Original Article

Effects of Steroidal and Nonsteroidal Drugs on Tooth Movement and Root Resorption in the Rat Molar

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ABSTRACT

Objective: To test the hypothesis that the administration of aspirin, acetaminophen, meloxicam, celecoxib, and prednisolone have no effect on root resorption and tooth movement.

Materials and Methods: A mesial force of 50 g was applied to the left maxillary first molars of sixty 10-week-old male Wistar rats using nickel titanium closed coil springs attached to the cervical area of the incisors. The rats were randomly divided into 12 groups of 5 each. High and low doses of aspirin, acetaminophen, meloxicam, celecoxib, and prednisolone were administered via drinking water for 2 weeks. The experimental control group had tooth movement but received no drug. The negative control group received neither tooth movement nor drugs. The amount of tooth movement was measured on digitized lateral cephalometric radiographs. Rats were sacrificed after 2 weeks. Mesial and distal roots (distobuccal and distopalatal) were examined using scanning electron and three-dimensional (3D) scanning laser microscopes. The surface area, depth, volume, and roughness of the root resorption craters were measured.

Results: When compared with experimental control rats, only prednisolone- and high-dose celecoxib-treated groups showed significantly less root resorption and less tooth movement. Although low dose celecoxib-treated group significantly decreased the tooth movement, root resorption was similar to the control group. Furthermore, resorption craters showed a smoother surface in the prednisolone-treated rats.

Conclusions: The hypothesis was rejected. Administration of prednisolone and high-dose celecoxib reduces root resorption and interferes with tooth movement in rats. Both drugs may interfere in the arachidonic acid cascade depending on dose thresholds. (*Angle Orthod.* 2009;79:715–726.)

KEY WORDS: Anti-inflammatory; NSAID; Steroid; Glucocorticoid; Cyclooxygenase; COX

INTRODUCTION

In spite of extensive research in animals and man, the exact mechanism by which teeth move has still not been determined.[1] Histologically, considerable evidence indicates that a major part of root resorption resulting from orthodontic treatment is associated with local overcompression of the periodontal ligament during tooth movement, and in particular is associated with the removal of the necrotic tissue of the hyalinized zone by perivascular macrophages.[2–6]

Orthodontic mechanical forces produce inflammation in periodontal tissues.[7] Prostaglandins (PGs), lipid mediators derived from arachidonic acid (AA), play central roles in the pathogenesis of inflammation, fever, and pain.[8] Evidence suggests that tooth movement significantly increased with prostaglandin injections.[9–12] PGs are generated by the oxygenation of AA to the unstable intermediate prostaglandin H_2 (PGH_2) by PGHS, of which there are two major isoforms—the constitutive PGHS-1 and the (generally) inducible PGHS-2. These enzymes are also commonly referred to as cyclooxygenase (COX) 1 and 2, respectively, in reference to the specific enzymatic active site that catalyzes AA oxygenation and provides the target for the majority of pharmacologic inhibitors of these enzymes.[13] Chandrasekharan et al[14] found an enzyme within the canine cerebral cortex, which they designated ''COX-3.'' This enzyme is the product of an al-

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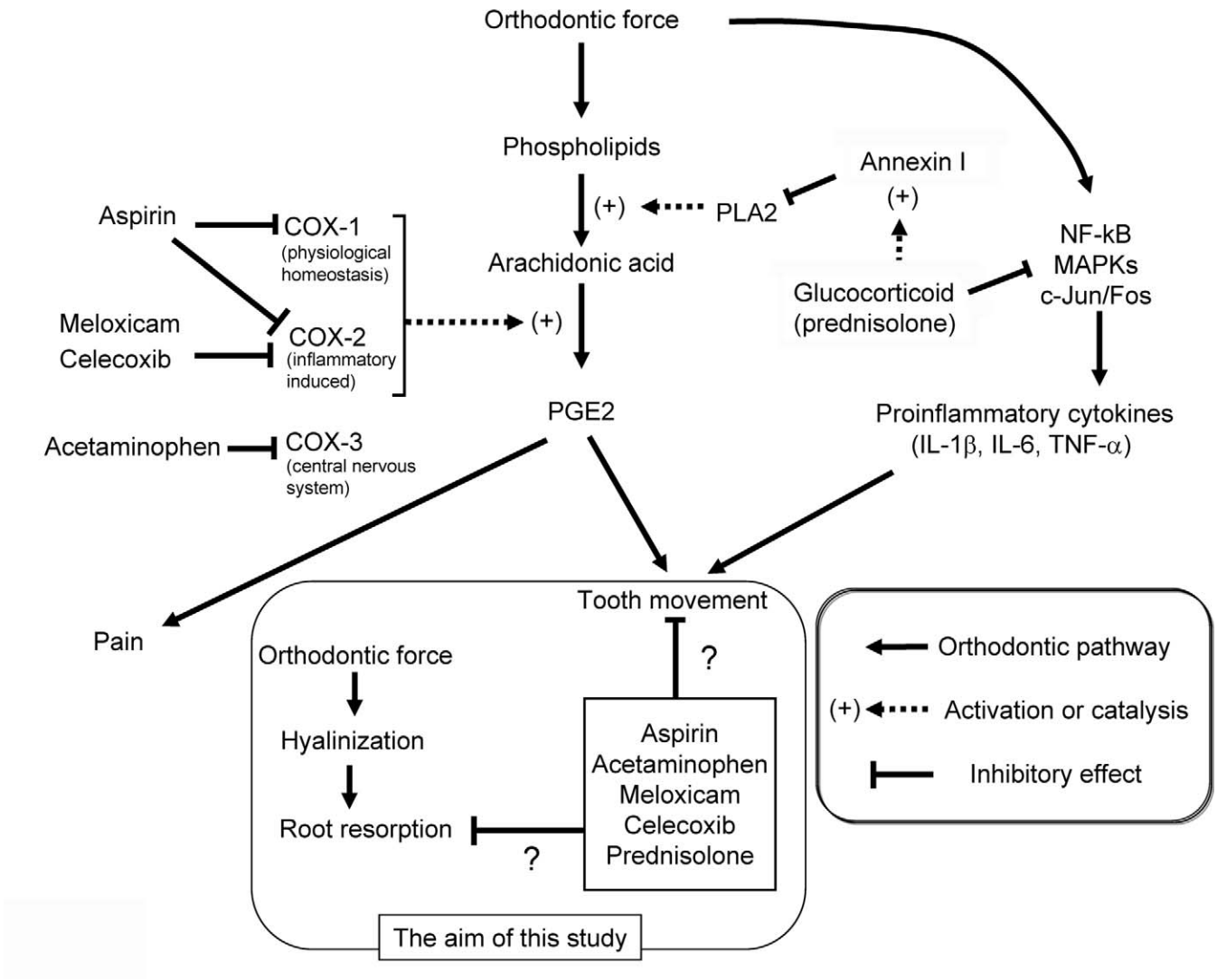

