The Effect of Three Weekly Intra-Articular Injections of Hyaluronate on Pain, Function, and Balance in Patients with Unilateral Ankle Arthritis

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Background: Ankle arthritis can cause substantial pain and functional limitation. Previous studies have indicated that five weekly intra-articular injections of hyaluronate were safe and effective in the treatment of ankle osteoarthritis. The purpose of this study was to evaluate the effect and safety of three weekly injections of hyaluronate in patients with unilateral ankle arthritis.

Methods: Fifty patients who had had unilateral ankle pain for at least six months and were classified radiographically as having Kellgren-Lawrence grade-2 or 3 ankle arthritis were recruited for a prospective study. Patients received three weekly intra-articular injections of hyaluronate. The primary outcome was the change in the Ankle Osteoarthritis Scale score at six months after the third injection. Secondary outcomes included the American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Score, four clinical tests of balance, consumption of rescue analgesics, and global patient satisfaction.

Results: Forty-six participants completed the study. A significant reduction in the mean Ankle Osteoarthritis Scale score was noted at one, three, and six months after the third injection (p < 0.05 for each follow-up visit compared with baseline). The mean AOFAS Ankle-Hindfoot Score improved from 60.5 points at baseline to 73.5, 75.5, and 76.7 points at one, three, and six months of follow-up, respectively (p < 0.05). The patients demonstrated significant improvement on all four balance tests at each follow-up visit (p < 0.05 for each test compared with baseline). Acetaminophen consumption dropped significantly following treatment (p < 0.05). The patients' satisfaction rate was high, and no serious adverse events were reported.

Conclusions: This study suggests that three weekly injections of hyaluronate are well-tolerated and can provide pain relief and improve function and balance in patients with unilateral ankle arthritis. Larger controlled trials with longer follow-up are necessary to verify the effects of hyaluronate in the treatment of ankle arthritis.

Level of Evidence: Therapeutic Level IV. See Instructions to Authors for a complete description of levels of evidence.

A nkle arthritis can cause substantial pain and functional limitation. Between 6% and 13% of all cases of osteoarthritis involve the ankle joint¹. Recent research has indicated that patients are being diagnosed with ankle osteoarthritis with increasing frequency². Treatment options include analgesics, anti-inflammatory medication, weight loss, physical and occupational therapy, activity modification, orthotic devices, corticosteroid injections, and surgery. Although some cases can be treated successfully with surgery, many patients are

either not good candidates for surgery or prefer not to have surgery. Therefore, a treatment that reduces chronic joint pain and improves function yet avoids the toxic effects of medications and the morbidity and mortality risks of surgery is needed. One such option for these patients may be the intraarticular injection of hyaluronate.

In osteoarthritis, the molecular weight and concentration of hyaluronate in the synovial fluid are both reduced, and this may be associated with an increased vulnerability of articular

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THE JOURNAL OF BONE & JOINT SURGERY · JBJS.ORG VOLUME 93-A · NUMBER 18 · SEPTEMBER 21, 2011

cartilage to damage³⁻⁵. Intra-articular injections of hyaluronate in joints with osteoarthritis can restore the viscoelasticity of the synovial fluid, augment the flow of joint fluid, normalize endogenous hyaluronate synthesis, inhibit hyaluronate degradation, reduce joint pain, and improve joint function^{6,7}.

Although viscosupplementation with three to five weekly intra-articular injections of hyaluronate is a well-established treatment option for osteoarthritis of the knee, and it is included in the treatment guidelines of the European League against Rheumatism and the American College of Rheumatology^{8,9}, evidence regarding its use in the ankle is limited¹⁰⁻¹³. Previous studies have indicated that five weekly hyaluronate injections can reduce pain and improve function in patients with ankle osteoarthritis¹⁰⁻¹². Witteveen et al. reported that a single intra-articular injection of hyaluronate (Synvisc; Wyeth, Philadelphia, Pennsylvania), with the option of a second injection after one to three months if pain relief is inadequate, is an efficacious treatment for patients with symptomatic ankle osteoarthritis¹³. The effect of three weekly injections of hyaluronate into the ankle has not been investigated, to our knowledge. The three-injection regimen may represent a costsaving therapy, and this remains an important area for investigation. Also, pain associated with ankle arthritis may cause loss of balance, leading to falls, injuries, and increased costs to the patient and society. To our knowledge, no previous study has assessed whether balance would change after hyaluronate injections in patients with ankle arthritis. The purpose of the current study was to investigate the efficacy and safety of three weekly intra-articular injections of hyaluronate in patients with unilateral ankle arthritis.

