Micro-osteoperforations: Minimally invasive accelerated tooth movement

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Safe, minimally invasive, and cost-effective treatments are being sought to shortened orthodontic treatment time. Based on the well-known principle that orthodontic force triggers inflammatory pathways and osteoclast activity, we hypothesized that controlled micro-trauma in the form of micro-osteoperforations (MOPs) will amplify the expression of inflammatory markers that are normally expressed during orthodontic treatment and that this amplified response will accelerate both bone resorption and tooth movement. We tested our hypothesis in an animal model and in a human clinical trial. In adult rats, MOPs treatment significantly increased molar protraction with concomitant increase in inflammatory cytokine expression, osteoclastogenesis, and alveolar bone remodeling. Likewise, in human subjects, MOPs increased the rate of canine retraction concomitant with increased TNFα and IL-1β levels in gingival crevicular fluid. Moreover, MOPs treatment did not produce additional pain or discomfort in the patients tested. Our data supports our conclusion that MOPs offers a safe, minimally invasive, and easy mechanism to accelerate orthodontic tooth movement. (Semin Orthod 2015; 21:162–169.)

A major challenge in orthodontics is decreasing treatment time without compromising treatment outcome. Assuming that mechanotherapy and cooperation are optimized for any given patient, the rate-limiting step in treatment time will be the patient's biological response to mechanotherapy. Thus, identifying and, more importantly, harnessing the cellular regulators of tooth movement are essential if we are to safely shorten orthodontic treatment time.

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New York University filed a patent on microperforations when the animal studies were completed (J Dent Res. 89:1135-41; 2010). Propel Orthodontics Inc. licensed this patent from NYU and developed a tool to facilitate the procedure. They did not participate in or support this study. NYU purchased the Propel tools used in this study.

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Biology of tooth movement

The now well-known sequence of biological responses to orthodontic forces begins with compression and tension in the periodontal ligament (PDL). Compression and tension immediately deform and constrict blood vessels, and damage cells in the periodontal tissues. The initial aseptic, acute inflammatory response is marked by a flood of chemokines and cytokines from localized cells, such as osteoblasts, fibroblasts, and endothelial cells. Many of these cytokines are pro-inflammatory and sustain the inflammatory response by recruiting inflammatory cells and osteoclast precursors from the PDLs extravascular space. Infiltrating inflammatory cells maintain high chemokine and cytokine levels to support osteoclast precursor differentiation into multinucleated giant cells that perform the time-consuming process of resorbing alveolar bone that is needed for teeth to move. Equally important is the continued presence of anti-inflammatory chemokines and cytokines, which temper the destructive pro-inflammatory and osteolytic processes. Thus, the more we know about the pro- and anti-inflammatory responses of

alveolar bone, PDL and inflammatory cells to orthodontic force, the better we can develop safe therapies that shorten overall orthodontic treatment time.

What we know about cytokine effects on the rate of tooth movement is very consistent—blocking pro-inflammatory cytokines increases the time needed to move teeth in different animal models.[1–6] Taken together, these studies strongly support the conclusion that pro-inflammatory cytokines are essential mediators of orthodontic tooth movement. More importantly, these data clearly compel us to develop methods to harness and titrate the pro-inflammatory responses to safely accelerate orthodontic tooth movement.

Accelerating tooth movement

In general, there are 2 methods to accelerate the rate of tooth movement. The first involves applying physical and chemical stimulants to activate bone remodeling pathways. Importantly, these pathways are not the pathways that are activated during routine orthodontic tooth movement. Rather, these stimulant-activated pathways trigger exaggerated *uncoupled* activation of localized cells to resorb, or form bone in ways that do not mimic the natural *coupled* cellular responses to orthodontic forces. In contrast, the second approach intensifies the naturally coupled bone remodeling pathways that are activated by orthodontic forces. Utilizing the latter approach here, we present a simple and safe method to accelerate tooth movement that harnesses and amplifies the patient's normal biological response to orthodontic forces.

