THE USE OF TOPICAL SUBGINGIVAL GELS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AS AN ADJUNCT TO NON-SURGICAL MANAGEMENT OF CHRONIC PERIODONTITIS

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ABSTRACT
The treatment of chronic periodontitis consists of conventional mechanical debridement and removal of plaque and calculus1. Topical NSAIDs could be used to complement the therapy as an adjunct to resolve the inflammatory process and clinical signs of the disease more rapidly.

A randomized clinical trial was performed on 33 systemically healthy patients diagnosed with chronic periodontitis, aged 21 to 40 years. All patients underwent scaling and root planing on one quadrant per week, and sub-gingival gel was applied 48 hours after each session. Patients were grouped into 4 treatment protocols with gels containing: (1) placebo, (2) 1% acetyl-salicylic acid (ASA), (3) 1% ketoprofen (KTP) and (4) 2% ketoprofen. The clinical variables studied were: probing depth, attachment level, tooth mobility, plaque index, gingival index and bleeding on probing. All protocols (groups 1, 2, 3 and 4) induced a reduction of probing depths, plaque and gingival indices and bleeding on probing. The 1% ASA and 2% KTP protocols (groups 2 and 4) significantly reduced the probing depth variable (ANOVA p<0.05).

Key words: NSAIDs, chronic periodontitis, topical administration.

INTRODUCTION
According to the American Academy of Periodontology, chronic periodontitis is an infectious disease resulting in inflammation within the tooth support tissues and leading to the progressive loss of attachment and bone, and is characterized by gingival inflammation, pocket formation and/or gingival recession1. The anti-infectious therapy of periodontal disease includes mechanical, surgical and non-surgical treatment as well as the use of antibiotics and anti-inflammatory drugs administered systemically2-7 and topically8,9.

There is currently sufficient evidence showing that both cyclooxygenase (COX) and lipoxygenase (LOX) products of arachidonic acid are involved in the pathogenesis of periodontal disease. Most research into the subject focuses on the COX pathway, specifically prostaglandins (PG). There are large quantities of PGs at inflamed sites, which is why the gingival crevicular fluid (GCF) is an ideal medium for monitoring changes during the periodontal health-disease process. PGs are associated to tissue destruction, metabolic changes in the fibroblast and bone.

RESUMEN
El tratamiento de la periodontitis crónica, consiste en el desbridamiento convencional mecánico de remoción de placa y cálculo1. El uso de AINEs en forma tópica como complemento de la terapia podría coadyuvar a resolver con más rapidez el proceso inflamatorio y los signos clínicos de la enfermedad.

Se realizó un estudio clínico randomizado en 33 pacientes crónicamente sanos de edades entre 21 y 40 años. A todos los pacientes se les realizó raspaje y alisado radicular en un cuadrante por semana, y gel sub-gingival se aplicó 48 horas después de cada sesión. Los pacientes fueron agrupados en 4 protocolos de tratamiento con geles conteniendo: (1) placebo, (2) ácido acetilsalicílico (AAS) 1%, (3) Ketoprofeno (KTP) 1% y (4) 2% ketoprofeno. Las variables clínicas estudiadas fueron: profundidad de sondaje, nivel de inserción, movilidad dentaria, índice de placa, índice gingival y sangrado al sondaje. Todos los protocolos (grupos 1, 2, 3 y 4) indujeron una disminución al sondaje, los índices de placa y gingival y el sangrado al sondaje. Los protocolos del AAS al 1% y el KTP 2% (grupos 2 y 4) redujeron significativamente la variable de profundidad al sondaje (ANOVA p<0,05).

Palabras clave: NSAIDs, crónica del periodontitis, administración tópica.

TOPICACIÓN SUBGINGIVAL CON GELES DE DROGAS ANTIINFLAMATORIAS NO ESTEROIDES (AINES) COMO COADYUVANTE EN EL MANEJO NO QUIRÚRGICO DE LA PERIODONTITIS CRÓNICA.

