscopy injections of hylan on the work performed by Adams et al (35), who compared several trials and concluded that 2 injections of hylan G-F 20 were statistically significantly better than placebo, and that a 3-injection course was statistically significantly better than 2 articular injections. Also, hylan G-F 20 comes packaged as 3 pre-filled syringes (Synvisc) for use in the treatment of knee osteoarthritis.

A number of potential biases were inherent to the design of this clinical investigation, and we realize that these threaten to some degree the validity of our results and conclusions. Probably most important is this regard is the fact that treatment allocation was not randomized. Rather, patients were enrolled consecutively as they presented for treatment of their ankle arthritis, and the decision as to which intervention would be used was determined at the discretion of the patient after discussion with the surgeon. Moreover, we did not use a visual analog pain scale to determine the pre- and post-intervention pain scores. Instead, we used a 10-point categorical scale that is commonly used in the clinical realm, and although it is likely that this form of pain measurement is not as valid as a visual analog scale, it is a method that is commonly used in clinical practice and, as such, conveyed a certain degree of external validity to our investigation. Finally, we did not perform an adjusted inferential analysis to determine the influence that any group of multiple variables had on a particular outcome. Instead, our interest was in trying to compile pilot data related to pain relief in association with ankle arthroscopy and articular instillation of hylan G-F 20 for the treatment of osteoarthritis of the ankle.

In the series of patients described in this article, we found that both treatment groups experienced statistically significantly decreased pain following the intervention ( $P = .002$  and  $P = .0009$  for the AAA and AA+H groups, respectively), and that those who received 3 intra-articular injections of hylan G-F 20 following ankle arthroscopy improved statistically significantly ( $P = .0014$ ) more than did those who underwent arthroscopy as a sole therapy. Although these results are preliminary in nature, they provide some evidence as to the beneficial effects that viscosupplementation, combined with arthroscopy, has in regard to pain relief in the treatment of osteoarthritis of the ankle. The results of this investigation may be useful in the development of future investigations into the treatment of ankle osteoarthritis by means of viscosupplementation.

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