

Efficacy and Safety of Celecoxib in the Treatment of Acute Pain due to Ankle Sprain in a Latin American and Middle Eastern Population

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Ankle sprains are common acute soft-tissue injuries. This 7-day open-label, multicentre, randomized study compared the efficacy and safety of celecoxib with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in treating acute ankle sprain with moderate-to-severe ankle pain in 278 patients. Patients received either celecoxib (400 mg loading dose followed by 200 mg twice daily) or standard doses of non-selective NSAIDs. The primary endpoint was a change in the patient's assessment of ankle pain on a 0 mm (no pain) – 100 mm (worst

possible pain) visual analogue scale (VAS) at day 3 compared with baseline. From a baseline of 73 mm, mean VAS pain scores decreased to 29 and 32 mm in the celecoxib and non-selective NSAID groups, respectively. The lower limit of the 95% confidence interval for the treatment difference with regard to change from baseline was greater than the pre-established non-inferiority margin of –10 mm. Using an initial loading dose, celecoxib was at least as efficacious as non-selective NSAIDs in treating acute pain due to ankle sprain.

KEY WORDS: CELECOXIB; NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs); NON-SELECTIVE NSAIDs; CYCLO-OXYGENASE-2 (COX-2) SELECTIVE NSAIDs; LOADING DOSE; ANKLE SPRAIN; ANKLE PAIN

Introduction

Ankle sprains are among the most common acute soft-tissue injuries sustained in everyday life and are particularly prevalent in individuals participating in sporting activities. Estimates for the USA indicate that ankle sprains occur at a rate of approximately one sprain per 10 000 people per day.¹ Management of acute ankle

sprains typically involves the 'rest, ice, elastic compression and limb elevation' (RICE) protocol, use of analgesic and anti-inflammatory drugs, and functional rehabilitation.²

Clinical trials have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) can ameliorate symptoms, reduce inflammation and hasten a return to full

function in sports-related injuries.³ Consequently, non-selective NSAIDs, such as diclofenac,^{4 - 7} piroxicam,^{8,9} naproxen,^{8,10} nimesulide¹¹ and ibuprofen,^{12,13} have become a common adjuvant therapy for acute ankle sprain.

The NSAIDs reduce pain and inflammation by inhibiting cyclo-oxygenase (COX),¹⁴ which exists in two distinct isoforms. The COX-1 isoform is present in many tissues and is necessary for physiological (homeostatic) functions, such as gastric mucosal protection and normal platelet aggregation.^{15 - 17} The COX-2 isoform is an inducible isoform mainly expressed locally in inflamed tissues.^{18,19} Non-selective NSAIDs inhibit both COX-1 and COX-2 while selective COX-2 inhibitors only inhibit COX-2.^{20,21} The analgesic efficacy of the COX-2 selective NSAID, celecoxib, in the treatment of acute ankle sprain has been demonstrated in previous clinical trials,^{15,22 - 24} but with efficacy endpoints only evaluated from 4 days after the onset of treatment. For acute pain, an initial celecoxib loading dose of 400 mg is recommended followed by subsequent doses of 200 mg twice daily. To date, this regimen has been used in only one ankle sprain study.¹⁵

No trials have studied the use of celecoxib in patients from the Middle East with acute ankle sprain. A study in patients of Latin American descent previously demonstrated that celecoxib was as effective as diclofenac in treating ankle sprain; however, no initial loading dose was used.²⁴

The COX-2 selective NSAIDs, including celecoxib, may offer advantages over non-selective NSAIDs in the treatment of acute ankle sprain because they have a more favourable gastrointestinal (GI) safety profile.^{15,16,22,25} Non-selective NSAIDs have been associated with upper GI mucosal injury (e.g. ulceration, perforation and

haemorrhage).^{25 - 28} They also significantly inhibit platelet aggregation,²⁹ which may be of concern in acute musculoskeletal injuries in which bleeding secondary to trauma is common. Platelet aggregation is involved in wound healing and plays an important role in disrupting the ecchymosis that often occurs with second-degree sprains.¹⁵

The trial reported in this paper was designed to evaluate the efficacy and safety of celecoxib compared with the non-selective NSAIDs that are used in recommended, real-life standard practice in the treatment of acute ankle sprain in Latin America and the Middle East. Compared with previous trials,^{22,23} the present study evaluated analgesic efficacy at earlier time points and assessed functional improvement following an initial loading dose. The primary objective was to assess the efficacy of a celecoxib 400 mg loading dose followed by 200 mg twice daily versus standard doses of oral non-selective NSAIDs in acute pain due to ankle sprain. The secondary objective was to evaluate the safety of celecoxib versus non-selective NSAIDs in the treatment of acute ankle sprain.

