The Clinical Application of Prostaglandin E₁ on Orthodontic Tooth Movement
– A Clinical Trial

Anand K. Patil MDS MORTH RCS Edinburgh,
Associate Professor,
Dept. of Orthodontics and Dentofacial Orthopedics,
SDM Dental Institute, Dharwad,
Karnataka, India.

K. M. Keluskar MDS,
Professor, Head,
Dept. of Orthodontics and Dentofacial Orthopedics,
KLE Dental Institute, Belgaum,
Karnataka, India.

S. D. Gaitonde MDS,
Professor,
Dept. of Orthodontics and Dentofacial Orthopedics,
KLE Dental Institute, Belgaum,
Karnataka, India.

Abstract
The purpose of the present study was to verify the effect of exogenous application of Prostaglandin E₁ (PG-E₁) in small dosage on Orthodontic tooth movement in routine orthodontic patients. Fifteen patients were selected after explaining the experimental procedure and obtaining the written consent. All these patients required extraction of first premolars for the correction of malocclusion. All the patients were banded and bonded with .018" Roth prescription. After the initial alignment of upper and lower arches, separate canine retraction was considered on .016" S.S round arch wire with light continuous force using Niti canine retraction coil springs. In all cases 1 microgram (gm) of PG-E₁ along with lignocaine as a vehicle was injected on three different days in the vestibular region distal to the right upper canine. The left side was the control side with injection of vehicle alone. Occlusograms of pre and 60 days post canine retraction was obtained and distal canine movement was calculated by using palatal rugae areas as stable landmarks. The results obtained showed significant increase in orthodontic distal canine tooth movement on Prostaglandin injected side as compared with matched control left side. Radiographically and clinically, no visible changes or any indications of root resorption was noted on the experimental side as compared to control side.

Keywords
Prostaglandin E₁, Orthodontic tooth movement.

Introduction
Tooth movement is primarily a Periodontal membrane phenomenon and it is a consequence of alveolar bone remodeling and bone cell turnover. As this knowledge of the physiological aspects of tooth movement became clearer with the help of recent research, it is obvious that there are various ways and means by which we can influence the rate of orthodontic tooth movement such as Mechanically, Chemically or Electro physiologically. Till date different chemical methods to affect the orthodontic tooth movement have been tried both in-vivo and in-vitro, in summary they can be listed as, application of prostaglandins¹-², injection of Vitamin D metabolite³, steroid therapy⁴, affecting bone metabolism by parathyroid hormone⁵, thyroxin intervention⁶ and injection of precursor of nitric oxide⁷-⁸.
Prostaglandins (PG's) are one such chemical mediators of tooth movement which can influence the rate of orthodontic movement.

The history of PG's dates back to 1939 with their discovery by Von Euler. It was in the 1970's that Klein and Raisz reported for the first time that PG's are important mediators for tooth movement. Following this, number of in-vivo and in-vitro experiments were conducted, prominent among them are by Davidovitch, Z. Shanfield JL et al,11,12,13,14, Yamasaki et al,2, Marks Junior15, Leewenchen16, Brudvik et al17, J.Leiker et al18, Boekenoojen Daryl I. etal19, Alireza Sekhavat et al20, Massoud Seifi et al21 and Kee-Joon Lee et al22. These above experiments successfully demonstrate the role of Prostaglandins in enhancing the Orthodontic tooth movement. It is evident from these experiments that the injection of Prostaglandins is associated with pain and some amount of root resorption. It is also clear that the root resorption is dosage dependent19. Until now only one human study of application of PG's on orthodontic tooth movement has been reported by Yamasaki et al2, where an increased orthodontic canine retraction was demonstrated with injection of Prostaglandins along with lignocaine as a vehicle. Certain other findings were also noted in the study conducted by Yamasaki et al. Firstly, the administration of large dosage of 30-40 gm/patient of PG-E, which caused tendency for root resorption at the injection site of canine retraction. Secondly, leakage of PG E, at site of injection causing anchor loss of molars After this initial single report of clinical application of PG E, in human Orthodontic tooth movement no further documented human studies have been reported till date although later invivo-in vitro studies indicated that the PG E, is equally effective to bring about orthodontic tooth movement in low doses thereby decreasing the amount of root resorption18. Thus, the purpose of our study was to verify the effect of exogenous application of low doses of Prostaglandin E, on orthodontic tooth movement, in routine orthodontic patients.

