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Differential Efficacy of 2 Vibrating Orthodontic Devices to Alter the Cellular Response in Osteoblasts, Fibroblasts, and Osteoclasts

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Abstract

Modalities that increase the rate of tooth movement have received considerable attention, but direct comparisons between devices are rare. Here, we contrasted 2 mechanical vibratory devices designed to directly transfer vibrations into alveolar bone as a means to influence bone remodeling. To this end, 3 cells types intimately involved in modulating tooth movements—osteoblasts, periodontal ligament fibroblasts, and osteoclasts—were subjected to in vitro vibrations at bout durations prescribed by the manufacturers. As quantified by an accelerometer, vibration frequency and peak accelerations were 400% and 70% greater in the VPro5 (Propel Orthodontics) than in the AcceleDent (OrthoAccel Technologies) device. Both devices caused increased cell proliferation and gene expression in osteoblasts and fibroblasts, but the response to VPro5 treatment was greater than for the AcceleDent. In contrast, the ability to increase osteoclast activity was device independent. These data present an important first step in determining how specific cell types important for facilitating tooth movement respond to different vibration profiles. The device that engendered a higher vibration frequency and larger acceleration (VPro5) was superior in stimulating osteoblast and fibroblast cell proliferation/gene expression, although the duration of each treatment bout was 75% shorter than for the AcceleDent.

Keywords

vibrations, tooth movement, cellular response, osteoblasts, fibroblasts, osteoclasts

Introduction

Osteoblasts, osteoclasts, and periodontal ligament fibroblasts are intimately involved in facilitating tooth movement and therefore are targeted by devices that aim at accelerating the movement of teeth. These cell types are sensitive to perceiving and responding to mechanical signals. Vibrations, a subcategory of mechanical signals produced by an oscillating device, can readily be applied to dental structures, and vibrational devices aimed at accelerating tooth movement are commercially available. The efficacy of these devices has been tested by a limited number of studies in vitro, in animals, or clinically. Results from these investigations have been mostly positive but also produced negative results, allowing interpretations within a wide range.[1-11] Direct comparisons between these studies are difficult, at least in part because it is sometimes neglected that not all vibrations are created equal and that altering specific vibration variables can significantly modulate the study outcome.

Technically, sinusoidal vibrations can be defined by specifying 2 of the following 3 variables: frequency (number of oscillations per second expressed in Hertz), magnitude of the induced peak acceleration (expressed typically with the acceleration of the Earth as a referent where 1 g = 9.81 m/s^2), and/or the total displacement produced by the oscillating vibrating actuator (expressed in μm, mm, or cm). Acceleration and frequency can be measured directly with an accelerometer attached to the actuator and should be verified, rather than relying on a manufacturer's data sheet.[12]

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Several investigations, primarily in long bones rather than craniofacial tissue, have aimed to answer the question which *vibration frequency* is most effective. Results suggest that cells tend to be more sensitive to higher (>60 Hz) frequencies rather than lower (<45 Hz frequencies). In the ovariectomized rat, for instance, vibrations applied at 90 Hz raised the levels of bone formation to a much greater extent than vibrations applied at 45 Hz.[13] Also in rats, 90 Hz vibrations but not 45 Hz vibrations, were able to prevent detrimental changes in the intervertebral disk induced by disuse.[14] Cell culture studies generally support the in vivo data. In mesenchymal progenitor cells exposed to vibrations, 100 Hz was significantly more effective than 30 Hz in increasing cell proliferation.[15] A similar observation was made in macrophages, with 100 Hz being more efficacious than 30 Hz.[16]

Very few studies have directly compared *vibration magnitudes* to each other, but the outcome of these studies has been relatively consistent in concluding that there is not a linear relationship, if any, between acceleration (vibration) magnitude and cellular output. In other words, more (greater acceleration magnitude) is not necessarily better. In a study in mice, for instance, increasing the acceleration magnitude from 0.1 to 0.3 g decreased efficacy while further raising acceleration magnitude to 1.0 g brought cellular output back to levels seen at 0.1 g.[17] Similarly, in an in vivo study that generated a large number of different vibration combinations, doubling the acceleration magnitude from 0.3 to 0.6 g did not change the cellular- or tissue-level response,[16] just as acceleration magnitude had no influence on bone's anabolic activity in rats exposed to vibrations.[13]

The question whether a longer treatment bout duration (min/d) is more effective than shorter ones has also been investigated. Most studies focusing on mechanical stimuli, including vibrations, suggest that increasing the number of loading cycles from as few as 3 increases the tissue/cellular response until it becomes saturated, and no more increases are observed.[18-20]

Two commonly used devices to stimulate tooth movement are the AcceleDent (OrthoAccel Technologies Inc, Bellaire, Texas) and VPro5 (Propel Orthodontics, Ossining, New York). According to the manufacturers' specifications, the AcceleDent and VPro5 produce distinct vibration frequencies and accelerations and are used for different treatment durations (20 min/d for the AcceleDent and 5 min/d for the VPro5). As discussed above, the substantially different vibration variables of the AcceleDent and VPro5 may be perceived differently by cells residing in craniofacial bone. In this study, we quantified the acceleration profiles of the AcceleDent and VPro5 devices and then contrasted the efficacy of these commonly used treatment tools to stimulate osteoblasts, periodontal ligament fibroblasts, and osteoclasts.

