Analgesia in ankle sprain: study with etoricoxibe*

Analgesia na entorse de tornozelo: estudo com etoricoxibe

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SUMMARY

BACKGROUND AND OBJECTIVES: Ankle sprain is one of the most frequent diseases in orthopedic emergencies. In general, analgesics and anti-inflammatory drugs are prescribed. This study aimed at evaluating whether 60 mg daily etoricoxib is as effective as 90 mg daily etoricoxib to treat pain and inflammation in patients with ankle sprain grades I and II.

METHOD: This is a clinic, randomized, double-blind, prospective and controlled study which has evaluated 43 patients with ankle sprain grades I and II, with mean age of 32 years. Patients were randomly distributed in two groups: group I, made up of 23 patients treated with 90 mg daily bolus etoricoxib, and group II, made up of 20 patients under 60 mg daily bolus dose. Patients were evaluated by the visual analog scale (VAS) and by functional evaluation after 7 and 15 days of treatment.

RESULTS: There has been significant pain improvement between visits before and after using the drug, with a mean of 4.1 VAS score (p < 0.001), however pain intensity improvement did not depend on therapeutic schedule. Drug was withdrawn from one patient due to tolerability, which was considered good for 90.7% of patients.

CONCLUSION: Both 60 mg and 90 mg etoricoxib doses were effective and well tolerated to control acute pain in ankle sprain patients.

Keywords: Acute pain, Ankle, Etoricoxib, Treatment.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A torção de tornozelo é uma das doenças mais frequentes nas emergências ortopédicas. Normalmente prescrevem-se analgésicos e anti-inflamatórios. O objetivo deste estudo foi avaliar se o etoricoxibe na dose diária de 60 mg é tão efetivo quanto à dose de 90 mg no tratamento da dor e inchaço em pacientes com torções de tornozelo graus I e II.

MÉTODO: Estudo clínico aleatório, duplamente encoberto, prospectivo e controlado foram estudados 43 pacientes com diagnóstico de entorse de tornozelo graus I e II, com idade média de 32 anos. Os pacientes foram divididos em dois grupos aleatoriamente: grupo I, constituído por 23 pacientes tratados com 90 mg de etoricoxib em dose única diária, e grupo II, constituído por 20 pacientes em uso de 60 mg em dose única diária. As avaliações pela escala analógica visual (EAV) e avaliação funcional foram feitas após 7 e 15 dias de tratamento.

RESULTADOS: Observou-se diminuição significativa da dor entre as visitas pré e pós o uso do medicamento, com uma média de 4,1 pontos na EAV (p < 0,001), porém a diminuição da intensidade da dor não dependeu do esquema terapêutico utilizado. Um paciente teve...
a medicação suspensa, devido à tolerabilidade, que foi considerada boa em 90,7% dos pacientes. **CONCLUSÃO:** As doses de 60 e 960 mg de etoricoxibe foram efetivas e bem toleradas para o controle da dor aguda em pacientes com entorse do tornozelo. **Descritores:** Dor aguda, Etoricoxibe, Tornozelo, Tratamento.

**INTRODUCTION**

Ankle sprain is a very frequent disease seen by orthopedic emergency sectors. International data from 1997 have shown that approximately 1 million people were annually affected by this problem in the United States\(^1\). A different North-American study has reported incidence of approximately 6 out of 1 thousand people/year, which in population terms is a high number. Most current recommendations favor early mobilization as an important aid for patients’ recovery\(^3\), and for this to be effective, both pain control and adequate immobilizing devices are necessary measures.

In spite of new advances in ankle immobilizers’ manufacture, the gain of the painless movement arch is still an important factor for patients to more rapidly recover joint function and to have adequate tissue healing. For such, physicians have analgesic and anti-inflammatory drugs which are routinely used by orthopedic departments.

There are several criteria for measuring treatment evolution, being the most important pain improvement when ambulating during both active and passive ankle mobilization\(^4,14\). A good analgesia is necessary to meet such objective.

Many drugs may be useful to decrease pain and tissue inflammation, ranging from those purchased over-the-counter to more potent analgesics. Since most sprains are part of Leach classification grades I and II (mild and moderate)\(^3\), in general non-opioid analgesics such as paracetamol, and non-steroid anti-inflammatory drugs (NSAIDs) are the most widely used. These, although safe for most cases, may lead to gastrointestinal and cardiovascular complications depending on usage time and patients’ profile\(^6\).

