Title
Ability of mini-implant–facilitated micro-osteoperforations to accelerate tooth movement in rats

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Ability of Mini-Implant Facilitated Micro-osteoperforations to Accelerate Tooth Movement in Rats

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Abstract

Introduction—While current techniques for accelerated tooth movement (ATM) often involve invasive surgical procedures, micro-osteoperforations (MOPs) using mini-implants (MI) may facilitate orthodontic tooth movement without raising flaps, reducing surgical risks and increasing patient acceptance. In this study, we evaluated the effectiveness of MI-facilitated MOPs in inducing ATM and investigated potential risks for root resorption.

Methods—Five MOPs were placed on the left side around the maxillary first molars in six rats using an automated MI driver, while the right side received no MOPs as a control. Closed-coiled springs were secured from incisors to first molars for orthodontic tooth movement. Tooth movement was measured and samples underwent radiological and histological analyses.

Results—The MOP side exhibited a 1.86-fold increase in the rate of tooth movement with decreased bone density and decreased bone volume around first molars compared to the control. H&E and TRAP analysis showed increased numbers of osteoclasts as well as new bone formation. Three dimensional volumetric analysis of all five roots of maxillary first molars demonstrated no statistically significant difference in root volumes.

Conclusions—MI-facilitated MOPs accelerated tooth movement without increased risk for root resorption, and therefore may become a readily available and efficient treatment option to shorten orthodontic treatment time with improved patient acceptance.

Keywords

INTRODUCTION

Many orthodontic patients are concerned with the physical and social discomfort associated with fixed appliances.[1–5] Approaches to reduce the length of orthodontic treatment have been actively pursued to reduce possible dental and periodontal complications, including external apical root resorption, increased level of dental caries, and subsequent gingivitis and periodontitis.[6–8]

Many techniques for accelerated tooth movement (ATM) based on regional acceleratory phenomenon (RAP) are invasive and involve surgery, requiring simultaneous treatment by a periodontist and orthodontist.[9] RAP occurs when tissues regenerate locally in response to noxious stimuli, in an intensified remodeling process that includes increased activity by osteoclasts, osteoblasts, and inflammation markers.[10] Wilckodontics, the first technique to utilize RAP, has proven effective in accelerating tooth movement. The technique however, requires surgical corticotomies, cuts in the cortical bone, by raising a split thickness flap and decorticating the bone with a round bur.[11] Although less invasive corticotomies have been subsequently developed, such as corticision using a mallet to hammer a surgical blade into

the alveolar bone[12] and using piezopuncture to penetrate the buccal cortex[13,14], patient acceptance of these methods can be low.

Recently, a new method of ATM using micro-osteoperforations (MOPs) [15] was introduced to stimulate alveolar bone remodeling without creating surgical trauma. This technique was developed based on previous animal studies showing that small and shallow perforations in alveolar bone increased the rate of tooth movement without the need for flaps, bone grafting or suturing.[16] Alveolar bone perforations activated the cytokine cascade and subsequently increased osteoclast activity, allowing for enhanced bone remodeling following orthodontic force.[17] A follow-up clinical study involving twenty adults showed that when perforations were delivered to one side of the maxilla, the procedure caused little discomfort to the patients and resulted in a 2.3-fold faster tooth movement than traditional orthodontics alone.[15] Due to the clinical nature of these studies, the effects of ATM using MOPs have yet to be observed histologically.

The objective of this study is to evaluate the ability of mini-implant (MI)-facilitated MOPs to accelerate orthodontic tooth movement. MIs represent a convenient tool that is already commonly utilized by orthodontists. Thus, our study not only aims to evaluate the effectiveness of MOPs in inducing ATM, but also to examine the use of MIs as an additional technique for MOP placement. In order to do so, we established a novel tooth movement model in rats that eliminates variation between animals and achieves higher statistical power by placing MOPs on one side of the mouth, with the other side remaining as a control. Additionally, we investigated the presence of external apical root resorption following MI-facilitated MOPs. By understanding the positive and adverse effects of this technique, which creates non-surgical trauma to the alveolar bone, orthodontic treatment can progress towards higher efficiency with reduced complications for widespread patient use.

