Effect of micro-osteoperforations on the rate of tooth movement

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Our objectives were to study the effect of micro-osteoperforations on the rate of tooth movement and the expression of inflammatory markers. Methods: Twenty adults with Class II Division 1 malocclusion were divided into control and experimental groups. The control group did not receive micro-osteoperforations, and the experimental group received micro-osteoperforations on 1 side of the maxilla. Both maxillary canines were retracted, and movement was measured after 28 days. The activity of inflammatory markers was measured in gingival crevicular fluid using an antibody-based protein assay. Pain and discomfort were monitored with a numeric rating scale. Results: Micro-osteoperforations significantly increased the rate of tooth movement by 2.3-fold; this was accompanied by a significant increase in the levels of inflammatory markers. The patients did not report significant pain or discomfort during or after the procedure, or any other complications. Conclusions: Micro-osteoperforation is an effective, comfortable, and safe procedure to accelerate tooth movement and significantly reduce the duration of orthodontic treatment. (Am J Orthod Dentofacial Orthop 2013;144:639-48)

One main issue in orthodontics is prolonged treatment time, leading patients, especially adults, to avoid treatment or seek alternative options such as implants or veneers with less than optimal results. Therefore, the search for methods that decrease the treatment duration without compromising the outcome is a main challenge in orthodontic research. Whereas clinician-optimized treatment through careful diagnosis and treatment planning, as well as patient cooperation, can affect treatment duration, the main factor controlling the rate of the tooth movement is the biologic response to the orthodontic forces. But what controls the biologic response is not clearly understood.

It is generally accepted that the rate of tooth movement is controlled by the rate of bone resorption, which in turn is controlled by osteoclast activity. Therefore, one can assume that the factors recruiting osteoclast precursors from the circulation and stimulating the differentiation of these cells into osteoclasts should play significant roles in tooth movement.

Many studies have reported an increase in the activity of inflammatory markers such as chemokines and cytokines in response to orthodontic forces. Chemokines play an important role in the recruitment of osteoclast precursor cells, and cytokines, directly or indirectly, through the prostaglandin E2 pathway and the RANK/RANKL pathway, lead the differentiation of osteoclasts from their precursor cells into mature osteoclasts.
The importance of these factors in controlling the rate of tooth movement can be appreciated in studies where blocking their effect, through medication or genetic manipulation, dramatically reduces the rate of tooth movement. Therefore, it is logical to assume that increasing the expression of these factors should accelerate tooth movement. Our previous animal studies have shown that performing micro-osteoperforations (MOPs) on alveolar bone during orthodontic tooth movement can stimulate the expression of these inflammatory markers, leading to increases in osteoclast activity and the rate of tooth movement.

To investigate whether this phenomenon occurs in humans, we designed a clinical trial to study the rate of canine retraction with or without MOPs. In addition, the effect of MOPs in the stimulation of inflammatory markers was studied at different time points. Finally, the pain and discomfort of the patients during the study were evaluated.

MATERIAL AND METHODS

A randomized, single-center, single-blinded study was approved by the institutional review board of New York University. The sample size was selected based on a type I error frequency of 5% and the power of the statistical test set at 90% (P = 0.9, β = 0.1) using our animal studies as a guide to detect at least a 50% difference in the rate of tooth movement. The inclusion and exclusion criteria are summarized in Table I. Subjects included in the study had fully erupted maxillary canines with a Class II Division 1 malocclusion that required the removal of both maxillary first premolars.

Two orthodontic residents (M.R. and E.K.), trained and calibrated by the principal investigator (M.A.), were responsible for examining the subjects, determining their eligibility, and performing the orthodontic treatment under the supervision of a faculty member who was not the principal investigator. Patients who met the selection criteria and completed an informed consent form were randomly assigned to one of the study groups. The experimental group received MOPs on either the right or left side. MOPs were randomly assigned to the patients’ left or right sides to eliminate the possibility of uneven occlusal forces because of habitual occlusion predominantly on 1 side. The control group received no MOPs. The subjects and the residents administering the treatment were aware of the group assignment and therefore were not blinded. The investigators performing the measurements and data analysis were blinded from the group assignments. Treatment was initiated by bonding fixed appliances in both arches (0.022-in McLaughlin, Bennett, and Trevisi [MBT] prescription) with an auxiliary vertical slot in the maxillary canine brackets (GAC International, Bohemia, NY). Patients were referred for extraction of the maxillary first premolars by the same surgeon to decrease variability. Both the experimental and control groups were leveled and aligned before retraction. At 6 months after the extractions, alginate impressions were taken. Before canine retraction, a periapical x-ray was taken to evaluate the canine root and estimate the center of resistance based on root length. Canine retraction was achieved using calibrated 100-g nickel-titanium closing-coil springs (GAC International) connected from a temporary anchorage device to a power arm on the canine bracket that allowed application of the force closer to the center of resistance of the tooth. At each visit, the force produced by the coil was checked, and the appliances were monitored for any deformation or change in position because of chewing. Load deflection analysis for the 100-g spring showed that the force level remained relatively constant for decreases of 0.5 to 1.5 mm in the length of the spring after initial activation (data not shown). Three MOPs were performed (in the left or right side) distal to the canines and before the retraction (Fig 1, A) using a disposable MOP device designed for this purpose by PROPEL Orthodontics (Ossining, NY) (Fig 1, B). Both temporary anchorage device delivery and MOPs were performed under local anesthesia (2% lidocaine with 1:100,000 epinephrine). No flap was made, and no pain or antibiotic medication was delivered.

