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The effect of budesonide on orthodontic induced root resorption

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ABSTRACT

Background: The aim of this study was to evaluate the hypothesis that budesonide increases the susceptibility of teeth to root resorption during the course of orthodontic treatment.
Materials and Methods: A randomized controlled trial design (animal study) was employed. Budesonide was administered in test group for 14 days during which orthodontic force was applied to upper right molar. Afterwards, root resorption was measured on mesio-cervical and disto-apical parts of the mesial root on transverse histological sections. ANOVA and Bonfferoni tests were used. Statistical significance was considered to be $P \leq 0.05$.
Results: In general, the subgroups in which the force was applied showed significantly greater root resorption. Where force was applied there was no significant difference, whether budesonide was administered or not. While where there was no force, a group who received budesonide showed significantly greater root resorption than the other, unless at the coronal level where the difference was not significant.
Conclusion: Within the limitations of this study, it seems budesonide could increase root resorption, but in the presence of orthodontic force this effect is negligible.

Key Words: Budesonide, histomorphomtery, orthodontics, rats, root resorption

INTRODUCTION

Orthodontic induced root resorption (OIRR) has shown to be the consequence of removing the hyalinization tissue by clastic cells.[1-5] Such tissue forms when the orthodontic force produces unphysiologic pressure in the periodontal ligament (PDL).[6]

Prostaglandins (PG) play an important role in the process of OIRR.[7-11] These cytokines reduce the production of collagen and increase cyclic adenosine monophosphate.[12-14] Orthodontic force activates the phospholipase (PLase) and arachidonic acid (AA) is produced. AA in turn converts to PG by means of cyclo-oxygenase (COX).[15]

Corticosteroids can influence OIRR.[16-19] Glucocorticoids inhibit the production of PG via three different mechanisms: Signal transduction suppression related to pro-inflammatory cytokines, inhibition of COX, and activation of anexin I, which suppresses the PLase and AA production.[20]

Budesonide is a second generation glucocorticoid with low systemic absorption and high 1st pass metabolism.[21,22] Compared with prednisolone, it has fewer systemic side-effects, less influence on the hypothalamic-pituitary-adrenal axis, and leads to bone loss less frequently.[23,24] Prescribed as an inhalant, the lungs keep drug efficiently; since budesonide forms lipophilic acid esters, it has a prolonged half-life in airways.[25] Budesonide is frequently used as an antiinflammatory agent in the treatment of asthma,[26] rhinitis,[27] and inflammatory bowel disease[28] and is

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currently in clinical trials for the prevention of lung cancer.

Several investigations have addressed the effect of corticosteroids on OIRR;[16,18,29,30] contradictory results have been achieved in this regard. However, the effect of inhaled corticosteroids such as budesonide has not been studied yet. This article is to evaluate this issue.

MATERIALS AND METHODS

Animals

Thirty male, 3 months old, 300-350 g weight, Wistar rats were included in this study. The animals were housed paired in cages, with 12 h light-darkness cycle. Food and water were provided *ad lib*. The National Research Council's guides for care and use laboratory animals were taken into consideration. This study was approved by the Ethics and Research Committee of the School of Dentistry, Shahid Sadoughi University of Medical Sciences. The animals were quarantined for a week to get acclimated with new situations before the study begins. The body weight was measured every other 3 days using a digital scale (Moment, model number 6836, Hungary).

Application of orthodontic force

The orthodontic appliance was installed using a previously described method.[31] The animal was generally anesthetized by 25 mg/kg of ketamine hydrochloride (Rotexmedica, Trittau, Germany) and 8 mg/kg of xylesine (Rotexmedica, Trittau, Germany), administered intra-peritoneally. A 50 g nickel-titanium closed coil spring (Sentaloy®, GAC, Iship, NY, USA) was ligated between right incisor and first molar. The lower incisors were cut every 4 days to prevent the animal from incising over the appliance. The rat was nourished with soft pellet, afterwards.

Budesonide administration

The animals were randomly divided into 2 15-rat groups, test and control. From first day, the test group was nebulized by 2.5 mg/rat/day of budesonide 0.5 mg/ml (Pulmicort, Astra Zeneca, Sweden); in the control group, normal saline was administered.

An exposure box was made of glass in dimensions of 20 cm × 50 cm × 70 cm. This box was then divided into 16 equal chambers, each to receive a specimen. This was to prohibit the animals from aggregation in a corner during nebulization. The animals were given 45 min before the nebulization began. This was to let the transformation stress to relief and the respiration rate to slow down to the base level. The exposure box was then connected to the nebulizer (OMRON®, model #NE-C28-E, Matsuzaca City, Japan). The rate of nebulization was set to 0.4 ml/min with 3 μ particle size.

Histopathology

All the animals were sacrificed by CO_2 overdose after 14 days of force application and nebulization. The maxilla was amputated, fixed in formalin 10%, and decalcified by formic acid 10%.

