Long-Term Efficacy and Safety of Periarticular Hyaluronic Acid in Acute Ankle Sprain

Michael J. Petrella, PhD; Anthony Cogliano, MD; Robert J. Petrella, MD, PhD

Abstract: The objectives of this study were to determine the long-term efficacy and safety of periarticular hyaluronic acid injections in acute lateral ankle sprain. A randomized controlled prospective trial in a primary sport medicine and emergency practice involved 158 competitive athletes who suffered an acute Grade 1 or 2 lateral ankle sprain, and who were randomized within 48 hours of injury. Patients were randomized at baseline to periarticular injection with hyaluronic acid (HA) + standard of care (rest, ice, elevation, and compression [RICE]) or placebo injection (PL) + standard of care (RICE) treatment at baseline assessment and Day 4 post injury. Follow-up was at 30, 90, and 712 days post treatment. Assessments at baseline and Days 4, 8, 30, 90, and 712 included visual analog scale (VAS) (0–10 cm) pain on weight bearing and walking 20 m, patient global assessment of ankle injury (5-point categorical scale), patient satisfaction with treatment (5-point categorical scale), time to return to pain-free and disability-free sport, recurrent ankle sprain, total number of days missing from primary sport activity, and adverse events (AEs). Time to intervention was 39 ± 4 hours with no difference between groups. A significant reduction in VAS pain on both weight bearing and walking was observed at all follow-up assessments for HA compared with PL ($P < 0.001$). Time to pain-free and disability-free return to sport was 11 (± 8) versus 17 (± 8) days for HA and PL, respectively ($P < 0.05$). At 24 months, in the PL versus HA group, there were 2 versus 0 lower limb fractures, 16 versus 7 second ankle sprains ($P < 0.05$), 3 versus 1 third ankle sprains, and a significantly greater number of days missing primary sport activity (41 versus 21; $P < 0.002$). Significantly greater patient satisfaction was also observed for HA versus PL at all follow-up assessments. No serious AEs were recorded throughout follow-up. Periarticular HA treatment for acute ankle sprain was highly satisfactory in the short and long term versus PL. This was associated with reduced pain, more rapid return to sport, fewer recurrent ankle sprains, fewer missed days from sport, with few associated AEs to 24 months.

Keywords: ankle sprain; hyaluronic acid; long-term efficacy and safety

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Introduction

Ankle sprains are among the most common of all sports injuries, with approximately 2 million people per year seeking medical treatment.[1–3] An epidemiological study of professional, competitive, and recreational athletes found a prevalence of ankle sprain as high as 73%[4] or a crude incidence rate of at least 52.7 per 10 000.[5] Ankle sprains are also the cause of significant morbidity in the longer term. A recent review by van Rijn et al[6] found up to 33% of patients still experienced pain after 1 year, while only 36% to 85% reported full recovery up to 3 years later. There is also a wide variation in subjective instability, of up to 33% to 53%. Hence, the impact of ankle sprain is of considerable concern to long-term function and performance of athletes beyond the acute event.

Compounding the impact of ankle sprain is the absence of a standard treatment approach that directly targets the injury. The American Academy of Orthopaedic Surgeons (AAOS) does recommend an initial rehabilitation program (up to 3 weeks) with nonsteroidal anti-inflammatory drugs (NSAIDs), rest, ice, compression, and elevation (RICE), as well as protected weight bearing, early mobilization, and isometric exercise.[7] Further, while NSAIDs may effectively reduce the pain and swelling associated with acute ankle sprain,[8–12] this may not alter the clinical course of ankle sprain regarding return to sport and may also cause significant adverse events (AEs) including gastrointestinal intolerance and serious events such as ulcers and bleeding.

The conservative treatment approach recommended by the AAOS may limit disability to an average of 8 days for a Grade 1 and 15 days for a Grade 2.[3–4] However, the longer-term efficacy in terms of

recurrent sprains and return to sport is limited. In one study of ankle sprain, pain and dysfunction was found to persist 6 to 18 months (average, 12.8 months) after initial ankle sprain in 73% of patients, with 40% reporting inability to walk 1 mile and 11% continuing to use medications for ankle symptoms,[14] while in a long-term follow-up study, nearly 40% of patients reported residual long-term symptoms and dysfunction 6.5 years after initial ankle sprain.[15]

Since recurrence rates are high ranging from 3% to 34% of the patients for periods ranging from 2 weeks to 96 months post injury,[6] the current approach to ankle sprain could benefit from new modalities and interventions.

