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Original Article

Combined effect of micro-osteoperforation and vibration on interleukin-1B, receptor activator of nuclear factor kappa-B ligand, C-C motif chemokine ligand 2, and tumor necrosis factor-alpha in orthodontic patients: A parallel-design randomized clinical trial

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ABSTRACT

Background: Bone remodeling is essential for orthodontic tooth movement. Techniques such as micro-osteoperforation (MOP) and vibration have been introduced to accelerate treatment by stimulating biological responses.

Materials and Methods: Randomized clinical trial study adult orthodontic patients who required bilateral extraction of maxillary first premolars were randomly assigned to two groups (n = 10) of intervention and control. Both groups received MOP at the onset of canine retraction. The intervention group also used a VPro5 vibrator for 28 days after the onset of canine retraction in addition to MOP. GCF samples were collected before the onset of orthodontic treatment (T0), right before canine retraction (T1), and after 24 h (T2), 7 days (T3), and 28 days (T4) by a paper point, and the GCF levels interleukin (IL)-1 B, receptor activator of nuclear factor kappa-B ligand (RANKL), C-C motif chemokine ligand (CCL) 2, and tumor necrosis factor-alpha (TNF)-α were measured. Data were analyzed using SPSS v25. Repeatedmeasures Analysis of Variance was employed to compare quantitative outcomes between groups and over time, with statistical significance set at $P < 0.05$.

Results: The GCF level of the four inflammatory factors was not significantly different between the two groups at any time point ($P > 0.05$). The trend of change in GCF level of the four inflammatory factors was also the same in the two groups over time, such that the lowest level of all four markers was recorded at T0. The highest level of TNF-α was recorded at T2, and the highest level of RANKL, IL1-B, and CCL2 was recorded at T2 and T3.

Conclusion: It does not seem that combined MOP with vibration can increase the level of inflammatory factors in GCF.

Key Words: Bone remodeling, inflammation mediators, physical stimulation, tooth movement techniques, vibration

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INTRODUCTION

A long course of orthodontic treatment is a drawback for both patients and orthodontists. Orthodontic treatments usually take 2–3 years to accomplish, depending on several factors such as the biological response of patients to orthodontic forces, complexity of treatment, degree of skeletal discrepancy, degree of dental camouflage in skeletal problems, mechanics of treatment, and patient cooperation.[1,2] Long course of treatment is often associated with complications such as pain, discomfort, development of white spot lesions and dental caries, and higher risk of root resorption, pulpal changes, periodontal problems, and temporomandibular disorders. Moreover, a long course of orthodontic treatment adversely affects the treatment outcome and patient cooperation.[3-5]

Several studies have reported increased activity of inflammatory markers such as chemokines and cytokines in response to orthodontic forces. Orthodontic tooth movement (OTM) is a modeling-remodeling process that depends on the activity of osteoclasts and osteoblasts, which is controlled by different inflammatory mediators. Some of the most important cytokines and chemokines involved in bone remodeling during OTM include tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1α, IL-1 β, C-C motif chemokine ligand (CCL) 3, CCL5, and CCL2. Furthermore, the pattern of expression of macrophage colony-stimulating factor, receptor activator of nuclear factor kappa-B ligand (RANKL), and osteoprotegerin by osteoblasts plays a role in OTM.[6-8] To date, several invasive and noninvasive modalities have been proposed to accelerate OTM and shorten the course of orthodontic treatment.[9,10]

The role of micro-osteoperforation (MOP) in the acceleration of OTM has been previously documented. A recent meta-analysis reported that MOP increased the speed of canine retraction by 0.45 mm/month, which was statistically significant.[11] Furthermore, this technique does not require flap elevation, and therefore, there is no need to refer the patients to a periodontist for this procedure, and orthodontists can easily do it whenever required. Furthermore, MOP is not associated with possible complications of other surgical procedures, such as wound dehiscence, alveolar bone loss, and severe pain and discomfort. Considering the high cost-effectiveness of MOP, this procedure appears to be more clinically acceptable than other surgical methods for acceleration of OTM, and is a more logical modality for this purpose.[12,13]

Vibrational appliances are noninvasive modalities proposed for the acceleration of OTM. Evidence obtained from animal experiments suggests that dynamic load can improve bone formation and increase OTM. A clinical study on humans also showed acceleration of OTM following the use of a vibrational appliance and confirmed its positive effects on bone remodeling.[14]