Material and Methods

Fifteen Patients were selected who were willing to participate in the study from the Department of Orthodontics and Dentofacial Orthopedics. Written informed approval from the Ethical Board of Institution & the Governing University of Medical & Dental Health Sciences was obtained after explanation of the proposed procedure of the study. Written consent of all the patients and parents (in case patient was minor) was obtained before the start of the treatment after complete explanation of the experimental procedure.

Criteria for selection of patients

Patients were in the age group between 13-25 years with good general physical health. All the patients had adequate bone support and good periodontal health, which was confirmed by clinical examination and orthopantamographs. Patients with history of any systemic disease and with any other medical problems were excluded. All the patients had undergone first premolar extraction for the correction of malocclusion.

Method of experimental procedure

All the patients were bonded and banded after the extraction of first premolars with .018" Roth prescription brackets. .016" Niti upper and lower archwires were used to align the arches. After the completion of alignment stage .016" round stainless steel Australian Wire with Molar stops and mild curve of spee, was ligated into all the brackets. Anterior segment was

Figure 1: 018 Roth set up with Niti Canine retraction coil springs on .016 round archwire. - Pre retraction right side. - PGE, inj site

Figure 2: Pre-retraction retraction left side. - Control site
consolidated into single unit. Niti - Medium force - Canine retraction coil springs of Lot 7412 sponsored by ORMCO, USA were used to retract canines of the right and left quadrants of the upper arch. Light continuous Force of 150gms as measured from a dynamometer was applied to the canine hooks using a ligature wire.

**Method of Administration of PGE$_1$**

Prostaglandin E$_1$(11α, 13E 155) 11,15 dihydroxy - 9 Ketoprost - 13Enoic Acid-Sigma Chemicals, approximately 99% TLC synthetic, was used in the study.

PGE$_1$ was prepared with the help of lignocaine as a vehicle in the concentration of 1ml of prepared solution containing 1 gm of PGE$_1$. Lignocaine in the prepared solution acts as a local anesthetic agent and reduces the risk of pain, which would have been caused after the injection of PGE$_1$ (PGs are chemical mediators of pain and inflammation). The right side of the upper quadrant was the experimental injection site and left side of the upper quadrant was the control site where only vehicle was injected. The method of injection was in the form of local infiltration in the vestibular area at the upper canine region.

**Figure 3:** Prostaglandin E$_1$ with lignocaine as vehicle.

**Figure 4:** Injection method of administration of Prostaglandin E$_1$.

**Table 1**: Particulars of each patient undertaken, anchorage considerations and days of prostaglandin E$_1$ injection.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Anchorage</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB.1</td>
<td>19 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops.</td>
</tr>
<tr>
<td>OB.2</td>
<td>15 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.3</td>
<td>18 Yrs</td>
<td>Male</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.4</td>
<td>26 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops, HG</td>
</tr>
<tr>
<td>OB.5</td>
<td>18 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.6</td>
<td>20 Yrs</td>
<td>Male</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.7</td>
<td>23 Yrs</td>
<td>Male</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.8</td>
<td>13 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.9</td>
<td>18 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.10</td>
<td>13 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.11</td>
<td>15 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.12</td>
<td>23 Yrs</td>
<td>Male</td>
<td>TPA, Molar Stops</td>
</tr>
<tr>
<td>OB.13</td>
<td>14 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops, HG</td>
</tr>
<tr>
<td>OB.14</td>
<td>14 Yrs</td>
<td>Female</td>
<td>TPA, Molar Stops</td>
</tr>
</tbody>
</table>
All the patients received PG E1 on the first day, sixth day and seventeenth day of the start of individual canine retraction. The injection days were selected on the basis of understanding of histological events of tooth movement.

**Anchorage consideration**

a. Transpalatal arch in the upper and lingual arch in the lower were soldered to the first molar bands from the beginning of alignment stage and was continued throughout the retraction of canines. b. Second molars were banded in cases where they were fully erupted and .016 round arch wire was passed into the second molar bands. First and second molars were ligated together and main arch wire was cinched back. c. Molars stops were given in upper and lower arch wires.