MATERIALS AND METHODS

Animal Study

Six male Sprague-Dawley rats (average body weight of 500 g) underwent orthodontic force application for tooth movement on both sides of the maxillary dentition and received MI-facilitated MOPs on only the left maxilla. The contralateral side, the right maxilla, was used as a control.

Surgical Procedure

After anesthesia was achieved, five MOPs were placed 1–3 mm apart, mesial and palatal to the left maxillary first molar, while none were placed around the right maxillary first molar (Fig 1). These MOPs were created by inserting a 1.2 mm diameter commercially available orthodontic MI to a depth of 1mm using an automated pre-programmed slow-speed implant driver at a constant 30 rpm torque. The MI successfully pierced the gingiva and created a shallow, consistent perforation in the alveolar bone. The MI was marked to ensure consistent MOP depth of 1mm and after reaching such depth, the MI was removed using the reverse function of the slow-speed driver engine. After MOPs were placed, hemostasis was achieved using cotton pellets and pressure.

Using a high-speed handpiece, retention grooves were placed on the mesial surface of the maxillary first molar and on the facial extending to the distal surface of the maxillary incisor on each side. A .09 inch stainless steel wire was bent and adapted to encircle the maxillary first molar and the maxillary incisor. Additional stability was achieved by bonding the wires into the retention grooves with bis-GMA composite resin. The wire was ligated to a 25 g nickel-titanium (Sentalloy) closed coil spring to provide consistent light force. Because rat incisors erupt continuously, appliances were checked daily and re-secured to the most apical position of the tooth as needed. Rats were euthanized at 21 days with CO_2 asphyxiation and their maxillae were consequently harvested and fixed in 10% buffered formalin.

MicroCT Analysis

Rat maxillae were scanned using high-resolution micro-computed tomography (SkyScan 1172, SkyScan N.V., Belgium) at an image resolution of 20 μm with 70 kV and 141 μA X-ray source and 0.5 mm aluminum filter. Three dimensional image datasets were then reconstructed from 2D X-ray images using NRecon software (SkyScan N.V., Belgium), which processes appropriate image correction steps including ring artifact correction, beam hardening correction and fine-tuning. The dynamic image range (contrast limits) was determined at 0–0.065 in units of attenuation coefficient and applied to all datasets for optimum image contrast. After acquisition and reconstruction of the datasets, the images were first viewed and reoriented on each 3D plane using DataViewer software (SkyScan N.V., Belgium) to align the palate parallel to the transaxial plane. To measure tooth movement, microCT images at day 21 were used to find the distance between the enamel on the most distal aspect of the first molar and the mesial aspect of the second molar, measuring from the heights of contour. To evaluate differences in bone mineral density (BMD, g/cm^3) and bone volume fraction (BV/TV, %) between the MOP and the control sides, the region of interest (ROI) was delineated to encompass the alveolar bone region surrounding the first molar, with limits at 1 mm mesial of the first molar until mesial of the second molar. Volumetric quantification of the root volume of first molars was performed following a previously established protocol.[18] After highlighting the root structure, reconstruction of slices produced a 3D representation of the root structure so that three buccal roots and two palatal roots could be digitally resected and their volumes could be analyzed individually. A global threshold of 80 was applied to all scans to extract physiologically accurate representations of the alveolar bone phase.

Histological Analysis

Samples were then decalcified in 14% neutral buffered EDTA for 21 days. After decalcification, the samples were dehydrated through graded ethanol and embedded in paraffin. The samples were sectioned coronally in 10 μm sections. Sections were stained with hematoxylin and eosin (H&E).

Three consecutive specimens from each side were immunostained with antibodies for tartrate-resistant acid phosphatase (TRAP) using TRAP staining kit (Sigma Aldrich, St. Louis, MO) according to the manufacturer's instructions. Slides were then counter-stained with Hematoxylin for 8 seconds to differentiate between soft and hard tissues. Osteoclasts were defined as multinucleated TRAP+ cells on the bone surface. For quantification, the

number of TRAP+ cells were counted for tension and pressure sides around the maxillary first molars under 100× magnification. The number was presented as number of TRAP+ cells/mm^2 bone area. Quantification was performed with a single operator blinded to the clinical information at two separate time points.