There is currently sufficient evidence showing that both cyclooxygenase (COX) and lipoxygenase (LOX) products of arachidonic acid are involved in the pathogenesis of periodontal disease. Most research into the subject focuses on the COX pathway, specifically prostaglandins (PG). There are large quantities of PGs at inflamed sites, which is why the gingival crevicular fluid (GCF) is an ideal medium for monitoring changes during the periodontal health-disease process. PGs are associated to tissue destruction, metabolic changes in the fibroblast and bone.
High levels of prostaglandin E2 (PGE2) in GCF are correlated positively to periodontal inflammation and tissue destruction in humans and animals, and many studies relate PGE2 levels to active periodontal disease. In 1992 Abramson et al. showed that levels of prostaglandin E2 and Thromboxane B2 in human gingival fluid remained constant during administration of flurbiprofen in patients with adult early periodontitis. Negai et al. showed that prostaglandin E2 stimulates bone resorption. Other studies showed that arachidonate metabolites in the LOX pathway, specifically 12-HETE and 15-HETE, are mediators of tissue inflammation in patients with gingival disease and advanced periodontal disease respectively.

The topical use of non-steroidal anti-inflammatory drugs (NSAIDs) to supplement periodontal therapy might help resolve the inflammatory process and the clinical signs of the disease sooner, because NSAIDs block PG synthesis by inhibiting the COX pathway in the arachidonic acid cascade.

The aim of this study was to find a safe NSAID which could be applied topically and intracrevicularly as an adjunct to the treatment of chronic periodontal disease, to revert its clinical variables.

MATERIALS AND METHODS

Patients
Thirty-three (33) patients aged 21 to 40 years were included in this study, which was approved by the bioethics committee of Rosario National University, Argentina.

Inclusion criteria: systemically healthy patients diagnosed with chronic periodontitis with periodontal pockets ≥ 4 millimeters deep on at least three teeth per quadrant. The systemically healthy condition was determined by means of clinical history, physical examination and laboratory studies.

Exclusion criteria: patients with chronic diseases, smokers, patients who had taken any kind of medication during the previous thirty days.

Intracrevicular gel preparation
To prepare the 1% ASA gel, 4 g sodium carboxymethyl cellulose (a fine, creamy-white, aqueous flowable powder, insoluble in ethanol, acetone and chloroform) were added to 200 ml distilled water, shaken and left to rest, thus producing an opalescent gel with pH 8. Separately, we prepared the 0.1% solution of ASA previously dissolved in the minimum amount of alcohol, citric acid and sodium bicarbonate, in the minimum amount of water, as excess water would reduce gel viscosity. The pH value for this solution was 6. The solution was added to the gel at room temperature, producing agglutination, which was corrected by shaking hard under gentle heat in order not to break down the solution. The final pH value of the preparation was 8.

The ketoprofen gel was prepared by adding 200 ml distilled water to 4 g sodium carboxymethyl cellulose, shaking and leaving to rest, thus producing an opalescent gel with pH 8. Separately, 2 g ketoprofen (for the 1% concentration) and 4 g ketoprofen (for the 2% concentration), citric acid and sodium bicarbonate were dissolved in the minimum amount of water and added to the previous solution under gentle heat and shaking to prevent agglutination. A placebo gel was prepared similarly, by adding 4 g carboxymethyl cellulose to 200 ml water.

Pharmacological treatment protocols
All patients received non-surgical periodontal treatment as follows: a scaling and root planing session on one mouth quadrant at seven-day intervals (4 consecutive weeks). Gel was applied intracrevicularly 48 hours after each session. Patients were divided into 4 experimental groups. Intracrevicular gel was applied to each group, delivered with syringes with 21Gauge x 11/2 0.80 x 40 needles after drying the area with a jet of air.

