OsteoArthritis and Cartilage (2006) **14,** 867–874

doi:10.1016/j.joca.2006.03.003

Osteoarthritis and Cartilage

International Cartilage Repair Society

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Efficacy of intra-articular hyaluronic acid in patients with osteoarthritis of the ankle: a prospective study[1]

Dr Shu-Fen Sun M.D.†*, Yi-Jiun Chou M.D.‡, Chien-Wei Hsu M.D.§, Chiao-Wen Hwang M.D.†, Pei-Te Hsu M.D.†, Jue-Long Wang M.D.†, Ya-Wen Hsu M.D.‖ and Mei-Chia Chou M.D.†

† *Department of Physical Medicine and Rehabilitation, Veterans General Hospital, Kaohsiung, Taiwan*

‡ *Department of Orthopaedic Surgery, Veterans General Hospital, Kaohsiung, Taiwan*

§ *Department of Internal Medicine, Veterans General Hospital, Kaohsiung, Taiwan*

‖ *Department of Health, Taipei Hospital, Taiwan*

Summary

Objective: To investigate the efficacy, safety and the duration of treatment effectiveness of intra-articular hyaluronic acid (Artz, Japan) in patients with ankle osteoarthritis (OA).

Method: As a prospective clinical trial, 93 patients with unilateral ankle pain for at least 6 months and radiographically classified as Kellgren–Lawrence grade I or II ankle OA were included. After five weekly intra-articular Artz injections, the Ankle Osteoarthritis Scale (AOS), the American Orthopaedic Foot and Ankle Society (AOFAS) ankle/hindfoot score, ankle sagittal range of motion (ROM), patients' global satisfaction, local adverse events and consumption of rescue analgesics were analyzed.

Results: Seventy-five patients completed the study. Significant improvement in AOS and AOFAS ankle/hindfoot scores was noted at 1 week, 1 month, 3 months and 6 months post the fifth injection ($P < 0.001$ compared with baseline). The mean reduction of AOS score was 1.9, 2.6, 2.5 and 2.6 at each following visit ($P < 0.001$). The mean AOFAS ankle/hindfoot score improved from 64 points at baseline to 75, 78, 78, and 78 points at 1 week, 1 month, 3 months and 6 months, respectively, post the fifth injection ($P < 0.001$). Ankle sagittal ROM did not improve significantly ($P > 0.05$). The majority of patients reported satisfaction at 1 week (100%), 1 month (100%), 3 months (90.7%) and 6 months (86.7%) follow-up. Local adverse events occurred in 6.7% of patients. Acetaminophen consumption dropped significantly following treatment ($P < 0.001$).

Conclusion: Five weekly intra-articular injections of Artz provide pain relief and functional improvements in patients with Kellgren–Lawrence grades I and II ankle OA. The clinical effect was rapid at 1 week and may last for 6 months or more.

Key words: Osteoarthritis, Hyaluronic acid, Ankle joint.

Introduction

Osteoarthritis (OA) is a common progressive degenerative joint disease with multiple etiologies, but similar biological, morphological, and clinical outcome[1,2]. Individuals with OA might suffer from pain, muscle weakness, loss of joint range of motion (ROM) and increasing disability. The disease process of OA is characterized by the progressive erosion of articular cartilage, leading to joint space narrowing, subchondral sclerosis, subchondral cyst, synovial inflammation and marginal osteophyte formation[3].

OA can be a functionally and emotionally limiting condition for which several treatment options exist. Current treatment options for OA include the use of simple analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, physiotherapy (including physical modalities, various stretching or strengthening exercises, shoe modifications, boots or assistive devices such as canes or crutches, etc.), weight reduction, orthotics and surgical treatment[4]. Prior to surgical management of OA, which is expensive and not risk-free, all other treatment options should be fully exploited.

Creamer and Hochberg presented the treatment protocol of OA and they stated that intra-articular hyaluronic acid (HA) played an important role[1]. HA is a high molecular weight polysaccharide contained within normal endogenous synovial fluid and it contributes to the elasticity and viscosity of synovial fluid. HA acts as a fluid shock-absorber and it helps to maintain the structural and functional characteristics of the cartilage matrix. It also inhibits the formation and release of prostaglandins, induces proteoglycan aggregation and synthesis, and modulates the inflammatory response[5,6]. A degradation of HA may be associated with increased vulnerability to articular cartilage damage. OA leads to a reduction in both molecular size and concentration of HA in the synovial fluid[6–8]. According to Balazs and colleagues, the injection of HA into joints with OA could restore the viscoelasticity of the synovial fluid, augment the

[1]The study was supported by a grant of VGHKS91-93 (an academic research fund for Kaohsiung Veterans General Hospital).

