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The Effect of Prostaglandin E2 and Vitamin D3 on Orthodontic Tooth Movement

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ABSTRACT

Background: The specialty of orthodontics is based on ability to produce controlled tooth movement. In our study we have compared the tooth movement by orthodontic force alone (Group-A) to tooth movement with orthodontic force along with Prostaglandin E_2 (Group-B) and tooth movement by orthodontic force along with Vitamin D_3 (Group-C). A sample of fifteen young male Albino rats of 6 weeks of age and weight of around 160 $\pm$10 gms were selected. These samples were divided in three groups containing five rats in each group. Results of our study depicted that Group B and Group C showed increase in the amount of tooth movement when compared to control group. Mean tooth movement showed by Group A is 1.69 $\pm$ 0.01mm, Group B is 2.27 $\pm$ 0.01mm, and for Group C is 2.18 $\pm$ 0.02mm. This difference was statistically not significant. With Prostaglandin E_2 group there is 34.31% more tooth movement compared to control group, and with Vitamin D_3 group there is 28.99% more tooth movement compared to control group. Orthodontic tooth movement was enhanced by local injections of both Prostaglandin E_2 and Vitamin D_3. The osteoclastic activity in the Prostaglandin E_2 group was greater than Vitamin D_3 group. The osteoblastic activity in the Vitamin D_3 group was greater than the Prostaglandin E_2 group favoring better coupling of formation and resorption of alveolar bone remodeling.

Keywords: Orthodontics, Vitamin D3, Tooth movement, Prostaglandin E2.

INTRODUCTION

Generally orthodontic treatment require more time-duration, to decrease the duration of treatment, many advancements regarding inducing faster tooth movement have been published in the literature[1-3]. A combination of mechanical, chemical, and perhaps electrical stimuli acting in combination might lead to more rapid bone turnover and hence faster orthodontic tooth movement. This will shorten the duration of treatment, so more patient satisfaction and also allow the orthodontists to offer their services to a larger number of populations. Mainly studied chemical substances for producing rapid tooth movement are, Prostaglandin, Vitamin D, Zileuton, Thromboxane analogue U 46619, Synthetic prostacyclin or analogues such as iloprost, corticosteroid, parathyroid hormones, thyroid hormone[4-6].

Among them the most commonly studied agents are prostaglandin E, and vitamin D. Prostaglandin stimulates bone resorption, directly acting on osteoclasts, and has effects similar to those of parathyroid hormone. Vitamin D_3 (1,25-DHCC) has been shown to stimulate bone resorption by inducing the differentiation of osteoclasts from their precursors and increasing the activity of existing osteoclasts. In addition to its bone-resorbing activity, Vitamin D_3 is known to stimulate bone mineralization and osteoblastic cell differentiation that occur in dose dependently manner.

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Prostaglandin E_2 and Vitamin D_3 are both claimed to enhance orthodontic tooth movement when applied locally in combination with mechanical forces. This study compares the effects of local administrations of Prostaglandin E_2 and Vitamin D_3 on orthodontic tooth movement in rats[7-11].

Aim- To compare and to evaluate the amount of orthodontic tooth movement caused due to orthodontic force alone (Group-A), to amount of orthodontic tooth movement due to orthodontic force along with Prostaglandin E_2 (Group-B), and amount of orthodontic tooth movement by orthodontic force along with Vitamin D_3 (Group-C).

Objectives:- to compare

1. The amount of bone resorption among different groups.
2. The number of osteoblast among different groups.
3. Any pre-treatment to post-treatment change in serum calcium, serum phosphate, and serum alkaline phosphatase activity level due to local administration of prostaglandin E_2 and vitamin D_3.

MATERIALS AND METHODS

Source of data – A sample of fifteen young male Albino rats of 6 weeks of age and weight of around 160 $\pm$10 gms have been selected. These samples were divided into three groups containing five rats in each group. Out of which one was control group (Group A) and other two were experimental groups (Group B, Group C). In control group only orthodontic force was applied and the effect was analyzed, whereas in experimental groups, Prostaglandin E2 (Group B) and Vitamin D3 (Group C) were administrated along with orthodontic force and the effect was analyzed. All animal were housed in cages. Five animal in each cage, at a constant temperature of 24.5^0C. They were fed with commercial rat chow which was provided them ad libitum. A modification of a fixed appliance, described by Boisson and Gianelly[12], was used to move maxillary incisors laterally. The appliance consisted of a helical loop which was 1.5 mm in diameter, constructed from 0.012-inch round stainless steel wire (By A.J.Wilcock, AUSTRALIA) and has two active arms which will be soldered to the incisor bands, constructed with 0.12 × 4.56 mm band material, and had a internal diameter of 4mm. The total length of appliance which extends in palatal direction was 18mm from the band to the loop.