Group 1: placebo gel (n=6)
Group 2: 1% ASA gel (n=9)
Group 3: 1% ketoprofen gel (n=8)
Group 4: 2% ketoprofen gel (n=10)

Clinical variables studied
The clinical indices were recorded before starting the scaling and planing (baseline) and at 30 days post-baseline (one week after the last gel application).

• Probing depth
  Measured from the free gingival margin to the bottom of the pocket, with a standardized pressure of 25 to 30 g using a second generation probe with pressure controlled by Marquis type marking, Pro Dentec brand Type I.

• Attachment level
  Determined from the cementoenamel junction to the bottom of the pocket with standardized pressure of 25 to 30 g using a second generation probe with
pressure controlled by Marquis type marking, Pro Dentec brand Type I.

- **Tooth mobility**

  Degree 1: 0.2 – 1 mm horizontal crown mobility
  Degree 2: more than 1 mm horizontal crown mobility
  Degree 3: horizontal and vertical crown mobility

- **Plaque index**

- **Gingival index**

- **Bleeding on probing** (Regardless of gingival index, and as a result of gentle probing) 0: Negative; 1: Positive.

**Statistical analysis**

Each protocol was compared statistically to its control group using Student’s T test. The results of all the protocols were compared using ANOVA with subsequent multiple comparisons using Dunnet’s test. In each case, a level of p<0.05 was considered significant.

**RESULTS**

All the protocols studied individually (groups 1, 2, 3 and 4) produced a significant reduction in probing depth, plaque index, gingival index and bleeding on probing (student t test p<0.05) (Table 1). Nevertheless, on comparing the differences between baseline and thirty days of all protocols to each other, it was found that probing depth decreased significantly in protocols using 1% ASA and 2% KTP (groups 2 and 4) and that ASA (group 2) was clinically the most effective in reducing it (Fig. 1). Gingival index, bleeding on probing and plaque index did not show significant differences for any of the groups (Table 2). None of the protocols significantly altered the gain in attachment level or the reduction in tooth mobility (Table 1).

![Fig. 1: Before treatment with 1% ASA (left) and after treatment with 1% ASA (right).](image_url)

| Table 1: Effects of each protocol on the clinical variables studied 30 days post-baseline. |
|---------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Placebo (group 1) n=6           | ASA 1% (group 2) n=9      | KPF 1% (group 3) n=8      | KPF 2% (group 4) n=10     |
| **Baseline**                   | **30 days**              | **Baseline**             | **30 days**              | **Baseline**             | **30 days**              |
| Probing Depth                  | 4.08 ± 0.72              | 4.16 ± 0.68              | 4.12 ± 0.56              | 3.98 ± 0.40              | 3.98 ± 0.40              |
| Attachment level               | 2.32 ± 0.58              | 2.41 ± 0.71              | 2.36 ± 0.81              | 2.52 ± 0.86              | 2.40 ± 0.69              |
| Tooth mobility                 | 1.68 ± 0.92              | 1.71 ± 1.06              | 1.58 ± 0.70              | 1.62 ± 0.81              | 1.21 ± 0.72              |
| Plaque index                   | 2.15 ± 0.75              | 2.06 ± 0.90              | 1.98 ± 0.71              | 2.10 ± 0.70              | 2.10 ± 0.74              |
| Gingival index                 | 2.32 ± 0.58              | 2.40 ± 0.59              | 2.37 ± 0.58              | 2.26 ± 0.70              | 1.93 ± 0.77              |
| Probing bleeding               | 0.92 ± 0.07              | 0.89 ± 0.11              | 0.78 ± 0.21              | 0.90 ± 0.09              | 0.31 ± 0.28              |

*: Statistically significant difference between baseline and 30 days after treatment (Student t test p<0.05).

