Adjunctive Benefits of Systemic Etoricoxib in Non-Surgical Treatment of Aggressive Periodontitis: Short-Term Evaluation

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Background: This pilot study assessed the effect of short-duration treatment with etoricoxib as adjuvant therapy to scaling and root planing (SRP) on the clinical and radiographic parameters and prostaglandin E_2 (PGE_2) levels in aggressive periodontitis.

Methods: Subjects were randomly allocated to test or control treatment (n = 10 in each group) and submitted to SRP and treatment with etoricoxib, 120 mg/day, or placebo for 7 days. Probing depth, clinical attachment level (CAL), gingival recession, visible plaque index, bleeding on probing, linear distance (LD) from the cemento-enamel junction to the alveolar crest, and analysis of the gray levels were recorded before and 1 month after the therapies. The prostaglandin E_2 (PGE_2) level in the gingival crevicular fluid (GCF) was measured by radioimmunoassay at the beginning of the study and 7 and 30 days after treatment.

Results: No significant difference in the clinical parameters was observed between the groups at the end of the experimental period, although both groups presented significant improvement in all variables examined. There was a decrease in CAL from 5.54 ± 0.47 mm to 3.59 ± 0.53 mm in the test group and from 5.92 ± 1.10 mm to 3.69 ± 0.80 mm in the control group. A significant reduction in PGE_2 was found after 7 days of treatment. LD differed between the groups.

Conclusion: Etoricoxib did not promote additional improvement in the clinical parameters; however, it produced an initial reduction in the PGE_2 levels in the GCF, which could be related to the discrete improvement in the bone condition. *J Periodontol 2008;79:1719-1725.*

KEY WORDS

Anti-inflammatory agents; clinical trial; dental scaling; etoricoxib; periodontitis; root planing.

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Aggressive periodontitis represents an inflammatory type of periodontal disease that generally affects individuals at an early age and is characterized by the rapid and debilitating destruction of the supporting periodontium.[1,2] Despite the severity and damage resulting from this pathology, studies[3-6] in this area are scarce and information on the factors involved and efficacy of therapeutic modalities is required.

Molecular and cellular immunology studies[7,8] of the pathogenesis of periodontitis showed that, although biofilm is the primary etiologic factor, the disease occurs as the result of interactions between specific bacterial pathogens and the susceptible host's immune and inflammatory responses. It was observed that there might be an exacerbation of this response, particularly with aggressive periodontitis, where non-surgical therapy, which is effective and sufficient in the majority of clinical situations,[9,10] may not result in limiting tissue damage.[11,12]

In view of the complex pathogenesis of periodontitis, different therapeutic modalities have been studied. Bearing in mind the immunoinflammatory nature inherent to this process, it is believed that modulation of specific cellular and humoral factors may potentially broaden the effect of mechanical therapies, e.g., the

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use of drugs that inhibit prostaglandin E_2 (PGE_2) biosynthesis.[13-18] Recent studies[14,17,18] pointed out the use of non-steroidal anti-inflammatory drugs (NSAIDs), associated with non-surgical periodontal therapy (scaling and root planing [SRP]), as a treatment potentially capable of producing additional benefits in the periodontal condition by modulating the host's immunoinflammatory response. However, few controlled clinical studies have been performed to evaluate the effect of cyclooxygenase (COX)-2–selective NSAIDs as an adjunct to non-surgical therapy in aggressive periodontitis. Therefore, the aim of this pilot study was to evaluate whether the use of the selective NSAID etoricoxib associated with SRP would be capable of producing, in the short-term, additional benefits on clinical and radiographic parameters and levels of PGE_2 in the gingival crevicular fluid (GCF) compared to non-surgical therapy alone.

