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Interleukin-1β levels, pain intensity, and tooth movement using two different magnitudes of continuous orthodontic force

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SUMMARY This study aimed to determine the optimum orthodontic force from a broader perspective. Interleukin (IL)-1β levels in human gingival crevicular fluid (GCF), pain intensity, and the amount of tooth movement were measured during canine retraction using different magnitudes of continuous orthodontic force.

Sixteen subjects (two males and 14 females), aged 18–24 years, diagnosed with Class I bimaxillary protrusion and treated with first premolar extractions participated in this study. The upper canines were retracted with continuous forces of 50 or 150 g using nickel–titanium coil springs on segmented archwires. One of the lower canines was used as a control. GCF was collected from the distal site of each tooth at specific time points. IL-1β concentrations, pain intensity, using the visual analogue scale (VAS), and the amount of tooth movement were evaluated. One-way analysis of variance, Friedman, and paired *t*-tests were used for comparisons of IL-1β in GCF, the plaque and gingival indices, and the efficiency of tooth movement on pain perception, respectively.

IL-1β concentration in the 150 g group showed the highest level at 24 hours and 2 months with significant differences compared with the control group ($P < 0.05$). The mean VAS score of pain intensity from the 150 g force was significantly greater than from the 50 g force at 24 hours ($P < 0.01$). However, no significant difference in the amount of tooth movement was found between these two different magnitudes of continuous force at 2 months. A 50 g force could effectively induce tooth movement similar to 150 g with less pain and less inflammation.

Introduction

Orthodontic force induces tissue remodelling around the teeth as a result of the reaction of the tissues or cells to mechanical stimulation. A number of studies have been conducted to identify the optimal magnitude or range of force for orthodontic tooth movement (Reitan, 1957; Hixon *et al.*, 1972; Storey, 1973; Boester and Johnston, 1974; Iwasaki *et al.*, 2000). The appropriate forces for tooth movement of human teeth reportedly range from a force as light as 18 g to one as heavy as 1515 g (Hixon *et al.*, 1972; Iwasaki *et al.*, 2000; Ren *et al.*, 2003). This argument still exists, and no evidence-based optimal force level can be recommended in clinical orthodontics (Ren *et al.*, 2003). In addition to the forces optimal for the velocity of human tooth movement, the inflammatory response and pain after orthodontic force is applied need to be studied.

Interleukin (IL)-1β has been shown to be the most potent cytokine to stimulate osteoclast activity and attract leukocytes and other cell mediators to process bone remodelling. It is the first polypeptide mediator of immune cell function to regulate bone resorption and bone formation by mechanical stress (Davidovitch *et al.*, 1988; Preiss and Meyle, 1994). Moreover, IL-1β is one of the inflammatory chemical mediators, which induce the secretion of pain-producing substances (Davidovitch *et al.*, 1989). Importantly, IL-1β is produced by the periodontal ligament (PDL) in sufficient quantities to diffuse into the gingival crevicular fluid (GCF) and has been identified as a biomarker of orthodontic tooth movement (Grieve *et al.*, 1994; Uematsu *et al.*, 1996).

Since teeth must be moved safely as well as efficiently, it is important to determine the possible adverse effects from various magnitudes of force application, cell biology by cytokines, and patient discomfort from pain intensity. The purpose of this study, therefore, was to compare two different magnitudes of orthodontic force used for canine retraction, with regard to IL-1β secretion in GCF, efficiency of tooth movement, and pain perception. The null hypothesis tested was that there is no difference between forces of 50 and 150 g concerning these measured variables.

Subjects and methods

This study protocol was approved by the Committee on Human Rights related to Human Experimentation of Mahidol University, Bangkok, Thailand. Informed consent was obtained from all subjects.

Patient selection

Sixteen patients aged 18–24 years (two males, mean age 20.8 ± 1.2 years; 14 females, mean age 20.2 ± 1.6 years) participated in this study. They all met the following criteria: (1) Class I molar relationship and bimaxillary protrusion with very mild crowding, especially in the posterior segment; (2) treatment plan involving extraction of all first premolars and distal retraction of the canines; (3) no evidence of periodontal or gingival disease; and (4) no history of antibiotic therapy during the previous 3 months and no anti-inflammatory drug use within 1 month before the start of the study. The reason for excluding patients with a history of recent antibiotic and inflammatory drug use was that they would affect some of the mediators released and immune functions.