Statistical Analysis

The data was expressed as means and standard deviations for each group. Paired Student's t-test was performed between the two groups to establish significance at an alpha of 0.05.

RESULTS

Linear distance between the first and second molars was measured on MicroCT images for accuracy and tooth movement at 21 days was significantly greater in the MOP side compared to the control side. On average, the MOP side (0.54±0.13mm) showed a 1.86-fold increase in tooth movement compared to the control side (0.29±0.15mm) (Fig 2). All the rats in the experimental group showed complete soft tissue and hard tissue healing of MOP sites at day 21. In addition, osteopenia illustrating decreased bone volume and bone density around the maxillary first molar was observed on the MOP side compared to the control side in all animals (Fig 3A and B). According to MicroCT volumetric analysis, the MOP side (76.06±2.72%) showed a statistically significant decrease in BV/TV compared to the control side (81.39±4.60%) in all animals (Fig 3C). The MOP side (2.50±0.13 g/cm^3) also showed a statistically significant decrease in BMD compared to the control side (2.74±0.22 g/cm^3) (Fig 3D).

Any type of orthodontic tooth movement is generally associated with root resorption.[19] To examine whether root resorption was induced during orthodontic movement after MI-facilitated MOPs, we evaluated root resorption and bone quality using H&E stained slides. Histological examination of the H&E slides showed that the MOP side experienced notable bone loss as indicated by the shortened interradicular trabecular bone height and increased number of multinucleated osteoclasts on all rats. Additionally, mild/moderate to moderate root resorption with blunted root apex on the MOP side was found in three animals (Fig 4A). On the other hand, the control side showed normal interradicular trabecular bone height, indicating minimal bone loss and no resorption with well-defined root apex and PDL space (Fig 4A). Further examination using MicroCT volumetric analysis on all five roots of the maxillary first molar revealed no statistically significant difference between root volumes of the control (2.71±0.41 mm^3) and the MOP sides (2.62±0.50 mm^3) (Fig 4B), indicating that MI-facilitated MOPs induced ATM without causing significant root resorption.

Although we found no difference in root volumes, closer examination of the bone surfaces showed an increased presence of multi-nucleated osteoclasts in the MOP side when compared to the control side (Fig 4A, middle panels). To quantitatively evaluate bone resorption, the number of osteoclasts was determined after TRAP staining (Fig 5A). The MOP side showed a significantly greater number of osteoclasts in the alveolar bone surrounding the maxillary first molar compared with the control side (Fig 5A). On average, there were 44% more osteoclasts in the total alveolar bone surrounding the first molar on the

MOP side compared with the control side and there were 55% more osteoclasts in the pressure side alveolar bone on the MOP side compared with the control side (Fig 5B).

Bone remodeling occurs by inducing bone resorption as well as bone formation.[20] Therefore, we also evaluated for new bone formation. H&E analysis also showed that the MOP side had an increase in new bone formation indicated by dark blue lines indicative of less organized woven bone and increased bone metabolic activity, as opposed to the predominantly organized and mature bone of the control side (Fig 6A). New bone formation was quantified on H&E by defining a fixed size rectangle enclosing the alveolar bone of the maxillary first molar for each rat. The areas of new bone were measured and percent new bone formation was calculated using the equation: Σ(new bone area)/(total alveolar bone area). The MOP side (11.0±4.7%) showed a statistically significant increase in new bone formation compared to the control side (6.2±5.8%) (Fig 6B).

