Efficacy of Celecoxib, a COX-2–Specific Inhibitor, and Naproxen in the Management of Acute Ankle Sprain

Results of a Double-Blind, Randomized Controlled Trial

Robert Petrella, MD, PhD, Evan F. Ekman, MD,† Reinhard Schuller, MS,‡ and John G. Fort, MD‡*

Objective: To assess the efficacy and safety of celecoxib and naproxen in the treatment of acute ankle sprain.

Design: Double-blind, parallel-group, randomized trial.

Setting: Multicenter outpatient.

Patients: Adult patients (n = 397) with acute first-degree or second-degree ankle sprain.

Interventions: Patients randomized to celecoxib 200 mg BID (n = 198) or naproxen 500 mg BID (n = 198) for 7 days.

Main Outcome Measures: Primary measures of efficacy were Patient's Assessment of Ankle Pain Visual Analogue Scale (VAS) and Patient's Global Assessment of Ankle Injury. Secondary efficacy measures included Physician's Global Assessment of Ankle Injury, Patient's Return to Normal Function/Activity, and Patients' and Physicians' Satisfaction Assessments. Adverse events (AEs) were reported by investigators during the study.

Results: For the primary endpoints at day 4, the mean pain VAS scores were 31.9 mm ± 1.96 for celecoxib and 29.0 mm ± 1.91 for naproxen, and the responder rate for Patient's Global Assessment of Ankle Injury was 71% in the celecoxib group and 72% in the naproxen group, differences that were not statistically significant. In addition, noninferiority analysis demonstrated treatment differences that were within prespecified minimal clinical important differences. Gastrointestinal AEs were the most common AE, accounting for 14% in the celecoxib group and 21% in the naproxen group. The incidence of dyspepsia was 3% for celecoxib compared with 12% for naproxen ($P = 0.032$).

Conclusions: Celecoxib is as effective as naproxen in treating acute first-degree or second-degree ankle sprains but causes significantly less dyspepsia.

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From the *Canadian Center for Activity and Aging, London, Ontario, Canada; †Southern Orthopedic Sports Medicine, Providence Hospital, Columbia, SC; and ‡Pfizer, New York, NY.

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Reprints: Robert Petrella, MD, PhD, Canadian Center for Activity and Aging, 1490 Richmond St. N., London, Ontario, Canada N6G 2M3 (e-mail: petrella@julian.uwo.ca).

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Ankle sprains are the single most common musculoskeletal sports-related injury, with about 2 million people a 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] Data from the National Hospital Ambulatory Medical Care Survey: 2000 Emergency Department Summary listed about 1.375 million emergency department (ED) visits in the US due to ankle sprains, representing about 1.3% of ED visits.[5]

Ankle sprains most commonly affect the lateral ligaments (inversion injury).[6] Symptoms include pain, swelling, tenderness, functional loss, and difficulty walking. Depending on the severity of the injury, ankle sprains are classified as first-degree, second-degree, or third-degree ankle sprains.[7] The assessment and treatment of ankle injuries is performed by emergency physicians, primary care, and orthopedic and trauma surgeons.[8]

The emphasis of therapy in ankle sprains is centered on reducing the inflammation and pain rapidly following injury.[7,9] Guidelines for the treatment of acute ankle sprain from the American Academy of Orthopaedic Surgeons recommend an initial rehabilitation program (up to 3 weeks) with nonsteroidal anti-inflammatory drugs (NSAIDs); rest, ice, compression, and elevation (RICE); protected weight bearing; early mobilization; and isometrics.[10] Conservative treatment may limit disability to an average of 8 days for a grade 1 sprain and 15 days for a grade 2 sprain.[3] Failure to provide adequate therapy can limit a patient's efforts in rehabilitation and prolong the recovery period. In long-term studies of ankle sprain, pain and dysfunction was found to persist for over 6 months in a significant portion of patients, including 40% of athletes.[6,11,12]

Nonsteroidal anti-inflammatory drugs effectively reduce the inflammation, pain, and disability associated with acute ankle sprain.[13–17] The rationale for their use include pain

control and anti-inflammatory effect to allow early activity and decrease inflammation to speed healing directly.[18] However, NSAIDs are nonspecific and inhibit both COX-1 and COX-2 and may cause significant adverse events (AEs) including UGI intolerance and serious events such as ulcers and bleeding. Celecoxib is one of several COX-2 specific inhibitors currently available (others include rofecoxib and valdecoxib) with effective anti-inflammatory and analgesic properties. Celecoxib and rofecoxib have been approved by the FDA for the management of acute pain. Specific COX-2 inhibitors are associated with significant improvement in UGI tolerability, significantly less serious UGI events, and, importantly, no significant effect on platelet function compared with traditional NSAIDs.[19–22]

This randomized, double-blind, controlled study was undertaken to compare the efficacy and safety of celecoxib 200 mg BID with that of the nonselective NSAID naproxen 500 mg BID in the management of grade 1 and 2 acute ankle sprain.

