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Safety and Efficacy of Intra-articular Sodium Hyaluronate (Hyalgan®) in a Randomized, Double-Blind Study for Osteoarthritis of the Ankle

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ABSTRACT

Background: **The potential benefit of hyaluronans in alleviating pain associated with osteoarthritis (OA) in joints other than the knee is of increasing interest. This double-blind, randomized, controlled study examined the safety and efficacy of intra-articular sodium hyaluronate (Hyalgan®) in the treatment of pain associated with ankle OA.** ***Materials and Methods:*** **Thirty consecutive patients with ankle OA documented by X-ray were randomized to treatment with five weekly injections of either sodium hyaluronate 2 mL (HYL) or phosphate-buffered saline 2 mL (control) in the tibiotalar joint. The primary endpoint was pain on movement and weightbearing using the Ankle Osteoarthritis Scale (AOS) 3 months after injection (a 100-mm visual analog scale [VAS]). Additional measures included the Western Ontario and McMaster Universities (WOMAC) OA Index and patient global assessment through 6 months; the Short Form-12 (SF-12) Health Survey at 3 months and 6 months; and all reported adverse events (AEs).** ***Results:*** **The study groups differed only in age, baseline WOMAC pain, and AOS total scores; 80% of the HYL and 73% of the control patients completed the study. At Month 3, the primary endpoint of the study, the HYL group demonstrated a significantly greater improvement from baseline in AOS total score than did the control group (HYL: -17.4 ± 5.0 mm; Control: -5.1 ± 4.0 mm; $p = 0.0407$). The incidence of AEs was low, with no significant differences between the groups. There were no post-injection flares.** ***Conclusion:*** **Our study suggests that sodium hyaluronate may be a safe and effective option for pain associated with ankle OA, although larger studies are needed.**

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INTRODUCTION

Hyaluronan (HA) is a large linear glycosaminoglycan, composed of repeating disaccharides of glucuronic acid and *N*-acetylglucosamine, which is present in all mammalian tissues.[3] HA is a lubricant at low shear and a shock absorber at high shear due to its ability to act as a viscous fluid and elastic solid. It has been shown to suppress cartilage matrix degradation and is reported to have an analgesic effect by directly buffering synovial nerve endings and stimulating synovial lining cells, inducing the production of normal HA.[11,22,24]

Osteoarthritis (OA) is a complex response of joint tissues to aging, genetics, and environmental factors, consisting primarily of cartilage degradation, bone remodeling, and overgrowth of bone.[12] It is well-recognized that synovial fluid removed from OA joints has decreased elasticity and viscosity compared with that of normal joints.[4] Administration of exogenous HA preparations addresses this problem by replacing the low viscoelastic synovial fluid with solutions of higher viscosity.[4] There are also substantial data to indicate that exogenously provided HA may also improve pain and function by non-mechanical, biologically based mechanisms within the synovial and articular environment.[1,9]

Intra-articular injections of a specific sodium HA (Hyalgan®; HYL; MW 500–730 kDa, sanofi-aventis, Bridgewater, NJ; Fidia Farmaceutici SpA, Abano Terme, Italy) have proven safe and effective for the treatment of pain associated with knee OA.[2,13] The manifestations of OA in the ankle are similar to those in the knee, providing a rationale for the evaluation of ankle viscosupplementation for the relief of OA pain in that joint. A recently published pilot study conducted in a total of 20 patients suggested that 5 weekly injections of HYL were well-tolerated, provided pain relief for up to 6 months, and improved function in patients with OA of the ankle.[20] To confirm and expand these results,

we report the results of a study investigating the benefits of intra-articular administration of HYL in reducing pain and improving function for patients with OA of the ankle. The objective of this study was to examine the safety and efficacy of five weekly injections of HYL in the treatment of ankle OA.