Figure 1. Mechanisms of orthodontic force-induced tooth movement, root resorption, and drugs related to this study.

ternatively spliced messenger ribonucleic acid (mRNA) of the COX-1 gene. However, the name COX-3 has been rejected by many authors because it is a product of alternative splicing of PGHS-1 and not a genetically distinct entity.[15,16]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common medications taken worldwide for the treatment of pain, inflammation, and fever.[17] Although chemically disparate, they produce their therapeutic effects by the common ability to inhibit the activity of COX enzymes.[18] Nonselective COX inhibition includes agents such as aspirin, acetaminophen, indomethacin, and naproxen, which provide effective pain relief for inflammatory conditions.

Acetaminophen (paracetamol) differs from the majority of NSAIDs and selective inhibitors of PGH_2 synthase (PGHS) 2 because it lacks significant anti-inflammatory activity.[13] Although acetaminophen has been used clinically for more than a century, its mode of action is still not clear. Indeed, inhibition of COX-3 is one of the more recent proposals that has been put forward to explain the unusual effects of acetaminophen, but further analysis has suggested that this interaction is unlikely to be clinically relevant. Hogestatt et al[19] identified a novel metabolite of acetaminophen (AM404) in the nervous system which inhibits purified COX-1 and COX-2, leading to PG formation in lipopolysaccharide-stimulated macrophages. The first NSAIDs developed as selective COX-2 inhibitors are celecoxib (Celebrex) and rofecoxib (Vioxx). Other COX-2 inhibitors include meloxicam (Mobic), nimesulide, and etodolac (Lodine).[20]

Steroidal anti-inflammatory drugs such as glucocorticoids are indicated for the treatment of inflammatory disorders such as allergies, asthma, autoimmune diseases, and sepsis. Their efficacy in alleviating inflam-

matory disorders results from the pleiotropic effects of the glucocorticoid receptor on multiple signaling pathways. Glucocorticoids are known to inhibit PG production through three independent mechanisms: suppression of signal transduction relating to proinflammatory cytokines, suppression of COX, and the activation of annexin I. Annexin I inhibits phospholipase $A_{2\alpha}$ (cPLA2), which results in the suppression of AA and its subsequent conversion to eicosanoids (ie, prostaglandins, thromboxanes, prostacyclins, and leukotrienes).[21] A schematic overview is shown in Figure 1.

As orthodontic tooth movement is considered to involve an inflammation process, many studies regarding the effect of anti-inflammatory drugs on tooth movement and root resorption have been reported. However, controversy still exists. The purpose of the present investigation is to provide a quantitative assessment of the effect of steroidal and nonsteroidal anti-inflammatory drugs on tooth movement and root resorption by using scanning electron and laser microscopes.

MATERIALS AND METHODS

Sixty 10-week-old male young adult Wistar rats (SLC, Shizuoka, Japan; body weight, 230–250 g) were allowed 1 week to acclimatize before the start of the experiments. The study was conducted under approval from the Animal Welfare Committee of Nagasaki University. All animals were housed individually in plastic cages in a colony room and fed standard pellet diet and water ad libitum.

A continuous force of 50 g-nickel titanium (NiTi) closed-coil spring (Sentalloy, Tomy Inc, Fukushima, Japan) was applied to move mesially the maxillary left molar. The appliance was set under anesthesia (intraperitoneal injection of pentobarbital) with a dosage of 60 mg/kg body weight. The appliance set has been previously described (Figure 2).[22] The force magnitude was measured with a tension gauge (DTN-150, Teclock, Tokyo, Japan) when the appliance was set and at the end of the experiments.

The rats were randomly divided into 12 groups of 5 rats each (Figure 3): 2 control groups (positive and negative controls) and 10 experimental groups. The negative control group received neither pharmacologic treatment nor tooth movement. The positive control group received orthodontic treatment for 2 weeks without any pharmacologic treatment. The experimental groups were divided into 10 groups receiving the following drugs in their drinking water: aspirin (high dose 300 mg/kg, low dose 60 mg/kg); acetaminophen (high dose 100 mg/kg, low dose 20 mg/kg); meloxicam (high dose 67 mg/kg, low dose 13 mg/kg); celecoxib (high dose 16 mg/kg, low dose 3.2 mg/kg); and prednisolone (high dose 0.67 mg/kg, low dose 0.13 mg/kg). All drugs except for celecoxib were purchased from Wako Pure Chemical Industries Ltd (Osaka, Japan). Celecoxib was provided by Pfizer (New York, NY). 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. All low doses were extrapolated from doses recommended for human use by the manufacturers.