*Address correspondence and reprint requests to: Dr Shu-Fen Sun, Department of Physical Medicine and Rehabilitation, Veterans General Hospital, Kaohsiung, No 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan. Tel: 886-73422121-4210; Fax: 886-73420243; E-mail: sfsun.tw@yahoo.com.tw

Received 2 December 2005; revision accepted 5 March 2006.

flow of joint fluid, normalize endogenous hyaluronate synthesis, inhibit hyaluronate degradation, reduce joint pain, and improve joint function[9,10]. Several trials have attempted to evaluate the effects of intra-articular HA in knee OA[11–18]. These studies relied on pain relief, joint function as well as ROM of the affected joint as parameters for the effectiveness of such a treatment. Pietrogrande showed a pain reduction from visual analogue scale values of 6 cm down to 2 cm 60 days after the intra-articular injections of HA[11]. Di Marco and Letizia found a reduction of weight-bearing pain from 6.7 to 4.7 cm following treatment with HA[13]. According to a recent review, intra-articular injection of HA reduced knee pain in patients with tibiofemoral disease by 20–40% over 6–12 months[18]. In general, previous trials have reported that intra-articular HA is a safe and well-tolerated treatment. OA can occur in several of the weight-bearing joints of the foot and ankle. To date there is only limited published literature on its use in the ankle and no viscosupplements have been approved for osteoarthritic joints other than the knee[19–21]. Theoretically viscosupplementation is an approach that should apply to all synovial joints. The clinical success of intra-articular HA in patients with knee OA suggests this would be a useful approach worthy of serious clinical investigation.

The purpose of this study was to investigate the efficacy, safety and the duration of its treatment effectiveness of five weekly intra-articular injections of HA in patients with unilateral ankle OA. Joint-specific functional outcome measures including the Ankle Osteoarthritis Scale (AOS)[22] and the American Orthopaedic Foot and Ankle Society (AOFAS) ankle/hindfoot scores[23], ankle sagittal ROM[24] and patients' global satisfaction were assessed.

Methods

PATIENTS

Patients in this study were referred from our outpatient orthopedic department with the diagnosis of unilateral ankle OA. All patients reported unilateral ankle pain for at least 6 months and had either reported no significant benefit from conservative treatment (including medication, physical modalities, various stretching or strengthening exercises, etc.) or were unable to tolerate side effects of medications. Ankle radiographs (weight-bearing anteroposterior and lateral views) taken within 6 months were reviewed by one author and were equivalent to grade I or II by Kellgren–Lawrence classification (grade 1, doubtful narrowing of joint space and possible osteophytic lipping; grade 2, definite osteophytes and possible narrowing of joint space; grade 3, moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour; and grade 4, large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour)[25]. In addition, all patients in this study (1) had a current total AOS score (described below) of >3 and <7.5 (possible range, 0–10); (2) were normally active, not bedridden or confined to a wheelchair, and were able to walk 30 m without the help of a walker, crutches, or cane; (3) were willing to discontinue all NSAIDs or other analgesic medication (except for rescue medication) for the duration of the study; and (4) did not receive physical therapy or trial of shoe modifications or orthotics for the study period.

Exclusion criteria included pregnant and lactating women, presence of joint infections of foot or ankle, bilateral ankle OA requiring treatment of both ankles, significant ankle deformity or instability, previous arthroscopy or surgery on the ankle within 12 months, intra-articular steroid or HA injection within the past 6 months, had substantial venous or lymphatic stasis in the legs, treatment with systemic steroid, immunosuppressives or anticoagulants (except for acetylsalicylic acid at dosages of up to 325 mg/day), history of rheumatoid arthritis, gout, or any other inflammatory arthropathy, history of chicken or egg allergy, presence of other comorbidity (neoplasm, diabetes mellitus, paresis, recent trauma, etc.) or poor health status that would interfere with the clinical assessments during the study.