MATERIALS AND METHODS

This was a randomized, double-blind, saline-controlled, 12-week pilot study. Thirty consecutive patients presenting for pain associated with ankle OA documented by X-ray were randomized to receive five weekly intra-articular injections of either HYL 2 mL or phosphate-buffered saline (control) 2 mL in the tibiotalar joint. Patients were scheduled for a total of 10 visits: Screening, Baseline (with first injection), four weekly visits for subsequent injections, and followup assessments at 2 weeks, 6 weeks, 3 months, and 6 months after completion of the treatment course. All injections were fluoroscopically guided.

The primary efficacy endpoint was the patient's evaluation of pain on movement and weightbearing at Month 3 with HYL compared to the control group using the Ankle Osteoarthritis Scale (AOS) in the intent-to-treat (ITT) population. This population included all patients who were randomized and treated with at least one injection.

Secondary efficacy endpoints included: Western Ontario and McMaster Universities (WOMAC) OA Index of pain, stiffness, and physical function scores[5] through Month 6; the patients' assessment of global disease status through Month 6; and a health-related quality-of-life (HRQoL) assessment using the Short Form-12 (SF-12) Health Survey which was administered at Baseline, 3 months, and 6 months.

The study population comprised eligible men or women over 50 years of age with a diagnosis of ankle OA established by pain associated with X-ray changes of OA,[14] and AOS values greater than or equal to 30 and less than or equal to 90 (range, 0 to 100). Patients had chronic ankle pain for greater than or equal to 3 months but for less than 5 years present at least 50% of the time and without improvement in the previous month, and must have discontinued all nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic medication with the exception of acetaminophen 500 mg $\times$ 1 to 2 tablets 4 times daily, as needed (maximum, 8 tablets or 4 g/day as rescue analgesia) and aspirin up to 325 mg/day used as an anticoagulant. All patients had X-rays and/or computerized tomography (CT) scanning confirming ankle arthritis with a Kellgren-Lawrence grade of 2, 3, or 4.[14] Patients must have been active and not bedridden or wheelchair-dependent, and able to ambulate 50 feet without the aid of a walker, crutches, or cane.

Key exclusion criteria included bilateral ankle OA requiring treatment for both ankles other than simple analgesics such as acetaminophen; change in physical therapy/occupational therapy within the last 3 months; treatment with NSAIDs during the last week (or 5 half-lives of the drug, whichever was longer) prior to the baseline visit; use of systemic corticosteroids (excluding inhalational or topical corticosteroids) or intra-articular injections of corticosteroids in the treated ankle within the last 3 months; HA injections within the last 9 months in the treated ankle; and arthroscopy or any other surgical procedure within the last 12 months in the treated ankle. Patients must not have had significant changes in activity relative to baseline. Other patients excluded were those with concomitant periankle tendonitis, Achilles tendonitis, chronic or acute enthesopathy, or arthritis in the adjacent hindfoot joints.

Evaluation instruments included the AOS, an 18-item instrument (50% pain, 50% disability) utilizing 0- to 100-mm visual analog scale (VAS) response mechanisms, in which the highest score indicates greatest pain or disability[8]; and the WOMAC Osteoarthritis Index, 3-dimensional (pain, stiffness, physical function) using 100-mm VAS scales.

Study blinding was accomplished by having a treating investigator administer the injections and an evaluating investigator (who was blinded to the randomization) conduct the assessments. Patients were not aware if they received HYL or control injections. The same evaluating investigator saw each patient at all visits, including the eligibility check at the screening visit.

All statistical analyses were performed using SPSS® 8.0 for Windows system (Chicago, IL). Between-group differences in AOS and WOMAC outcomes were tested with the Wilcoxon rank sum test. Two-tailed p values less than or equal to 0.05 were considered significant.

RESULTS

Study population

A total of 30 patients were randomized to treatment: 16 to the HYL and 14 to the control group. One patient from the HYL group and one patient from the control group were screened but declined therapy prior to receiving an injection. Hence, 15 HYL and 13 control patients were included in the ITT efficacy and safety analyses. There were no significant differences between the study groups in demographics or disease characteristics, with the exception of mean age and mean baseline AOS total scores and WOMAC pain scores (Table 1).