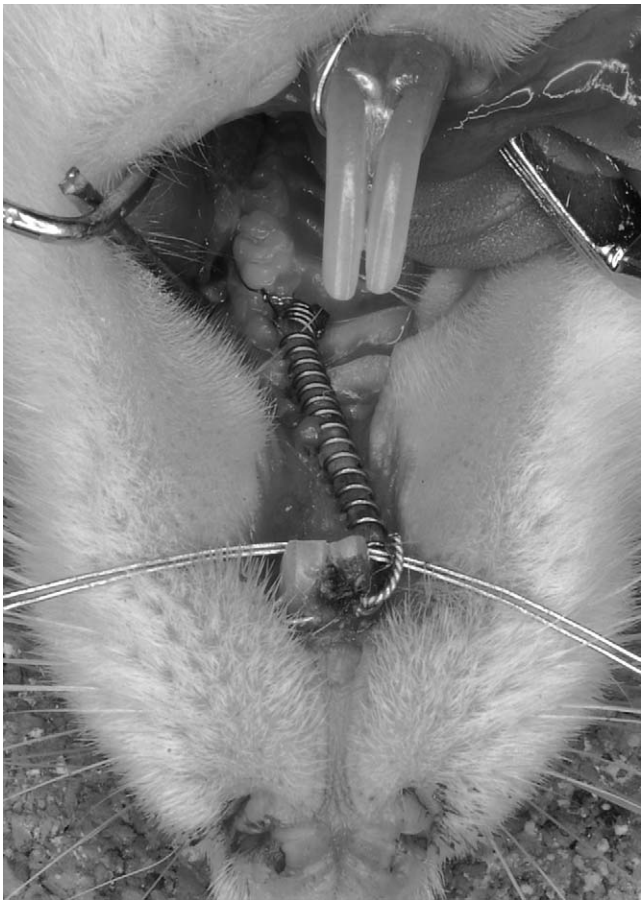

Figure 2. Intraoral picture of the appliance.

Tooth movement was measured on digitized lateral cephalometric radiographs, as previously described.[22] The amount of tooth movement was determined by the change in the distance between the most posterior point of the posterior border of the maxillary first molar crown and the most anterior point of the anterior border of the maxillary second molar crown. At the end of the experiments, the rats were sacrificed by an overdose of CO_2.

The left upper first molar, including its surrounding bone, were cut as a block, followed by delicately removing the alveolar bone to avoid any root surface damage. The molars were submerged in 1% sodium hypochlorite to eliminate remaining periodontal liga-

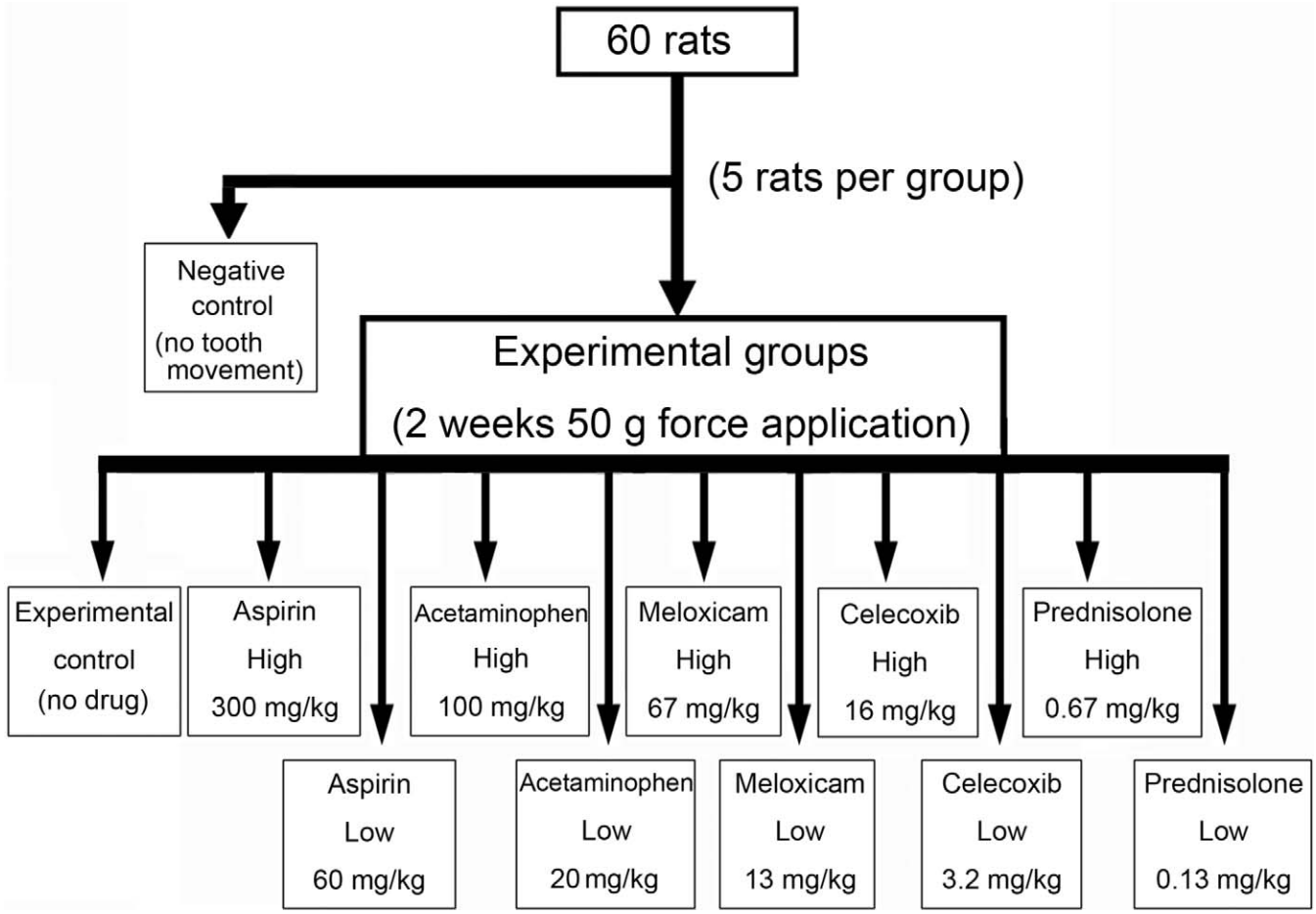

Figure 3. Design of the experiment showing the control and experimental groups. Each group consists of five rats.

ment remnants. The molars were then sectioned buccolingually through the crown near the cemento-enamel junction with a thin diamond disc. Root resorption craters on the apical region were not evaluated due to anatomic variations and difficulties in delimitating the craters. The mesial and distal surfaces of distobuccal, distopalatal, and mesial roots were evaluated with a scanning electron microscope (TM-1000, Hitachi, Tokyo, Japan) and three-dimensional (3D) laser scanning microscope (VK-8500, Keyence, Kyoto, Japan). Since resorption craters in the distal surfaces of the roots were scarcely detectable they were also excluded from the study. All craters scattered on the cervical and middle thirds of the roots (mesial side) were digitally obtained. Surface area was measured by means of commercial software (Mimics 11.11; Materialise Software, Leuven, Belgium). The deepest point and the surface roughness of the resorption craters were calculated with the laser microscope program (VK-8500). The roughness in this study was defined as the arithmetical average roughness with a resolution of 0.01 μm.