**Time duration and record maintained**

Total period of 60 days was considered for the study.

Records maintained during pre and post retraction of right and left canines.

1. OPG at the beginning, IOPA of right and left canines after 60 days.
2. Study Models after the alignment phase and end of 60 days.
3. Photographs – Pre and post retraction of right and left canines.

**Method of Assessment of Canine Retraction**

Occlusograms of pre and post retraction of all the study models obtained and following landmarks were marked:

a. Mid-palatine raphe was marked and a mid palatine line was drawn.

b. Median points of first rugae line

c. Tip of the right and left canines.

The intersection of median rugae line and the mid palatine line was drawn and the distance traveled by the tip of canine was measured in relation to this median rugae line from Electronic Digital Caliper.

Out of fifteen patients selected initially, one patient was not considered as the patient did not keep appointment and returned after 3 months of first injection. Therefore for all practical and statistical result purpose it was only 14 patients which were considered in the study.

**Results**

The Results of 60 days of post canine retraction, shown with Fig. 7 and Fig 8.
Table II: Canine retraction in prostaglandin E<sub>1</sub> injected and control group.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>PGE&lt;sub&gt;1&lt;/sub&gt; (mm)</th>
<th>CONTROL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB.1</td>
<td>4.44</td>
<td>2.06</td>
</tr>
<tr>
<td>OB.2</td>
<td>3.02</td>
<td>2.02</td>
</tr>
<tr>
<td>OB.3</td>
<td>4.05</td>
<td>2.00</td>
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<tr>
<td>OB.4</td>
<td>2.71</td>
<td>1.47</td>
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<tr>
<td>OB.5</td>
<td>4.60</td>
<td>3.00</td>
</tr>
<tr>
<td>OB.6</td>
<td>4.00</td>
<td>2.70</td>
</tr>
<tr>
<td>OB.7</td>
<td>3.14</td>
<td>2.10</td>
</tr>
<tr>
<td>OB.8</td>
<td>3.93</td>
<td>1.80</td>
</tr>
<tr>
<td>OB.9</td>
<td>2.59</td>
<td>2.02</td>
</tr>
<tr>
<td>OB.10</td>
<td>2.86</td>
<td>1.65</td>
</tr>
<tr>
<td>OB.11</td>
<td>3.94</td>
<td>1.88</td>
</tr>
<tr>
<td>OB.12</td>
<td>3.80</td>
<td>2.30</td>
</tr>
<tr>
<td>OB.13</td>
<td>2.80</td>
<td>1.00</td>
</tr>
<tr>
<td>OB.14</td>
<td>2.90</td>
<td>2.10</td>
</tr>
</tbody>
</table>

Mean value of PGE<sub>1</sub> injected canine movement on the right side is 3.5 mm in two months. Corrected to nearest decimal place: (3.484)

Mean value of canine movement on the left side is 2 mm in two months. Corrected to nearest decimal place: (2.004)

The ratio of injection side to non injected Side of PGE<sub>1</sub> is 1.7:1 was recorded for one month. Corrected to nearest decimal place: (1.738:1)

Discussion

Bone remodeling consists of osteoclastogenesis and osteogenesis<sup>23,24</sup>. Molecular determinants of osteoclastogenesis are now identified and are membrane bound proteins, Receptor activator nuclear factor ŒB Ligand (RANKL), and soluble Macrophage colony stimulating factor (M-CSF)<sup>22,25</sup>. These are produced by osteoblasts and bone marrow stromal cells. At the same time osteoprotegerin (OPG), soluble tumor necrosis factor receptor homologues were identified as inhibitor of osteoclastogenesis competing with RANKL.

Mechanical loads applied to PDL cells are known to induce expression of cyclooxygenase-2(Cox-2) which facilitates formation of PG's. They are proved to be one of the potential regulators of osteoclastogenesis. Exogenous PGE<sub>1</sub> treatment increases RANKL mRNA expression in PDL cells.<sup>25</sup>
The previous researches also have proved that, the PG's not only stimulate osteoclasts but osteoblasts as well either directly or indirectly\(^\text{15,24}\).