Methods

Acceleration Measurements

For both devices, an accelerometer (Slamstick C; Mide Technology Corp, Medford, Massachusetts) was attached to the top surface of the mouthpiece and inserted into the mouth cavity of a volunteer as instructed by the manual of the manufacturer (light bite force). All data were recorded for 20-second intervals at a recording frequency of 800 Hz. During recording, the mouthpiece was kept in the horizontal plane. Fast Fourier Transform was applied to determine the frequency content of the recordings. Three devices from each manufacturer were tested consecutively. Measurements were confirmed in a slightly modified standard-sized dental teaching model (AZDENT Dental Typondont Demonstration Teeth Model; Amazon, Seattle, WA) to which a bite force of approximately 500 g was applied.

Cells

Commercially available human osteoblasts, human periodontal ligament fibroblasts, and human osteoclasts were cultured according to the manufacturer's instructions (Lonza Walkersville Inc, Walkersville, Maryland). For all experiments, cells were plated at a cell density of 7500 cells/cm^2 on the day prior to starting the experiment.

Application of Vibrations to Cells

Osteoblasts, periodontal ligament fibroblasts, and osteoclasts were subject to vibrations generated either by the AcceleDent or VPro5 device for 20 min/d (AcceleDent) or 5 min/d (VPro5). To this end, we designed an experimental setup that induced vibration frequencies and acceleration magnitudes similar to those measured in the first part of our study (acceleration measurements). Briefly, the device was sandwiched between a plastic box and the tissue culture plates containing the cells. Two industrial elastic bands isolated vibrations from being transmitted into the countertop (and changing the inertial mass of the setup) and vertically secured the 4 layers to each other (Figure 1).

Immediately prior to treatment, cells were taken out from the incubator. Nonvibrated control cells were handled identical to vibrated cells using a setup that did not contain a vibration device sandwiched between the boxes. Treatment was applied at room temperature. After vibration treatment, cells were returned to the incubator. While outside the incubator, cells from all groups were exposed to room temperature for the same duration, although treatment duration differed between the 2 devices. In other words, cells vibrated with the VPro5 were left at room temperature for an additional 15 minutes following the 5-minute treatment to match the 20-minute room temperature exposure of AcceleDent-treated cells.

Cellular Outcome Variables

In osteoblasts and periodontal ligament fibroblasts, we used cell proliferation (cell density, cells/cm^2) over a 3-day period as a marker for a cell's *responsivity* to the vibration stimuli. A standard spectrophotometric assay was used according to the manufacturer's instructions (XTT Cell Proliferation Assay Kit; ACTT, Manassas, VA). To determine osteoclast biochemical

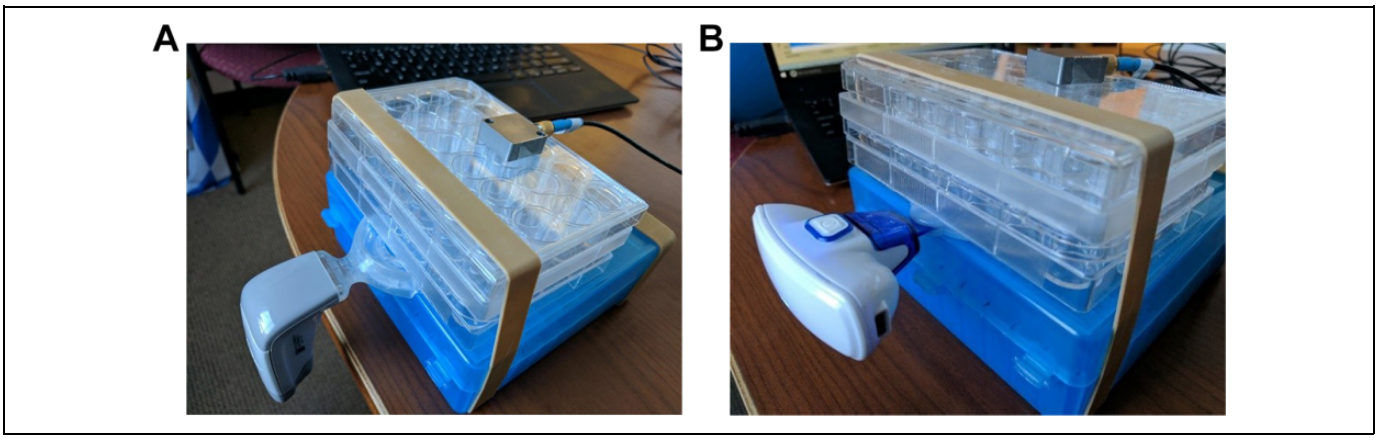

Figure 1. Pictures showing how vibrations were transmitted from the (A) AcceleDent or (B) VPro5 to the cell culture plates (2 transparent plastic boxes on top of each decive). An accelerometer attached to the top of the cell culture plates verified the applied vibration frequency and acceleration.