Medical records for each patient were reviewed. Baseline characteristics (age, sex, weight, height, employment status as light workers or heavy labors, side of involvement, etiology of OA and disease duration) were recorded before the first injection. The etiology of OA was determined based on medical history, physical examination, and imaging studies. The cause was determined whenever possible. If no cause could be elucidated, then by a process of elimination, the case was classified as OA of unknown etiology.

STUDY DESIGN

This was a prospective clinical trial with a 6-month follow-up period. The trial 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 investigation and all subjects provided signed informed consent before being enrolled in the study.

After completing the baseline survey within 2 weeks of entry into this study, the patients were then given five weekly intra-articular injections of HA. The test medications (Artz) were provided by Seikagaku Corporation, Tokyo, Japan. Each ampoule of the active medication contained 25 mg of sodium HA in 2.5 ml of phosphate buffered saline. The sodium HA was extracted from rooster combs and the purified material had a molecular weight of 6.2×10^5 to 11.7×10^5 Da. The preparations were injected into the ankle joints at a dose of one ampoule per week for a total of 5 weeks. The injections were done by an experienced physician who took no part in the clinical assessment of patients throughout the study. Either the lateral or medial approach for injection could be used at the discretion of the injector. An intake of analgesics or NSAIDs was not permitted and physical therapy was not carried out during the study period. Only acetaminophen (500 mg), up to 4 g/day was allowed as rescue medication. If the treatment dose was above the stipulated limit (acetaminophen 4 g/day), the patient was regarded as a clinical failure. Patients taking analgesics or NSAIDs stopped them at least 7 days before the preinjection assessment. Administration of acetaminophen 8 h before the time of follow-up assessment was prohibited. The administration of all analgesic medications during the study period was recorded on a diary card by the patient.

CLINICAL ASSESSMENT

The clinical assessment was documented by the same investigator for every patient prior to the first injection and at intervals of 1 week, 1 month, 3 months and 6 months post the fifth injection. The clinical assessment included the following items:

(1) The AOS is a patient-rated, validated outcome measure that includes nine items on a pain subscale and nine items on a disability subscale. Using the

AOS, a score of 0 represents no pain or disability and 10 represents worst pain or disability imaginable (Appendix 1)[22].

(2) AOFAS ankle/hindfoot score 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 alignment (Appendix 2)[23].

(3) Ankle sagittal ROM was measured with a hand-held goniometer. The axis of the goniometer is located at the intersection of the foot and the shank. Measure ankle dorsiflexion and ankle plantar flexion range while the patient is supine with knee flexed to 90 degrees[24]. Ankle sagittal ROM is the sum of ankle dorsiflexion and plantar flexion angles.

(4) Patients were asked to rate the level of global satisfaction with regard to ankle pain relief on weight bearing compared to their preinjection condition at each follow-up visit. The rating was based on a 7-point categorical scale weighted from completely satisfied, satisfied, somewhat satisfied, no change, somewhat unsatisfied, unsatisfied to completely unsatisfied. The data of the patients' global satisfaction are expressed as the number of the patients in each of the seven categories.

(5) To monitor the safety of each injection, the occurrence of systemic and local adverse events, defined as any unwanted events whether it was thought to be related to the study drugs or not, was recorded on a diary card.

STATISTICAL ANALYSIS

A total of 75 patients completed the study through the 6-month follow-up and the statistical analysis was done on completers. All statistical procedures were conducted with the Statistical Package for the Social Sciences (version 12.0; SPSS Inc., Chicago, Illinois). Change of outcome measures was analyzed using paired *t* test comparing baseline value with each follow-up score. *P* values less than 0.05 were regarded as statistically significant.

Table I
Demographic data and disease characteristics of the patients

Characteristic	Ankle OA ($n = 75$)	Range
Age (years)	50.2 ± 14.3	22–84
Sex (F/M)	34/41	
Weight (kg)	71.5 ± 11.9	50–92
Height (cm)	164.4 ± 7.6	150–176
Employment status (light worker/heavy labor)	35/40	
Side of ankle OA (Lt/Rt)	37/38	
Etiology of OA (unknown/known)	23/52	
Radiographic stage (Kellgren–Lawrence stage)		
Grade I	32	
Grade II	43	
Disease duration (years)	5.3 ± 4.7	

Data are mean ± standard deviation.