DISCUSSION

Orthodontics is a continuously developing field that strives to effectively and efficiently achieve desired results. Due to the discomfort and complications that can arise from lengthy treatment duration, new methods have been pursued to decrease orthodontic treatment time. MOP procedures aim to accelerate the rate of tooth movement by boosting bone remodeling activities of bone resorption and new bone formation, in a process known as RAP.[10] In previous rat studies, Teixeira *et al.* demonstrated that shallow perforations of the cortical plate using a round bur and handpiece significantly increased the rate of bone remodeling and tooth movement by stimulating the expression of inflammatory cytokines[17]. In a follow-up human clinical study by Alikhani *et al.*, a commercially available disposable MOP device designed for this purpose was used to show that alveolar MOPs safely and effectively accelerated tooth movement in humans during orthodontic treatment.[15] Due to the clinical nature of their study however, no histological findings were observed. Here, utilizing an MI driver to pierce through the gingiva with subsequent decortication of the alveolar bone in rats, we demonstrated for the first time that MOPs accelerated tooth movement at the histological level. We further demonstrated that ATM induced by MOPs did not induce root resorption.

Our work differs from prior studies on orthodontic tooth movement in that we developed a novel experimental design to protract the first maxillary molar using the maxillary incisor as an anchor, in which MOPs were placed on the left side, with the right side remaining a control. Studies such as this in which the experimental and control groups are compared within a single animal are considered to provide optimal conditions for studying a treatment effect on tooth movement as they minimize confounding variables within the different groups and maximize statistical power within a fixed number of observations.[21] With MOPs and orthodontic tooth movement on one side of the maxilla versus orthodontic tooth movement alone on the contralateral side, much of the inter-animal variability was removed from the results of the treatment effect. In addition, our animal model was able to secure the appliance for orthodontic tooth movement in a non-destructive way without drilling a hole in animals' teeth, which could add discomfort to the animals.[17,22–24] Another method to increase retention for the appliance would have been to place an implant to be used as an

anchor for tooth movement; however, the additional inflammation either from implant placement or tooth damage would have presented confounding factors in the study.[25,26]

Orthodontic tooth movement is generated by the coupling of bone resorption on the pressure side—where the periodontal ligament (PDL) is compressed—and new bone formation on the tension side—where the PDL is stretched.[27–30] In our study, the maxillary first molar on the MOP side moved a greater distance during the treatment time by almost two-fold because the bone on the pressure side had been demineralized with MOPs (Fig 3), which decreased the resistance to movement.[31] Bone remodeling occurs in response to forces applied to teeth, and HW Chang *et al.* demonstrated that the direction of tooth movement is associated with a greater reduction in alveolar bone density.[32] Evidently, a decrease in BV/TV and BMD in the MOP side underlies regulatory processes that initiate accelerated tooth movement. Our results confirmed a study by Baloul *et al.* demonstrating that BV/TV and BMD were decreased significantly after 7 days when tooth movement was combined with alveolar decortication.[25] Thus, our results demonstrate that MOPs can indeed increase the rate of orthodontic tooth movement by inducing more rapid bone remodeling.

Osteoclast activation occurs during inflammation, particularly following the release of IL-1, TNF-α and other pro-inflammatory cytokines, resulting in increased bone resorption and subsequent accelerated tooth movement.[33] It was shown that MOPs increase inflammation and cause osteoporosity of alveolar bone.[17] Similarly, our results showed an increase in osteoclast quantity as well as an increase in new bone formation on the MOP side, confirming that osteoclast-osteoblast coupling occurs following decortication. Osteoclast-osteoblast coupling, regulated by intricate interactions of cytokines and growth factors, activates osteoblasts, forming new bone to sufficiently replace lost bone that resulted from osteoclast activity.[34–36] This coupling process may be a fundamental basis for accelerated bone remodeling and tooth movement. While there is greater bone resorption and bone formation with MOPs, decreased bone fraction (BV/TV) and bone mineral density (BMD) were observed, representing more bone resorption than bone formation during our treatment duration of 21 days. Furthermore, although the conventional theory behind the biology of tooth movement stipulates that osteoclast activity is confined to the pressure side, a newer study suggests that the periodontium remodels as a continuous unit.[37] Similarly, our study showed an increase in osteoclast quantity in all areas of alveolar bone surrounding the maxillary first molar with MI-facilitated MOPs, while a more dramatic difference was observed on the pressure side (Fig 5).