Some approaches to longer-term prevention of recurrent sprains have focused on prophylactic external bracing and rehabilitative training but have shown variable results.[13] Further, prophylactic approaches may impact performance and even increase risk of other injury. What is missing is a targeted approach to ankle sprain that would provide superior efficacy, low risk of AEs, and improved rates of recurrence.

Hyaluronic acid is a naturally occurring biological substance which has been shown to have a positive clinical impact in intra-articular as well as intradermal indications.[16] As hyaluronic acid relieves pain and stiffness related to its rheologic modification of intra-articular matrix as well as "filling" intradermal space, it may be hypothesized to have a similar effect on the extra-articular complex including ligamentous structures affected by acute ankle sprain, including structural and inflammatory interruption. Further, hyaluronic acid injected locally at the site of injury would not precipitate systemic risk of AEs. We previously reported the short-term efficacy and safety of periarticular hyaluronic acid in acute ankle sprain versus placebo.[17] Periarticular hyaluronic acid was not only superior in terms of pain relief and patient satisfaction, but resulted in a faster return-to-sport activity. In the current study, we report for the first time the long-term efficacy, safety, return-to-sport, and subsequent recurrence rate of ankle sprain at 2 years post injury.

Methods

This randomized controlled study was conducted between March 2003 and December 2005 with follow-up to June 2008 in 3 primary care sport medicine facilities in Ontario, Canada. The study and follow-up was approved by the institutional ethics committee and was conducted according to the Declaration of Helsinki Good Clinical Practice guidelines. All patients signed informed consent prior to participation.

The study methodology was previously described.[17] Briefly, the study included a screening phase where patients were assessed based on selected inclusion and exclusion criteria. Prior to enrollment, a diagnosis of first- or second-degree ankle sprain was made by athletic trainers affiliated with university athletic programs, emergency physicians at affiliated local hospitals, and family physicians in the referral base for the 3 sport medicine clinics. Enrolled patients were required to report to the sport medicine clinics within 48 hours of their injury. Pain severity at enrollment was assessed using a pain visual analog scale (VAS) and included eligibility of a VAS at rest of $>$ 4.5 cm (0–10 cm). Patients were excluded if they had bilateral ankle sprain, third-degree ankle sprain, or had previous sprain in the last 6 months. An x-ray of the ankle joint was performed prior to enrollment to exclude other pathologies. Patients were randomized (1:1) to 1 of the 2 treatment groups using a computer-generated randomization schedule: periarticular hyaluronic acid (HA) (MW range, 750–1 million kDal, 20 mg) + usual standard of care RICE or periarticular placebo (PL) + usual standard of care RICE. The first dose of study treatment was administered on Day 1 (within 48 hours of injury) and the second dose was administered on Day 4 ($\pm$ 1 day).

Assessments were done at baseline, and Days 4, 8, 30, 90, and 712 (Table 1). Efficacy measures included patients' VAS of pain on weight bearing (0–10 cm) and walking 20 m (0–10 cm), patients' global assessment of ankle injury (5-point categorical scale), patients' assessment of return to normal function/activity in sport (5-point categorical scale), patients' satisfaction assessment (10-point categorical scale), number of recurrent ankle sprains, number of other injuries, number of days missing from incident sport due to ankle sprain and AEs as per World Health Organization (WHO) definition.

Following measurement of the outcome assessments, those randomized to HA treatment received a single injection of HA (0.7–1.2 mL) or placebo (normal saline 0.7–1.2 mL). Injections were performed using previously[18,19] described blinded syringes affixed to a 27-gauge, 1-inch needle.[17] Briefly, skin was prepped using Betadine 1%. Injections were delivered by the study physician using a standard approach along the anterior talofibular ligament using clinical landmarks. The injection

Table 1. Schedule of Time and Events

Evaluations	Baseline/Day 1	Day 4	Day 8	Day 30	Day 90	Day 712
Informed consent	X					
Medical history	X					
Vital signs and physical examination	X					
X-Ray Evaluation	X					
Patients VAS of pain on weight bearing	X		X	X	X	X
Patients VAS of pain on walking (20 m)	X		X	X	X	X
Patients global assessment of ankle injury	X		X	X	X	X
Patients assessment of normal function/activity	X		X	X	X	X
Patients satisfaction assessment			X	X	X	X
Number of recurrent ankle sprains						X
Number of all injuries						X
Days missing from incident sport						X
HA administration	X	X				
Concomitant medications	X	X	X	X	X	X
Adverse events		X	X	X	X	X

Abbreviations: VAS, visual analogue scale; HA, hyaluronic acid.