Results

Ninety-three patients with unilateral OA of the ankle were recruited in the study. Five patients withdrew from the study before the final injection (one fear of injection, two moving to another city and two because of traffic accident and unrelated intercurrent illness). Eleven patients were lost to follow-up because of noncompliance. Two patients withdrew from study due to subsequent ankle surgery. A total of 75 participants (34 females; 41 males) with an average age of 50.2 ± 14.3 years completed the study. Demographic data and disease characteristics of the patients were shown in Table I. OA without traceable history of trauma or purulent arthritis was attributed as OA of unknown etiology in 23 patients. OA due to ligamentous injury, malleolar fracture, plafond fracture, talar fracture, previous purulent arthritis or other causes were noted in 52 patients.

Table II provided a summary of outcome measures. Mean change from baseline in AOS and AOFAS ankle/hindfoot scores at each following visit was shown in Table III. Ankle sagittal ROM did not improve significantly following treatment ($P > 0.05$). All the other treatment outcomes improved significantly at each follow-up visit ($P < 0.001$). These effects were rapid at 1 week post the fifth injection, and the treatment effects could last for at least 6 months.

Table II
Summary of outcomes before and after treatment

	OA ankle ($n = 75$)					
	Baseline	1 week	1 month	3 months	6 months	*P* value
Total AOS†	5.1 ± 1.9	3.2 ± 2.1	2.5 ± 2.0	2.6 ± 1.7	2.4 ± 1.9	AB* AC* AD* AE*
Pain subscale†	4.8 ± 1.7	2.8 ± 2.0	2.1 ± 1.7	2.1 ± 1.6	2.1 ± 1.8	AB* AC* AD* AE*
Disability subscale†	5.5 ± 2.4	3.7 ± 2.3	2.9 ± 2.3	3.1 ± 2.1	2.8 ± 2.1	AB* AC* AD* AE*
AOFAS ankle/hindfoot score	64 ± 17	75 ± 15	78 ± 16	78 ± 15	78 ± 14	AB* AC* AD^{+} AE*
Ankle sagittal ROM	36.9 ± 14.6	37.7 ± 15.0	37.8 ± 14.4	38.1 ± 14.3	38.7 ± 13.6	AB = 0.086, AC = 0.255, AD = 0.414, AE = 0.258
Acetaminophen (tablets/week)	14.3 ± 2.4	5.1 ± 2.3	3.4 ± 2.1	3.1 ± 2.3	3.3 ± 2.2	AB* AC* AD* AE*

Note: Values are the mean ± standard deviation; AOS = Ankle Osteoarthritis Scale, AOFAS = the American Orthopaedic Foot and Ankle Society, and ROM = range of motion. The possible range for the AOS score was 0–10; the possible range for the AOFAS score was 0–100. *$P < 0.001$ vs baseline. AB is the comparison before and 1 week after the intra-articular Artz injections; AC is the comparison before and 1 month after the intra-articular Artz injections; AD is the comparison before and 3 months after the intra-articular Artz injections; and AE is the comparison before and 6 months after the intra-articular Artz injections.

†Higher scores represent worse pain or function.

Table III
Mean change from baseline in AOS and AOFAS ankle/hindfoot scores at each postinjection following visit

	Total AOS†	Pain subscale†	Disability subscale†	AOFAS ankle/ hindfoot score
1 week	-1.9 ± 1.0*	-2.0 ± 1.2*	1.8 ± 1.1*	11 ± 9*
1 month	-2.6 ± 1.6*	-2.7 ± 1.4*	2.5 ± 2.0*	14 ± 8*
3 months	-2.5 ± 1.6*	-2.7 ± 1.8*	2.4 ± 1.8*	14 ± 10*
6 months	-2.6 ± 1.8*	-2.8 ± 2.0*	2.5 ± 2.0*	14 ± 11*

AOS = Ankle Osteoarthritis Scale; and AOFAS = the American Orthopaedic Foot and Ankle Society ankle/hindfoot score. The possible range for the AOS score was 0–10; the possible range for the AOFAS ankle/hindfoot score was 0–100. *$P < 0.001$ vs baseline.

†Higher scores represent worse pain or function.