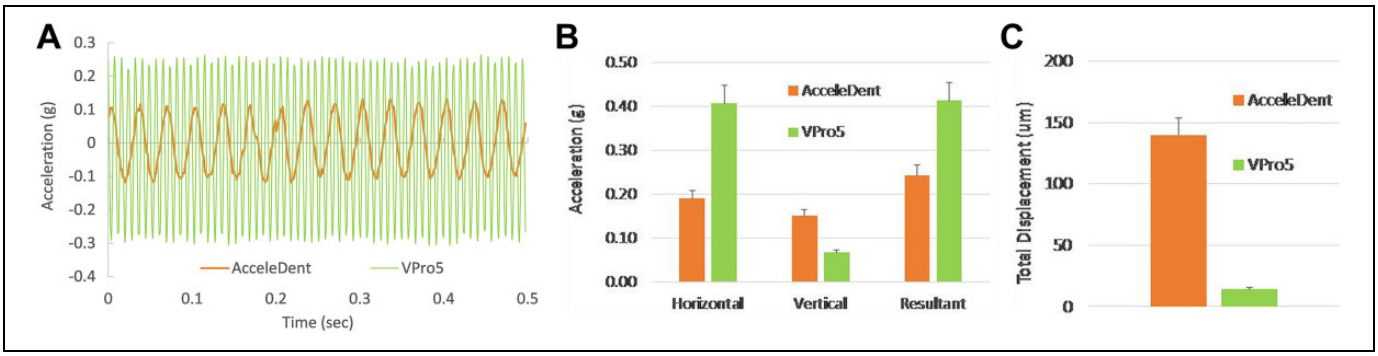

Figure 2. A, Superimposed sample recordings (0.5 seconds) from the x-axis (horizontal) of the accelerometer attached to either the AcceleDent (orange) or VPro5 (green) unit showing the distinct acceleration profiles of the 2 devices. B, Comparison of peak acceleration magnitudes between the AcceleDent and VPro5 in the horizontal and vertical direction as well as the total resultant of horizontal and vertical directions. C, Total displacement produced by the AcceleDent and VPro5. The VPro5 generated smaller displacements in spite of greater generated peak accelerations by using a vibration frequency that is 4× greater than that of the AcceleDent (120 vs 30 Hz).

activity, tartrate-resistant acid phosphatase (TRAPc) activity was measured over a 3-day period using a staining kit (Acid Phosphatase Kit; Sigma-Aldrich, St. Louis, MO) and a microplate reader (Bio-Rad, Hercules, CA) operating at 540 nm. The sample size for the proliferation experiments was n = 6 (osteoblasts/fibroblasts) and for the osteoclast experiments n = 12.

Molecular Markers

After 3 days of vibration treatment with either AcceleDent or VPro5, cells were lysed immediately to prevent RNA degradation and RNA was extracted according to the instructions of the manufacturer (RNeasy Mini Kit; Qiagen, Germantown, MD). RNA was reverse transcribed to complementary DNA (Qiagen). For osteoblasts, we quantified transcriptional levels of collagen type I alpha 1 (COL1A1), alkaline phosphatase (ALPL), and runt-related transcription factor 2 (RUNX2) with COL1A1 as an indicator of osteoblast proliferation/activity and ALPL and RUNX2 as indicators of osteogenic differentiation. For fibroblasts, we quantified fibroblast growth factor 2 (FGF2), connective tissue growth factor (CTGF), and ALPL with FGF2 and CTGF as indicators of fibroblast proliferation/activity and ALPL as indicator of differentiation. For osteoclasts, we quantified phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), receptor activator of nuclear factor κ B (RANK), and nuclear factor of activated T cells 1 (NFATC1) with PI3K as indicator of the Akt signaling pathway (reflecting osteoclast activation/proliferation) and NFATC1 and RANK as indicators of osteoclast differentiation during osteoclastogenesis. All genes were selected based on their importance as indicators of processes including cellular activity/signaling/differentiation. Because of the large number of genes involved in these processes, this selection was not unique, and a different set of 3 genes per cell type could have served a similar purpose.