(1.2 mL total) was delivered during a single penetration along 3 planes from anteroposterior, medial, and lateral from the proximal ligamentous landmark. Assessments and injections were repeated on Day 4 (± 1 day). All randomized patients received standard care consisting of RICE, assistive devices as determined by the study physician including crutches, taping, or bracing but not physiotherapy, and oral or topical medications such as NSAIDs. These latter interventions could be used after Day 8 at the patient's discretion.

Rescue medication (500 mg acetaminophen tablets, up to 4 tablets daily) was allowed in both groups but not for the 24 hours prior to study visit. Patients were free to withdraw at any time during the trial.

Follow-up assessments were completed at Days 8 (± 2 days), 30 (± 7 days), 90 (± 7 days), and 712 (± 7 days). Adverse events and concomitant medications were assessed throughout the patients' participation in the study.

Demographic and baseline data were compared within the 2 groups using Student's t-tests for continuous and χ^2 statistics for noncontinuous variables. Statistical analysis was based on the intent to treat (ITT) population. Efficacy and safety variables were analyzed between groups using appropriate statistical methods including Student's t-test for quantitative, χ^2 test for nominal, and Mann-Whitney U test for ordinal variables. The data analysis was performed using the SAS® version 8.2 (SAS Institute, Cary, NC). All statistical tests were 2-tailed at a 5% level of significance.

