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Evaluation of effectiveness of pge2 gel on orthodontic tooth movement: An invivo study

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Abstract

Introduction: Orthodontic treatment is an expensive procedure partly because of the long duration of treatment required and is dependent on bone metabolism being influenced by chemical mediators causing bone resorption and deposition where mediators like PGE2 causing bone resorption can be used for faster retraction. Enhancing the rate of tooth movement pharmaco-therapeutically will be an ultimate goal for present-day researchers, and among the chemical mediators affecting orthodontic tooth movement, prostaglandins head the list.

Aim: This study aims to evaluate and compare the orthodontic tooth movement rate during the en-masse retraction of the maxillary anterior using PGE2 as a biomodulator.

Methodology: Sixteen patients seeking orthodontic treatment were divided into two equal groups based on the inclusion and exclusion criteria and coded as Group I & II. They underwent a fixed orthodontic proposed procedure, and written informed consent was obtained. Also, clearance from the ethical board of institutions was obtained before commencing the study.

Group-I: Control group: Eight subjects underwent en-masse retraction with conventional friction mechanics.

Group-II: Experimental group: Eight subjects who underwent en-masse retraction with conventional friction mechanics received an application of PGE2 gel at an interval of fifteen days. Patients have been explained the proposed procedure and written informed consent was obtained.

Results: The amount of movement was obtained by calculating the differences between sequential measurements (T0-T1-T2-T3). The total amount of movement was considered to be the difference between the values of T0 and T3. The test group showed a two-fold increase in tooth movement than in previous studies.

Conclusion: There was a significant increase in orthodontic teeth movement of about two-fold when PGE2 was used as a biomodulator. PGE2 gel of about

1microgram is sufficient to accelerate the teeth movement without any side effects.

Keywords: OTM - Orthodontic tooth movement, PGE2- Prostaglandin E 2, OPG – Osteoprotegerin, RANKL - Receptor activator of nuclear factor-kappa ligand, RANK - Receptor activator of nuclear factor-kappa, cAMP - Cyclic amino monophosphate, MMP - Matrix metalloproteinase, TRAP - Tartrate resistant acid phosphatase, RAP - Regional acceleration phenomena, COX – Cycloxygenase, CGRP - Calcitonin gene-related peptide, GCF - Gingival crevicular fluid.

Introduction

We live in an era where science and technology know no limits. Our Orthodontic world is no less; it has evolved into its best at present. Research involving Orthodontic tooth movement is an interesting field as we are trying to answer many questions to meet the demands of this ultramodern era. [1] In the orthodontic treatment, the bone is resorbed in pressure areas and formed in tension areas. Remodeling processes by mechanical stimuli and biochemical mediators work together & coordinate the bone remodeling activity. Among these mediators, pharmacological agents like prostaglandins play an essential role in the resorbing process and bone apposition. They belong to a family of hormones called eicosanoids. They are paracrine hormones that act on cells near hormone synthesis instead of being transported through the blood to act on cells in other tissues or organs. All eicosanoids were derived from arachidonic acid, from which they take their general name (eikosi in Greek means twenty). The three essential eicosanoid classes are prostaglandins, thromboxanes, leukotrienes, where thromboxanes are produced in the human body by platelets and act in blood clot formation leukotrienes are involved in inflammation. Their overproduction causes asthmatic attacks. Prostaglandins act on many tissues by regulating the synthesis of cyclic AMP. As cyclic AMP mediates various hormones' mode of action, prostaglandins affect a wide range of cellular and tissue functions. Kurzrok and Lieb (1930) first observed that strips of the human uterus relax or contract when exposed to human semen. A few years later, Goldblatt in England and Von Euler in Sweden independently reported smooth muscle contracting and vasodepressor action in seminal fluid. Euler identified it as a lipid-soluble substance and named it prostaglandin, secreted from the prostate gland. Bergstrom and Samelson demonstrated that prostaglandins were, in fact, a family of compounds. They elucidated the structure of PGE1 and PGF2 in 1962. In 1964, Bergstrom and coworkers, and Van dorp independently achieved the biosynthesis of PGE2 from arachidonic acid. Research into prostaglandins' properties by Klein and Raisz, Raisz et al., Dowsett et al. demonstrated that prostaglandins had an essential role in promoting bone resorption in the human body. Though prostaglandins' exact role in bone resorption is not clear, it stimulates cells to produce cyclic AMP, an important chemical messenger for bone resorption. Goldhaber et al. reported on the association of increased levels of prostaglandins with bone loss in periodontal disease.