A recent study confirmed the optimal clinical efficacy of high-frequency vibration (HFV) for the enhancement of complex OTM with orthodontic aligners.[15] However, a review study could not confirm the clinically significant efficacy of vibration for OTM, highlighting the need for randomized clinical trials on this topic.[9]

Finding an effective method for acceleration of OTM with minimal side effects, which is well accepted by patients and can be easily performed by orthodontists, can decrease complications associated with a long course of treatment, reduce patient concerns regarding a long course of treatment, and improve the acceptance of orthodontic treatment by patients. Other studies have examined the effect of HFV and MOP just as a single intervention. Considering the confirmed role of MOP in the enhancement of OTM, this study aimed to assess the combined effect of MOP and vibration on the concentration of inflammatory factors in gingival crevicular fluid (GCF) as indices of OTM in patients under fixed orthodontic treatment. The null hypothesis was that no significant difference would be found between the intervention and control groups in the level of inflammatory markers.

MATERIALS AND METHODS

Trial design

This parallel-design single-blind randomized clinical trial with a 1:1 allocation ratio was conducted at the Department of Orthodontics, School of Dentistry, Tehran University of Medical Sciences, between April 2021 and December 2021. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.DENTISTRY.REC.1399.058) and registered in the Iranian Registry of Clinical Trials (IRCT20200928048869N1).

Participants, eligibility criteria, and setting

The inclusion criteria were age between 18 and 45 years, completely erupted canine teeth, the need for extraction of both maxillary first premolars, presence of 3 mm of extraction space after initial alignment, and good oral hygiene.

The exclusion criteria were systemic diseases affecting bone metabolism, medication intake, periodontal disease, smoking, and pregnancy.

The sample consisted of 20 eligible healthy adults who signed informed consent forms.

Interventions

Orthodontic treatment of participants was performed by two postgraduate students of orthodontics under the supervision of an orthodontist. Three months after the extraction of first premolars and following aligning and leveling of maxillary anterior teeth by a preadjusted edgewise appliance (0.022 inch MBT, DB orthodontics, United Kingdom), canine retraction was initiated in both groups with maximum anchorage (by involving the maxillary second molars). For this purpose, canine sliding was performed using 0.022-inch × 0.016-inch stainless steel wire (American Orthodontics, United States) and a 9 mm-inch × 0.010-inch NiTi coil (American Orthodontics, United States) with 150 g force. A tension gauge (Correx; Haag Streit, Bern, Switzerland) was used for this purpose. To prevent unwanted spacing between the maxillary incisors, the four anterior teeth were ligated by a 0.010-inch stainless steel ligature (DB Orthodontics, United Kingdom). Right before canine retraction, three MOPs were created in the buccal and three in the palatal bone surface distal to canine teeth in the right and left sides using a first-generation MOP appliance (PROPEL Orthodontics; Ossining, NY, USA). The protocol for creating MOPs was as follows:

The patients were initially asked to rinse their mouths with 0.2% chlorhexidine mouthwash for 20 s, and then spit it out. After drying of the respective area, a topical anesthetic gel (20% xylocaine) was applied over the site. Next, infiltration anesthesia was administered by injection of 2% lidocaine with 1:100,000 epinephrine. The respective area was isolated with cotton rolls. After ensuring optimal depth of anesthesia, the MOP device was removed from its sterile pack, and MOP was created at the respective site. The device had an indicator that showed reaching the desired depth. At this depth, perforation (created by screwing in a clockwise direction) was stopped. Three MOPs were created with a 3 mm distance from each other, extending from the crest to the root apex in the buccal and palatal surfaces (a total of six perforations). The area was gently pressed with sterile gauze to prevent bleeding. The patients received necessary hygienic instructions. No antibiotic or analgesic was prescribed for patients.

In addition to MOP, patients in the intervention group also used a 120 Hz vibrational appliance (Vpro5, Propel Orthodontics, Ossining, NY, USA) with 0.3 g force for 5 min daily for 28 days upon initiation of the retraction phase. During the study period, the researchers sent text messages to participants at a specific time of the day to remind them to use the vibrational appliance.