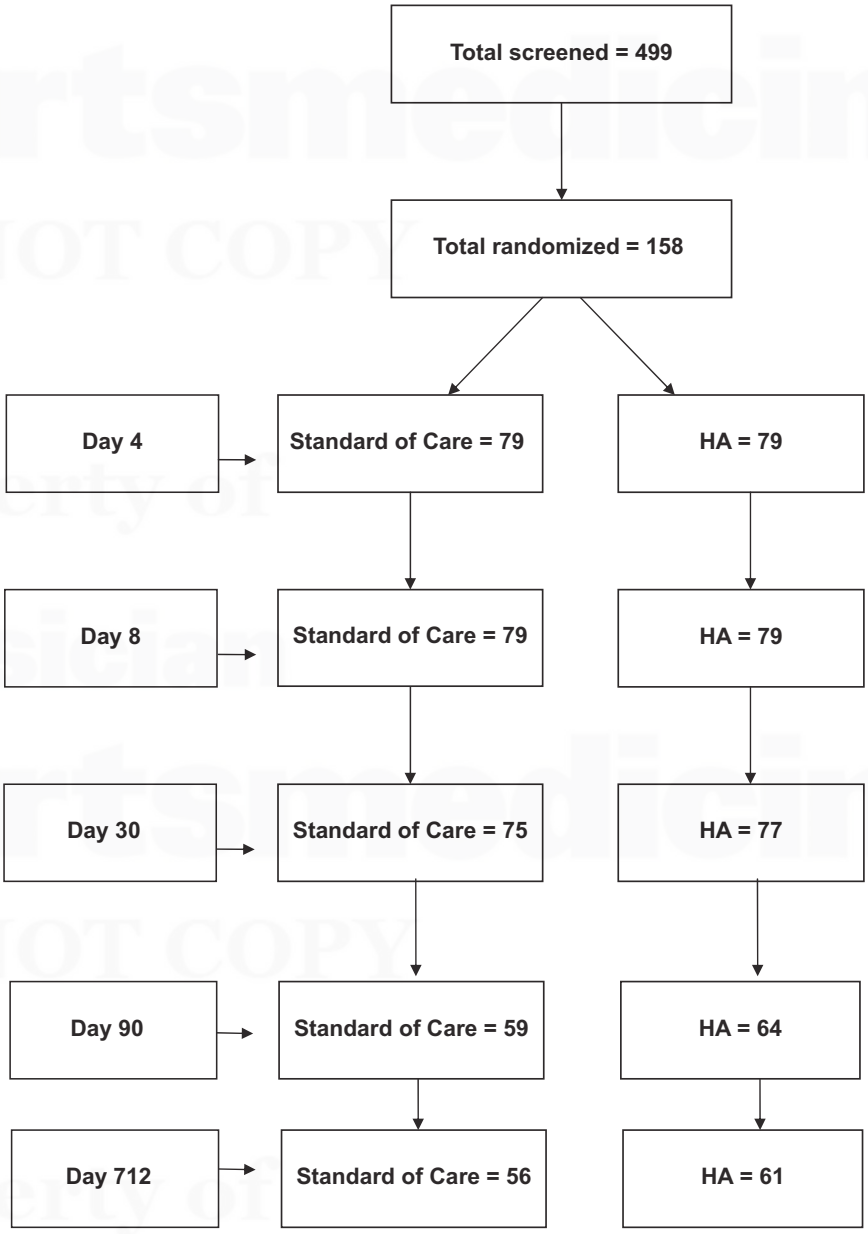
Results

A total of 499 patients were screened and the ITT population was 158 patients (Figure 1). The average age was 26 ± 7 years and 24 ± 8 years for the HA and PL groups, respectively, with equal male to female representation between groups. Thirty percent of sprains were first events and 65% were Grade 1 with no difference between groups. There was no difference between the groups at baseline. We obtained 100% compliance with the injection series throughout the treatment phase and 70% to 75% retention at 2 years (Figure 1). Time to intervention was not different between groups (39 ± 4 hours).

The primary efficacy criterion was the decrease from baseline to visit 2 (Day 8 ± 1) in weight-bearing pain calculated in the ITT population (Table 2). This, and changes in walking pain, were −3.16 ± 1.18 cm and −1.83 ± 1.1 cm (%) (weight-bearing pain) and −4.99 ± 2.02 cm and −3.76 ± 2.43 cm (%) (walking pain) in the HA and PL groups, respectively ($P < 0.0001$), giving an inter-group difference of 1.31 cm and 1.23 cm in favor of treatment.

The differences between groups were also significant at visit 3 (Day 30), visit 4 (Day 90), and visit 5 (Day 712) in favor of the treatment group (Table 2).

Figure 1. Treatment algorithm for the study.



Globally, all efficacy parameters improved during the study in both groups. However, intergroup comparisons showed a statistically significant difference in favor of HA on most efficacy parameters (Table 2). For parameters where such a difference was not obtained for all visits, the improvement was more marked in the HA than in the control. The results for the secondary efficacy variables were therefore globally consistent with those concerning the primary outcomes.

Fewer recurrent sprains were observed in the HA (7) versus PL (16) group at 2 years (Figure 2). Further, this was associated with fewer days missing (21) versus (41) for the HA and PL groups, respectively (Figure 3). There was a small but nonsignificant difference favoring HA in number of total MSK injuries (18 vs 24) reported at 2 years, suggesting that missing days from sport in patients post ankle sprain is primarily driven by recurrent ankle sprain.

Table 2. Subject Characteristics, Efficacy, and Safety Outcomes

EFFICACY: Double-Blind Treatment Phase				Follow-up Phase		
	Baseline	Day 4	Day 8	Day 30	Day 90	Day 712
Characteristics	(n = 158)	(n = 158)	(n = 158)	(n = 152)	(n = 123)	(n = 123)
VAS pain of weight bearing change in cm, mean (SD)						
HA		–3.16 (1.18)*°	–4.11 (1.81)*°	–4.04 (1.16)*°	–4.07 (1.27)*°	–3.0 (1.1)*°
PL		–1.83 (1.12)	–2.38 (1.72)*	–2.42 (1.09)*	–2.67 (1.47)*	–1.7 (1.3)*
VAS pain on walking change in cm, mean (SD)						
HA		–4.99 (2.02)*°	–5.62 (2.54)*°	–5.68 (2.55)*	–5.10 (1.92)*	–6.1 (0.9)*°
PL		–3.76 (2.43)*	–4.2 (2.16)*	–4.67 (1.89)*	–4.78 (1.99)*	–4.0 (1.2)*
Patient global assessment of ankle injury, mean (SD)*						
HA	1.3 (1.8)	3.8 (1.8)*	4.8 (0.3)*	4.9 (1.8)*	4.9 (1.3)*	4.9 (0.2) *
PL	1.5 (1.5)	2.1 (2.4)	3.5 (1.8)*	3.8 (2.7)*	4.8 (1.5)*	4.8 (1.0) *
Time - return to pain free sport in %, mean (SD)*						
HA		3	27	70	100	91
PL		0	5	42	81	71
Patient satisfaction with treatment, mean (SD)						
HA	NA	7.4 (2.8)*°	7.7 (2.4)*°	9.5 (1.2)*	9.6 (0.7)*	9.4 (0.2)*
PL	NA	4.8 (2.9)*	5.7 (1.7)*	7.6 (1.6)*	9.6 (1.1)*	9.4 (0.8)*
Adverse events (n, HA/PL)						
Erythema		1/0	1/2	0/0	0/0	0/0
Pain		2/1	3/1	0/0	0/0	3/5
Swelling		0/0	0/1	0/0	0/0	1/3
Other		0/0	0/0	0/0	0/0	0/2