The real-time polymerase chain reaction gene expression of all samples was analyzed via Taqman primers (Qiagen). The TaqMan primers for human cells were COl1A1 (Hs00164004_m1), ALPL (Hs01029144), RUNX2 (Hs01047973), FGF2

(Hs00266645_m1), CTFG (Hs00170014), PI3K (Hs01046353), RANK (Hs00921372), and NFATC1 (Hs00542675). Gene expression was calculated by $2^{-\Delta\Delta Ct}$ with respect to GAPDH (glyceraldehyde-3-phosphate dehydrogenase; Qiagen) and nonvibrated control cells. To minimize variability, RNA concentration was 3.5 µg/mL in all samples. The sample size for each gene and experimental condition was n = 6, averaged across triplicates.

Collagen I and TRAPc Staining

We stained cells subject to experimental (AcceleDent or VPro5) or control (no vibration) conditions for collagen type I (human osteoblasts and periodontal fibroblasts) or TRAPc (human osteoclasts) to allow for qualitative observation. Briefly, upon exposure to vibrations for 7 days (or no vibration), osteoblasts and fibroblasts were fixed in 37% paraformaldehyde at room temperature for 5 minutes. Subsequently, cell membranes were permeabilized with 0.1% Triton X-100 for 10 minutes, and nonspecific binding was blocked with 1% BSA at room temperature for 1 hour. Cells were then incubated overnight with primary collagen I antibody at 4°C before incubation with a secondary immunoglobulin G (ThermoFisher, Waltham, MA) antibody conjugated Alexa Flour 488 for 3 hours at 4°C. Cells were counterstained with DAPI (4′,6-Diamidino-2-phenylindole dihydrochloride; Sigma Aldrich) for 2 to 3 minutes. Collagen I was visible in green color with the nucleus in blue. A photon laser scanning confocal system (LSM 510; Carl Zeiss, Germany) was used for visualization.

Osteoclasts were fixed (2.5 mL citrate solution, 6.5 mL acetone, and 0.8 mL of 37% paraformaldehyde) at room temperature for 30 seconds. Cells were then rinsed twice with dPBS (Dulbecco's phosphate buffered saline; Sigma-Aldrich, and allowed to air dry prior to exposure to a Tartrate-Resistant Acid Phosphatase Kit (Sigma-Aldrich). Cells in TRAPc solution were incubated at 37°C in the dark for 1 hour, rinsed several times with dPBS, and air dried before microscopic visualization.

Table 1. Peak Acceleration Magnitudes (Expressed as Fractions of the Acceleration on Earth, g) Recorded with an Accelerometer in Horizontal (X,Y) and Vertical Directions.

Acceleration	AcceleDent	VPro5
X, g	0.12	0.23
Y, g	0.15	0.33
Resultant horizontal, g	0.18	0.41
Vertical, g	0.15	0.07
Total resultant, g	0.24	0.41

Statistics

Data were presented as means and standard deviations. The 3 groups were statistically compared via Fisher tests. A significance value of .05 was used throughout.

Results

Acceleration Data

Accelerations were quantified experimentally in 3 dimensions with a triaxial accelerometer directly attached to each device (Figure 2). The frequency of the oscillatory accelerations was verified for each of the 3 AcceleDent devices to measure 30 Hz. The frequency content of the sinusoidal accelerations generated by the VPro5 was 120 Hz for each of the 3 devices. Thus, the measured vibration frequencies matched those specified by the manufacturers.

Mean peak accelerations of the AcceleDent measured 0.12 g in the medial–lateral, 0.15 g in the anterior–posterior, and 0.15 g in the vertical direction (Table 1). For the VPro5, mean peak accelerations were 0.23 g in the medial–lateral, 0.33 g in the anterior–posterior, and 0.07 g in the vertical direction. When the acceleration magnitudes in the 2 horizontal directions were combined to produce a horizontal resultant peak acceleration, this horizontal component of the acceleration vector was 0.18 g for the AcceleDent and 0.41 g for the VPro5 (Table 1). Combining all 3 acceleration magnitudes in the 3 directions into a *Total Resultant* yielded 0.24 g for the

