

Celebrex Offers a Small Protection From Root Resorption Associated With Orthodontic Movement

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ABSTRACT

Tooth movement results from alveolar bone resorption/deposition following application of orthodontic forces, and root resorption can be an undesirable complication associated with this process. No treatment for external root resorption is available to date.

Objective: To determine if COX-2 inhibitors like Celebrex are effective in protecting root resorption associated with orthodontic forces.

Methods: A force of 80 grams was applied to the left maxillary first molars of 7-week-old female Wistar rats using nickel titanium closed coil springs attached to the cervical area of the incisors with 0.010 stainless-steel ligature wires. Twenty animals were divided into three experimental groups: one receiving no treatment, the second receiving 25mg/kg, and the third receiving 50 mg/kg of celecoxib (Celebrex) in their drinking water. Rats were maintained on a soft diet and euthanized two weeks after initial placement of the force. Paraffin-embedded sections of the right (control) and left (experimental) maxillae were stained with H&E and the areas of root resorption were examined by counting the number of lacunae in the roots.

Results: No difference in the distance of tooth movement (0.5 mm/two weeks) was seen in all three groups. The rats that received the low dose of Celebrex showed no statistically significant difference in root resorption than that of the rats that received no dose. The rats that received the high dose of Celebrex showed a lower number of lacunae (mean = 3.5) than that of the control group (mean 10.2; $p=0.02$).

Conclusions: Administration of Celebrex during the application of orthodontic forces does not interfere with tooth movement and appears to offer some slight protection against root resorption.

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Orthodontic treatment is reliant on the resorption and apposition of bone adjacent to the root structure with none or minimum resorption of the root. It is believed root tissues are resistant to resorption and that cementum is not remodeled as is bone.^{1,2} The resistance of cementum to resorption appears to be derived from the cellular layer known as precementum, and the etiology and pathogenesis of root resorption would depend on the amount of damage caused to the periodontal ligament, PDL. Thus, when there is limited mechanical damage to the precementum, superficial resorption will occur. This type of resorption is reversible and not detectable radiographically. On the other hand, inflammatory resorption is present when larger and deeper resorption lacunae reach dentinal tubules, which leads to an infected leukocyte zone and consequently destruction of the root.^{3,4} Replacement resorption or ankylosis occurs after extensive necrosis of the PDL and the root is incorporated in the alveolar bone.³

Clinical observations in patients with apical hypercementosis, where Sharpey's fibers are more spaced and an increase in cementum turnover is found, suggest the PDL could be involved in this resistant process, and that Sharpey's fibers lack recognition for osteoclasts. This idea is supported by studies in which, after the removal of periodontal tissue from deciduous teeth, osteoclasts got easy access to the root surface.⁴ Some other investigators support the idea that cementum and dentine are more resistant to resorption

than bone because of differences in vascularity. While relative abundance of blood vessels is present in bone, few are close to the tooth side of the periodontal ligament.^{4,5} The presence of proteinase inhibitors in cementum and PDL has also been suggested as being responsible for the resistance of roots to resorption.¹ More recent studies suggest that when an orthodontic force is applied, there is remodeling of the adjacent bone and cementum, with the later repair occurring at a relative

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passive rate after force levels decline. Therefore, root remodeling appears to be also a constant feature in orthodontic tooth movement, and permanent loss of root structure will occur only if repair does not replace the initial resorbed cementum.^{6,7}

It is a common belief the use of strong orthodontic forces will increase the risk of apical root resorption. It has been shown that in cases where compression of the PDL is strong and of long duration, root resorption tends to increase.⁸⁻¹¹ However, other studies suggest the force magnitude is probably not as decisive for root resorption as much as the duration of the force application. The more teeth are displaced, the more root resorption will occur and therefore intermittent forces will cause less severe root resorption than continuous forces.¹² A recent meta-analysis of the literature suggests the treatment-