Materials and Methods

Participants

Patients with a diagnosis of unilateral ankle arthritis were referred by our outpatient orthopaedic department between October 2007 and October 2008. All patients fulfilled the following inclusion criteria: (1) an age of at least twenty years; (2) unilateral ankle pain that had lasted for at least six months, with no significant benefit from conservative treatment or with an inability to tolerate the side effects of medications; (3) grade-2 or 3 arthritis, according to the Kellgren-Lawrence grading system¹⁴, demonstrated on ankle radiographs made within the previous six months; (4) a current total Ankle Osteoarthritis Scale (AOS) score (see Appendix) of >3 and \leq 9 (out of a possible range of 0 to 10); (5) a normal activity level-i.e., not bedridden or confined to a wheelchair, and able to walk 30 m without the aid of a walker, crutches, or cane; (6) willingness to discontinue all nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic medication (except for rescue medication) for the duration of the study; and (7) no use of physical therapy or changes in shoes or orthotic devices during the study period.

Exclusion criteria included pregnancy or lactation in women; bilateral ankle arthritis; lower-extremity trauma in a location other than within the ankle; previous surgery involving the spine, hip, or knee; the presence of an active infection of the ankle; surgery involving the affected ankle within the previous twelve months; previous hyaluronate injections into the ankle; corticosteroid injection into the ankle within the previous six months; treatment with anticoagulants or immunosuppressives; a history of rheumatoid arthritis, gout, or other inflammatory arthropathy; a history of allergy to avian protein; and the presence of visual or vestibular impairments or poor health status (such as a neoplasm, diabetes mellitus, or paresis) that would interfere with the clinical assessments conducted during the study.

EFFICACY OF THREE WEEKLY INJECTIONS OF HYALURONATE IN PATIENTS WITH ANKLE ARTHRITIS

TABLE I Patient and Osteoarthritis Characteristics (N = 46)				
	Value	Range		
Age* (yr)	51.7 ± 14.4	23-71		
Sex (F/M)	26/20			
Weight* (kg)	68.6 ± 10.7	50-95		
Height* (cm)	163.9 ± 5.7	153-173		
Body-mass index* (kg/m²)	25.5 ± 3.7 17.5-3			
Side of ankle arthritis (left/right)	29/17			
Etiology of arthritis (unknown/known)	9/37			
Radiographic Kellgren-Lawrence grade				
2	32			
3	14			
Disease duration* (yr)	3.7 ± 5.0	0-30		
*Values are given as the mean a	nd the standard de	eviation.		

Fifty patients satisfied these criteria and consented to take part in the study. One of these patients withdrew his consent, and one developed a fear of injection prior to receiving the first injection. Two patients withdrew from the study before the third injection (one because of an unrelated concurrent illness and one because of a move to another city). Thus, forty-six participants completed the study. Demographic data for these patients, including the characteristics of the osteoarthritis, are presented in Table I. The arthritis was of unknown etiology-without a traceable history of either trauma or a recent infection-in nine patients. The arthritis was due to an infection in three patients and due to a ligamentous injury, malleolar fracture, plafond fracture, talar fracture, or another cause in the remaining thirty-four patients.

The medical records of each patient were reviewed, and the etiology and duration of the arthritis were recorded, prior to the first injection. The etiology was determined on the basis of the medical history, physical examination, and imaging studies. If no cause could be elucidated, the case was classified as arthritis of unknown etiology.