Root resorption continues to be a significant clinical problem in orthodontics that has been studied extensively throughout the years. However, evidence-based knowledge regarding etiology and predictors remains elusive.[38] Currently, there are few studies evaluating whether accelerated tooth movement and decortication has an effect on root resorption.[15] The same cytokines that promote inflammation also activate cementoclasts, which cause root resorption.[39] Conversely, decortication and demineralization of the alveolar bone might allow teeth to move more readily through bone with less resistance, resulting in decreased root resorption. Tsai et al. recently reported that MOP-facilitated ATM resulted in decreased root resorption upon H&E analysis.[40] Similarly, while half of the H&E samples in our study showed moderate root resorption on the MOP side, our volumetric analysis of all five roots

of the maxillary first molar showed no significant increase in root resorption with MOPs, suggesting that MI-faciliated MOPs induced ATM without causing significant adverse effects on roots. A larger sample size however, is needed to further validate this finding.

While some decortication methods have been previously proven to be effective in accelerating tooth movement, patient acceptance of these techniques was challenged by the degree of invasiveness. MOPs using a round bur and hand piece or a commercially available device specifically designed for MOP creation has been developed for minimally invasive ATM treatment option, eliminating the need for concomitant periodontal surgery.[15,17] Here, we created the alveolar perforations by inserting and removing an orthodontic MI. This utilization of conventional orthodontic MIs for MOP creation offers great potential, as these MIs are readily available in some orthodontic offices and most orthodontists are already trained in the use MIs for multiple orthodontic cases such as Class II correction and extraction space closure. The universal acceptance and wide usage of orthodontic MIs should also help patient acceptance, as many orthodontic patients are already familiar and comfortable with MIs. Furthermore, this method potentially allows for more consistent and uniform defects to be created compared to previously utilized MOP methods such as round burs. Based on our results, which demonstrate that MI-facilitated MOPs successfully accelerated tooth movement, MIs offer an attractive method for MOP placement with promising clinical acceptance both from orthodontic patients and orthodontists. Consequently, future studies should compare the effectiveness of this technique in inducing ATM with those currently being used.

While our study shows strong evidence for the effectiveness of ATM using MI-facilitated MOPs, certain limitations should be considered; particularly as orthodontic ATM based on RAP has been questioned in the past.[41,42] The 21 day treatment period was chosen because it represented the time of maximum RAP response in rats according to Yaffe et al. and has since been used in other studies examining RAP-based ATM in rats.[43–45] Even so, future studies should consider additional time points to examine long-term effects and further studies are required to establish the number and frequency of MOPs to optimally induce ATM and maximally reduce treatment duration in clinical cases.

CONCLUSIONS

The outcomes of this study demonstrate the following.

1. MI-facilitated MOPs can effectively accelerated tooth movement in rats.

2. These MOPs acted by inducing bone remodeling, as evidenced by an increase in osteoclast quantity and a decrease in bone volume and bone density.

3. MI-facilitated MOPs did not cause significant root resorption.

4. MI-facilitated MOPs may become a readily available and effective treatment modality to accelerate orthodontic treatment with excellent patient acceptance.

5. Additional studies should compare the effectiveness of MI-facilitated MOPs in inducing ATM with other methods such as corticotomies using flaps, corticision, and currently used MOP techniques.