related causes of root resorption appear to be the total distance the apex moved and the time it took.¹³⁻¹⁵ Root shortening has also been associated with age, agenesis, duration of contraction period, treatment group, trauma, application of continuous forces, etc.^{16,17} Apical root resorption appears to be influenced also by root approximation to the palatal cortical plate during orthodontic treatment.¹⁸ Larger teeth appear to have a greater amount of root resorption, but the amount of alveolar

bone, thickness of cortical bone, density of the trabecular network, and fractal dimension have no correlation with apical root resorption.¹⁹ The idea that root resorption of the upper first molars by the use of nighttime extraoral traction has been rejected and no rela-

tionship between root resorption and the number of activations has been found.^{9,20} In other studies, it has been found that adults experienced more resorption than children, but only in the mandibular anterior segment; that Caucasian and Hispanics experienced more root resorption, that an increased overjet, but not overbite, was significantly associated with greater root resorption. Duration of treatment and the horizontal (but not vertical) displacement of the incisor apices were also significantly associated with root resorption. No difference between male and female patients was found.^{21,22} It has been suggested that genetic factors account for at least 50 percent of the variation in external apical root resorption.²³ Amongst the genes implicated are variations in the Interleukin 1-beta gene and a member of the tumor necrosis factor (TNFRSF11A) family.²⁴⁻²⁶

Treatment for Root Resorption

Successful treatment, depending upon the degree and position (internal or external) of the resorption, when the resorption is mild and internal, can be treated by interrupting the treatment and/or root canal therapy.²⁷ However, when the resorption is external and has penetrated the dentin layer, there is no known successful treatment. Several studies are now being focused at finding ways to either prevent or treat root resorption. Amongst them is a recent study which tested the effect of clodronate, a type of bisphosphonate that strongly inhibits bone resorption and has anti-inflammatory properties, as treatment for root resorption using a rat animal model. Although the local injection of clodronate was somehow successful

in reducing root resorption, it had to be injected every third day, and caused a significant reduction in tooth movement.²⁸ Other studies tested the effect of a noninvasive method like low-intensity pulsed ultrasound (LIPUS) in reducing root resorption in human studies. It was shown that LIPUS can enhance healing of various types of traumatized connective tissues and stimulate dental tissue formation. These studies are more promising since LIPUS-exposed human premolars had a significant decrease in the areas of resorption, the number of resorption lacunae, and showed healing of the resorbed root surface by hypercementosis.²⁹

Objective of This Study

Since for the most part, the process of resorption results from inflammation, in this study the authors wanted to test if administration of nonsteroid

anti-inflammatory, NSAIDs, had a protective effect on root resorption without altering the rate of tooth movement. There are more than 50 NSAIDs on the market, all with varying degrees of therapeutic and side effects. Traditional NSAIDs such as aspirin, ibuprofen, Aleve, Vioxx, Bextra, Celebrex, and other prescription drugs, act by interfering with the synthesis of prostaglandins, chemical mediators released when tissue is injured. NSAIDs provide analgesia and suppress inflammation by inhibiting

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the action of the enzyme cyclooxygenase, resulting in decreased prostaglandin synthesis. Cyclooxygenase exists in two isoenzymatic forms, cyclooxygenase-1, COX-1, and cyclooxygenase-2, COX-2. COX-1 appears to be constitutively expressed in many tissues and produces prostaglandins, which regulate normal cellular functions like the synthesis of eicosanoids that have important homeostatic functions, for example, in the gastric mucosa and platelets.³⁰

However, COX-2 activity is induced by proinflammatory cytokines and produces prostaglandins that mediate the inflammatory response and pain signaling transmission. The suppression of prostaglandin synthesis can also produce gastric and renal toxicity, as well as impair normal platelet function. Thus, NSAIDs are associated with potentially harmful side effects. Traditional nonspecific NSAIDs inhibit

both COX-1 and COX-2, and in doing so, not only decrease inflammation and pain, but also promote gastrointestinal tract damage and bleeding. A class of anti-inflammatory medications has been developed that primarily inhibits COX-2 while sparing the enzymatic activity of COX-1 at therapeutic dosages like rofecoxib and celecoxib.³¹ The authors selected celecoxib, Celebrex, for these studies and a rat animal model previously established in the laboratory, in which root resorption consistently resulted after the application of orthodontic forces of 80 grams or greater.