Study Design

This prospective study was conducted in the outpatient rehabilitation department at a university-affiliated tertiary-care medical center. The study was approved by the institutional review board for human investigations, and all subjects provided signed informed consent before being enrolled in the study. The trial was registered at ClinicalTrials.gov (number NCT00918736).

Patients were instructed to discontinue all analgesics and NSAIDs at least seven days before the baseline assessment. Patients completed this assessment within one week of entry into the study and then received three weekly intraarticular injections of 2 mL of sodium hyaluronate (Hyalgan [molecular weight, 500 to 730 kDa]; Fidia Pharmaceuticals, Abamo Terme, Italy) into the ankle joint. Hyalgan has been reported to be well-tolerated and effective in the treatment of pain associated with knee or ankle osteoarthritis^{10,12,15,16}. The injections were performed by a single experienced physician (S.-F.S.), who took no part in the clinical assessment of the patients or in the data analysis. Patients were instructed not to take anti-inflammatory drugs or pain medications on a regular basis during the study period. Only acetaminophen (500 mg/tablet, up to 4 g/day) was allowed for breakthrough pain. If the treatment dose exceeded this stipulated limit, the patient was regarded as a clinical failure. Administration of acetaminophen within eight hours prior to any of the follow-up assessments was prohibited.

The Journal of Bone & Joint Surgery • JBJS.org Volume 93-A • Number 18 • September 21, 2011 EFFICACY OF THREE WEEKLY INJECTIONS OF HYALURONATE IN PATIENTS WITH ANKLE ARTHRITIS

Outcome Measures

A single investigator (C.-W.H.) performed a clinical assessment of each patient prior to the first injection and at one, three, and six months after the third injection. The primary outcome measure was the AOS score¹⁷, which is a validated patient-rated outcome measure that contains a nine-item pain subscale and a nine-item disability subscale (see Appendix). The range of possible scores for the AOS and for its subscales is 0 to 10. A score of 0 represent no pain or disability, and a score of 10 represents the worst pain and/or disability imaginable¹⁷.

The secondary outcome measures included four clinical tests of balance. (1) The single-leg stance test involved raising the unaffected foot, without touching it to the affected lower extremity, and maintaining balance for as long as possible. Each participant performed three trials, and the best result was recorded¹⁸. (2) The functional reach test evaluated the maximum distance that the participant could reach forward while maintaining a fixed base of support in a standing position¹⁹. Each participant performed three trials, and the average was recorded. The validity of the functional reach test has been previously demonstrated by a significant correlation (r = 0.71)between the results and laboratory center-of-pressure measurements¹⁹. A longer functional reach suggests that the participant has a larger anterior margin of stability, and therefore better dynamic balance control. (3) The timed "up-and-go" test, which measures functional mobility and dynamic balance²⁰, involved rising from an armchair, walking 3 m at a safe and comfortable pace, turning around, walking back to the chair, and sitting down again. The total time (in seconds) required to complete this series of tasks once was recorded. (4) The Berg Balance Scale was used to evaluate performance during fourteen functional tasks, such as rising, turning, and reaching for an object on the floor. Static and dynamic balance is evaluated with use of tasks of increasing difficulty, progressing from sitting to single-leg standing. The result is scored on a 56-point scale, and a higher score indicates better balance skills. The Berg Balance Scale has high interobserver and intraobserver reliability, and scores have been shown to correlate with laboratory tests of balance²¹.

Four other secondary measures were also employed. (1) Pain, function, and alignment were assessed with use of the American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Score, which is a 100-point scale that devotes 40 points to pain, 50 points to function, and 10 points to alignment. The maximum score of 100 points denotes no pain and normal function and alignment²². (2) The patient recorded the use of analgesic medication during the study period on a diary card. (3) The patient rated his or her level of global satisfaction relative to the state before the treatment. The rating was based on a seven-point categorical scale on which 7 = completely satisfied, 6 = satisfied, 5 = somewhat satisfied, 4 = no change (neither satisfied nor dissatisfied), 3 = somewhat unsatisfied, 2 = unsatisfied, and 1 = completely unsatisfied. (4) The safety of each injection was monitored by recording the occurrence of systemic and local adverse events on a diary card.