MATERIALS AND METHODS

Selection of Subjects

Individuals with aggressive periodontitis,[2,19] aged between 18 and 35 years, were selected from those seeking care at the undergraduate and postgraduate clinics in periodontics at the Bahian School of Medicine and Public Health (EBMSP). Subjects were enrolled from January 2006 to April 2007. The final sample consisted of 21 subjects who had ≥20 teeth and at least four sites in different teeth with probing depth (PD) ≥4 mm and two sites with PD ≥7 mm. Because aggressive periodontitis is not a very common pathology,[20,21] this sample size was considered sufficient. All evaluations performed considered only the sites that presented PD >3 mm (gingival increase was excluded) at the beginning of the study. The exclusion criteria were hypersensitivity to NSAIDs; systemic conditions that could modify the progression or treatment of periodontal diseases, including diabetes and immunodeficiencies; the need for antibiotic coverage for periodontal procedures; periodontal treatment during the last 6 months; use of NSAIDs in the last 30 days or antibiotics in the last 60 days; use of drugs that could interfere in the inflammatory response, immunologic system, or bone metabolism during the last 60 days; smoking; pregnancy; lactation; and significant alteration in the hemogram or coagulogram. Sites with furcation involvement were also excluded.

Experimental Design

This study was a randomized, placebo-controlled, parallel-design, double-masked clinical trial. Ethical approval was obtained from the EBMSP joint Research and Ethics Committee, and the study was conducted according to the principles outlined in the Declaration of Helsinki of 1975, as revised in 2000, on experimentation involving human subjects. All subjects agreed to and signed the "Free and Informed Term of Consent."

Therapeutic Procedures

Subjects were randomly allocated, by coin toss, into two groups: the test group (n = 11) underwent SRP (40-minute session per sextant) and the daily ingestion of one pill of etoricoxib[#] (120 mg) for 7 days (test); the control group (n = 10) received the same SRP procedure and daily ingestion of placebo for the same time interval. The mechanical therapy was conducted over a maximum of 7 days during which the medication was administered. The delivery of medication was performed by a professional not involved in the study. Subjects were telephoned daily to remind them to take the medication and to remind them about the appointment to perform the SRP; the number of pills was counted to evaluate the compliance with treatment. SRP was performed with Gracey periodontal curets,[**] under local anesthetic when required. Oral hygiene instructions (OHI), which include explanations about brushing techniques and auxiliary resources, were provided before the therapies were instituted. OHI reinforcement and prophylaxis were done weekly until the reassessment 30 days later. Side effects were reported and recorded.

Examiner Calibration

The periodontist examiner calibration was conducted in two subjects with clinical conditions similar to study subjects and involved PD, clinical attachment level (CAL), and gingival recession (GR) (two examinations, with an interval of 72 hours between them). This calibrated examiner performed all treatment and clinical examinations. The radiologist examined 55 random sites in eight volunteers involved in this study (two examinations with an interval of 7 days between them) for the calibration.

Data Collection

Clinical parameters. Clinical parameters were measured to the nearest millimeter prior to the first session of SRP at six sites per tooth (mesio-buccal, buccal, disto-buccal, disto-lingual, lingual, and mesio-lingual) in all teeth, excluding third molars, using a standardized periodontal probe with 1-mm markings.[††] PD, CAL, GR, visible plaque index (VPI),[22] and bleeding on probing (BOP) were recorded at the beginning of the study (T0) and 30 days after treatment (T1).

PGE_2 values. Four samples of GCF were collected (involving the deepest pockets) at T0, after 7 days, and T1. An absorbent paper cone[‡‡] was inserted into the bottom of the pocket; after 30 seconds, it was removed and placed in 100 μl phosphate buffered saline.

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The samples were centrifuged, and the supernatant was stored at –70°C and evaluated by radioimmunoassay.[23] The standard curve was obtained by using PGE_2 at concentrations that ranged from 0.007 to 40 ng/ml. The PGE_2 values were obtained in scintillations per minute and converted into pg/ml.