Methods and Materials

Twenty 7-week-old female Wistar rats were used in this study. All animals were treated under the most humane conditions according to protocols approved by the University of Southern California Institutional Animal Care and Use Committee. The average weight of the rats was 105-115 grams, and the rats were anesthetized by intraperitoneal injection of phenobarbital (0.1 mg/gm of body weight). A modified technique described by Brudvik and Rygh was used.³² A nickel titanium closed coil spring with an additional spring eyelet was attached to the cervical area of the incisors and left molar of the maxilla with 0.010 stainless-steel ligature wire. A continuous force of 80 gm using a nickel titanium (Sentalloy) closed coil spring (GAC, N.Y.; 10-00-02 NiTi with M hooks) was applied to the left maxillary first molar with the right side being the control. The force applied was measured using a dynamometer (Dentaurum No 040711, Newtown, Pa). After the appliance was tied on

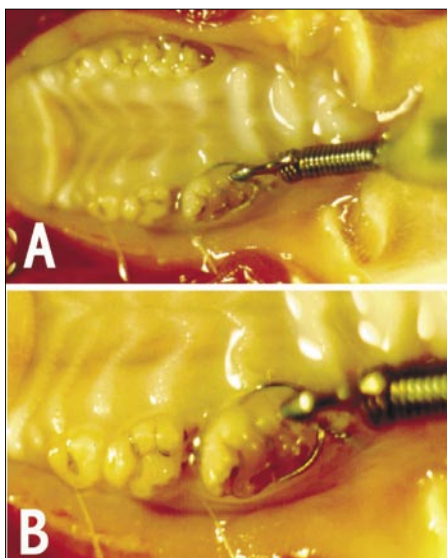


Figure 1. (A) Tooth movement on rat maxillary first molar after 14 days of force application. (B) High magnification of A.

the molar, the coil spring was stretched until its mesial eyelet touched the distolingual surface of the anterior teeth, and the force registered by the dynamometer indicated 80g. The force applied was measured twice to guarantee equal force delivery in all rats. A notch in the middle third of the distal surfaces of the incisors was placed with a low-speed carbide bur to prevent occlusal migration of the ligature. In order to avoid possible breakage of the wire, the surface of the maxillary incisors was etched for 20 seconds with 37 percent phosphoric acid and then covered with self-cured orthodontic composite (Ormco orthodontic bonding kit), the incisal edge of the mandibular incisors was reduced, and the rats were maintained on a soft food diet under standard conditions in the central animal care facilities. All animals were housed in facilities maintained by the University's Vivaria. Rats were divided into three groups:

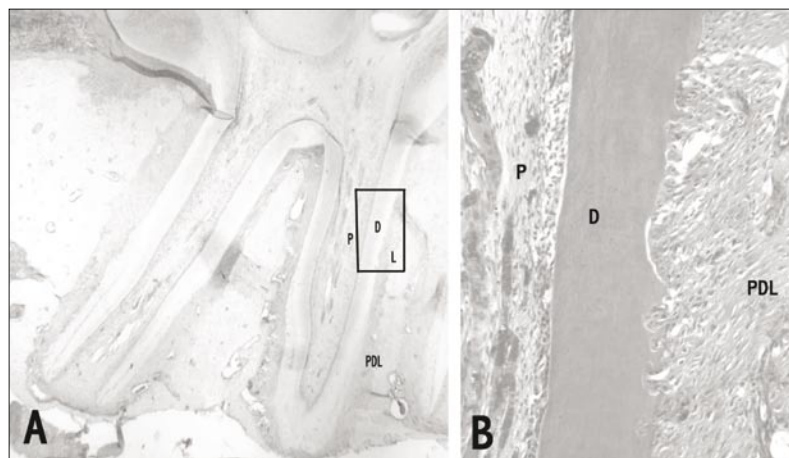


Figure 2. (A) Sagittal section of the rat maxillary first molar after two weeks of application of an orthodontic force of 80g and (B) the area of lacunae showed at a 20x magnification. P=Pulp, D=Dentin, PDL=Periodontal ligament, L=Lacunae.

