Clinical and Biochemical Evaluation of Short-Term Systemic Ibuprofen as an Adjunct to Non-Surgical Periodontal Therapy of Chronic Periodontitis

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Both periodontopathogens and destructive host response play important roles in the pathogenesis of chronic periodontitis and ideal therapy must address both components. Therefore, management of the disease may require additional interventions that will modulate the host response, for example by the use of non-steroidal anti-inflammatory drugs (NSAIDs). The present study was designed to evaluate the efficacy of adjunctive ibuprofen clinically and also biochemically by detecting gingival crevicular fluid (GCF) matrix metalloproteinase-8 (MMP-8) and prostaglandin E_2 (PGE_2) levels, in the treatment of chronic periodontitis. Twenty chronic periodontitis patients were randomly placed in two groups. The control group received initial periodontal therapy, while the test group additionally received systemic ibuprofen for two weeks. Plaque index (PI), sulcus bleeding index (SBI), probing pocket depth (PPD) and relative attachment level (RAL) were recorded and GCF samples were obtained at the first, third and sixth months following therapy. GCF levels of MMP-8 and PGE_2 were evaluated using enzyme immunoassay technique. Treatment outcomes were analysed by Mann-Whitney U test for treatment modalities and Wilcoxon signed rank test for changes within each group. Both groups showed significant improvements in all parameters following therapy ($p < 0.05$). The comparisons between the two groups revealed that neither mean PI scores, nor the improvements in SBI, PPD, RAL or GCF MMP-8 and PGE_2 levels demonstrated statistical significance ($p > 0.05$). Adjunctive use of systemic ibuprofen demonstrated no beneficial effect on the clinical or biochemical outcome of periodontal treatment of chronic periodontitis. The lack of beneficial effect may be due to short period usage of ibuprofen.

Key words: NSAID, gingival crevicular fluid (GCF), GCF MMP-8, GCF PGE_2, chronic periodontitis

INTRODUCTION

Chronic periodontitis is a progressive and site-specific disease, characterized by the destruction of tooth supporting structures (Socransky et al, 1984). Microbial dental plaque is the primary etiological factor for the initiation of the disease. However, a large body of evidence suggests that host response to the presence of microorganisms is actually responsible for the breakdown of periodontal tissues and disease progression (Page et al, 1997; Page, 1997). Perpetuation of the host response against persistent bacterial insult distrupts homeostatic mechanisms and as a result some inflammatory mediators, such as proteases and prostaglandins, are released. In return, these mediators may promote extracellular matrix destruction and bone resorption in the periodontium (Eley and Cox, 1998; Golub et al, 1998).

Matrix metalloproteinases (MMPs) are believed to be responsible for the degradation of collagen fibers in the periodontal ligament during periodontal disease process (Ryan and Golub, 2000). MMP-8 (neutrophil-type collagenase, collagenase-2) is implicated as the main type of collagenase in gingival crevicular fluid (GCF) of individuals with chronic periodontitis (Golub et al, 1995; Golub et al, 1997). Pathological elevation of MMP levels in periodontal disease may also be regulated intracellularly by prostaglandins, particularly PGE_2 (Ryan and Golub, 2000; Ryan et al, 1996; Buduneli et al, 2002). This arachidonic acid metabolite is synthesised in case of tissue damage and has many pro-inflammatory effects on periodontal tissues, including release of collagenase by inflammatory cells, activation of osteoclasts and mediation of bone resorption (Paquette and Williams, 2000; Goodson et al, 1974; Offenbacher et al, 1984; Offenbacher et al, 1986; Genco 1992).

Conventional therapeutic approach for chronic periodontitis is based on standard mechanical procedures. Since both periodontopathogens and destructive host response play important roles in the pathogenesis of the disease, ideal therapy must address both the bacterial component and the destructive host response. Therefore management of the disease may require additional interventions that will modulate the host response (Golub et al, 1998; Ng and Bissada, 1998; Caton, 1999).