Radiographic parameters. Six radiographs were taken for each subject by the same examiner, consisting of the regions of the molars (vertical interproximal technique) and incisors (periapical bisectrix technique with positioner). For standardization, individual occlusal positioners (stents), made of acrylic material, were positioned for each region to be radiographed, and the same stents were used at T0 and T1. The stents were attached to film holders to restrain the field of interest and keep the same angulation for T0 and T1. The same radiographic equipment (70 kV [peak] and 8 mA) and type of radiographic film§§ were used. Similarly, the focal distance was maintained at 20 cm, and the exposure time was 0.5 seconds. Processing was also standardized with regard to time and temperature control. The radiographs were interpreted by the same calibrated radiologist. Analysis of the linear distance (LD) was performed with a ×2 magnifying glass, on the negatoscope, with uniform lighting. The examiner indicated the extent of alveolar bone loss or gain in the two radiographs (T0 and T1), using a millimeter ruler and a dry-tipped compass, and distances were quantified with a digital caliper with 0.01 mm resolution. LD was obtained by measuring the vertical distance from the cemento-enamel junction (static reference point) to the alveolar bone crest. Only differences (T1 – T0) >1 mm (cutoff point) were considered changes (increase or reduction). For digital analysis of the gray levels (GL), the radiographs were digitized in pairs (T0 and T1) by a scanner with a transparency reader, with spatial resolution of 300 dots per inch, enlargement of 100%, in the gray-scale mode and 8 bits. Corrections of the image size and brightness were made by commercial programs‖¶¶ from a control area;[24] next, a rectangle containing ~100 pixels was traced onto the most coronal portion of the remaining interalveolar septum, and the mean ± SD for GL was obtained. The cutoff point of 5 units was used to establish the changes in bone density.

Data Analysis

Twenty subjects were involved in the analysis. All statistical analyses were performed with a commercial statistical program.## For clinical parameters, the mean was calculated considering the subject as the experimental unit. Repeated-measures analysis of variance (ANOVA) was used to detect intra- and intergroup differences in clinical parameters (PD, CAL, GR, VPI, and BOP). The Mann-Whitney test was used to compare the variation in PGE_2 levels between groups. For the PGE_2 levels and radiographic analysis, the site was used as the experimental unit. Analysis of LD was performed by the Fischer exact test to evaluate the prevalence of variation among sites. The χ^2 test was used to analyze the frequency of variations of GL. The level of significance was set at 5% ($P < 0.05$).

RESULTS

The present study, conducted by two calibrated examiners (a periodontist and a radiologist), involved a coefficient of agreement >85% for the intraclass correlation for both evaluations (data not presented).

Clinical and Sociodemographic Data

During the study, one subject from the test group was excluded because she did not return for reassessment. The baseline clinical data of 20 subjects are summarized in Table 1. No statistically significant differences were found between the groups ($P > 0.05$) with regard to the subject's age, number of teeth evaluated, and number of sites with PD >3 mm (Table 1). The test group presented 19.3% shallow pockets (4 mm), 60.8% moderately deep pockets (5 or 6 mm), and 19.9% deep pockets (≥7 mm). The control group presented 27% shallow pockets, 46.7% moderately deep pockets, and 26.3% deep pockets. With regard to gender, only one subject in each group was male.

At the end of the experimental period, no statistical differences were observed between the groups in any clinical parameter evaluated. However, all variables presented significant alterations within each group between the beginning and the end of the study, with a decrease in all values, with the exception of GR, which increased. Mean CAL decreased from 5.54 ± 0.47 mm to 3.59 ± 0.53 mm in the test group and from 5.92 ± 1.10 to 3.69 ± 0.80 mm in the control group ($P = 0.47$; (Table 2). Analysis of the data allowed us to infer that both treatments were capable of causing a reduction in CAL ≥2 mm; 67% and 64% of the pockets presented this decrease in the test and control group, respectively.

Assessment of the variations in PGE_2 levels in GCF revealed a significant difference between the groups after 7 days ($P = 0.0351$); a greater reduction was found in the test group. After 30 days, the groups presented similar results ($P = 0.40$; (Fig. 1).