Primary outcome

At Month 3, the HYL group demonstrated a significantly greater improvement from baseline in AOS total score than the control group (HYL: -17.4 ± 5.0 mm; control: -5.1 ± 4.0 mm; $p = 0.0407$). At Week 2, Week 6, Month 3, and Month 6, the percent improvements from baseline in the AOS total score in the HYL group were 19%, 22%, 36%, and 31%, respectively, as compared with 5%, 11%, 9%, and 13% in the control group (Figure 1). Although a trend toward greater improvement in the HYL group compared with that in the

Table 1: Demographics and baseline characteristics (Safety Population)

	HYL ($n = 15$)	Control ($n = 13$)	p value
Age, years (mean ± SD)	56.2 ± 15.1	43.4 ± 14.9	$p = 0.01$
Men (n, %)	14 (93%)	11 (85%)	n.s.
Body mass index, kg/m^2 (mean ± SD)	30.5 ± 5.3	29.5 ± 4.2	n.s.
Right ankle involvement (n, %)	10 (67%)	7 (54%)	n.s.
History of trauma (n, %)	11 (73%)	10 (77%)	n.s.
Kellgren-Lawrence grade (mean ± SD)	2.8 ± 1.2	2.8 ± 0.9	n.s.
Signal ankle range of motion (degrees ± SD)	19.0 ± 9.1	21.8 ± 11.6	n.s.
AOS pain (mean ± SD)	58.8 ± 16.3	51.9 ± 14.6	n.s.
AOS disability (mean ± SD)	69.4 ± 12.1	52.9 ± 18.7	n.s.
AOS total (mean ± SD)	64.1 ± 12.8	52.5 ± 14.6	$p = 0.03$
WOMAC pain (mean ± SD)	53.4 ± 16.6	45.9 ± 17.3	$p = 0.01$
WOMAC stiffness (mean ± SD)	62.7 ± 18.9	65.0 ± 21.0	n.s.
WOMAC function (mean ± SD)	55.9 ± 15.6	43.6 ± 19.3	n.s.
WOMAC total (mean ± SD)	55.9 ± 15.1	45.9 ± 17.5	n.s.

AOS = Ankle Osteoarthritis Scale; n.s. = not statistically significant; WOMAC = Western Ontario and McMaster Universities.

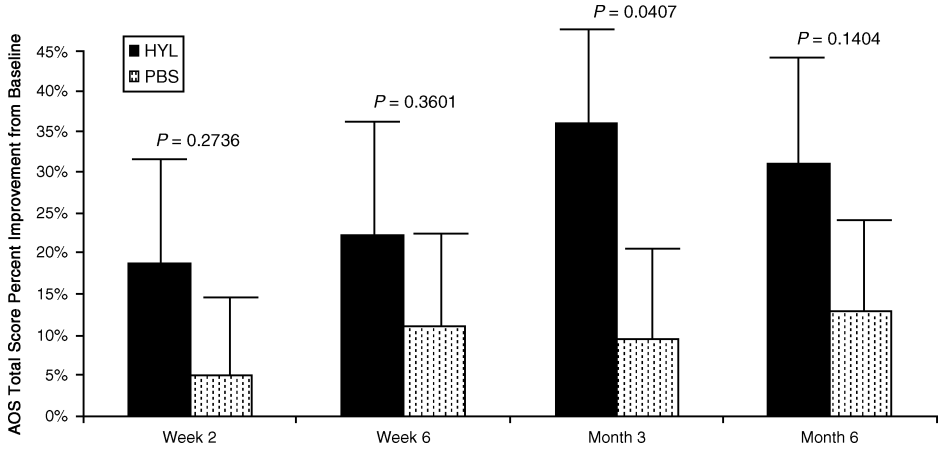

Fig. 1: Percent improvement (± standard error) from baseline in AOS total score at Week 2, Week 6, Month 3, and Month 6 after completion of a treatment course with 5 injections of HYL ($n = 13$) or control ($n = 11$). P values for the HYL versus control were calculated based on the Wilcoxon rank sum test.

control group was noted at Week 2, Week 6, and Month 6, the between-group comparisons were not statistically significant at these times (Table 2).