Statistical Analysis

The primary outcome measure was the change in the AOS score from baseline to the six-month follow-up visit. The sample size was calculated on the basis of a previous report by our group in which five weekly intra-articular injections were used for the treatment of ankle arthritis in seventy-five patients. The mean reduction in the AOS score in that study was 2.6 points, and the standard deviation was 1.8 points¹¹. Therefore, assuming a similar mean reduction in the AOS score of 2 ± 2 points six months after a series of three weekly injections, we calculated that we would require at least forty-two patients in order to have >90% power to detect a reduction of >1 point in the AOS score with use of the paired t test. Allowing for the possible drop-out of participants, we recruited fifty patients into the current study.

The data are presented as the mean and the standard deviation except where otherwise noted. The AOS score, the AOFAS score, the clinical balance test results, and the consumption of rescue analgesics at each follow-up visit were compared with the corresponding baseline value with use of the paired t test. A p value of <0.05 was considered significant.

Subgroup Analysis

After data collection was complete, we stratified patients by age and by radiographically determined osteoarthritis severity. We then used an independentsample t test to determine whether the change in each outcome measurement after treatment varied depending on the age of the patient. Similarly, an independent-sample t test was used to determine the effect of osteoarthritis severity on the change in each outcome measurement. A power analysis was conducted if the null hypothesis was rejected in any of these subgroup analyses.

Source of Funding

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Results

Table II summarizes the change in the total AOS score, the AOS pain and disability subscores, the AOFAS Ankle-Hindfoot Score, and acetaminophen consumption at each follow-up visit. Each of these outcome measures improved significantly, compared with the baseline value, at each follow-up visit. Thus, the treatment effect lasted for at least six months.

The mean AOS pain subscore (and standard deviation) decreased from 5.0 ± 2.2 points prior to injection to 3.2 ± 2.0 , 3.0 ± 1.7 , and 3.0 ± 1.9 points at one, three, and six months,

TABLE II AOS and AOFAS Scores and Analgesic Usage Before and After Treatment*					
Test	Baseline	1 Mo	3 Mo	6 Mo	
AOS					
Total	5.5 ± 2.1	$\textbf{3.5} \pm \textbf{1.9}$	3.4 ± 1.7	3.2 ± 1.9	
Pain subscore	5.0 ± 2.2	$\textbf{3.2}\pm\textbf{2.0}$	3.0 ± 1.7	3.0 ± 1.9	
Disability subscore	5.9 ± 2.2	$\textbf{3.8} \pm \textbf{2.0}$	$\textbf{3.8} \pm \textbf{1.9}$	3.3 ± 2.0	
AOFAS	$\textbf{60.5} \pm \textbf{19.1}$	$\textbf{73.5} \pm \textbf{18.4}$	75.5 ± 17.7	76.7 ± 19.5	
Acetaminophen (tablets/wk)	16.1 ± 6.4	6.7 ± 2.8	7.2 ± 2.1	9.6 ± 2.9	

*AOS = Ankle Osteoarthritis Scale (possible range, 0-10; higher scores represent poorer outcome), and AOFAS = American Orthopaedic Foot & Ankle Society Ankle-Hindfoot Score (possible range, 0-100). N = 46 ankles. Values are given as the mean and the standard deviation. All values were significantly better than before intra-articular injection of hyaluronate (p < 0.05).