In the late 1990s, studies were aimed at the development of selective cyclooxygenase-2 inhibitor NSAIDs, called coxibs. These drugs proved to be safe for the gastrointestinal tract when compared to traditional NSAIDs\(^7\), and started to be widely used worldwide.

More recently there has been concern with the chronic use of these drugs, especially due to cardiovascular adverse events. Although the literature has published studies supporting the safety of such drugs\(^8\), several studies appeared in recent years deeply discussing coxibs-related complications. Due to these studies, several international regulatory agencies have determined that these coxibs should be limited to specific cases, and that further studies should confirm the lowest effective dose possible, to prevent complications.

Taking into consideration that all patients suffering ankle sprain have to be immobilized as part of their treatment, it is believed that this, by itself, is a major aid to treat joint pain of these patients, allowing supposing that analgesia may be effective with decreased routine coxib analgesic doses, when patients are adequately immobilized. In the specific case of etoricoxib, recommended daily dose is 120 mg for acute pain and there are no studies about the efficacy of a lower dose in analgesia and joint mobility improvement. Another important point is that acute pain studies have evaluated dental pain models, which is not necessarily the best comparison for the acute orthopedic pain model.

Given this premise, we decided to study other doses of this drug to check the efficacy of decreasing the recommended drug dose to control acute orthopedic pain. This pilot study primarily aimed at testing the hypothesis that 90 mg daily etoricoxib is as effective as 60 mg to treat initial pain and inflammation in patients with ankle sprain grades I and II. Secondarily, we have observed the tolerability of such drug when used for two weeks.

**METHOD**

This is a clinical, double blind, randomized and prospective study with two active treatment arms, including 50 patients with ankle sprain grades I and II, seen by the emergency sector of a tertiary hospital of the city of São Paulo, from August 2009 to February 2010. After initial contact with the evaluator, who was a physician, patients were invited to read and sign the free and informed consent term for voluntary participation in the study. Patients’ age varied from 18 to 50 years with mean age of 32 years. Inclusion criteria were history of acute ankle sprain during sports practice, with time interval less than 24 hours between the injury and the first evaluation.

Exclusion criteria were patients with less than 18 years of age and more than 50 years of age, with history of previous ankle sprain submitted or not to treatment, in one or both ankles; patients with foot and/or ankle fractures previous or simultaneous to current sprain; patients under anti-inflammatory drugs or chronic steroids; pa-
patients with heart diseases, vascular failure, previous or current deep venous thrombosis, vascular diseases being treated, congenital deformities with lack of limb, amputations, hypertension, rheumatic diseases, wounds and scars with deformities, cardiovascular diseases such as angina, acute myocardial infarction, heart failure, renal diseases, kidney diseases, allergic reaction to acetylsalicylic acid or other anti-inflammatory drugs, history of stroke or transient ischemic attack.

Patients were blindly and randomly distributed in two groups being group I made up of 25 patients treated with 90 mg daily etoricoxib in bolus dose for 14 days, and group II, made up of 25 patients with 60 mg daily bolus. To assure randomization, 50 numbers of 3 digits were generated by a computer program and only the chief researcher, who had no contact with patients would have information about the therapeutic schedule.

**Clinical evaluation protocol**

The study was divided in four visits and a telephone call, being the first visit on day zero, that is, the day patients would enter the emergency sector. In this visit, a questionnaire was filled with personal data, clinical data and ankle sprain history, followed by additional tests: total blood count, biochemistry, beta-HCG for female patients, urine test I and simple ankle X-rays to rule out the possibility of fractures.

After collecting additional tests, the protocol was started with visit I on day zero. In this visit, patients were submitted to physical evaluation where blood pressure was measured, edema was generally inspected and measured by volumetry and perimetry in 8. Visual analog pain scale (VAS) was used to evaluate pain intensity, where 0 = no pain and 10 = maximum pain ever experienced by patients. Pain was evaluated in three situations: at rest, during ankle passive and active mobilization. After this, ligament stability was checked with specific tests and movement amplitude was evaluated with a goniometer.

Finally, patients were oriented to stay in orthostatic position on both feet, in orthostatic position on the injured foot and in orthostatic position on the tip of the injured foot. In each position, the researcher would ask patients about pain intensity according to VAS. At the end of visit I, patients were immobilized with Aircast® and the first drug dose was administered.

Visit II could be simultaneous to visit I day zero because the protocol applied to visit I was repeated in visit II, plus pain evaluation with VAS during counter-resistance evaluation and drug control item.

Visit III was carried out on the 8th day after injury and the evaluation protocol was the same used during visit II, plus the following items: adverse reactions, drug efficacy and tolerability.