■ **Group No. 1 or Control:** Rats were fed a soft diet and regular drinking water.

■ **Group No. 2 or Low Dose:** Rats were fed a soft diet, drinking water with Celebrex (25 mg per kg of body weight), and a little sugar to induce them to drink the water. The water was changed daily and the amount of water consumed was monitored by measuring the level of water remaining in the bottle after 24 hours.

■ **Group No. 3 or High Dose:** Rats were fed a soft diet, drinking water with Celebrex (50 mg per kg of body weight), and a little sugar to induce them to drink the water. The water was changed daily and the amount of water consumed was monitored by measuring the level of water remaining in the bottle after 24 hours.

Doses of Celebrex were extrapolated from doses recommended for human use by the manufacturers. All animals were euthanized with CO₂ after two

weeks of initial placement of the orthodontic forces. The rats were decapitated, the appliances were removed, and the tooth movement was measured as the distance between the first and second molars. Whole palate samples were cut in half and fixed in 10 percent neutral buffered formalin, NBF, solution for 24 hours. Tissues were then washed with distilled water in vials for one to two hours with four changes and decalcified with EDTA at 4°C for six weeks. Tissues were processed for paraffin embedding procedures and sagittal 5 microns sections were prepared using a microtome and stained with hematoxylin and eosin or Mallory, and analyzed under light microscopy.

The data was analyzed using histomorphometric measurements of root resorption. The numbers of lacunae and the resorption surface area were checked and recorded in those cases where signs of root resorption were present. Each section was independently evaluated by

Table 1**Analysis of the number of lacunae, intensity of lacunae and position**

Control (right) no drug											
Rat#	Lacunae	Total score	MM	MD	DM	DD	Cervical	Middle	Apical	Comp	Tension
C1	3	3	3	0	0	0	0	3	0	3	0
C2	2	3	0	0	0	2	2	0	0	0	2
C3	3	3	0	0	0	3	0	3	0	0	3
C5	1	3	0	1	0	0	0	1	0	1	0
C6	2	3	2	0	0	0	2	0	0	2	0
Avg	2.2	3	1	0.2	0	1	0.8	1.4	0	1.2	1
STDE	0.836660027	0									
Experimental (left) no drug											
Rat#	Lacunae	Total score	MM	MD	DM	DD	Cervical	Middle	Apical	Comp	Tension
C1	8	10	4	2	2	0	1	7	0	6	2
C2	10	13	4	2	2	2	1	9	0	6	4
C3	10	17	3	2	1	4	1	9	0	4	6
C5	9	11	3	1	3	2	1	5	3	6	3
C6	12	15	4	4	2	2	2	10	0	6	6
Avg	9.8	13.2	3.6	2.2	2	2	1.2	8	0.6	5.6	4.2
STDE	1.483239697	2.863564213									
Control (right) low dose											
Rat#	Lacunae	Total score	MM	MD	DM	DD	Cervical	Middle	Apical	Comp	Tension
L1	3	4	3	0	0	0	3	0	0	3	0
L2	2	3	0	1	0	1	0	1	1	1	1
L3	3	5	3	0	0	0	0	3	0	3	0
L4	3	5	3	0	0	0	1	2	0	3	0
Avg	2.75	4.25	2.25	0.25	0	0.25	1	1.5	0.25	2.5	0.25
STDE	0.5	0.957427108									
Experimental (left) low dose											
Rat#	Lacunae	Total score	MM	MD	DM	DD	Cervical	Middle	Apical	Comp	Tension
L2	8	12	4	0	0	4	1	6	1	4	4
L3	6	11	3	0	2	1	1	4	1	5	1
L4	6	10	3	3	0	0	1	5	0	3	3
L6	10	14	3	4	3	0	1	7	2	6	4
Avg	7.5	11.75	3.25	1.75	1.25	1.25	1	5.5	1	4.5	3
STDE	1.914854216	1.707825128									
Control (right) high dose											
Rat#	Lacunae	Total score	MM	MD	DM	DD	Cervical	Middle	Apical	Comp	Tension
H1	5	5	1	0	4	0	1	0	4	5	0
H4	3	3	3	0	0	0	1	2	0	3	0
H5	1	2	1	0	0	0	1	0	0	1	0
H6	4	6	4	0	0	0	4	0	0	4	0
Avg	3.25	4	2.25	0	1	0	1.75	0.5	1	3.25	0
STDE	1.707825128	1.825741858									
Experimental (left) high dose											
Rat#	Lacunae	Total score	MM	MD	DM	DD	Cervical	Middle	Apical	Comp	Tension
H1	8	11	0	4	3	1	1	4	1	3	5
H3	5	9	3	0	2	0	1	2	1	5	0
H4	6	10	0	4	0	2	1	4	1	0	6
H6	6	11	3	0	3	0	3	3	0	6	0
Avg	6.25	10.25	1.5	2	2	0.75	1.5	3.25	0.75	3.5	2.75
STDE	1.258305739	0.957427108									