EFFICACY OF THREE WEEKLY INJECTIONS OF HYALURONATE IN PATIENTS WITH ANKLE ARTHRITIS

TABLE III Clinical Balance Test Scores Before and After Treatment*				
Test†	Baseline	1 Mo	3 Mo	6 Mo
SLS	17.3 ± 21.5	22.4 ± 24.0	25.6 ± 25.0	25.6 ± 26.0
FRT	$\textbf{23.1}\pm\textbf{6.3}$	26.6 ± 6.7	27.2 ± 7.6	26.3 ± 6.7
TUG	9.6 ± 3.3	8.2 ± 2.7	8.0 ± 2.9	7.9 ± 2.6
BBS	51.1 ± 5.2	52.6 ± 4.0	53.2 ± 3.6	52.9 ± 3.5

*Values are given as the mean and the standard deviation. N = 46 ankles. All values were significantly better than before intra-articular injection of hyaluronate (p < 0.05). †SLS = single-leg stance test, FRT = functional reach test, TUG = timed up-and-go test (higher scores represent poorer performance), and BBS = Berg Balance Scale (possible range, 0-56).

respectively, after the third injection (p < 0.05 for each value compared with baseline). The mean AOS disability subscore improved from 5.9 ± 2.2 points at baseline to 3.8 ± 2.0 , 3.8 ± 1.9 , and 3.3 ± 2.0 points at one, three, and six months after the third injection (p < 0.05 for each value compared with baseline).

The mean AOFAS Ankle-Hindfoot Score (on which a higher score is better and the maximum possible score is 100 points) improved from 60.5 ± 19.1 points at baseline to 73.5 ± 18.4 , 75.5 ± 17.7 , and 76.7 ± 19.5 points at one, three, and six months after the third injection (p < 0.05). Mean analgesic (acetaminophen) usage decreased from 16.1 ± 6.4 tablets weekly at baseline to 6.7 ± 2.8 , 7.2 ± 2.1 , and 9.6 ± 2.9 tablets weekly at one, three, and six months of follow-up (p < 0.05 compared with baseline).

All patients demonstrated significant improvement on each of the clinical balance tests at each follow-up visit (p < 0.05 for each test compared with baseline) (Table III). Again, the treatment effect lasted for at least six months.

Nearly all of the improvement in the total AOS score, the AOS pain and disability subscores, the AOFAS Ankle-Hindfoot Score, and the scores on the four clinical balance tests attained during the study period had occurred by the time of the onemonth follow-up visit. Thereafter, the AOS and timed up-andgo test scores trended downward (better) with time, the AOFAS ankle-hindfoot and single-leg stance scores trended upward (better), and the functional reach test and Berg Balance Scale scores trended upward (better) until three months and then trended downward (poorer). Thus, the efficacy of three injections of hyaluronate appeared to begin to wane at six months, as did patient satisfaction.

The treatment resulted in a high rate of patient satisfaction (with 97.8% at least somewhat satisfied) at the onemonth follow-up visit (Table IV). The degree of satisfaction decreased at the three-month and six-month follow-up visits. However, no patient reported dissatisfaction or aggravation of the ankle symptoms compared with the baseline condition at any of the follow-up visits.

The injections were well-tolerated, and no serious adverse events were observed. Three patients experienced brief post-injection pain, and one had local pruritus that resolved within seventy-two hours. The rate of local adverse reactions was 8.7% per patient and 5.8% per injection. No patient withdrew from the study because of an adverse event.

Subgroup Analyses

The severity of the arthritis was grade 2 in thirty-two patients and grade 3 in fourteen according to the Kellgren-Lawrence system (Table I). With the numbers available, the subgroup analysis revealed no significant difference in the AOS, AOFAS, or clinical balance test scores between patients with grade-2 and grade-3 arthritis at any time point.