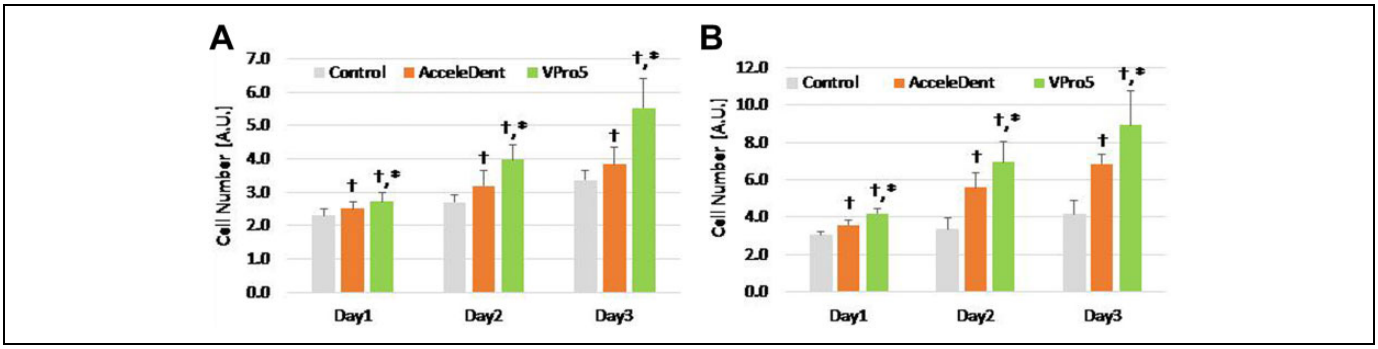

Figure 3. Cell number of nonvibrated control cells (gray bars), cells exposed to vibration with the AcceleDent (orange bars), and cells exposed to the VPro5 (green bars) quantified over 3 days. Shown are means and standard deviations for (A) osteoblasts and (B) periodontal ligament fibroblasts. For both cell types, VPro5 treatment produced a greater increase in cell number (proliferation) than AcceleDent after 2 and 3 days of treatment. Daggers mark statistically significant differences between experimentally treated (either by AcceleDent or VPro5) and control samples. Asterisks mark statistically significant differences in cell number between V5Pro treatment versus AcceleDent treatment.

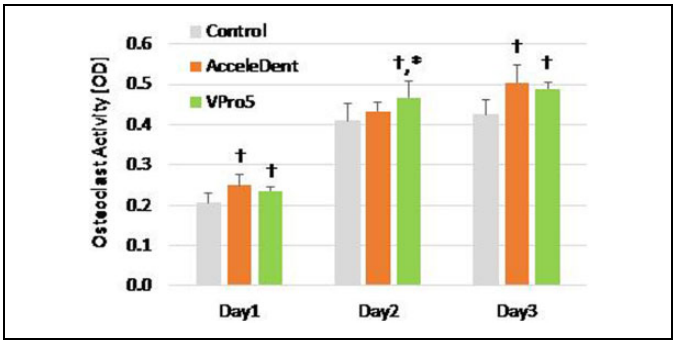

Figure 4. Osteoclast activity of nonvibrated control cells (gray bars), cells exposed to vibration with the AcceleDent (orange bars), and cells exposed to the VPro5 (green bars) quantified over 3 days. Shown are means and standard deviations. On day 1 and day 3, osteoclast activity was raised by both devices with no differences between them. On day 2, only the VPro5 significantly increased osteoclast activity. Daggers mark statistically significant differences between experimentally treated (either by AcceleDent or VPro5) and control samples. Asterisks mark statistically significant differences in cell number between V5Pro treatment versus AcceleDent treatment.

AcceleDent and 0.41 g for the VPro5 (Figure 2). For both the AcceleDent and VPro5, variability was low across the 3 devices from each manufacturer (Figure 2). The total displacement of the oscillatory motions yielded 140 µm for the AcceleDent and 14 µm for the VPro5. When using a dental teaching model rather than a volunteer, acceleration data were similar. For both data collections, human and a dental teaching model, transmissibility of the mechanical signal was good for the light bite force. While not quantified in this study, transmissibility decreased noticeably when bite force was substantially increased (>1200 grams), in particular for the AcceleDent device.

Cellular Data

Both devices were capable of significantly increasing ($P < .05$) cell proliferation over 3 days in human osteoblasts and periodontal ligament fibroblasts (Figure 3). However, the VPro5 device initiated significantly greater ($P < .05$) cell proliferation than the AcceleDent device on days 1 to 3 after commencing vibration treatment (Figure 3). Both devices also moderately increased osteoclast activity with only few quantitative differences between the AcceleDent and the VPro5 (Figure 4).

Gene Expression

In human osteoblasts and compared to nonvibrated controls, COLA1 and ALPL, measured as indicators of human osteoblast activity and differentiation, respectively, were significantly upregulated by both the AcceleDent and the VPro5 devices (Figures 5 and 6). Significantly greater ($P < .05$) upregulation resulted from VPro5 than from AcceleDent exposure (Figure 5). RUNX2, an indicator of osteoblast differentiation