This novel method to accelerate tooth movement is based on the natural inflammatory response of the body to physical trauma. We hypothesize that controlled micro-trauma in the form of micro-osteoperforations (MOPs; which maintain the integrity and architecture of hard and soft tissue) will amplify the expression of inflammatory markers that are normally expressed during orthodontic treatment and that this amplified response will accelerate both bone resorption and tooth movement. To test our hypothesis, we used MOPs in an animal model of accelerated tooth movement,[7] followed by human clinical trials of the MOPs protocol.[8,9]

From rats to humans

In our study on rats, the rate of tooth movement increased significantly, with tooth movement occurring twice as fast in the MOP group compared with the O group (Fig. 1B). Cytokine/cytokine receptor expression increased significantly 24 hours after force application in the MOP and O groups compared with the C group (Fig. 1C). Moreover, 21 cytokines were significantly higher in the MOP group than the O group. Histology revealed increased alveolar bone resorption in both the MOP and O groups compared to the C group. The MOP group showed a significantly greater rate of alveolar bone resorption than in the O group, and a subsequent increase in PDL thickness (Fig. 1D). Immunohistochemical staining of TRAP-positive osteoclasts (Fig. 1D) revealed a threefold increase in osteoclast number in the MOP group compared with the O group.

Using a canine retraction model in humans, we confirmed the results of our animal study. After 28 days of canine retraction, we observed a significant increase in canine retraction in the MOP group compared with both C group and CL side (Fig. 2B). Dental cast measurements showed a 2.3-fold increase in canine retraction compared with both C group and CL side (Fig. 2C). GCF protein analysis showed increased cytokine and chemokine expression after 24 hours of force application compared with pre-retraction levels for the same patients. Moreover, cytokines were significantly higher in the MOP group than in the C group (Fig. 2D). After 28 days, all cytokine levels were decreased back to pre-retraction levels with the exception of interleukin-1-beta (IL1-β). In the MOP group, IL1-β levels at 28 days was still significantly higher (5.0- and 3.6-fold, respectively) than the pre-retraction levels (Fig. 2D). In addition, we recorded pain and discomfort levels using a self-reporting numeric scale which ranged from 0 to 10 (0 = "no pain" and 10 = "worst possible pain") on the day of appliance placement, the day of canine retraction, and 24 hours, 7 days, and 28 days after retraction was initiated. All patients reported mild to moderate discomfort compared to pre-retraction levels (Table). Importantly, MOPs treatment did not produce increased levels of pain compared to conventional, non-MOPs canine retraction treatment, with patients

