

Prognostic Factors after Intra-Articular Hyaluronic Acid Injection in Ankle Osteoarthritis

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Purpose: The goal of this study was to identify baseline prognostic factors of outcome in ankle osteoarthritis patients after intra-articular hyaluronic acid injection.

Materials and Methods: Patients with ankle osteoarthritis who received hyaluronic acid injection therapy were retrospectively reviewed. Each patient received weekly intra-articular hyaluronic acid injections (2 mL) for 3 weeks. Six predictors including gender, age, symptom duration, radiographic osteoarthritis stage, radiographic subchondral cyst, and fracture history were evaluated. Visual analogue scale (VAS) and patient satisfaction were evaluated as outcome measures. These predictors and outcome measurements were included in a logistic regression model for statistical analysis. **Results:** Total of 40 consecutive patients (21 male, 19 female) were included in this study. Mean age was 60.6. Average follow up period was 13 months. The mean VAS recorded 3, 6, and 12 months after the first injection was 3.6 (SD 2.54, $p < 0.001$), 4.33 (SD 2.9, $p < 0.001$), and 5.3 (SD 2.7, $p = 0.0071$), respectively, when compared to baseline VAS. Early stage disease was identified as an independent predictor associated with 'positive VAS outcome' at 3 and 6 months. Early stage disease and duration of pain less than 1 year were independent predictors associated with higher satisfaction. **Conclusion:** While hyaluronic acid injection for ankle osteoarthritis is a safe and effective treatment, careful selection of patients should be made according to the above prognostic predictors.

Key Words: Ankle, osteoarthritis, hyaluronic acid, prognosis

INTRODUCTION

While the prevalence of ankle joint osteoarthritis (OA) is approximately <1% of the adult population, far lower than knee joint OA, its disease and socioeconomic burden cannot be overlooked.¹ Nearly 70% of ankle OA is post-traumatic, affecting a relatively younger population compared to other joints.²⁻⁴ Ankle OA thus hinders the performances at work and athletics in this otherwise healthy population.⁵

Treatment methods for ankle OA differ according to disease severity and activity level of the patient. These include exercise, weight loss, orthosis, simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injection and surgery. Surgical treatments, which include total ankle arthroplasty and ankle

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fusion, carry numerous complications and are only indicated for end stage disease. Ankle OA patients with milder stages are relatively young, not yet surgical candidates, and many wish to be active without the burden of pain medications.⁶

Viscosupplementation with hyaluronic acid (HA) may be an effective treatment modality for such ankle OA patients.⁷ Intra-articular HA injection has been approved by the U.S. Food and Drug Administration for the treatment of knee OA in 1997, and has since been used for treatment of OA in many other joints, including the ankle.⁷⁻¹⁰ The intra-articular injection of HA replaces lost HA in the arthritic joint and possibly stimulates the endogenous production of HA, providing symptomatic relief and improving biomechanical function.¹¹ Several authors have reported favorable short term results after intra-articular HA injection in ankle OA patients.^{12,13} The optimal indications for this treatment, however, have not yet been established. The goal of this study was to identify prognostic predictors in ankle OA patients that are easily identifiable in an outpatient clinic setting after intra-articular HA injection.

MATERIALS AND METHODS

Study design

Consecutive patients clinically diagnosed with ankle OA who had received intra-articular HA injection therapy were retrospectively reviewed. The study was carried out in a single tertiary institution outpatient clinic. Before intra-articular HA injection, all patients signed a consent form fully disclosing the risk and benefits of the treatment. The study, along with the treatment protocol, was approved by our Institutional Review Board. Inclusion criteria were as follows; 1) patients diagnosed with ankle OA by clinical and radiologic evidence, 2) patients who had discontinued pain control medication (anti-inflammatory drugs and analgesics) for at least 12 months after intra-articular HA injection, excluding intermittent rescue medication, 3) self-ambulatory patients able to walk at least 50 meters without the assistance of a wheel chair or crutches, and 4) patients who were followed by our outpatient clinic for at least 12 months after intra-articular HA injections. Rescue medication was defined as acetaminophen (<4 g/day) administered not for more than 3 consecutive days, and no more than 10 days per month. All patients receiving intra-articular HA injections had no symptomatic improvement with oral NSAIDs for at least 3 months prior to HA injection. Exclusion criteria were

as follows; 1) patients who had prior history of surgery for ankle OA, such as arthroscopic debridement, 2) bilateral ankle OA, 3) patients with prior intra-articular injection history, including HA or corticosteroid, 4) any other diagnosis for ankle pain, such as rheumatoid arthritis, 5) patients unable to complete the 3 week treatment protocol, and 6) patients lost during outpatient clinic follow up for at least 12 months or unwilling to fill out our questionnaires for data collection.

