Received: 20 August 2018 | Revised: 14 April 2019 | Accepted: 15 April 2019

DOI: 10.1002/jbio.201800311

JOURNAL OF BIOPHOTONICS

FULL ARTICLE

Photobiomodulation increases intrusion tooth movement and modulates IL-6, IL-8 and IL-1β expression during orthodontically bone remodeling

Marcella R. U. Fernandes* | **Selly S. Suzuki** | **Hideo Suzuki** | **Elizabeth F. Martinez** | **Aguinaldo S. Garcez**

Department of Orthodontics, São Leopoldo Mandic, R. Dr. José Rocha Junqueira, Campina, São Paulo, Brazil

***Correspondence**
Marcella R. U. Fernandes, Department of Orthodontics, São Leopoldo Mandic, R. Dr. José Rocha Junqueira, 13 Ponte Preta, Campinas, São Paulo 13045-755, Brazil.
Email: marcellafern@hotmail.com

Abstract



This study investigated the effects of photobiomodulation (PBM) on upper molar intrusion movement, regarding acceleration of orthodontic movement and its molecular effects. The sample consisted of 30 patients with indication of tooth intrusion for oral rehabilitation. Teeth were divided into three different groups: G1 (n = 10) premolars without force or laser application (control); G2 (n = 10) upper molar intrusion; and G3 (n = 10) upper molar intrusion and PBM. On PBM treated molars, the teeth were irradiated with a low-power diode laser (808 nm, 100 mW), receiving 1 J per point, density of 25 J/cm^2, with application of 10 s per point, 10 points (5 per vestibular and 5 per palatal region). Orthodontic force of intrusion applied every 30 days and PBM was performed immediately, 3 and 7 days after force application for 3 months. Gingival crevicular fluid was collected at the same time periods as the laser applications and interleukins (IL) 1-β, -6 and -8 were evaluated by enzyme-linked immunosorbent assay. Clinical measures were performed monthly to verify the amount of intrusion. The levels of IL-6, IL-8 and IL-1β increased under orthodontic force (G2 and G3) when compared to control group (G1), however, the cytokines levels were significantly higher after PBM (G3). The mean intrusion velocity was 0.26 mm/month in the irradiated group (G3), average duration of 8 months vs 0.17 mm/month for the non-irradiated group (G2), average duration of 12 months. This study suggests that PBM accelerates tooth movement during molar intrusion, due to modulation of IL-6, IL-8 and IL-1β during bone remodeling.

KEYWORDS

accelerated movement, cytokines, molar intrusion, PBM

 © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

1 | INTRODUCTION

Orthodontic treatment is based on forces applied to the wires and brackets and these forces when transmitted to the dental structure, produce a distortion of the periodontal ligament, and a consequent change in cellular configuration and bone remodeling [1]. Nowadays with the increase number of adults looking for orthodontic treatment, the pressure for faster treatment time was also increased. Many studies have reported different methods for orthodontic movement acceleration, which can be divided into three categories: biological pathway with local or systemic delivery of drugs (local injections of prostaglandins or administration of muscle relaxants); physical or mechanical stimulation (photobiomodulation (PBM)-laser or vibratory forces); and surgically facilitated orthodontic treatment (corticotomies) [2–4].

The administration of systemic substances has already been described in animal studies [5], but further studies are needed to assess its efficacy, safety and specificity for human dentoalveolar tissues, before it can become a common practice. Injection of local drugs, or electrical or vibratory stimulation, has several side effects, including, pain and discomfort. In addition, surgically facilitated treatment is an invasive procedure, which is hardly acceptable by the patient [4]. Therefore, the use of PBM, using laser irradiation, may be an alternative with a good degree of acceptance due to its non-invasive characteristic, as well as being a type of equipment which can be widely used in different areas of dentistry [6–9].

PBM have been highlighted in dentistry literature, mainly regarding its pain inhibitory effects and tissue repair [10, 11]. These modulatory effects are the result of the ability of PBM to accelerate metabolic changes and increase bone resorption and neoformation, which are necessary for orthodontic movement [12].

When treating adult patients, there may be a reduction in the amount of tooth movement due to decreased vascularity in areas of compression, and an increase in bone density. In these situations, the application of PBM, that has angiogenic stimulating effects may be beneficial for adult patients [13–15].

A common problem in adult patients is the extrusion of upper molars, typically caused by the early loss of the antagonist tooth. The position of these teeth usually impairs oral rehabilitation and can cause both occlusal and functional problems, as well as compromise periodontal health, requiring an interdisciplinary treatment approach [16].

Gingival crevicular fluid (GCF) sampling is a non-invasive and non-destructive method to examine cell dynamics. Since inflammatory process occurs during tooth movement, several mediators such as chemokines, cytokines and growth factors can be detected in GCF [17]. During orthodontic tooth movement, an increase in expression of inflammatory mediators (cytokines) [18, 19], such as interleukins (ILs) is expected. These cytokines are released during orthodontic tooth movement from various cell types, such as periodontal ligament fibroblasts and osteoclasts modulating the inflammatory response, and bone remodeling, especially IL-1β, IL-6 and IL-8 [20–22]. IL-1β is a highly studied cytokine due to its ability to stimulate osteoclastic activity and to recruit leukocytes and other cellular mediators to act in the bone remodeling process. Previous studies have reported the relationship between increased IL-1β levels and tooth movement [23, 24]. IL-6 is responsible for the regulation of immune responses at inflammation sites, and stimulates the formation of osteoclasts and the bone resorption activity of osteoclasts [25]. IL-8 is responsible for stimulating the differentiation of osteoclasts in orthodontically driven tooth compression zones [26].

Furthermore, the effect of PBM on proinflammatory cytokine expression during orthodontic movement is still unknown due to large variations of laser's parameters and protocols found in literature, and also patients of different ages, use of different teeth, forms of measurement and orthodontic techniques.

Since upper molar intrusion is commonly required for patients who need oral rehabilitation, the present study aimed to evaluate the effects of PBM on orthodontic movement acceleration, and on pro-inflammatory cytokine expression.

2 | MATERIALS AND METHODS

2.1 | Study design

The protocol of this study was reviewed and approved by the Institutional Review Board of the São Leopoldo Mandic Institute and Dental Research Center, and all trial procedures were conducted according to the principles of the Declaration of Helsinki (protocol number #1.745.149). Before participating, all patients were informed individually about the nature of the proposed study, as well as the risks and benefits, and signed an informed consent form.