**Table I. Inclusion and exclusion criteria for the study**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Male and female</td>
<td>Long-term use of antibiotics, phenytoin, cyclosporin, anti-inflammatory drugs, systemic corticosteroids, and calcium channel blockers</td>
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<tr>
<td>Age range, 18-45 years</td>
<td>Poor oral hygiene for more than 2 visits</td>
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<tr>
<td>Class II Division 1 malocclusion</td>
<td>Extreme skeletal Class II malocclusion, overjet &gt;10 mm, Pg-Nper &gt;18 mm, ANB &gt;7°, SN-GoGn &gt;38°</td>
</tr>
<tr>
<td>No systemic disease</td>
<td>Systemic disease</td>
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<tr>
<td>No radiographic evidence of bone loss</td>
<td>Evidence of bone loss</td>
</tr>
<tr>
<td>No history of periodontal therapy</td>
<td>Past periodontal disease</td>
</tr>
<tr>
<td>No current active periodontal disease</td>
<td>Current periodontal disease</td>
</tr>
<tr>
<td>No smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>No gingivitis or untreated caries</td>
<td>Gingivitis and caries</td>
</tr>
<tr>
<td>Probing depth &lt;4 mm in all teeth</td>
<td>Probing depth &gt;4 mm in any tooth</td>
</tr>
<tr>
<td>Gingival index ≤1</td>
<td>Plaque index ≤1</td>
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was prescribed. The timetable of events is summarized in Table II. After 4 weeks of canine retraction, impressions were taken again, and the study was concluded. Patients continued treatment in the Department of Orthodontics at New York University, and routine final records were taken at the end of treatment.

Gingival crevicular fluid (GCF) samples were collected from each subject to evaluate the level of inflammatory response. GCF was collected before orthodontic treatment, immediately before the start of canine retraction, and at each subsequent visit, between 10 AM and 12 noon. These samples were taken from the distobuccal crevices of the maxillary canine. If present, supragingival plaque was removed, and cotton rolls were used to isolate the regions before GCF samples were collected with filter-paper strips (Oraflow, Smithtown, NY) inserted 1 mm below the gingival margin into the distobuccal crevices of the canine for 10 seconds. Sample volume was assessed with Periotron 8000 (Oraflow) according to the manufacturer’s instructions. An estimated volume of 0.6 to 1.2 mL of GCF was collected and diluted to obtain 50 to 100 μL of sample, required for analysis, using a glass slide-based protein array. Cytokine levels were measured using a custom protein array for the following cytokines: CCL-2 (MCP1), CCL-3, CCL-5 (RANTES), IL-8 (CXCL8), IL-1α, IL-1β, IL-6, and TNF-α (Raybiotech, Norcross, Ga) according to the manufacturer’s instructions.

Alginate impressions were taken at the beginning of the study, immediately before canine retraction, and 28 days after canine retraction began to monitor the rate of tooth movement. The impressions were immediately poured up with plaster (calcium sulfate). The casts were labeled with the patient’s number and date and stored. Vertical lines were drawn on the cast over the palatal surface of the canine from the middle of the incisal edge to the middle of the cervical line. The distance between the canine and the lateral incisor was assessed before and after canine retraction at 3 points: incisal, middle, and cervical thirds of the crowns. All cast measurements were made using an electric digital caliper (Orthopli Corp, Philadelphia, Pa) with an accuracy of 0.01 mm. Both intraobserver and interobserver errors

<table>
<thead>
<tr>
<th>Groups</th>
<th>Start time (mo) Ortho</th>
<th>Ortho + MOPs</th>
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<tbody>
<tr>
<td>Extraction of maxillary first premolars</td>
<td>0 ✔ ✔</td>
<td></td>
</tr>
<tr>
<td>Leveling to stage of 16 × 22-in stainless steel</td>
<td>0-6 ✔ ✔</td>
<td></td>
</tr>
<tr>
<td>Placement of temporary anchorage devices</td>
<td>6 ✔ ✔</td>
<td></td>
</tr>
<tr>
<td>MOP</td>
<td>6 ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Canine retraction</td>
<td>6 ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Monitoring OH</td>
<td>0-7 ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Monitoring TM</td>
<td>6-7 ✔</td>
<td>✔</td>
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</tbody>
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Ortho, Control group; Ortho + MOPs, experimental group; OH, oral hygiene; TM, tooth movement.