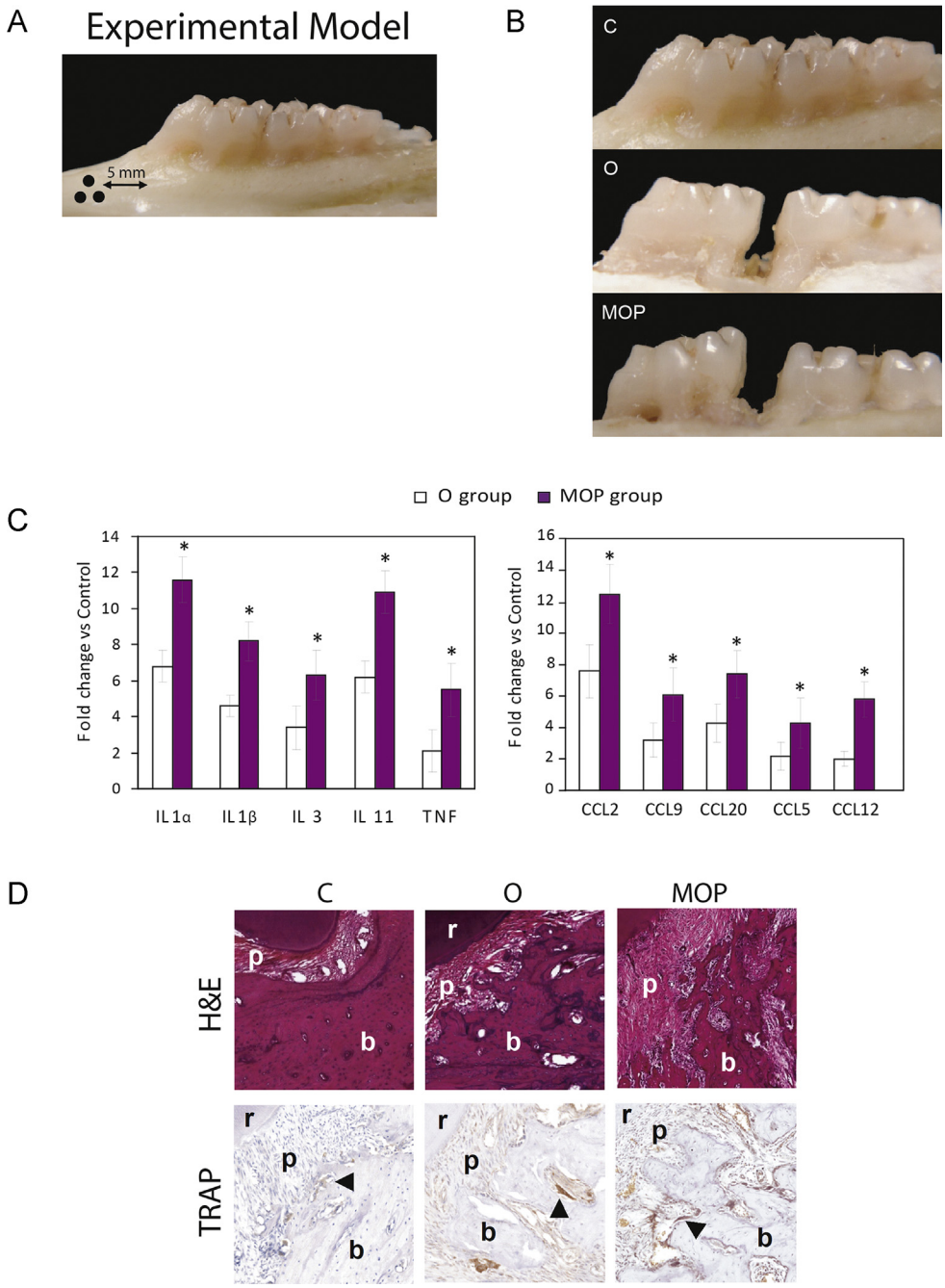

Figure 1. MOPs accelerate tooth movement in rats. Rats were divided into 3 groups. The experimental group (MOP) received 3 shallow MOPs (black dots) in the cortical bone 5 mm mesial to the maxillary first molar and a spring connecting the maxillary first molar to the incisors to apply a mesial force (A). The sham group (O) received the same mesializing spring but no MOPs. The control group (C) received passive springs and no MOPs. (B) Magnitude of tooth movement after 28 days of orthodontic force (C, control; O, orthodontic force only; MOP, orthodontic force + micro-osteoperforations). The MOP group showed the greatest magnitude of movement. (C) RT-PCR analysis of cytokine gene expression. Data presented as fold increase in cytokine expression in the O and MOP groups compared with C group. Data shown is mean ± SEM of 3 experiments. (D) Histological sections stained with hematoxylin and eosin (top panels) show increased periodontal space (*p*) thickness around the mesiopalatal root (*r*) of the first molar and increase in bone (*b*) resorption in both the O and MOP groups. Immunohistochemical staining (bottom panels) shows an increase in osteoclast activity represented by the increased number of TRAP-positive osteoclasts (*arrowhead*) in both the O and MOP groups.