2.2 | Patient screening

Thirty patients were selected for this study. Twenty patients undergoing orthodontic treatment for molar intrusion (ages from 35 to 65) were selected according to the following inclusion criteria (a) good systemic health condition; (b) indication of intrusion of first upper molar for esthetic or prosthetic rehabilitation; (c) presence of adjacent teeth; adequate oral hygiene; (d) absence of previous orthodontic

treatment; and (e) absence of teeth (molars) with curved roots. The exclusion criteria were: (a) pregnant and breastfeeding women, (b) infants, (c) use of medications that could alter the response to orthodontic treatment (such as non-steroidal anti-inflammatory drugs); (d) use of antibiotics.

The selected patients were treated in the period from 2016 to 2017, at Orthodontics Division of São Leopoldo Mandic Institute and Dental Research Center, Campinas (SP, Brazil). All the patients had been indicated to receive upper molar intrusion—2 to 2.5 mm from occlusal plane, for posterior prosthetic rehabilitation. After the end of the experiment, all the patients received orthodontic treatment according to appropriate indication and planning. The other 10 patients selected did not receive orthodontic treatment and were classified as the control group (G1).

At their first appointment, all the patients were assessed clinically and radiographically, and an accurate treatment plan was made. Afterwards, two mini-implants (PecLab, Belo Horizonte, MG, Brazil) were installed in each patient, as an anchorage device, to perform the intrusion movement, one in the inter roots vestibular region, and the other in the palatal region. The location and dimensions of the mini-implant were chosen based on the amount of cortical bone present in the region for proper anchorage and primary stability [16].

After installation, a metallic orthodontic button (Morelli, Sorocaba, SP, Brazil) was bonded to the palatal face, and a standard edgewise bracket (Morelli, Sorocaba, SP, Brazil), to the buccal side of the molar to be intruded. An elastomeric memory chain (American Orthodontics, Sheboygan, Wisconsin) was used to impose a light force of 150 g in all the cases, regardless of the tooth position. This elastic chain was changed every 30 days until the tooth reached the desired position (Figure 1). The force used in all activations was measured with a Correx tensiometer (Haag-Streit Diagnostics, Koeniz, Switzerland).

The patients were divided into three groups: G1, control: without orthodontic movement and without premature contact (n = 10), G2, orthodontic movement (n = 10) and G3, orthodontic movement plus laser irradiation (PBM) (n = 10).

2.3 | Photobiomodulation

In G3, after the patients underwent upper molar intrusion, they received PBM at three different moments: immediately after force application (T0), after 3 (T1) and 7 days (T2), as well as, whenever a new elastic chain was placed to activate the intrusion, during a total of 3 months. A low-power diode laser (Laser Duo, MMOptics, São Carlos, SP, Brazil) emitting at 808 nm, with 100 mW, was applied for 10 seconds to each point (energy of 1 J per point). Irradiation was performed along 10 points on the gingival tissue (five points per vestibular and five per palatine region): two points on the cervical third (one mesial and one distal gingiva), two points on the apical third (one mesial and one distal), and one point in the middle third (root center) [6, 28]. The laser beam (area = 0.04 cm^2) was positioned at each point, creating an energy density of 25 J/cm^2 per irradiation (Figure 2).

The entire study was performed in 90 days, the samples and rate of tooth movement were collected immediately after installation of the orthodontic device, and then 30, 60 and 90 days later. After the experimental period, the patients were followed up until they completed the planned dental intrusion and thereby received oral rehabilitation.

2.4 | Crevicular fluid sampling

The samples were collected from four sites, including the buccal, lingual, mesial and distal sites of the uppers molars or premolars (control). The premolars were used to compare the molecular differences between teeth under orthodontic force and non-treated teeth. An absorbent paper point (#20—Dentsply, Brazil) was inserted into the gingival sulcus at each site, until smooth resistance was felt. The paper point was then kept in place for 60 seconds to allow the GCF to be absorbed from the sulcus (Figure 3). Paper points that were visibly contaminated by blood were discarded. Each tip was placed in a sterile polystyrene tube (Eppendorf, Sigma, California) containing 250 μL of RIPA buffer supplemented with protease inhibitor at 1% of the mixture (Sigma-Aldrich, Saint Louis, Missouri). The tube was then sealed and identified with the patient's details and with the

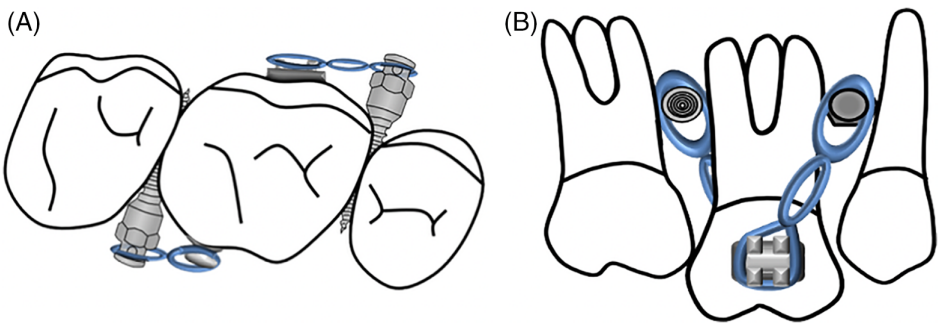


FIGURE 1 A, Occlusal view of the orthodontic mechanics used; B, vestibular view of the orthodontic mechanics used for upper molar intrusion