METHODS

The protocol and written informed consent were approved by an Institutional Review Board or Ethics Committees at each study site. The study was conducted in accordance with Good Clinical Practice and in compliance with the requirements of the International Conference on Harmonization and the Declaration of Helsinki.

The study was a multicenter, double-blind, parallel-group, randomized controlled trial with a 7-day treatment period. In each arm of the study, patients took the blinded study drug with a matching placebo of identical characteristics (double-dummy). There were a total of 46 investigator sites, including 22 sites in Canada, of which 14 were sports centers. Other sites included orthopedic centers and EDs. Outpatients 18 years or older were eligible to participate in the study if they (1) had sustained a first-degree or second-degree lateral ankle sprain within 48 hours of administration of study drug and (2) reported moderate (45–60 mm) to severe (>60 mm) ankle pain on full weight bearing on the Patient's Assessment of Ankle Pain using a 100-mm visual analogue scale (VAS).

Patients with bilateral ankle sprain, ipsilateral knee injury, third-degree sprain, or previous ankle sprain within 6 months were excluded, as were patients who had used prescription or over-the-counter anti-inflammatory or analgesic medications, muscle relaxants, neuroleptics, tricyclic antidepressants, sedative-hypnotics, or anxiolytics 48 hours prior to enrollment. In addition, patients with sensitivity or allergy to NSAIDs or sulfonamides, patients with a history of serious gastrointestinal, renal, or hepatic disease, and patients with other rheumatic diseases or a history of drug or alcohol abuse were excluded.

Prior to enrollment, patients underwent a screening assessment that included a physical examination. Investigators determined a diagnosis of first-degree or second-degree ankle sprain based on established criteria on the classification of ankle sprain (grades 1–3) described in the study protocol. Patients rated pain on a 100-mm VAS, with 0 representing no pain and 100 representing maximal pain. After enrollment, patients were randomized (1:1) to 1 of 2 oral treatments using a computer-generated randomization schedule: celecoxib 200 mg BID or naproxen 500 mg BID for 7 days. The first dose of study drug was administered immediately after completing assessment procedures. Patient's treatment assignment was known only by the supplier's clinical packaging group and was kept in a sealed envelope by the statistician until the database was closed. The data were collected by the study sponsor.

Clinical assessments were performed at baseline, on day 4, and on day 8 (end of study). Investigator-identified AEs were recorded at postbaseline visits. The primary measures of efficacy were the Patient's Assessment of Ankle Pain VAS on weight bearing and the Patient's Global Assessment of Ankle Injury (1–5 point categorical scale of very poor, poor, fair, good, and very good). These assessments were performed at day 4 (primary endpoints) and day 8 (secondary endpoints). Response rate for Patient's Global Assessment was defined as the percentage of patients who improved by 1 or more grades. Secondary assessments included Physician's Global Assessment (1–5 point categorical scale) at days 4 and 8, Patients' and Physicians' Satisfaction Assessments using a 10-point scale at day 8, and Patient's Assessment of Normal Function/Activity at day 8 (defined as all activity that a patient performs on a routine basis, including work and recreation), which rates the impact of ankle pain on walking and normal activity on a 5-point scale, with 1 representing no pain and normal activity and 5 representing severely restricted walking and activities. Adverse events were classified using standard World Health Organization dictionary of AE terminology and codes. Withdrawals due to treatment failure were determined by the investigator. Compliance was determined by the percentage of capsules consumed.

In addition to the study drug, physicians were permitted to prescribe standard nonpharmacological treatments including RICE and the use of crutches, a cane, an ankle brace, and so forth. Patients were not permitted to use additional over-the-counter or prescription analgesics or antiulcer medications. Aspirin at dosages not exceeding 325 mg/d for cardiovascular prophylaxis was permitted.

