

# The efficacy of paracetamol in the treatment of ankle sprains in comparison with diclofenac sodium

Cemil Kayali, MD, Haluk Agus, MD, Levent Surer, MD, Ali Turgut, MD.

## ABSTRACT

**Objectives:** To assess the efficacy of paracetamol in comparison with diclofenac sodium.

**Methods:** Between February - November 2006, a prospective, double blinded, parallel group study of 100 patients suffering from first or second degree lateral ankle sprain within 48-hours of admission in Tepecik Education and Research Hospital, Izmir, Turkey. Patients with bilateral injury, ipsilateral knee injury, third degree sprain, previous sprain within 6 months, and ankle pain less than 45 according to visual analogue score (VAS) were excluded. Patients rated pain on a 100 VAS, representing 0 no pain, 100 maximal pain. After enrollment, patients were randomized (1:1) with diclofenac sodium 150 mg/day or paracetamol 1500 mg/day for 5 days. Clinical assessments were carried out at baseline; on second, tenth days, and sixth week (end of study). In each visit, VAS and adverse effects of medication were questioned.

**Results:** The mean VAS of the diclofenac group was 81 and 82.3 with paracetamol group at the first visit. These scores decreased to 20.7, 9.9, 4.6 in diclofenac group and 11.9, 6.3, 3 in paracetamol group at the second, tenth days and last examination. Similar reductions in pain were observed at the end of study ( $p>0.05$ ) in both groups. However, cases treated by paracetamol group showed accelerated decrease in VAS at day 2 and 10 in comparison with diclofenac group ( $p<0.05$ ). Of the ankle range of motion, there was a similar improvement in both groups ( $39.6^\circ$ ,  $37.5^\circ$ ) ( $p>0.05$ ). The incidence of gastrointestinal adverse effects on diclofenac group was much more than the paracetamol group, however, there was no significant difference ( $p>0.05$ ).

**Conclusion:** It was concluded that diclofenac sodium and paracetamol are effective and well tolerated as a short term treatment alternatives for acute ankle injuries.

*Saudi Med J 2007; Vol. 28 (12): 1836-1839*

*From Tepecik Education and Research Hospital, Second Clinic of Orthopedics and Traumatology, Karsiyaka, Izmir, Turkey.*

*Received 21st March 2007. Accepted 17th June 2007.*

*Address correspondence and reprint request to: Dr. Cemil Kayali, Orthopedic Surgeon, 6445 sokak No: 10/4, 35550 Karsiyaka, Izmir, Turkey. Tel. +90 (232) 469 6969 Ext. 1226. Fax. +90 (232) 433 0756. E-mail: cemilkayali@yahoo.com*

Ankle sprains are reported as the most common acute injury seen in sports.<sup>1</sup> Most ankle sprains are the result of an inversion force when the ankle is in plantar flexion position. Pain, swelling, hemorrhage, tenderness, functional loss, and disability of walking are the most common symptoms seen. Inversion injuries are graded from I to III depending on the ligament injuries. Grade I sprains are mild, single ligament injuries involving the anterior talofibular ligament (ATFL) having negative anterior drawer test and talar tilt on stress x-ray. Grade II refers to complete disruption of the ATFL, and damage in calcaneofibular ligament (CFL) with positive anterior drawer sign ( $>4\text{mm}$ ), but talar tilt normal to minimally positive ( $5-15^\circ$ ). Grade III sprains are due to complete tear of some or all 3 ligaments including ATFL, CFL, and posterior talo-fibular ligament (PTFL).<sup>2-4</sup> The intervention in ankle injuries focuses on reducing the inflammation and pain. Guidelines for the treatment include rest, ice, compression, and elevation (RICE), protected weight bearing, early mobilization and rehabilitation program.<sup>2,5</sup> The rationale for non-steroid anti-inflammatory drugs (NSAID) use is pain control effect and decrease of inflammation to obtain rapid healing. However, the NSAID inhibit both cyclooxygenase (COX)-1 and COX-2, which may cause some adverse effects such as ulcers and bleeding in the gastrointestinal tract,<sup>6</sup> while paracetamol is a simple, with low adverse effect risk and economical analgesic drug. In this current study, the aim is to evaluate the effectiveness of paracetamol in comparison with diclofenac sodium in acute ankle sprains.

