CLINICAL EFFICACY OF LOCALLY INJECTED CALCITRIOL IN ORTHODONTIC TOOTH MOVEMENT

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ABSTRACT
Orthodontic treatment has two major problems: being lengthy and costly procedure. The present study was designed to evaluate the clinical efficacy of locally injected vitamin D3 (calcitriol) in accelerating orthodontic teeth movement (OTM) and reducing treatment time and cost in humans. The study was performed on 15 Iraqi adult orthodontic patients within the age range 17-28 years, they are randomly allocated into three groups, each of five patients and treated with either 15 pg, 25 pg, or 40 pg/0.2ml calcitriol diluted with 10% dimethylsulfoxide (DMSO). The maxillary arch of every patient was divided into control (right) and experimental (left) sides. In addition to force application, the right canine received 0.2 ml DMSO injections while the left canine received the calcitriol injections. The follow up period for every patient included five visits at one week intervals through which they received two injections three times and evaluated for OTM, GCF collection and radiographic examination. Statistically non-significant differences were reported for OTM between control and experimental sides, and among the three groups. However, on clinical efficacy basis, the dose of 25 pg calcitriol produced about 51% faster rate of experimental canine movement compared to control, while each of the 15 pg and 40 pg doses resulted in about 10% accelerated OTM. Moreover, the periapical radiographs showed no any damaging effect of calcitriol to the surrounding tissues. In conclusion, for the first time we reported that locally injected calcitriol, in dose dependent pattern, is clinical and cost effective in humans.

Keywords: Orthodontic, Calcitriol, Local injection, OTM

INTRODUCTION
Application of mechanical forces to teeth causes tooth movement as a result of the biological responses of the periodontal tissues. In orthodontic tooth movement, mechanical stress appears to evoke biochemical and structural responses in a variety of cell types both in vivo and in vitro. Although current clinical systems in orthodontics use mechanical forces to induce bone remodeling, several researchers have suggested that there might be ways to increase cellular activity with agents more potent than mechanical force alone. Considerable scientific interest has been focused on chemical or electrical stimuli in combination with mechanical forces for more rapid bone turnover and faster orthodontic tooth movement. One of the most commonly studied agents in animal and clinical models is prostaglandin E2 (PGE2) and prostaglandin E1 (PGE1) stimulated bone resorption, directly acting on osteoclasts, and had effects similar to those of parathyroid hormone. The role of vitamin D in the maintenance of calcium homeostasis in human beings has been well documented. In particular, the active form of vitamin D, 1, 25- dihydroxycholecalciferol (Vitamin D3, Calcitriol) is one of the most potent stimulators of osteoclastic activity known. It is also involved in the formation of osteoclasts from precursor monocytes and may produce these effects at much lower doses than other hormones such as prostaglandins. Collins and Sinclair as well as Kale et al. have reported that the local administration of vitamin D increases the rate of tooth movement in cats and rats respectively; they have emphasized that administration of vitamin D results in a good balance between deposition and resorption of bone and well-modulated bone turnover compared to prostaglandin administration. It has been shown to be a potent stimulator of bone resorption by inducing differentiation of osteoclasts from their precursors, as well as increasing activity of existing osteoclasts. In vitro studies have shown that, upon administration of 1, 25-DHCC, osteoblast cell cultures demonstrate a two- to fourfold increase in osteoclastic bone resorption compared to controls. The same results are seen when 1, 25-DHCC is added to osteoclasts incubated alone. But upon administration of actinomycin D, a known inhibitor of osteoblast activity, 1,25-DHCC was unable to stimulate osteoclastic resorption. Moreover, in vivo studies appearing in the orthodontic literature have shown increased levels of orthodontic tooth movement upon daily PDL injections of 1, 25-DHCC. The amount of increased tooth movement compared to controls has been reported to be as high as 60% in experimental animal models. According to literature survey, no data available about using vitamin D in human trials; so, the present study was designed to evaluate the effect of locally injected 1,25-Dihydroxy-cholecalciferol (Vitamin D3, Calcitriol) in accelerating orthodontic tooth movement in humans.