Efficacy analyses were performed with data from the ITT and evaluable cohorts. The ITT cohort consisted of all randomized patients who took at least 1 dose of study drug. The evaluable cohort was used for testing noninferiority, which excluded data from patients with major protocol violations. The hypothesis of noninferiority of celecoxib relative to naproxen in the pain VAS was accepted if the upper 95% CI of the treatment difference (celecoxib-naproxen) was less than 20 mm (on a 100-mm scale). The study sample size was calculated based on a Patient's Global Assessment responder rate of

90% with a difference in the responder rate of less than 15% for celecoxib relative to naproxen. The hypothesis of noninferiority of celecoxib relative to naproxen using the Patient Global Assessment was accepted if the lower 95% confidence limit of the odds ratio (OR; celecoxib/naproxen) was greater than 0.33. Two-sided 95% CIs for treatment differences were estimated on all secondary outcome variables. Changes in Ankle Pain VAS scores were evaluated with an analysis of variance. Patient's Assessment of Ankle Pain VAS scores were evaluated to determine the proportion of treatment responders on days 4 and 8. In addition, mean scores for return to normal function were tabulated. The ITT cohort was used in the safety analyses. The Fisher exact test was used to compare incidences of AEs between treatments.

RESULTS

A total of 397 patients were enrolled in the study. One hundred ninety-nine patients were randomized to receive celecoxib and 198 to receive naproxen (Fig. 1). Baseline demographic characteristics, ankle sprain characteristics, and therapies other than study drug that were prescribed by investigator for the treatment of ankle sprain are included in Table 1. Compliance with study drug was similar in the groups.

Primary Efficacy Measures

Pain VAS measures are described in Table 2. Similar reductions in pain were seen with naproxen and celecoxib at day 4 (primary assessment) and day 8 (secondary assessment). These differences were not statistically significant. Assessing noninferiority (evaluable cohort) at day 4 (primary assessment), the treatment difference was 2.86 mm, with the upper 95% CI at 5.79 mm ($P = 0.1$), and at day 8, the treatment difference was −0.43 mm, with the upper 95% CI at 2.62 mm ($P = 0.8$). Both of these were within the prespecified definition of clinical equivalency. Regarding the Patient's Global Assessment, the percentage of patients classified as responders on day 4 was 71% for celecoxib and 72% for naproxen (OR, 0.89; 95% CI, 0.53–1.49; $P = 0.7$) and on day 8 was 89% for celecoxib and 90% for naproxen (OR, 0.78; 95% CI, 0.38–1.62; $P = 0.5$), differences that were not statistically significant. In assessing noninferiority, at day 4 (primary assessment), the treatment difference OR was 0.88 (lower 95% CI of 0.59; $P = 0.62$), and at day 8, the treatment difference OR was