A significant difference was detected in changes in the radiographic parameter LD based on treatment ($P = 0.01$). In the majority of sites in both groups, no alteration ≥1 mm was observed in LD (test: 78%; control: 96%); however, 20% of the sites in the test group

§§ IP-21 Insight, Eastman Kodak Company, Rochester, NY.
‖ Photoshop, v.7.0, Adobe Systems, Mountain View, CA.
¶¶ Image Tool v.2.0 for Windows, Department of Dental Diagnostic Science Center, San Antonio University, San Antonio, TX.
SAS 9.1, SAS Institute, Cary, NC.

Table 1.

Characteristics (mean ± SD) of the 20 Subjects at the Beginning of the Study

Characteristic	Control	Test	*P* Value*
Age (years)	34.6 ± 7.6	32.4 ± 6.5	0.25
Teeth evaluated (n)	27.5 ± 3.3	28.5 ± 2.8	0.24
Sites with PD >3 mm (n)	42.2 ± 19.3	46.4 ± 26.0	0.31

* Student *t* test.

Table 2.

Clinical Parameters (mean ± SD) at Baseline and 30 Days After Therapy*

	Control		Test	
Parameter	Baseline	30 Days	Baseline	30 Days
PD†	5.74 ± 0.89	3.26 ± 0.44‡	5.32 ± 0.44	3.15 ± 0.45‡
CAL†	5.92 ± 1.10	3.69 ± 0.80‡	5.54 ± 0.47	3.59 ± 0.53‡
GR†	0.21 ± 0.26	0.48 ± 0.47§	0.24 ± 0.20	0.47 ± 0.26‡
VPI	92.17 ± 8.19	26.35 ± 9.93‡	91.28 ± 11.56	33.45 ± 16.60‡
BOP	73.45 ± 17.89	25.87 ± 12.82‡	77.58 ± 10.60	20.14 ± 11.21‡

ANOVA in split-plot scheme (α = 5%).
* No difference was observed between groups (*P* >0.05).
† Mean ± SD of sites with PD >3 mm.
‡ Significant change from baseline (*P* <0.0001) by ANOVA.
§ Significant change from baseline (*P* <0.001).

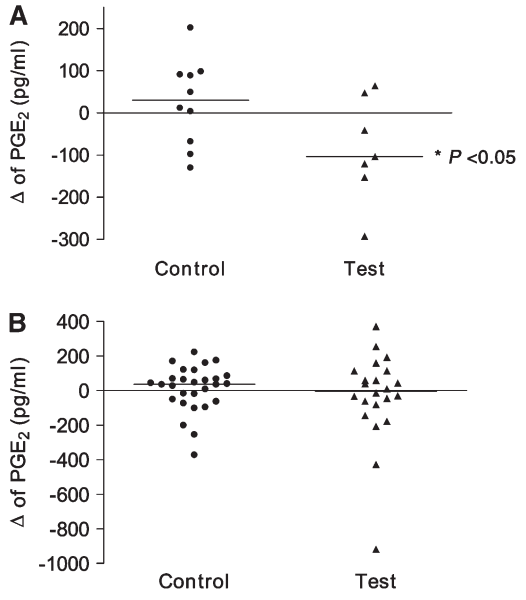

Figure 1.
Variations in PGE_2 level (pg/ml) in GCF at 7 days ***(A)*** *and 30 days* ***(B)*** *in the etoricoxib and control groups. Mann-Whitney test.*

and 4% of the sites in the control group had a reduction in LD, whereas 2% of the sites in the test group and no site in the control group were associated with an increase in LD (Table 3).

Digital analysis of the variations in GL after treatment revealed that, in the test group, the majority (40%) of sites presented an increase in GL, whereas in the control group, a lower percentage (29%) showed an increase. Despite the percentage differences, no significant difference was observed in the changes in GL as a function of the treatment performed ($P = 0.16$) (Table 4).