Using a microtome (Leica, Wetzlar, Germany), the mesial root of right and left first molar was dissected in a horizontal plane. The dissections were done in 2 levels: Cervical, defined as the first section containing alveolar bone, and apical, at a distance of 1150 μ from the cervical level. At each level, 3 sections were obtained, 7 μ in thickness and 150 μ apart from each other. The sections were then stained by hematoxiline and eosine. Using a light microscope (Magnum®, Ceti Co., GB), with ×40 magnification, images were shot by a digital camera (Dsch50 cybershot®, Sony, Japan).

The images where transferred to Photoshop software ver.8 (Adobe, San Jose, CA), where the periphery of mesial and distal halves of the root was delineated in cervical and apical sections, respectively. On each periphery, the scalloped parts were considered as the resorptive lacunae regardless of the existence of cementoclasts. These parts were delineated separately [Figure 1]. The delineated curves were then transferred to AutoCAD 2009 (Autodesk Inc., San Rafael, CA, USA), where the length of each was measured. Ten randomly selected sections were reevaluated by the

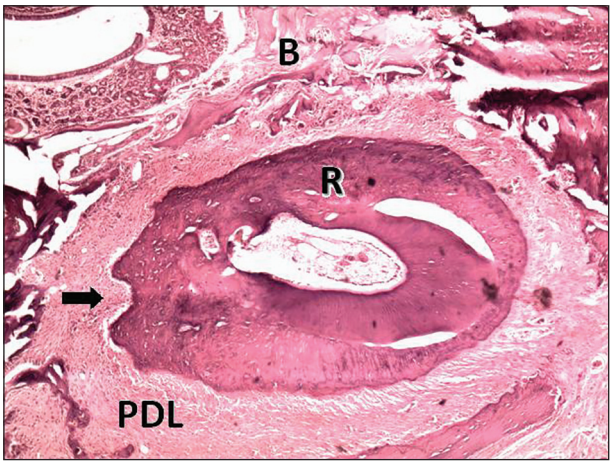

Figure 1: Histological section of the root at cervical level. Note the resorption lacuna (black arrow). B: Bone; R: Root; PDL: Periodontal ligament.

same examiner. The *t*-test revealed a $P < 0.05$ and intra-examiner error was considered to be negligible.

The amount of root resorption was defined as the mean length of the root periphery to the sum of the length of resorptive lacunae in the 3 sections obtained at cervical or apical level.

Groups and subgroups

The test group (B) where budesonide was administered was further divided into 2 subgroups: B-F; the right side molar to which the orthodontic force was applied, and B-nF; the left side molar to which no force was applied. As well in the control group (nB) where budesonide was not administered, the subgroups nB-F and nB-nF formed by the same manner. In each subgroup, root resorption was measured at three levels: Cervical (C), apical (A), and total (T), which was the mean of C and A.

Statistical analysis

The changes in weight were analyzed by repeated measure ANOVA and Bonfferoni tests. As for the amount of root resorption, ANOVA and Bonfferoni tests were used. The level of significance was determined at 0.05. Statistical analyses were performed using SPSS version 11.5 (SPSS Corporation. Chicago, IL, USA).

RESULTS

Table 1 demonstrates the amount of root resorption in each group. The values varied from 5.7% ± 2.1% at apical level where both force and budesonide were applied, to 1.4% ± 0.8% in cervical level where neither force nor budesonide was applied.

Table 2 demonstrates the comparison between groups. In general, the subgroups in which the force was applied showed significantly greater root resorption. Where force was applied there was no significant difference, whether budesonide was administered (B-F subgroup) or not (nB-F subgroup). While where there was no force, the group who received budesonide (B-nF sub group) showed significantly greater root resorption than the other (nB-nF), unless at the coronal level where the difference was not significant.

DISCUSSION

During the first 3 days, the animals' weight showed a slight decrease; nonetheless, this was not significant ($P = 0.052$). This can be attributed to the trauma of appliance placement and also change in the diet after the lower incisors where cut-off. For the rest of the course of study, a gradual weight gain was observed ($P < 0.05$). The difference between test and control groups was insignificant ($P > 0.05$).

The rats were exposed to budesonide for a 2-week period which could be considered as acute administration. The budesonide is usually prescribed for acute situations such as asthma.[26] It was also proposed that this is during the acute phase of corticosteroid administration that the tooth is significantly susceptible to OIRR; afterward remodeling would increase due to secondary hyperparathyroidism and OIRR is no longer a special consideration.[30]

The rationales for choosing the mesial root for evaluating root resorption were that this root is the largest one from which better sections could obtain, and is located centrally in the buccolingual dimension

Table 1: The percentage of root resorption in each group

Groups	B			nB		
	C	A	T	C	A	T
F	5.7±24	5.7±21	5.7±22	5.1±24	5.2±11	5.2±18
nF	2.4±0.7	3.4±1.0	2.9±1.0	1.4±0.8	1.6±0.7	1.5±0.7

Data were shown in the form of mean±SD. B: Test group with two subgroups; nB: Control group with two subgroups; B-F: The right side molar to which the orthodontic force was applied; B-nF: The left side molar to which no force was applied; C: Cervical, A: Apical, T: Total; SD: Standard deviation; For the meaning of the abbreviations refer to section materials and methods; groups and subgroups