Patients and methods

STUDY POPULATION

Adults (aged > 18 years) presenting with pain due to first- or second-degree ankle sprain (involving the anterior talofibular ligament and/or the calcaneofibular ligament) \leq 48 h before the first dose of study medication and with a patient-assessed ankle pain measurement \geq 45 mm on a 0 - 100 mm visual analogue scale (VAS; 0 mm, no pain; 100 mm, worst possible pain) on full weight bearing, were eligible to participate in the trial. All patients provided written informed consent before entering the trial.

All women of childbearing age had to be using adequate contraception, not be breast

feeding and were required to have a negative urine or blood pregnancy test. Patients were also excluded if any of the following criteria applied: a similar injury of the same joint within the previous 6 months; osteoarthritis; a history of clinically significant renal, hepatic, cardiovascular or cerebrovascular disease; active GI disease; a history of oesophageal, gastric or duodenal ulcer; clinically significant coagulopathy or current treatment with an anticoagulant; treatment with an intra-articular injection of a corticosteroid or hyaluronic acid in any joint within 8 weeks of the first dose of study medication; treatment with any oral or intramuscular corticosteroid, non-selective NSAID or COX-2 selective inhibitor within 14 days of the first dose of study medication (except aspirin \leq 325 mg/day for cardiovascular prophylaxis); and use of an analgesic or other agent that could potentially confound the assessment of analgesia (e.g. antidepressants, sedatives, muscle relaxants, narcotics or corticosteroids) within 4 h of the first dose of study medication.

Paracetamol up to a dose of 2 g/day could be taken as add-on analgesia during the trial. No other analgesic medications, including opioids and tramadol, were permitted (except low-dose aspirin for cardiovascular prophylaxis). Other medications prohibited during the trial included anticoagulants, muscle relaxants, neuroleptics, tricyclic antidepressants, sedative hypnotics, anxiolytics, lithium and digoxin. Non-pharmacological treatments were permitted if considered to be standard care by the investigator.

STUDY DESIGN AND ASSESSMENTS

This was an open-label, multicentre, randomized, comparative study conducted at 24 centres (emergency departments at

orthopaedic hospitals and general hospitals, and doctors' surgeries) in Brazil, Costa Rica, Ecuador, Egypt, Jordan, Mexico, Panama and Peru between May 2007 and April 2008. The institutional review board and/or independent ethics committee at each centre approved the protocol. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines and local regulatory requirements.

The trial consisted of three clinic visits and one telephone assessment during a 7-day treatment period. The first visit (day 1) included screening and baseline evaluations, randomization to treatment and administration of the first dose of study medication. The telephone assessment on day 2 was conducted 24 – 30 h after the first dose of study medication. The second visit was on day 3, and the final visit was on day 7 (\pm 2 days) or at the time of early termination. Assessments conducted on day 1 included medical history, prior and concomitant medications, physical examination, vital signs, weight, pregnancy test for women and baseline assessments of pain, function and injury (patients' VAS assessments of ankle pain on weight bearing and normal function/activity, patients' global assessments [PGA] and physicians' global assessments [PhyGA] of ankle injury).³⁰

After screening and baseline assessments were completed on day 1, patients were randomized to a treatment group according to a computer-generated randomization schedule in the order in which they were enrolled in the trial. Patients randomized to celecoxib received two capsules (200 mg/capsule) as a loading dose at the day 1 visit. Subsequent doses of 200 mg twice daily were administered at home or elsewhere from day 2 to day 7. Patients

randomized to non-selective NSAIDs received daily doses according to standard treatment practice for up to 7 days.

Patients' VAS assessments of ankle pain on weight bearing, normal function/activity, ankle injury and pain relief were recorded on days 2, 3 and 7, and the PhyGA of ankle injury was recorded on days 3 and 7. In addition, the self-administered modified Brief Pain Inventory-Short Form (mBPI-sf) questionnaire was used to assess pain severity and pain interference with functional activities on days 2, 3 and 7.^{31,32} Patients' assessments of ankle pain VAS on weight bearing were measured on a 100-mm scale ranging from 0 mm (no pain) to 100 mm (worst possible pain). Patients' assessments of normal function/activity were measured on a 5-point scale ranging from 1 (normal walking/activity without pain) to 5 (severely restricted walking due to pain and inability to resume normal activities). The PGA of ankle injury was measured on a 5-point scale ranging from 1 (very good; no symptoms and no limitation of normal activities) to 5 (very poor; very severe, intolerable symptoms and inability to carry out all normal activities). Patients' assessments of pain relief, with reference to the baseline level of pain, were measured on a 5-point scale ranging from 0 (none) to 4 (complete). The PhyGA of ankle injury graded injury severity on a 5-point scale ranging from 1 (very mild; very mild signs and symptoms of ankle sprain) to 5 (very severe; very severe signs and symptoms of ankle sprain).

Safety assessments included monitoring for adverse events and any clinically significant changes from baseline to final visit in vital signs, weight and findings at physical examination.