Secondary Outcomes

Secondary endpoints included change from baseline in AOS pain and disability subscores through Month 6. For the HYL group, the AOS pain subscore was significantly different from baseline at 2 weeks ($p = 0.042$), 3 months ($p = 0.0009$), and 6 months ($p = 0.0016$), while the AOS disability subscore was significantly different from baseline at 6 weeks ($p = 0.0106$), 3 months ($p = 0.0011$) and 6 months ($p = 0.0025$). For the control group, the AOS scores were not significantly different from baseline at each evaluation for either subscale. In a comparison between treatments, no statistically significant differences in either the AOS pain or AOS disability subscores were detected between the HYL and control groups at any evaluation (Table 2).

The percent improvements from baseline in WOMAC total score were 21%, 18%, 35%, and 32% at Week 2, Week 6, Month 3, and Month 6, respectively, for the HYL group, and 13%, 10%, 9%, and 12%, respectively, for the control group. At Month 3, there was a statistically significant difference ($p = 0.0332$) in the WOMAC total score between the HYL and control treatment groups (Table 2).

The WOMAC pain subscore for the HYL group was significantly different from baseline at 2 weeks ($p = 0.0003$), 3 months ($p < 0.0001$), and 6 months ($p = 0.0013$). At Month 3, there was a statistically significant difference ($p = 0.0062$) in the WOMAC pain subscore between the HYL and

Table 2: Percent improvement (± standard error) from Baseline in AOS and WOMAC total and subscale scores at Week 2, Week 6, Month 3, and Month 6

Score	Week 2			Week 6			Month 3	Month 6				
	HYL ($n = 15$)	Control ($n = 13$)	p value	HYL ($n = 15$)	Control ($n = 13$)	p value	HYL ($n = 15$)	Control ($n = 13$)	p value	HYL ($n = 15$)	Control ($n = 13$)	p value
AOS—pain	17.8 (±8.2)	2.9 (±8.9)	0.23	17.3 (±9.1)	10.0 (±9.9)	0.59	34.3 (±8.9)	10.3 (±9.3)	0.07	28.6 (±7.9)	9.4 (±8.3)	0.11
AOS—disability	16.6 (±9.3)	6.7 (±10.1)	0.49	23.5 (±8.4)	10.4 (±9.1)	0.31	34.3 (±9.1)	7.4 (±9.6)	0.06	30.7 (±8.9)	16.0 (±9.4)	0.28
AOS—total	18.6 (±8.3)	4.8 (±9.0)	0.27	22.2 (±8.0)	11.1 (±8.7)	0.36	35.9 (±8.3)	9.4 (±8.7)	0.04	30.9 (± 8.0)	12.9 (±8.46)	0.14
WOMAC—pain	27.8 (±6.5)	10.9 (±7.0)	0.09	17.9 (±9.6)	9.2 (±10.4)	0.54	42.4 (±8.2)	6.5 (±8.6)	0.01	35.4 (±9.5)	16.8 (±10.0)	0.19
WOMAC—stiffness	11.0 (±7.8)	0.6 (±8.4)	0.38	18.0 (±8.1)	12.1 (±9.1)	0.15	32.7 (±9.4)	8.4 (±9.7)	0.09	26.5 (±11.5)	4.2 (±12.4)	0.20
WOMAC—function	18.4 (±7.9)	13.2 (±8.6)	0.67	16.6 (±8.5)	7.4 (±9.3)	0.48	31.9 (±8.6)	6.6 (±9.1)	0.06	30.3 (±9.2)	7.9 (±9.7)	0.11
WOMAC—total	21.2 (±6.6)	12.7 (±7.2)	0.40	18.2 (±8.1)	10.1 (±8.8)	0.50	35.2 (±8.1)	8.5 (±8.5)	0.03	32.4 (±8.6)	12.0 (±9.1)	0.12

AOS = Ankle Osteoarthritis Scale; WOMAC = Western Ontario and McMaster Universities; HYL = sodium hyaluronate 2 mL.

