Pulpitis, external root resorption, and pain may be experienced during orthodontic movement. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been suggested to control these changes. The purpose of this study was to observe pulp-dentinal reactions, root resorption, tooth pain, and tooth movement after the application of a 4-ounce intrusive orthodontic force to human maxillary first premolars in patients given the NSAID nabumetone. Thirty-four maxillary first premolars were evaluated. A placebo was prescribed to 17 patients after an intrusive force was activated and reactivated for an 8-week period on the right side. The same procedure was repeated on the left side after patients were given nabumetone. Pulp-dentinal reactions and external root resorption were evaluated by histology. Pain and movement were also evaluated. Nabumetone was found to be useful in reducing pulpitis, external root resorption, and pain caused by intrusive orthodontic movement, without altering tooth movement in response to the application of orthodontic force.

Some researchers have demonstrated that orthodontic treatment alters pulpal blood flow (1–4) and the activity of the odontoblastic layer (2, 5), generating an obliteration of the pulp space by producing tertiary dentine (6). Other findings related to orthodontic treatment are inflammatory external root resorption in which cementum and dentin loss due to trauma to the periodontal ligament can be observed (6). Some authors maintain that this can be a consequence of the orthodontic treatment and is part of a multifactorial process (2, 7–10). Changes in the cellular metabolism of the alveolar bone and the periodontal ligament have been described in teeth subjected to orthodontic movement in which a hyalinization area is created, and this is where the root resorption can be initiated (6, 7, 11, 12).

It is known that external root resorption is caused mainly by high-magnitude intrusive forces (2, 7, 9, 13, 14). Stenvik (2) and McFadden et al. (15) found that the longer the orthodontic treatment, the greater the degree of root resorption observed. If root resorption can be prevented, it would be an important contribution to decrease the undesired consequences of orthodontic treatment.

The trigger mechanism of external root resorption is a root surface that lacks its protective blastic layer. The lack of protection can be the result of damage to the cementoblastic layer. For resorption to progress, stimuli such as constant application of intense orthodontic force is required, and it must generate inflammatory changes such as the liberation of prostaglandins and interleukins (16). Inhibiting cyclooxygenase and the subsequent production of prostaglandins with nonsteroidal anti-inflammatory drugs (NSAIDs) can be useful to decrease bone and root resorption. It has been proposed that the systemic use of NSAIDs in the initial stages of an orthodontic treatment could be useful (2, 17). Some authors do not agree with this proposal, based on studies that show that the expected tooth movement is affected by the use of these drugs (18–20). However, other studies show that the use of NSAIDs has no influence on the rate of tooth movement (17).

The mechanism whereby the application of orthodontic forces causes pulpal and periradicular pain is not yet fully understood, but there are indications that these perceptions are due to changes in blood flow in the periodontal ligament and are correlated with the presence of prostaglandins, substance P, and other substances. The subjective perception of pain is difficult to measure, and there is a wide range of individual response even when similar forces are applied to teeth (21–23). The use of NSAIDs could help patients who have severe pain during the first days after activation (23, 24). Because of the wide range of individual responses when the same force is applied to different teeth, pain is difficult to measure. NSAIDs such as aspirin and ibuprofen have been used to ease pain and discomfort (21, 25, 26).

METHODS AND MATERIALS

Before the study began, all patients received a full explanation of the aims and design of the study and signed an informed consent.
form. The design of the study was approved by the CES University Dental School Research and Ethical Committee (Medellin-Colombia). This study consisted of 25 patients of both sexes, 13 female and 12 male patients, without any systemic compromise, aged 12 to 25 years. The children weighed at least 45 kg. These patients needed maxillary first premolar extractions as part of their orthodontic treatment. The selected teeth were healthy, had complete root formation, and did not have any history of trauma. Fifty teeth were evaluated, and 16 of them were used to establish normal healthy controls of teeth not exposed to orthodontic forces. An intrusive force was applied to the other 34 maxillary first premolars and were divided into two groups. Patients in the first group (right premolars) were prescribed a placebo (crystalline microcellulose). In the second group (left premolars), patients were prescribed an NSAID, nabumetone (Nadorex Laboratorios Best, Bogotá, Colombia) after an intrusive force was activated and reactivated.

In each patient a palatal bar was placed to obtain anchorage. An orthodontic system (0.017 × 0.025 stainless steel) was designed to produce an intrusive force of 4 ounces. A Dontrix gauge (ETM Corporation) was used to measure the magnitude of the intrusive force.

Each patient had a two-phase orthodontic movement that lasted 8 weeks. During the first phase an intrusive force was applied to the maxillary right first premolar, and each patient was prescribed a placebo. In the second phase, the same force was applied to the maxillary left first premolar, and each patient was prescribed nabumetone.