STUDY ENDPOINTS

The primary endpoint was the change in the

patient's assessment of ankle pain VAS from baseline to day 3. Secondary efficacy endpoints were: change from baseline in the patient's VAS assessment of ankle pain at day 2 (24 – 30 h) and day 7; responder rates (the proportion of patients improving by ≥ 20 mm on the ankle pain VAS) at days 2, 3 and 7; PGA of ankle injury at days 2, 3 and 7; PhyGA of ankle injury at days 3 and 7; pain relief at days 2, 3 and 7; and the patient's assessment of normal function/activity scores at days 2, 3 and 7. The secondary health outcomes endpoint was mBPI-sf scores at days 2, 3 and 7. Secondary safety endpoints were incidences of adverse events and premature discontinuations from the trial, and any clinically significant changes in vital signs, weight and findings at physical examination.

STATISTICAL ANALYSIS

The trial was intended to show non-inferiority of celecoxib versus non-selective NSAIDs. The sample size was based on the expected change from baseline in ankle pain VAS at day 3. The maximum clinically acceptable difference for declaring non-inferiority was -10 mm. Assuming a SD of ± 25 mm and a type I error rate of 0.050, the trial was designed to have 80% power to reject the null hypothesis in favour of the alternative hypothesis of non-inferiority. Based on a differential of 10% between the modified intent-to-treat (mITT) and the per-protocol (PP) populations, a total of 111 subjects were planned to be randomized per treatment group.

The safety population included all randomized patients who received at least one dose of study medication. The mITT population included all randomized patients receiving at least one dose of study medication who had at least one follow-up pain VAS measurement. The PP population

included all patients without major protocol violations up to and including day 3 (including the use of prohibited concomitant medications), who took a full loading dose on day 1, had acceptable drug compliance up to and including day 3 and had valid ankle pain VAS measurements at baseline and day 3.

The primary efficacy endpoint was analysed using an analysis of covariance (ANCOVA) model with effects for treatment, country and the baseline ankle pain VAS score. To conclude non-inferiority, the lower limit of the two-sided 95% confidence interval (CI) of the difference in change scores between the two treatment groups (non-selective NSAIDs minus celecoxib) had to be greater than -10 mm. Consistent with ICH guidelines for testing non-inferiority, the primary efficacy analysis was conducted on the PP population.

Changes from baseline in the ankle pain VAS score at days 2 and 7 were analysed in the same manner as the primary endpoint, but were analysed for the mITT and PP populations. Other secondary efficacy endpoints were analysed for the mITT population only. Categorical responses (PGA and PhyGA of ankle injury, and patient's assessments of normal function/activity and pain relief) were analysed using the Cochran–Mantel–Haenszel test, controlling for country and responder rates using a logistic regression model with effects for treatment and baseline ankle pain VAS.

Modified BPI-sf scores (individual item, pain severity composite and pain interference composite scores) were analysed for the mITT population only using ANCOVA with effects for treatment and country. Safety data are presented descriptively.

For all secondary analyses, a *P*-value of < 0.05 was considered to be statistically significant.