In contrast, Harris et al. reported that dental cysts' bone resorption was not due to pressure but by prostaglandin-like substances' secretion. Goodson et al. produced calvarium bone and alveolar bone resorption in rats by repeated injections of PGE1. All these studies served to show the critical role of prostaglandins in the process of bone resorption. Yamasaki and associates were among the earliest researchers to investigate prostaglandin roles in the bone resorption associated with orthodontic tooth movement. They conducted experiments on rats to examine whether prostaglandins' synthesis was induced by orthodontic force, whether exogenous prostaglandins can

produce bone resorption similar to orthodontic force. They reported that the orthodontic force application caused increased prostaglandin synthesis, which stimulated osteoclastic bone resorption. They also attempted to clarify the prostaglandin effect on the orthodontic tooth movement rate in monkeys and examined possible side effects on gingival tissues. Another key objective was to explore the possibility of local administration of prostaglandins, in conjunction with orthodontic tooth movement, to increase tooth movement and decrease the treatment time. Experiments on two Macaca fuscata monkeys showed that the local administration of PGE1 or PGE2 in gingiva near the distal area of canines should be retracted, which caused double the tooth movement rate on the opposite control side. Also, saw no side effects in the gingiva. Orthodontic treatment has the goal of achieving good occlusion. [2] It needs a relatively longer treatment time than other dental treatment kinds with a mean of 28.5–29 months. The longer the orthodontic treatment, it may increase the adverse effect, such as caries, gingivitis, and root resorption. There are many ways to shorten the treatment time, e.g., self-ligating system, electromagnetic usage, surgical corticotomy prostaglandin E2 (PGE2) injection buccal mucosa. The studies have shown that PGE2 injection could accelerate the tooth movement 1.6–2 times faster than control. That is why PGE2 injection becomes an alternative to enhance the tooth movement to shorten the orthodontic treatment time. The study of PGE2 was done on an experimental animal with a PGE2 injection dose, in the range of 0.1–10 µg/mL, in a cycle of 2–3 weeks (21 days). Although PGE2 injection could enhance the tooth movement, there are adverse effects of over resorption on alveolar bone and tooth root, also pain during needle infiltration

The needle usage may cause pain; the infiltration depth, needle penetration, and PGE2 acted as an inflammation trigger, which was painful. So it is needed to develop a new kind of PGE2 in gel form. Gel has an advantage in simple usage. It could be applied to oral mucosa without pain so that the effects are expected to be better. Carboxymethylcellulose (CMC) is the chosen gel. CMC is one of the cellulose derivative, a natural structural polymer found in plants. CMC's physical properties are pH 2,5–3, white, fluffy acidic, and hygroscopic powder with a slight characteristic odor. CMC characteristics as a bioadhesive polymer are a common component in bioadhesive dosage forms, unaffected by temperature variations, hydrolysis, oxidation, and bacterial growth resistance. CMC is known as one of the mucoadhesive polymers capable of attaching to the oral mucosa surface. The dosage of PGE2 gel is bigger than injection due to mucosal thickness, for PGE2 to affect bones. Orthodontic tooth movement means that a sustained force is directly delivered into a tooth or teeth using an orthodontic appliance. Orthodontic force and increased vascular permeability and cellular infiltration trigger inflammatory processes in the involved dental and paradental tissues. Neutrophil, lymphocyte, and monocytes called PMN cells were invaded on the tissues, enhancing PGE2 release, which indirectly causes the elevation in PGE2. PGE2 is an inflammation stimulator to trigger the capillary vasodilatation that brings the acute inflammation where the amount of PMN cells increase, and its topical applications could trigger tissue inflammation. [3]

Materials & method

This study is designed to assess and compare the orthodontic tooth movement rate during the en-masse retraction of maxillary anterior using PGE2 as a biomodulator.