Fig 1. Experimental model. A, A temporary anchorage device (TAD) was placed between the second premolar and the first molar, 5 mm from the alveolar crest and loaded immediately. Three small MOPs were performed in the extraction space at equal distances from the canine and the second premolar. Each perforation was 1.5 mm wide and 2 to 3 mm deep. B, Handheld appliance designed by Propel Orthodontics (Ossining, NY) for performing MOPs. The appliance has an adjustable length and a light signal that turns on upon achieving the desired depth during the procedure. C, Clinical application of MOPs with the perforation device.
were evaluated. For the evaluation of the intraobserver error, 10 models were measured twice at least 2 weeks later. For the interobserver error, a second investigator (S.A.) measured the same set of models twice, and the mean values of the 2 measurements by each investigator were compared. The random and systematic errors were calculated using a formula described by Dahlberg and Houston. Both the random and systematic errors were found to be small and insignificant. Random errors were 0.026 mm for the intraobserver evaluation and 0.034 mm for the interobserver evaluation. Systematic errors were 0.025 mm for the intraobserver evaluation and 0.034 mm for the interobserver evaluation. Systematic errors were 0.026 mm for the intraobserver evaluation and 0.033 mm for the interobserver evaluation (P <0.001).

The participants were asked to assess their level of discomfort on the day of appliance placement, the day of canine retraction, and subsequently at 24 hours, 7 days, and 28 days after canine retraction with a numeric rating scale, a high reliability tool comparable with a visual analog scale. The patients were instructed to choose a number (from 0 to 10) that best described their pain: 0 would mean “no pain” and 10 would mean “worst possible pain.”

STATISTICAL ANALYSIS

Comparisons between groups were assessed by analysis of variance (ANOVA). Pairwise multiple comparison analysis was performed with the Tukey post hoc test. In some experiments, paired and unpaired t tests were used to compare the 2 groups. Two-tailed P values were calculated, and P <0.05 was set as the level of statistical significance.

RESULTS

Twenty patients were recruited and completed the study with no loss to follow-up. The subjects were selected from patients that came to the Department of Orthodontics at New York University for comprehensive orthodontic treatment between September 2009 and May 2012. Their age range was 19.5 to 33.1 years, with mean ages of 24.7 years for the control group and 26.8 years for the experimental group. The patients were divided randomly into 2 groups with similar severities of malocclusion (P >0.05) (Table III). The control group had 3 men and 7 women, and the experimental group included 5 men and 5 women. All patients maintained good oral hygiene throughout the study and took no additional medications, including analgesics.

Both groups received similar treatment until initiation of canine retraction. Then the experimental group was randomly assigned to receive 3 small MOPs between the canine and the second premolar on 1 side (Fig 2, A; right panel); the control group or the contralateral side of the experimental group (Fig 2, A; left panel) did not receive MOPs. Twenty-four hours after application of the MOPs, no signs or symptoms of trauma were observed in the sides that received the MOPs (Fig 2, B; right panel), in the control group, or in the contralateral sides of the experimental group; the groups were indistinguishable (Fig 2, B; the left side shows the contralateral side representing the absence of MOPs). After 28 days, canine retraction in the group that received MOPs was clinically obvious (Fig 2, C; right panel), whereas canine retraction in the control group and the contralateral side that did not received MOPs was minuscule (Fig 2, C; left panel; Fig 2, D, shows the contralateral side representing the absence of MOPs).

Canine retraction was measured on the dental casts at 3 points: incisal, middle, and cervical thirds of the crowns (Fig 3, A). On average, MOPs increased the rate of canine retraction by 2.3-fold when compared with the control group and contralateral side of the experimental group, which was statistically significant (P <0.05). No difference in the magnitude of canine retraction between the control group and the contralateral side of the experimental group was observed (P >0.05) (Fig 3, B).