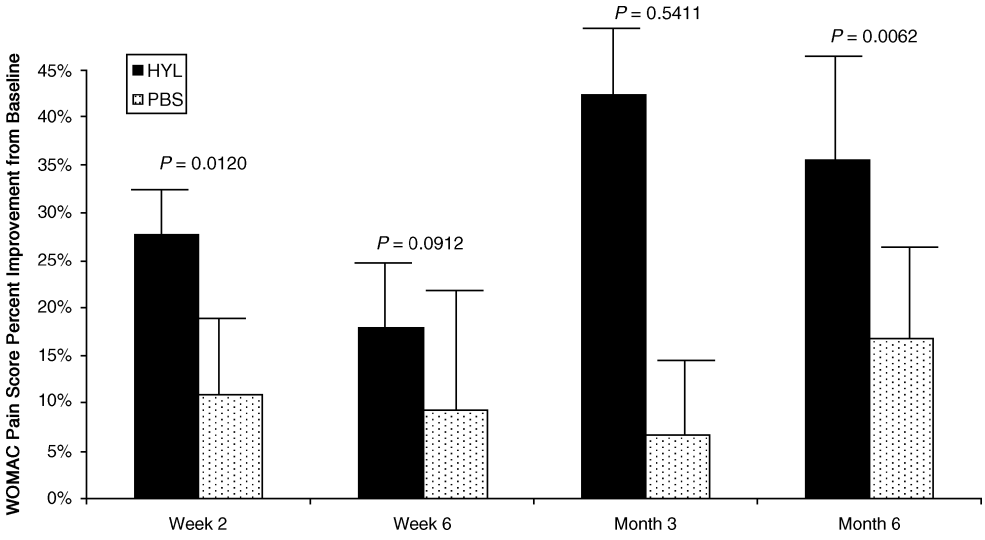

Fig. 2: Percent improvement (± standard error) from baseline in WOMAC pain subscale score at Week 2, Week 6, Month 3, and Month 6 after completion of a treatment course with 5 injections of HYL ($n = 13$) or control ($n = 11$). P values for the HYL versus control were calculated based on the Wilcoxon rank sum test.

control treatment groups (Figure 2). However, there were no statistically differences between the treatments for either the WOMAC stiffness or function subscores at any evaluation. Both groups improved in patient global assessment, with no significant differences between the treatment groups. There were no significant changes in the SF-12 assessments for either treatment group.

The incidence of AEs was low, with no significant differences between the treatment groups. There were no post-injection flares in either group. One patient in the HYL group presented to an emergency room 2 days post-injection with an effusion and erythema around the ankle. An aspiration of the joint revealed calcium pyrophosphate crystals consistent with pseudogout, which resolved without therapy or sequela.

DISCUSSION

The results of this randomized, placebo-controlled study indicate that for OA of the ankle, five intra-articular injections of HYL were safe and well-tolerated in this patient population. Significant pain relief and improvement in function were noted for at least 3 months after the conclusion of treatment. Although the difference between the active and control treatments was no longer significant at the 6-month time point, there was still a clear improvement from baseline in the primary outcome variable, the AOS pain score, at Month 6 in the HYL group. The results of this study confirm and extend those of a recently published pilot study by Salk et al.[20] involving 20 patients, which demonstrated that HYL was safe and effective for the treatment of pain associated with ankle OA. In comparison with this earlier trial, our study was more rigidly controlled and had a larger patient pool; in addition, it had tighter exclusion criteria, and was a single-center trial, which enhanced its consistency. Our results are also consistent with those of a recent uncontrolled pilot study indicating that another sodium hyaluronate formulation, Artz™ (Seikagaku Corporation, Tokyo, Japan), was effective and well-tolerated in patients with ankle OA,[21] and with a preliminary open-label study of another visco-supplementation agent, hylan G-F 20, indicating that this preparation was generally well tolerated and efficacious for the treatment of ankle OA pain.[25]