Materials used:

1. Diagnostic instruments (mouth mirrors, probes, explorers)

2. Alginate impression material
3. Impression trays
4. Type III Dental stone
5. NiTi coil spring (9mm)
6. PGE2 gel
7. Microbrush
8. Digital vernier caliper
9. Force measuring Gauge

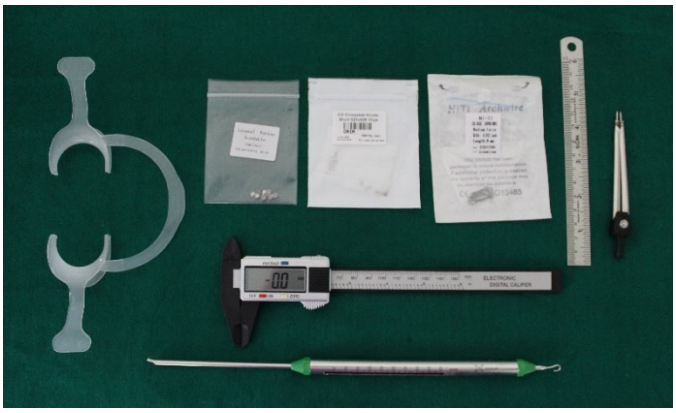


Fig. 1: Orthodontic armamentarium

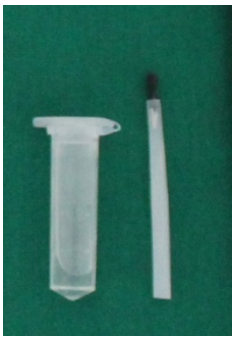


Fig. 2: PGE2 gel & Microbrush

Methodology

Sixteen patients who visited the Department of Orthodontics, Drs Sudha & Nageswarao Siddhartha Institute of Dental Sciences, seeking orthodontic treatment were divided into two equal groups based on the inclusion and exclusion criteria and coded as Group I & II. They underwent a fixed orthodontic proposed procedure and written informed consent. Also, clearance from the ethical board of institutions was obtained before commencing the study.

Group-I: Control group: Eight subjects underwent en-masse retraction with conventional friction mechanics.

Group-II: Experimental group: Eight subjects who underwent en-masse retraction with conventional friction mechanics received an application of PGE2 gel at an interval of fifteen days. Patients have been explained the proposed procedure, and written informed consent was obtained.

Method of data collection

The study was conducted from the beginning of space closure of fixed orthodontic treatment for two months. Initially, patients were treated with MBT prescription 0.022 x 0.028 slot for preadjusted edgewise appliance. After leveling and alignment, with 19×25" SS as working archwire, the retraction was started using NiTi retraction coil spring with PGE2 gel application at each interval of fifteen days using a continuous force of 150 gm per side from crimpable hook placed between lateral incisor and canine to molar hook.