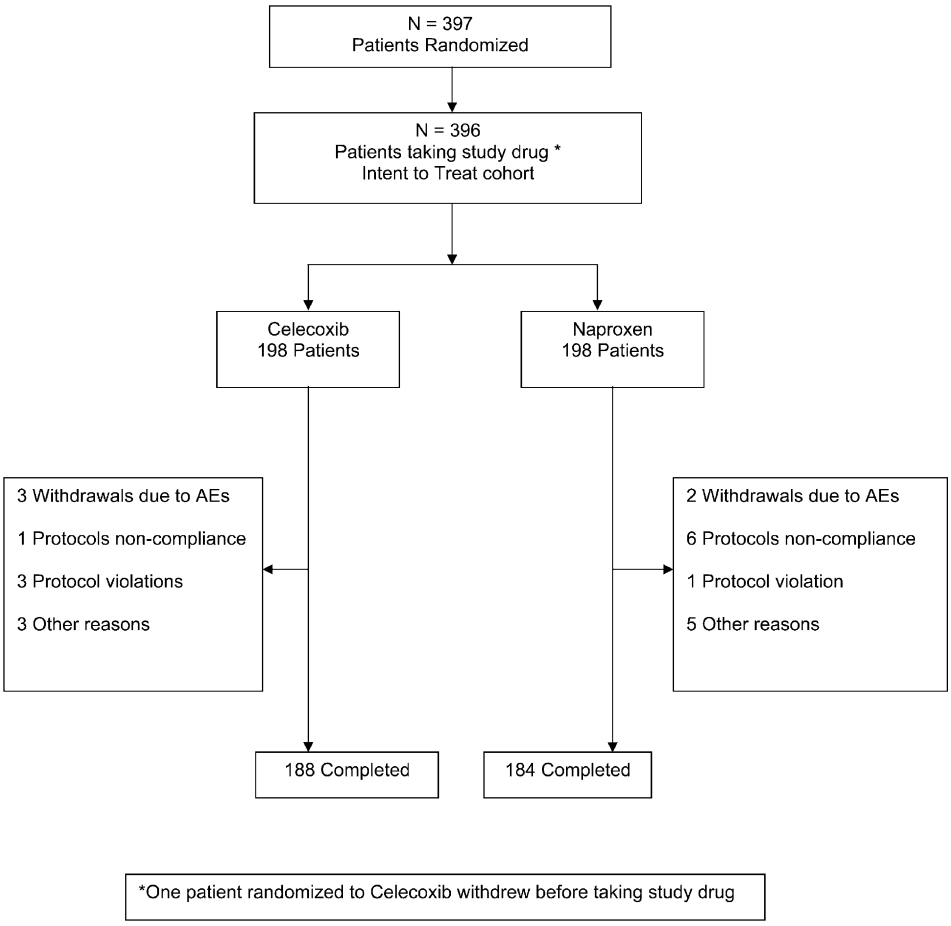

FIGURE 1. Patient disposition.

TABLE 1. Baseline Demographics and Characteristics of All Randomized Patients

	Celecoxib n = 199	Naproxen n = 198
Age (y ± SE)	29.5 ± 0.78	30.6 ± 0.90
Male	133 (67%)	133 (67%)
Caucasian	187 (94%)	185 (93%)
Duration of injury (h ± SE)	21.8 ± 0.97	24.6 ± 0.97
Sports Related Injury	106 (53%)	109 (55%)
Degree of sprain		
First	43 (22%)	53 (27%)
Second	156 (78%)	145 (73%)
Severity of pain		
Severe (>60 mm)	134 (67%)	130 (66%)
Moderate (45–60 mm)	63 (32%)	67 (34%)
Mild (<45 mm)	2 (1%)	1 (1%)
Nonpharmacological therapy		
RICE	192 (96%)	182 (92%)
Crutches	89 (45%)	83 (42%)
Ankle band/tape	73 (37%)	68 (34%)
Strengthening exercises	38 (19%)	31 (16%)
Air cast	36 (18%)	41 (21%)

0.78 (lower 95% CI of 0.47; $P = 0.41$). Both of these were within the prespecified definition of clinical equivalency.

Secondary Efficacy Measures

The Physician's Global Assessment of Ankle Injury showed a significantly greater improvement at day 4 with naproxen ($P = 0.025$) compared with celecoxib; however, at day 8, this difference was no longer observed, with complete or moderate recovery in 92% with celecoxib and 93% with naproxen ($P = 0.96$). Patient's Assessment of Normal Function/Activity at the final visit demonstrated that 77% (n = 148) of patients on celecoxib and 78% (n = 150) of patients on naproxen achieved clinically significant improvement, defined as normal walking/activity with no pain or normal walking/activity with pain. This difference was not statistically significant, with an OR of 0.93 (95% CI, 0.64–1.35; $P = 0.688$). The median time to normal function/activity was obtained by day 5 for both celecoxib and naproxen. Patient's Satisfaction Assessment performed at end of the study demonstrated a mean assessment of 8.8 with celecoxib and 8.7 with naproxen, and Physician's Satisfaction Assessment demonstrated a mean assessment of 8.7 with celecoxib and 8.6 with naproxen. These differences were not statistically significant. Last, the number of treatment failures was 3 (2%) for patients on celecoxib and 4 (2%) for patients on naproxen.

Forty-six subjects in the celecoxib group (23%) compared with 59 in the naproxen group (30%) experienced 1 or more AEs. The most common AEs were gastrointestinal, which occurred in 14% (n = 28) of the celecoxib group and 21% of the naproxen group (n = 42). Adverse events occurring in 2% or more of patients are depicted in Table 3. Individual gastrointestinal AEs were similar across both groups except for dyspepsia, which was significantly greater in patients on naproxen. Regarding AEs leading to withdrawals, there were 3 patients on celecoxib who reported 4 AEs (vertigo, vomiting, nervousness, and rash) and 2 patients on naproxen who reported 3 AEs (abdominal pain, melena, and stomatitis). There were no serious AEs reported and no deaths.