The volume was measured by multiplying the crater area by the average depth. The same investigator performed all measurements, and every measurement was repeated three times. The mean value was used as the final measurement. To assess measurement reproducibility, serial measurements of area, depth, surface roughness, and volume were performed 10 times in one randomly selected distobuccal root from the experimental control group. Each value of mean and standard deviation was 34.1 $\pm$ 0.3 % for the area; 117.5 $\pm$ 0.37 μm for the depth; 12.9 $\pm$ 0.05 $\times$ 10^6 μm^3 for the volume; and 18.7 $\pm$ 0.5 μm for surface roughness.

Statistical Methods

Statistical analysis was performed with SPSS version 16.0 (SPSS, Chicago, Ill). Univariate analyses of variance (ANOVA) followed by Bonferroni adjustments were performed.

Table 1. Descriptive Statistics of Mesial, Distopalatal, and Distobuccal Roots[a]

	Area, %		Depth, mm		Volume, $\times 10^6$ μm^3		Roughness, mm	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Mesial root								
Negative control	0.3	0.2	2.2	0.4	0.3	0.1	1.4	0.3
Experimental control	5.0	2.2	5.0	2.1	0.9	0.6	6.2	1.0
Asp-high	3.6	1.1	3.6	1.1	0.9	0.1	4.5	0.3
Asp-low	4.9	0.8	4.9	0.8	0.9	0.1	5.2	0.8
Ace-high	4.3	1.3	4.2	1.3	0.8	0.1	4.8	1.1
Ace-low	4.9	0.9	4.9	0.8	0.9	0.1	7.1	0.9
Mel-high	3.9	0.9	3.9	0.9	0.7	0.1	3.8	0.2
Mel-low	5.7	1.5	5.7	1.4	0.7	0.1	3.9	0.5
Cel-high	2.7	1.5	2.7	1.7	0.3	0.1	3.0	0.4
Cel-low	5.2	1.3	5.2	1.3	0.6	0.2	3.4	1.1
Pre-high	1.4	0.6	1.4	0.6	0.1	0.0	2.8	1.2
Pre-low	4.8	0.7	4.8	0.7	0.5	0.1	4.3	1.2
Distopalatal root								
Negative control	1.1	0.2	2.3	0.4	0.8	0.1	7.4	0.6
Experimental control	28.8	2.1	76.1	14.0	10.7	1.6	14.9	1.7
Asp-high	27.5	1.6	68.7	7.2	10.5	1.2	13.7	2.0
Asp-low	28.3	1.0	71.7	1.9	11.1	1.6	14.7	3.1
Ace-high	27.4	1.2	65.6	2.3	10.7	1.8	15.0	2.8
Ace-low	26.2	2.2	72.7	1.6	10.4	1.1	16.7	1.2
Mel-high	27.6	0.7	65.1	4.0	10.9	1.2	13.2	2.2
Mel-low	28.4	1.1	64.2	2.2	10.6	0.8	17.5	0.7
Cel-high	20.1	1.6	53.5	1.4	3.3	0.7	15.0	1.4
Cel-low	28.9	0.9	58.3	4.6	10.7	0.7	14.9	2.5
Pre-high	9.2	1.7	31.1	8.1	2.7	0.2	8.6	3.3
Pre-low	24.5	2.1	47.9	5.9	3.9	0.8	9.6	1.6
Distobuccal root								
Negative control	1.2	0.0	2.5	0.4	0.9	0.1	7.2	0.6
Experimental control	34.8	2.1	117.6	5.1	13.7	1.1	18.7	2.1
Asp-high	31.6	1.6	107.6	1.6	12.7	1.2	16.4	2.0
Asp-low	33.9	2.4	115.5	2.8	13.1	0.5	18.3	1.5
Ace-high	34.5	2.3	113.9	7.8	13.7	1.1	14.3	1.9
Ace-low	34.5	1.8	114.1	4.1	13.1	0.3	17.3	1.4
Mel-high	33.9	2.5	109.6	4.2	12.4	1.2	17.2	1.8
Mel-low	34.6	1.1	117.7	3.4	12.3	0.7	18.0	2.8
Cel-high	29.7	1.9	84.6	2.4	7.9	0.6	16.8	1.5
Cel-low	34.8	0.7	118.6	2.7	13.5	1.4	18.3	1.9
Pre-high	17.0	2.5	64.0	3.4	4.3	0.2	9.5	2.4
Pre-low	33.6	2.3	89.5	2.1	7.7	0.3	11.3	1.7

[a] Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone.

RESULTS

The rat's weight was recorded on a daily basis after the appliance set. The initial weight of the rats was 239.4 ± 6.7 g, and no statistical difference was found among the groups. At the end of the experiments, the weight of experimental control rats was 270.4 ± 10.4 g, and that of aspirin and prednisolone groups was 240.4 ± 21.3 g ($P < .03$) and 238.0 ± 14.0 g ($P < .01$), respectively. The drug administration via drinking water was well tolerated by all the rats. This was confirmed by measuring the amount of water each rat drank per day (25–30 mL).

Examination using SEM showed that the negative control roots were covered by undamaged cementum with a characteristic smooth surface. The apical third of the roots was covered with thick cementum with a rough and irregular surface that, occasionally, contained resorption craters. In all experimental groups, isolated lacunae, wide shallow resorption pit, and deep resorption craters were found. Small isolated lacunae were mainly seen scattered on the mesial roots (cervical half of its mesial surface). Wide shallow and deep resorption craters were observed on the distal roots covering cervical and middle portions of the root. The bottom of the root resorption cavities revealed an extensive, irregular, disorganized, and rough layer with irregular borders (Figure 4).