Experimental design

After first premolar extractions, all subjects received oral hygiene instruction and were advised to have a soft food diet and to chew on both sides 1 month before and throughout the experimental period. To prevent plaque formation and the development of gingivitis, all subjects started rinsing with chlorhexidine mouthwash twice daily until the end of the experiment. At each appointment, the oral hygiene of each subject was evaluated using the plaque index (PI) as described by Dababneh *et al.* (2002) and the modified gingival index (GI; Lobene *et al.*, 1986). A transpalatal arch attached on molar bands (0.022 inch slot, Ormco Corp., Orange, California, USA) was inserted at least 1 week before the experimental procedures.

Brackets (0.022 inch slot, Ormco Corp.) and segmented archwires (0.018 × 0.025 inch stainless steel wire) were placed on the upper posterior teeth. The upper right and left canines of the same patient were randomly retracted using a continuous force of 50 or 150 g with nickel-titanium coil springs (Tomy®, Tokyo, Japan). The accuracy of the force was measured before canine retraction with a calibrated orthodontic force gauge (Gram Gauges, Mecmesin Asia Co. Ltd., Bangkok, Thailand). A lower right or left canine with no appliance was used as the control (Uematsu *et al.*, 1996; Lee *et al.*, 2004).

GCF sampling

GCF was collected from the distal site of the experimental and control canines before retraction (baseline) and after retraction at 1 and 24 hours, 1 week, 1 month, and 2 months without any reactivation of the coil spring. A paper strip (Periopaper; Proflow™ Incorporated, Amityville, New York, USA) was carefully inserted 1 mm into the gingival crevice on the distal side and left there for 30 seconds (Offenbacher *et al.*, 1986; Uematsu *et al.*, 1996; Figure 1). After an interval of 90 seconds, a second strip was carefully placed at the same site. The absorbed fluid volume was measured with a Periotron 8000 (Proflow™ Incorporated). The two periopapers of each sample site were pooled into a sealed tube and immediately frozen at −80°C.

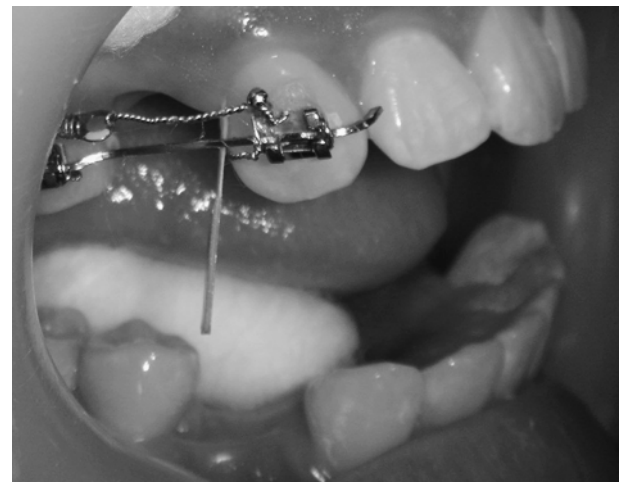

Figure 1 Gingival crevicular fluid collection at the distal side of an experimental canine.

The periopapers in each tube were eluted with 100 μl of 0.05 M Tris HCl buffer (pH 7.5) and centrifuged at 5000 g, 4°C, for 20 minutes. A further 50 μl of buffer was then applied, and the procedure was repeated. Subsequently, the supernatants were placed in a new tube and prepared for measurement of protein and IL-1β concentrations.

Protein assay and IL-1β determination

Protein concentrations of each sample site were measured by BCA Assay (Micro BCA™ Protein Assay Kit, Pierce, Rockford, Illinois, USA), with bovine serum albumin as a standard. IL-1β levels were determined using the enzyme-linked immunosorbent assay (Quantikine, R&D Systems, Minneapolis, Minnesota, USA). Total IL-1β was calculated in picograms, and IL-1β concentration in each sample site was calculated from the amount of IL-1β divided by the total protein content in GCF samples (picograms/milligrams of total protein).