All patients in this study visited our clinic at least 7 times; baseline (with first injection), weekly second and third injection, 1 week after third injection, and 3, 6, and 12 month visits after the first injection. At baseline, bilateral, weight-bearing ankle radiographs were taken (AP and lateral view). Information was gathered regarding demographic data, medical and surgical history, duration of ankle pain, medication history and current level of pain using a 100 mm visual analogue scale (VAS) by a blinded observer who did not participate in this study. During each visit, changes in VAS were recorded. Any adverse effects were also recorded if present.

Treatment protocol

Each patient received weekly intra-articular HA injections (20 mg/2 mL, MW 3 MDa) for 3 weeks. The antero-medial portal for ankle arthroscopy was used as an injection site. Aseptic principles were followed during the injections.

Outcome measures and groups for analysis

Primary outcome measure for evaluating effectiveness of intra-articular HA injection was pain, measured by 100 mm VAS during each visit. We have used 4 respective endpoints; 1 week after third injection, and 3, 6, 12 months after the first injection. Patients were dichotomized into 'positive outcome' group (50% or more decrease in VAS compared to baseline VAS) and 'negative outcome' group (negative or no change in VAS, or <50% improvement in VAS compared to baseline VAS) for each end point. Secondary outcome measure was assessed by subjectively asking each patient's level of satisfaction with the question "How satisfied are you with the injected ankle?" 1 year after injection. The response was recorded using a 4 point Likert scale (1; completely satisfied, 2; satisfied, 3; somewhat satisfied, and 4; not satisfied). Patients were also dichotomized into 'satisfied' group (1 and 2) and 'dissatisfied' group (3 and 4).

Predictors

The following factors were included in the statistical analysis as independent variables.

Age

The mean age of the sample patients (60.6) was used as a cutoff point to dichotomize all patients into two groups. As a result, 19 patients were included in the <60 group, and 21 in the ≥ 60 group.

Gender

Twenty-one patients were male, and 19 patients were female.

Duration of pain

Sample patients were dichotomized into two groups; pain lasting ≤ 12 months and >12 months. As a result, 24 patients had pain duration of >12 months, and 16 patients had pain duration of ≤ 12 months.

Staging of ankle OA

Ankle radiographs of all patients were evaluated using Takakura classification (stage I; early sclerosis and osteophyte formation without joint space narrowing, stage II; narrowing of medial joint space, stage III; partial obliteration of joint space, and stage IV; obliteration of whole joint space).¹⁴ Results were dichotomized as ‘early stage’ group, which included stage I and II ankles, and ‘late stage’ group, which included stage III and IV ankles. Twenty-eight patients were allocated in the ‘early stage’ group, and 12 patients were allocated in the ‘late stage’ group.

History of fracture

Seven patients had a history of fracture around the ankle joint.

Presence of radiographic subchondral cyst

Six patients showed radiographic subchondral cysts.

Statistical analysis

Mean VAS values from each time point were compared using Wilcoxon signed-rank test. The dichotomized variables were assessed using Fisher’s exact test for changes in VAS and satisfaction. Multivariable logistic regression model was used to identify independent predictors of prognosis for satisfaction. A p value of <0.05 was defined as significant. Statistical Analysis Software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for data analysis.

RESULTS

Patient demographics

A total of 40 consecutive patients (21 male, 19 female) met our criteria for this study. The mean age was 60.6 years (range 35–80). The mean duration of pain was 49.63 months (SD 91.66). Takakura OA classification revealed 16 stage I patients (40%), 12 stage II patients (30%), 5 stage III patients (12.5%), and 7 stage IV patients (17.5%). Seven out of 40 patients (18%) had a history of fracture around the ankle. Six out of 40 patients (15%) had radiographic subchondral cyst formation.