Root resorption was quantitatively evaluated by

Table 2A. Mesial Root: ANOVA of Groups of Rats (Pairwise Comparisons) With Area, Depth, Volume, and Surface Roughness as Dependent Variables

(I) Experimental Control Group	(J) Drugs Group[a]	Mean Difference (I − J)	SE	Significance[b]	95% CI for Difference[b]	
					Lower Bound	Upper Bound
Area (%)	Asp-high	1.40	0.57	0.88	−0.56	3.37
	Asp-low	−0.45	0.61	1.00	−2.57	1.67
	Ace-high	0.57	0.55	1.00	−1.35	2.48
	Ace-low	0.06	0.59	1.00	−1.98	2.09
	Mel-high	1.16	0.59	1.00	−0.87	3.20
	Mel-low	−1.12	0.61	1.00	−3.23	1.00
	Cel-high	1.77	0.64	0.40	−0.45	4.00
	Cel-low	0.12	0.68	1.00	−2.24	2.48
	Pre-high	3.57	0.57	0.00**	1.60	5.54
	Pre-low	1.52	0.61	0.86	−0.60	3.63
Depth (μm)	Asp-high	3.24	6.93	1.00	−21.42	27.90
	Asp-low	3.23	6.93	1.00	−21.43	27.88
	Ace-high	2.88	6.53	1.00	−20.37	26.13
	Ace-low	−7.97	6.53	1.00	−31.22	15.28
	Mel-high	−4.59	6.53	1.00	−27.84	18.66
	Mel-low	6.08	6.05	1.00	−15.44	27.60
	Cel-high	9.51	6.26	1.00	−12.75	31.77
	Cel-low	0.71	6.53	1.00	−22.54	23.96
	Pre-high	11.25	6.53	1.00	−12.00	34.50
	Pre-low	4.20	6.93	1.00	−20.46	28.85
Volume ($\times 10^6$ μm^3)	Asp-high	0.15	0.12	1.00	−0.25	0.55
	Asp-low	0.11	0.12	1.00	−0.32	0.54
	Ace-high	0.21	0.11	1.00	−0.18	0.60
	Ace-low	0.11	0.12	1.00	−0.30	0.52
	Mel-high	0.37	0.12	0.14	−0.04	0.79
	Mel-low	0.35	0.12	0.34	−0.08	0.78
	Cel-high	0.78	0.13	0.00*	0.33	1.23
	Cel-low	0.47	0.14	0.06	−0.01	0.95
	Pre-high	0.96	0.12	0.00**	0.56	1.36
	Pre-low	0.47	0.14	0.06	−0.01	0.95
Roughness (μm)	Asp-high	1.70	0.83	1.00	−1.28	4.69
	Asp-low	0.94	0.83	1.00	−2.05	3.92
	Ace-high	1.35	0.83	1.00	−1.63	4.34
	Ace-low	−0.86	0.83	1.00	−3.85	2.13
	Mel-high	2.37	0.76	0.19	−0.36	5.10
	Mel-low	2.28	0.83	0.51	−0.71	5.26
	Cel-high	3.19	0.79	0.00*	0.36	6.03
	Cel-low	2.78	0.83	0.10	−0.21	5.77
	Pre-high	2.49	0.79	0.17	−0.35	5.32
	Pre-low	1.82	0.76	1.00	−0.91	4.55

[a] Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone.
[b] Bonferroni adjustment for multiple comparisons.
* Mean difference significant at .03 level; ** mean difference significant at .01 level.

measuring the root resorption crater surface area, depth, volume, and surface roughness. The difference in the measurements among the groups was observed only in the celecoxib and prednisolone groups. The volume of the resorption craters in the celecoxib high dose and prednisolone (high and low dose) groups was significantly smaller than the experimental control groups. Interestingly, the surface of resorption craters showed a smoother structure only in the prednisolone groups (Figure 5; Tables 1 and 2A,B,C).

All coil springs were still active after 14 days, indicating that force was delivered throughout the experiment. After 2 weeks of tooth movement, experimental control rats exhibited 0.28 ± 0.02 mm of tooth movement (Figure 5E; Table 3A,B). Among the experimental groups, prednisolone and celecoxib-treated rats showed less amount of tooth movement.

DISCUSSION

In relation to NSAIDs in this study, only celecoxib suppressed tooth movement as well as root resorp-

Table 2B. Distopalatal Root: ANOVA of Groups of Rats (Pairwise Comparisons) With Area, Depth, Volume, and Surface Roughness as Dependent Variables

(I) Experimental Control Group	(J) Drugs Group[a]	Mean Difference (I − J)	SE	Significance[b]	95% CI for Difference[b]	
					Lower Bound	Upper Bound
Area (%)	Asp-high	1.51	0.72	1.00	−0.99	4.00
	Asp-low	−1.45	0.82	1.00	−4.27	1.37
	Ace-high	1.64	0.70	1.00	−0.79	4.06
	Ace-low	3.17	0.75	0.00	0.58	5.75
	Mel-high	1.35	0.75	1.00	−1.23	3.93
	Mel-low	0.54	0.78	1.00	−2.14	3.22
	Cel-high	8.54	0.82	0.00**	5.72	11.36
	Cel-low	−1.92	0.87	1.00	−4.91	1.07
	Pre-high	19.86	0.75	0.00**	17.27	22.44
	Pre-low	4.55	0.75	0.00**	1.96	7.13
Depth (μm)	Asp-high	7.36	3.34	1.00	−4.44	19.15
	Asp-low	4.40	3.51	1.00	−8.02	16.82
	Ace-high	10.51	3.51	0.22	−1.91	22.92
	Ace-low	3.34	3.51	1.00	−9.07	15.76
	Mel-high	11.03	3.51	0.15	−1.39	23.45
	Mel-low	11.81	3.51	0.08	−0.61	24.23
	Cel-high	22.64	3.51	0.00**	10.21	35.05
	Cel-low	17.79	3.51	1.00	5.36	30.21
	Pre-high	45.01	3.34	0.00**	33.21	56.81
	Pre-low	28.14	3.51	0.00**	15.71	40.56
Volume ($\times 10^6$ μm^3)	Asp-high	−0.51	0.57	1.00	−2.49	1.48
	Asp-low	−0.50	0.62	1.00	−2.63	1.64
	Ace-high	−0.09	0.56	1.00	−2.02	1.84
	Ace-low	−0.30	0.59	1.00	−2.35	1.75
	Mel-high	−0.82	0.59	1.00	−2.87	1.24
	Mel-low	−0.11	0.62	1.00	−2.24	2.03
	Cel-high	7.15	0.65	0.00**	4.91	9.39
	Cel-low	−0.47	0.69	1.00	−2.85	1.91
	Pre-high	7.56	0.57	0.00**	5.58	9.55
	Pre-low	−0.70	0.59	0.00**	−2.75	1.35
Roughness (μm)	Asp-high	1.20	1.16	1.0	−2.95	5.36
	Asp-low	0.23	1.36	1.00	−4.64	5.11
	Ace-high	−0.06	1.36	1.00	−4.93	4.81
	Ace-low	−1.75	1.36	1.00	−6.62	3.12
	Mel-high	1.75	1.36	1.00	−3.12	6.63
	Mel-low	−2.57	1.36	1.00	−7.45	2.30
	Cel-high	−0.07	1.36	1.00	−4.94	4.80
	Cel-low	0.07	1.36	1.00	−4.81	4.94
	Pre-high	6.29	1.27	0.00**	1.74	10.84
	Pre-low	5.33	1.36	0.02	0.46	10.20