Intensity of pain

For evaluation of pain intensity, all subjects were instructed to place a mark on a 100 mm visual analogue scale (VAS), corresponding to their current level of spontaneous pain intensity, including a feeling of discomfort for the right and left experimental canines separately as well as the control tooth at all experimental time periods without any stimulation. The left end of the line was given a VAS score of 0, indicating no pain, and the right end 100, indicating maximum pain. The distance from the left side to the mark indicating pain intensity was measured three times and averaged.

Determination of the amount of tooth movement

Dental models of all subjects taken before and at 2 months were evaluated with a measuring microscope (MM-11

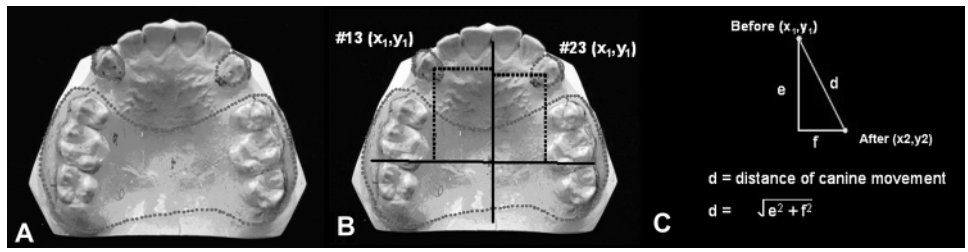

Figure 2 (A) Templates of the canines and posterior segments; (B and C) Calculation of linear changes in the position of the canines before (x_1,y_1) and after canine retraction (x_2,y_2), *d* is the distance the canine moved from the start of treatment to 2 months.

Measurescope, Nikon Inc., Tokyo, Japan). The occlusal plane of the model was set parallel to the measurement plane of the microscope connected to the computer for the reference plane. This standardized orientation was used for the subsequent model of the same subject. An orientation template that fitted the posterior teeth on the subsequent model confirmed the relative stability of the anchor segment component during canine retraction. A canine template was also made to fit over the crown of each upper canine. The position of the marker was recorded on the canine template relative to the defined axis system and references on the anchor template. The linear changes in the position of the canine at the start of treatment and at 2 months were recorded and computed in millimetres to two decimal places (Figure 2).

To assess the measurement error, the linear changes of the canine position of each patient were re-measured by the same investigator (SL) after 1 week. A paired *t*-test showed no statistically significant difference between the first and second measurement.

Statistical analyses

Data analysis was performed using the Statistical Package for Social Sciences version 14.0 (SPSS Inc., Chicago, Illinois, USA). Means and standard deviations of total protein and IL-1β concentrations from the GCF samples of all groups were calculated. For comparison of the protein or IL-1β concentrations at each observation time point within each group, repeated-measures one-way analysis of variance (ANOVA) was performed. One-way ANOVA was used for comparison of concentrations of protein and IL-1β among the groups and Friedman test for comparisons of the PI and modified GI among the groups. A paired *t*-test was used for comparing VAS scores of pain intensity or the amount of canine movement between the 50 and 150 g force. The significance level was set at $P < 0.05$.

Results

All subjects showed good gingival and periodontal status at all experimental time points with no significant difference in PI and modified GI scores (Figures 3 and 4). GCF volumes showed no significant difference among or within groups at any time point (Table 1). The mean value of total protein concentrations in the GCF samples of all groups was approximately 12 mg/ml at all time points (data not shown).