**Methods.** A prospective study was carried out between February and November 2006 in the out patient clinic of Tepecik Education and Research Hospital, Izmir, Turkey, including 100 patients. The study was a double blind, parallel group, randomized controlled trial with 6 weeks treatment period. Patients were randomly assigned to one of 2 treatment groups. Eligible cases were 18 years or older and had sustained first or second degree lateral ankle sprain within 48 hours of admission to the emergency room or out patient clinic. Another necessity for inclusion was reported ankle pain as moderate (45-60) to severe (>60) on full weight bearing on the patient's assessment of ankle pain using a 100 mm visual analogue score (VAS). Exclusion criteria included fractures, pregnancy, a history of gastrointestinal, renal or hepatic disorders, and systemic inflammatory disease such as arthritis. In addition, patients with bilateral ankle sprain, ipsilateral knee injury, third degree sprain, and previous ankle sprain within 6 months were excluded from the study. After consent was obtained, eligible patients underwent an assessment including full physical examination. Physicians classified the ankle injuries as grade I to grade III based on the ligaments injured.<sup>3</sup> Patients were instructed to rate pain on a 100 mm VAS, representing 0 no pain, 100 maximum pain. After enrollment to study, patients were randomized (1/1) to one of 2 treatment protocols. These protocols included diclofenac sodium 150 mg/day (in 2 doses) or paracetamol 1500 mg/day (in 3 doses) for 5 days. After which, the range of motion and stretching exercises were instructed to patients for rehabilitation program.<sup>2,5</sup> Clinical assessments were carried out on admission, day 2, 10, and on the sixth week. Patient's dependent measures were ankle pain VAS on weight bearing and the number of days required to return to recreational activities. The investigator's evaluations were physician's global assessments on day 2, 10, and 6th week (1-4 scale: 1; poor, 2; fair, 3; good, 4; very good), swelling on day 0, 2, and 10 (0-3 scale: 0; none, 1; slight, 2; moderate, 3; severe), active range of ankle motion in degrees (ROM) on day 0 and on the 6th week, and adverse effects of oral medications. Patients were allowed to apply the non pharmacological treatments including RICE and crutches.

Statistical analysis was performed using the Statistical Package for Social Sciences for windows. Student t test and Fisher's chi-square test were used,  $p < 0.05$  was accepted as significant.

**Results.** One hundred patients were enrolled in this study, 50 patients were randomized to receive diclofenac sodium and the remaining 50 to receive paracetamol. There were no significant difference in the demographic data including gender, age, height, and weight of the 2 treatment groups (gender: OR, 0.78; 95% CI, 0.35-1.72;  $p=0.68$ ), (age: mean difference [MD], 2.26; 95% CI, -0.33 to 5.45;  $p=0.082$ ), (height: MD, 2.2:

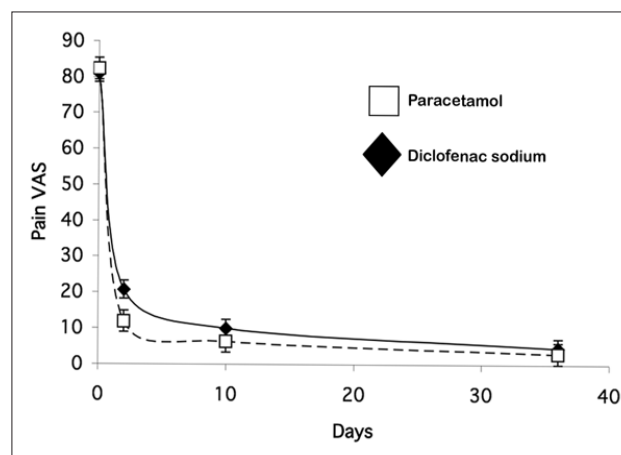
95% CI, -1.51 to 5.91;  $p=0.24$ ), (weight: MD, 4.08, 95% CI, -0.7 to 8.86;  $p=0.09$ ) (Table 1).