[a] Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone.

[b] Bonferroni adjustment for multiple comparisons.

* Mean difference significant at .03 level; ** mean difference significant at .01 level.

tion. On the contrary, aspirin, acetaminophen, and meloxicam do not seem to affect orthodontic tooth movement. Our results are in disagreement with Jerome et al[23] and De Carlos et al,[24] who found that celecoxib and parecoxib did not interfere with tooth movement, while no tooth movement was found in rats treated with rofecoxib.

Some other controversial conclusions regarding the effect of NSAIDs on tooth movement have been reported. Chumbley and Tuncay[25] showed that indomethacin inhibited orthodontic tooth movement. Arias and Marquez-Orozco[26] applied expansion force to upper incisors in rats and reported that aspirin (100 mg/kg) and ibuprofen (30 mg/kg) diminish the number of osteoclasts and reduce orthodontic tooth movement, whereas, acetaminophen (200 mg/kg) did not affect tooth movement. Sandy and Harris[1] found that the NSAID flurbiprofen inhibited the appearance of osteoclasts, but had no significant effect on tooth movement. Wong et al[27] examined the influence of aspirin (65 mg/kg) on orthodontic tooth movement in guinea pigs and found that aspirin did not significantly inhibit

Table 2C. Distobuccal Root: ANOVA of Groups of Rats (Pairwise Comparisons) With Area, Depth, Volume, and Surface Roughness as Dependent Variables

(I) Experimental Control Group	(J) Drugs Group[a]	Mean Difference (I − J)	SE	Significance[a]	95% CI for Difference[a]	
					Lower Bound	Upper Bound
Area (%)	Asp-high	3.26	0.93	0.04	0.01	6.51
	Asp-low	0.92	1.01	1.00	−2.57	4.41
	Ace-high	0.27	0.91	1.00	−2.88	3.43
	Ace-low	0.29	0.97	1.00	−3.06	3.64
	Mel-high	3.78	0.97	1.00	0.43	7.14
	Mel-low	0.15	1.01	1.00	−3.34	3.64
	Cel-high	5.12	1.06	0.00*	1.46	8.79
	Cel-low	0.00	1.12	1.00	−3.89	3.90
	Pre-high	17.83	0.93	0.00*	14.58	21.08
	Pre-low	1.20	1.12	1.00	−2.63	5.15
Depth (μm)	Asp-high	9.94	2.01	0.00*	2.84	17.05
	Asp-low	2.03	2.11	1.00	−5.44	9.51
	Ace-high	3.62	2.01	1.00	−3.48	10.73
	Ace-low	−0.49	2.11	1.00	−7.97	6.98
	Mel-high	3.95	2.11	1.00	−3.52	11.43
	Mel-low	−0.17	2.01	1.00	−7.28	6.92
	Cel-high	33.01	2.11	0.00**	25.52	40.48
	Cel-low	−1.03	2.11	1.00	−8.51	6.44
	Pre-high	53.56	2.11	0.00**	46.08	61.04
	Pre-low	28.02	2.11	0.00**	20.54	35.50
Volume ($\times 10^6$ μm^3)	Asp-high	−0.55	0.37	1.00	−1.84	0.73
	Asp-low	−0.72	0.40	1.00	−2.11	0.66
	Ace-high	−1.24	0.36	0.52	−2.50	0.00
	Ace-low	−0.52	0.38	1.00	−1.85	0.80
	Mel-high	−0.01	0.38	1.00	−1.33	1.33
	Mel-low	0.06	0.40	1.00	−1.32	1.45
	Cel-high	4.59	0.42	0.00**	3.13	6.04
	Cel-low	−1.12	0.44	0.79	−2.66	0.42
	Pre-high	8.10	0.37	0.00**	6.81	9.39
	Pre-low	−0.05	0.44	0.00**	−1.59	1.49
Roughness (μm)	Asp-high	2.31	1.16	1.00	−1.86	6.48
	Asp-low	0.38	1.29	1.00	−4.28	5.04
	Ace-high	4.40	1.29	0.09	−0.26	9.06
	Ace-low	1.45	1.29	1.00	−3.21	6.11
	Mel-high	1.60	1.29	1.00	−3.05	6.26
	Mel-low	0.75	1.29	1.00	−3.91	5.41
	Cel-high	1.94	1.29	1.00	−2.72	6.60
	Cel-low	0.45	1.29	1.00	−4.21	5.11
	Pre-high	9.31	1.29	0.00**	4.65	13.97
	Pre-low	7.40	1.29	0.00**	2.74	12.06

[a] Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone.
[b] Bonferroni adjustment for multiple comparisons.
* Mean difference significant at .03 level; ** mean difference significant at .01 level.

tooth movement. Roche et al[28] investigated the effect of acetaminophen (500 mg/kg) on tooth movement in rabbits. No statistically significant differences were found. Kehoe et al[29] demonstrated that misoprostol increased tooth movement due to PGE_1 activity, ibuprofen inhibited tooth movement due to PG inhibition, and acetaminophen had no effect on the tooth movement process. Although the effects of NSAIDS on tooth movement are still controversial, COX-2/PGE-2 pathway certainly influences orthodontic tooth movement. COX-2 selective inhibitor such as celecoxib might have a high suppressive effect on the target molecule COX-2, which leads to the suppression of root resorption along with tooth movement.

