

# THE EFFECTS OF PGE<sub>1</sub> AND INDOMETHACIN ON ORTHODONTIC TOOTH MOVEMENT IN RAT

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**Abstract** - Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and indomethacin, a nonsteroidal antiinflammatory drug, were separately administered during orthodontic tooth movement in rats. At the beginning, an orthodontic appliance was placed and activated in male albinus rats. In the first examination, the experimental group received submucosal injections of PGE<sub>1</sub> (10 mg/kg/day) near the first maxillary right molars, and alcohol was injected to control group animals as a vehicle similarly. In the second examination, indomethacin (10 mg/kg/day) and methyl cellulose subcutaneously injected to experimental and control groups respectively. Tooth movement was measured at 1,3,5,7,9 and 11 days. In PGE<sub>1</sub> group, tooth movement increased significantly at the beginning of seven days as compared to the vehicle injected group and the number of osteoclast and Howship's lacunae were markedly increased. A significant inhibition of tooth movement occurred beginning at seven days in the indomethacin group compared to the control group.

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## INTRUDUCTION

Tooth movement during orthodontic treatment requires remodeling of periodontal tissues, especially in alveolar bone. The role of local bone metabolism associated with orthodontic tooth movement has been considered to be related to the biologic response of periodontal tissues to applied mechanical forces. Davidovitch and co-workers have demonstrated that orthodontic forces bring about change in the organization and function of the alveolar bone cells and as a result of these changes, there is localized bone remodeling and ultimately movement of teeth to new positions. Indeed, they found that changes occur in chemical composition and enzymic profile of the periodontal tissues during orthodontic treatment (1).

Recently, great advances have been achieved in understanding the role of some endogenous compounds such as cyclic adenosine monophosphate (CAMP), calcium, collagenase, prostaglandins (PGs), in cellular responses to orthodontic forces. However, the exact

mechanisms of these phenomena are not understood (2,3). Yamasaki and co-workers reported the role of prostaglandins as biochemical mediators of bone resorption induced by orthodontic tooth movement. In rats (4), it was suggested that orthodontic mechanical stress induced synthesis and secretion of PGs by localized cells, which stimulated osteoclastic bone resorption. Although the involvement of PGs in mediating orthodontic tooth movement is well established (2, 4,5,6), the exact role of these mediators is not very clear. However, mechanical forces by themselves may not be the most efficient means for moving teeth, because they are exceedingly variable and the clinical response to their application remains unpredictable.

Recently, Yamasaki and co-workers showed that local administration of PGE<sub>1</sub> or PGF<sub>2</sub> in gingiva near the distal area of canines might almost double the rate of monkey canine tooth movement seen in the vehicle injected side, no macroscopically evident side effects in the gingiva (5). In another study, these authors reported the same effects in clinical cases with local administration of PGE<sub>1</sub> in gingiva near the orthodontically treated teeth.

It has also been shown that indomethacin, a specific inhibitor of PG synthesis, reduced the rate of orthodontic tooth movement (7,8).

In the present study, the effects of locally and systemically administered PGE<sub>1</sub> and indomethacin respectively upon orthodontic tooth movement in rat were examined and possible side effects of PGE<sub>1</sub> on the gingival tissues and associated structures were also studied.

## MATERIALS AND METHODS

120 male albinus rats weighing 30 ± 20 g were used. The animals were housed in standard cages at a constant temperature (68 °F) with free access to food and water. Animals were divided into two main groups containing 60 animals and each main group was subdivided into control and experimental subgroups. The latter were divided into six subgroups containing five animals with orthodontic tooth movement.

An orthodontic appliance was placed and activated in all the animals. Animals were anesthetized by intraperitoneal injection of 50 mg/kg ketamine and 10 mg/kg chlorpromazine to provide masticatory muscle relaxation during appliance insertion. The orthodontic force delivery system consisted of a 0.08 by 0.022 inch closed-coil spring (Unitek m 341-110). A 6 mm length of spring was attached between the first right maxillary molar and right incisor by means of light stainless steel ligature. A hole was drilled through the incisor at its gingival margin to permit attachment. The ligature was passed interproximally between the first and second molars and ligated around the cervical area of the first molar. The device was activated for 1 mm to deliver 60 g of initial force and was not reactivated during the course of experiment (9).

#### Application of PGE<sub>1</sub> and indomethacin

In the first examination, the experimental group received submucosal injections of PGE<sub>1</sub> (10 mg/kg/day) near the first maxillary right molars by a 1 ml syringe and a 28-gauge, 1/2 inch needle for 10 days. Alcohol was similarly injected to the control group as a vehicle.