When active (both arms touching), the appliance would exert a reciprocal lateral force of 20 $\pm$ 0.1 gms. When the appliance was passive, the arms were 9 mm apart (figure no 1). Group A served as a baseline control group in which only orthodontic force was given. Group B (PGE_2 group) samples received both orthodontic force as well as a single injection of 0.1 ml of 0.1µg PGE_2 on the day of appliance placement. The Prostaglandin E_2 (figure no 2) was first dissolved in ethanol (1 mg/mL) and diluted with 2% lidocaine to the concentration of injection. The Group C (vitamin D_3 group) samples received orthodontic appliances and a 0.1 ml injection of vitamin D_3 (figure no 3) containing 5mg/ml (50pg/ml) of vitamin D_3 on days 0 and 7. To achieve this concentration, 5ml of commercially available vitamin D_3 injection (Arachitol-61 having 15 mgs of vitamin D_3 per ml) was mixed in 10ml of dimethyl sulfoxide (DSMO) solution.

The experimental period was 9 days. The injections were administered with a microsyringe with 30 guage needle to the gingiva distal to the maxillary incisors. All procedures were carried out under light anaesthesia with intramuscular injection of kitamine (22 mg/kg body weight). The injection site was lower left abdomen. On the 9th day of the experiment, the distance between maxillary incisors was measured intraorally with a digital caliper accurate to 0.01 mm (By Yamayo JAPAN). The measurements were recorded at the level of gingival margins of the bands of the appliances. After measuring the distance the rats were sacrificed by heavy dose of kitamine. Their premaxillae, including the incisors, were immediately dissected for histological examination. The excised tissues were kept in 10% neutral formalin solution for fixation for 2 days. These tissues were decalcified in 10% nitric acid for 7 days. Then the tissue was embedded in Paraffin wax (By Merck Specialities Private Limited, INDIA) and 5 serial cross-sections of 3 µm thickness from distal side of the right central incisor were made from beginning to the end of the root surface at 20 µm difference. The sections were stained with hematoxylin and eosin stains then the stained

section is examined under light microscope (Lawrence and Mayo, INDIA) with 40x magnification. For the haematological examination 1mm blood collected prior to the treatment and after completion of treatment from the tail vein of each rat. The site chosen for drawing the blood was distal 1/3 of tail, as it gave better visualization of vein. Haematological examinations were done to check the difference in pre-treatment and post-treatment values of calcium, phosphate and alkaline phosphatase activity. All the blood samples were taken in early evening between 5 P.M. to 6 P.M. to avoid any variation due to circadian rhythm. (figure no 4-7)

Data obtained from the clinical and laboratory findings were fed into S.P.S.S 15 statistical analysis software package for the analysis and two tail student t-test was performed to check any significant difference in values. Paired t-test was used to check any significant difference between pre-treatment and post-treatment values.

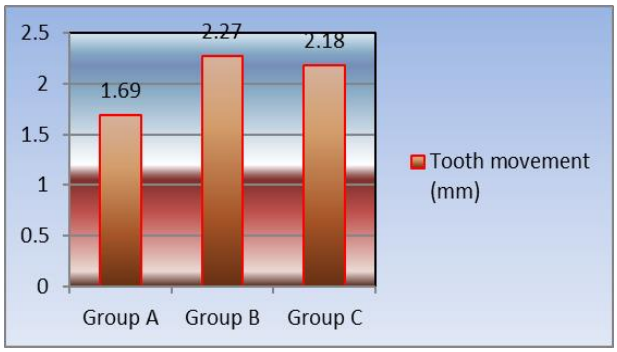
RESULTS

Table 1: Clinical & Histological variables.