Acknowledgments

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Highlights

1. The ability of micro-osteoperforations to accelerate tooth movement was evaluated.

2. Orthodontic mini-implants were used to create the micro-osteoperforations in rats.

3. This treatment significantly accelerated tooth movement compared to controls.

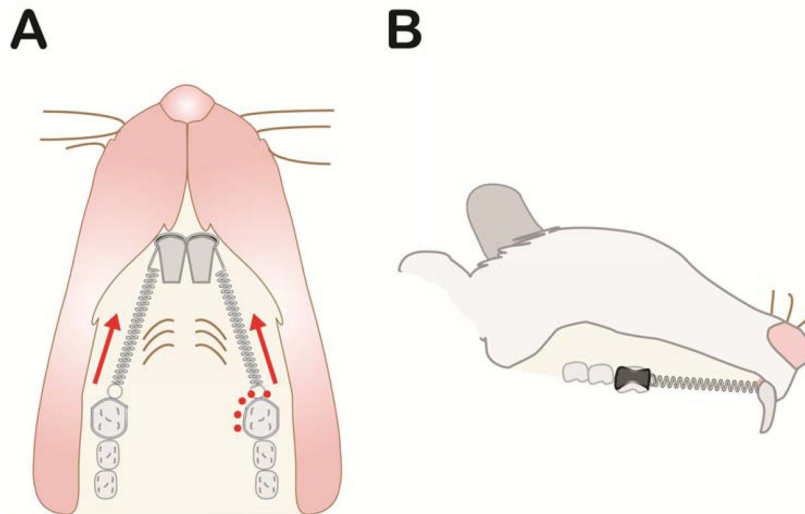4. Micro-osteoperforations did not result in significant root resorption.

Fig 1. Illustration of the orthodontic tooth movement animal model
The orthodontic appliance protracts the first maxillary molar using the maxillary incisor as an anchor on both sides, while micro-osteoperforations (red dots) are placed around the first maxillary molar only left side using commercially available orthodontic mini-implants. A closed coil spring provides consistent orthodontic force (red arrows). **A)** Palatal view. **B)** Lingual view
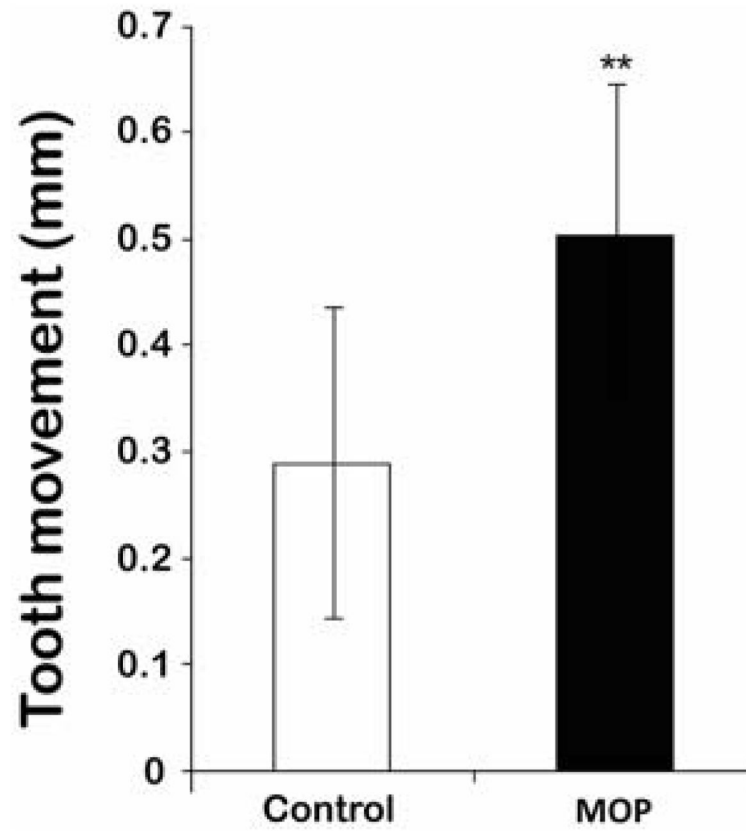
Fig 2. Comparison of the rate of tooth movement