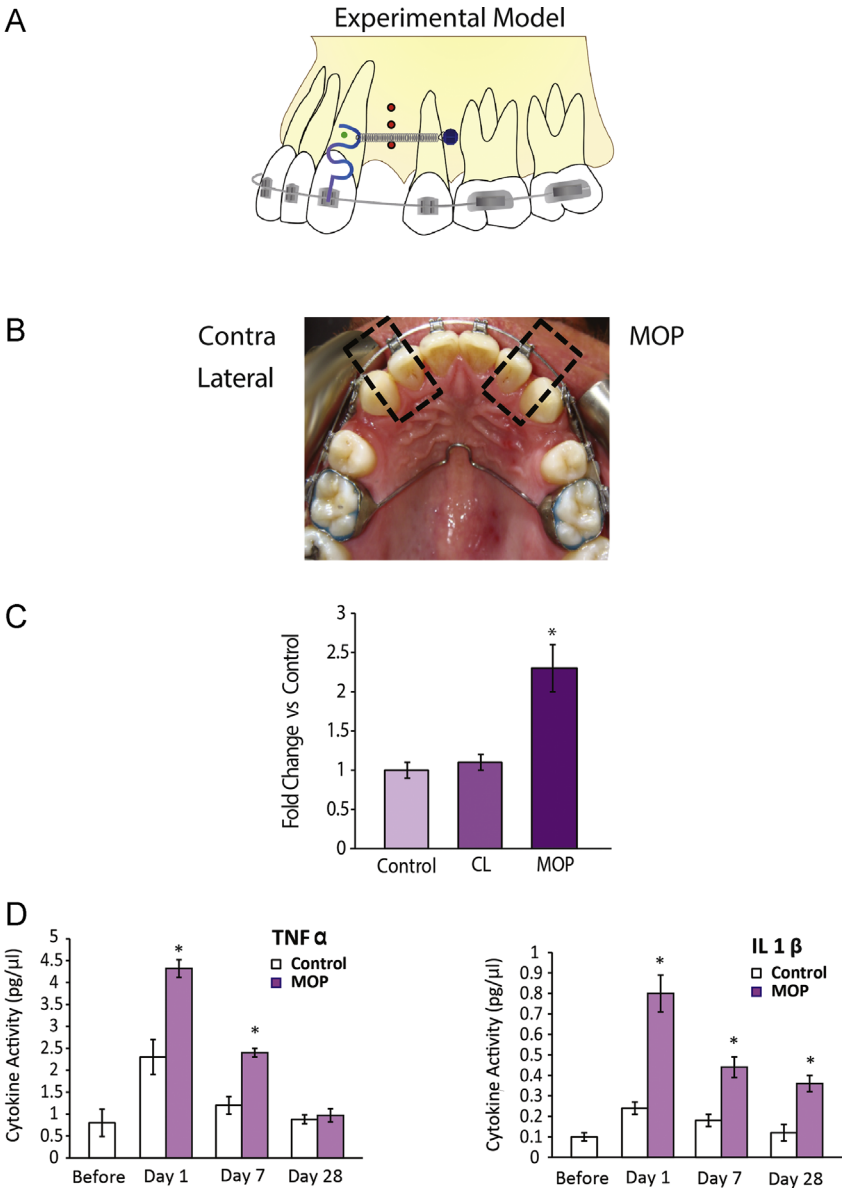

Figure 2. MOPs treatment accelerated canine retraction in a human clinical study. In a randomized, single-center, single-blinded study, 20 subjects were randomly divided into control and experimental groups. Both groups received similar treatment until the initiation of canine retraction. At that time, the experimental group received 3 MOPs between the canine and the second premolar on one side only, while the contralateral side served as additional control (CL). The control group (C) did not receive MOPs. The rate of canine retraction was determined from dental cast analysis of impressions taken immediately before initiating canine retraction and after 28 days of retraction. (A) Diagram showing the setup during canine retraction. A power arm extending from the vertical slot of the canine bracket to the level of the canine center of resistance (*green dot*) was connected by a NiTi coil (continuous 50 cN force) to a temporary anchorage device (*blue dot*) placed between the second premolar and the first molar at the level of the CR of the canine. The 3 MOPs (*red dots*) were placed between the canine and the second premolar prior to retraction. (B) After 28 days of force application, the distance between the canine and the lateral incisors was measured using a digital caliper. The canine retraction is significantly greater in the MOP group than in the O group (orthodontic force alone or contralateral side). (C) Canine retraction in MOP group increased 2.3-fold after 28 days of retraction compared with the control group and the contralateral side of the experimental group. (D) Cytokine levels in the gingival crevicular fluid collected from the distobuccal crevices of the canine before retraction and 24 hours, 7 days, and 28 days after force application cytokine protein activity was assayed by enzyme-linked immunoassay (ELISA) and shows significantly higher levels in the MOP group than in the C group. Data is presented as pg/uL. *Significantly higher than control ($p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table. Pain and Discomfort Assessment for Control (O) and Experimental (MOP) Groups Using a Numerical Rating Scale (NRS)