	Group A	Group B	Group C	"t" value of Group A and Group B	"t" value of Group B and Group C	"t" value of Group A and Group C
Tooth movement (mm)	1.69 ± 0.01	2.27 ± 0.01	2.18 ± 0.02	-0.659	0.092	-0.542
No. Of howship's lacunae (per mm^2)	3.2 ± 0.11	21.5 ± 0.21	19.2 ± 0.13	-10.327*	1.279	-9.870*
No. Of osteoblast (per mm^2)	11.4 ± 0.61	20.8 ± 0.31	25.2 ± 0.17	-3.679*	-2.173	-5.754*

*= statistically significant difference at P value >0.05.

Group A- Control group (Orthodontic force alone)
Group B- Experimental group (orthodontic force along with PGE_2)
Group C- Experimental group (orthodontic force along with Vitamin D_3)



Graph 1. Tooth movement

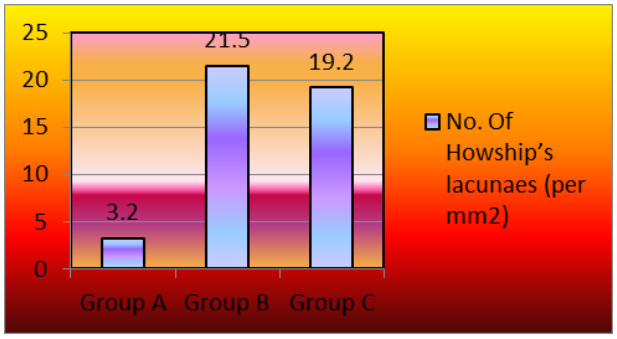
Group A :- Control Group
Group B:- Experimental Group (Prostaglandin E_2 Group)
Group C :- Experimental Group (Vitamin D_3 Group)

Table 1 shows the summary of all the clinical and histological variables for different groups in this study. The mean tooth movement seen in Group A is 1.69 ± 0.01mm, compared to which Group B and Group C show 34.31% and 28.99% more tooth movement respectively. Same can be seen in Graph 1. There is no significant difference in tooth movement among all groups. When we consider number of Howship's lacunae, it was found to be 3.2 ± 0.11 (per mm^2) in Group A, while in Group B and in Group C mean values were 21.5 ± 0.21 (per mm^2) and 19.2 ± 0.13 (per mm^2) respectively. The experimental groups show significant increase in number of Howship's lacunae compared to control group, and there is no significant difference between experimental groups for the same. Graph 2 represents the numbers of Howship's lacunae among different groups and reveals the same information. When taking the account of numbers of osteoblasts, mean were 11.4 ± 0.61 (per mm^2) in Group A, 20.8 ± 0.31 (per mm^2) in Group B, and 25.2 ± 0.17 (per mm^2) in Group C. Statistically Group B and Group C show significant increase in number of osteoblasts compare to Group A, and there was no statistically significant difference between Group B and Group C for the same. Graphs 3 unfold the same information.

Table 2: Haematological variables.

	Group A	Group B	Group C	"t" value of Group A and Group B	"t" value of Group B and Group C	"t" value of Group A and Group C
Pre-treatment serum calcium level (mmol/L)	2.48 ± 0.01	2.52 ± 0.04	2.54 ± 0.01	-0.036	-0.0183	-0.069
Post-treatment serum calcium level (mmol/L)	2.86 ± 0.01	2.71 ± 0.05	2.62 ± 0.01	0.131	0.0797	0.265
Pre-treatment serum phosphate level (mmol/L)	2.43 ± 0.01	2.42 ± 0.01	2.42 ± 0.01	0.011	0	0.011
Post-treatment serum phosphate level (mmol/L)	2.51 ± 0.01	2.62 ± 0.01	2.69 ± 0.01	-0.012	-0.079	-0.200
Pre-treatment serum ALP activity level (K.A. Unit)	21.52 ± 0.19	21.48 ± 1.07	20.79 ± 0.17	0.0138	0.021	0.396
Post-treatment serum ALP activity level (K.A. Unit)	19.79 ± 0.01	18.79 ± 0.01	18.52 ± 0.01	1.173	0.321	1.524

*= statistically significant difference at P value >0.05. mmol= millimole/liter. K.A. Unit= kiloannum.