Clinical efficacy

The overall mean VAS at baseline was 8.1 (SD 1.533). On short term follow up, where VAS was recorded a week after the first, second, and third injection, the mean VAS decreased to 5.3 (SD 1.636, $p<0.001$), 3.53 (SD 2.1, $p<0.001$), and 3.17 (SD 2.2, $p<0.001$), respectively, when compared to baseline VAS (Fig. 1A). On longer term follow up, where VAS was recorded 3, 6, and 12 months after the first injection, the

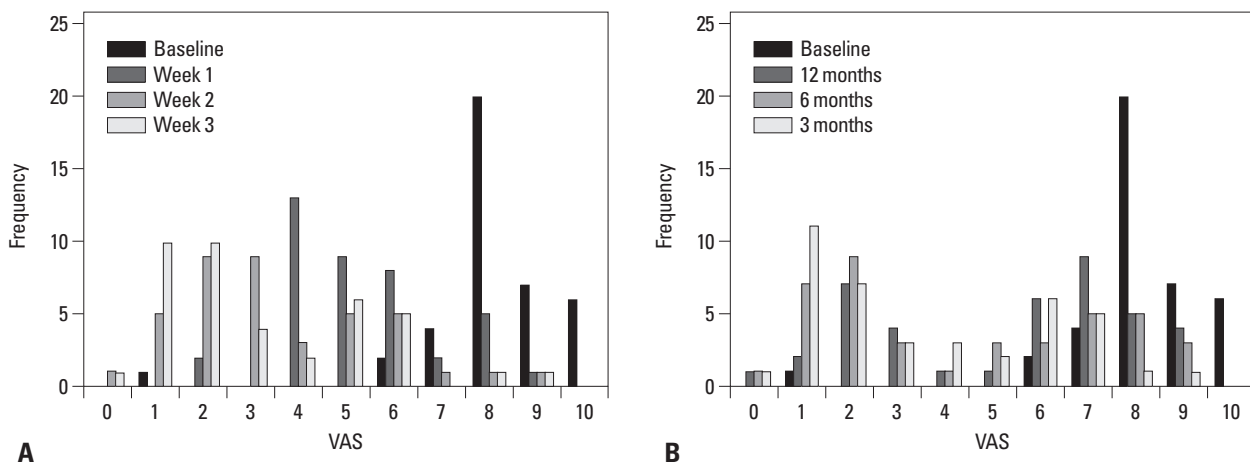


Fig. 1. Histogram of VAS change according to time. (A) Short term changes after intra-articular HA injection. (B) Long term changes after intra-articular HA injection, compared to baseline VAS. Baseline, before injection; Week 1, 1 week after first injection; Week 2, 1 week after second injection; Week 3, 1 week after third injection; VAS, visual analogue scale; HA, hyaluronic acid.

mean VAS was 3.6 (SD 2.54, $p<0.001$), 4.33 (SD 2.9, $p<0.001$), and 5.3 (SD 2.7, $p=0.0071$), respectively, when compared to baseline VAS (Fig. 1B). After 12 months follow up, 16 patients were 'completely satisfied' (40%), 5 were 'satisfied' (12.5%), 5 were 'somewhat satisfied' (12.5%), and 14 were 'not satisfied' (35%) with the treatment.

Patients with positive outcome VAS vs. negative outcome VAS

At 3 months after the first injection, 25 patients showed 'positive outcomes' in VAS (62.5%), while 15 showed 'negative outcomes' (37.5%). Patients with 'positive outcome' in

VAS were more likely to have early stage disease (Takakura stage 1 or 2, $p=0.0032$) (Table 1). Other predictors did not show statistically significant differences. At 6 months after the first injection, 21 patients showed 'positive outcomes' in VAS (52.5%), while 19 patients showed 'negative outcomes' (47.5%). Patients with 'positive outcome' in VAS were also more likely to have early stage disease (Takakura stage 1 or 2, $p=0.005$) (Table 2). At 12 months after the first injection, 16 patients showed 'positive outcomes' in VAS (40%), while 24 patients showed 'negative outcomes' (60%). No predictors showed statistically significant differences (Table 3).

