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Effectiveness of Diclofenac, Ketorolac and Etoricoxib in the Treatment of Acute Pain from Ankle Fracture

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Abstract

Tissue degeneration, infection, inflammation, cancer, trauma, surgery and limb fractures all produce pain. Each of these physiological abnormalities requires a therapeutic approach different from the last. In acute pain, caused by fracture, several classes of analgesics have been utilized. These basic remedies for analgesia, however, are still confined to a small number of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics and opioids. In addition, most of these drugs have side effects, limiting their use in clinical practice. The purpose of this study was to compare the efficacy of three NSAIDs to relief acute pain caused by ankle fracture. Sixty subjects with ankle fracture were randomized to receive ketorolac, diclofenac, or etoricoxib, every 12 hours in a prospective, double-blind study. Forty-nine patients completed the study. The subjects' assessments of ankle pain on the visual analog scale and a Likert scale showed a significant reduction from baseline over 24 hr, regardless the treatment group. All treatments showed a similar profile in pain reduction. Etoricoxib, diclofenac and ketorolac twice daily are a rapid and effective treatment for acute pain. All the regimens were well tolerated in this study.

Introduction

Toxic effects induced by nonsteroidal anti-inflammatory drugs (NSAIDs) have been attributed to their ability to decrease prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (prostaglandin endoperoxide synthase complex), an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins, prostacyclin and thromboxane.

Two cyclooxygenase isoforms are know, cyclo-oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is the major isoform in normal tissues and produces prostanoids that are required for various maintenance functions, such as gastric cytoprotection, renal homeostasis and platelet aggregation. COX-2 is also located in certain healthy tissues, but this isoform is especially expressed in some tissues in response to an inflammatory stimulus or mitogens [1-3].

Some NSAIDs such as ibuprofen, diclofenac, ketorolac, indomethacin, naproxen and aspirin inhibit the two isoforms of the enzyme cyclooxygenase (COX-1 and COX-2) in a non-selective manner. Rofecoxib, celecoxib, etodolac, meloxicam, nimesulide, valdecoxib, etoricoxib and lumiracoxib are selective inhibitors of COX-2 [4]. The lack of specificity of nonselective NSAIDs has been proposed as a major factor in the development of ulcers and gastrointestinal bleeding. It has been shown that complications of gastro-duodenal ulcers associated with NSAIDs use have been responsible for about 107,000 hospitalizations and 16,500 deaths per year in North America [5].

Due to their anti-inflammatory and analgesic properties, NSAIDs are particularly useful in the treatment of rheumatic and other musculoskeletal disorders, such as fractures, sprains, etc. There are few studies evaluating the effectiveness and safety of different NSAIDs in patients with moderate to severe pain caused by severe soft tissue injury or bone caused by trauma. For this reason the objective of this study was to evaluate the efficacy and safety of three NSAIDs (ketorolac, etoricoxib and diclofenac) in patients with acute pain caused by fracture of ankle.

MATERIAL AND METHODS

The participants of the study were patients with closed ankle fractures ranging in age from 18 to 55 years, with acute pain ≥ 5 cm according to a 10-cm visual analog scale (VAS; 0 = no pain and 10 = worst pain), good health determined by clinical history, without sanguineous dyscrasias or hypersensitivity to drugs to be employed and that consented to participate voluntarily. This study was approved by the ethics and investigation committees and carried out according to the guidelines delineated by the Helsinki Declaration.

After consent, patients rated their pain on a VAS and were then randomized into one of three groups receiving 10 mg ketorolac (Dolac®), 60 mg etoricoxib (Arcoxia®) or 70 mg diclofenac (Flotac®) twice daily (*p.o.*). Patients were

hospitalized in the trauma service for evaluation and subsequent surgical treatment. Patient evaluations of pain intensity were recorded with VAS at 0, 2, 4, 8, 12 and 24 hr. At 24 hr after initiation of treatment, the degree of pain relief was assessed with a Likert scale, where: 0 = complete relief: no pain during treatment; 1 = slight relief, pain intermittently throughout the study, which is very tolerable; 2 = moderate relief, pain intermittently throughout the study, which causes inconvenience and discomfort to the patient, but not leaving the study; and 3 = None: no pain subsided with treatment.