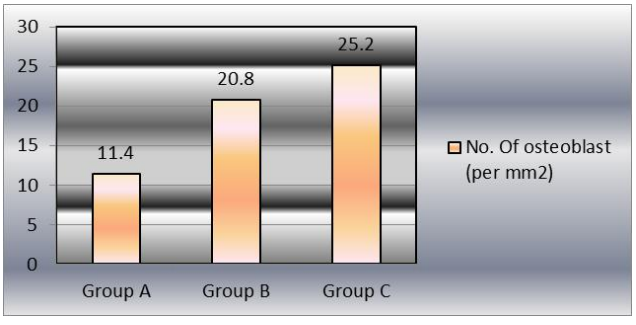
Graph 2. Numbers of Howship's lacunaes

Table 2 shows the summary of all the Haematological variables for different groups in this study. The pre-treatment serum calcium level showed the mean value of 2.48 ± 0.01 mmol/L for Group A, 2.52 ± 0.04 mmol/L for Group B, and 2.54 ± 0.01 mmol/L for Group C. These differences were not statistically significant among the groups. While post-treatment serum calcium level showed the mean of 2.86 ± 0.01 mmol/L, 2.71 ± 0.05 mmol/L, 2.62 ± 0.01 mmol/L for Group A, Group B and Group C respectively. Statistically these differences were not significant. When considering mean values for pre-treatment serum phosphate level it was found to be 2.43 ± 0.01 mmol/L for Group A, 2.42 ± 0.01 mmol/L in Group B, and 2.42 ± 0.01 mmol/L for Group C. Statistically these differences were found to be non-significant. While the post-treatment serum phosphate level were 2.51 ± 0.01 mmol/L, 2.62 ± 0.01 mmol/L, 2.69 ± 0.01 mmol/L for Group A, Group B and Group C respectively. This difference was also found statistically non-significant. Mean values for pre-treatment serum ALP activity level was 21.52 ± 0.19 K.A. Unit for Group A, 21.48 ± 1.07 K.A. Unit for Group B, 20.79 ± 0.17 K.A. Unit for Group C. Statistically these difference were not significant. When we considered the post-treatment serum ALP activity level it was seen that the mean was 19.79 K.A. Unit for Group A, 18.79 K.A. Unit for Group B, And 18.52 K.A. Unit for Group C, even these differences were not statistically significant.

Table 3: Comparisons of pre-treatment and post-treatment haematological values.

Groups	Serum calcium level (mmol/L)	Serum phosphate level (mmol/L)	Serum ALP activity level (K.A. Unit)
Group A	0.719	0.339	0.930
Group B	0.652	0.430	1.033
Group C	0.339	2.721	1.159

*= statistically significant difference at P value >0.05. mmol= millimole/liter. K.A. Unit= kiloannum



Graph 3: Numbers of osteoblasts

Table 3 show the significant difference between pre-treatment and post-treatment haematological values. All parameters show that there were no statistically significant differences between any group for pre-treatment and post-treatment values of serum calcium level, serum phosphate level, serum ALP activity level. Graph 4, 5, 6 gives the same information.

DISCUSSION

In this study, the effect of local injection of Prostaglandin E_2 and Vitamin D_3 on orthodontic tooth movement were compared clinically, histologically as well as haematologically in rats. Many kind of animals including cats, monkeys, guinea pigs, etc. can be used for this types of study but the rat model was used in this study as rat is considered suitable for the study of skeletal adaptation to mechanical forces and has been used in many studies concerning experimental orthodontic tooth movement[3]. The experimental studies related with the rats were reviewed, and nine days of experimental period and 20 g of force were selected because 20 g was found to be the optimal force necessary for orthodontic separation without creating separation of the inter-premaxillary suture or transfer of non-physiologic forces to the teeth or supporting tissues in the rat. Because the short cycles in female rats cause hormonal variations, our study was carried out with male rats. Traumatic effects of the springs on the soft tissues were not observed during the experiment[2,4].

The present study utilized an experimental model suggested by Gianelly. In our study same appliance was modified to an extent by removing the eyelet attachment and by directly soldering the wire to the band was used to check the similar tooth movement. This model was preferred as it provided ease in application, good durability, and good adaptation to oral soft tissues. Appliance was cemented to teeth with help of glass ionomer luting cement. For the measurement of amount of tooth movement that had occurred at the end of the experimental period of nine days, an electronic calliper was used. It gives maximum accuracy and visualization compared to other manual methods.