	Day of Canine Retraction	*1 d*	*7 d*	*14 d*	*28 d*
Control (O)	18 ± 0.3	3.4 ± 0.5	2.1 ± 0.7	1.6 ± 0.5	1.1 ± 0.4
Experimental (MOP)	1.4 ± 0.2	3.1 ± 0.4	2.2 ± 0.6	1.4 ± 0.5	1.2 ± 0.2

Pain scores in the control and experimental groups, Values represent the average for each group ± SD.

reporting only moderate discomfort that was bearable and did not require any medication.

Using the same canine retraction model in humans, the effect of number of MOPs on the rate of tooth movement was studied. In this study, rate of tooth movement was compared in 3 groups: control that only received orthodontic force (O), O + 1 MOP group that in addition to orthodontic force received 1 MOP between canine and second premolar, and O + 4 MOP group that in addition to orthodontic force receive 4 MOPs in the same position. At different time points after canine retraction, the rate of tooth movement and levels of inflammatory marker IL1-α were evaluated as described before. In response to 4 MOPs, IL1-α activity in the gingival crevicular fluid increased fivefold when compared with O group, 24 hours after MOPs procedure and coil activation, and 3.5-fold after 28 days (Fig. 3A), which was statistically was significant ($p < 0.05$). While a slight increase was observed in the O + 1 MOP group in comparison to O group at all time points studied, these changes were not statistically significant. Similar to the results of the previous clinical trial, 4 MOPs were able to increase the rate of tooth movement more than 2 folds ($p > 0.05$), while no significant difference between O group and O + 1 MOP group was observed (Fig. 3B and C). These results demonstrate a direct relation between the magnitude of the trauma to the alveolar bone and activation of inflammatory markers, and therefore, the rate of tooth movement.

Discussion

The demand for accelerated tooth movement is heard from both orthodontists and their patients. Delivering on this demand has led researchers down varied paths, including vibration, piezoelectricity, and light; just to name a few. We hypothesize that harnessing and amplifying the body's natural inflammatory responses to orthodontic tooth movement using microosteoperforations in the alveolar bone would produce a minimally invasive, safe and easily performed protocol to accelerate tooth movement. Our data from both the animal and human studies strongly support our hypothesis. We confidently conclude that MOPs treatment is a viable option for orthodontists who seek to shorten overall treatment time for their patients.

Shortening orthodontic treatment time offers significant value to clinicians and patients alike. Less time in fixed appliances reduces the risk for external apical root resorption[10] and demineralization/caries[11]; patient burn-out is less likely; young patients will miss less school; parents or older patients will miss less work. Our MOPs protocol not only offers these advantages by shortening treatment time, its minimally invasive application accelerates tooth movement without additional discomfort for the patients.

Mechanistically, our animal studies showed that MOPs significantly stimulated expression of inflammatory markers and significantly increased the number of osteoclasts and bone resorption, as anticipated. Interestingly, we observed that the increase in bone remodeling was not limited to the area of the moving tooth, but extended to the tissues surrounding the adjacent teeth (data not shown). This most likely contributed to the increase in the rate and magnitude of tooth movement observed in this study, thereby suggesting that the perforations do not need to be very close to the tooth to be moved to accelerate the rate of tooth movement.

The results of our human clinical trial were similar to the rat study. Canine retraction in the presence of MOP resulted in twice as much distalization as observed with the orthodontic forces alone. When compared to invasive surgical approaches to accelerate tooth movement, it is obvious that MOPs offers a number of advantages. This procedure is minimally invasive and flapless, allowing orthodontists to deliver care in their offices.