Results of the AOS score with respect to pain and disability were shown in Table II. The average pain subscale score of AOS prior to injection was 4.8 ± 1.7 cm. The score decreased to 2.8 ± 2.0, 2.1 ± 1.7 and 2.1 ± 1.6 cm at 1 week, 1 month and 3 months after the fifth injection ($P < 0.001$ for each score compared with baseline), the reduction remained significant until 6 months post the fifth injection ($P < 0.001$) (Table II). Improvement in average disability subscales score of AOS from 5.5 ± 2.4 cm at baseline to 3.7 ± 2.3, 2.9 ± 2.3 and 3.1 ± 2.1 cm was noted at 1 week, 1 month and 3 months, respectively, post the fifth injection ($P < 0.001$ for each score compared with baseline). The benefit also persisted to 6 months ($P < 0.001$) (Table II). The mean reduction of total AOS score was 1.9, 2.6 and 2.5 at 1 week, 1 month and 3 months, respectively, after the fifth injection ($P < 0.001$ for each score compared with baseline). The effect still remained significant at the 6-month follow-up ($P < 0.001$) (Table III).

The mean AOFAS ankle/hindfoot score improved from 64 ± 17 out of 100 points at baseline (higher score better) to 75 ± 15, 78 ± 16, 78 ± 15 and 78 ± 14 out of 100 points, respectively, at 1 week, 1 month, 3 months and 6 months after the fifth injection ($P < 0.001$). The improvement in AOFAS score averaged 14 points at the 6-month follow-up ($P < 0.001$) (Table II).

After treatment, ankle sagittal ROM increased in 48 of the 75 patients. ROM decreased in 12 patients and remained unchanged in 15 patients at the 6-month follow-up. Average ankle sagittal ROM increased 1.8 degrees, but this change in ROM from baseline was not statistically significant ($P > 0.05$) (Table II).

Table IV
Satisfaction to viscosupplementation for the treatment of ankle OA

	Completely satisfied	Satisfied	Somewhat satisfied	No change	Satisfaction rate (%)
1 week	32	24	19	0	100
1 month	29	29	17	0	100
3 months	22	24	22	7	90.7
6 months	22	24	19	10	86.7

Numbers referred to number of patients who reported their level of global satisfaction with regard to pain relief on weight bearing when comparing the situation after viscosupplementation with that before injection. No patients reported dissatisfaction throughout the study period.

Patient satisfaction is a fundamental goal in the treatment of OA. Satisfaction reflects the summation of all factors relating to successful clinical treatment. Results of patients' global satisfaction with regard to pain relief on weight bearing were shown in Table IV. Treatment of the ankles in this series resulted in high patients' satisfaction. At 1-week follow-up, 32 patients reported completely satisfied, 24 reported satisfied and 19 reported somewhat satisfied. The overall satisfaction rate was 100%. A shift in distribution of patients to different categories was observed at 1 and 3 months. At 6 months post the fifth injection, the reported satisfaction slightly diminished as 22 patients reported completely satisfied, 24 satisfied and 19 somewhat satisfied. Ten patients reported no change compared to their preinjection condition. Sixty-five patients were satisfied with their overall response to treatment and the overall satisfaction rate was 86.7%. No patients reported dissatisfaction or aggravations of the ankle symptoms compared to preinjection condition throughout the study period.

The injections were well tolerated. Five patients experienced transient pain and erythema at the injection site that resolved within 48 h and did not interfere with the remaining injections. The local adverse reaction rate was 5.3% per injection and 6.7% per patient. No case of septic arthritis or other severe systemic adverse events was observed during the study.

Patients who received intra-articular HA injections used much less rescue analgesics during the study period. Acetaminophen consumption fell from an average of 14 tablets weekly at baseline to 5, 3, 3 and 3 tablets weekly at 1 week, 1 month, 3 months and 6 months, respectively, post the fifth injection ($P < 0.001$ at each time point compared with baseline) (Table II).

Discussion

This prospective, open pilot study in patients with unilateral ankle OA had demonstrated that a regimen of five weekly intra-articular injections of Artz was safe and efficacious in the areas of pain and ankle function. The patients' satisfaction rate was high with only relatively few local adverse events. These effects were rapid at 1 week post the fifth injection and could last for 6 months or more.

In this study, the average pain subscale score decreased significantly from 4.8 cm before injection to 2.1 cm at 6 months post the fifth injection. It appeared that the pain relief reported in previous studies of HA in knee OA was also documented in this study of ankle OA.