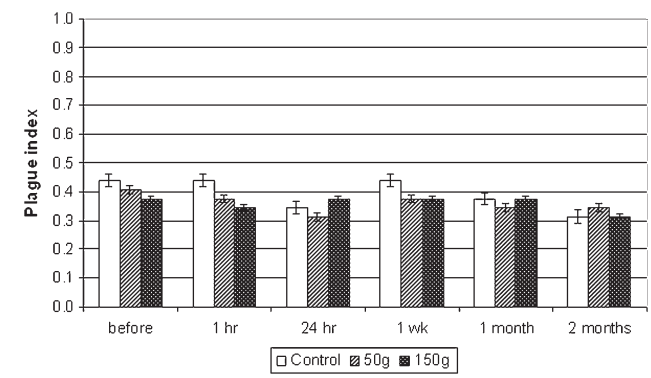

Figure 3 Plaque index score for the control and experimental groups (n = 16). There was no significant difference among or within the groups (P > 0.05).

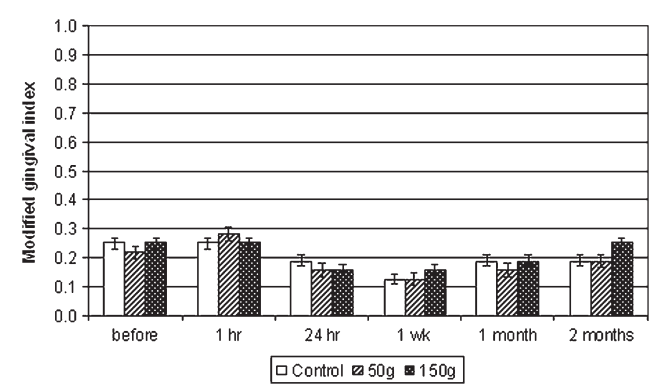

Figure 4 Modified gingival index score for the control and experimental groups (n = 16). There was no significant difference among or within the groups (P > 0.05).

IL-1β concentrations in the 50 and 150 g groups increased, with the greatest mean amounts at 24 hours, declined to approximately normal levels during 1 week to 1 month, and increased again at 2 months (Table 2). Significant differences were found between the control and a force of 150 g at 24 hours and 2 months ($P < 0.05$). Although there were no significant differences in IL-1β levels between the 50 and

Table 1 Mean ± standard deviation (SD) of gingival crevicular fluid volumes for the control and experimental groups (average volume of two periopapers in microlitres; $n = 16$).

Groups	Statistics	Before	1 hour	24 hours	1 week	1 month	2 months
Control	Mean	0.45	0.43	0.37	0.28	0.37	0.33
	SD	0.29	0.29	0.24	0.21	0.26	0.21
50 g	Mean	0.41	0.32	0.33	0.32	0.45	0.42
	SD	0.23	0.24	0.30	0.16	0.34	0.25
150 g	Mean	0.38	0.42	0.40	0.34	0.34	0.42
	SD	0.22	0.37	0.41	0.16	0.21	0.26

There was no significant difference among or within the groups ($P > 0.05$).

Table 2 Inteleukin-1β concentrations (picograms/milligrams of total protein) in the gingival crevicular fluid samples of the three groups ($n = 16$).

Groups	Statistics	Before	1 hour	24 hours	1 week	1 month	2 months
Control	Mean	0.054	0.056	0.041[a]	0.051	0.061	0.030[b]
	SD	0.044	0.050	0.045	0.052	0.080	0.030
50 g	Mean	0.059	0.052	0.073	0.058	0.051	0.069
	SD	0.064	0.080	0.129	0.053	0.038	0.078
150 g	Mean	0.054[c]	0.073	0.112[a,c]	0.068	0.078	0.111[b]
	SD	0.048	0.068	0.095	0.073	0.119	0.148

Significant differences between [a]the control and 150 g group at 24 hours, [b]the control and 150 g group at 2 months and [c]the 150 g group before and at 24 hours ($P < 0.05$).

Table 3 Means ± standard deviation (SD) of visual analogue scale scores of pain intensity from canine retraction forces of 50 and 150 g ($n = 16$).