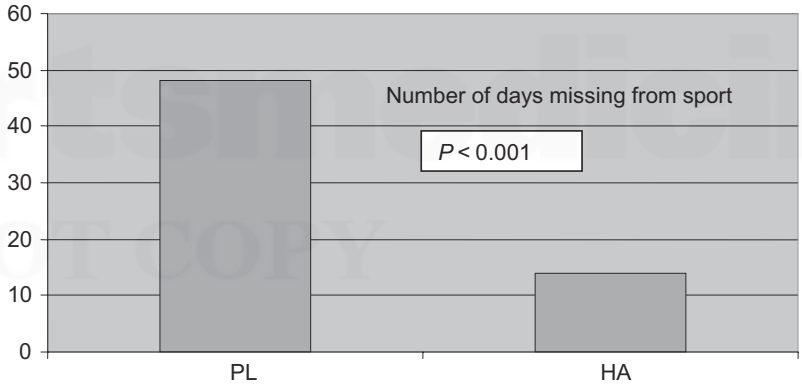
Abbreviations: HA, hyaluronic acid group; PL, usual care group; SD, standard deviation.
Sprain grade is percent presenting with Grade 1 sprain; VAS pain on weight bearing is the score decrease from baseline in cm on 10-point Likert scale; VAS pain on walking is the score decrease from baseline in cm on 10-point Likert scale; patient global assessment of ankle injury is self reported score from 1–5 where 1 = very poor assessment of injury on health and 5 = very good assessment of injury on health; patient assessment of return to normal activity in sport is self reported score from 1 = severely restricted to 5 = normal activity; patient satisfaction with treatment is self reported score from 1 = not satisfied to 10 = completely satisfied with treatment; adverse events are the self reported adverse events at each study visit.
*Statistically significant differences within treatment groups for these parameters.
*°Statistically significant difference between treatment groups for these parameters.

Patient satisfaction with treatment scores among subjects showed that 75% versus 48% and 77% versus 57% were satisfied at Days 4 and 8 while 95% versus 76% were satisfied at Day 30, 93% vs 67% at Day 90, and 95% versus 60% at Day 712 (χ^2 test, $P < 0.001$) (Table 2).

Three AEs were observed among all subjects and consisted of pain requiring the self-medication with NSAID (2 HA, 1 PL) including 1 mild erythema and pain (HA) at the injection site not requiring further intervention at Day 4, and 3 pain and 1 mild erythema at the injection site in the HA vs 2 erythema, 1 pain and 1 swelling at Day 8 in PL (Table 2). The pain AEs in the 2 groups did not differ in intensity. At 712 days, 3 pain AEs for HA and 5 pain AEs for PL were reported (Table 2). There were no serious AEs.

No difference in concomitant treatment or physical therapy between groups was observed to Day 90. At Day 712 more patients in PL had used at least 7 days of NSAID compared with HA ($P < 0.001$) and more had utilized physical therapy ($P < 0.001$).

Figure 2. Number of recurrent ankle sprains with days missing from sport at 2 years.