In our study we have used Prostaglandin E_2 and Vitamin D_3 injections. Lidocaine was preferred vehicle for Prostaglandin E_2 as there were no known antagonistic or synergistic effects when used in conjunction with Prostaglandin E_2. Furthermore, it has been used successfully as a vehicle for Prostaglandin E_2 in previous study by Selin Kale et al.

Local injection of Prostaglandin E1 or Prostaglandin E2 in humans, and rats has been reported to accelerate orthodontic tooth movement. A major disadvantage of the local administration of Prostaglandin is pain at the site of injection, which was shown to be alleviated by dissolving Prostaglandin in dental lidocaine. However, dental lidocaine solutions induce peripheral vasoconstriction at the site of administration and suppress local inflammatory reaction, which is necessary for bone resorption. In addition, local injection of Prostaglandin is technically difficult. Some leakage occurs, and the full effect might not be achieved in all cases. In comparison with local injection, systemic intravenous administration of Prostaglandin E1 has been shown to have a more marked effect on bone resorption. The reason behind choosing 0.1ml dose of Vitamin D_3 was due to the fact that it nearly matched the physiological concentration of Vitamin D_3 in rats, moreover it has maximum stimulatory effects on tooth movement as found by other study by Collins M.K. and Sinclair P.M..[10] Other studies have also found that above this dose there will be a biphasic effect of Vitamin D_3 and can cause lowering or inhibitory effect.

When the comparison was done for orthodontic tooth movement in different groups, it was found that in Prostaglandin E_2 group there was 34.31% more tooth movement compared to control group, and with Vitamin D_3 there was 28.99% more tooth movement compared to control group. This is of great clinical significance regarding increased amount of tooth movement. Additionally there was 4.12% more tooth movement in Prostaglandin E_2 group compared to Vitamin D_3 group. However there existed no statistically significant differences among the 3 groups ($P>0.05$). Contrasting results indicating difference in amount of tooth movement with Vitamin D_3 and Prostaglandin E_2 were reported in previous studies, but similar finding of no significant difference between control group and Vitamin D_3 group regarding tooth movement was found in study by Takano T. They found significant increase in tooth movement between these groups

only after 14th day of experiment. The possible explanation for these contrasting reports may be the small sample size and short experimental period of the present study when compared to other studies. The results of our measurements agreed with the current literature,[7-10] in which the orthodontic tooth movement was enhanced by local injections of both Prostaglandin E_2 and Vitamin D_3.

Goodson et al[17]. reported that local Prostaglandin's stimulate bone resorption in vivo and they demonstrated that repeated injections of 50 µg of Prostaglandin E_1 directly into rat alveolar bone produced marked changes in bone morphology with increased resorption, such as extensive loss of bone matrix, fibrous replacement, and increased vascularity. Prostaglandin administration did not mimic the periodontal disease process but there are at least three aspects in which prostaglandin-induced bone resorption resembled that of the disease. It involved the action of live cells on viable bone; resorbing surfaces were sculptured with covelike lacunae; and there was a strong suggestion of vascular component to the resorption process. Prostaglandin-induced bone resorption differed from the histological appearance of periodontal disease in its absence of inflammatory cells[13]. However, there is considerable evidence that oral bacteria stimulate the formation of chemotactic factors. This could account for the inflammatory cell infiltration that is characteristic of periodontal disease. Leukocytes may be especially important in this connection because there is evidence that they release prostaglandins and another osteolytic principle.

The mechanism and the role of Prostaglandins to induce osteoclastic bone resorption are still unknown, though cyclic AMP and intracellular calcium have been reported to be involved in the action of Prostaglandins. Prostaglandin injection lead to an increase in cyclic AMP, which cause increase in bone resorption.

To evaluate the amount of bone resorption, the number of Howship's lacunae per 1-mm^2 area on the surface of the alveolar bone adjacent to the periodontal ligament in the pressure zone was counted. The number of osteoclasts were not taken into consideration, because Vitamin D_3 not only promotes the fusion of osteoclasts but also enhances the fusion of macrophages to form polykaryons. It is very difficult to differentiate macrophage polykaryons from multinucleated osteoclasts under a light microscope.[9] In the Vitamin D_3 and Prostaglandin E_2[14] groups, the numbers of Howship's lacunae were significantly greater than the control groups. This finding agrees with many other studies in which Prostaglandin E_2 and Vitamin D_3 were found to increase the number of active osteoclasts. [7-10,16] The comparison of the 2 experimental groups showed that the number of Howship's lacunae in the Prostaglandin E_2 group was greater than in the Vitamin D_3group. Holtrop and Raisz[15] reported similar results in their in vitro study. In our study a 11.97% increase in numbers of howship's lacunae in Prostaglandin E_2 group compared to Vitamin D_3 group was observed, this however was not statistically significant.