However, some interesting findings emerged when patients were stratified by age. The median age of our study population was fifty-five years. Using fifty-five years of age as the cutoff point, patients were classified into a younger group (up to fifty-five years, n = 25) and an older group (older than fifty-five years, n = 21). The improvements in the AOS score,

TABLE IV Satisfaction with Outcome of Viscosupplementation for the Treatment of Ankle Arthritis*						
	Completely Satisfied	Satisfied	Somewhat Satisfied	No Change	Satisfaction Rate	
1 mo	9 (20%)	25 (54%)	11 (24%)	1 (2%)	98%	
3 mo	4 (9%)	26 (57%)	13 (28%)	3 (7%)	93%	
6 mo	4 (9%)	16 (35%)	23 (50%)	3 (7%)	93%	

*Values are given as the number (and percentage) of patients who reported the indicated level of global satisfaction when comparing the status after viscosupplementation with that before the injections. No patient reported dissatisfaction at any of the time points.

The Journal of Bone & Joint Surgery - JBJS.org Volume 93-A - Number 18 - September 21, 2011 EFFICACY OF THREE WEEKLY INJECTIONS OF HYALURONATE IN PATIENTS WITH ANKLE ARTHRITIS

AOFAS Ankle-Hindfoot Score, and clinical balance test scores were compared between the two age groups at each follow-up time period (see Appendix). Although most of the improvements were similar in the two groups, we found significantly greater improvement in two of the clinical balance test scores (the single-leg stance and the functional reach test) in patients in the younger age group than in the older age group at the one-month follow-up visit (with 59% and 52% power, respectively). In addition, patients in the younger age group demonstrated significantly greater improvement than patients in the older age group on the single-leg stance test at the threemonth and six-month follow-up visits (with 50% and 71% power, respectively). Patients in the older age group demonstrated significantly greater improvement than patients in the younger age group on the Berg Balance Scale at the threemonth and six-month follow-up visits (with 71% and 77% power, respectively).

Discussion

This prospective study provides evidence that a regimen of three weekly intra-articular injections of hyaluronate can be a safe and effective treatment for patients with unilateral ankle arthritis, resulting in improvements in pain, function, and balance. The patients' satisfaction rate was high, and there were no serious adverse events. These effects can last for at least six months.

Our results are consistent with those of a recent pilot study of twenty patients by Salk et al. that demonstrated that five weekly intra-articular injections of hyaluronate could improve function and ameliorate pain in patients with ankle osteoarthritis¹⁰. In another pilot study, we reported a mean reduction of 2.6 points in the AOS score and a mean improvement of 14 points in the AOFAS Ankle-Hindfoot Score at the six-month follow-up visit after five weekly injections of another hyaluronate formulation (ARTZ; Seikagaku Corporation, Tokyo, Japan) in patients with Kellgren-Lawrence grade-1 or 2 ankle arthritis¹¹. Although a similar improvement in pain and disability was also documented in our present study, the results of our previous study and current study were difficult to compare because of differences in the formulation of the injection and in the radiographic severity of the arthritis as well as in the number of injections.

The characteristics of the ideal candidate for hyaluronate injection have yet to be defined. Previous large openlabel studies involving knee osteoarthritis have suggested that patients with early and intermediate-grade disease (as measured radiographically) obtained better results than patients with end-stage disease did²³. In a meta-analysis, Wang et al. found that patients who were more than sixty-five years of age and had more advanced osteoarthritis were less likely to benefit from intra-articular hyaluronate injections than their younger counterparts with less severe disease were²⁴. In the current study, we stratified patients by radiographically measured arthritis severity but we did not have a sufficient number of patients to demonstrate a significant difference in outcome between patients with grade-2 and grade-3 ankle arthritis. One interesting finding from our study was that the improvement in the scores on two of the four balance tests was significantly greater in the younger age group than in the older age group. However, this could potentially be due to a ceiling effect if there are age-related differences in performance on these balance tests; older patients may have poorer performance normally, and that may limit their ability to improve to the same extent as younger individuals. Furthermore, the results of subgroup analyses should be interpreted with caution when the statistical power is low. Future studies with larger treatment group sizes should better elucidate the factors associated with a favorable patient response and thus help to identify patients who would benefit the most from viscosupplementation in the ankle joint.