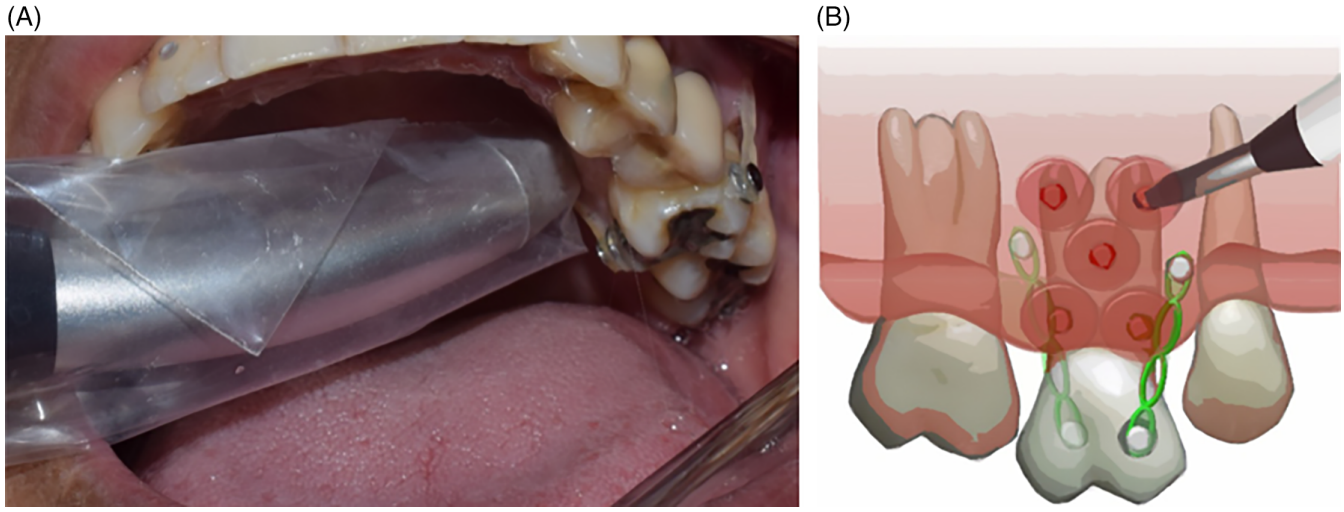


FIGURE 2 PBM on G3 patients: A, Real representation; B, Figure demonstrating the five points chosen to apply the PBM



FIGURE 3 Crevicular fluid sampling

sample collection site. The samples were frozen at −70°C for subsequent experiments.

2.5 | Enzyme-linked immunosorbent assay

The samples were centrifuged for 15 minutes at 4°C, at 10000 g. The concentration of the inflammatory mediators (IL1-β, IL-6 and IL-8) present in the GCF was evaluated by enzyme-linked immunosorbent assay (ELISA), following manufacturers' recommendations (eBioscience, San Diego, California). In brief, 100 μL of detection antibody was added to all the wells, with the exception of the blank well, mixed gently and incubated overnight (16–24 hours) at 4°C. The plates were washed 3 times; standards and supernatant were then added to their respective wells, in duplicate. After incubation, the plates were washed again and incubated with 200 μL of conjugate for 60 min at room temperature. After washing the plates three more times and adding 200 μL of substrate, the plates were incubated for 15 min at room temperature in the dark. The reaction was stopped by adding 50 μL of stop solution, and the color was measured in an automated microplate spectrophotometer (Epoch, Biotek, Winooski, Vermont), using λ 450 nm. The total concentration of cytokines present was determined in picograms per milliliter (pg/mL). The results were calculated using the standard curves created in each assay. All ELISA analyses were performed in a blind manner and in triplicate.

2.6 | Clinical measurement

The amount of intrusion was measured every month in all patients that underwent orthodontic force (G2 and G3), by using a digital caliper (Mitutoyo, São Paulo, Brazil) and a dry-tip compass (Integra LifeSciences, Plainsboro, New Jersey). The occlusal plane of each patient, as well as the distobuccal (DB) and mesiobuccal (MB) cusps of adjacent teeth, was used as a reference. These measurements were recorded in millimeters, on each patient's chart, for future comparison (Figure 4.

2.7 | Root resorption

The amount of root resorption was measured in all patients that underwent orthodontic force (G2 and G3). To evaluate if root resorption occurred after the intrusion movement, linear measurements were taken from CT scans performed before and after the procedure. CT scans were used to avoid the possible distortion in periapical radiographs. Using Horos software (Horos project—open source medical image viewer), a standard position for patient's head was stipulated in the sagittal, axial and coronal sections. Since first upper molars have three roots, three measurements were made (also standardized on the three cuts). The measure used started from cementoenamel junction to the apex of each intruded tooth. Measurements obtained from initial CT scans

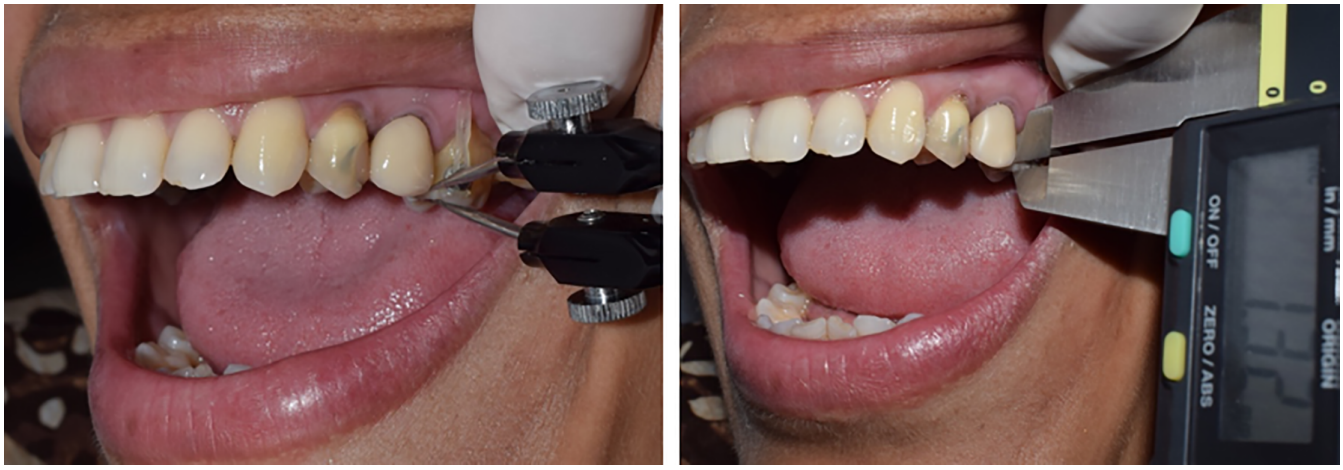


FIGURE 4 Clinical measurement with a dry-tip compass and a digital caliper

were compared with measurements of final CT scans to calculate the amount of root resorption.