DISCUSSION

Musculoskeletal trauma is a common condition, and the ankle is 1 of the most common sites for acute musculoskeletal injuries. Data from the National Hospital Ambulatory Medical Care Survey of Emergency Departments list about 1.96 million injury-related ED visits involving the lower leg and ankle.[5] The Emergency Medicine Model assesses sprains and strains as a lower patient acuity injury with a low probably of progression to more serious disease or development of complications.[23] However, more than 40% of ankle sprains have the potential to cause chronic problems, and care should be taken when prescribing appropriate care to limit this risk.[7]

The present study tested the effects of 2 drug treatments—celecoxib (a COX-2–specific inhibitor) at a dose of 200 mg BID and naproxen (a traditional NSAID) at a dose of 500 mg BID—in the management of the symptoms of acute ankle sprain, especially pain. Several issues were critical to the design of this study. First, all patients had to have sustained the ankle injury at least 48 hours before entering the study. Second, all patients had to a have a minimum amount of pain on a VAS greater than or equal to 45 mm, which is generally considered moderate to severe pain. Third, the primary assessments to measure drug effect were taken at day 4 of the study, which was felt to be early enough to measure an effect and not so late that near-complete recovery would have occurred in most patients. Last, this trial used a noninferiority design.[24]

Under these design conditions, the study demonstrated that patients on celecoxib experience improvement in pain comparable to improvement in patients taking a traditional NSAID, naproxen. As a noninferiority trial, the study required the identification of a minimal clinically important difference (MCID). In this study, the MCID was prespecified on a pain VAS as less than 20 mm. This differs from other suggested MCIDs, which may be as low as 13 mm.[25] Nevertheless, the study conclusions did not change given that the upper 95% CIs of the observed differences in this trial were 5.79 mm (day 4) and 2.62 mm (day 8). These numbers are well within even the more stringent 13 mm MCID. Thus, the results of this trial are consistent with a recently published article comparing celecoxib (400 mg/d), ibuprofen (2400 mg/d), and placebo added to standard nonpharmacological therapy.[16] Patients on anti-

TABLE 2. Patient Assessment of Pain (ITT Cohort)

Pain VAS mm (0–100 mm)	Celecoxib 200 mg BID n = 198	Naproxen 500 mg BID n = 198	Non inferiority*: Treatment Differences (Upper 95% CI)
Baseline	67.6	67.5	
Day 4	31.9 ± 1.96	29.0 ± 1.91	
Change from baseline	−35.7	−38.5	2.86 mm (5.79 mm; $P = 0.1$)
Day 8	15.0 ± 1.70	15.3 ± 1.65	
Change from baseline	−52.6	−52.2	−0.43 mm (2.62 mm: $P = 0.8$)

*Noninferiority based on evaluable cohort.

TABLE 3. Incidence of Individual Adverse Events Occurring in ≥2% of Patients (ITT Cohort)

	Celecoxib n = 198 n (%)	Naproxen n = 198 n (%)
Patients with ≥1 AE	46 (23)	59 (30)
AE*		
Abdominal pain	10 (5)	9 (5)
Nausea	6 (3)	9 (5)
Diarrhea	5 (3)	7 (4)
Dyspepsia	3 (2)	12 (6)†
Flatulence	3 (2)	4 (2)
Headache	4 (2)	6 (3)
Insomnia	3 (2)	1 (1)
Rash	4 (2)	1 (1)
Somnolence	3 (2)	2 (1)
Fatigue	2 (1)	4 (2)

*Individual patients may have reported more than 1 AE.
†Celecoxib vs. naproxen, $P = 0.032$.

inflammatory therapy appeared to have a slightly faster return to normal function/activity.

The treatment of acute ankle sprains has been outlined in a number of guidelines and reviews. The American Academy of Orthopedic Surgeons defines 4 treatment approaches depending on initial and follow-up assessments: an initial rehabilitation program, a home rehabilitation program, functional bracing, and a supervised rehabilitation program.[10] In a recent review, Wolfe et al[7] outlined several steps in the management of ankle sprains, including (1) initial management with RICE and NSAIDs and (2) early and advanced functional rehabilitation. The important elements of treatment appear to include RICE, anti-inflammatory therapy, and rehabilitation. It should be noted that swelling, a common feature of ankle sprain that contributes significantly to disability, may not be influenced by anti-inflammatory drug therapy.