Table 1. Patient Predictors of Prognosis According to 3 Month VAS Changes

Demographic predictors	Descriptive (n)	3 month VAS change		Odds ratio	95% CI		p value
		Positive (n=25, 62.5%)*	Negative (n=15, 37.5%)†		Lower	Upper	
Age (n, % of group)	<60 (19, 48)	12 (30)	7 (18)	1.055	0.2925	3.805	1.0000
	≥60 (21, 53)	13 (33)	8 (20)				
Sex (n, % of group)	F (19, 48)	14 (35)	5 (13)	2.545	0.6712	9.654	0.2037
	M (21, 53)	11 (28)	10 (25)				
Pain duration (n, % of group)	<12 m (11, 28)	8 (20)	3 (8)	1.882	0.1163	2.427	0.486
	≥12 m (29, 73)	17 (43)	12 (30)				
Stage (n, % of group)	1, 2 (28, 70)	22 (55)	6 (15)	11.000	2.246	53.863	0.0032
	3, 4 (12, 30)	3 (8)	9 (23)				
Fx. history (n, % of group)	- (33, 83)	22 (55)	11 (28)	2.667	0.5059	14.069	0.392
	+ (7, 18)	3 (8)	4 (10)				
Radiographic cyst (n, % of group)	+ (6, 15)	4 (10)	2 (5)	1.238	0.1979	7.7744	1.0000
	- (34, 85)	21 (53)	13 (33)				

VAS, visual analogue scale; CI, confidence interval.

*50% or more decrease in VAS compared to baseline VAS.

†Negative or no change in VAS, or <50% improvement in VAS compared to baseline VAS.

Table 2. Patient Predictors of Prognosis According to 6 Month VAS Changes

Demographic predictors	Descriptive (n)	6 month VAS change		Odds ratio	95% CI		p value
		Positive (n=21, 52.5%)*	Negative (n=19, 47.5%)†		Lower	Upper	
Age (n, % of group)	≥60 (21, 53)	10 (25)	9 (23)	1.010	0.2914	3.501	1.0000
	<60 (19, 48)	11 (28)	10 (25)				
Sex (n, % of group)	F (19, 48)	11 (28)	8 (20)	1.513	0.4332	5.281	0.5450
	M (21, 53)	10 (25)	11 (28)				
Pain duration (n, % of group)	<12 m (11, 28)	7 (18)	4 (10)	1.875	0.4494	7.823	0.4882
	≥12 m (29, 73)	14 (35)	15 (38)				
Stage (n, % of group)	1, 2 (28, 70)	19 (48)	9 (23)	10.556	1.903	58.553	0.0050
	3, 4 (12, 30)	2 (5)	10 (25)				
Fx. history (n, % of group)	- (33, 83)	19 (48)	14 (35)	3.393	0.5724	20.112	0.2258
	+ (7, 18)	2 (5)	5 (13)				
Radiographic cyst (n, % of group)	+ (6, 15)	2 (5)	4 (10)	0.3947	0.0635	2.455	0.3976
	- (34, 85)	19 (48)	15 (38)				

VAS, visual analogue scale; CI, confidence interval.

*50% or more decrease in VAS compared to baseline VAS.

†Negative or no change in VAS, or <50% improvement in VAS compared to baseline VAS.

Patients with 'satisfied' vs. 'dissatisfied' results

At 12 months, patients with 'satisfactory' outcomes (patients who answered either 'completely satisfied' or 'satisfied') were more likely to have early stage disease (Takakura stage 1 or 2, $p=0.0015$) (Table 4). Logistic regression analysis identified pain duration of ≤ 12 months, and early stage disease to be independent predictors associated with 'satisfactory' results (Table 5).