An important example of host response modulation is the use of non-steroidal anti-inflammatory drugs (NSAIDs) in order to suppress inflammation and alveolar bone loss in periodontal disease (Paquette and Williams, 2000; Ng and Bissada, 1998). Cross-sectional human studies and prospective clinical trials regarding the adjunctive use of systemic NSAIDs have reported promising results (Jeffcoat et al, 1991). In a previous study, two weeks use of systemic ibuprofen in the treatment of chronic periodontitis has been reported to provide significantly greater reduction in gingival inflammation and pocket depth (Taiyeb Ali and Waite, 1993). Also, according to the findings of another study, systemic ibuprofen administration following periodontal therapy of chronic periodontitis resulted in pocket depth reduction and gain of attachment (Socransky and Haffajee, 1993).

It has been demonstrated that GCF levels of MMP-8 and PGE_2 decreased significantly after mechanical periodontal therapy (Buduneli et al, 2002; Chen et al, 2000). The adjunctive use of ibuprofen might provide additional benefits to non-surgical treatment of chronic periodontitis, through the inhibition of these mediators. Therefore the present study was planned to evaluate the short-term clinical and biochemical efficacy of adjunctive ibuprofen in the treatment of chronic periodontitis.

MATERIALS AND METHODS

Study Population

A total of 20 individuals (9 females, 11 males) with chronic periodontitis, having at least 16 interproximal sites with probing pocket depth (PPD) ≥ 4 mm, four of which were in the anterior region, were selected for the study. Detailed medical and dental histories of the patients revealed that they were systemically healthy, non-allergic to NSAIDs, non-smokers and they had neither used any antibiotics/anti-inflammatory drugs, nor received any kind of periodontal treatment within the last 3 months. No pregnancy was reported among female patients and written informed consent was obtained for each individual prior to participation. Their radiological examination demonstrated an average loss of ≥ 30 % in alveolar bone height. The study protocol was approved by the Ethical Committee of the Istanbul University.

Clinical Measurements

Prior to clinical examination, customised acrylic stents with six markings were fabricated from the study models of each patient and used as references during recordings of attachment level and probing pocket depth. The clinical parameters including plaque index (PI) (Silness and Löe, 1964), sulcus bleeding index (SBI) (Mühleman and Son, 1971), probing pocket depth (PPD) and relative attachment level (RAL), were measured with a Williams probe (Hu-Friedy, Chicago, IL, USA) by the same examiner, initially and at the first, third and sixth months following periodontal therapy.

Clinical Study Design

All subjects were randomly and equally assigned in two treatment groups. Initial periodontal therapy, which consisted of scaling and root planing procedures and oral hygiene instruction, was performed in each group and completed in 2 weeks.

While the control group received no additional therapy, the test group received ibuprofen tablets via oral administration (800 mg per day for 2 weeks).

GCF Sample Collection

Prior to clinical measurements, four GCF samples were collected from pockets with at least 4 mm probing depth, in the anterior teeth of each patient, using standardised paper strips (Periopaper, Proflow, Amityville NY, USA), at baseline and at 1, 3 and 6 months following therapy. Mesio-buccal or disto-buccal aspects of anterior teeth were selected in order to facilitate isolation from saliva. The selected area was dried for 10 seconds and the filter paper strip was then inserted to the base of the pocket until a slight resistance was felt, and left in place for 30 seconds. Samples containing blood were discarded. Each paper strip was then placed into a uniquely labelled microcentrifuge tube and stored at –30°C until the assay procedures.

The laboratory procedures were carried out as described in detail previously (Preshaw et al, 1998).