In all participants, GCF was collected before the onset of orthodontic treatment (T0), right before canine retraction (T1), and after 24 h (T2), 7 days (T3), and 28 days (T4) between 10 am and 12 pm. Samples were collected from the distobuccal sulcus of maxillary canine teeth. Before the collection of GCF, supragingival plaque was removed if present. Next, the area was isolated with cotton rolls, and a #30 paper point (DMX dent, China) was gently inserted into the gingival sulcus and remained there for 30 s. Care was taken not to traumatize the gingival sulcus. Immediately after collection, labeled paper strips were placed in plastic microtubes containing 0.1 mL of Tris buffer. The microtubes were then sent to an immunology laboratory to measure the GCF levels of IL-1 β, RANKL, CCL2, and TNF-α by the sandwich ELISA using Estbiopharm kits (Hangzhou Estbiopharm Co. Ltd, Hangzhou, China). The samples were stored at −20°C until the collection of all samples from all patients. The concentration of factors was reported in picograms/microliters (pg/μL).

Outcomes (primary and secondary)

The primary objective of this study was to compare the concentration of IL-1 β, RANKL, CCL2, and TNF-α between the intervention and control groups as indicators of the speed of OTM.

Sample size calculation

The minimum sample size was calculated to be 10 in each group (a total of 20) according to a study by Alikhani *et al*.,[16] assuming $\alpha = 0.05$, $\beta = 0.2$, and a standard deviation of IL-6 to be 0.35 and 0.4 in the two groups to find a significant difference equal to 0.5 units using PASS 11 software (NCSS, LLC, Kaysville, Utah, USA).

Interim analysis and stopping guidelines

No interim analysis was performed, and no stopping guidelines were established.

Randomization

The patients were randomly assigned to two groups of intervention and control by balanced block randomization using Microsoft Excel (Microsoft Office 2016, Microsoft, Redmond, USA). For this purpose, four equal-sized blocks (envelopes) were created. Each block (envelope) contained a piece of paper displaying B (control group) or A (intervention group), determined randomly by the RAND feature of Excel software. Randomization was performed by the statistician, and the researcher was not aware of the group allocation of patients until the treatment onset (concealment). The statistician placed paper sheets displaying A (intervention) or B (control) in sealed envelopes. The envelopes were coded 1–4. On enrollment of participants, they received envelopes #1 to #4 in an orderly manner. The clinician opened the envelope to find the type of intervention that needed to be performed for each patient.

Blinding

This study had a single-blind design. Due to the specific design of the study, blinding of patients and clinicians was not possible. However, the technician who measured the GCF level of factors and the statistician who analyzed the data were blinded to the group allocation of participants.

Statistical analysis

The mean and range were reported for demographic variables of participants in each group. Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

. Repeated measures Analysis of Variance (ANOVA) was applied to compare quantitative variables between the two groups, and also for comparison of these variables within each group over time at a $P < 0.05$ level of significance.

RESULTS

Participant flow

Figure 1 shows the CONSORT flow diagram of patient selection. A total of 20 healthy adults with a mean age of 21.2 years (range 18–45 years), including seven males and 13 females, who required extraction of both maxillary first premolars were evaluated. There were no dropouts.

Demographic data

Table 1 presents the demographic information of the participants. The two groups had no significant difference in terms of age or gender ($P > 0.05$).