2.8 | Statistical analysis

Statistical analysis was performed using only the data obtained from the patients who completed the study. The Kolmogorov-Smirnov test was applied prior to data analysis to assess the normality of each parameter. Two-way analysis of variance (ANOVA) followed by the Bonferroni test were used to compare all the measurements. All tests were performed using Graphpad Prism 5 (GraphPad Software, San Diego, California). The significance level was set at $P < 0.05$.

3 | RESULTS

The GCF levels of cytokines evaluated are shown in Figures 5–6 and 7. In the control group (G1), as expected no significant change was observed in the levels of all mediators, at all the evaluation time points. However, regardless of laser irradiation, the cytokine levels were increased whenever orthodontic force was applied (G2 and G3).

Especially after 30 days of sample collection, a significant increase in IL1-β, IL-6 and IL-8 was observed in the laser-irradiated group (G3), compared with groups G1 and G2 ($P < 0.05$). In addition, this increase was found to be more significant at the 3rd day of analysis (T1).

Evaluating each inflammatory cytokine, we could observe that there was a slightly decrease in the IL-1β levels over time, compared with IL-6 and IL-8, which increased during the 90th day of analysis, compared with T0. Additionally, after the second activation (T1) and throughout the experimental period, IL-6 and IL-8 levels (but not IL-1β) were higher in the irradiated group (G3) than the others ($P < 0.05$).

In regard to the amount of intrusion per month, Figure 8 shows the distance to reach the occlusal plane after irradiation (G3) or non-irradiation (G2). The laser group (G3) had a higher intrusion rate than the non-irradiated group (G2), in all the experimental periods ($P < 0.05$). The mean total intrusion was completed after 8 months for G3, and 12 months for G2 (Figure 5). The mean velocity required for intrusion in each group was 0.26 mm/month and

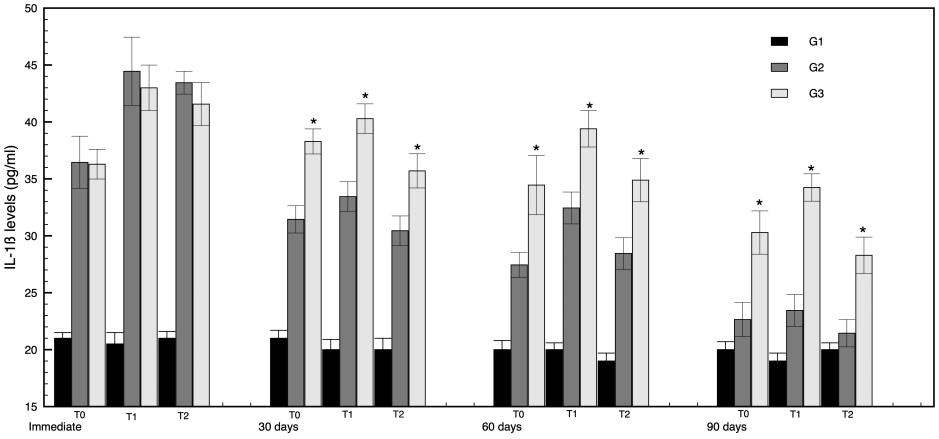


FIGURE 5 Concentrations of IL-1β at T0 (day 1), T1 (day 3) and T2 (day 7), after orthodontic force application. The data represent mean and the error bars represent the SD. The symbol + at the top of each bar indicates significant difference determined by intragroup analysis ($\alpha = 0.05$; Bonferroni test)

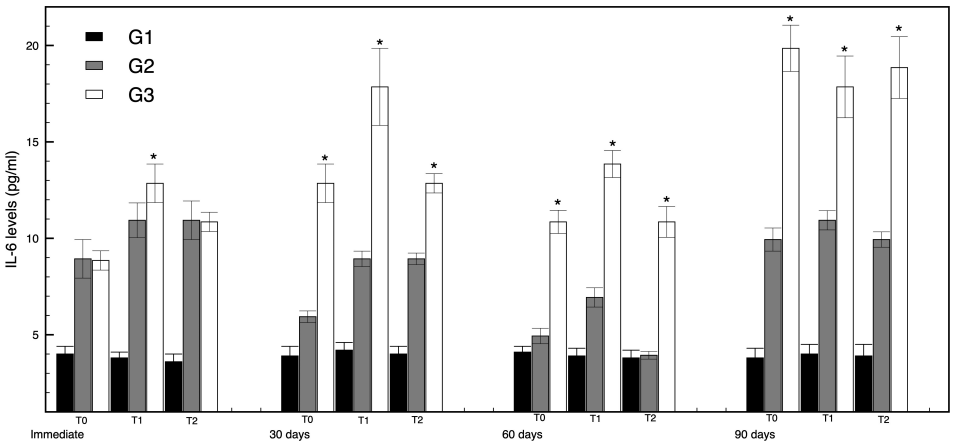


FIGURE 6 Concentrations of IL-6 at T0 (day 1), T1 (day 3) and T2 (day 7), after orthodontic force application. The data represent mean and the error bars represent the SD. The symbol + at the top of each bar indicates significant difference determined by intragroup analysis ($\alpha = 0.05$; Bonferroni test)

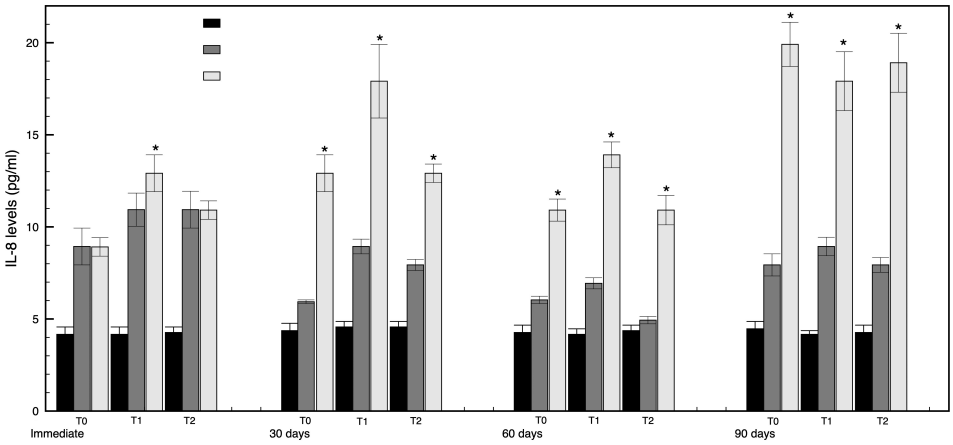


FIGURE 7 Concentrations of IL-8 at T0 (day 1), T1 (day 3) and T2 (day 7), after orthodontic force application. The data represent mean and the error bars represent the SD. The symbol + at the top of each bar indicates significant difference determined by intragroup analysis ($\alpha = 0.05$; Bonferroni test)