The duration of treatment effectiveness after HA is unclear. Most studies report that clinical improvement begins with a delayed onset between 2 and 5 weeks, lasting 6 months or up to 1 year[26–28]. In this ankle OA study, we demonstrated that the clinical effect was rapid at 1 week and may last for 6 months or more. The mechanisms by which HA mediates their clinical benefit seem to be multifactorial and biologically related, in contrast to the notion that they provide only viscous fluid replacement. Studies have shown that the half-life of injected HA may be as short as 2 days[29]. Multiple injections attempt to increase its residence time within the joint. Temporary restoration of the rheologic homeostasis may trigger normal native

HA metabolism[9]. HA also fulfills an anti-inflammatory role by reducing white cell aggregation and activation. With this postulated disease-modifying behavior, its clinical effects may persist beyond its physical duration within the joint[6,15,28,30].

Most patients in this study with Kellgren–Lawrence grade I or II ankle OA had good response to viscosupplementation. This suggested that viscosupplementation was effective in mild to moderate ankle OA. Whether severe cases would likely respond to viscosupplementation remained unknown. Neustadt reported that intra-articular HA was an effective and safe treatment for pain in difficult-to-treat patients with moderate to severe OA of the knee[31]. Evanich *et al.* recommended that patients with a complete collapse of joint space not to receive this treatment given their poor clinical response[32]. Theoretically, patients with severe OA might have a poor and shorter response. In future studies, we would like to recruit patients with higher X-ray grades to see whether intra-articular HA injections can improve function in severely obliterated ankle joints. As the treatment group increases, additional studies should better elucidate favorable patient response factors that may identify patients with OA who would benefit the most from viscosupplementation.

Evaluation of adverse reactions is important because untoward effects may limit the use of a specific treatment option. Significant and frequently occurring adverse reactions likely would prohibit the use of a certain modality, no matter how great the benefit. A wide range of local adverse reaction rates had been reported after intra-articular HA. For the five individual Artz trials, the incidence varies from 1 adverse event/589 (0.17%) to 11 adverse events/215 (5.1%)[33]. Altman and Moskowitz described injection site pain in 23% of knees treated with HA, 13% with saline placebo, and 9% with subcutaneous local anesthesia[16]. Lussier *et al.* reported an adverse reaction rate of 2.7% per injection and 8.3% per patient, most effects were mild to moderate local reactions[14]. In this ankle OA study, local pain of varying intensity and erythema at the injection site occurred in five patients, but was mild and resolved within 48 h without sequela in all cases. The adverse reaction rate was 5.3% per injection and 6.7% per patient. The occurrence of adverse events was difficult to predict. They sometimes occurred after several injections without any reaction previously, and sometimes they did not occur in subsequent injections. Interestingly, we found that local adverse reactions did not predict treatment failure. All of these patients received subsequent injections and they still improved clinically and reported high satisfaction. The tolerability and safety of the treatment regimen were shown in the study.

The result of the study using HA in the ankle is consistent with previously published studies using HA in the knee. The study results provide important information for patients who suffer from OA of the ankle. As surgery to treat ankle OA is often quite painful, HA may offer patients who may not have had success with traditional pain medications, another option to treat their OA. This study is encouraging as it stimulates interest in research to assess the potential role of viscosupplementation in treating ankle OA and it continues to build on the existing data suggesting benefits from the use of HA in the treatment of joints other than the knees.

Several limitations existed in the study. One limitation includes the absence of a control group, thus the placebo effects associated with joint injections were not investigated. Several previous trials have used saline controls without report of adverse responses; some researchers speculate that saline injection might have a clinical benefit. We did not make use of a saline control group since saline injection could not be excluded as a source of a noxious stimulus and we thought it would be inappropriate and ethically difficult to subject these patients to a placebo. The very early significant benefits with high satisfaction rate reported in the treatment course with HA are a remarkable achievement. However, it might also suggest possibility of a strong placebo effect. The patients and the injector were not blinded throughout the study period. The injector, however, did not take part in analysis of the data. Since the numbers of patients studied were relatively small, the results were not analyzed on the basis of severity of OA, cause of OA, or pre-injection functional levels. The postinjection period was also not controlled for subject activity level or assistive devices usage. These factors might have a role in determining the candidates who would benefit most from this treatment and might help determine the best overall treatment plan for these patients. Failure to perform a dose response assessment is another limitation of this study. Large, randomized clinical trials that carefully assess clinical outcomes are necessary in order to establish the efficacy.