Visit IV was on the 15th day, the protocol was maintained and the chief researcher requested patients to repeat complementary tests.

A telephone call was made by the chief researcher 45 days after the injury, when patients were asked about the presence of pain and edema, and about the subjective final result of the treatment.

**Statistical analysis**

SPSS 15.0 software was used for statistical analysis and the following variables were calculated for descriptive analysis: mean, standard-deviation, minimum, median, maximum and frequency.

Numeric variables were compared by visits and by group. ANOVA for repeated measures was used for variables with normal distribution. Non-parametric Wilcoxon test p-value was used for numeric variables without normal distribution where significance level was equal 0.05 divided by the number of comparisons of each variable.

Non-parametric Nc Nemar test was used to compare categorical variables by visits and by group, with significance level of 0.05 divided by the number of comparisons of each variables.

In comparisons between visits I and III, I and IV and III and IV for numeric variables not meeting normality assumptions, p-value of non-parametric Wilcoxon test at significance level of 0.0167. Divisions were made by the number of comparisons.

In comparisons between visits I and III, I and IV and III and IV for categorical variables, the p-value of non-parametric Wilcoxon test was significant at the level of 0.0167. This study was approved by the Institution’s Ethics Committee, process 25000.188.520/2007-41.

**RESULTS**

From 50 patients starting the protocol, 43 were included in the final analysis. Seven patients were excluded because they missed the 3rd and/or 4th visit.

From 43 patients included in the final evaluation, 23 (GI) (53.5%) used the therapeutic schedule 1 – 90 mg etoricoxib; 20 patients (GII) (46.5%) used the therapeutic schedule 2 – 60 mg etoricoxib. From all 43 patients, 9.3% were females and 90.7% were males.

Final results were not statistically different between
Analgesia in ankle sprain: study with etoricoxibe

Analgesia in ankle sprain - study with etoricoxibe.indd   107 6/21/12   2:36 PM

both therapeutic schedules in any time and for any variable: pain evaluation at rest (VAS), passive mobilization, active mobilization and counter-resistance mobilization (Graph 1).

Graph 1 – Decreased pain intensity by the visual analog scale between visits 1 and 4 by measurement tools (clinical outcomes) and therapeutic schedule. Schedule 1 = 90 mg etoricoxib; Schedule 2 = 60 mg etoricoxib

Significant pain decrease was observed between visits I and IV according to VAS during pain evaluation at rest. This improvement was either general, regardless of the therapeutic schedule, or when considered each therapeutic schedule separately. There has been a higher trend for pain decrease in group I, using 90 mg etoricoxib, but difference was not statistically significant. There has been significant pain decrease during visits I and IV with mean of 4.1 points ($p < 0.01$), being interesting to stress that this decrease was not therapeutic schedule-dependent.

From 43 studied patients, only one patient had the drug withdrawn following medical orientation because he presented stomach discomfort and diarrhea after starting the protocol. The protocol was maintained until study completion, even after drug withdrawal. Both groups had tolerability of 90.7%, considered good, and just 4.7% had poor tolerability.

DISCUSSION

This study has shown that 90 and 60 mg etoricoxib doses were effective for analgesia of immobilized patients after ankle sprain. There was a trend of patients under 90 mg dose to report further pain decrease measured by VAS, however this difference was not significant. In addition, both doses were well tolerated by patients. The analysis of this study has shown that there is still a very interesting research field in the area of sports orthopedics and traumatology, especially in acute pain models.

It is known that patients with acute contusions and traumas should be treated with pain killers, but some studies do not report different manners to induce analgesia, such as affected joint immobilization. What can be observed in sprain patients is that reported pain is not that severe as compared to pain at rest. VAS measures for ankle movement pain were significantly higher than those reported at rest (Graph 2).

Graph 2 – Pain intensity at rest.

Studies showing the benefits of orthosis to treat acute ankle sprain do not mention the coadjuvant treatment with analgesic or anti-inflammatory drugs, leaving these data as secondary for patients’ analgesia. It is known that most patients looking for orthopedic services after ankle sprain will have some type of immobilization, even if for a short period. Peripheral nociceptive pain in these cases may also be controlled by joint immobilization, which acts as a factor to promote analgesia.