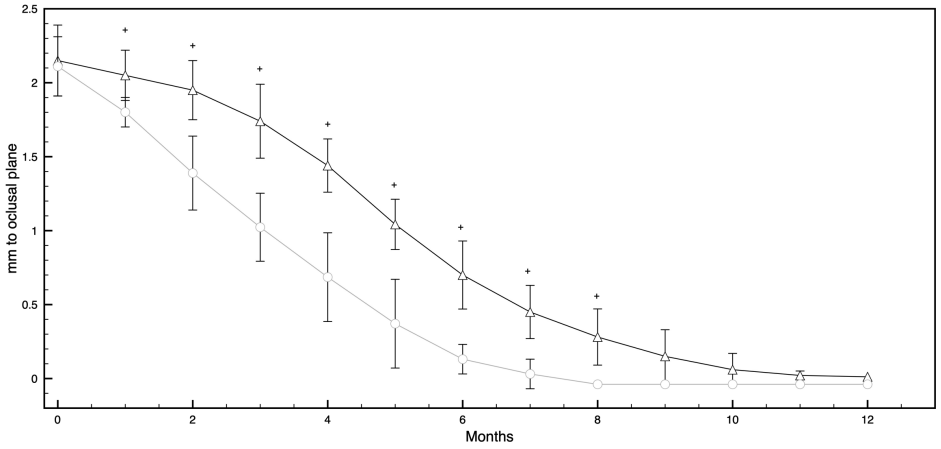


FIGURE 8 Mean tooth movement throughout the experimental period. The + symbol indicates statistical difference in relation to the other groups ($P < 0.05$)

0.17 mm/month, for G3 and G2, respectively. These data represent a 34% acceleration rate in dental movement when PBM was performed (G3).

In regard to the amount of root resorption, there was a significant difference between the measurements of all roots for G2 before and after molar intrusion ($P < 0.05$). However, there was no difference between the measures of length of all roots in G3, before and after intrusion ($P > 0.05$). When comparing root shortening between G2 and G3, MB and DB roots showed greater shortening in G2 ($P < 0.05$). There was no difference in the shortening of palatal root between groups ($P = 0.066$) (Figure 9).

4 | DISCUSSION

Recently many researches have been indicating PBM to speed tooth movement. In patients, Cruz et al. [6], Youssef

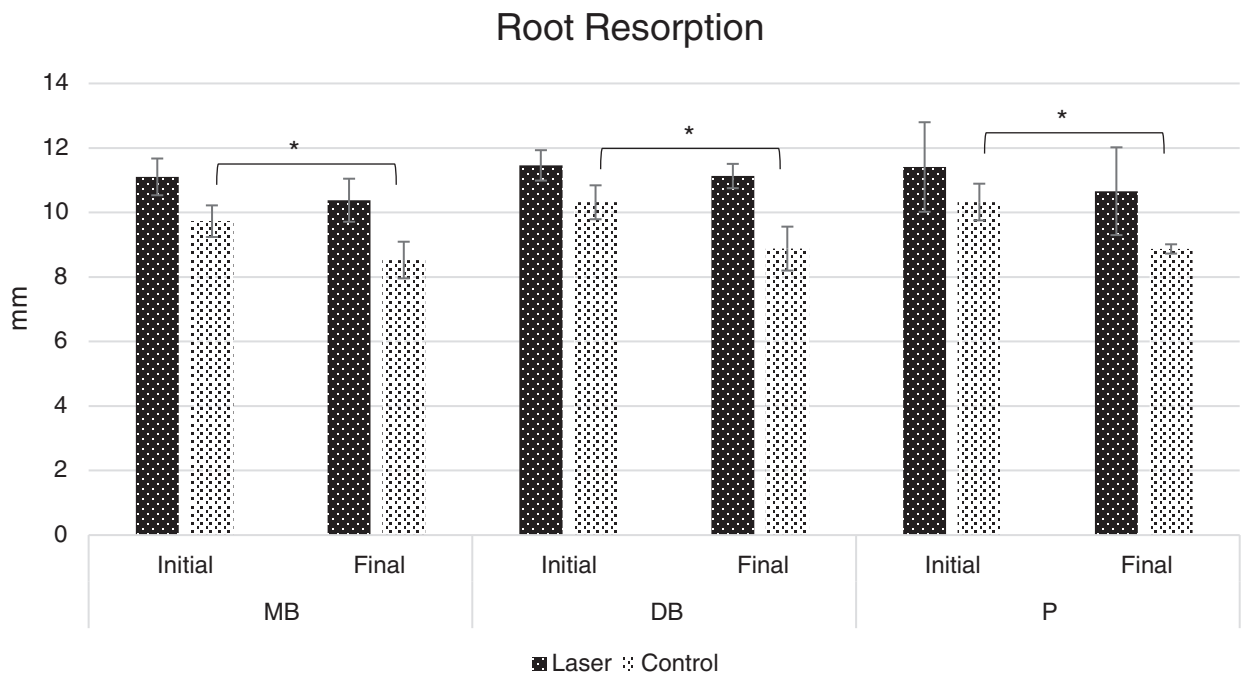


FIGURE 9 Amount of root resorption before and after intrusion movement

et al. [30], Sousa et al. [29] and Genc et al. [3] showed increases of 20% to 40% or even doubled in rate of movement in 6 months. These clinical researches were performed in premolar extraction cases, using mesialization orthodontic mechanic and applied to young patients presenting healthy periodontal conditions. In our study, since criteria for patient selection included extruded molars with indication for intrusion, the majority of patients were mature adults seeking for a faster orthodontic treatment and prosthetic rehabilitation on the lower arch. PBM is known for its benefits including pain relief, increased blood microcirculation, modulatory effects on tissue physiology, biomechanical and proliferative activities [31, 32]. To the best of our knowledge, this is the first study to focus on PBM effects on bone remodeling and tooth movement in more mature patients.