MMP-8 and PGE_2 Analysis

Two of the four GCF samples obtained from each patient were used in MMP-8 detection and the other two samples were used in PGE_2 evaluation procedures. Human MMP-8 enzyme immunoassay kit (Quantikine, R&D Systems, Minneapolis, USA) was used in order to determine the level of MMP-8 and High-Sensitivity PGE_2 enzyme immunoassay kit (Assay Designs Inc., Ann Arbor, MI, USA) was used for detecting PGE_2 in GCF samples. Immediately before the assay, the paper strips were removed from storage and a 50 µl of corresponding assay buffer (Tris-buffered saline), which was provided within each kit, was pipetted onto each tube. The tubes were left at room temperature for 30 minutes and vortexed every 5 minutes. The aliquots of the extracted samples were used in the assay procedures, as described within the kit instructions. Finally, enhancement solution was added to stop the reaction and the optical density of the colour produced was measured immediately using a microplate reader (450 nm for MMP-8 and 405 nm for PGE_2). The concentrations of MMP-8 and PGE_2 in GCF samples were determined using optical density values and expressed as ng/ml.

Statistical Analysis

The patient was considered as the unit of observation. The differences between groups were compared using Mann-Whitney U test. During intergroup comparisons, regarding all biochemical and clinical data except PI, mean differences between baseline and the first, third and sixth months following therapy were taken into consideration; whereas in PI, the mean PI scores at baseline and at the first, third and sixth months following therapy were evaluated. The changes in PI were not used in order to analyse the actual amount of plaque at each measurement interval, which is clinically more important. In order to overcome this inconsistency, the percentage of the improvement in PI at 6 months after therapy was calculated.

Wilcoxon signed rank test was used in evaluations of repeated measurements within each group.

Statistical analysis of the study was carried out using a software program (SPSS for Windows, Release 10.0, 1999, SPSS Inc., USA) and statistical significance was established at $p < 0.05$.

RESULTS

The patients enrolled in the study had a mean age of 41.98 ± 9.17 (and were aged between 31 and 66).

Plaque Index

Both groups demonstrated statistically significant improvements in PI scores at 1, 3 and 6 months following therapy, according to baseline ($p < 0.05$). No statistically significant differences, regarding the PI scores, were observed between two groups. Also the percentage of the improvement in plaque index at the sixth month after therapy did not represent statistical significance between groups ($p > 0.05$) (Table 1).

Sulcus Bleeding Index

A statistically significant improvement in SBI scores was observed in both groups at the first, third and sixth months following treatment, when compared with baseline ($p < 0.05$). There were no statistically significant differences between two groups when the decrease in SBI scores was compared ($p > 0.05$) (Table 2).

Table 1 Comparison of PI scores in the test and control groups as expressed over time and between groups at baseline and after therapy.

PI	Group	Median (MIN–MAX)	Z	p
Baseline	Test Control	1.99 (1.09–3.00) 2.15 (1.33–3.00)	–1.101	0.271
1st month	Test Control	0.41* (0.09–0.77) 0.21* (0.03–0.69)	–1.399	0.162
3rd month	Test Control	0.16* (0.00–0.32) 0.06* (0.00–0.15)	–1.592	0.111
6th month	Test Control	0.07* (0.00–0.19) 0.04* (0.04–0.14)	–1.179	0.238
Change % at 6th month	Test Control	96 (91.20–100) 98 (93.52–100)	–1594	0.111

** Significant difference according to baseline ($p < 0.05$).*
Statistical significance at $p < 0.05$.

Table 2 Comparison of SBI scores in the test and control groups as expressed over time and the change after therapy.

SBI	Group	Median (MIN–MAX)	Z	p
Baseline	Test Control	2.73 (2.04–4.00) 3.00 (2.00–4.00)	–0.796	0.426
Baseline–1st month	Test Control	2.09* (1.79–3.23) 2.82* (1.77–3.75)	–1.587	0.112
Baseline–3rd month	Test Control	2.47* (2.01–3.85) 3.00* (2.00–3.91)	–0.984	0.325
Baseline–6th month	Test Control	2.63* (2.04–3.93) 2.94* (1.95–3.91)	–0.681	0.496

** Significant difference according to baseline ($p < 0.05$).*
Statistical significance at $p < 0.05$.

Table 3 Comparison of PPDs in the test and control groups as expressed over time and the change after therapy