DISCUSSION

The results of the present pilot study demonstrated that etoricoxib was capable of significantly reducing PGE_2 levels during the period in which it was administered, signifying that it had a full pharmacologic effect on the organism, attaining sufficient serum levels for the anti-inflammatory action to be established. Because the action of etoricoxib is centered precisely on the inhibition of PGE_2 biosynthesis,[25,26] the decrease found was expected. At 30 days, the groups presented comparable results, which were equally expected because in this period the medication had already been excreted from the subjects' organisms. Based on the data presented, it is possible to infer that the reduction in the PGE_2 levels during the initial stages may have generated a beneficial effect by producing a more effective modulation of the host's immunoinflammatory response and promoting an effect in addition to that of the non-surgical therapy. The importance of this supposition or inference resides in the observation that, over the medium- and long-term, the reduction in PGE_2 levels may proceed with improvement of clinical condition and gain of bone.[27] This could be an additional benefit of the use of NSAIDs associated with non-surgical therapy,[28] which, itself, could be the cause of aggression of the periodontal soft tissues and the initial exacerbation of the inflammatory response. Therefore, it is possible that the use of etoricoxib for 7 days, concomitantly with mechanical therapy, may also contribute to modulating an eventual inflammatory response to this therapy itself, broadening its benefits to the periodontal condition.

Analysis of the clinical parameters demonstrated that, despite the clinical improvement after the implementation of treatments, the lack of a statistical difference between the groups does not allow for the suggestion of any additional effect of the anti-inflammatory medication used on the evaluated variables.

Table 3.

Frequency (%) of Sites That Showed an Increase, Decrease, or No Change in LD 30 Days after Treatment

Change in LD	Control	Test
Increase	0 (0)	1 (2)
Decrease	2 (4)	12 (20)*
No change	49 (96)	47 (78)
Total	51 (100)	60 (100)

Fischer exact test.
* Significant difference between groups ($P = 0.01$).

Table 4.

Frequency (%) of Sites That Showed an Increase, Decrease, or No Change in GL 30 Days After Treatment

Change in GL	Control	Test
Increase	21 (29)	30 (40)
Decrease	18 (25)	22 (29)
No change	33 (46)	23 (31)
Total	72 (100)	75 (100)

Chi-square test ($P = 0.16$).

The literature supports these findings, demonstrating that the clinical trials[29,30] that compared the association of other NSAIDs with SRP and SRP alone in aggressive periodontitis found similar results, i.e., clinical improvement, irrespective of the systemic therapy instituted. Thus, this study provided additional evidence that even in aggressive periodontitis, mechanical therapy associated with motivation and OHI are effective for producing improvement in the clinical parameters.

The representativeness of the gain in CAL obtained (mean gain of 1.95 mm in test and 2.23 mm in control groups) is confirmed when the data of the present study are compared to the results of another study[31] that evaluated the adjunctive use of NSAIDs in subjects with aggressive periodontitis. In that study, the reevaluation at 3 months after SRP treatment, associated with the use of naproxen, revealed a mean attachment gain of 0.41 mm. Another study[29] on aggressive periodontitis showed a maximum attachment gain of 0.86 mm obtained 3 months after SRP associated with sodium meclofenamate. It may be speculated that the relevant attachment gain observed in the present study is justified, in part, by the mechanical intervention performed by a calibrated periodontist, instead of a dental hygienist, as seen in the studies mentioned. Reiterating the findings of the current study, a recent investigation[32] demonstrated a mean attachment gain of 1.77 mm 10 weeks after mechanical therapy that was also performed by a specialist, emphasizing the importance of experience and dexterity in SRP for obtaining satisfactory clinical results. Another aspect to be considered is the time spent on SRP in the present study. Recent reports[6,10,32] showed that even a single episode of one-stage debridement in a limited time of 45 minutes achieved results similar to those observed with the gold standard therapy. However, further longitudinal studies are needed to confirm the application of this approach to other types and severities of periodontal disease.