The mean intrusion rate on irradiated group, in this study was 0.26 mm/month, therefore 0.09 mm/month higher than the non-irradiated group, which had a mean velocity of 0.17 mm/month. Resulting in an average of 34% faster tooth movement. As cited above, these results are similar to those found in previous studies related to PBM and acceleration of tooth movement [2, 6, 31, 32]. Since the age selection was relatively wide for the present study, female patients aged more than 45 years may have presented the influence of osteoporosis [33, 34] on the tooth movement. This could be a potential shortcoming and needs further review on future studies.

Irradiation parameter used in this study was energy 1 J per point, 25 J/cm energy density[2]: two points in the cervical third (one mesial and one distal), two points in the apical third (one mesial and one distal) and one point in the middle third (root center) [3, 6, 28]. Genc et al. [3] used an energy density of 0.71 J/cm^2 and an exposure time of 10 seconds, the laser was applied on 0, 3rd, 7th, 14th, 21st and 28th days after the application of orthodontic force. Cruz et al. [6] used a dose of 5 J/cm^2 and exposure time of 10 seconds, the laser was applied on 0, 3rd, 7th and 14th days. Sousa et al. [28] used an energy density of 5 J/cm^2 with application of 10 seconds per point, the laser was applied on 0, 3rd and 7th days. All of the previous studies used the same applications points as the ones used in our study. The laser beam (area = 0.04 cm^2) was positioned at each point, creating an energy density of 25 J/cm^2 per point. This protocol, with 10 points of irradiation was chosen to allow light to be distributed throughout the alveolar bone around molar roots. In this respect, the wavelength used for irradiation is an important factor to be considered, since in vivo studies reporting the effects of PBM use wavelengths greater than 780 nm [35] to allow light penetration into tissue, such as that used in the present study (808 nm).

In orthodontic treatment, single molar intrusion is a challenge when using conventional orthodontic mechanics. Generally, this approach relies on the adjacent teeth for anchoring and requires patient collaboration [16]. This study used mini-implants, in both buccal and palatal sides, to provide absolute anchorage, controlled movements, absence of complex surgical procedures, low cost and patient acceptance [36]. Also, this chosen biomechanics for orthodontic movement enabled the application of a more accurate and controlled force.

Regarding the amount of force used for intrusion, previous studies have suggested different protocols. Some authors suggested 90 g per tooth for molar intrusion, other authors, 50 g for upper molars in adults and 200 to 300 g for teeth with 3 roots [37–39]. Considering the anatomy of posterior teeth, it is reasonable to apply forces 2 or 3 times greater than those used in anterior teeth (50 g) [40]. Based on this, in the present study, 150 g of intrusion force was used in upper molars, and an average of 0.21 mm of intrusion was achieved per month without noticeable root resorption.

Regarding the relation between root resorption and PMB, previous studies have suggested that this technique improves periodontal tissue repair and decreases inflammation and root resorption [41–44]. As found in our study, when comparing root shortening between G2 and G3, MB and DB roots showed greater shortening in G2 ($P < 0.05$).

Our results showed that levels of IL-1β, IL-6 and IL-8 collected in the GCF of upper first premolars (which were untreated and did not receive any orthodontic forces) were relatively stable during the entire period of experiment, as expected. On the contrary, force application (150 g) in both, irradiated and non-irradiated teeth, led to an increase in all cytokine levels, indicating an inflammatory response to orthodontic-induced tooth movement, as previously reported [45–47].

IL-8 is a cytokine responsible for involvement of neutrophils during inflammation and is important for regulation of alveolar bone resorption during tooth movement, acting on the inflammatory response. Previous studies showed a significant enhancement of IL-8 release in the first hour after force application, reaching a peak in GCF on day 6, whereas other cytokines were reported as increasing on days 7 and 21 [46, 47]. In the present study, IL-8 levels increased significantly in both groups at T1, and presented peak values after the 3rd day. In addition, higher levels of IL-8 may explain the greater amount of tooth displacement found in laser group. The increase in peak levels on the 3rd day after force application can be attributed to the elastomeric material used in this study, since they remain active during the first 3 days, and suffer elastic degradation later on.

IL-8 also acts on migration, invasion and proliferation of endothelial cells through their receptors, as well as angiogenesis [48]. Studies have found an effect on vascular response after PBM irradiation [49]. Colombo et al. [50] observed that PBM positively influenced angiogenesis and vasodilation. The increase in IL-8 levels found in this study may induce angiogenesis at the periodontal ligament, therefore, favoring accelerated tooth movement, possibly by increasing the number of osteoclasts involved in the mechanism of tooth movement [51].

IL-6 and IL-1β are known to induce differentiation and proliferation of osteoclasts, stimulating bone resorption. Therefore, during orthodontic movement, high expression of these cytokines is found to promote bone resorption, mainly on the compression side [36, 52, 53]. In addition, IL-1β is an IL-6 induce and participate in the complex mechanism of mediators that regulate bone remodeling [32, 54], by recruiting osteoclast cells and inducing bone resorption [31, 55]. Similar results were found by Yanaguizawa et al. [31] after insertion of mini screws, the bone trauma promoted by miniscrew installation also promote rise in IL-6 levels and PBM significantly promoted a further increase in this cytokine. Our study revealed an increased level of cytokines whenever orthodontic force was applied (G2 and G3), regardless of laser irradiation, especially after 30 days of sample collection, a significant increase in IL1-β, IL-6 and IL-8 was observed in the laser-irradiated group (G3), compared with groups G1 and G2 ($P < 0.05$). Varella et al., [53] also presented a study where IL-1β increased especially due to PBM. Yanaguizawa et al. [31] stated that PBM promoted a significant modulation of IL-8 levels when compared to a non-irradiated group. Their results also showed that the level of IL-6 was higher for the laser group at T1. This study demonstrated that increase in IL-1β, IL-6 and IL-8 levels at GCF promoted by PBM have led to a faster dental intrusion over the 3-month period of this experiment. This result may be explained by the fact that these cytokines are related to bone resorption, recruitment of osteoclasts and are currently found in the periodontal ligaments of patients under orthodontic treatment. Mature adult patients can benefit from this approach, especially when the main objective of orthodontic treatment is prosthetic rehabilitation, considering that patient seeks for a quicker treatment involving a particular site of the dental arch. Furthermore, PBM also have a positive effect on bone remodeling, as reported by Suzuki et al. [42] that showed an increase in bone mineral density, bone volume fraction, and trabecular thickness after PBM. Also, Kawasaki and Shimizu [56] observed that orthodontic movement associated to PBM resulted on an acceleration of alveolar bone remodeling, indicated by increases in the number of osteoclasts, cellular proliferation of periodontal ligament cells and mineralized bone formation, and Hsu et al. [57] concluded that PBM can accelerate orthodontic tooth movement because the activation of bone cells leads to rapid turnover of alveolar bone.