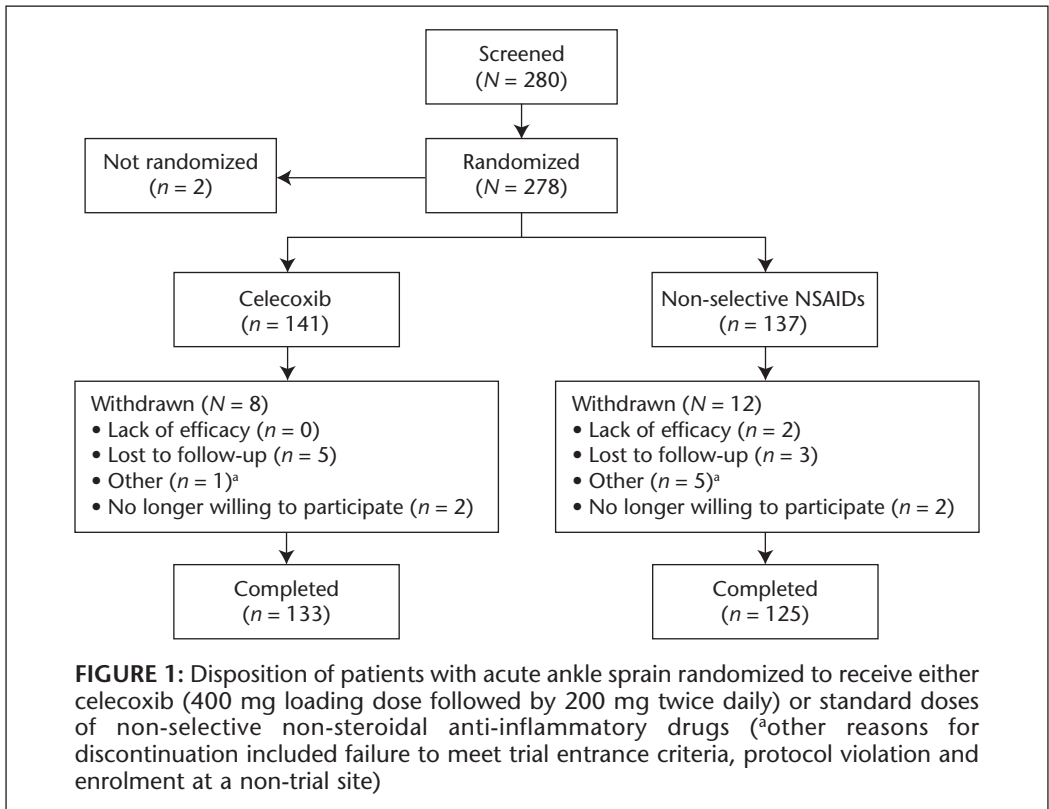
Results

PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

A total of 280 patients were screened and 278 patients were randomized to celecoxib (141 patients) or a non-selective NSAID (137 patients) (Fig. 1). Non-selective NSAIDs taken were diclofenac (55/137), nimesulide (21/137), ibuprofen (17/137), meloxicam (17/137), piroxicam (9/137), ketoprofen (8/137), naproxen (5/137), cholestyramine/diclofenac (3/137) and tiaprofenic acid (2/137) (Table 1). Twenty patients discontinued treatment; eight patients

TABLE 1:
The distribution of patients with regard to the type and total daily dose of non-selective non-steroidal anti-inflammatory drugs taken ($n = 137$)

| Drug/Total daily dose (mg) | No. (%) of patients |
|----------------------------|---------------------|
| Diclofenac | |
| 100 | 36 (26.3) |
| 150 | 10 (7.3) |
| 200 | 9 (6.6) |
| Nimesulide | |
| 200 | 21 (15.3) |
| Ibuprofen | |
| 800 | 2 (1.5) |
| 1200 | 14 (10.2) |
| 1600 | 1 (0.7) |
| Meloxicam | |
| 15 | 17 (12.4) |
| Piroxicam | |
| 20 | 2 (1.5) |
| 40 | 7 (5.1) |
| Ketoprofen | |
| 100 | 1 (0.7) |
| 200 | 7 (5.1) |
| Naproxen | |
| 1100 | 5 (3.6) |
| Cholestyramine diclofenac | |
| 150 | 3 (2.2) |
| Tiaprofenic acid | |
| 600 | 2 (1.5) |
| Total | 137 (100.0) |



discontinued treatment with celecoxib (5.7%) and 12 patients with non-selective NSAIDs (8.8%); of these, two patients (1.5%) in the non-selective NSAIDs group discontinued treatment due to a lack of efficacy (Fig. 1). Other reasons for discontinuation included loss to follow-up, failure to meet the trial's entrance criteria, protocol violation, unwillingness to continue participation and enrolment at a non-trial site.

All 278 patients were included in the safety analyses. The mITT population comprised 268 patients (celecoxib, 135 patients; non-selective NSAIDs, 133 patients), and the PP population comprised 257 patients (celecoxib, 131 patients; non-selective NSAIDs, 126 patients).

The patients' ages ranged from 18 to 74 years, with a mean of approximately 30 years in each treatment group (Table 2). Gender distribution was the same in each

group (60% males). Rescue medication was taken by eight (6%) patients in each treatment group. Non-pharmacological treatments were prescribed at similar frequencies in the two groups (celecoxib, 103 [73.0%] patients; non-selective NSAIDs, 97 [70.8%] patients). The median duration of treatment in both groups was 7 days. The range of treatment duration was 1 – 9 days and 2 – 9 days in the celecoxib and non-selective NSAIDs groups, respectively.

EFFICACY ENDPOINTS

Mean scores for the patients' VAS assessments of ankle pain on full weight bearing decreased from approximately 73 mm at baseline in both groups to 29 mm in the celecoxib group and 32 mm in the non-selective NSAID group at day 3 in the PP analysis (Fig. 2). The least squares (LS) mean

TABLE 2:

Demographics and injury characteristics at baseline of all patients ($n = 278$) with acute ankle sprain randomized to receive either celecoxib (400 mg loading dose followed by 200 mg twice daily) or standard doses of non-selective non-steroidal anti-inflammatory drugs (NSAIDs)

| Demographic/Injury | Celecoxib 200 mg twice daily ($n = 141$) | Non-selective NSAIDs ($n = 137$) |
|--|--|---------------------------------------|
| Age (years) | | |
| Mean \pm SD | 30.6 \pm 10.1 | 30.4 \pm 12.1 |
| Range | 18 – 66 | 18 – 74 |
| Gender, n (%) | | |
| Male | 85 (60) | 82 (60) |
| Female | 56 (40) | 55 (40) |
| Race, n (%) | | |
| White | 79 (56) | 74 (54) |
| Black | 4 (3) | 4 (3) |
| Other | 58 (41) | 59 (43) |
| Severity of ankle pain (VAS), n (%) ^a | | |
| Severe (> 60 mm) | 109 (77) | 104 (76) |
| Moderate (45 – 60 mm) | 31 (22) | 31 (23) |
| Low (< 45 mm) | 1 (1) | 1 (1) |

^aData for one subject missing.