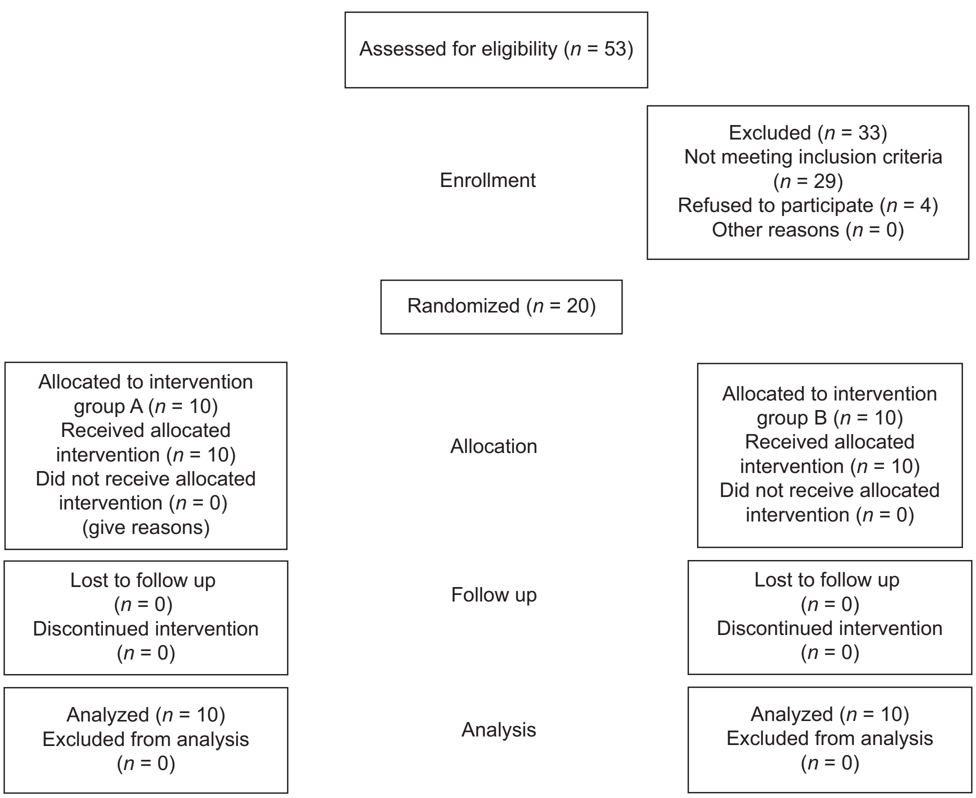

Figure 1: CONSORT flow diagram of patient selection and allocation.

Numbers analyzed for each outcome, estimation and precision, subgroup analyses

Data from all 20 patients were analyzed. Quantitative variables were compared between the two groups at different time points of T0 to T4 using repeated measures ANOVA.

No significant difference was found between the two groups in GCF levels of IL-1 B, TNF-α, CCL2, and RANKL at T0 to T4 (P = 0.303, P = 0.133, 0.193, and 0.328, respectively). The trend of change in inflammatory factors was also the same in the two groups.

The lowest level of IL-1 B, TNF-α, CCL2, and RANKL inflammatory factors was recorded in T0 and the highest in T2 and T3. The level of CCL2 was the same at T1 and T4, such that the level of this factor at the end of week 4 was similar to the time of initiation of canine retraction (P = 0.517). The level of RANKL at T4 was significantly higher than its value at T1 (P = 0.032). The lowest level of TNF-α was recorded at T0 and the highest at T2. Furthermore, the level of this factor at T4 was still significantly higher than its level at T1 (P = 0.021). Diagram 1 shows the trend of change in inflammatory factors.

Table 1: Demographic information of the participants

Group	Age (range)	Age (mean)	Male (*n*)	Female (*n*)
Intervention	18–25	20.9	4	6
Control	18–35	21.5	3	7

Harms

No patients were harmed during the study.

DISCUSSION

In this study, the level of the most important inflammatory factors known as indices of tooth movement (IL-1 B, TNF-α, CCL2, and RANKL) has no significant difference between the control and intervention groups.

The duration of comprehensive orthodontic treatment widely varies among different individuals. However, evidence-based prospective studies indicate that comprehensive orthodontic treatment typically lasts approximately 2 years. Several factors can affect the course of treatment, including the severity of malocclusion, the need for tooth extraction, the expertise of the clinician, and patient cooperation. For instance, correction of class II malocclusion takes approximately 5 months more than correction of class I malocclusion, and the severity of overjet is responsible for 46% of variations in the duration of treatment.[17-19]

Prolonged orthodontic treatment is associated with an increased risk of root resorption and decalcification.