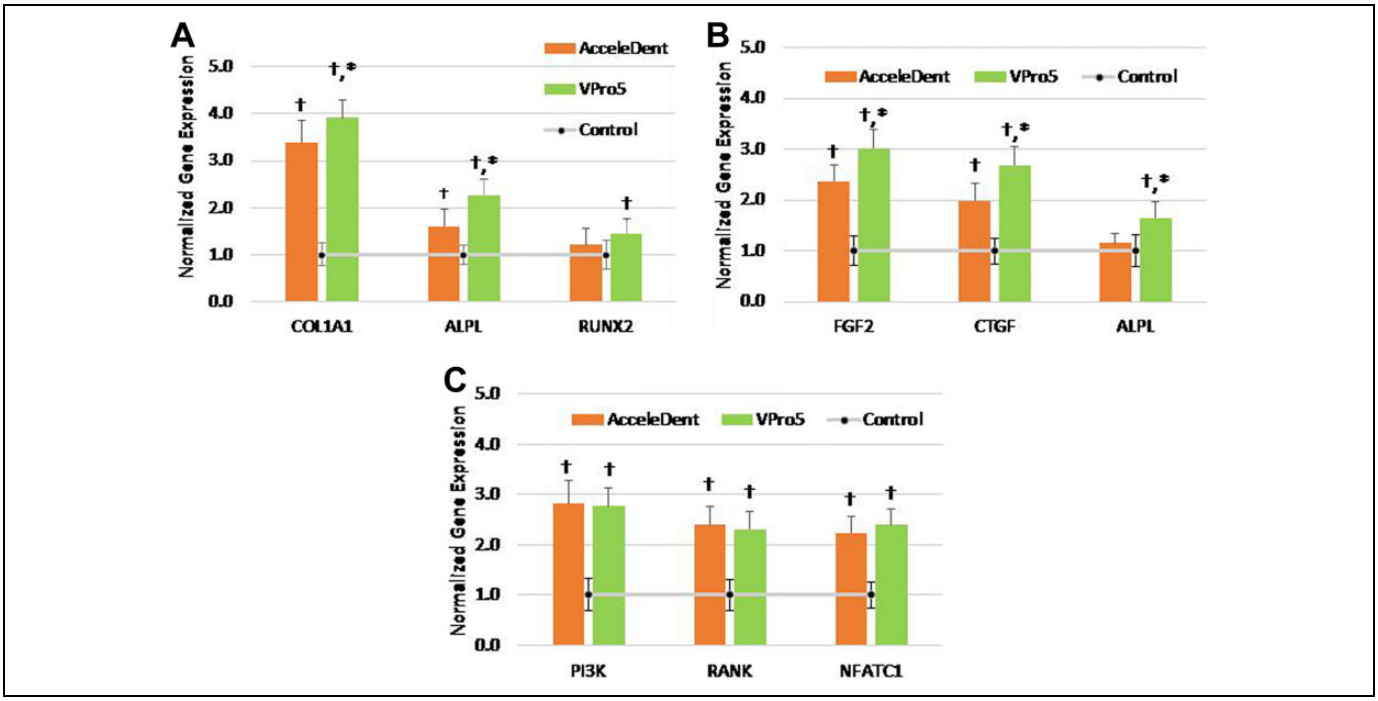

Figure 5. Gene expression levels of cells exposed to vibration with the AcceleDent (orange bars) or VPro5 (green bars) normalized to nonvibrated control cells (gray line that runs through 1.0). Gene expression was calculated by $2^{-\Delta\Delta Ct}$ with respect to GAPDH (housekeeping gene). Shown are means and standard deviations for (A) osteoblasts, (B) periodontal ligament fibroblasts, and (C) osteoclasts. Changes in transcriptional levels as a function of vibration treatment were largely consistent with proliferation data. Daggers mark statistically significant differences between experimentally treated (either by AcceleDent or by VPro5) and control samples. Asterisks mark statistically significant differences in gene expression between V5Pro treatment versus AcceleDent treatment.