VAS, visual analogue scale (0 mm, no pain; 100 mm, worst possible pain).

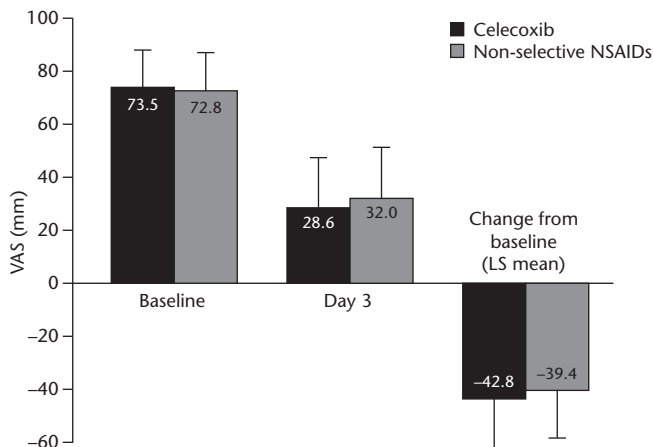


FIGURE 2: Primary efficacy endpoint: change from baseline in ankle pain visual analogue scale (VAS) score at day 3 in patients with acute ankle sprain randomized to receive either celecoxib (400 mg loading dose followed by 200 mg twice daily) or standard doses of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (per protocol population – all randomized patients without major protocol violations up to and including day 3 [including use of prohibited concomitant medications] who took a full loading dose on day 1, had acceptable drug compliance up to and including day 3, and had valid pain VAS measurements at baseline and day 3; LS mean, least squares mean)