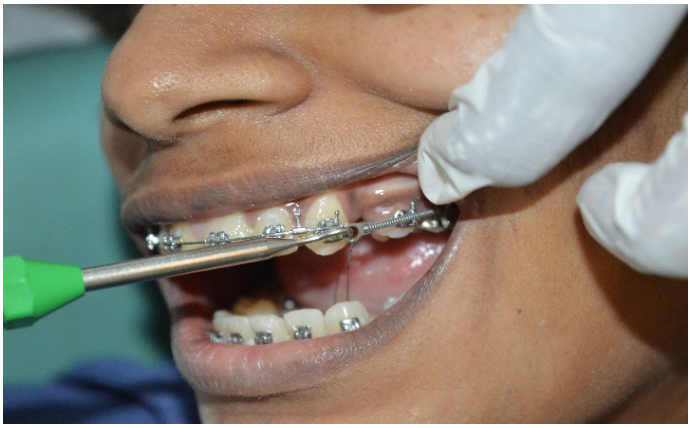


Fig. 3: NiTi coil spring with 150 gms of force

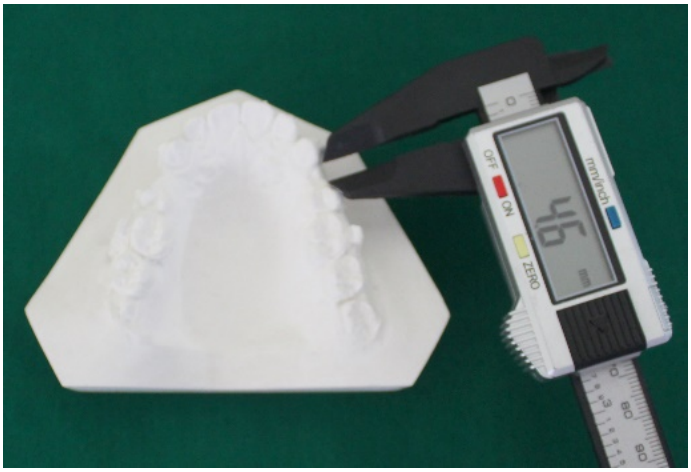


Fig. 4: Measurements were done on the cast

Prostaglandin (PGE2) gel preparation

Gel was prepared in the Department of Pharmacology in Siddhartha pharmaceutical college, Vijayawada. From 1g of Prostaglandin (PGE2) initially, Stock Solution was prepared where 0.1 µg/ml is required. Stock solution 1mg/ml (1000 µg/ml) was obtained. Later ten microliters of stock solution were added to 10ml of ethanol to get the intermediate solution. A solution of 0.1ml was taken from an intermediate solution, and a 1microgram of the gel was made. So for the preparation of 1 microgram of PGE2 gel from 1 gram of PGE2, Prostaglandin E2 (10%), HPMC (Hydroxypropyl Methylcellulose)E5 (5%), Ethanol (40%), Distilled Water (45%) was used.

Method of gel application

The PGE2 gel was applied at about 7mm from each anterior tooth's marginal gingiva. The teeth movement was recorded by measuring the distance between the canine's distal surface to the second premolar's mesial surface using a digital vernier caliper bilaterally. The tooth movement amount was obtained by calculating the differences between sequential measurements. The amount of movement was obtained by calculating the differences between sequential measurements (T0-T1-T2-T3). The total amount of movement was considered to be the difference between the values of T0 and T3.

Result

This study compares the orthodontic tooth movement rate during the en-masse retraction of maxillary anteriors using PGE2 as a biomodulator. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 21. Descriptive statistics like mean and standard deviation were calculated. Group differences were analyzed with a one-way analysis of variance (ANOVA). When the P-value was less than 0.001, the statistical test was regarded as highly significant. If the P-value was less than 0.05, the statistical test was regarded as significant. When the P-value was greater than 0.05, the statistical test was regarded as non-significant. The obtained data is subjected to statistical analysis to determine the amount of orthodontic tooth movement obtained by calculating the differences between sequential measurements. The amount of movement was obtained by calculating the differences between sequential measurements (T0-T1-T2-T3). The total amount of movement was considered to be the difference between the values of T0 and T3.

When a comparison was made between the test and control groups regarding tooth movement rate, the test group showed statistically significant results. The amount of tooth movement was more generous in the test group than in the control group.

Table 1: Comparison of mean AMT tooth movement among the two groups at given time intervals.

GROUPS		T0-T1	T1-T2	T2-T3	T0-T3
Test	Mean	1.20	0.95	0.60	2.75
	SD	0.25	0.18	0.12	0.48
Control	Mean	0.56	0.48	0.31	1.36
	SD	0.16	0.09	0.09	0.24
Total	Mean	0.88	0.71	0.45	2.06
	SD	0.39	0.28	0.18	0.81

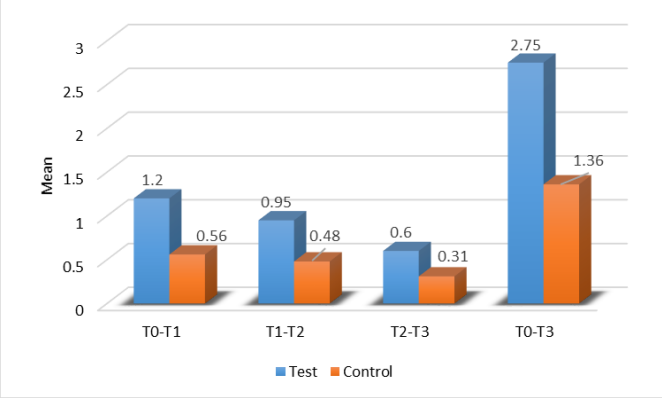
When an intragroup comparison was made, the results showed high significance.