**Patient's dependent measures.** Ankle pain VAS changes of both groups were displayed in Figure 1. There was no significant difference in the initial and last follow up pain VAS's (VAS<sub>initial</sub>: MD, 1.3; 95% CI, -2.61 to 5.21;  $p=0.51$ ), (VAS<sub>last</sub>: MD, -1.6; 95% CI, -4.0 to 0.83;  $p=0.19$ ) between both groups. However, on days 2 and 10, the paracetamol group showed more decrease than the diclofenac sodium group (VAS<sub>day 2</sub>: MD, -8.8; 95% CI, -14.0 to -3.5;  $p=0.0013$ ), (VAS<sub>day 10</sub>: MD, -3.66; 95% CI, -6.82 to -0.49;  $p=0.02$ ). In addition, there was no significant difference according to the days required to return to recreational activities as  $9.66 \pm 1.5$  in diclofenac sodium group and  $9.84 \pm 1.6$  in paracetamol group (MD, 0.18; 95% CI, -0.46 to 0.82;  $p=0.58$ ).

**Investigator's evaluations.** The physician's global assessment of ankle injury showed significant improvement in both groups. The mean assessment of the diclofenac sodium group increased from  $1.46 \pm 0.5$  to  $3.18 \pm 0.59$  on day 10 and  $3.76 \pm 0.43$  on the 6th week. The mean assessment of the paracetamol group improved from  $1.42 \pm 0.49$  to  $3.14 \pm 0.53$  on day 10, and  $3.72 \pm 0.45$  on the 6th week. These improvements

**Table 1** - Demographic data of the patients, n=50.

Demographics	Diclofenac sodium	Paracetamol
	n (%)	
<b>Gender</b>		
Male	23 (46)	26 (52)
Female	27 (54)	24 (48)
Age (mean)	27.3±6.7	29.9±7.8
Height (cm)	168.48±9.7	170.68±9
Weight (kg)	72.3±13.4	76.4±10.47



**Figure 1** - Change in pain visual analogue (VAS) score of the study groups.

were similar and there was no significant difference ( $P_{\text{day}2}=0.69$ ,  $P_{\text{day}10}=0.72$ ,  $P_{\text{week}6}=0.65$ ). The rates of swelling of the ankles displayed improvement in both groups compared on day 0, day 2, and day 10. In diclofenac sodium group it decreased from  $2.12\pm 0.68$  on day 0 to  $1.2\pm 0.67$  on day 2, and  $0.42\pm 0.53$  on day 10. Similar decrease was observed in paracetamol group from  $2.14\pm 0.75$  on day 0 to  $1.28\pm 0.67$  on day 2, and  $0.5\pm 0.58$  on day 10. On statistical analysis, there was no significant difference ( $P_{\text{day}0}=0.89$ ,  $P_{\text{day}2}=0.55$ ,  $P_{\text{day}10}=0.47$ ).

The range of ankle motion of patients of both groups on the 6th week increased when compared with initial examination. In the diclofenac sodium group initial and last ROM were  $28.8^{\circ}\pm 9.3$  and  $68.4^{\circ}\pm 3.1$ . In the paracetamol group ROM improved from  $30.2^{\circ}\pm 8.5$  to  $67.7\pm 3.6^{\circ}$ . There was no significant difference in the initial and last follow up ankle ROM between both groups ( $P_{\text{initial}}=0.43$ ,  $P_{\text{last}}=0.30$ ).

Fifteen subjects of the diclofenac sodium group (30%) compared with 9 subjects of the paracetamol group (18%) reported at least one adverse effect. However, in the statistical analysis, we do not find significant difference (OR, 1.95; 95% CI, 0.76-5.0,  $p=0.24$ ). These adverse effects were mostly in the gastrointestinal system as dyspepsia, constipation, and diarrhea.