Table 2: Pairwise comparison of the groups

Groups	B-F			B-nF			nB-F		
	C	A	T	C	A	T	C	A	T
nB-nF	0.000	0.000	0.000	0.934	0.007	0.009	0.000	0.000	0.000
nB-F	1.000	1.000	1.000	0.001	0.003	0.000			
B-nF	0.000	0.000	0.000						

B: Test group with two subgroups; nB: Control group with two subgroups; B-F: The right side molar to which the orthodontic force was applied; B-nF: The left side molar to which no force was applied; C: Cervical; A: Apical; T: Total; *P* values (for the meaning of the abbreviations refer to section materials and methods, groups and subgroups)

in the same plane as the force applied. In addition, it was used by several other investigations.[29-34]

In order to quantify root resorption, different methods have been used in studies. Some have evaluated the root surface on a longitudinal sagittal section. While this method could reveal the defects from the cervical area to apical, it omits the buccal and lingual. In this study, the buccolingual sections were obtained in cervical and apical region. One shortcoming of this method is the underestimation of the defect due to the fact that the section could simply pass through a narrow part of the defect. To overcome this, at each level 3 parallel sections were passed with 150 μ interval.[30]

To evaluate the spread of defect, some investigators used a grid and counted the lines passing through the defect.[30] Due to the ovoid geometry of the root, the buccal and lingual regions would receive fewer grid lines. Thus, the spread of the defects in this area could be underestimated. In this study, software was used to delineate the border of the defect and measure its length that could give a more realistic image. Another point is that, in this study, the ratio of defect to root surface was less than other studies that used a grid.[30] Beside the study parameters such as the drug used, one explanation lies in the fact that the defect located in mid-part has received more grid lines than the intact root surface in buccal and lingual parts.

Root resorption was evaluated on mesio-cervical and disto-apical region. Since the tooth was undergoing simple tipping movement in which the center of rotation is located in mid-root region,[35] regarding the relation between OIRR and compression area in the PDL,[1-6] the reason for this selection becomes clear. A pilot study undertaken by the authors also justified this selection.

Review of data reveals that the root resorption increased between the study subgroups by the following order: (1) nB-nF, (2) B-nF, (3) nB-F, and 4. B-F; although the difference between the last 2 was not significant ($P > 0.05$).

An interesting observation is that, in nF group, root resorption was also observed. This could be due to several factors: Occlusal trauma,[36] dentinal antibody,[37] and the last but not least, the systemic side-effect of budesonide.

This study revealed that budesonide could increase root resorption, since the root resorption was more in B-nF than nB-nF (P at apical level = 0.007, and at total = 0.009). The budesonide may stimulate the odontoclastic activity and/or suppress the reparative action of cementoblasts. It should also be mentioned that at cervical level the difference between B-nF and nB-nF was insignificant ($P = 0.934$). Although difference in biomechanical parameters as well as the effect of systemic factors at cervical level may be responsible, this finding could not easily be explained and further investigations on this issue are recommended.

The difference between nB-F and B-F was insignificant ($P > 0.05$) that is, when the orthodontic force was applied, it made no difference whether budesonide was administered or not. This finding revealed that the major factor in root resorption was the application of force and that the effect of budesonide faded out in the presence of force.

The clinical conclusion of the above mentioned results is that, in an orthodontic patient, during the acute phase of budesonide administration, there is no need to cease the course of treatment, nevertheless monitoring the root resorption by means of radiographs is a safe caution.

The results of this study are in contrast with those of other investigations. Ong *et al.*[18] administered 1 mg/kg of prednisolone in rats. The result was decreased root resorption. Gonzales *et al.*[29] investigated the effect of high dose (0.67 mg/kg) and low dose (0.13 mg/kg) prednisolone on a rat model and observed the same results. On the other hand, Ashcraft *et al.*[16] exposed a rabbit model to osteoporotic dose of cortisone (15 mg/kg) and found the root resorption to increase significantly. The same result was achieved by Verna *et al.*[30] who found that during the acute phase of administration, 8 mg/kg of prednisolone increased the root resorption in rats. The differences can be explained by various animal models and methods used, for example in the study performed by Ashcraft *et al.*[16] rabbit model and osteoporotic dosage of the drug have been used. Rabbit's molars have continuous eruption which may flaw the results. Ong *et al.*[18] used a lower dosage in rat and did not report information about root resorption occurrence, therefore, direct comparison was impossible. The total experimental period of Ong *et al.*[18] study was only half the period used in the study done by Verna *et al.*[30] (24 days against 49 days). The reason for these differences could be found in several factors such as

animal model, the type of corticosteroid administered, method of administration, duration of administration, and method for evaluating root resorption. One should pay special attention to the type of corticosteroid administered; inhaled budesonide compared to other types of corticosteroid, has low systemic absorption, high first pass metabolism, and affect the hypophyseal-pituitary-adrenal axis less frequently. These mean less systemic side-effects.

CONCLUSION

Within the limitations of this study, Budesonide could increase root resorption, but in the presence of orthodontic force, this effect is negligible. It seems in an orthodontic patient, during the acute phase of Budesonide administration, there is no need to cease the course of treatment, nevertheless monitoring the root resorption by means of radiographs may be advisable.

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