5 | CONCLUSION

Our study suggests that PBM accelerates tooth movement during molar intrusion, by modulating the levels of cytokines (IL-1β, IL-6 and IL-8), which are increased in comparison with non-irradiated areas, during the entire experimental period. The total treatment time was

significantly reduced in the irradiated group, compared with the non-irradiated group.

AUTHOR BIOGRAPHIES

Please see Supporting Information online.

ORCID

Marcella R. U. Fernandes https://orcid.org/0000-0002-9443-8876

REFERENCES

[1] J. Tasanapanont, T. Wattanachai, J. Apisariyakul, P. Pothacharoen, S. Ongchai, P. Kongtawelert, et al., *Int J Dent* **2017**, *2017*, 2689642.
[2] G. Doshi-Mehta, W. A. Bhad-Patil, *Am. J. Orthod. Dentofacial Orthop.* **2012**, *141*, 289. https://doi.org/10.1016/j.ajodo.2011.09.009.
[3] G. Genc, I. Kocadereli, F. Tasar, K. Kilinc, S. El, B. Sarkarati, *Lasers Med. Sci.* **2013**, *28*(1), 41.
[4] F. Uribe, S. Padala, V. Allareddy, R. Nanda, *Am J Orthod Dentofac Orthop* **2014**, *145*, S65. https://doi.org/10.1016/j.ajodo.2013.12.015.
[5] M. Seifi, *Eur J Orthod* **2003**, *25*, 199. https://doi.org/10.1093/ejo/25.2.199.
[6] D. R. Cruz, E. K. Kohara, M. S. Ribeiro, N. U. Wetter, *Lasers Surg. Med.* **2004**, *35*, 117.
[7] D. Makedonas, H. Lund, K. Gro, *Angle Orthod* **2012**, *82*, 196.
[8] S. S. Baloul, L. C. Gerstenfeld, E. F. Morgan, R. S. Carvalho, T. E. Van Dyke, A. Kantarci, *Am. J. Orthod. Dentofacial Orthop.* **2011**, *139*, S83. https://doi.org/10.1016/j.ajodo.2010.09.026.
[9] M. Nishimura, M. Chiba, T. Ohashi, M. Sato, Y. Shimizu, K. Igarashi, H. Mitani, *Am. J. Orthod. Dentofacial Orthop.* **2008**, *133*, 572.
[10] F. Topolski, A. Moro, G. M. Correr, S. C. Schimim, *J. Pain Res.* **2018**, *11*, 589.
[11] V. P. Wagner, L. Meurer, M. A. Martins, C. K. Danilevicz, A. S. Magnusson, M. M. Marques, M. S. Filho, C. H. M. M. Squarize, *J. Biomed. Opt.* **2013**, *18*, 128002.
[12] A. Ekizer, G. Türker, T. Uysal, E. Güray, Z. Taşdemir, *Lasers Surg Med* **2016**, *48*, 936. https://doi.org/10.1002/lsm.22516.
[13] F. R. Beckwith, R. J. Ackerman, C. M. Cobb, D. E. Tira, *Am. J. Orthod. Dentofacial Orthop.* **1999**, *115*, 439.
[14] L. C. Filho, S. A. Braga, A. D. O. Cavassan, Ozawa TO, *Dent Press Ortodon Ortop Facial* **2001**, *6*, 63.
[15] A. C. Esteves de Oliveira Melo, L. Oliveira Thiers Carneiro, L. Farias Pontes, R. Lobão Cecim, E. Rufinod, J. N. Mattos, D. Normando, *Dental Press J Orthod* **2013**, *18*, 59 Available from: http://search.ebscohost.com/login.aspx?direct=true&db=ddh&AN=96358343&site=ehost-live.
[16] S. Baumgaertel, S. Smuthkochorn, J. M. Palomo, *Am. J. Orthod. Dentofacial Orthop.* **2016**, *149*, 411. https://doi.org/10.1016/j.ajodo.2015.10.016.
[17] I. Andrade Jr., T. SRA, S. PEA, *YSODO* **2012**, *18*, 257. https://doi.org/10.1053/j.sodo.2012.06.004.
[18] J. Capelli Jr., R. Fidel Junior, C. M. Figueredo, R. P. Teles, *Dental Press J Orthod* **2010**, *15*, 52.
[19] V. Krishnan, Z. Davidovitch, *Am. J. Orthod. Dentofacial Orthop.* **2006**, *129*, 1.
[20] Y. Ren, A. Vissink, *Eur. J. Oral Sci.* **2008**, *116*, 89.
[21] A. M. Alhadlaq, *J Contemp Dent Pr.* **2015**, *16*, 578.
[22] M. Bakhiet, N. Alhashimi, L. Frithiof, P. Brudvik, *Am. J. Orthod. Dentofacial Orthop.* **2001**, *119*, 307.
[23] C. Giannopoulou, A. Dudic, S. Kiliaridis, *J. Pain* **2006**, *7*, 367.
[24] Y. Yao, X. Feng, X. Jing, *Shanghai Kou Qiang Yi Xue* **2003**, *12*, 331.
[25] J. K. Maclaine, A. B. M. Rabie, R. Wong, *Eur J Orthod* **2010**, *32*, 435.
[26] P. Proff, C. Reicheneder, A. Faltermeier, D. Kubein-meesenburg, P. Römer, *J Orofac Orthop* **2014**, *75*, 191.
[27] M. V. da Silva Sousa, M. A. Scanavini, E. K. Sannomiya, L. G. Velasco, F. Angelieri, *Photomed Laser Surg* **2011**, *29*, 191. https://doi.org/10.1089/pho.2009.2652.
[28] M. Youssef, S. Ashkar, E. Hamade, N. Gutknecht, F. Lampert, M. Mir, *Lasers Med. Sci.* **2008**, *23*(1), 27.
[29] P. R. Arany, *J Dent Res* **2016**, *95*, 977.
[30] M. S. Yanaguizawa, S. S. Suzuki, E. F. Martinez, H. Suzuki, M. C. J. Pelegrin, A. S. Garcez, *Photomed Laser Surg* **2017**, *35*(1), 57-63. https://doi.org/10.1089/pho.2015.3959.
[31] P. Palmqvist, P. Lundberg, I. Lundgren, L. Hänström, UHL, *J Dent Res.* **2008**, *87*(6), 558-63.
[32] S. A. Samara, A. Z. Nahas, T. A. Rastegar-lari, *Lasers Dent Sci* **2018**, *2*(2), 109-118.
[33] M. B. Ashcraft, K. A. Southard, E. A. Tolley, *Am J Orthod Dentofacial Orthop* **1992**, *102*(4), 310-9.
[34] I. Sirisoontorn, H. Hotokezaka, M. Hashimoto, C. Gonzales, S. Luppanapornlarp, M. A. Darendeliler, N. Yoshida, *Am. J. Orthod. Dentofacial Orthop.* **2012**, *141*, 563. https://doi.org/10.1016/j.ajodo.2011.11.016.
[35] Y. Maegawa, T. Itoh, T. Hosokawa, *Lasers Surg Med* **2000**, *437*, 427.
[36] J. Volpato, C. Paccini, F. A. Cotrim-ferreira, F. V. Ferreira, *Dental Press J Orthod* **2016**, *21*, 56.
[37] V. Kalra, C. J. Burstone, R. Nanda, *Am J Orthod Dentofacial Orthop* **1989**, *95*, 467.
[38] M. Umemori, J. Sugawara, H. Mitani, H. Nagasaka, H. Kawamura, *Am J Orthod Dentofac Orthop* **1999**, *115*, 166.
[39] Y. C. Park, S. Y. Lee, D. H. Kim, S. H. Jee, *Am. J. Orthod. Dentofacial Orthop.* **2003**, *123*, 690.
[40] R. Burstone, *Am J Orthod* **1977**, *72*, 1.
[41] D. Ng, A. K. Chan, A. K. Papadopoulou, O. Dalci, P. Petocz, M. A. Darendeliler, *Eur J Orthod* **2018**, *40*, 317.
[42] S. S. Suzuki, A. S. Garcez, H. Suzuki, E. Ervolino, W. Moon, M. S. Ribeiro, *J. Biophotonics* **2016**, *9*, 1222.
[43] S. S. Suzuki, A. S. Garcez, P. O. Reese, H. Suzuki, M. S. Ribeiro, W. Moon, *Lasers Med. Sci.* **2018**, *33*, 811.
[44] P. D'Andrea Fonseca, F. M. De Lima, D. T. Higashi, D. F. V. Koyama, D. De Oliveira Toginho Filho, D. IFL, et al., *Lasers Med. Sci.* **2013**, *28*(1), 49.
[45] N. Hamamcı, F. A. Kaya, E. Uysal, B. Yoku, *Eur J Orthod* **2012**, *34*, 357.