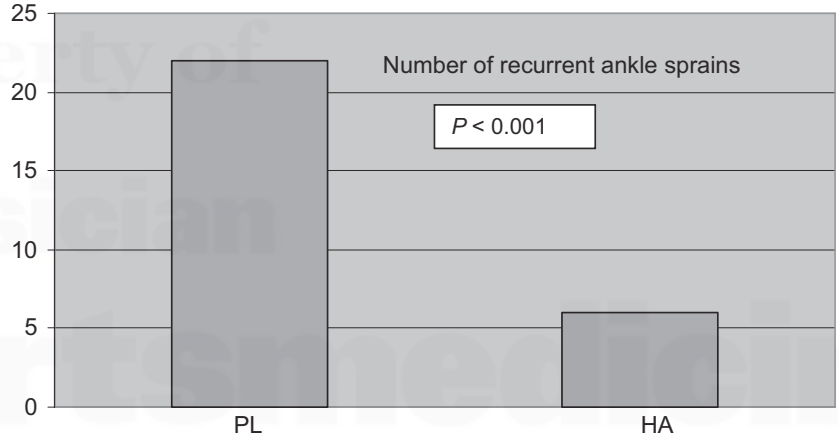
Abbreviations: HA, hyaluronic acid group; PL, usual care group.

Discussion

Conservative treatment of acute ankle sprain may limit disability to an average of 8 days for a Grade 1 and 15 days for a Grade 2,[3,4] but this treatment is not ideal as it remains that a significant number of patients will have ongoing disability including instability, recurrent sprains, and time away from sport. Further, while NSAIDs effectively reduce the pain and swelling associated with acute ankle sprain,[8–12] they are nonselective and may cause significant AEs including gastrointestinal intolerance, serious events such as ulcers and bleeding, as well as potential negative cardio-renal effects. Hence, therapeutic options for ankle sprains have been limited while both the short- and long-term recovery suggest that alternative treatments, particularly those that improve return-to-sport with minimal sequelae, are needed.

Hyaluronic acid is a naturally occurring biological substance representing an unbranched, high-molecular-weight polysaccharide as a major component of ligamentous, cartilaginous, and synovial ultrastructure[16] with no demonstrated effect on gastrointestinal and platelet function. It has proven efficacy and safety in the treatment of osteoarthritis.[20] We have previously reported the short-term efficacy and safety of periarticular administration of HA in acute ankle sprain compared with standard of care treatment.[17]

Figure 3. Number of recurrent ankle sprains.



Abbreviations: HA, hyaluronic acid group; PL, usual care group.

In the current study, we extend our previous findings that periarticular HA was associated with fewer recurrent ankle sprains and fewer injury days missing from sport compared with PL. This is the first study to our knowledge, regardless of management, that has demonstrated impact on future ankle injury and morbidity from a standardized treatment of acute ankle sprain. The primary efficacy criterion was a decrease in pain in the first 8 days in the ITT population. Based on this criterion, periarticular HA was found to be significantly more effective than control. This change of 3 cm is considered clinically significant.[11] Furthermore, almost all the secondary criteria, including patient global satisfaction, were also improved during the trial compared with control, even up to 90 days.

Further, clinical implications of our results were confirmed by the fact that the number of patients who withdrew for AE or lack of efficacy was small for both groups, and that our short-term results are consistent with other treatments of ankle sprain with topical NSAIDs [10,21,22] and oral NSAIDs and COX-2 inhibitors.[9,12] Importantly, we reported a very low incidence of AEs with high satisfaction both in the short- and longer-term.

Further, less use of concomitant medication for ankle pain and fewer physical therapy sessions was observed at 2 years in the HA versus PL group, suggesting that this new treatment modality could have added value to clinicians and their patients. Currently, those with ankle instability after an acute sprain may be advised that wearing a prophylactic external brace to reduce the risk of a future sprain, although the results including costs and performance to date are not clear.[13] Investigation of the costs and benefits of periarticular HA versus conventional therapy requires attention to return-to-sport and recurrent ankle injury across the range of sport settings, including amateur to professional, to allow clinicians and athletes to make informed decisions regarding their therapy options.

Summary

Our results showed superior short- and long-term therapeutic response of periarticular HA in patients with acute ankle sprain versus standard of care treatment. Further, periarticular HA resulted in fewer recurrent ankle sprains, less use of concomitant treatments, and fewer days missing from sport 2 years after the initial injury. Given that this treatment is easily performed in primary care sport medicine and has high patient satisfaction, these results suggest that periarticular HA in acute ankle should be considered an important alternative by physicians and their patients.

Acknowledgments

The authors acknowledge the participation of study investigators at the Fowler-Kennedy Sport Medicine Clinic, London, Canada.

Conflict of Interest Statement

Michael J. Petrella, PhD, Anthony Cogliano, MD, and Robert J. Petrella, MD, PhD declare no conflicts of interest.

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