Groups	Statistics	1 hour	24 hours	1 week	1 month	2 months
50 g	Mean	12.24	20.24[a,b,c]	8.05[b]	9.44[c]	10.97
	SD	15.33	24.11	12.18	19.06	18.50
150 g	Mean	18.84[d]	35.15[a,d,e,f,g]	8.09[e]	10.45[f]	15.03[g]
	SD	18.19	16.89	10.84	16.79	22.02

Significant difference [a]between the 50 and 150 g groups ($P < 0.01$), [b]within the 50 g group at 24 hours and at 1 week ($P < 0.05$), [c] within the 50 g group at 24 hours and at 1 month ($P < 0.05$), [d]within the 150 g group at 1 and 24 hours ($P < 0.01$), [e] within the 150 g group at 24 hours and at 1 week ($P < 0.01$), [f] within the 150 g group at 24 hours and at 1 month ($P < 0.01$) and [g] within the 150 g group at 24 hours and at 2 months ($P < 0.01$).

150 g groups at any time point, the increases in IL-1β concentration in the 150 g force group at 24 hours and at 2 months were almost twice that of the 50 g group. Within-group comparison showed a significant difference before treatment and after 24 hours in the 150 g group ($P < 0.05$).

The mean VAS scores of pain intensity with forces of 50 and 150 g are shown in Table 3. A significant difference was found between the groups at 24 hours ($P < 0.01$). This pain intensity subsequently reduced to some extent towards the end of the experiment. Although there were no significant differences in pain intensity between the 50 and 150 g groups, except at 24 hours, the 50 g showed less pain than the 150 g throughout the study.

The average amount of retraction of the canines with forces of 50 and 150 g at 2 months was 1.13 mm (±0.63) and 1.28 mm (±0.70), respectively (Figure 5). No significant difference in the amount of canine distance between the two groups was found.

Discussion

In this study, an attempt was made to evaluate the efficacy of different amounts of orthodontic force (50 and 150 g) for tooth movement in conjunction with levels of IL-1β as well as intensity of pain. Because a force of 100–200 g has been recommended for canine retraction (Burstone *et al.*, 1961;

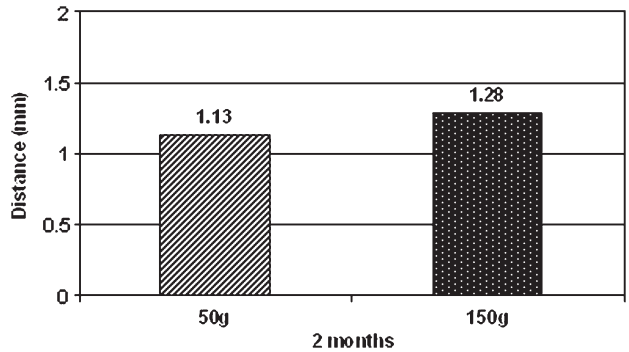

Figure 5 The mean amounts of canine retraction after 2 months of application of continuous orthodontic forces of 50 and 150 g. No significant difference was found between the two experimental groups ($P > 0.05$).

Quinn and Yoshikawa, 1985), an average force of 150 g was chosen in this study. A low magnitude of 50 g, the efficacy of which has also been reported (Boester and Johnston, 1974; Iwasaki *et al.*, 2000, 2006), was used for comparison. It was expected that these different magnitudes of force would result in differences in stress distribution in the PDL and therefore might lead to different biological responses. The patients selected were aged from 18 to 24 years and as they presented with only Class I bimaxillary protrusion, segmental archwires were used in order to reduce the confounding factors.

GCF collection, which is a non-invasive method that has been widely used for analysis of human tooth movement, enables easy detection of various biochemical markers (Grieve *et al.*, 1994; Uematsu *et al.*, 1996). Because the level of IL-1β in GCF increases with plaque accumulation and gingival inflammation (Zhang *et al.*, 2002), all subjects were instructed to maintain good oral hygiene practices throughout the period of the study. The PI and GI results for all subjects showed no sign of gingival inflammation or significant changes at any time point. Moreover, as there was no change in GCF volume, this demonstrated good gingival health throughout experimental period.