The movement of the canine was not completely bodily; in both the control and experimental groups, the incisal edge of the crown moved slightly more (0.2 mm in the experimental group and 0.1 mm in the control group) than did the cervical part of the crown (Fig 3, C). However, this difference was not statistically significant (P <0.05).

CGF samples were obtained from the distobuccal sides of the canines at different times (Fig 4, A). Protein analysis showed an increase in the level of cytokines after
24 hours in both the control and experimental groups, when compared with their levels before retraction. In both groups, these increases were statistically significant (P < 0.5). IL-1α, IL-1β, TNF-α, and IL-6 increased by 4.6-, 2.4-, 2.3-, and 1.9-fold, respectively, in the control group, and by 8.6-, 8.0-, 4.3-, and 2.9-fold, respectively, in the experimental group (Fig 4, B). The levels of chemokines increased significantly after 24 hours of canine retraction in both the experimental and control groups compared with their levels before retraction (P < 0.05). The levels of CCL-2, CCL-3, CCL-5, and IL-8 showed 4.2-, 2.1-, 1.6-, and 6.7-fold increases, respectively, in the control group, and 16.9-, 4.8-, 2.8-, and 13.4-fold increases, respectively, in the experimental group (Fig 4, C). The differences between the 2 groups in cytokine and chemokine levels were statistically significant (P < 0.05). At day 28, only the activity of IL-1 in the control group was still significantly higher than its level before retraction (2.8-fold; P < 0.5), whereas the rest of the inflammatory markers decreased to pre-retraction levels. In the experimental group, the activity levels of IL-1α and IL-1β were 5.0 and 3.6 times higher than before retraction; these were statistically significant (P < 0.5). Even though the levels of all other cytokines and chemokines at 28 days were higher in the experimental group than in the control group, the differences were not statistically significant (P > 0.5). No difference in expression of cytokines was detected between the control group and the contralateral side of the experimental group that did not receive MOPs (data not shown).

Pain and discomfort levels were assessed using a numeric rating scale from 1 to 10 (Table IV). Data analysis indicated that at 24 hours after the beginning of canine retraction, both the control and experimental
groups reported higher levels of discomfort compared with the levels before retraction; this was statistically significant (\(P < 0.5\)). However, the difference between the control and experimental groups was not statistically significant (\(P > 0.5\)). The patients reported local discomfort at the site of the MOPs that was bearable, and no medications were necessary. At 7 days after retraction began, pain and discomfort were still higher compared
with the levels before retraction, but the difference between the groups was not statistically significant \( (P > 0.5) \). At days 14 and 28, the patients reported little to no pain or discomfort.

**DISCUSSION**

This clinical trial, similar to our animal studies, demonstrates that the application of MOPs can increase the rate of canine retraction by more than 2-fold. But many factors could affect the rate of tooth movement and need further study. It has been shown that the forces of occlusion can affect the rate of tooth movement significantly.\(^24\) To rule out the effect of occlusion in this study, we selected patients with similar severities of malocclusion (Table III). Patients with crossbite or deviation during closure caused by occlusal interference were not included in this study. In addition, to eliminate the possibility of uneven occlusal forces from habitual occlusion predominantly on 1 side, MOPs were randomly assigned to the left or right side of each patient. Furthermore, the canines were selected because they were free from occlusal interferences because of the Class II Division 1 relationship. Occlusal interferences during canine retraction were checked, but none was found that required occlusal adjustment.

Another major factor affecting the rate of tooth movement is the type of movement.\(^25,26\) In this study, an attempt was made to achieve bodily movement. Although our results suggest that retraction of the canines was not completely bodily and some tipping was involved, the magnitude of tilting was not significant (Fig 3, C) and was observed in both groups; this cannot explain the difference in the rates of tooth movement.

Age can play a significant role in the rate of tooth movement. This effect has been related to bone density...
or rate of osteoclast recruitment or activation.\textsuperscript{27-30} To eliminate the effect of age on the rate of tooth movement, only adults between 18 and 45 years were selected for this study, and the average ages in both groups were similar. Another confounding variable that can affect the rate of bone remodeling and tooth movement is the levels of sex hormones in women throughout the estrous cycle.\textsuperscript{31,32} Unfortunately, we could not eliminate this variable because of the limited number of men willing to participate in this study.

Poor oral hygiene, periodontal disease, alveolar bone loss, systemic diseases, and consumption of anti-inflammatory medications can affect the rate of tooth movement significantly.\textsuperscript{17,33,34} To reduce these variables, there was strict discipline in maintaining excellent oral hygiene and clear exclusion criteria (Table I).