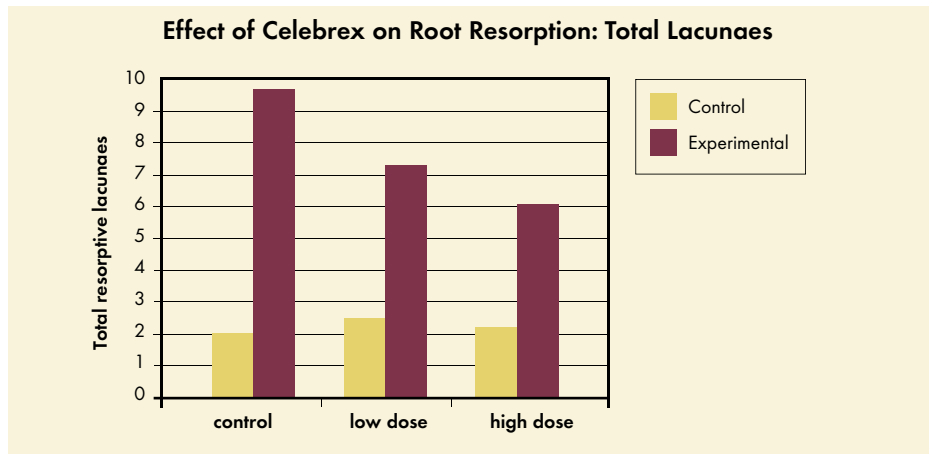


Figure 3. Effect of Celebrex on the number of lacunae formed as consequence of orthodontic forces.

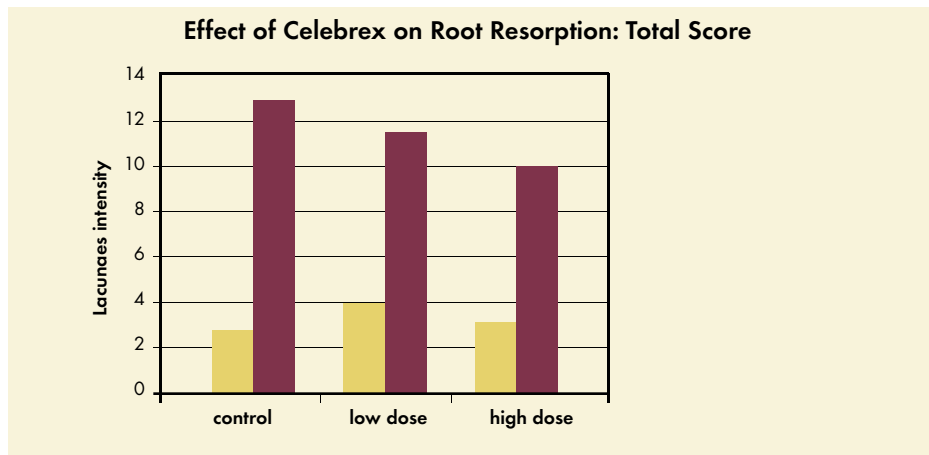


Figure 4. Effect of Celebrex on the number and intensity of lacunae produced as consequence of application of orthodontic forces.