The data of this study confirmed that IL-1β was expressed in GCF both from a healthy control canine with no force and the experimental canines subjected to continuous forces of either 50 or 150 g. The mean levels of IL-1β in GCF of the control and experimental canines were similar at baseline. The IL-1β concentrations subsequently increased significantly after application of an orthodontic force of 150 g with the greatest mean amount at 24 hours which declined to about the normal level in 1 week to 1 month. These findings are similar to those of other studies with different forces and designs (Uematsu *et al.*, 1996; Lee *et al.*, 2004). However, in this experiment, the IL-1β level with a force of 150 g increased again at 2 months and was significantly different when compared with the control group. The 50 g force also showed the same pattern but was not statistically significantly different when compared with the 150 g and the control at any time point. IL-1β at baseline for all experimental and control teeth implied that IL-1β is generally released and involved in bone metabolism of healthy periodontal tissues. When orthodontic forces are applied to teeth, the mechanical stress from the applied orthodontic forces evokes biochemical and structural reactions of many cell types in and around the teeth and leads to an acute inflammatory response during early orthodontic tooth movement (Davidovitch *et al.*, 1988). A human study by Lee *et al.* (2004) found a significant increase in IL-1β concentration at 24 hours after canine retraction with a force of 100 g, which then declined, with no significant difference towards the end of the experiment of 3 weeks. In the present study where a force magnitude of 150 g was used for canine retraction, a pattern similar to that found by Lee *et al.* (2004) was observed. However, in the current research, the concentrations of IL-1β were studied for 2 months, and a significant increase was found again at that time point compared with the control. The reason for the significantly increased IL-1β concentration at 2 months might be because the 150 g force caused chronic inflammation. Although the 150 g force at 24 hours and 2 months were not significantly different when compared with the 50 g force, the increase of IL-1β concentration with the 150 g force was higher at all time points and almost twice that of the 50 g group at 24 hours and 2 months. The reason why a significant difference was not detected between the 50 and 150 g group might be due to the small sample size. Additional research is needed to elucidate this trend.

Interestingly, there was no significant difference between the mean amount of canine movement with forces of 50 and 150 g at 2 months, implying that force magnitudes less than 100 g could produce the same rate of tooth movement as a greater force (Reitan, 1957; Gianelly and Goldman, 1971). Iwasaki *et al.* (2000, 2006) used continuous average forces of 18 and 60 g for canine retraction and found that effective tooth movement could be produced with lower forces and that the lag phase was eliminated.

The immediate painful response from initial orthodontic force has been reported to be due to the development of an acute inflammatory process and changes in blood flow in the PDL (Burstone, 1962). To evaluate pain intensity, a VAS was used as this method has been found to be valid and reliable in previous research (Carlsson, 1983; Krebs *et al.*, 2007). In this study, because of the well-aligned posterior teeth, canine retraction by continuous coil springs could be performed immediately after placement of brackets and segmented archwires. The maxillary first molar bands with the transpalatal arch had been placed more than 1 week earlier to ensure that pain from the band phase had subsided (Jones and Richmond, 1985). The highest pain intensity was found in the 150 g group at 24 hours, similar to other studies (Ngan *et al.*, 1989; Polat and Karaman, 2005), while pain in the 50 g group was significantly less.

In the present study, at 24 hours, IL-1β concentration from a force of 150 g showed the highest data, which was consistent with the reported pain. Thus, the concentration of IL-1β was to

some extent related to the pain intensity. It could be considered that there might be a concentration of IL-1β, which induced sufficient tooth movement but not strong pain. A force of 50 g could be considered optimum for canine retraction.

Similar to other studies, there appeared to be great variability within and among individual patients with regard to the amount of applied force, tooth movement, and pain intensity (Lee *et al.*, 2004; Başaran *et al.*, 2006). Further research is needed with respect to the difference among individuals concerning bone metabolic capacity and bone density, including morphology and genetic factors, to clarify the mechanisms that create these variations.

Conclusions

1. A continuous force of 150 g resulted in significantly higher IL-1β levels at 24 hours and after 2 months of initial canine tooth movement when compared with the control teeth.
2. A continuous force of 50 g produced significantly less pain intensity at 24 hours compared with a 150 g force.
3. Both forces resulted in movement of the canines after 2 months, but without a statistically significant difference.
4. A continuous force of 50 g could effectively induce canine movement similar to a 150 g force, but with less pain.

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