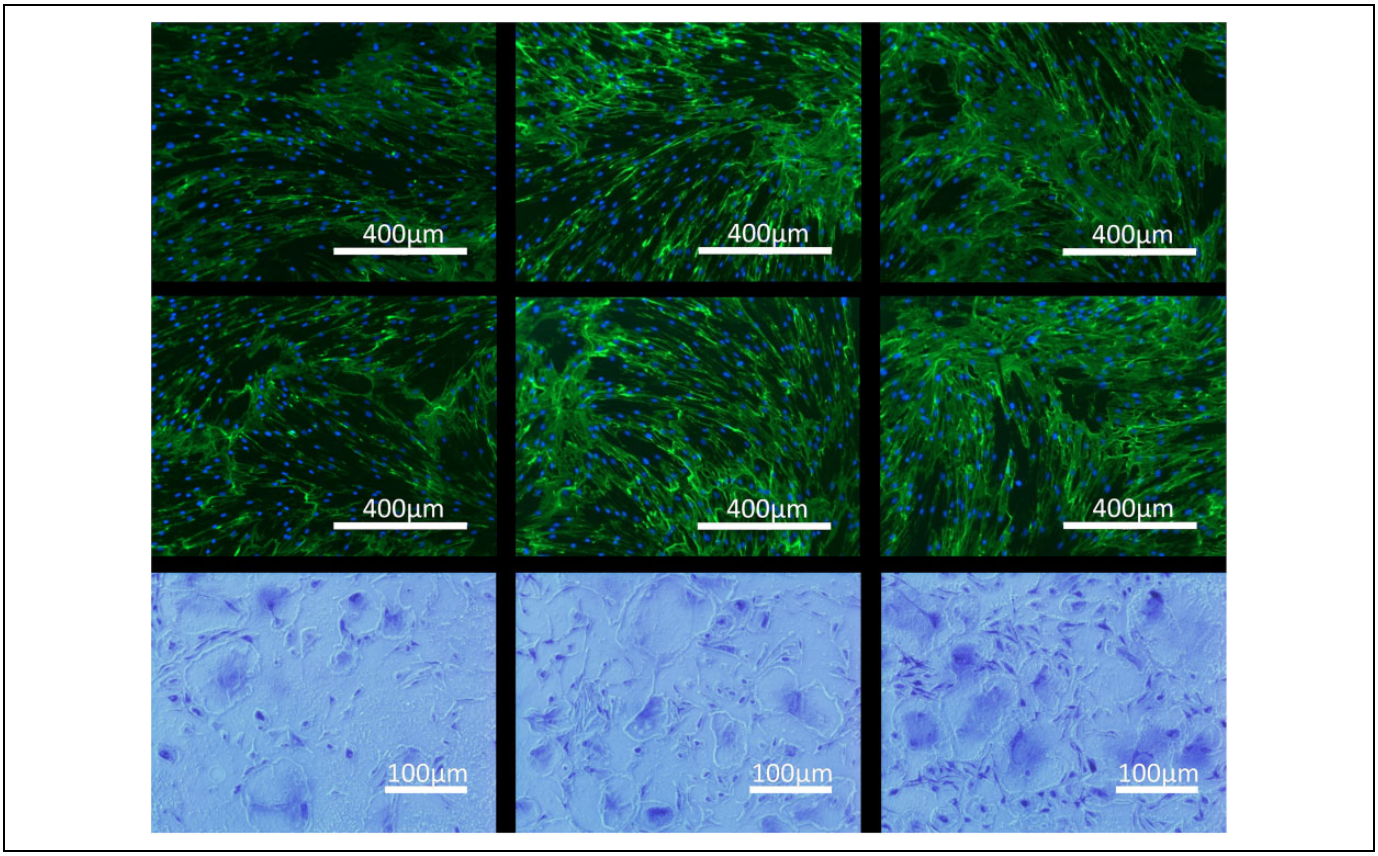

Figure 6. Stained human osteoblasts (first row), periodontal fibroblasts (second row), and osteoclasts (third row) subjected to either control conditions (first column) or 7 days of vibration with the AcceleDent (second column) or VPro 5 (third column). In osteoblasts and fibroblasts, collagen type I can be observed in green and the cell nucleus is stained blue. Tartrate-resistant acid phosphatase (TRAPc) staining visualized active multinucleated osteoclasts (and much smaller preosteoclasts). Staining in all 3 cell types confirmed cell phenotypes and quantitative results from the proliferation/gene expression experiments.

level, was significantly upregulated by VPro5 but not AcceleDent treatment (Figure 5).

Fibroblast growth factor 2 and CTGF were used as indicators of activity in human periodontal ligament fibroblasts. The FGF2 and CTGF levels were upregulated ($P < .05$) by both devices, but their levels were 30% and 40% greater ($P < .05$) in VPro5 samples than in AcceleDent samples (Figures 5 and 6). The ALPL, a gene indicating osteogenic differentiation, was not upregulated with AcceleDent but experienced significantly greater expression levels in VPro5 samples compared to both control and AcceleDent samples (Figure 5).

The PI3K, RANK, NAFATC1 gene expression levels were probed as indicators of Akt pathway initiation (PI3K) and osteoclastogenesis (RANK, NAFATC1). All 3 genes were significantly upregulated by both devices without significant differences between devices (Figures 5 and 6).

Discussion and Conclusions

We compared 2 orthodontic devices that aim at accelerating tooth movement, the AcceleDent and VPro5, to each other and tested which one is more effective at raising cell proliferation and transcriptional activity in human osteoblasts, periodontal ligament fibroblasts, and osteoclasts. Accelerometer measurements verified the manufacturers' specification of a 30-Hz vibration frequency in the AcceleDent and a 120-Hz vibration frequency in the VPro5. The different vibration frequencies were accompanied by different vibration (acceleration) magnitudes. Peak accelerations generated by the VPro5 were 70% greater than those generated by the AcceleDent. The greater vibration frequency and peak accelerations of the VPro5 coincided with greater cell proliferation/gene expression in human periodontal ligament fibroblasts and osteoblasts. In contrast, the devices' ability to increase osteoclastic activity was comparable.