Our experiments show a higher level of inflammatory markers in the experimental group in response to MOPs. Although in humans it is difficult to establish a cause-and-effect relationship, our previous animal study clearly supports increased cytokine expression as the key factor in the role of MOPs in accelerated tooth movement. Therefore, one can assume the same role for inflammatory markers in humans, if one considers the known function of the elevated cytokines and chemokines. One chemokine released during tooth movement is monocyte chemotactrant protein-1 (MCP-1 or CCL-2), which plays an important role in recruiting monocytes.\textsuperscript{3} These cells leave the bloodstream and enter the surrounding tissue to become tissue macrophages or osteoclasts. Similarly, the releases of CCL-3,\textsuperscript{35} CCL-5 (RANTES),\textsuperscript{4} and IL-8 (CXCL8)\textsuperscript{36} during orthodontic tooth movement have been related to recruitment and activation of osteoclasts.\textsuperscript{37} The result of the early hours of exposure to orthodontic forces is a further release of a broader spectrum of inflammatory markers. In addition to chemokines, many other proteins are released during orthodontic treatment that can be categorized as members of the cytokine family. These extracellular proteins play an important role in regulating the inflammatory process. Many cytokines have proinflammatory roles and help to amplify or maintain the inflammatory response and activation of bone resorption machinery, whereas some proteins have anti-inflammatory roles, preventing unrestrained progress of the inflammatory response. The main proinflammatory cytokines that are released during orthodontic tooth movement are IL-1 (α and β), TNF-α, and IL-6.\textsuperscript{6-8} These cytokines are produced by inflammatory cells such as macrophages and by local cells such as osteoblasts, fibroblasts, and endothelial cells. Our study demonstrates that these chemokines (CCL-2, CCL-3, CCL-5, and IL-8) and cytokines (IL-1, TNF-α, and IL-6) were elevated during orthodontic tooth movement. MOPs increased the expression of these factors significantly. Since all these factors play significant roles in recruitment and activation of osteoclast precursor cells, one can assume that increased release of these factors should be accompanied by higher osteoclast activation and therefore a higher rate of tooth movement (Fig 5).\textsuperscript{8-11}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{Schematic representation of the effect of MOPs on osteoclastogenesis: A, expression of inflammatory markers and osteoclast formation in response to orthodontic forces; B, MOPs increase the levels of inflammatory markers such as CCL-2, CCL-3, CCL-5, IL-8, IL-1, TNF-α, and IL-6, leading to increased osteoclastogenesis.}
\end{figure}
Extractions can change the rate of tooth movement by increasing the activity of inflammatory markers, which could obscure the effect of MOPs. To minimize this possibility in our study, extraction was done at the start of the treatment, 6 months before canine retraction. Extractions can be a great source of elevation of inflammatory markers; therefore, when possible, the extractions should be delayed until the time of major tooth movement. This would reduce the need for MOPs.

No differences in the rate of tooth movement and the level of inflammatory markers were observed between the control group and the contralateral side of the experimental group that did not receive MOPs. This suggests that MOPs on 1 side cannot affect the rate of tooth movement on the opposite side. Although our previous animal study demonstrated that the osteopenic effect of MOPs can extend to adjacent teeth, it seems that this effect is not strong enough to extend to the other side of the arch.  

Pain and discomfort caused by MOPs were not different from the control group; this indicates that this procedure can be adopted in routine clinical practice with no distress for the patient. The discomfort caused by a small injection can be bypassed by using a strong topical anesthetic.

In this project, root resorption was not investigated because of the short duration of the study (terminated after 1 month of canine retraction). Any long-term effect of MOPs on root resorption would be difficult to study because many variables can contribute to root resorption; the longer the study, the more difficult it would be to control these variables. No patient in this clinical trial showed any evidence of root resorption or alveolar bone loss in the routine panoramic radiographs taken as final records. However, panoramic or periapical radiographs are not precise for measuring the magnitude of root resorption, and future studies are necessary.

This was the first study of the effect of MOPs on the rate of tooth movement in humans. We have shown that MOPs are an effective, comfortable, and safe procedure that accelerates tooth movement significantly and could result in shorter orthodontic treatments. Future studies on the effect of the number and frequency of MOPs are necessary.

CONCLUSIONS

1. MOPs significantly increased the expression of cytokines and chemokines known to recruit osteoclast precursors and stimulate osteoclast differentiation.
2. MOPs increased the rate of canine retraction 2.3-fold compared with the control group.
3. Patients reported only mild discomfort locally at the spot of the MOPs. At days 14 and 28, little to no pain was experienced.
4. MOPs are an effective, comfortable, and safe procedure to accelerate tooth movement during orthodontic treatment.
5. MOPs could reduce orthodontic treatment time by 62%.

REFERENCES