In the present study, the volume of root resorption and tooth movement decreased in the prednisolone-treated group. This is in agreement with Ong et al[30] who administered prednisolone, 1 mg/kg daily, for a 12-day induction period to rats and found less root resorption and fewer TRAP-positive cells within the periodontal space on the compression side. However, they did not find significant differences in the magni-

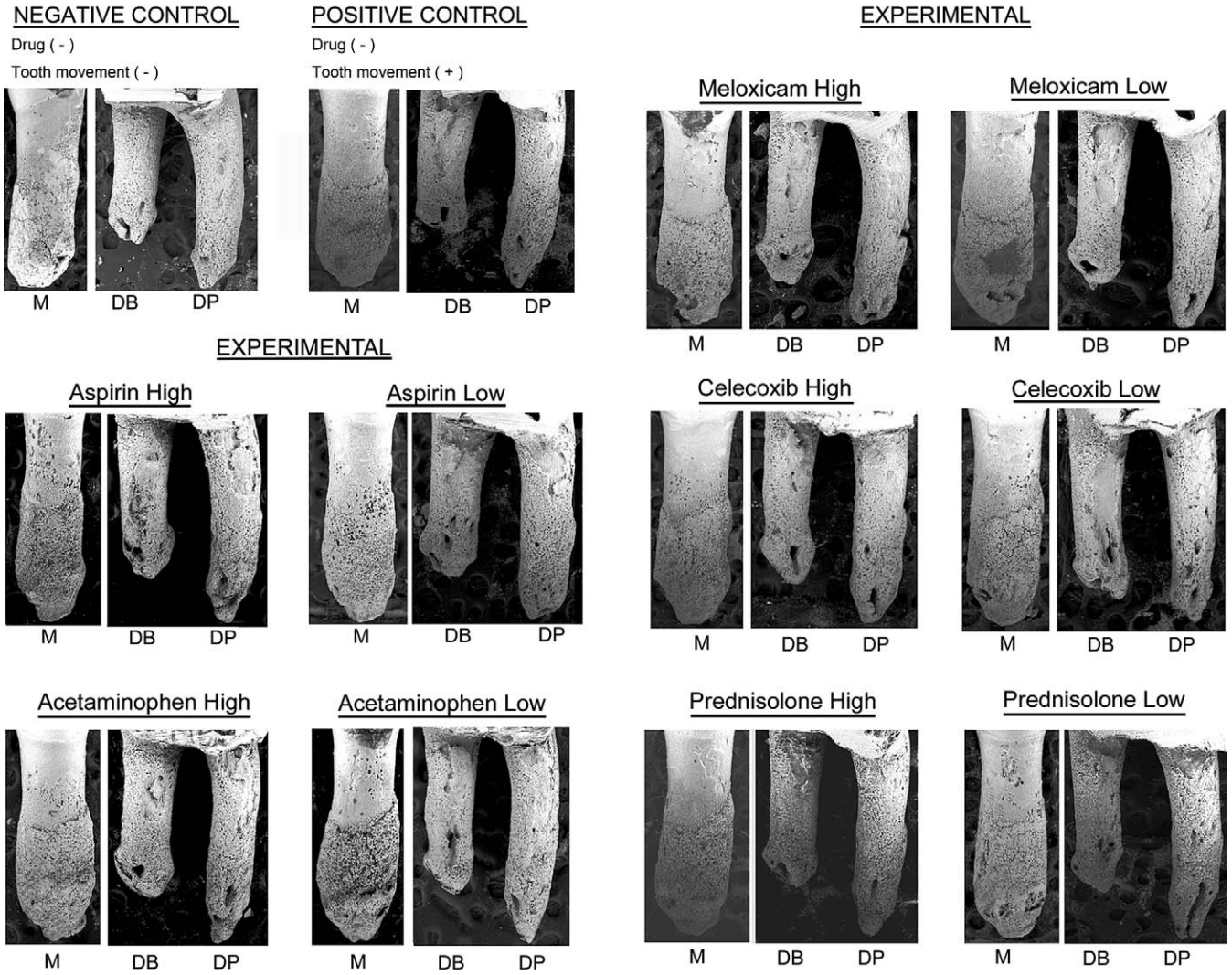

Figure 4. Scanning electron micrographs (60×) of the upper left distal roots (mesial view). M, indicates mesial; DB, distobuccal; and DP, distopalatal root.

Table 3A. Descriptive Statistics of Tooth Movement (mm)[a]

	Mean	±SD
Negative control	0.00	0.00
Experimental control	0.28	0.02
Asp-high	0.24	0.02
Asp-low	0.28	0.03
Ace-high	0.25	0.04
Ace-low	0.27	0.01
Mel-high	0.25	0.01
Mel-low	0.26	0.01
Cel-high	0.16	0.02
Cel-low	0.20	0.02
Pre-high	0.07	0.02
Pre-low	0.15	0.02

[a] Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone.

Table 3B. ANOVA of Groups of Rats (Pairwise Comparisons) With Tooth Movement (mm)

(I) Positive Control Group	(J) Experimental Group[a]	Mean Difference (I − J)	SE	Significance[b]	95% CI for Difference[b] Lower Bound	95% CI for Difference[b] Upper Bound
	Asp-high	−0.01	0.03	1.00	−0.09	0.08
	Asp-low	−0.04	0.03	1.00	−0.13	0.05
	Ace-high	−0.01	0.03	1.00	−0.10	0.08
	Ace-low	−0.04	0.03	1.00	−0.13	0.05
	Mel-high	−0.01	0.03	1.00	−0.10	0.08
	Mel-low	−0.02	0.03	1.00	−0.11	0.06
	Cel-high	0.08	0.03	0.00**	−0.01	0.17
	Cel-low	0.03	0.03	0.00**	−0.05	0.12
	Pre-high	0.16	0.03	0.00**	0.08	0.26
	Pre-low	0.09	0.03	0.00**	0.00	0.18

[a] Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone.

[b] Bonferroni adjustment for multiple comparisons.