Table 2: Intragroup comparison between the two groups at a given time

		Sum of Squares	df	Mean Square	F	Sig.
T0-T1	Between Groups	1.645	1	1.645	3748	0001*
	Within Groups	.614	14	.044		
T1-T2	Between Groups	.903	1	.903	42.83	.0001*
	Within Groups	.295	14	.021		
T2-T3	Between Groups	.331	1	.331	28.26	.0001*
	Within Groups	.164	14	.012		
T0-T3	Between Groups	7.742	1	7.742	53.12	.0001*
	Within Groups	2.040	14	.146		

Note: **P<0.001– highly significant. ANOVA test applied.

Graph 1: Comparison of mean AMT tooth movement among the two groups at given time intervals.



Graph 1 showing the increased amount of tooth movement in the test group

Table 3: Comparison of mean anchor loss among the two groups at given time intervals.

Anchor Loss		Before 2 Months	After 2 Months
Test	Mean	17.12	17.12
	SD	1.246	1.24
Control	Mean	16.62	16.62
	SD	1.41	1.40
Total	Mean	16.87	16.87
	SD	1.31	1.31

Table 3 showed no anchor loss between the two groups

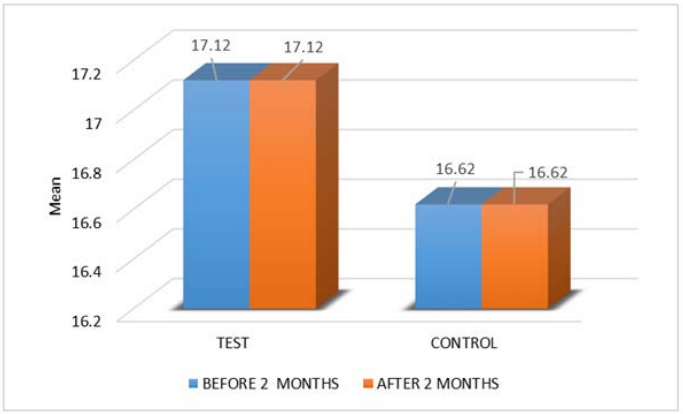
Table 4: Intragroup comparison between the two groups at a given time

ANOVA		Sum of Squares	Df	Mean Square	F	Sig.
Before two months	Between Groups	1.000	1	1.000	.566	.464
	Within Groups	24.750	14	1.768		
After two months	Between Groups	1.000	1	1.000	.566	.464
	Within Groups	24.750	14	1.768		

ANOVA test applied

When an intragroup comparison was made, there was no anchor loss.

Graph 2: Comparison of mean anchor loss among the two groups at given time intervals.



Discussion

In everyday life, in physiological conditions, the teeth are in constant motion, slow, minor and invisible, and are accomplished by permanent remodeling of the alveoli in which they are placed. Although they are always in discrete motion in healthy periodontitis, they remain firmly fixed in the alveoli without luxation. In this case, the forces are controlled. But throughout life, teeth are regularly exposed to the effects of various forces (weaker or stronger) due to mastication, phonetics, or maybe because of the result of many other causes that are transmitted from the tooth to the alveoli surrounding support apparatus. The forces are not always within the permissible force or direction. In many situations, they overlap with the tooth's axial axis and are vertically oriented, and can also be longitudinal, sloping, and even horizontal.[4]

In essence, the supportive tooth apparatus is the primary harmonizing system that balances strength in physiological stresses. During pathological stresses, tolerance is limited; thus, if compensatory mechanisms cannot continue balancing, alterations appear. The consequences depend on the strength, duration of force, and the tissues' capacity around the crowded teeth. Of course, in these conditions, individuals' immune response significantly influences the tissue response should not be forgotten. There is a balance between osteoclastic resorption and osteoblastic bone formation; hence in the absence of excessive forces, these two processes are in equilibrium. The resorption on one side of the tooth is balanced by the deposition of newly created bone on the opposite side. Simultaneously, these processes are aided by continuous cementum deposition, which throughout life manages to maintain, more or less, a constant relationship between the root surface and the alveolar cup.[4]