[46] B. B. Tuncer, N. Özmeriç, C. Tuncer, I. Teoman, B. Çakilci, A. Yücel, et al., *Angle Orthod.* **2005**, *75*, 631.
[47] G. Basaran, T. Özer, *Filiz Acun Kaya and OH. Interleukins 2, 6, and 8 Levels in Human Gingival Sulcus during Orthodontic Treatment. Am J Orthod Dentofacial Orthop.* **2006**, 130(1), 7. e1-6.
[48] Y. Ning, P. C. Manegold, Y. K. Hong, W. Zhang, A. Pohl, T. Winder, et al., *NIH Public Access.* **2012**, *128*, 2038.
[49] S. C. Núñez, G. E. C. Nogueira, M. S. Ribeiro, A. S. Garcez, JLL-M, *Lasers Surg Med* **2004**, *368*, 363.
[50] F. Colombo, A. Neto Ade, A. Sousa, A. Marchionni, A. Pinheiro, S. Reis, *Braz. Dent. J.* **2013**, *24*, 308.
[51] M. Soleimani, E. Abbasnia, M. Fathi, H. Sahraei, Y. Fathi, G. Kaka, *Lasers Med. Sci.* **2012**, *27*, 423.
[52] A. Z. N. Bergamo, P. Nelson-Filho, C. do Nascimento, C. RCV, M. Z. Casati, A. MCD, et al., *Arch. Oral Biol.* **2018**, *85*, 79.
[53] A. M. Varella, A. V. Revankar, A. K. Patil, *Am J Orthod Dentofac Orthop* **2018**, *154*, 535. https://doi.org/10.1016/j.ajodo.2018.01.012.
[54] A. Vujacic, A. Konic, J. Pavlovic, V. Todorovic, V. Vukicevic, D. Jevremovic, N. Milosevic-Jovcic, *Vojnosanit. Pregl.* **2017**, *74*, 219.
[55] G. Basaran, T. Ozer, F. Kaya, O. Hamamci, *Am. J. Orthod. Dentofacial Orthop.* **2006**, *130*(1), 7.e1.
[56] K. Kawasaki, N. Shimizu, *Lasers Surg. Med.* **2000**, *26*, 282.
[57] L. F. Hsu, M. H. Tsai, B. E. Chang, Y. J. Chen, C. C. J. Yao, *J Photochem Photobiol B Biol* **2018**, *186*, 41-50. https://doi.org/10.1016/j.jphotobiol.2018.05.011.

How to cite this article: Fernandes MRU, Suzuki SS, Suzuki H, Martinez EF, Garcez AS. Photobiomodulation increases intrusion tooth movement and modulates IL-6, IL-8 and IL-1β expression during orthodontically bone remodeling. *J. Biophotonics*. 2019;12:e201800311. https://doi.org/10.1002/jbio.201800311