two investigators, each evaluating the resorption two times. The total number of lacunae was determined (lacunae) and the extent of the resorption was scored in a scale of 1 to 5, depending on the severity of the resorption, "1" being minimal severity and "5" being maximum severity. The sum of all the lacunae scores per histological section was the "total score." The loca-

tion of the resorption was noted as apical, middle or cervical third of the root; and, the root surface the resorption occurred was noted as mesial root mesial aspect, mesial root distal aspect, distal root mesial aspect, or distal root distal aspect. Lacunae in the compression vs. tension sites were also noted. A T-test was performed to determine the statistical significance of the data.

Results

Analysis of the "gap" created between the first and second molars was used as an indication of the amount of tooth movement resulting from the application of the orthodontic forces (Figure 1). No differences were found between the three groups of rats. A representative histological section of a first molar showing the resorption lacunae can be seen in Figure 2. The analysis of the data can be seen in Table 1. When the total number of lacunae in the three different groups was plotted, the number of "natural" resorption in the right molars, where no appliance was placed remained constant. However, the number of lacunae decreased in the rats treated with both low and high doses, with the last one decreasing even more (Figure 3). When the total score (number and deepness of the lacunae) was plotted, the results were very similar, although the differences appeared to be slightly less (Figure 4). Application of a T-test indicated that the difference between the low dose and the control has a p-value of 0.07, and does not represent a statistically significant difference. However, the difference between the high dose and the control has a p-value of 0.02, and indicated that the results were statistically significant, suggesting that Celebrex does provide some protection from root resorption.

Analysis of the distribution of resorption lacunae by site (Figure 5) indicated that in the control, the majority of the lacunae were present in the middle portion of the root, whereas only 6 percent were present in the apical portion, and 12 percent in the cervical portion. In the low dose group, this distribution changed slightly with an increase in the apical resorption while the proportion of lacunae in the middle portion diminished. In the high dose

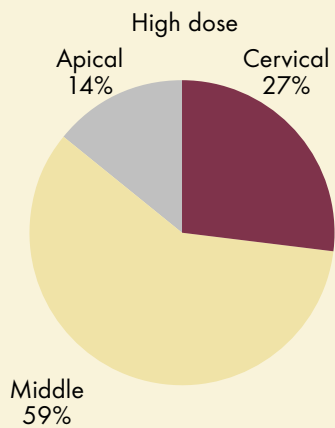
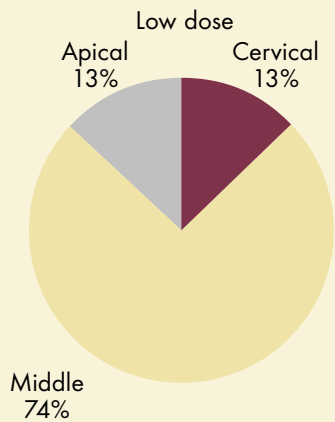
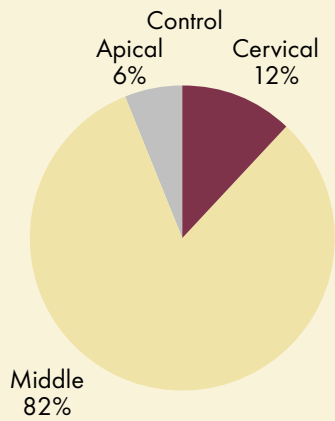


Figure 5. Distribution percentage of lacunae in cervical, middle, and apical regions of the experimental molars.