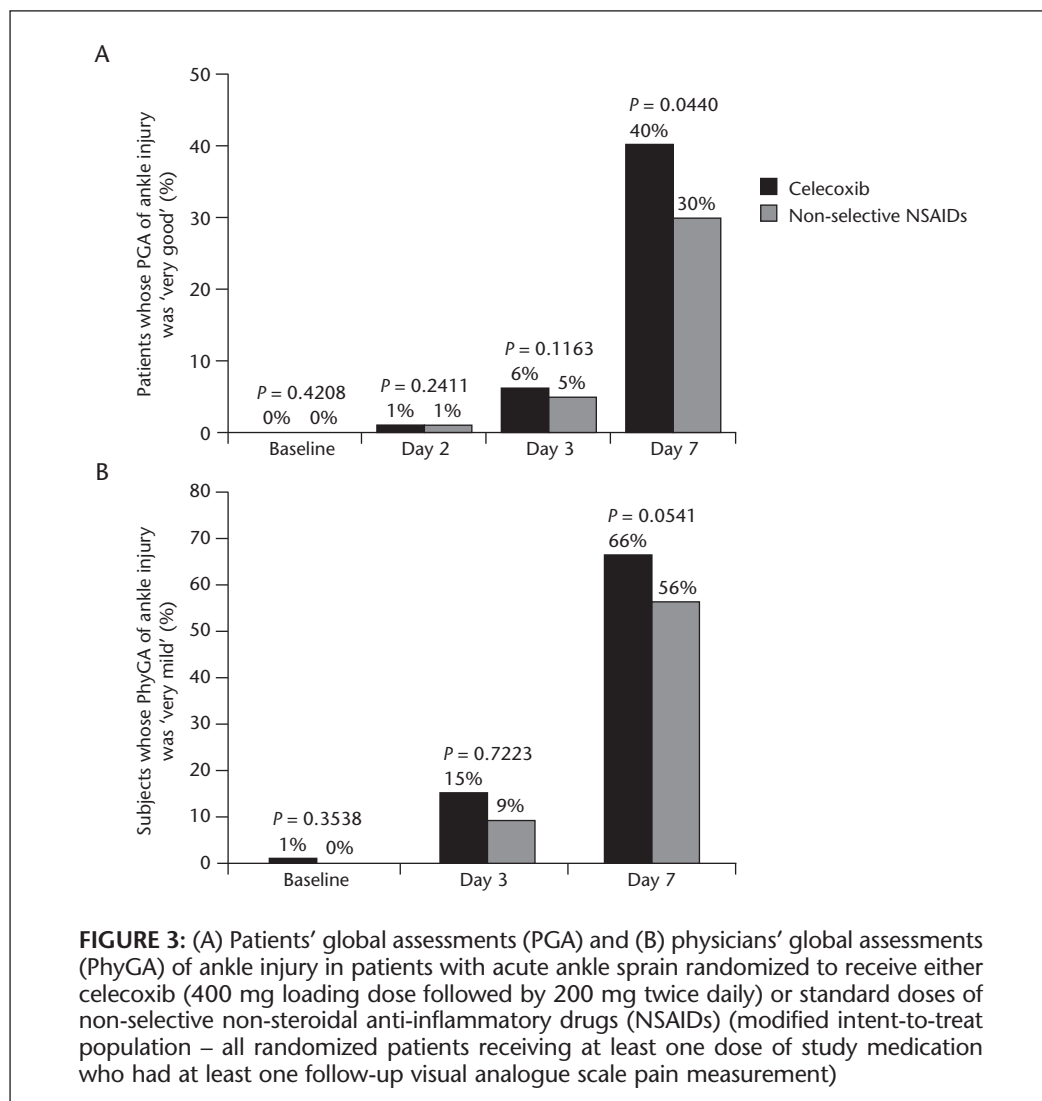
Celecoxib for pain due to ankle sprain

difference between the two treatment groups in the change from baseline in ankle pain VAS at day 3 was 3.39 mm (95% CI -0.76, 7.55), supporting the non-inferiority of celecoxib versus non-selective NSAIDs. Similar results were also obtained for the mITT population at day 3 (LS mean difference 3.46; 95% CI -0.55, 7.48).

In the celecoxib group, the percentages of patients responding with an improvement of ≥ 20 mm in ankle pain VAS at days 2, 3 and

7 were 67.9%, 91.9% and 97.0%, respectively. Corresponding responder rates for the non-selective NSAIDs group were 59.4%, 88.5% and 96.0%, respectively. The differences between the groups were not statistically significant.

On day 7, a significantly greater proportion of patients in the celecoxib group had an ankle injury PGA of 'very good' compared with the non-selective NSAIDs group ($P = 0.0440$) (Fig. 3). At baseline, day 2 and



day 3, the assessment was similar for both treatment groups. On day 7, 66% of patients in the celecoxib group had a PhyGA of ankle injury of 'very mild' compared with 56% in the non-selective NSAIDs group (Fig. 3). This inter-group difference bordered on statistical significance ($P = 0.0541$). There were clearly no statistically significant differences for the assessments at baseline or day 3.

The level of pain relief improved consistently in both treatment groups during the trial (Fig. 4). No statistically significant inter-group differences were observed at days 2 and 7. At day 3, 'a lot' or 'complete' pain relief was reported by a significantly greater proportion of patients in the celecoxib group compared with the non-selective NSAIDs group ($P = 0.0157$). Patient's assessment of normal function/activity also improved consistently in both treatment groups during the trial (Fig. 5), although there was no statistically significant inter-group difference at any time point.

HEALTH OUTCOMES ENDPOINT – mBPI-sf SCORES

In general, results for the individual item and composite scores for pain severity were similar for the two treatment groups, with the following exceptions. On day 3, patients in the celecoxib group reported significantly less pain than patients in the non-selective NSAIDs group (LS means: celecoxib 2.92; non-selective NSAIDs 3.34; $P = 0.027$). The item describing the level of worst pain was the only individual item that showed a statistically significant difference at day 3 (LS means: celecoxib 3.80; non-selective NSAIDs 4.46; $P = 0.004$). On day 2, the item describing the level of pain 'right now' was significantly improved in the celecoxib group compared with the non-selective NSAIDs group (LS means: celecoxib 3.74; non-selective NSAIDs 4.35; $P = 0.017$).

No significant inter-group differences were observed in the pain interference index or individual item scores (general activity,

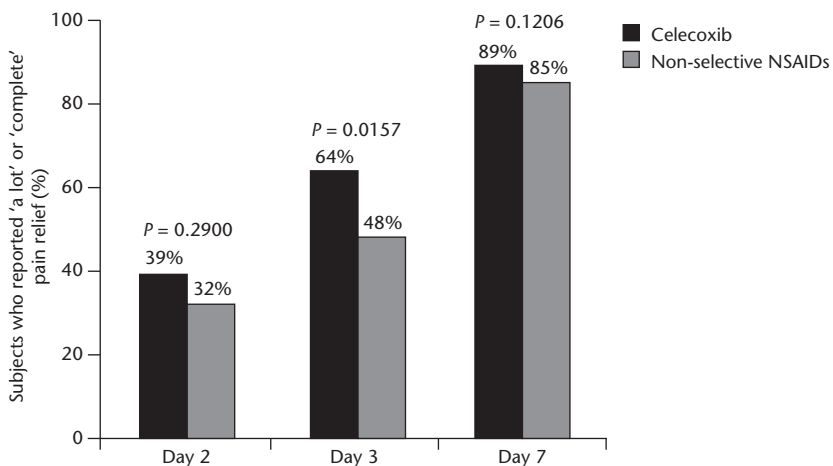


FIGURE 4: Patient-reported pain relief in patients with acute ankle sprain randomized to receive either celecoxib (400 mg loading dose followed by 200 mg twice daily) or standard doses of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (modified intent-to-treat population – all randomized patients receiving at least one dose of study medication who had at least one follow-up visual analogue scale pain measurement)