DISCUSSION

Ankle OA remains a major clinical problem due to the bur-

den that the disease places on the daily activities of patients. These patients may benefit from non-surgical treatment modalities such as intra-articular HA injection that may delay end-stage surgery. Currently, there is no consensus or guideline highlighting who will actually benefit from intra-articular HA injection in ankle OA patients. The goal of this study was to identify independent prognostic predictors in ankle OA patients after intra-articular HA injection. We have analyzed predictors that are easily identifiable in an outpatient clinic, in order for our results to be directly applicable in clinic. As a result, patients with shorter symptom duration (≤ 12 months) and early stage disease (Takakura stage 1, 2) were more likely to show improvement in VAS and satis-

Table 3. Patient Predictors of Prognosis According to 12 Month VAS Changes

Demographic predictors	Descriptive (n)	12 month VAS change		Odds ratio	95% CI		p value
		Positive (n=16, 40%)*	Negative (n=24, 60%) [†]		Lower	Upper	
Age (n, % of group)	<60 (19, 48)	10 (25)	9 (23)	2.778	0.7518	10.264	0.1965
	≥ 60 (21, 53)	6 (15)	15 (38)				
Sex (n, % of group)	F (19, 48)	8 (20)	11 (28)	1.182	0.3328	4.197	1.0000
	M (21, 53)	8 (20)	13 (33)				
Pain duration (n, % of group)	<12 m (11, 28)	3 (8)	8 (20)	0.4615	0.1014	2.101	0.4732
	≥ 12 m (29, 73)	13 (33)	16 (40)				
Stage (n, % of group)	1, 2 (28, 70)	14 (35)	14 (35)	5.000	0.9229	27.089	0.0788
	3, 4 (12, 30)	2 (5)	10 (25)				
Fx. history (n, % of group)	- (33, 83)	14 (35)	19 (48)	1.842	0.3108	10.920	0.6808
	+ (7, 18)	2 (5)	5 (13)				
Radiographic cyst (n, % of group)	+ (6, 15)	2 (5)	4 (10)	0.7143	0.1146	4.453	1.0000
	- (34, 85)	14 (35)	20 (50)				

VAS, visual analogue scale; CI, confidence interval.

*50% or more decrease in VAS compared to baseline VAS.

[†]Negative or no change in VAS, or <50% improvement in VAS compared to baseline VAS.

Table 4. Patient Predictors of Prognosis According to Satisfaction at 12 Months

Demographic predictors	Descriptive (n)	Satisfaction		Odds ratio	95% CI		p value
		Positive (n=19, 48%)*	Negative (n=21, 53%) [†]		Lower	Upper	
Age (n, % of group)	<60 (19, 48)	10 (25)	9 (23)	1.481	0.4251	5.163	0.7518
	≥ 60 (21, 53)	9 (23)	12 (30)				
Sex (n, % of group)	F (19, 48)	10 (25)	9 (23)	1.481	0.4251	5.163	0.7518
	M (21, 53)	9 (23)	12 (30)				
Pain duration (n, % of group)	≤ 12 m (16, 40)	11 (28)	5 (13)	4.4	1.134	17.075	0.0515
	>12 m (24, 60)	8 (20)	16 (40)				
Stage (n, % of group)	1, 2 (28, 70)	18 (45)	10 (25)	19.8	2.219	176.70	0.0015
	3, 4 (12, 30)	1 (3)	11 (28)				
Fx. history (n, % of group)	- (33, 83)	17 (43)	16 (40)	2.656	0.4494	15.699	0.4124
	+ (7, 18)	2 (5)	5 (13)				
Radiographic cyst (n, % of group)	+ (6, 15)	1 (3)	5 (13)	0.1778	0.0187	1.688	0.1856
	- (34, 85)	18 (45)	16 (40)				

VAS, visual analogue scale; CI, confidence interval.

*50% or more decrease in VAS compared to baseline VAS.

[†]Negative or no change in VAS, or <50% improvement in VAS compared to baseline VAS.

Table 5. Independent Predictors of Prognosis of 'Satisfactory' Results at 12 Months Post-Injection

Predictors	'Satisfactory' results at 12 months		
	Odds ratio	95% CI	<i>p</i> value
Pain duration ≤12 m	4.405	0.133–16.949	0.0322
Early stage (stage 1 and 2)	19.607	2.2–166.67	0.0075

CI, confidence interval.

Identified using logistic regression analysis.

fraction. To the best of our knowledge, this is the first study to analyze independent prognostic predictors in ankle OA patients after HA injection.