Orthodontics has been developing extensively in achieving the desired results both clinically and technically. For therapeutic purposes in certain situations, tooth movement during orthodontic treatment (OTM) is desirable, predictable, and expected. Nowadays, it is still very challenging to reduce the duration of orthodontic treatments. It is one of the common deterrents that faces orthodontist and causes irritation among adults plus increasing risks of caries, gingival recession, and root resorption. Several attempts have been made to create different approaches, both preclinically and clinically, to achieve quicker results. [5

It has always been interesting for clinicians to understand the basic concept of tooth movement to reduce the treatment time, resulting in patient satisfaction. Extensive research has been done on the mechanical forces and tooth movement than the focus on cellular biology. Although there are many innovative mechanical devices for tooth movement, we have not successfully prevented periodontal injuries. Understanding the specific remodeling pathways is essential to target those cells and achieve an impeccable prognosis. The other advantage of knowing these cells can also stimulate the body directly or indirectly to produce or activate these cells. [6]

Orthodontic tooth movement(OTM) is a biological process that requires the relay of mechanical loading to biological signals by a periodontal ligament (PDL) and alveolar bone (AB) cells such as osteoblasts, osteocytes, and osteoclasts. The mechanotransduction signals involve dynamic cellular communication that allows for a coordinated cellular response of alveolar bone remodeling and periodontal tissue homeostasis to orthodontic force. This complex process depends on adaptive tissue remodeling of periodontium for both anabolic and catabolic events. Compression and tension forces from orthodontic treatment create stress and strain to the PDL and AB cells and their surrounding extracellular matrices (ECM), which respond to the stress and strain from orthodontic forces by expressing and secreting biologic mediators and inflammatory cytokines, osteoclast differentiation factors, and ECM proteins such as collagen I, III, V, and their modifying enzymes and proteases. These biomolecules will initiate the activation of fibroblasts, osteoblasts, osteocytes and lead to the recruitment and differentiation of osteoclasts, causing anabolic activities on the tension side and increased osteoclastic activity, with the evidence of low bone density on the compression side of tooth movement.[7

Hatch suggested that Blood vessels and periodontal fibroblasts reside in between the periodontal ligament collagen fibers. Inactive osteoblasts line along the alveolar bone surface, and quiescent osteocytes reside in their bony lacunae. Initial cellular events in periodontal

ligament after force loading during tooth movement. The blood vessels are squeezed, then local hypoxia and fluid flow change are initiated from the loading force. The mechanical strain affects the periodontal fibroblasts and osteoblasts in the periodontal ligament space. This creates fluid flow shear stress and strain on the osteocytes in their bone lacunae. The mechanical strain induces the release of inflammatory cytokines and biological signaling mediators, including interleukins, prostaglandins, tumor necrosis factors, nitric oxide, growth factors, proteinases, and cell differentiation factors. These mediators, in turn, activate the periodontal fibroblasts, osteoblasts, and osteocytes. The blood vessels dilate due to the response to the released mediators and cytokines. The activated fibroblasts, osteoblasts, and osteocytes are ready to secrete M-CSF and RANKL to activate preosteoclasts from blood and bone marrow. Besides, the activated osteoblasts release OPG to act as competitive decoits for RANKL. The PDL fibroblasts release MMPs to degrade collagen fibers in the periodontal ligaments. The activated osteoclast is derived from the fusion of preosteoclasts, which creates a ruffle border, seals the bone surface area, and releases MMP9, TRAP, and acid to resorb bone matrix minerals. Apoptotic osteocytes also release the biomolecules and mediators to activate osteoclast recruitment for bone resorption leading to tooth movement.[8]

Biomarkers are identified as essential mediators during orthodontic therapy. In essence, biomarkers are objectively measured and evaluated as indicators of normal biological, pathological processes, pharmacological response status following applied therapeutic procedures in tissue, and most commonly in GCF.[9] In addition to the metabolic substances and enzymes in the group of biomarkers that participate in bone shaping during orthodontic tooth movement, an important site belongs to the inflammatory mediator's group. This group includes the following biological substances: prostaglandin E, neuropeptides (calcitonin related gene peptide and substance p), transforming growth factor-α1, epidermal growth factor, α2 microglobulin and insulin-like growth factor-1, interleukin-1 (receptor antagonist) 1β, 2, 6, 8, tumor necrosis factor, macrophages colony-stimulating factors, receptor activator of nuclear factor-kappa/receptor activator of nuclear factor-kappa ligand/osteoprotegerin system, myeloperoxidase, markers of root resorption. Prostaglandins are among the most critical groups of inflammatory mediators involved in bone loss and bone formation processes. [10]