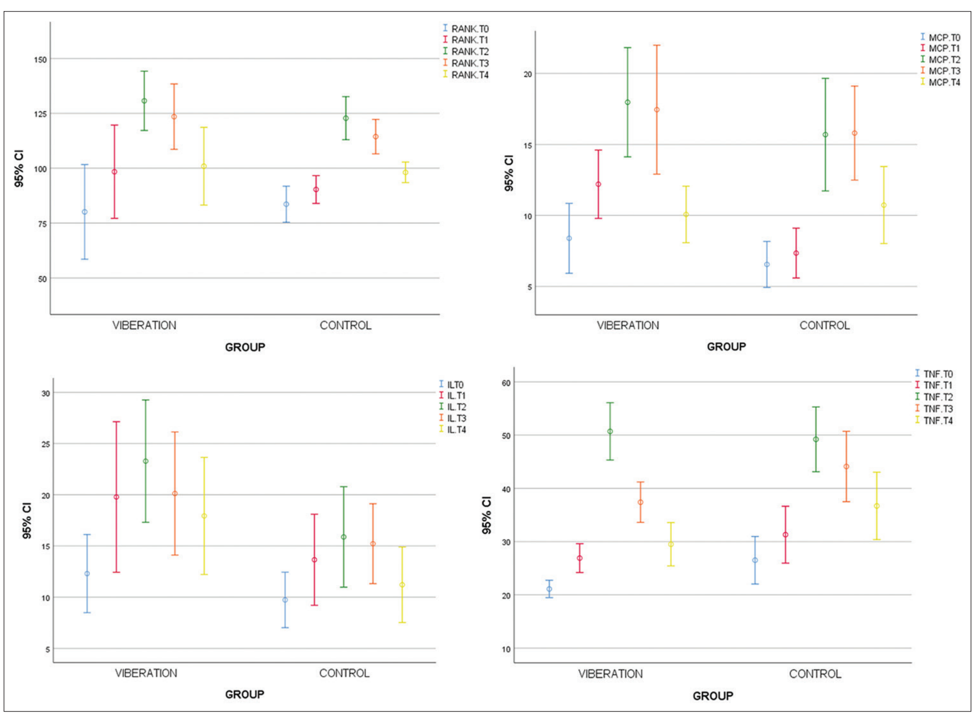

Diagram 1: Trend of change in inflammatory factors at different time points.

Since patients also demand shorter treatments, the manufacturers have been in search of strategies to accelerate OTM. At present, several manufacturers of orthodontic appliances have proposed bracket types, techniques, and devices to decrease the course of treatment.[20] In some cases, patients insist on fast treatments, and dental clinicians use restorative and cosmetic procedures instead of orthodontic treatment to improve the smile appearance of patients and satisfy them; however, some of these procedures may cause serious complications for the teeth and periodontium in the long term.[21]

The role of MOP in the enhancement of OTM has been well documented. Considering its cost-effectiveness, MOP has gained clinical acceptance and is a logical strategy for the acceleration of OTM.[12,13] Thus, MOP was used for both groups in the present study.

Alikhani *et al*.[16] evaluated the effect of MOP on the concentration of inflammatory factors in GCF. They reported the highest level of factors in both the intervention and control groups at 24 h after the onset of canine retraction; this increase was greater in the intervention group, and then the level of factors decreased. At 28 days, only the activity of IL-1 was still significantly higher than that at baseline before the canine retraction, while the level of other inflammatory markers returned to their baseline level before retraction.[16]

In the present study, all patients underwent MOP, and the changes in inflammatory markers had a relatively similar trend in both groups, such that the maximum concentration of factors occurred at 24 h after the onset of retraction, and their level was still high at 7 days. However, the level of RANKL and TNF-α at 28 days was still higher than the value at the onset of retraction. Furthermore, Flórez-Moreno *et al*.[22] evaluated the level of RANKL at different time points after the onset of orthodontic treatment. The highest level was recorded at 8 weeks after the onset of alignment.[22] Such variations in the results may be due to differences in the tools used for the collection of GCF, the solution used for the storage of specimens, the ELISA kit used, and the study population.

Among the different methods suggested for the enhancement of OTM, vibrational appliances have gained attention since they can be used by patients at home. They do not require costly equipment, unlike low-level laser therapy, and should be used for only a short period daily.[23] Since no consensus has been reached regarding the effects of vibrational appliances on OTM, this study aimed to assess the effect of vibration in combination with MOP on inflammatory markers.

In the present study, vibration had no significant effect on inflammatory markers; thus, it does not seem that the combined use of vibration and MOP has an additional effect compared with MOP alone on OTM. A meta-analysis on the effect of vibration on OTM found no significant evidence supporting the efficacy of vibrational appliances for the enhancement of OTM.[24] Nonetheless, a clinical trial with a split-mouth design showed a significant effect of HFV on canine retraction. This difference in the results may be due to the evaluation of children, instead of adults, in their study, no conduction of simultaneous MOP, and the different frequency of the vibrational appliance (102 Hz).[25]