A number of authors have published favorable results of intra-articular HA injection in the OA ankle joint.^{12,13,15-18} Results from our present series share the short term, favorable outcomes in pain score. At 3 and 6 months post-injection, 63% and 53% of patients, respectively, showed 50% or more decrease in VAS compared to baseline VAS. Cohen, et al.¹⁶ reported statistically different ankle osteoarthritis score pain sub-scores at 3, and 6 months post-injection compared to baseline, and Luciani, et al.¹⁸ reported a statistically significant step decrease over the first 6 months.

The exact duration of efficacy after HA injection is unknown. Cohen, et al.¹⁶ has reported a duration of at least 3 months, while Salk, et al.¹² has reported ongoing efficacy over 6 months. We have followed our patients at least 12 months in this series and have found statistically significant improvement of pain for up to 1 year. This ongoing pain relief may have been due to direct HA effect on the intra-articular environment as well as secondary increase in joint motion and resultant muscle strengthening. The peak improvement in our series was at 3 weeks after the first injection. Significant symptomatic relief started as early as 1 week after the first injection. Similar therapeutic trajectory has been reported for knee OA, as HA was efficacious by 4 weeks, followed by peak effectiveness at 8 weeks. Detectable, residual efficacy has been found up to 24 weeks post-injection in knee OA.¹⁹

Symptom duration and radiographic stage were two independent predictors of prognosis in our series. Previous studies have failed to define an ideal candidate for intra-articular HA in ankle OA patients. Sun, et al.¹³ attempted to stratify patients according to radiographic Kellgren-Lawrence grading, but did not have sufficient number of patients to demonstrate differences: age-wise, there was significant improvement on balance test results in the younger group, yet authors noted that this phenomenon may be due to a ceiling effect. The fact that age was not a significant predictor in our study may have also resulted from a ceiling

effect. Dichotomized age does not necessarily correlate with ankle OA severity, with younger (<60) patients often presenting with advanced stage disease.¹⁻³ As for the history of fracture, our results indicate that it is not a negative prognostic factor. Similar results were observed in a number of HA trials in ankle OA, where the diagnoses of the majority of patients were post-traumatic OA. Efficacy of intra-articular HA injection was similar to our results, indicating that post-traumatic ankle OA may not hinder the efficacy of HA injection.^{15,16} Subchondral bone cysts of the ankle often form as a result of osteochondral defects,²⁰ and pain originating from bone cysts may occur due to elevated intraosseous pressure.²¹ Intra-articular HA injection in patients with radiographic subchondral bone cysts may have no effect, or even exacerbated cyst-originated pain by increasing intra-articular pressure.²⁰

Current literature extrapolates results from knee OA studies to define predictors of prognosis.^{13,17,22} Lussier, et al.²³ reported that patients with radiographic early stage knee OA obtained better results compared to late stage knees after intra-articular HA injection. Meta-analysis revealed that older (>65) patients and patients with advanced knee OA were less likely to benefit from HA injections.²⁴ A study in knee OA patients, with purpose similar to our study, recommended against treating patients showing complete collapse of joint space with HA injections.²⁵ While our results on disease stage agree with previous results shown in knee OA studies, symptom duration was also an independent prognostic factor. Biological explanation for these factors could be that, quality and quantity of endogenous HA in advanced OA are already altered, having lower molecular weight and smaller size compared to HA synthesized from healthy joints.²⁶ The high molecular-weight HA produced from healthy joints also serves to insulate pain fibers.²⁷ Longer duration of pain may signify that this insulation effect of HA has been inadequate for a long time, along with sensitization of pain fibers.

This study is limited by the retrospective design. Although patients were consecutively enrolled, only patients who have met our inclusion criteria were reviewed. This may have left out some 'non-responders', creating a selection bias. The

sample size was also small compared to knee OA studies, thus resulting in a weak statistical power to delineate positive and negative predictors. There are also certain differences among published data depending on the regimen, dosage, and type of HA injection. Other protocols may result in different results.^{7,20}

In conclusion, while hyaluronic acid injection for ankle osteoarthritis is a safe and effective treatment, careful selection of patients should be made according to the above prognostic predictors. Suboptimal results may occur in ankle OA patients with symptom duration over 1 year and advanced stage disease after intra-articular HA injection.

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