A typical Artz treatment cycle for knee OA consists of five injections given at weekly intervals by a doctor. The effectiveness of a single treatment cycle or less than three injections has never been established. Cost-effective issues need to be addressed, particularly as five injections are administered in our study. The long-term clinical benefit and the reduced apparent need for medications or alternative OA-modifying therapies might contribute to favorable cost/benefit ratio of this therapy. Many clinical uncertainties on the use of HA remain. Future studies regarding optimal number of injections in a course of treatment, optimal dosing per injection, different concentration and molecular weight options for long-term effect of HA as well as the biochemical, morphologic, and histopathologic effects on cartilage are warranted. Comparison studies with other treatment options, such as intra-articular steroid injections and NSAIDs, are also needed.

Conclusion

On the basis of this prospective clinical trial of patients with unilateral Kellgren–Lawrence grades I and II ankle OA, we concluded that five weekly intra-articular injections of HA provided pain relief and functional improvements with high patients' satisfaction. It was a useful and well-tolerated treatment with rapid onset of action at 1 week post the fifth injection and the treatment effects lasted for 6 months or longer.

Acknowledgments

We wish to express our sincere gratitude to all the investigators who participated in the trial. The authors also wish to thank Yung-Yen Gau, MPH, for her skillful assistance. The study was supported by funds received from the hospital's medical research council.

Appendix 1

Ankle Osteoarthritis Scale

Pain

The line next to each item represents the amount of pain you typically had in each situation. On the far left is "No pain" and on the far right is " The worst pain imaginable". Place a mark on the line to indicate how bad your ankle pain was in each of the following situations during the past week. If you were not involved in one or more of these situations, mark that item NA.

How severe was your ankle pain	No pain	Worst pain imaginable	NA
1. At its worst?	_____		--------
2. Before you get up in the morning?	_____		--------
3. When you walked barefoot?	_____		--------
4. When you stood barefoot?	_____		--------
5. When you walked wearing shoes?	_____		--------
6. When you stood wearing shoes?	_____		--------
7. When you walked wearing shoe inserts or braces?	_____		--------
8. When you stood wearing shoe inserts or braces?	_____		--------
9. At the end of the day?	_____		--------

____/____==_____%

Disability

The line next to each item represents the amount of difficulty you had performing an activity. On the far left is "No difficulty" and on the far right is " So difficult unable". Place a mark on the line to indicate how much difficulty you had performing each activity because of your ankle during the past week. If you did not perform an activity during the past week, place an "X" in the column under the heading NA.

How much difficulty did you have	No difficulty	So difficult unable	NA
1. Walking around the house?	_____		-------
2. Walking outside on uneven ground?	_____		-------
3. Walking four or more blocks?	_____		-------
4. Climbing stairs?	_____		-------
5. Descending stairs?	_____		-------
6. Standing on tip toes?	_____		-------
7. Getting out of a chair?	_____		-------
8. Climbing up or down curbs?	_____		-------
9. Walking fast or running?	_____		-------

Appendix 2

AOFAS ankle/hindfoot score (100 points total)

Pain (40 points)	
•None	40
•Mild, occasional	30
•Moderate, daily	20
•Severe, almost always present	0
Function (50 points)	
•Activity limitations, support requirement	
○No limitations, no support	10
○No limitation of daily activities, limitation of recreational activities, no support	7
○Limited daily and recreational activities, cane	4
○Severe limitation of daily and recreational activities, walker, crutches, wheelchair, and brace	0
•Maximum walking distance, blocks	
○Greater than 6	5
○4–6	4
○1–3	2
○Less than 1	0
•Walking surfaces	
○No difficulty on any surface	5
○Some difficulty on uneven terrain, stairs, inclines, and ladders	3
○Severe difficulty on uneven terrain, stairs, inclines, and ladders	0
•Gait abnormality	
○None, slight	8
○Obvious	4
○Marked	0
•Sagittal motion (flexion plus extension)	
○Normal or mild restriction (30° or more)	8
○Moderate restriction (15–29°)	4
○Severe restriction (less than 150)	0
•Hindfoot motion (inversion plus eversion)	
○Normal or mild restriction (75–100% normal)	6
○Moderate restriction (25–74% normal)	3
○Marked restriction (less than 25% normal)	0
•Ankle/hindfoot stability (anteroposterior, varus–valgus)	
○Stable	8
○Definitely unstable	0
•Alignment (10 points)	
○Good, plantigrade foot, ankle/hindfoot well aligned	10
○Fair, plantigrade foot, some degree of ankle/hindfoot malalignment observed, no symptoms	5
○Poor, nonplantigrade foot, severe malalignment, symptoms	0

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