It should be noted that different types of vibrational appliances are used in orthodontics, such as low-frequency vibration (LFV) and HFV.[15,26] Alikhani *et al*.,[27] in an animal study, revealed that application of 30 Hz frequency increased the speed of OTM by 1.45 times. Increasing the frequency to 60 and 120 Hz increased the speed of OTM by 2.1 and 2.4 times, respectively. Thus, a higher frequency of vibration had a greater effect on OTM.[27] Judex and Pongkitwitoon[28] compared the effects of different HFV and LFV appliances and showed that both types increased cell proliferation and gene expression in osteoblasts and fibroblasts. However, HFV gave a higher response than LFV. Collagen1alpha, alkaline phosphatase, Runt-related transcription factor 2, Fibroblast growth factor 2, and connective tissue growth factor were measured as indices of the activity of osteoblasts, osteoblastic differentiation, level of differentiation of osteoblasts, and activity of human periodontal ligament fibroblasts. Both appliances caused an increase in the level of collagen1alpha, alkaline phosphatase, fibroblast growth factor 2, and connective tissue growth factor; however, higher levels were recorded in the use of HFV. Application of HFV upregulated Runt-related transcription factor 2, but LFV did not have such an effect.[28]

Considering the reported results regarding the optimal efficacy of HFV in increasing the level of inflammatory factors and acceleration of OTM, the Propel VPro 5 vibrational appliance was used in this study, which has the highest frequency among the currently available vibrators. Studies that showed optimal efficacy of HFV for upregulation of inflammatory factors and acceleration of OTM were animal[27] and *in vitro*[28,29] studies, which cannot be generalized to the clinical setting. Nonetheless, the results regarding the effects of vibration on OTM are controversial. A previous study showed a significant effect of LFV on OTM,[14] while another study did not show any positive effect and even reported higher bone density in the vibration group.[30] An animal study reported a reduction in OTM due to vibration.[31] Some clinical studies revealed that AcceleDent increased the rate of OTM in patients with fixed orthodontic appliances.[32,33] Nonetheless, none of the aforementioned two studies had a prospective design, and thus, they both were susceptible to potential bias and overestimation of treatment effect.[34] Interestingly, a randomized prospective clinical trial used another type of vibrational appliance (Tooth Masseuse) and found no significant difference in the alignment of teeth in the two groups after a 10 week.[26] Shipley *et al*.[35] found that HFV, along with clear aligners, shortened the treatment course because vibration decreased the time interval of replacement of aligners from 8.7 days in the control group to 5.2 days in the intervention group. It was claimed that firm contact of the aligner with the entire tooth surface and more efficient transfer of vibration to the root and the surrounding bone may explain this finding.[36] Thus, these results may not be applicable to fixed orthodontic treatment. Moreover, their study was retrospective and susceptible to bias. The results of the clinical trial that showed HFV, along with clear aligners, shortened the course of treatment and increased the level of inflammatory factors cannot be compared with the present study, either, since they used clear aligners while patients received fixed orthodontic appliances in the present study.[37]

The present study did not find any positive effect for the combined use of HFV in combination with MOP on IL-1 B, TNF-α, CCL2, and RANKL levels. Since these factors are important mediators in OTM, it does not appear that this combination is more effective than MOP alone. However, this finding does not completely deny the efficacy of vibration since vibration alone may be effective, but it may not be able to elevate the level of inflammatory factors to a statistically significant level in combination with MOP.

Limitations

Due to limited budget, time restrictions, and difficult patient enrollment, having a separate group for assessment of the effect of vibration alone, and also a no-intervention control group, was not possible. Vibration alone may have a significant effect on the level of inflammatory markers, which needs to be investigated in future studies. Furthrmore, due to the unavailability of the Periotron device, it was not possible to measure the volume of collected GCF from patients. The authors selected periodontally healthy patients, standardized the sampling protocol, and followed the randomization principles to control for this confounding effect as much as possible.

Generalizability

This study was conducted at the Orthodontics Department of School of Dentistry, Tehran University of Medical Sciences, by a senior postgraduate student of orthodontics under the supervision of an orthodontist. The participants were healthy adults who required bilateral extraction of maxillary first premolars. No limitation was set concerning the type of malocclusion. The present results can be generalized to adult patients with similar treatment parameters.

CONCLUSION

Based on the findings of this study, it appears that the combination of MOPs with vibration does not significantly enhance the levels of inflammatory factors in gingival crevicular fluid. It can be inferred that, due to the lack of a significant increase in cytokine levels, the combined application of MOP with vibration is unlikely to increase the rate of tooth movement.

Registration

The study protocol was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.DENTISTRY.REC.1399.058) and registered in the Iranian Registry of Clinical Trials (IRCT20200928048869N1).

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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