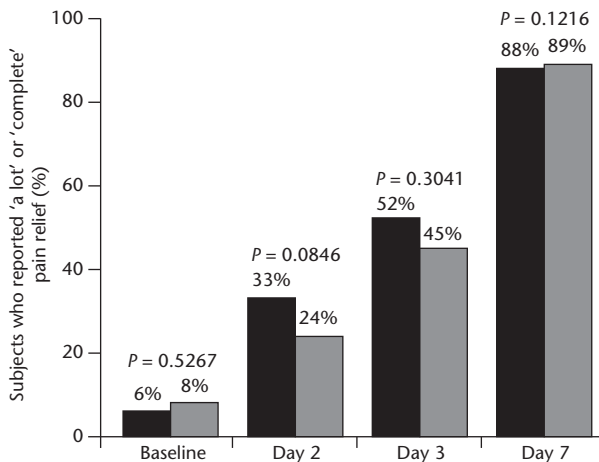


FIGURE 5: Patients' assessments of normal function/activity in patients with acute ankle sprain randomized to receive either celecoxib (400 mg loading dose followed by 200 mg twice daily) or standard doses of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (modified intent-to-treat population – all randomized patients receiving at least one dose of study medication who had at least one follow-up visual analogue scale pain measurement)

mood, walking ability, normal work, relations, sleep, and enjoyment of life) on days 2, 3 and 7.

SAFETY

Two serious adverse events (dengue fever and tendon rupture) were reported during the study; both occurred in the non-selective NSAIDs group but neither was considered treatment related. Treatment-related adverse events were reported for almost twice as many patients in the non-selective NSAID group (19/137 [13.9%]) compared with the celecoxib group (10/141 [7.1%]). The most common treatment-related adverse event in the celecoxib group was somnolence, and in the non-selective NSAIDs group was gastritis (Table 3). Treatment-related GI disorders were reported for four patients (2.8%) in the celecoxib group and 16 patients (11.7%) in the non-selective NSAID group. Two patients in the celecoxib group reported gastritis but neither was considered to be related to

treatment. Three subjects in the non-selective NSAID group had their dose reduced or were temporarily discontinued due to treatment-related GI adverse events (gastritis or dyspepsia). One patient in the celecoxib group with gastroenteritis unrelated to treatment had treatment temporarily discontinued.

Discussion

The results of the present study showed that celecoxib (400 mg loading dose followed by 200 mg twice daily for 7 days) was as efficacious as non-selective NSAIDs in treating acute pain due to ankle sprain from as early as 24 h after the start of treatment. Using standard efficacy measures, patients in both treatment groups demonstrated a clinically significant reduction in pain from baseline and a rapid return to normal function. More than 70% of patients in both groups received concurrent non-pharmacological therapies. While celecoxib

TABLE 3:

Incidence of adverse events (all-cause and treatment-related) seen in two or more patients randomized to receive either celecoxib (400 mg loading dose followed by 200 mg twice daily) or standard doses of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (safety population – all randomized patients who received at least one dose of study medication)

| Adverse event | All-cause, <i>n</i> (%) | | Treatment-related, <i>n</i> (%) | |
|---------------------------|--------------------------------|--|---------------------------------|--|
| | Celecoxib (<i>n</i> = 141) | Non-selective NSAIDs (<i>n</i> = 137) | Celecoxib (<i>n</i> = 141) | Non-selective NSAIDs (<i>n</i> = 137) |
| Any adverse event | 19 (13.5) | 24 (17.5) | 10 (7.1) | 19 (13.9) |
| Any serious adverse | 0 | 2 (1.5) | 0 | 0 |
| Any GI event ^a | 7 (5.0) | 17 (12.4) | 4 (2.8) | 16 (11.7) |
| Gastritis | 2 (1.4) | 5 (3.6) | 0 | 5 (3.6) |
| Hyperchlorhydria | 1 (0.7) | 3 (2.2) | 0 | 3 (2.2) |
| Dyspepsia | 1 (0.7) | 2 (1.5) | 1 (0.7) | 2 (1.5) |
| Nausea | 1 (0.7) | 2 (1.5) | 1 (0.7) | 2 (1.5) |
| Diarrhoea | 1 (0.7) | 2 (1.5) | 1 (0.7) | 1 (0.7) |
| Upper abdominal pain | 0 | 2 (1.5) | 0 | 2 (1.5) |
| Abdominal distension | 0 | 1 (0.7) | 0 | 1 (0.7) |
| Dry mouth | 0 | 1 (0.7) | 0 | 1 (0.7) |
| Constipation | 1 (0.7) | 0 | 0 | 0 |
| Vomiting | 1 (0.7) | 0 | 1 (0.7) | 0 |
| Somnolence | 5 (3.5) | 2 (1.5) | 5 (3.5) | 2 (1.5) |
| Headache | 3 (2.1) | 0 | 1 (0.7) | 0 |
| Nasopharyngitis | 2 (1.4) | 1 (0.7) | 0 | 0 |
| Rash | 1 (0.7) | 1 (0.7) | 0 | 1 (0.7) |

^aOne patient could have experienced more than one adverse event; therefore, the total number of adverse events may not coincide with the total number of patients.

and non-selective NSAIDs provided similar outcomes on all other endpoints, the PGA of ankle injury scores was significantly better for the celecoxib group than the non-selective NSAIDs group at the final visit, suggesting sustained improvement with celecoxib.