The second examination, indomethacin (10 mg/kg/day) and methylcellulose 1% (vehicle) were submucosally injected to experimental and control groups from 0 to 10 days experimental.

#### Histological examination

Upper molar region (consisted of right hemimaxilla and left hemimaxilla from experimental and control group respectively) was dissected on the 9th day and was prepared for histologic examination.

All specimens were fixed in formalin (10%). They were then washed and decalcified in formic acid (5%) and imbedded in paraffin.

All hemimaxillas were sectioned at 7mm and stained with either hematoxylin or eosin. Serial sections were cut parasagittally, and were five sections at four section interval for each animal.

The selected parasagittal sections of each hemimaxilla were photographed and one area in each section, at a magnification of x63, was measured for alveolar bone reaction. The mesial aspect of the mesial root of the first maxillary molar which was selected for assessment.

#### Orthodontic tooth movement

All animals in each subgroup were killed at 1,3,5,7, 9 and 11 days by ether. Each rat was decapitated and tooth movement was determined by measuring the space created between the first and second maxillary molars with a calibrated thickness gauge (10). The distance from the distal face of the third molar to the mesial face of first molar was measured before and after insertion of calibrated thickness gauge by a digital collis.

## RESULTS

Animals tolerated the appliance well and no side effects were observed as a result of drugs administration. Changes in the body weight of the animals were measured at the beginning and during the experiment and were found to be normal.

Tooth movements in all groups consisted of three different phases (Table 1, Fig. 1). A rapid movement occurred at the first day caused by the compression of the tissues surrounding the teeth, followed by a period of cessation of movement for 4 to 5 days due to the formation of the hyalinization zone. Finally, the late phase of tooth movement occurred from the 7th day to the end of the experiment.

Rate of tooth movement in PGE<sub>1</sub> group significantly increased compared to the control group ( $P < 0.05$ ) (Table 1).

In the indomethacin group, rate of tooth movement was less than the control group and this difference was significant ( $P < 0.05$ ). However, there was no significant difference between the control groups of the two experiments (Table 2,3).

Tooth movement was similar in all animals from day 0 day to 5.

Superimposition of the different tooth movement cycles during the experimental period showed that the indomethacin-treated group had the least tooth movement (Fig. 2), while the PGE<sub>1</sub> treated group had the highest tooth movement.

#### Histologic Evaluation

All tissue specimens were prepared for light microscopic evaluation on the 9th day, when the late changes in surrounding tissues appeared. The early changes consisted of transient ischemia of PDL in the pressure side with the formation of transient ischemia of hyalinized tissues, and stretched PDL on the tension side. There was no evidence of disease in periodontal ligaments or on the root surface of the teeth in PGE<sub>1</sub> or indomethacin groups.

In assessment of the alveolus opposite the mesial aspect of the mesial root of the maxillary first molar in all six groups the major difference was found on the pressure side of the alveolar bone of the PGE<sub>1</sub> injected teeth. The alveolar bone of the PGE<sub>1</sub> group demonstrated an entire resorption front covered with a large number of multinucleated and mononuclear osteoclasts and osteoclast precursor cells and Howship's lacunes (Fig. 3). Evidence of increased bone resorption on the frontal surfaces of the alveolus and bone surrounding the vascular haversian system within the depth of alveolus was present. Bone formation and osteoblastic activity was also apparent so. (Fig. 4a,b).

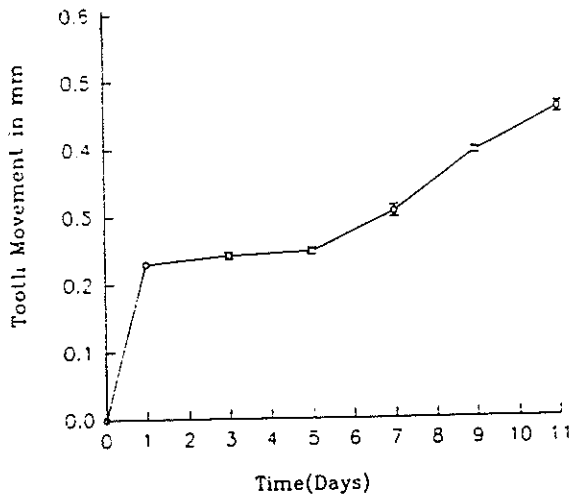


Fig. 1. Tooth movement in control group with local injection of alcohol :