Analysis of the frequency of the variations in LD, a parameter that evaluates the gain or loss in bone height, demonstrated that the percentage of sites in the test group that presented a reduction in LD (20%) was five times greater than in the control group (4%). This difference was statistically significant, suggesting a better bone-remodeling pattern in subjects who were treated with the NSAID. Supporting these results, a systematic review[17] found that the majority of studies showed that NSAIDs seemed to affect bone progression but did not have an apparent effect on the clinical condition. In this respect, a relevant study[33] demonstrated that there was a significant decrease in bone loss in subjects with periodontitis 12 and 18 months after the use of flurbiprofen for 6 months. Similarly, Jeffcoat et al.[31] found a difference between the LDs in the test (gain of 0.27 mm) and placebo (loss of 0.14 mm) groups 3 months after the daily ingestion of naproxen by subjects with aggressive periodontitis. In addition, another study[29] demonstrated that subjects with aggressive periodontitis presented a gain in bone height after using sodium meclofenamate. Similarly, a subsequent study[28] evaluated the effect of flurbiprofen and ketorolac, not associated with non-surgical therapy, in subjects with periodontitis and found that the use of both NSAIDs correlated with a gain in bone height, in contrast to the untreated group, which showed statistically significant bone loss. In the present study, all efforts were taken to standardize the radiographic methodology. However, a distortion related to methodologic error cannot be discounted.

The study of GL, which indicates bone radiopacity or radiolucency, revealed no statistical difference between the test and control groups. It is important to consider that, because of the short duration (30 days) of this study and the period of remodeling, the results could be related to the immaturity and instability of the patterns that involve bone density and height. Conversely, a recent study[32] pointed out the clinical

relevance of short-term evaluations, because the periodontal reassessment in clinical practice is usually performed 30 to 60 days after the non-surgical therapy, when new therapeutic decisions are made. Moreover, there is scientific evidence that minimal changes can be seen as early as 1 month after implementation of the therapy.[34-36] Another study by Matteson et al.[37] warned about the need for early evaluations and interventions using sensitive diagnostic resources, with the goal of preventing future bone loss. However, medium- and long-term consolidation of the results obtained is necessary through further studies with similar designs.

Data in the literature, including the work of the authors' group, demonstrated that etoricoxib reduced inflammation and bone loss in experimental periodontal disease.[38,39] The present study showed an effect of etoricoxib on the level of PGE_2 in the GCF in periodontal disease and suggested a discrete positive effect on the bone condition in humans. In this study, only one subject reported a bitter taste in the mouth, and no other side effect was detected during the use of etoricoxib. The drug is a highly selective inhibitor of COX-2 and, as such, has a lower index of gastrointestinal side effects than the non-selective NSAIDs. The use of etoricoxib for a short period also makes it improbable that there will be any risk for cardiovascular complications associated with the long-term use of selective COX-2.[26]

Moreover, with regard to the efficacy of NSAIDs as adjunct therapy, a large gap exists in the literature from 1999 onward for clinical trials that evaluated their use in periodontitis, especially in aggressive periodontitis (only two publications exist).[29,31] In the systematic review,[17] the investigators affirmed that they had not found sufficient data for performing a meta-analysis of the studies involving the modulation of the host's response to the use of NSAIDs and considered that the interpretation of this hypothesis is complex, because it involves multiple experimental designs, variations in sample size and population characteristics, errors and biases inherent to the study design, the dilemma of statistical significance versus clinical significance, and the inability to reproduce the results found in private practice. Despite this, the reviewers recognized that such drugs could play a potential role as an adjuvant in periodontal therapy.

CONCLUSIONS

Although treatment with etoricoxib as an adjunctive therapy to SRP in aggressive periodontitis did not promote additional improvement in the clinical parameters, the data presented in this pilot study suggested that it produced an initial reduction in PGE_2 levels in GCF, which could be related to the discrete beneficial effect on the bone condition.

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