Prostaglandin E (PGE2) can primarily mediate inflammatory responses and induce bone resorption by activating osteoclastic cells. [11] They directly stimulate osteoclast production and form a ruffled border to affect bone resorption. Besides, the GCF level of PGE2 reflects the biologic activity in periodontium during OTM, significantly high in both tension and compression sides. [12] Clinical and animal studies by various authors have identified PGE1 and PGE2 role in stimulating bone resorption. [13,14]

Recent research advances suggested that these biological modulators enhance or inhibit the recruitment, differentiation, or activation of osteoclasts, which could be used to provide new adjunctive approaches to orthodontic treatment. In other words, local injections of biomodulators could be used to accelerate OTM, reduce root resorption, enhance anchorage, and improve the stability of orthodontic results. [15]

Taba and his associates suggest that although PGs' exact role in bone resorption is not clear, it is thought to stimulate cells to produce cyclic adenosine monophosphate, an important chemical messenger for

bone resorption. Their research proved that the orthodontic force's application increased PGs' synthesis, which stimulated osteoclastic bone resorption.[16]

Sari noted that Prostaglandins are lipid compounds derived enzymatically from fatty acids and have essential functions in human and animal organisms. Each prostaglandin contains 20 carbon atoms, five of which form a ring. One of them is Prostaglandin E. Specifically, PGE2 is a primary mediator of inflammatory and vascular events. It plays a significant role in the destructive and absorptive processes based on increased osteoclast activity in the body.[17]

Among the subclasses of prostaglandins, PGE2 is strongly related to bone resorption, inhibits osteoprotegerin, and stimulates the nuclear factor receptor kappa-B ligand (RANKL), which regulates the increase in COX- 1 and COX-2. One of the factors being investigated for their effects on tooth movement is prostaglandins (PG), especially E2, which are potent multifunctional regulators of bone metabolism. [18]

Mechanical force loading triggers various cell signaling pathways in osteoblasts such as calcium (Ca2+), NO, IL1β, adenosine triphosphate (ATP), [19,20,21] and compression associated with elevated COX-2, which catalyzes the production of PG, including PGE2, from arachidonic acid. [22,23]

Forsberg noted that specific synthases are involved in the pathway of the synthesis of each type of prostaglandins(e.g., PGE and PGD synthases), and many of them have been cloned and could provide drug targets for the regulation of the synthesis of specific prostaglandins, such as PGE2 in the case of OTM. [24]

The activity of PGE2 and IL-1β is known, but their role in bone remodeling is confirmed in Ren's review. [25]

Yamasaki demonstrated that osteoclast increases after injecting prostaglandin, and Balaji and his associates conducted studies on rabbits and found that the tooth movement rate increased after injecting prostaglandin locally. [26,27] During mechanical stimulation, prostaglandins are produced directly by inflammatory cells or indirectly by cytokines like TNF-alpha. [28]

Krishna and his associates suggested that administration of PGE2 into the alveolar bone of mice induces both osteoclasts and osteoblasts. During orthodontic tooth movement, pain sensation occurs, and, coincidentally, substance P and calcitonin gene-related peptide (CGRP) are generated to be secreted during the tooth movement. They enhance cellular secretion of inflammatory cytokine and increase vasodilation and permeability of surrounding blood vessels resulting in inflammation in the alveolar bone, promoting tooth movement. [29]

Studies by Dudic and associates have been conducted to predict PGE2 values on compression and tension in patients undergoing orthodontic forces during the early phase of orthodontic tooth movement. Increases in fundamental values have been seen in most of the cases on the tension side. In control teeth throughout the study values of PGE2. Results suggest that PGE2 reflects biological activity in the periodontium. [30]