We found that the number of osteoblasts on the external surface of the alveolus in both the Vitamin D_3 and Prostaglandin E_2 groups were significantly greater than in the control group. This can be explained by the hypothetic model for the activation of osteoclasts and its regulation[16]. The model proposes that the activation of osteoclasts by bone resorbing agents is mediated by osteoblasts that respond directly to these agents by exposing the bone mineral to osteoclasts or by releasing a soluble factor that activates these cells. The greatest number of osteoblasts were in the Vitamin D_3 group. There is 21.15% increase in numbers of osteoclasts in Vitamin D_3 group compared to Prostaglandin E_2 group. However there was no statistical significant difference in between these two groups regarding numbers of osteoblasts at 5% level of significane. This might be because Vitamin D_3 acts directly on the nucleus of the osteoprogenitor cells with a mechanism independent from the cyclic nucleotide cascade. Another reason might be that osteoblasts but not osteoclasts are the target cells for Vitamin D_3.Vitamin D_3 stimulate the osteoclast to increase in their number and their size, it is because bone resorption by Vitamin D_3 is mediated primarily by increasing the activity of existing osteoclasts, which was shown by increased size of the ruffled borders and the clear zones of osteoclasts. Furthermore, Vitamin D_3 stimulates osteoclasts to enlarge their size, their nuclei, and to increase the numbers of osteoclasts.These findings suggest that physiological doses of Vitamin D_3 have direct local

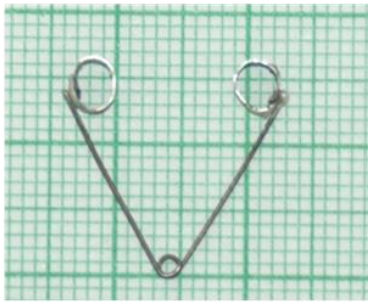


Figure 1- Appliance used

Figure 2-Prostaglandin injection

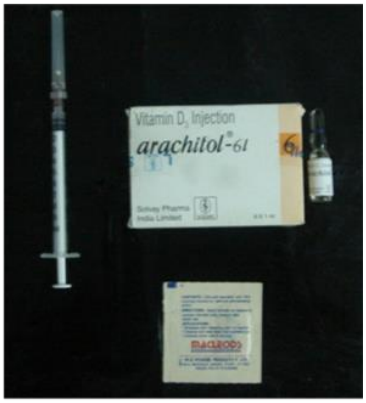


Figure 3-Vitamin D injection

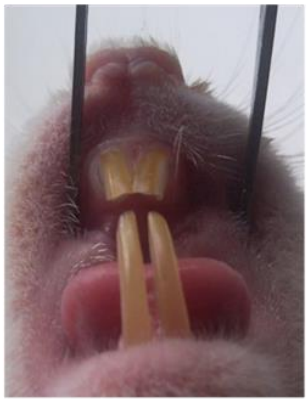


Figure 4-Pretreatment

effects on bone by increasing the size of the osteoclast and their population and eventually alveolar bone resorption by increasing the activity of individual osteoclasts. The results suggest that Vitamin D_3 is more effective in modulating bone turnover during orthodontic tooth movement, because of its well-balanced effects on bone formation and bone resorption[18].

From the study following conclusions are drawn:

- Orthodontic tooth movement was enhanced by local injections of both Prostaglandin E_2 and Vitamin D_3.
- Both Prostaglandin E_2 and Vitamin D_3 caused no detectable systemic adverse effects.
- The osteoclastic activity in the Prostaglandin E_2 group was greater than Vitamin D_3 group.
- The osteoblastic activity in the Vitamin D_3 group was greater than the Prostaglandin E_2 group favoring better coupling of formation and resorption of alveolar bone remodeling.
- The physiological doses of Prostaglandin E2 and Vitamin D_3 have direct local effects on size and activity of osteoclasts and osteoblasts.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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