**Discussion.** Ankle injuries are the most common musculoskeletal injuries seen in active adults.<sup>7</sup> Treatment of uncomplicated ankle sprain should focus on early protected mobilization, RICE, NSAIDs, and rehabilitation.<sup>2,5</sup> The American Academy of Orthopedic Surgeons defined 4 treatment approaches depending on initial and follow up assessments including different rehabilitation programs and functional bracing.<sup>8</sup> Wolfe et al<sup>9</sup> recommended several steps of management of acute ankle sprains including initial management with RICE, NSAID's, and rehabilitation. It should be noted that swelling, a common feature of ankle sprain that contributes to disability, may be influenced by RICE rather than NSAID therapy.<sup>8</sup>

Paracetamol (nonopioid analgesic), administered orally, is the active metabolite of the phenacetin responsible for analgesic effect.<sup>10</sup> It is a weak prostaglandin inhibitor and has no significant anti-inflammatory effect. The peak blood concentration is usually reached in 30-60 minutes. Alone, it is not an adequate indication for inflammatory conditions such as rheumatoid arthritis but its analgesic effect is equivalent to aspirin. Paracetamol is a well tolerated drug at therapeutic doses (15-20 mg/kg, up to 4 g/day) and this excellent tolerability is a major factor in its wide usage.<sup>11</sup> Hepatotoxicity as a result of metabolism of the drug

to reactive compounds after overdosage of paracetamol is well known, and is the major problem with use of this drug. This excellent tolerability has been confirmed in the recent meta-analyses of case control studies. Lewis et al<sup>12</sup> found no significant effect of paracetamol on the gastrointestinal system at any dose. Paracetamol is also recommended for pain arising from orthopedic and non-orthopedic conditions such as migraine and postoperative conditions.<sup>13-15</sup> Sachs<sup>16</sup> pointed out that when efficiency, side effects, and cost are considered, the treatment algorithm for oral acute pain therapy should begin with paracetamol. It can be dangerous in patients whether it used in alcohol abuse, concomitant use of warfarin and liver damage though with a neutral and protective role in the cardiovascular system.<sup>17</sup>

Classical NSAID's including diclofenac sodium has been widely used for the treatment of musculoskeletal inflammatory disorders, traumatic, post operative or low back pain.<sup>18-21</sup> This anti-inflammatory effect depends on the inhibition of COX enzymes. The COX has 2 isoform as COX-1 and COX-2. It was reported that COX-1 is responsible for maintenance of such physiological functions as platelet aggregation, gastric cytoprotection, and COX-2 for the progression of inflammatory process.<sup>22</sup> Diclofenac is a NSAID characterized by short half time with potent anti-inflammatory, analgesic, and antipyretic effects. The sustained form of the diclofenac sodium yields 0.4  $\mu\text{g}/\text{ml}$  maximum concentrations reached on average 5 hours after the oral intake of 75 mg tablet. The plasma level is 13  $\text{ng}/\text{ml}$  16 hours after the ingestion of 75 mg tablet, however twice daily administration of this dose results in a mean plasma concentration of 25  $\text{ng}/\text{ml}$ .<sup>23</sup> The NSAIDs have excellent efficacy with higher incidence of adverse effects such as gastrointestinal, platelet function inhibition, and renal dysfunction. Dubois et al<sup>6</sup> recommended the use of gastro protective co therapy should be considered in patients at higher risk of NSAID-related complications.

The current study compared the efficacy of 2 drugs in the management of symptoms of acute ankle sprains. Several points were considered to be identical while designing the study. Subjects with grade III ligament injury, sustaining ankle sprain more than 48 hours, having ankle pain VAS less than 45 were excluded from the study. In addition patient's dependent and physician's dependent measurements were recorded on admission, on day 2, 10, and 6th week to get more knowledge on the efficacy of treatment. The pain VAS on the 6th week showed significant decrease in both treatment groups when compared with initial examination measurements. However, as seen in **figure 1**, the paracetamol group had accelerated pain VAS decrease on days 2 and 10. This difference may depend on the sustained release of diclofenac sodium. The number of days required to return the recreational activities were similar. On the other

hand, physician's assessments, swelling examination measures, range of ankle motion were not significantly different in all the examinations. At the 6th week, both groups reached to maximum healing stature. The use of classical NSAIDs for the treatment of acute ankle injuries may be limited for some reasons especially the high risk of serious gastrointestinal events.<sup>6,24</sup> However, the adverse effects were similar between 2 drugs though there were a greater number of gastrointestinal side effects in diclofenac sodium group.

As a result, we may conclude that paracetamol 1500 mg/day was comparable to diclofenac sodium 150 mg/day for the treatment of grade I and II ankle sprains. Although both drugs were well tolerated by the patients, future studies with larger series should be carried out to make a stronger conclusion.

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