Studies by Shetty and Yamasaki showed that dosage of orthodontic force supplemented with PGE2 injection in animal models (monkeys and rats) resulted in advanced alveolar bone resorption, which caused increased tooth mobility. Studies by Shetty also showed that increased levels of PGE2 in GCF by 24-48 hours of the application had been reported in the human population where orthodontic controlled forces have been applied. [31,32,33]

Studies conducted by Grieve and his associates suggested that PGE2 and IL1β are considered to be potent stimulants of bone resorption and apoptosis and are a type of responsto mechanical stress. This activity's dynamics depends on their concentration, reflected in the clinical

finding in orthodontic loading conditions. Values increase at the early stage of orthodontic treatment and then normalize, i.e., are returned to their initial values in 7 days. [11]

Brudvik and Yamaguchi suggested that the main side effect associated with PGs' local injection is hyperalgesia, which is due to the release of noxious agents such as histamine, bradykinin, serotonin, acetylcholine, and substance P, from nerve endings both peripherally and centrally. [34,35]

The relationships of the two inflammatory mediators have been confirmed in a study done by Amella Cana, revealing different patterns of regulation. Namely, PGE 2 and IL-1 beta jointly participate in orthodontic tooth movement. IL-1 beta responds primarily to mechanical stress, and PGE 2 is more responsive to the synergistic regulation of IL-1 beta. The results of the analysis suggest the application of light continuous forces in the orthodontic treatment of patients. [4]

Jain suggested that the Prostaglandin solution prepared in a gel form is feasible due to its ease of administration and improved patient compliance with no systemic side effects, so gel was preferred in the present study instead of injection.[36]

A study conducted by Miyauchi attempted to examine the effects of exogenously applied PGE2 on osteoclastic résorption of alveolar bone by morphometric methods after topical application of PGE2 on the gingiva. Topically applied-PGE2 also caused distinct alveolar bone résorption associated with an increase of active osteoclasts. The JE is generally recognized to be more porous than other oral epithelia. They also concluded that one microgram PGE2 applied topically to the gingival tissue caused an increase of osteoclasts at 1 hour to 2 days after treatment and reached a maximum at 12hours. Their values were about 2 to 3 times those of the untreated control groups. So that is the reason why one microgram of PGE2 gel was preferred in the present study. [37]

Saito suggested the widening of JE's intercellular spaces with marked PMN migration o after PGE2 application indicating increased JE permeability. Furthermore, various changes in JE's subepithelial connective tissue, such as dilatation of blood vessels, PMN infiltration, and edematous change, indicate penetration of PGE2 through the JE into the subepithelial connective tissues. Therefore, it is reasonable to consider that PGE2 topically applied through the gingival sulcus passed through JE to the periodontal ligament and caused an increase of osteoclasts along the alveolar bone surface. [38]

The total dosage of 3microgram per patient injected in local infiltration method at the upper canine vestibular region used in Patil's study was absolutely safe and very well below the dosage used for producing any therapeutic and systemic effects.

In studies conducted by Patil and Yamasaki, the effect of PGE1 on orthodontic tooth movement was observed at a dose of 10 micrograms by injection and one microgram by injection, which showed a 1.7 fold increase in teeth movement. [39]

In Jain's study, they considered three micrograms for local application due to the uncertainty of bioavailability of the drug in the gel form, which showed a 1.6 fold increase in teeth movement. [36]

A comparison of PGE2 values in GCF during orthodontic force application revealed different findings. Namely, the young population has increased levels of PGE2 in the GCF, which increased to 21 days. From 21 to 28 days, the concentration of this biomarker has been decreased. So that is the reason why PGE2 was preferred and was applied once in 15 days. [40]

From the results, it was evident that when a comparison was made between the amount of teeth movement

between test and control groups, the test group showed a two-fold increase in tooth movement than previous studies with no anchor loss. Lesser bioavailability of the drug in the gel form might be one reason for variation in OTM in the test group. Some limitations were the study duration being inadequate for space closure and limited knowledge of the drug's bioavailability in its gel form. No severe side effects or root resorption, or anchor loss was noted in any patient.

Conclusions

There was a significant increase in orthodontic teeth movement of about two-fold when PGE2 was used as a biomodulator.PGE2 gel of about 1microgram is sufficient to accelerate the teeth movement without any side effects.

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