The present study supports the findings from previous studies in patients with ankle sprain where celecoxib has been shown to have similar efficacy to other non-selective NSAIDs. For example, in a trial comparing celecoxib 400 mg/day and naproxen 1000 mg/day, celecoxib was as efficacious as naproxen when assessed using the patient's VAS assessment of ankle pain and the PGA of ankle injury.²³ In another trial, celecoxib 400

mg/day had similar efficacy to ibuprofen 2400 mg/day when evaluated in terms of the patient's VAS assessment of ankle pain and the time to return to normal function.²² Similar findings were observed in a trial comparing celecoxib 400 mg/day and diclofenac sustained release 150 mg/day.¹⁵

A loading dose of 400 mg celecoxib was given in the present study followed by 200 mg twice daily. This follows the licensed regimen for acute pain in many countries, including the USA, of 400 mg initially followed by an additional 200 mg dose on the first day (as needed) and 200 mg twice daily on subsequent days.³³ At the time of publication, however, this loading dose regimen has only been used in one other

ankle sprain study.¹⁵ The loading dose is important to ensure a high enough concentration of celecoxib is reached quickly to treat the acute pain, which can then be maintained by taking further lower doses daily.

The safety data also suggest that celecoxib may be a better tolerated alternative to non-selective NSAIDs. Consistent with other trials in ankle sprain, the incidence of treatment-related GI adverse events was lower in the celecoxib group than the non-selective NSAID group.^{15,22,23} Dose reduction or temporary discontinuation as a result of treatment-related GI adverse events occurred in three patients in the non-selective NSAID group. The potential GI advantage of celecoxib over non-selective NSAIDs used short term for treatment of acute pain in the present study is consistent with longer studies in chronic pain where celecoxib has demonstrated improved GI tolerability versus non-selective NSAIDs and where the non-selective NSAIDs have been associated with upper GI mucosal injury (e.g. ulceration, perforation and haemorrhage).^{25,34,35}

Non-selective NSAIDs have also been associated with an increased risk of bleeding due to a reduction in platelet aggregation^{36–38} even after a single dose,²⁹ and a number of studies have shown reduced platelet aggregation and prolonged bleeding time in healthy patients with non-surgical injuries treated with these agents.^{39,40} Platelet aggregation is involved in wound healing and is essential for interruption of the ecchymosis that often occurs with second-degree ankle sprains.¹⁵ Celecoxib, which has COX-1-sparing properties, may offer an advantage over non-selective NSAIDs in the treatment of acute ankle sprain, as it does not significantly affect platelet function.²⁹ With its platelet-sparing properties and improved GI tolerability profile, celecoxib

may offer advantages over conventional non-selective NSAIDs in the treatment of acute ankle sprain.

In general, ankle sprains will heal within 1 – 2 weeks without pharmacological treatment.^{15,41,42} Inflammation associated with the injury may, however, result in tissue damage and delayed return to normal function;^{15,42} if the patient does not receive adequate rehabilitation this can lead to prolonged symptoms, decreased sporting performance and increased risk of recurrence.⁴³ Long-term ankle sprain studies show that pain and dysfunction can persist for > 6 months in a significant number of athletes (40%).^{44,45} The return to normal function after acute injury such as ankle sprain is particularly important for these patients, as well as those involved in physically demanding employment or taking part in Muslim prayer activities, where a maximum ankle flexion of 45° is required.⁴⁶

In accordance with current treatment recommendations,^{47–50} patients requiring non-selective NSAIDs, who are at an increased GI risk, should be co-prescribed a gastroprotective agent such as a proton pump inhibitor (PPI). Along with dizziness and tachycardia, PPIs are also known to cause minor GI disturbances.^{51,52} Because athletes and, in particular, endurance athletes such as long-distance runners, have reported abnormal GI effects such as nausea, diarrhoea, vomiting and even bleeding⁵³ during 'normal' training, the use of PPIs may not be an appropriate treatment option. Celecoxib, which can be used without co-prescription of a PPI may, therefore, be more suitable in these patients.

Overall, the findings of the present study support the use of celecoxib for the treatment of acute pain caused by ankle sprain and are a further addition to the body of evidence regarding its use in the management of

acute pain conditions such as post-operative dental pain,^{54,55} acute shoulder pain,^{56,57} osteoarthritis flare,⁵⁸ acute low-back pain⁵⁹ and post-operative pain.⁶⁰ In conclusion, celecoxib is at least as effective as standard non-selective NSAIDs treatment for acute ankle sprain pain.

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Conflicts of interest

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