** Mean difference significant at .01 level.

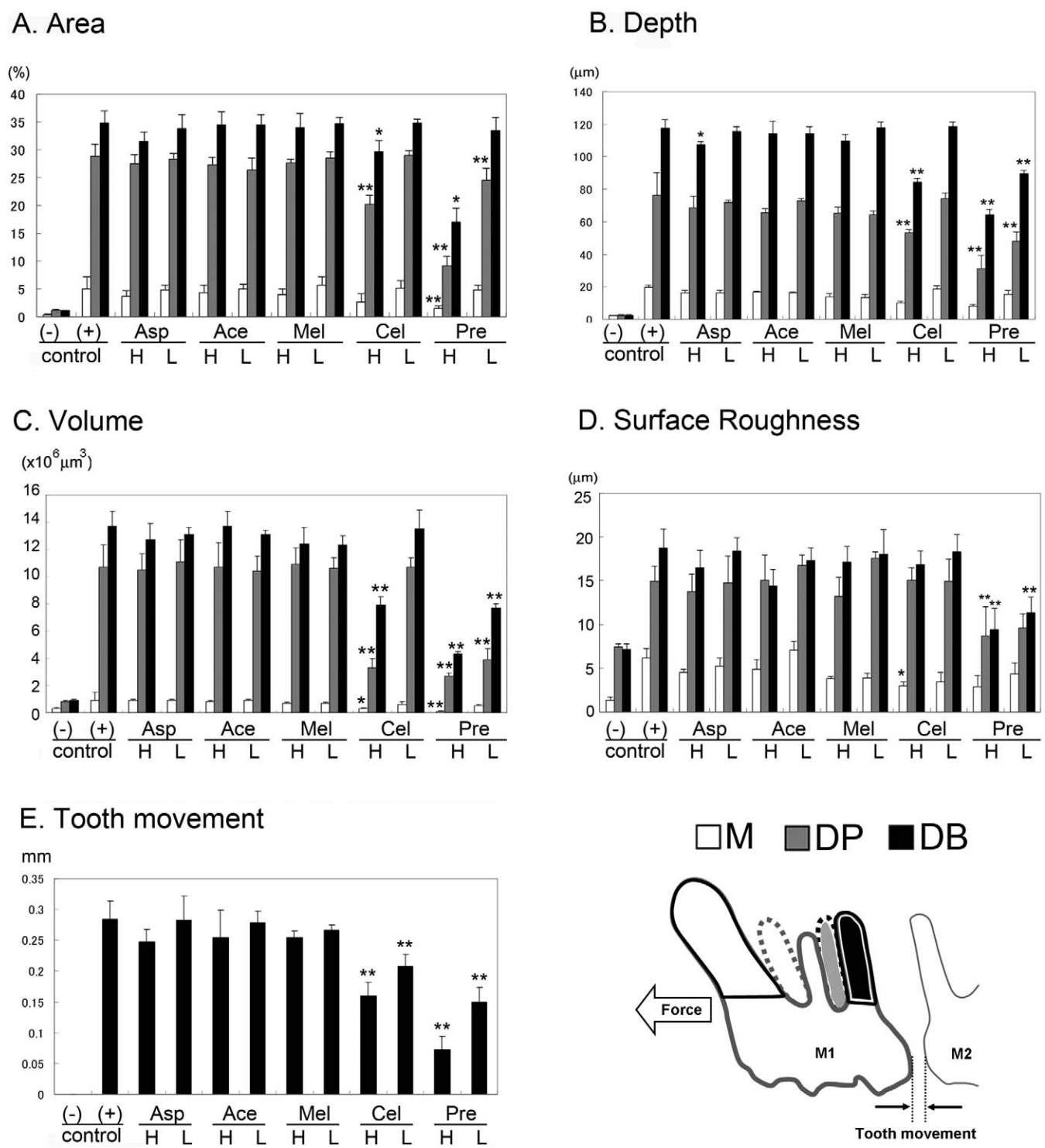

Figure 5. (A) Area of the resorption craters is expressed as the percentage of the resorbed portion of the root in relation to the whole root two-dimensional (2D) area in the scanning electron microscopic image. (B) Depth, (C) volume, (D) surface roughness of the resorption craters, and (E) tooth movement after 50-g force application for 2 weeks. M indicates mesial; DB, distobuccal; and DP, distopalatal root. Asp indicates aspirin; Ace, acetaminophen; Mel, meloxicam; Cel, celecoxib; and Pre, prednisolone. H indicates high dose; L, low dose. * Mean difference significant is at .03 level; ** mean difference significant at .01 level.

tude of tooth movement. Verna et al[31] administered 8 mg/kg/day for 3 and 7 weeks and evaluated root resorption after 25 g-force application. They found that the 3-week group showed significantly more root resorption. The inconsistencies among the above mentioned reports may be caused by different experimental conditions such as animal age, drug administration frequency, and duration.

Among the investigated drugs, celecoxib and prednisolone suppressed tooth movement and root resorption. Though the mechanism for suppression of root resorption is totally unknown, it may differ from the mechanism for suppression of tooth movement. Celecoxib and prednisolone may have an inhibitory effect on osteo/odontoclastic activity. Although a low dose of celecoxib decreased tooth movement, it did not affect root resorption. The threshold dose for celecoxib to initiate the odontoclastic activity may be higher than that to initiate osteoclastic activity. This implies that root resorption through hyalinization of periodontal ligament is not simply related to tooth movement and those different dose thresholds that affect tooth movement and root resorption exist. In this regard, albeit the volume of root resorption in prednisolone and celecoxib high-dose groups was similar, the surface roughness of the prednisolone group was clearly smoother (Figure 5C,D). This may be related to some specifically involved mechanism for root resorption when prednisolone is administered.

The similarities and dissimilarities between tooth movement and root resorption mechanisms remain to be elucidated.

CONCLUSIONS

In rats, after the administration of anti-inflammatory drugs during orthodontic tooth movement for 2 weeks, the following conclusions were obtained:

- Prednisolone and celecoxib suppress orthodontically induced tooth movement and root resorption.
- High dosage (16 mg/kg) of celecoxib suppresses root resorption significantly more than low dosage (3.2 mg/kg). The mechanisms between tooth movement and root resorption are suggested to be different, which may lead to different dose thresholds of celecoxib affecting tooth movement and root resorption.

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