| Table 2: Comparison of the reduction in the clinical variables induced by each protocol. |
|---------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Placebo (group 1)               | ASA 1% (group 2)         | Ketoprofen 1% (group 3)  | Ketoprofen 2% (group 4)  |
| Probing depth                   | 0.76 ± 0.24              | 1.26 ± 0.13 *            | 1.02 ± 0.21              | 1.08 ± 0.28 *            |
| Plaque index                    | 0.99 ± 0.61              | 1.04 ± 0.84              | 0.93 ± 0.80              | 1.09 ± 0.74              |
| Gingival index                  | 0.92 ± 0.64              | 1.42 ± 0.76              | 1.21 ± 0.83              | 1.23 ± 0.77              |
| Probing bleeding                | 0.29 ± 0.18              | 0.61 ± 0.49              | 0.52 ± 0.34              | 0.59 ± 0.38              |

*: Significant difference in the reduction of clinical variables for each protocol (ANOVA followed by multiple comparisons with Dunnet’s test).
DISCUSSION
Until the nineteen-nineties, there were only a few studies on humans providing evidence of the effectiveness of NSAIDs on reducing the progression of periodontal disease. The first studies performed by Paolantonio et al.\textsuperscript{28} using subgingival irrigation with 1\% ASA in patients with periodontitis reduced the subclinical inflammation of the periodontal pockets. Corry and Moran\textsuperscript{29} suggest that using strips of polymethacrylate cement as a delivery vehicle for sustained release of NSAIDs such as indometacin, tolmetin and mfenamic acid might be an important tool for treating periodontal diseases.

Our studies showed that administering intracrevicular 1\% ASA and 2\% KTP gel as an adjunct to periodontal treatment in patients with chronic periodontitis can significantly reduce probing depth. We propose using 1\% ASA and 2\% KTP with bioadhesive gels as a delivery vehicle\textsuperscript{30} instead mouthrinses\textsuperscript{28,29,31,32}, because gel pharmaceutical presentations have the advantage or remaining \textit{in situ} longer than irrigants and the technique is simpler than manipulating polymethacrylate strips in the periodontal pockets. Moreover, an effective means for treating the inflammatory lesion, which is limited to the periodontal tissues, will reduce the gastrointestinal and renal adverse effects often produced by NSAIDs\textsuperscript{33,34}.

None of our protocols altered the clinical attachment level or tooth mobility. Although there is evidence of the effectiveness of systemically administered NSAIDs on periodontal disease\textsuperscript{33} the studies are controversial regarding the alteration of attachment level. Del Puente et al.\textsuperscript{35} showed that patients suffering from adult periodontitis who were taking systemic NSAIDs suffered less periodontal attachment loss. In contrast, Heasman and Seymour\textsuperscript{36} report that systemic NSAIDs do not affect the amount of attachment loss. Since the reduction of attachment loss depends directly on the reduction of the inflammatory exudate in the crevicular fluid, it is logical to assume that a systemically administered NSAID, which remains for a longer time and at a higher concentration in the crevicular fluid than a topical NSAID does, should more effectively induce attachment gain. However, considering that clinical data on the effects of systemic administration of NSAIDs are not conclusive and have not been shown to be clinically superior to topical administration, it would be prudent to consider local administration in order to avoid adverse systemic effects.

The topically administered NSAID protocols used in this study did not alter the plaque index or gingival index more than the placebo did. As the infectious agents that produce and maintain the inflammation need to be reduced to enable NSAID anti-inflammatory action, the plaque index may be expected to be a variable independent from NSAID application, and more related to mechanical debridement, base therapy or changes in the patient’s brushing technique. Finally, although the base therapy is the conventional and unarguably the most effective treatment for chronic periodontitis, we believe that the use of adjuncts such as 1\% ASA or 2\% KTP administered topically by means of intracrevicular gel, as suggested, could aid the clinical reduction of probing depth in this disease. Thus, by changing the patient’s hygiene habits plus periodontal therapy, a mechanical anti-infectious action on bacterial plaque could be achieved, after which the anti-inflammatory action of NSAIDs could be used on a relatively germ-free terrain as an adjunct for tissue repair.

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REFERENCES

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