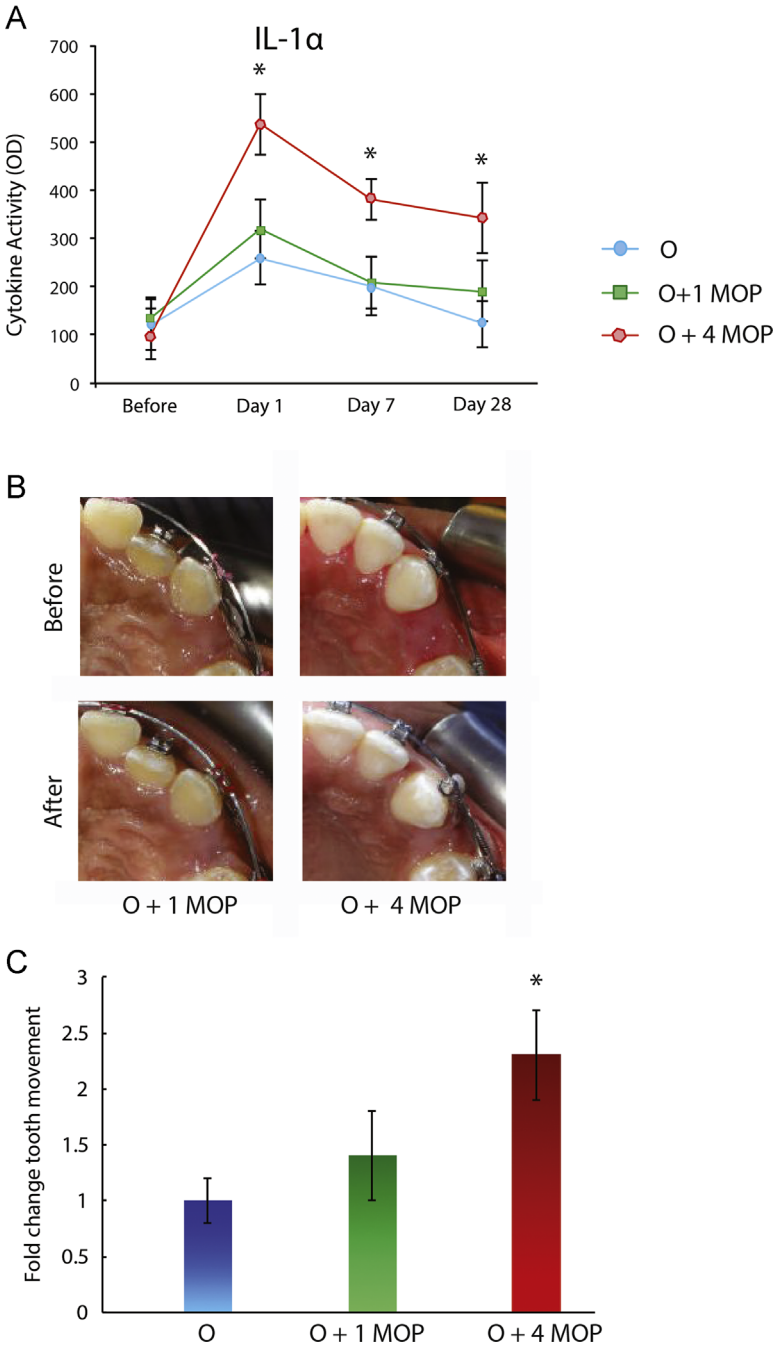

Figure 3. Increasing the number of micro-osteoperforations increases the catabolic effect in humans. A total of 15 subjects were randomly divided into control (O) and experimental groups. Using the same canine retration model previously described, experimental groups received either 1 (O + 1 MOP) or 4 (O + 4 MOP) MOPs between the canine and the second premolar prior to retraction, on one side of maxilla. (A) Levels of IL1α in the gingival crevicular fluid—as measured by protein activity was measured by enzyme-linked immunoassay (ELISA) before retraction, 24 hours, 7 days, and 28 days after force application. Data show significantly higher levels in the group that received 4 MOPs in comparison to control (O) and the O + 1 MOP group. Data is presented as pg/uL. *Significantly higher than O and O + 1 MOP groups ($p < 0.05$). (B) Intraoral photos showing canine retraction after 28 days of force application. (C) Canine retraction measured in casts was significantly greater in the O + 4 MOP group than in the O + 1 MOP and O groups. *Significantly different from O and O + 1 MOP groups ($p < 0.05$).