To our knowledge, this was the first study to examine the effect of hyaluronate injection on balance in patients with ankle arthritis. We previously reported significant improvements in pain, physical function, and balance after five weekly hyaluronate injections in elderly patients with knee osteoarthritis²⁵. A limited number of other studies have evaluated balance in patients with knee arthritis²⁶⁻²⁸; Hassan et al.²⁷ and Wegener et al.²⁸ demonstrated increased postural sway when subjects with knee osteoarthritis were standing on a firm surface. These studies utilized expensive force platforms that are not readily available to most physicians in a clinical setting. Furthermore, loss of balance and falls occur most commonly during dynamic tasks such as walking, and it is therefore important that an evaluation of balance incorporate testing procedures that reflect the dynamic nature of such locomotor tasks. In the current study, we chose simple, inexpensive, and easy-toadminister clinical tests to assess both static and dynamic balance. Control of balance depends on sensory input from the vestibular, visual, and somatosensory systems as well as precise motor control and coordinated neuromuscular responses²⁹⁻³¹. In our study population, balance deficits were likely a result of a combination of impaired proprioception and impaired neuromuscular control, since we ensured that the subjects had no vestibular or vision impairment. Hubbard et al. reported significant impairments in mechanical and sensorimotor function in patients with ankle arthritis compared with healthy controls³². Pain associated with arthritis frequently leads to a reduced activity level and weakening of muscles, resulting in a secondary increase in instability. Reduced muscle strength and deficits in lower-limb proprioception associated with arthritis could compromise effective and timely motor responses in maintaining balance^{27,33}. Although the mechanism by which hyaluronate results in a clinical improvement in balance remains unknown, we believe that pain reduction might be one of the major contributing factors and that balance may therefore represent a surrogate measure for pain. Since we did not directly measure proprioception or neuromuscular control in the current study, we do not know which system may have been responsible for the improvement in balance. More research on the impact of arthritis on balance may allow the mechanism to be elucidated and thus permit more effective management of patients with ankle arthritis.

The Journal of Bone & Joint Surgery · JBJS.org Volume 93-A · Number 18 · September 21, 2011

The current study was limited by the lack of a control

group for comparison. Therefore, we were unable to determine what proportion of the improvement in the pain level may have been due to a placebo effect. Several previous trials

have used saline solution controls; no adverse responses were

reported, and some researchers have speculated that saline solution injection may actually have a clinical benefit^{10,15}. The six-month trial period in our study was relatively short, and it is unclear how much longer the clinical benefits would have

been maintained. Since the number of patients studied was

relatively small, the results were not analyzed on the basis of

the cause of the arthritis or the patient's baseline functional

level or activity level. Future studies with a direct comparison

between three-injection and five-injection protocols are

needed to determine which patients might benefit more from

one regimen than the other, and larger studies are necessary to

investigate the variables that are predictive of a good outcome.

Several studies have reported the efficacy of and possible adverse events associate with repeat injections of hyaluronate to

treat knee osteoarthritis³⁴⁻³⁹. However, the efficacy and safety

of repeat courses of hyaluronate therapy in patients with ankle

arthritis have not been reported. Finally, studies comparing

hyaluronate injection with other treatment options such as intra-articular corticosteroid injections, NSAIDs, or thera-

peutic exercise, as well as studies involving the combination of

hyaluronate injection with such alternate treatment options,

may help to determine the best overall treatment plan for

patients with ankle arthritis.

EFFICACY OF THREE WEEKLY INJECTIONS OF HYALURONATE IN PATIENTS WITH ANKLE ARTHRITIS

Appendix

The Ankle Osteoarthritis Scale questionnaire and a table comparing the outcomes in the younger and older patient subgroups are available with the online version of this article as a data supplement at jbjs.org.

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THE JOURNAL OF BONE & JOINT SURGERY • JBJS.ORG VOLUME 93-A • NUMBER 18 • SEPTEMBER 21, 2011

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EFFICACY OF THREE WEEKLY INJECTIONS OF HYALURONATE IN PATIENTS WITH ANKLE ARTHRITIS

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