Ankle sprains are managed by a number of physicians. IMS data based on diagnostic coding suggest that most ankle injuries are managed by primary care physicians (Table 4) but that orthopedic surgeons, emergency medicine physicians, pediatrics, and podiatry also treat a large number of these cases.[26]

TABLE 4. Diagnostic Visits for Ankle Injury by Medical Specialty (5 Most Common) and Relative Pharmacological Treatments Prescribed*

Medical Specialty	Percent of Diagnostic Visits	Percent Use of Nonspecific NSAIDs	Percent Use of COX-2–Specific Inhibitors	Percent Use of Narcotic Analgesics	Percent Use of Nonnarcotic Analgesics
Primary care	44.5	33.6	20.7	12.3	27.7
Orthopedic surgeons	17.7	23.0	30.6	17.4	24.7
Emergency medicine	13.2	25.8	0.7	38.0	34.9
Pediatrics	12.2	22.4	NA†	2.2	68.9
Podiatry	10.8	45.9	22.6	12.0	13.0

*From Projected Drug Uses Associated With Ankle Injury Diagnoses: Moving Annual Total September 2000–2002.[26]
†COX-2–specific inhibitors are approved for use only in adults.

Anti-inflammatory therapy seems to be relatively highest with podiatrists (68.5%), followed by primary care (54.3%) and orthopedics (53.6%). The rate of use with ED physicians is lower, at (26.5%). ED physician rely more on analgesics, with use evenly split between narcotics and nonnarcotics. The reason for these differences is not clear. This may be related to a perception that anti-inflammatory drugs are not as effective as low-dose oral narcotics. However, recent data in dental pain and orthopedic surgery models suggest that COX-2 inhibitors are as effective as low-dose oral narcotics.[27–29] In addition, analgesics may be easier to titrate to the desired effect and have a lower incidence of some AEs. Moreover, the drug costs associated with COX-2–specific inhibitors may be greater than those of some analgesics and NSAIDs.

The use of nonselective NSAIDs for the treatment of acute ankle sprains may be limited for a number of reasons. NSAIDs are associated with an increased risk for serious UGI events even following a few days of therapy, as is typical in the treatment of ankle sprains. This may be more important in populations with risk factors such as age, comorbid conditions, concomitant therapies, and so forth. On the other hand, COX-2–specific inhibitors are associated with a significant reduction in serious UGI events compared with NSAIDs. However, this is based on studies of longer duration, in different medical conditions, and in an older population than the present study. In addition, NSAIDs are known to inhibit platelet aggregation significantly even after a single dose.[22] This may be important in patients with acute musculoskeletal injuries in which bleeding secondary to trauma is inherent in the injury. COX-2–specific inhibitors have been shown to have no effect on platelet aggregation (similar to placebo). Thus, in patients with bleeding potential, specific COX-2 inhibitors may provide an advantage.

The AE profiles were similar between the 2 drugs, although there were a greater number of gastrointestinal side effects with naproxen. In larger studies, celecoxib and other COX-2–specific inhibitors have been shown to be better tolerated than traditional NSAIDs.[19–21] This study was not powered to detect statistical differences in AEs. In addition, the current study population was younger (mean age is about 30 years). This population may be less susceptible to UGI side effects of traditional NSAIDs, although the rate of dyspepsia may be relatively age-independent.

In this trial, a majority of the patients experienced sports-related ankle injuries (54%). These patients appeared to have a similar response to treatment than those suffering from no sports-related injuries. Patients who are active in sports may benefit from a more comprehensive rehabilitation approach to help restore both time to activity and level of activity. The mean age of the study population was about 30 years. This age group may not be representative of ankle sprains seen in other clinical settings.

Results from this study suggest that treatments used are consistent with published guidelines. For instance, most patients were prescribed RICE. However, exercise for strengthening or proprioception was low. IMS data suggest that the use of anti-inflammatory therapy with either NSAIDs or COX-2–specific inhibitors is not as widespread as suggested by published guidelines. Physicians treating patients with ankle sprain should consider published guidelines and rehabilitation and appropriate anti-inflammatory therapy.

The present study confirms previous studies on the potential benefit of anti-inflammatory therapy in patients with acute ankle sprain. COX-2–specific inhibitors appear to be as effective as NSAIDs as anti-inflammatory therapy for this condition. COX-2–specific inhibitors provide safety advantages that should be considered when prescribing anti-inflammatory therapy for patients with acute ankle sprain.

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