As it was discussed earlier osteoclast recruitment depends on inflammatory marker expression. This begs the question does inflammatory marker expression depend on the magnitude of the trauma? Our clinical studies demonstrate that by increasing the number of MOPs, inflammatory maker expression, and magnitude of tooth movement increased significantly. Therefore, one should expect procedures such as orthognathic surgery, corticotomies (where a flap is raised and numerous cuts and perforations are made in the alveolar bone), or piezocision (where no flap is raised, and bone is accessed through small cuts through the gingiva, followed by bone injury by a piezoelectric device) to significantly increase the level of inflammatory cytokines beyond levels induced by MOPs, which in comparison to these procedures is considered a very conservative insult to alveolar bone. Unfortunately, the increase in inflammatory marker expression is not sustained for a long time and after 2–3 months a significant decrease in cytokine activity is observed regardless of the type of procedure or the magnitude of injury. Due to the need to repeat the procedures over the course of orthodontic treatment, some of the above procedures lose their practicality. Therefore, based on these observations the orthodontists should be able to decide which procedure best fits the needs of their patients.

Pain and external apical root resorption

The 2 main concerns about MOPs are pain and root resorption. MOPs are done under infiltration of local anesthetic. Patients who received MOPs did not demonstrate additional pain or discomfort when compared with patients who received only orthodontic treatment and did not require additional pain medications or additional care other than regular oral hygiene. External apical root resorption (EARR) is not increased following MOPs treatment. One main reason for EARR is high stress that produces a cell-free zone when a tooth is pushed towards dense bone.[12] In these areas, osteoclasts are recruited from the surrounding PDL and endosteal surfaces. The prolonged presence of osteoclasts, rather than the number of osteoclasts, causes EARR. While MOPs significantly increased the number of osteoclasts, these osteoclasts are on the adjacent endosteal bone surface not in the PDL (data not shown). Moreover, since MOPs decreases the density of the adjacent alveolar bone, the cell-free zone is smaller and cleared faster, which would prevent prolonged osteoclast activity adjacent to tooth roots. Thus, EARR risk decreases significantly in MOPs treatment, even during tooth movement over long distances.

Clinical applications

MOPs can easily be incorporated into our orthodontic mechanics. Application of MOPs during leveling and aligning stages should be postponed until adequate space has been created. While MOPs can increase the number of osteoclasts, it will not change the side effects of the biomechanics plan and therefore similar to classic mechanics, the teeth without adequate space will not be able to engage in the main archwire. MOPs can facilitate one of the most difficult movements to accomplish in orthodontics; root movement. By activating osteoclasts and decreasing the bone density, application of similar bodily movement mechanics can produce faster tooth movement and less stress on anchor teeth, since movement occurs in less time. For these reasons, MOPs are an excellent adjunct technique during protraction/retraction of a single tooth or group of teeth. MOPs between the roots of teeth decreases the bone density while the bone density around anchor teeth remains unchanged. This procedure is especially useful when a tooth is moved into an edentulous space where alveolar bone is dense with a narrow ridge. MOPs can significantly decrease the bone density and allow faster and safer tooth movement while enhancing alveolar bone remodeling in that area. MOPs should also be considered during segmental intrusion, during which there is a possibility of root resorption due to high stress area around the root apex. While keeping the force light, MOPs application around the apex prevents the prolonged cell-free zone that can cause root resorption. Clinicians should take into consideration that since the increase in cytokine activity decreases after 2 months of MOPs application, repeating the procedure every other month is recommended. And if TADs are being used to increase anchorage, application of MOPs adjacent to the location of the TADs should be avoided since decreased bone density around the TADs will likely decrease their stability.

Conclusion

MOPs can be incorporated into routine orthodontic mechanics and at different stages of treatment, facilitating alignment and root movement, reducing the possibility of root resorption, stimulating bone remodeling in areas of deficient alveolar bone, and reducing the stress on anchor units. Therefore, MOPs offers a practical, minimally invasive and safe procedure that can be repeated as needed to maximize the biological response to orthodontic forces.

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