The data obtained were analyzed using the statistical program Sigma Stat for Windows version 2.03. The level of statistical significance was $P < 0.05$.

RESULTS AND DISCUSSION

A total of 49 patients completed the study. Fifteen patients for the ketorolac group, 17 for the etoricoxib group and 17 for the diclofenac group. There was no statistically significant differences in the characteristics of the population studied in the 3 treatment groups, the average age was 38.9 $\pm$ 14 years of the ketorolac group, 38.1 $\pm$ 19.4 years in the etoricoxib group and 36.7 $\pm$10.1 years for the diclofenac group.

The perception of pain from skeletal muscle trauma is mediated by peripheral nociceptors; prostaglandins being some of the signaling intermediaries [6]. The immediate goals of treatment for a broken ankle are to relieve pain and inflammation and protect the structures of the ankle from further damage. For relief of acute pain for a broken ankle, the following 4 strategies can be used: administration of opioids, local anesthesia, regional nerve block or NSAIDs administration such as diclofenac or other NSAIDs to cause a decrease prostaglandinas synthesis [7]. Unfortunately, NSAIDs propensity to cause gastrointestinal damage and patient discomfort limits their use.

It is known that as many as two to four percent of patients who take NSAIDs regularly during long-term therapy may have a serious gastrointestinal side effects such as perforation, ulceration, or bleeding [8, 9]. Therefore, a possible strategy to decrease these adverse effects is to use a selective COX-2 inhibitor such as etoricoxib. In the present study, etoricoxib, ketorolac and diclofenac were able to decrease the pain 24 hr after the initiation of the treatments. The values of VAS among the three treatments were not statistically different (21.2 ± 4.3 mm for the ketorolac group, 20.1 ± 4.5 mm for etoricoxib group and 21.9 ± 5.0 mm for the diclofenac group; Fig. 1).

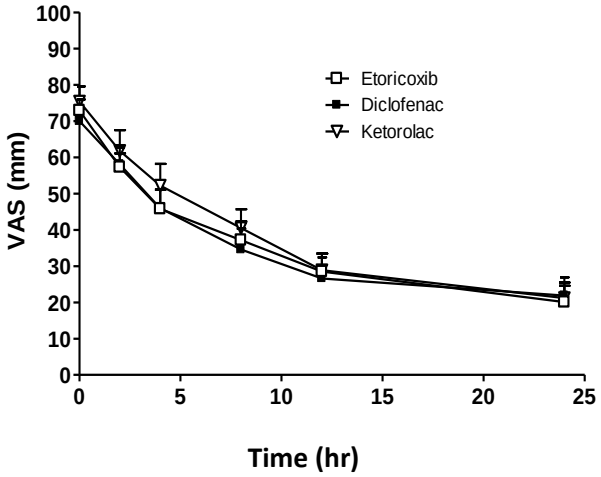

Figure 1. Effect of administration of ketorolac, etoricoxib or diclofenac in the pain of ankle fracture. The points represent the mean ±SEM of the values of visual analogue scale (VAS) assessed at different times.

The decrease in the level of pain evaluated in percentages, were a 74.5% in the ketorolac group, a 74.3% in the etoricoxib group and 70.9% for the diclofenac group (Figure 1). Likewise, regarding the assessment of the pain relief at 24 hr after starting treatment (Likert scale), we obtained a value 1.13 ± 0.8 for the ketorolac group, 1.13 $\pm$ 0.9 for etoricoxib and 1.07 ± 0.7 for diclofenac; not statistically different.

The time used in this study for the evaluation of patients was only 24 hr. During this time of monitoring, patients received only 2 doses for each of the different treatments. Therefore, in general, all treatments were well tolerated without any adverse event reporting by patients.

In conclusion, ketorolac, diclofenac or etoricoxib proved to be equi-effective in reducing the acute pain caused by fracture of ankle. Furthermore, the selective inhibitor of COX-2 etoricoxib proved to be as effective as ketorolac and diclofenac. All treatments used were shown to be safe in a 24-hr evaluation.

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