Tooth movement was significantly greater on the micro-osteoperforation side compared to the control side. MOP, micro-osteoperforation; **p<0.05
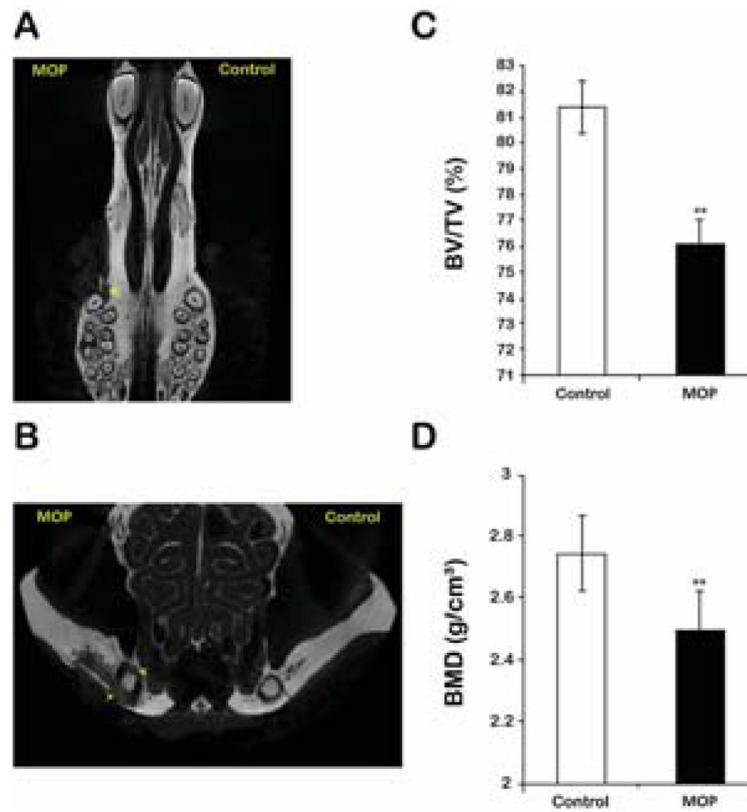
Fig 3. MicroCT analysis of bone quality comparison
Axial **A)** and Coronal **B)** of images of microCT scan showed osteopenia with decreased bone volume and bone density around the maxillary first molar on the micro-osteoperforation side compared to the control side in all animals. **C)** Quantification of bone fraction (BV/TV) **D)** Quantification of bone mineral density (BMD). MOP, micro-osteoperforation;.**p<0.05.
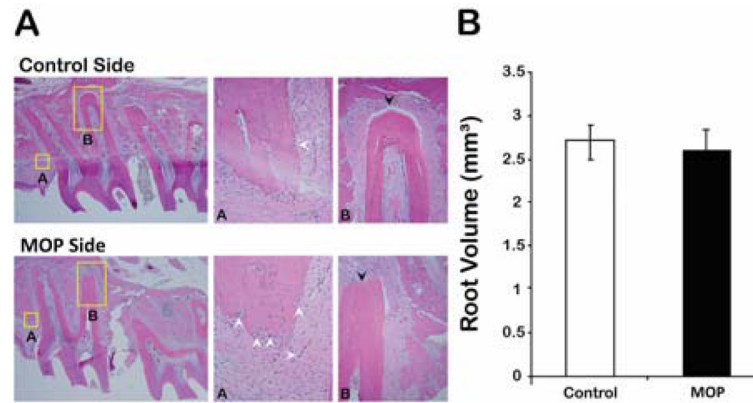
Fig 4. Evaluation of root resorption and bone loss

A) Histomorphometric analysis with H&E showed more bone loss (yellow box A) and root resorption (yellow box B) in the micro-osteoperforation side compared to the control side. Increased number of osteoclasts (white arrow) were detected on the micro-osteoperforation side. **B)** MicroCT volumetric analysis of all five roots of maxillary first molar showed no significant difference in root volume between the two groups. MOP, micro-osteoperforation.
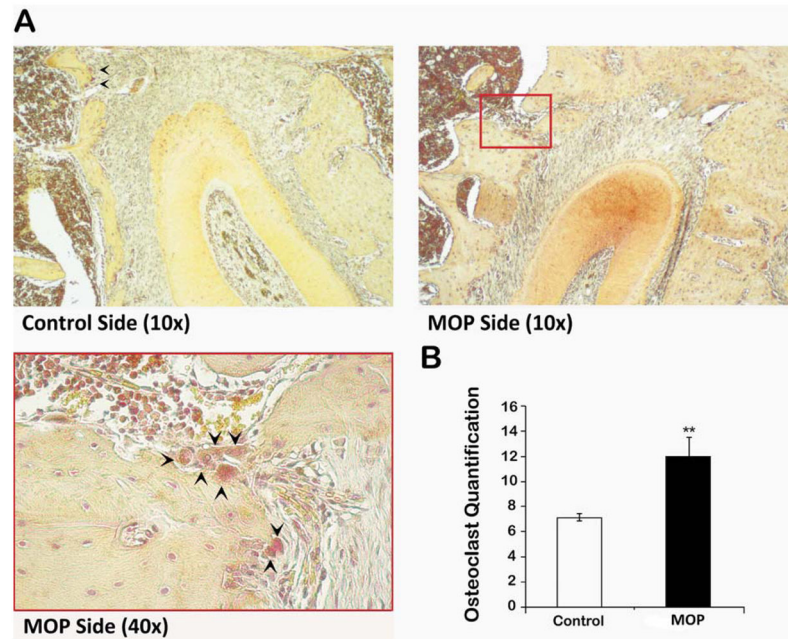
Fig 5. Evaluation of TRAP+ osteoclasts