- 1- Early tooth movement (First day)
- 2- Late phase (2-5 days)
- 3- Late movement (5-11 days)

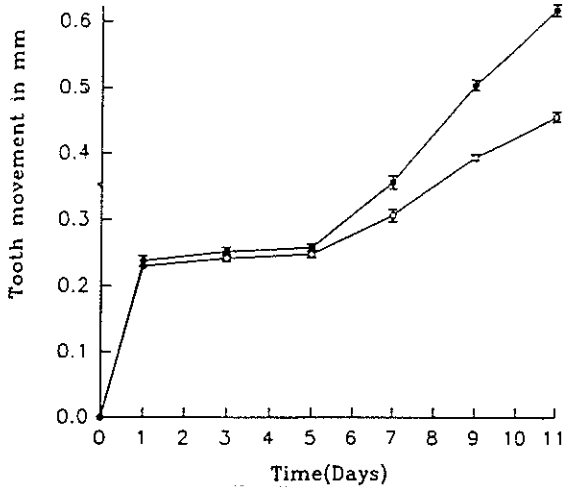


Fig. 2. Movement time in first test

- treatment group
- control group

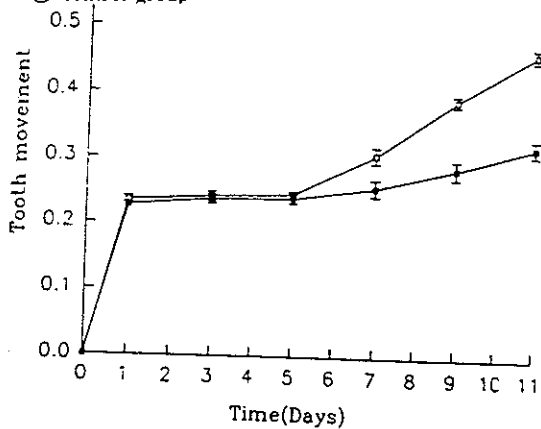


Fig. 3. Movement time in second test

- indomethacin group
- control group

In the pressure side of the alveolar bone (right hemimaxilla) of indomethacin-treated group, histologic findings were significantly different. Low level of osteoclastic activity and increased fibrotic tissue was shown in this group (Fig. 5a,b).

Histologic findings of the left hemimaxilla in PGE<sub>1</sub> and indomethacin, treatment group were similar. These findings showed that indomethacin did not bring about any significant change on the surrounding tissues of teeth either.

Table 1. Tooth movement in the PGE<sub>1</sub> treated and control groups

Days	Control group (X±SD) m.m	Experimental group PGE <sub>1</sub> (X±SD) m.m	significance
1	0.230±0.008	0.2380±0.019	NS
3	0.242±0.013	0.252±0.014	NS
5	0.248±0.011	0.258±0.014	P < 0.05
7	0.306±0.020	0.356±0.023	P < 0.01
9	0.394±0.011	0.504±0.018	P < 0.01
11	0.456±0.018	0.618±0.021	P < 0.01

NS : not significant

Table 2. Tooth movement in the indomethacin and control groups

Days	Control group (X±SD) m.m	Experimental group Indomethacin (X±SD) m.m	significance
1	0.236±0.011	0.228±0.010	NS
3	0.242±0.016	0.238±0.016	NS
5	0.245±0.011	0.240±0.015	NS
7	0.308±0.026	0.258±0.029	P < 0.01
9	0.392±0.016	0.288±0.032	P < 0.01
11	0.462±0.023	0.324±0.028	P < 0.01

NS : not significant



Fig. 4a- The root surface of next tooth. (in control group)

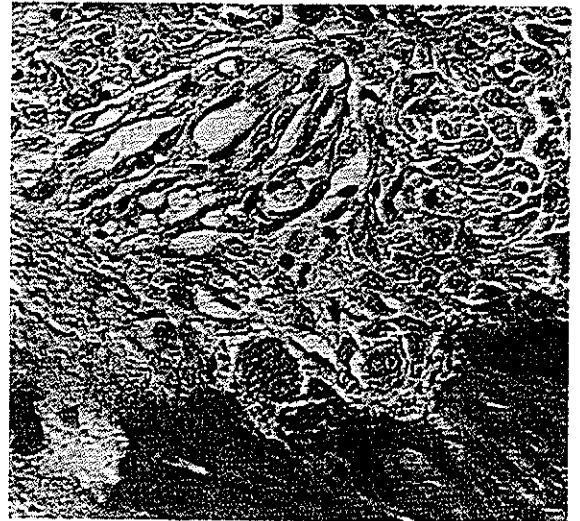


Fig. 4b- Microscopic view in PGE<sub>1</sub> group, showing clear inflammation and resorption