PPD	Group	Median (MIN–MAX)	Z	p
Baseline	Test Control	4.75 (3.98–5.72) 4.25 (3.64–4.92)	–1.890	0.059
Baseline–1st month	Test Control	2.25* (1.90–3.27) 2.22* (1.45–2.86)	–0.681	0.496
Baseline–3rd month	Test Control	2.40* (1.94–3.29) 2.41* (1.45–2.95)	–0.529	0.597
Baseline–6th month	Test Control	2.40* (1.94–3.29) 2.23* (1.45–2.92)	–0.454	0.650

** Significant difference according to baseline ($p < 0.05$).*
Statistical significance at $p < 0.05$.

Table 4 Comparison of RALs in the test and control groups as expressed over time and the change after therapy.

RAL	Group	Median (MIN–MAX)		Z	p
Baseline	Test Control	7.92 7.81	(6.92–10.29) (6.77–9.85)	–0.529	0.597
Baseline–1st month	Test Control	1.78* 1.72*	(0.55–2.31) (0.95–2.49)	–0.340	0.734
Baseline–3rd month	Test Control	1.78* 1.79*	(0.61–2.43) (0.97–2.65)	–0.227	0.821
Baseline–6th month	Test Control	1.79* 1.86*	(0.61–2.46) (0.96–2.67)	–0.076	0.940

** Significant difference according to baseline ($p < 0.05$).*
Statistical significance at $p < 0.05$.

Table 5 Comparison of CGF MMP-8 levels in the test and control groups as expressed over time and the change after therapy.

GCF MMP-8	Group	Median (MIN–MAX)		Z	p
Baseline	Test Control	8.52 7.78	(6.00–10.50) (6.10–10.20)	–0.718	0.473
Baseline–1st month	Test Control	5.35* 4.95*	(4.05–6.80) (4.02–7.05)	–0.643	0.520
Baseline–3rd month	Test Control	5.85* 5.41*	(4.55–8.55) (4.40–7.18)	–1.248	0.212
Baseline–6th month	Test Control	6.18* 5.78*	(4.85–8.73) (4.43–7.30)	–1.248	0.212

** Significant difference according to baseline ($p < 0.05$).*
Statistical significance at $p < 0.05$.

Probing Pocket Depth

When compared with baseline, statistically significant improvements in PPD were observed in both groups, at the first, third and sixth months after therapy ($p < 0.05$). There were no statistically significant differences, when the decrease in PPD was compared between the groups ($p > 0.05$) (Table 3).

Relative Attachment Level

According to baseline, statistically significant improvements in RAL were observed in both groups at 1, 3 and 6 months after therapy ($p < 0.05$). No statistically significant differences regarding the change in RAL were found between the groups ($p > 0.05$) (Table 4).

GCF MMP-8 and PGE_2 Levels

At 1, 3 and 6 months after therapy, statistically significant improvements in GCF MMP-8 and PGE_2 levels were observed in both groups ($p < 0.05$). There were no statistically significant differences when the change in GCF MMP-8 and PGE_2 levels were compared between the groups ($p > 0.05$) (Tables 5 and 6).

DISCUSSION

The present study was designed to evaluate the clinical and biochemical efficacy of systemic ibuprofen administration as an adjunct to non-sur-

Table 6 Comparison of GCF PGE_2 levels in the test and control groups as expressed over time and the change after therapy.

GCF PGE_2	Group	Median (MIN–MAX)	Z	p
Baseline	Test Control	66.15 (55.60–71.20) 64.67 (56.90–69.70)	–0.038	0.970
Baseline–1st month	Test Control	19.30* (10.20–26.10) 20.65* (11.75–25.00)	–0.832	0.405
Baseline–3rd month	Test Control	22.75* (14.60–27.50) 22.46* (17.90–28.15)	–0.417	0.677
Baseline–6th month	Test Control	23.62* (15.70–29.95) 24.07* (18.70-31.80)	–0.378	0.705

** Significant difference according to baseline ($p < 0.05$).*
Statistical significance at $p < 0.05$.

gical periodontal treatment for chronic periodontitis. The rationale for such a treatment approach is to target simultaneously both the bacterial component of periodontal disease and the destructive host response.