MATERIALS AND METHODS
Subjects Selection and Study Design
The present open label study was conducted at Baghdad Teaching Hospital- College of Dentistry/Baghdad University, during the period from October 2010 to April 2011. The study protocol was in accordance with the ethics of the clinical research and approved by the committee of graduate studies in the College of Pharmacy/Baghdad University. After getting consent of the Orthodontic Department at Baghdad Teaching Hospital, sample selection was started by examining patients seeking orthodontic treatment at the postgraduate clinic. Selection of subjects has been done according to that they are orthodontic patients within the age range 17-28 years, with class I and II malocclusion cases that require bilateral maxillary 1st premolars extraction and bilateral maxillary canines retraction (distalization). They should not have any history of chronic systemic illness, syndromes, craniofacial deformities; i.e. clinically healthy subjects, no previous orthodontic treatment, and no history of chronic drug intake; they should have vital teeth with healthy periodontium and no root resorption (examined by dental panoramic radiographs). After clinical examination of 48 patients indicated for the sample criteria and full interpretation of the research aims, signed consents were obtained only from 22 patients and/or their parents to participate as volunteers. Of those 22 patients, only 15 patients completed the research requirements.

Instruments, Chemicals and Methods
All subjects received Pre-adjusted Fixed Appliance treatment (Stainless Steel Roth 0.022” System, Dentaurum Co., Germany), and finished the 1st (leveling and alignment) phase. Maxillary Canine retraction started in the 2nd phase using stainless steel round 0.018” base archwire with a distalizing force of 150 g measured by a pressure gauge. The anchorage for canine retraction included stoppers mesial to 1st molars, 3 orders bends, ligation of 2nd
premolar and 1st molar, and transpalatal bar. All subjects also have been given orthodontic tooth brushes and chlorhexidine mouth wash to maintain good oral hygiene and prevent gingivitis; they have been instructed to take paracetamol only, if an analgesic treatment was required, for the relief of orthodontic treatment pain. The subjects were randomly allocated to the control (C) and experimental (E) sides for PDL injections and force applications. For both sides, PDL injections have been given locally to the distal side of the canines, the distance between the canine and the nearest 0.01 mm. After that, injections and force applications were done. At the first visit before applying the force for retraction (distalization) of the canines, the distance between the canine and the control side and control (right canine) side as previously reported 15. In the experimental side, the specified dose of calcitriol was locally injected, while the control side received 0.2 ml of DMSO only; these injections were repeated three times for every subject (at 1st, 2nd, and 3rd visits). For both sides, PDL injections have been given locally to the distal side of canines.

Measurement of the Rate of Canine Movement and Gingival Fluid Collection
At each of the 1st three visits, before applying the force for retraction (distalization) of the canines, the distance between the canine and second premolar (at the widest contact areas) was measured (for the control and experimental E sides) using a digital vernier to the nearest 0.01 mm. After that, injections and force applications were done. At the first visit after deciding the target dose to each patient, the gingival fluid volume was measured before and 1-1.5 hr after the 1st injection. The same is done at the 2nd and 3rd visits. Also it was measured after 7 days of the third injection. The fluid was carefully collected from the distal gingival sulci of maxillary right and left canines, while the surrounding gingival tissues were isolated with cotton rolls and dried carefully with a gentle blast of air directed in an occlusal direction; this was done until there was no evidence of wetness about the gingival margin. A paper point (size 30) was carefully guided into the distal sulcus depth until a slight resistance was felt, the paper point was left in place for 30 seconds and then was immediately stained with 2% alcoholic ninhydrin solution (for 5 seconds) and left to dry. Quantification of the GCF volume was determined by measuring the stained length of the paper point using a digital vernier to the nearest 0.01 mm 16.

Radiographic Evaluation
Periapical x-rays were performed for the right and left maxillary canines of each patient at the 5th visit (i.e. 30 days after the first injection) to compare the peri-apical and peri-radicular areas at the control and experimental sides 14.