All studied pain models and analgesic therapies take into account the extent to which chemical pain mediators may be blocked. For acute injuries, analgesics and NSAIDs are widely used. NSAIDs have a very good analgesic potential for the acute phase because they block the production of prostaglandin (PG) which induces tissue inflammation. Studies have shown that at least 80% of PG production should be blocked to obtain a satisfactory analgesic effect in the acute phase and this depends on the drug, usage time and on the dose. This blockade should be constant, and for such it is necessary to know the adequate dose of a certain anti-inflammatory substance.

Traditional NSAIDs and coxibs are major examples of this group of drugs used during the acute phase of such sprains to control pain. Even simple analgesics, such as paracetamol and ibuprofen have already
been studied for acute orthopedic pain. A study with 260 ankle sprain patients has shown that 3.9 mg/day extended release paracetamol in three doses of 1.2 g a day has good analgesic efficacy, comparable to 1.2 g ibuprofen in three doses of 400 mg. The major problem of this study was the dose, since it is known that paracetamol has a maximum allowed dose of 4 g a day and that possibly 1.2 g ibuprofen could have been insufficient to control acute pain. Since in this study patients were also immobilized and ankle sprains were limited to grades I and II, it might be that in patients with high pain intensity these drugs may have limited effects. Other authors have described the benefits of other NSAIDs, such as diclofenac and piroxicam and even pain improvement of acute orthopedic injuries with the use of dermal patches with diclofenac and ketoprofen as active substances. By the time, little was known about gastrointestinal complications, but today we know that even with the short term use of these drugs, which do not selectively inhibit COX-2, there might be severe gastrointestinal complications.

A study carried out from 1999 to 2001 in the Canadian public system has evaluated 726 admitted patients (first visit) from a sample of 1,054,532 people/year. This population was compared to 20,002 controls to perform a regression logistic analysis to estimate odds ratio (OR) with 95% confidence interval (CI-95) to evaluate the risk of confirmed upper gastrointestinal (GI) complications and their association with NSAIDs. Rofecoxib and naproxen users had higher GI risk with adjusted OR of 3.6 (CI-95 from 2.2 to 5.7) and 3.4 (CI-95 from 1.8 to 6.7), respectively. No association was found between GI risk and celecoxib (OR 1.1 with CI-95 from 0.7 to 1.8) or diclofenac associated to misoprostol, a gastric protector widely used in the USA and Canada (OR 0.7 with CI-95 from 0.3 to 1.8).

No study was found in the literature with etoricoxib, used in our study, and because it is a more selective Cox-2 inhibitor we believe that it would be interesting to evaluate results with doses lower than 120 mg, recommended for acute pain. This drug had already recommended doses for more chronic pain: 90 mg for rheumatoid arthritis and 60 mg for osteoarthritis, and these doses associated to immobilization, could be effective to control pain, which has been proven.

Clinical coxibs utilization has been shown to be effective to handle GI complications, for leading to a selective blockade of arachidonic acid cascade inhibition. This is interesting because it prevents upper GI complications, common with non-selective NSAIDs. But there has been also concern with cardiovascular events, and major regulatory agencies have indicated that further studies are needed and that the lowest most effective dose should be looked for in this group of drugs. In addition, drugs should be used for the shortest possible time after obtaining the desired clinical effect.

In our study, patients have greatly benefited from both therapeutic schedules with a mild trend to further pain decrease with 90 mg etoricoxib. This shows the extent to which acute orthopedic pain models should be studied because immobilization itself has helped local ankle pain improvement, which probably has helped analgesia of patients under 60 mg to the point that there was no statistical difference between both doses. Recommended etoricoxib dose for acute pain is 120 mg, and with this study it is also possible to include at least the dose of 90 mg to this indication spectrum.

Another important aspect of this study is that it is the first to prove the efficacy of this drug in a model of acute orthopedic pain, since all other studies have proven its efficacy in models of dental pain and postoperative pain in general.

A limitation of this study was the number of patients, since the analysis of just 50 individuals may lead to some bias, which could be avoided with a larger sample. We have also not studied the anatomic level of ligament and capsule injury, deciding to consider the practical part of pain control, which is a major factor during sprain acute phases. As from the results of this pilot study, we intend to carry out a larger study to improve the understanding of this acute orthopedic pain control model.

This study may encourage further studies in this area because we were able to prove with this drug, and also with other drugs, that a lower dose is effective for acute pain and may prevent major clinical complications.

CONCLUSION

This study has shown that 60 and 90 mg etoricoxib doses are effective and well tolerated to control acute pain in patients with ankle joint sprain.

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REFERENCES

23. Malmstrom K, Kotey P, Coughlin H, et al. Randomized, double-blind, parallel-group study com-

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