Previous articles report that MMP-8 is implicated as the main type of collagenase, and significant elevations in PGE_2 concentrations are observed in the GCF of individuals with chronic periodontitis (Golub et al, 1995; Golub et al, 1997; Offenbacher et al, 1981; Offenbacher et al, 1984). Sites with elevated levels of MMP-8 were also reported to have significantly higher levels of PGE_2 and the production of these mediators has been shown to be prevented or reduced by the use of NSAIDs (Söder, 1999). Therefore the present study was planned to evaluate MMP-8 and PGE_2 concentrations in GCF, in order to supplement clinical findings with objective tests.

The results of this study indicated statistically significant improvements in all clinical parameters at 1, 3 and 6 months following therapy, in both groups. This finding is the expectable outcome with regard to non-surgical periodontal therapy (Lowenguth and Greenstein, 1995). Similar to the results of the present study, Ng and Bissada reported a parallel improvement regarding PI, whereas significant elevations in gingival index (Löe and Silness, 1963), probing depth and clinical attachment values were observed after therapy in the placebo and ibuprofen groups (Ng and Bissada, 1998).

At 1, 3 and 6 months after therapy, statistically significant improvements in GCF MMP-8 and PGE_2 levels were observed in both groups. This finding is compatible with the results of previous investigations in which non-surgical periodontal therapy was employed alone or in combination with systemic NSAIDs and can be explained by the reduction of inflammation in periodontal tissues (Buduneli et al, 2002; Chen et al, 2000; O' Brien et al, 1996; Preshaw et al, 1999).

In the present study, the improvements in PI, SBI, PPD and RAL did not demonstrate statistical significance between the two groups, revealing that systemic ibuprofen had no clinically beneficial effect. In a similar investigation in which the same dosage of systemic ibuprofen was applied alone or combined with systemic doxycycline versus non-surgical periodontal therapy alone, Ng and Bissada reported that there were no significant differences regarding PI between the placebo and ibuprofen groups (Ng and Bissada, 1998). In contrast to the findings of the current investigation, they also reported that the ibuprofen-treated group demonstrated significantly lower gingival index scores, PPD and clinical attachment level values compared with the placebo group (Ng and Bissada, 1998). However, the findings of SBI, PPD and RAL in the present study cannot be compared directly with the results reported by Ng and Bissada, since they had compared the means of clinical parameters between groups, instead of mean differences according to baseline (Ng and Bissada, 1998). In another study, Taiyeb Ali and Waite applied the same dosage and regimen of systemic ibuprofen for 2 weeks and observed significantly greater reductions in gingival bleeding, colour and pocketing in the test group (Taiyeb Ali and Waite, 1993).

As was the case in clinical results, no significant differences were observed when the decrease in GCF MMP-8 level was compared between the groups, indicating that systemic ibuprofen had no additional benefit. On the contrary, another study has reported early findings of a different NSAID, meloxicam, to show a tendency to reduce GCF MMP-8 levels on the tenth day of drug intake (Buduneli et al, 2002).

Within the limitations of this study, it may be speculated that adjunctive use of systemic ibuprofen did not provide any additional clinical benefit to the non-surgical periodontal treatment of chronic periodontitis. Also, the adjunctive use of systemic ibuprofen demonstrated no improvement to MMP-8 or PGE_2 levels sampled from the GCF. It may be concluded that the ibuprofen regimen employed in this study did not possess the capacity to achieve significant clinical or biochemical benefit, depending possibly on the relatively short period of usage; prolonged periods of time taking the medication may be necessary for significant differences to become apparent. Also, the results of this study need to be confirmed in further investigations with a larger population sample.

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