Each patient was prescribed two tablets of the placebo or of nabumetone (500 mg) every 24 hours for 7 days (27). They began to take the tablets 2 days before the orthodontic system was activated, to achieve maximum blood level concentration. After the force was activated, they took the drug for 4 more days. The reason was because studies have shown that pain and discomfort caused by the activation of orthodontic forces may last for 3 to 5 days (28). Patients completed a visual analog scale, consisting of one line with a scale from 0 to 10, where 0 represented absence of pain and 10 represented intense pain; each patient reported his or her own perception of pain. They did this from the first day of activation and for 4 more days. Four weeks after the orthodontic system was activated, it was reactivated again with the same force. Patients followed the same guidelines regarding the use of the drugs and pain perception.

After 8 weeks, the premolars from the first group were extracted, stored, and fixed with 10% formalin for at least 36 hours. One week after the first extraction, the same protocol was followed with the premolars of the second group.

To obtain the proper histologic sections, a pilot test was designed in the histologic laboratory of the Universidad de Antioquia and the Instituto Colombiano de Medicina Tropical. Six hundred buccal-lingual longitudinal sections were obtained. Histologic sections were 2 µm thick. They were stained with hematoxylin and eosin, Masson’s trichromic, and Mallory’s trichromic and read by a previously standardized histologist. Standardization was done by analyzing 192 histologic sections of 16 healthy teeth used to establish the patterns of normality.

Histologic sections were divided into three zones: coronal, middle, and apical thirds. In each histologic section, changes in the predentin and odontoblast layer were observed. Changes in collagen fiber density and quantity, central and periphery pulp angiogenesis, and odontoblast vacuolization were examined. Finally, the size, degree, and amount of root resorption were studied. These variables were standardized as shown in Tables 1 and 2.

### Amount of Tooth Movement

The amount of tooth movement achieved by the maxillary first premolar was obtained with a precision of 0.01 millimeter. Measurements were made with a digital Vernier calibrator (Nitutoyo) on the initial casts of each patient with an acrylic record placed on the incisal border of the maxillary lateral and canine. The acrylic record had a stainless wire (0.017 × 0.025) that was placed on the occlusal vertex of the premolar’s buccal cusp and was extended to the first molar zone. From the reference point, the distance was measured vertically from the inferior edge of the wire to the premolar’s vertex in casts taken after the orthodontic movement was made. Two measurements were made by the same person on different days to decrease the amount of error. Only the intrusive movement was measured.

### Amount of Pain

Amount of pain was defined as the amount of painful sensation registered in 5 days by each patient on a visual analog scale for pain after an intrusive force was activated and reactivated.

This was a double-blind study, in which neither the patients nor the histologist knew which teeth were moved under the effect of nabumetone or placebo.

### Statistical Analysis

Information obtained from the histological analysis, tooth movement, and pain evaluation were run on the SPSS 8.0 and Epi Info 6.04 statistical program. The χ² test was used to compare the histologic variables between groups (placebo and nabumetone). Because the amount of dental movement has no normal distribution, the Mann-Whitney nonparametric test was used to compare the amount of tooth movement in both groups (placebo and nabumetone). To compare the level of pain, the analysis of variance was used for repeated samples. When the level of significance was significant, the Duncan post-hoc analysis was used.

### RESULTS

#### Pulp-Dentine Complex

The coronal third of the odontoblastic layer of teeth subjected to an intrusive force was altered. The apical third was normal. When the amount of predentin was analyzed, no statistically significant differences were found between the control group and the experimental group. It is important that the thickness and pattern of calcification in predentin in the coronal third were altered in both groups. Meanwhile, normal features were observed in the middle and apical thirds.

Vacuolization of the odontoblastic layer was mild in the coronal third and became less toward the apical third in both groups. It was almost absent (94.1% of cases were negative) in the apical third in the group that used nabumetone.

Central angiogenesis was higher in the placebo group (p = 0.000). Also, peripheral angiogenesis was higher in this group (p = 0.002) (Figs 1D, 1F). These values became less from the coronal third to the apical third. No severe central angiogenesis was found in any teeth under the effect of nabumetone (Figs 1E, 1G). In both
groups there was an increase in the number of collagen fibers, and they became thicker in all thirds observed.

**Root Resorption**

The external root resorption observed in the experimental group (nabumetone) was smaller than in the control group ($p = 0.0032$).

In the placebo group, the external root resorption was in the middle third in 76.4% of the cases. Most of the root resorption in both groups was in the apical third, 64.7% and 76.5%, respectively, and was small. None of the teeth under the effect of nabumetone showed large root resorption areas.