Fig. 5a- Microscopic view of tooththe vicinity of bone (X10) control group



Fig. 5b- Microscopic view of indomethacin trated group showing clear fibrotic tissue

## DISCUSSION

The results reported in this study show that local administration of PGE<sub>1</sub>, combined with mechanical tooth movement, accelerated tooth movement, whereas indomethacin, a nonsteroidal anti-inflammatory drug, slowed tooth movement. The mechanism of acceleration of tooth movement in PGE<sub>1</sub>-treated cases may be related to *in vivo* stimulation of bone resorption by local PGs (11). Results of histologic evaluation in the present study confirm this idea. Yamasaki has described the role of cyclic AMP and calcium in the induction of osteoclasts incident to experimental tooth movement in rats (12). These intracellular second messengers are important modulators of osteoclasts and bone resorption. PGs cause a significant increase in the content of cyclic AMP in calvara isolated from fetal rats *in vitro* (6) and intracellular calcium is important in the mechanism of bone resorption of PGs *in vitro* (6). These effects of PGs on periodontal tissues are probably related to the acceleration of the rate of tooth movement shown here. Yamasaki and co-workers (2) reported the effects of PGE<sub>1</sub> and indomethacin on orthodontic tooth movement with another model.

The effect of indomethacin on bone resorption is primarily mediated by inhibition of cyclooxygenase and PGs synthesis although this drug can inhibit prostaglandin 15-dehydrogenase, collagenase and phosphodiesterase (7). Clinical studies have demonstrated that patients that taking aspirin or aspirin like drugs show very slow tooth movement.

Our histological evaluation, in agreement with recent studies (4,12) showed that PGs are involved in bone resorption induced by orthodontic mechanical forces. Therefore, to appear exogenous PGE<sub>1</sub> causes osteoclasts and bone resorption, but indomethacin, an inhibitor of PGs synthesis, inhibits the appearance of osteoclasts and bone resorption of alveolar bones was induced by an orthodontic appliance.

## REFERENCES

1. Davidovitch Z. and Shanfeld JL. Cyclic AMP Levels in alveolar bone of orthodontically - treated cats. Archives of oral biology 20: 567-574; 1975.
2. Yamasaki K. The role of cyclic AMP, calcium and prostaglandins in the induction of osteoclastic bone resorption associated with experimental tooth movement. Journal of Dental Research. 62: 877-881; 1983.
3. King GJ, Gollier J, A bone resorptive agent extracted from orthodontically - treated tissues of the rat, The Angle Orthodontist, October 299-308; 1986 .
4. Yamasaki K. and Miura S. Prostaglandin as a mediator of bone resorption induced by experimental tooth movement in rats. Journal of Dental Research. 59: 1635-1642; 1980.
5. Yamasaki K., Shibata Y. and Fukhata. The effect of prostaglandins on experimental tooth movement in monkey (Macaca fuscata) Journal of Dental Research 61L 1444-1446; 1982.
6. Yamasaki K., shibata Y., Imai S., Tani Y., Shibusaki Y., Fukuhara T. Clinical application of prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) Upon orthodontic tooth movement. American Journal of Orthodontics 85: 508-518; 1984.
7. Chumbley AB. and Tuncayoc. The effect of indomethacin can aspirin Like drug) on the rate of orthodontic tooth movement. American Journal of Orthodontic. 89: 312-314; 1986. .
8. Ohkawa S. Effects of orthodontic forces and anti-inflammatory drugs on the mechanical strength of the periodontium in the rat mandibular first molar. American Journal of Orthodontics. 81: 498-502; 1982.
9. Heller LJ. and Nanda R. Effect of metabolic alteration of periodontal fibers on orthodontic tooth movement. American Journal of Orthodontics. 75: 239-257; 1979 .
10. Mohammad AH., Tatakis DN. and Dziak R. Leukotrienes in orthodontic tooth movement. American Journal of Orthodontics and Dentofacial Orthopedics 95: 231-237; 1989.
11. Goodson JM., McClatchy K. and Revell C. Prostaglandin induced resorption adult rat calvarium. J. Dent. Res. 53: 670-677; 1974.
12. Yamasaki K. The role of cyclic AMP, calcium and prostaglandins in the induction of osteoclastic bone resorption associated with experimental tooth movement. J. Dent Res. 62: 877-881; 1983.