Evaluation of Time and Cost Effectiveness
The greatest influence of calcitriol on E side rate of canine movement has been compared with the control side and the normally known canine movement in order to calculate if there is any treatment time reduction effectiveness of calcitriol. Assuming that the canine retraction usually requires on the average 6 mm space closure, then canine retraction will require normally about 24 weeks. Again the greatest influence of calcitriol on E side has been compared with the C side and the normally known canine movement in order to calculate if there is any cost reduction effectiveness of calcitriol.

Table 1: Effect of locally injected different doses of calcitriol (15pg, 25pg and 40pg) on the rate of canine movement (OTM in mm) after three weeks treatment

<table>
<thead>
<tr>
<th>Time intervals</th>
<th>OTM (mm) in C side</th>
<th>OTM (mm) in E side</th>
<th>% difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (15pg calcitriol)</td>
<td>1.29±0.61</td>
<td>1.42±0.63</td>
<td>10.4</td>
<td>0.893</td>
</tr>
<tr>
<td>Group 2 (25 pg calcitriol)</td>
<td>1.04±0.33</td>
<td>1.57±0.84</td>
<td>50.9</td>
<td>0.138</td>
</tr>
<tr>
<td>Group 3 (40pg calcitriol)</td>
<td>1.04±0.3</td>
<td>1.14±0.36</td>
<td>9.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD; number of sides=5 at each occasion; C= control, E= experimental; values with non-identical superscripts among different experimental groups are significantly different.

Table 2: GCF volume before and 1.0-1.5 hr after injection of either different doses of calcitriol (14pg, 25pg and 40pg) or vehicle (DMSO)

<table>
<thead>
<tr>
<th>Timing of GCF collection in each group</th>
<th>GCF volume (mm)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C side (before injection)</td>
<td>3.58±1.22</td>
<td>0.175</td>
</tr>
<tr>
<td>E side (before injection)</td>
<td>5.57±1.38</td>
<td>0.175</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD; number of sides=5 at each occasion; C= control, E= experimental; values with non-identical superscripts among different experimental groups within the same timing are significantly different.
Fig. 1: Right and left peri-apical radiographs for two patients in group 1

Fig. 2: Right and left periapical radiographs for subject in group 2

Fig. 3: Right and left periapical radiographs for subject in group 3

Table 3: Approximate estimation of treatment time and cost reduction effectiveness for using locally injected calcitriol in orthodontic procedures

<table>
<thead>
<tr>
<th>Variable</th>
<th>normal</th>
<th>C</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (weeks)</td>
<td>24</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Cost</td>
<td>X</td>
<td>3X/4</td>
<td>X/2</td>
</tr>
</tbody>
</table>
DISCUSSION

Different methods have been utilized to increase tooth movement and minimize root resorption, such as modifying force magnitude, using a vitamin D metabolite injection 18, steroid therapy 19, altering bone metabolism by PTH 20 and thyroxin intervention. Reports of patients at high risk of developing root resorption suggest the impact of factors other than force 21 and although not definitely proven, a close correlation has been observed between root resorption and hypothyroidism. As previously stated, low levels of serum calcium can also evoke bone and root resorption and a change in serum calcium level is a determining factor for root resorption despite the decisively greater role of PTH in regulation of bone resorption 22. This reason likely that raised serum calcium levels may inhibit PTH secretion and therefore inhibit root resorption. According to the previously mentioned reports, calcitriol was suggested as a promising choice in orthodontic procedures, and for the first time we decide to evaluate the clinical utility of such approach; so, the volunteers have been classified into 3 groups that receive different doses of calcitriol (15 pg, 25 pg, and 40 pg). The rational behind choosing these doses is attributed to previous reports about calcitriol, which showed its efficacy in mild and non significant systemic influence of calcitriol which led the authors gratefully thank University of Baghdad for supporting the study.

The present data was abstracted from M. Sc. theses submitted to the Department of Clinical Pharmacy, University of Baghdad. The authors gratefully thank University of Baghdad for supporting the project.

REFERENCES