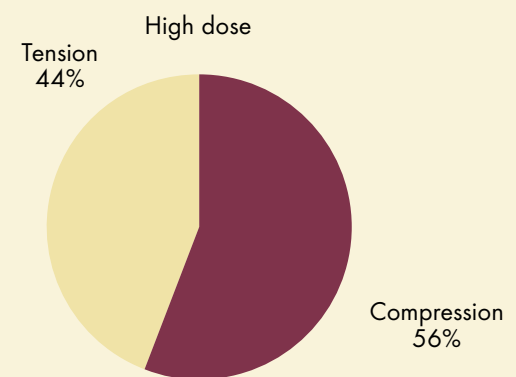
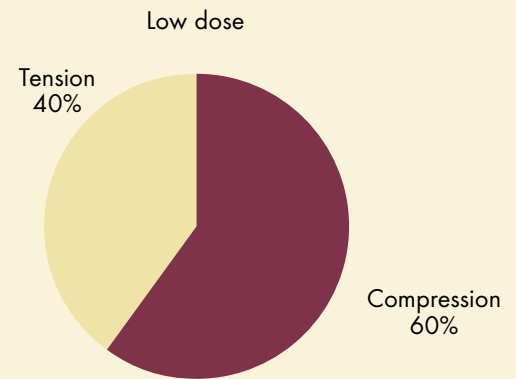
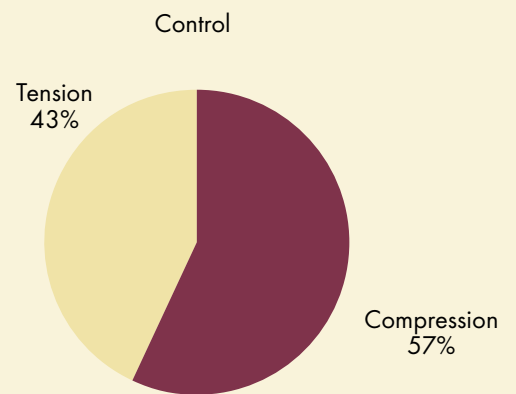


Figure 6. Distribution of lacunae in the compression and tension sites of experimental molars.

group, there was an increase in the cervical resorption, while the apical resorption did not appear to change (Figure 4). When the presence of lacunae was plotted by tension or compression sites, all three groups appeared to have had similar distribution, with the resorption being more prevalent (56 percent to 70 percent) in the compression site than in the tension site (40 percent to 44 percent).

Discussion

The results presented in this study suggest that the use of the NSAID Celebrex concomitant with the application of orthodontic forces might offer not only pain relief but also some mild protection from root resorption associated with this process. Although extrapolation from animal studies to humans is not always perfect or completely accurate, animal models offer several advantages as compared to human studies that can provide good insights as to possible mechanisms that may well work also in humans. Animal studies offer several advantages that make these type of studies possible; for example, a reliable system where we know that application of an orthodontic force of 80g will result in root resorption in a relatively brief period of time that can be detected early and accurately and can be measured. Therefore, although taken with caution, the authors' results suggest that the use of NSAIDs may be of benefit for patients undergoing orthodontic treatment.

The effectiveness of NSAIDs like ibuprofen in relieving the pain associated with orthodontic force activation in human studies has been reported.³³ However, one animal study suggested that administration of NSAIDs (or prostaglandin inhibitors) will interfere

with tooth movement and therefore will slow down progress in treatment.³⁴ The authors did not find this to be the case in their studies. Pain relievers like acetaminophen have been recommended for patients undergoing orthodontic treatment since they do not interfere with tooth movement.³⁵ Unfortunately, acetaminophen does not have anti-inflammatory properties and will not offer much protection against inflammatory root resorption.

The use of a COX-2 inhibitor, rather than a COX-1 and COX-2, has the advantage that it protects the GI tract from the side effects of other NSAIDs.³⁶ Since this study was initiated, the use of COX-2 inhibitors has been questioned due to their potential to produce cardiovascular problems, although the evidence for Celebrex is still being evaluated.³⁷ Perhaps the use of other NSAIDs might be as, or more effective than Celebrex in protecting from root resorption associated with orthodontic treatment.

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