The total dosage of 3 gm per patient injected in local infiltration method at the upper canine vestibular region used in our present study was absolutely safe and very well below the dosage used for producing any therapeutic and systemic effects\(^\text{9,20}\). In the present study, the experimental procedure was explained to all the orthodontic patients and their parents and written consent was taken. Furthermore, throughout the experimental study and subsequent follow up until the end of active orthodontic treatment of two years, no side effects were observed macroscopically or radiographically around prostaglandin E\(_1\) injected site.

Ali Reza et al pointed out associated pain and leakage of drug as the shortcoming of using PG's injection\(^\text{20}\). In the present study Prostaglandin E\(_1\) was used along with Lignocaine as vehicle. Local anesthetic effect of lignocaine eliminated pain associated with the PG E\(_1\) injection. Epinephrine content in lignocaine solution may induce contraction of local blood vessels causing prolonged local action of prostaglandin E\(_1\), and thereby increasing its effectiveness. Among the fourteen patients, three patients showed anchor loss on the prostaglandin injected quadrant. All the three patients showed average to vertical growth pattern. The probable hypothesis for anchor loss could also be due to diffusion of the injected prostaglandin E\(_1\) up to the molars as pointed out by Ali Reza et al.

The results of the present research support the conclusion of earlier study conducted by Yamasaki et al, that injection of Prostaglandin E\(_1\) enhances rate of orthodontic tooth movement\(^\text{1}\.\)

The ratio 1.7:1. Prostaglandin E\(_1\), injected side tooth movement to the control side as obtained in the present study was statistically significant. The statistical ratio obtained showed 57.6 % increase in Orthodontic Tooth Movement on the Prostaglandin E\(_1\) injected side.

The certain merits of present study as compared to the previous reported human study conducted by Yamasaki et al are as follows:

1. The low concentration of dose i.e. 3 gm in the present study was equally effective in enhancing the orthodontic tooth movement as compared to previous human study where in 30 to 40 gms/pt. was used.

The significantly reduced dosage of PG E\(_1\) injection has resulted in no side effect such as root resorption in the present study as observed by periapical intraoral radiographs at the end of 60 days of canine retraction.

2. Yamasaki et al. considered the distal canine movement as decrease in distance between canine and anchor molar space. This method did not clarify the exact amount of distal canine movement and the amount of anchor loss. In the present study the exact amount of canine retraction in distal direction was accomplished with light continuous force and was defined with reference to stable palatal rugae landmarks\(^\text{27,28,29}\). This helped us predominantly to determine the factor of leakage of drug and the anchor loss.

During the entire course of study prostaglandin E\(_1\), with lignocaine was four times freshly prepared and it was found that the effect of tooth movement was more during the initial injection of the freshly prepared solution.

At present, when the clinician is aiming to achieve painless orthodontics the injection mode of administration of Prostaglandins and the local leakage of drug seems to be disadvantages in the use of Prostaglandins. The researches suggest the other modes of the administration of PG's such as Oral administration of PG's analog and systemic intravenous administration both reported in animal studies\(^\text{10,20}\). These alternative methods though definitely show increase in orthodontic tooth movement but also have some systemic side effects such as phlebitis and local irritation.

There were certain shortcomings noted in our study to list them:

Firstly, our sample size was small as it comprised of only fourteen Orthodontic patients who were willing to participate.

Secondly, our study was short term study of 60 days and long term study needs to be conducted to supplement our findings. (Though we observed significantly faster space closure on the PG E\(_1\) injected side at the end of active treatment, this finding was not statistically noted)

**Conclusion**

The results obtained clearly showed a significant increase in orthodontic tooth movement on the Prostaglandin E\(_1\) injected side as matched with control
side even in very minimum dosage. All though ours was a short term clinical study, similar studies of such kind involving various possible chemical mediators within the sphere of ethics and safety can make a miraculous difference to "Future Orthodontics"

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Communications

Anand K. Patil
Associate Professor,
Dept. of Orthodontics and Dentofacial Orthopedics,
SDM Dental Institute, Dharwad.
Karnataka, India.
Cell No: 09886279490
Ph. No – 91 + 836 – 2462090 Extn. 137
Fax – 91 + 836 – 2467212
E-mail: akptimes@yahoo.com

References