Studies have been performed with various HA preparations in the treatment of a diverse array of articular joints aside from the knee, including the temporomandibular joint,[6,10] the shoulder,[16,18,19,26] and the hip.[7] Although these studies have been generally limited in design and scope, HA therapy was reported to be safe and efficacious in alleviating pain associated with OA in a number of joints. Although the specific mechanisms of action that account for the clinical benefit of HA in relieving OA pain are not precisely defined, several have been proposed and are supported by experimental data. In addition to increased viscosity and mechanically mediated amelioration of pain, other potential mechanisms of pain relief include an exogenous HA-mediated anti-inflammatory action, enhanced synthesis and decreased degradation of articular cartilage, and direct analgesia through inhibition of pain receptors.[1,9] Each of these proposed mechanisms of action has the potential to play a role in the beneficial effects of HAs for the treatment of OA of the ankle joint.

As has been noted in patients with OA of the knee, the onset of pain relief following HYL treatment in our patients was rapid, apparent within 2 weeks of starting treatment, and statistically significantly superior to control at the 3-month time point. Although the between-group difference was no longer significant at the 6-month secondary

outcome, a separation between the groups for the primary outcome was still observed at this time point. As has been noted in a number of previous studies comparing sodium hyaluronate and saline control injections, substantial pain relief compared with baseline was noted in the control patients, which could have an effect on the significance of between-group comparisons. This pain reduction may represent a true beneficial effect of saline solution in the damaged joint, in addition to a pure placebo effect.[2,15,23] This possibility represents a limitation of any controlled OA study that employs vehicle injections as a control. The duration of pain relief noted in this study is consistent with evaluations of HYL for treatment of pain associated with OA of the knee, in which pain relief has been noted for periods of 6 months up to more than a year.[2,15,17]

The improvement in AOS total score over the 6-month period of this investigation points to the likely benefits of HYL in alleviating chronic ankle pain in patients with OA with similar disease features to the population we studied; i.e., patients who have been without improvement in the previous month and who have been experiencing OA pain at least 50% of the time for greater than or equal to 3 months but less than 5 years. Although we did not quantify the costs of treatment, HYL may represent a cost-effective alternative therapy in particular OA subgroups such as: (1) patients who fail to respond to other treatments; (2) patients who are unable to tolerate oral medications such as NSAIDs, especially those with comorbidities; and (3) those in whom intra-articular corticosteroid injections have been ruled out because of their potential hazards. Further studies of its cost-effectiveness in specific subgroups, eg, those with a particular Kellgren-Lawrence grade of OA or in whom other therapies are ineffective or not tolerated, will clarify its optimal place in therapy in the future.

Overall, the results of this study involving 28 patients extend previous data from a pilot study indicating that HYL provides a safe and effective treatment option for improvement of pain and function in patients with OA of the ankle. Patients treated with HYL were older and had more pain based on AOS and WOMAC at baseline, which could have affected the ability to demonstrate pain relief. However, the analysis of treatment effect as percent changes from baseline would have accounted for this difference in the primary and secondary evaluations. Further evaluation in greater patient numbers of patients treated for longer periods and in specific subgroups of OA patients is warranted.

CONCLUSION

For OA of the ankle, five weekly intra-articular injections of Hyalgan (MW, 500 to 730 kDa) provided safe and effective pain relief for at least 3 months. Additional studies in larger patient populations are recommended to confirm these findings.

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