Greater numbers of osteoclasts were found on the micro-osteoperforation pressure side: **A)** TRAP staining of the mesial root apex showed osteoclasts on the pressure side, where catabolic activity was taking place. **B)** The mean number of osteoclasts for the micro-osteoperforation and control side was obtained for each rat. MOP, micro-osteoperforation.
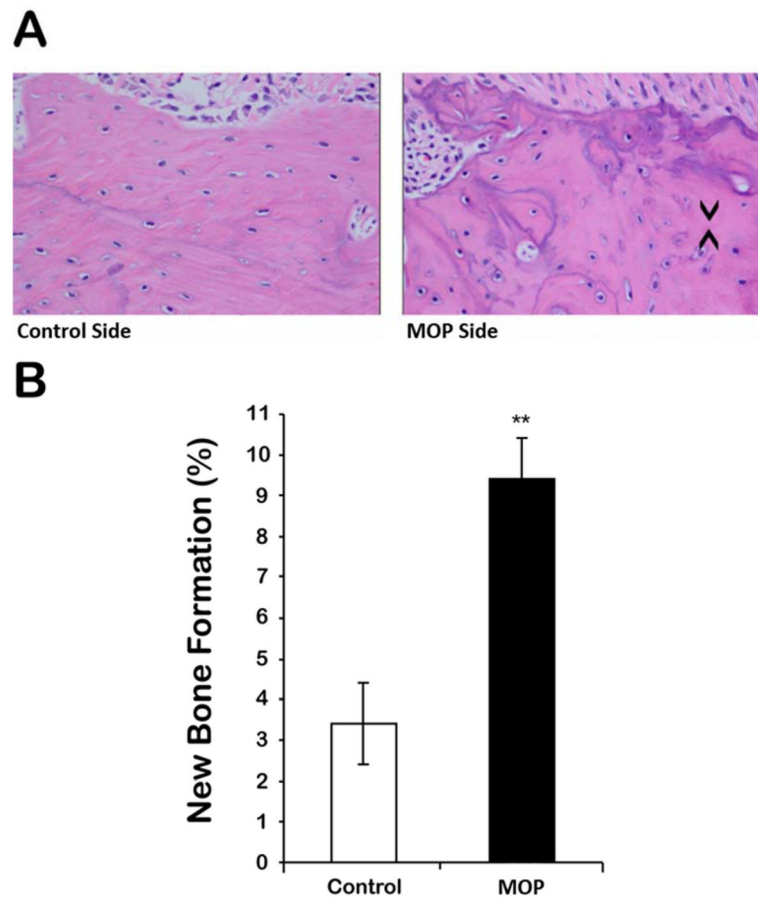
Fig 6. Evaluation of new bone formation

More new bone formation on the micro-osteoperforation side bone: **A)** Mature and organized lamella bone predominated in the control side. Dark blue lines (black arrows) in the micro-osteoperforation side represent new or woven bone, indicative of increased bone metabolic activity. **B)** Quantification of new bone formation showed more bone formation in the micro-osteoperforation side. MOP, micro-osteoperforation. **p<0.05