In 64.7% of the cases, the placebo group had two or more resorption lacunae in the middle third, whereas only 17.6% of the

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**Table 1. Standardization of dentine and pulp variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Histological Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predentine</strong></td>
<td>Thickness of 10–50 microns (Fig 1-A)</td>
</tr>
<tr>
<td></td>
<td>Increase in thickness and irregular</td>
</tr>
<tr>
<td></td>
<td>calcification pattern</td>
</tr>
<tr>
<td><strong>Odontoblast</strong></td>
<td>Empalisade form (Fig 1-A)</td>
</tr>
<tr>
<td><strong>Vacuolization</strong></td>
<td>Irregular form (Fig 1-B)</td>
</tr>
<tr>
<td><strong>Collagen Fibers</strong></td>
<td>Disperse fibers between the pulp’s cells (Fig 1-A)</td>
</tr>
<tr>
<td></td>
<td>Dense mesh between the pulp’s cells</td>
</tr>
<tr>
<td><strong>Central Angiogenesis</strong></td>
<td>Normal pulp with few arterioles (Fig 1-A)</td>
</tr>
<tr>
<td><strong>Peripheral Angiogenesis</strong></td>
<td>Normal peripheric pulp morphology (Fig 1-A)</td>
</tr>
<tr>
<td><strong>Vacuolization</strong></td>
<td>Odontoblasts maintain normal form (Fig 1-A)</td>
</tr>
<tr>
<td></td>
<td>Small vacuoles that do not alter the odontoblast layer</td>
</tr>
<tr>
<td></td>
<td>Altered odontoblast layer with vacuoles (Fig 1-B)</td>
</tr>
<tr>
<td></td>
<td>Form is lost in the odontoblast layer</td>
</tr>
</tbody>
</table>

**Table 2. Standardization of root resorption variables**

<table>
<thead>
<tr>
<th>Size</th>
<th>External Root Resorption (ERR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Absence of ERR</td>
</tr>
<tr>
<td>Quantity</td>
<td>Absence de RRE</td>
</tr>
<tr>
<td>Quality</td>
<td>Immature ERR without evidence of repair with a cementoid substance, and the periodontal ligament is in contact with the dentine (Fig 1-C)</td>
</tr>
<tr>
<td></td>
<td>Loss of cement but dentine integrity is kept (Fig 1-C)</td>
</tr>
<tr>
<td></td>
<td>Loss of cement and dentine is beginning to be lost</td>
</tr>
<tr>
<td></td>
<td>Undermining of the root’s dentine</td>
</tr>
<tr>
<td></td>
<td>One ERR lagoon</td>
</tr>
<tr>
<td></td>
<td>Two or three ERR lagoons</td>
</tr>
<tr>
<td></td>
<td>More than three ERR lagoons</td>
</tr>
<tr>
<td>Quality</td>
<td>Mature ERR with a cementoid substance separating dentine from the periodontal ligament indicating repair</td>
</tr>
<tr>
<td>Quality</td>
<td>Repaired The root’s form is kept but there is evidence of cement repair in the ERR lagoons</td>
</tr>
</tbody>
</table>

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In the placebo group, the external root resorption was in the middle third in 76.4% of the cases. Most of the root resorption in both groups was in the apical third, 64.7% and 76.5%, respectively, and was small. None of the teeth under the effect of nabumetone showed large root resorption areas.

In 64.7% of the cases, the placebo group had two or more resorption lacunae in the middle third, whereas only 17.6% of the
teeth in the NSAID-treated group had the same findings. Teeth in the placebo group had more than three resorption lacunae in the apical third in 64.7% of cases, whereas teeth in the NSAID group had more than three resorption lacunae in the apical third in only 35% of cases.

Amount of Movement

The amount of intrusive movement with an orthodontic force of 4 ounces was 1.711 mm in the control group and 1.449 mm in the NSAID group with p = 0.02 (Student’s t test). Figure 2 indicates the individual responses to the application of orthodontic forces in both groups.

Pain Level

Pain levels were lower in patients to whom nabumetone was administered (p = 0.005). Pain perception was higher during the first activation phase than during the second activation.

DISCUSSION

The findings in this study were the result of high experimental intrusive forces (4 ounces) applied for 2 months used to observe different behaviors patterns in the pulp-dentine complex, cement, tooth movement, and pain under the effect of nabumetone.

Angiogenesis was evaluated in the central zone (pulp) and in the peripheral area of the pulp (zone rich in cells, free cells zone, and odontoblastic layer). The results showed angiogenesis in the central and peripheral areas of the pulp, with a statistically significant difference that indicated more microvasculature in the control group. The vacuolization of the odontoblastic layer was slight in both groups. The calcification pattern of predentine was altered in the coronal third of both groups and maintained its normal characteristics in the middle and apical thirds. The external root resorption in the NSAID group was less than in the control group; this suggests that nabumetone is effective in reducing external root resorption during orthodontic treatment. In this study, nabumetone did not impede orthodontic movement; there was a slight decrease of 0.13 mm per month, and it was very useful to decrease the perception of pain during treatment.