The difference in vibration profiles induced by the 2 devices is striking. Although the AcceleDent produced peak accelerations on the order of 0.15 g in all 3 directions, peak accelerations of the VPro5 were much greater in the horizontal than vertical direction. This spatial anisotropy in acceleration magnitudes generated by the VPro5 may have directly contributed to greater rates of periodontal ligament fibroblast and osteoblast proliferation/gene activity rates seen with this device, as cells may sense vibrations preferentially in the horizontal direction.[15] The resultant acceleration magnitude, including both horizontal and vertical directions, was 70% greater in the

VPro5. The in vivo impact of significantly greater horizontal in-plane oscillations (VPro5) is unclear but conceivably is useful for seating clear aligners. The greater acceleration magnitude of the VPro5 was achieved via a greater vibration frequency (120 vs 30 Hz) and not a greater displacement magnitude. In fact, the displacement magnitude of the VPro5 was an order of magnitude smaller than in the AcceleDent, possibly perceived as inducing less discomfort. Also, application of these devices induces a relatively unconstrained motion both in our in vitro setup and in vivo. Thus, it is expected that stresses generated in alveolar bone by either device would be small, but these stresses were not measured here. As an alternative, and a perhaps more likely pathway to one that is based on stress/strain, cells have the ability to sense high-frequency oscillatory accelerations directly,[21-23] and it is therefore entirely possible that stress/strain plays no role in the mechanobiology of vibration-induced tooth movement.

Mechanobiologic activities at the periodontal ligament, containing cell types including osteoblasts, fibroblasts, and osteoclasts[24] can modulate successful tooth movement.[25] We probed cell proliferation and gene expression in this article because they are indicators of tissue turnover and remodeling,[26,27] processes critical to increase orthodontic tooth movement.[28,29] Vibrations upregulated RANK in osteoclasts, RUNX2 in osteoblasts, and FGF2 in periodontal ligament fibroblasts, specific markers for cellular differentiation and activity.[30,31] Although the understanding of cell–cell interactions among these 3 different cell types would require coculture and/or triculture, extrapolated to the clinical environment, these data suggest that vibrations promote proliferation/differentiation and thereby can enhance tissue turnover and accelerate tooth movement.

Inherently, one needs to be cautious when attempting to extrapolate data from in vitro cell culture studies to the orthodontic in vivo environment; however, the results collected here are coherent with the peer-reviewed literature showing that a number of different cell types and tissues are more responsive to vibrations applied at higher frequency (>60 Hz) rather than lower frequency (<45 Hz) vibrations.[13-16] Further, the biologic responses observed here echo, at least to some degree, the in vivo biologic responses witnessed in alveolar bone, where 100 Hz vibrations were more efficacious in increasing bone volume fraction than 30 Hz vibrations.[32,33] Thus, data collected here do not answer the question whether treatment with the AcceleDent or the VPro5 is more effective at accelerating tooth movement but, together with the published literature, suggest that cells favor higher vibration frequencies over lower frequencies. Of the other 2 vibration variables that were different between the AcceleDent and the VPro5, acceleration magnitude, and displacement magnitude, it is likely that only acceleration magnitude modulated the cellular response because displacement magnitude by itself has not been associated with altering biologic events. The influence of the higher acceleration magnitude of the VPro5 on the results is unclear. Although acceleration magnitude can readily change the potency of the applied vibration regime, the relationship between acceleration magnitude and cellular output may be highly nonlinear.[13,15-17,21]

In summary, we quantified the 3D vibration profile of 2 orthodontic devices that target to increase the rate of tooth movement. There were large relative differences in the generated vibration frequency and vibration magnitude (acceleration magnitude). These relative differences between the 2 devices are likely retained in vivo, although this in vitro investigation did not allow us to determine accurate acceleration levels experienced by cells in vivo. The device that produced the higher vibration frequency (VPro5) enhanced proliferation and differentiation of human osteoblasts and periodontal ligament fibroblasts to a significantly greater level than the device operating at the lower frequency (AcceleDent). The levels of osteoclast activity stimulated by the applied vibrations were not substantially different between the 2 devices. From an applied perspective, the shorter bout duration and lower overall displacement may improve compliance with regular at-home use. Whether the differential in vitro response between the 2 devices observed here will produce a differential rate of tooth movement remains to be investigated.

Authors' Note

The right to a final decision on the content was retained by the authors without requiring approval from a third party. The corresponding author (S.J.) has worked as a consultant for Propel Orthodontics in the past. He did not participate in data collection for the biologic experiments.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Professor Judex holds (provisional) patents on the effect of vibrations in biologic systems.

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