Experimental tooth movement induces dynamic changes in the density and distribution of periodontal and pulp nerve fibers and blood vessels, indicating their involvement in periodontal remodeling and regenerative processes of the periodontal ligament (29). Angiogenesis is an important factor in pulp response, and angiogenic growth factors have been found in dentine matrix, which are released in a biologically active form after a traumatic injury (30). Orthodontic forces produce an inflammatory pulp response with liberation of angiogenic growth factors and proliferation of microvasculature (31, 32), allowing more oxygen supply and nutrients to cells that are acting as part of a defense mechanism against an
inflammatory process. It also allows carbon dioxide and other waste products to be removed easily. A higher blood flow may contribute to the increased presence of inflammatory cells and the cell activity of odontoblasts and fibroblasts, enhancing the production of collagen fibers.

To our knowledge, no other studies have compared pulp angio-genesis after orthodontic movement in subjects under the influence of NSAIDs. However, some authors have evaluated pulp reactions to intrusive movements with results similar to those in this study (31–33).

An increase in thickness of the predentin from moderate to severe was observed in most of the teeth (85.3%), indicating a higher level of odontoblastic activity during orthodontic treatment. However, there was no statistically significant difference between the placebo and the NSAID groups, in contrast to reports by other authors (34). The calcification pattern observed in the predentin was irregular and included dentine zones with no calcification, consistent with a rapid synthesis process.

Similar to reports by Stenvik and Mjor (2), most of the teeth had little or no vacuolization in the odontoblastic layer, and there were no differences between groups. This indicates that the forces used generated inflammatory changes without producing important cell degeneration in the odontoblastic layer.

Pharmacologic regulation of bone resorption has been suggested by means of the use of antiinflammatory drugs such as dexamethasone (35). The use of other substances such as alendronate, a third-generation biphosphonate, and taurine, a B-amino acid considered an essential parenteral nutrient, have been suggested for the prevention and management of external root resorption mediated by osteoclasts and caused by bacteria (36). Few studies have reported the effects of NSAIDs on external root resorption in patients undergoing orthodontic treatment. This study found that nabumetone is effective in the prevention of external root resorption mediated by osteoclasts and subsequent bone resorption, and increase of prostaglandins. NSAIDs not only achieve their desired anti-inflammatory effects but also inhibit the increased production of prostaglandins. NSAIDs including ibuprofen, ketoprofen, ibuprofen and isoxsuprofen, and nabumetone inhibit 5-lipoxygenase activity and thereby decrease the production of leukotrienes, a class of inflammatory leukotrienes that are produced from arachidonic acid by means of different cyclooxygenase enzymes and subsequent production of prostaglandins (37). However, this in turn stimulates osteoblasts to release interleukin-6 (IL-6) and prostaglandin E2 (PGE2). These mediators recruit and activate osteoclasts and may therefore lead to bone resorption (39).

Prostaglandins have been shown to elicit and participate in inflammatory responses, increase osteoclast activity and subsequent bone resorption, and increase osteoblast activity and new bone formation by inhibiting the cyclooxygenase enzymes and the subsequent production of prostaglandins. NSAIDs not only achieve their desired anti-inflammatory effects but also inhibit the increased production of prostaglandins that is necessary for bone healing to occur (40, 41).

Some authors have suggested that the use of NSAIDs during orthodontic treatment does not influence the amount of tooth movement (17, 18). By contrast, some studies indicate that the rate of tooth movement is slower when NSAIDs are used (18–20, 42). This study concluded that the use of nabumetone does not block orthodontic movements. There was a decrease of only 0.13 mm per month.

The perception of pain is difficult to measure because of the wide range of individual response when the same force is applied to different teeth. Patients’ response after an initial archwire is placed was studied by Jones (24), who reported that patients experienced severe discomfort days after activation. This shows the need to prescribe an analgesic during this period. Pain perception was higher during the first activation phase than during the second reactivation. Finally, pain was significantly less when nabumetone (p = 0.005) was administered, because of its analgesic effect.

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Dr. Villa, Dr. Oberti, Dr. Moncada, Dr. Jaramillo, Dr. Tobon, and Dr. Aguadela are affiliated with the Instituto de Ciencias de la Salud CES, Medellin, Colombia. Dr. Vasseur is affiliated with the Universidad de Antioquia, Medellin, Colombia.

Address requests for reprints to Paula A. Villa, Instituto de Ciencias de la Salud, Medellin, Colombia. E-mail: paulavilla@epm.net.co.

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