Effect of low-level laser on the rate of tooth movement

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Low-level laser therapy (LLLT) has been introduced in orthodontic procedures with its initial purpose to alleviate the pain after adjustment of the appliances and to enhance healing of the sore spot caused by appliance impingement. Recent studies have shown that LLLT may increase the differentiation and proliferation of the cells associated with bone remodeling machinery and therefore affect the rate of orthodontic tooth movement. The effects of LLLT in regards to orthodontic tooth movement have been controversial. This article reviews the previous studies on the biological effects of LLLT on orthodontic tooth movement in animals and human subjects, and thereby aims to set the optimal protocol to accelerate tooth movement in orthodontic avenue. (Semin Orthod 2015; 21:210–218.) © *2015 Elsevier Inc. All rights reserved.*

Introduction

The biological cascades along with the conventional biomechanics allow tooth movement for less than 1 mm per month; therefore, the orthodontic treatment usually takes approximately 2–3 years. Most orthodontists have long yearned for shorter treatment period since the extended treatment duration may increase the risk of dental caries and/or root resorption. In addition, the actual treatment duration occasionally surpasses the estimated treatment period, leading to the attrition of patients' cooperation.

The orthodontic mechano-therapeutic systems presently in use apply mechanical force to the teeth in order to derive tooth movement by remodeling the periodontal tissues surrounding the teeth. Cellular and molecular studies on the biological mechanism of tooth movement conducted to date signify that mechanical force is not the only mean to stimulate such cellular reactions. Other stimuli such as osteotomy and corticotomy are among the first procedures suggested to increase the rate of tooth movement. Nonetheless, these procedures involve relatively invasive surgical interventions such as full thickness flap and extensive alveolar bone decortication.

Recently, wide diversity of clinical trials to accelerate orthodontic tooth movement by non-invasive approaches such as electromagnetic provisions, cytokine administration, or endocrine/paracrine regimens has been suggested. The low-level (energy) laser therapy (LLLT) has been suggested to accelerate turnover of periodontal tissue through its biostimulatory effect, which in turn is postulated to accelerate tooth movement. Low-level laser may also be known as low-power laser, soft laser, cold laser, biostimulation laser, therapeutic laser, and laser acupuncture.

The present article reviews the existing literature on the effects of LLLT at the cellular level and the experimental tooth movement in animal models to provide the basis for clinical applications on human subjects.

Biostimulatory effect of the low-level laser therapy (LLLT)

The laser has diverse mechanisms for application in the biomedical domain. It is primarily used for optical instruments such as fluoroscopy or high definition coherence tomography. Laser causes

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Table 1. Laser–tissue Interactions According to Intensity and Irradiation Time

		Intensity (W/cm^2)	Irradiation Time (s)
High-level laser therapy (HLLT)	Plasma-induced ablation	$10^{12} – 10^{14}$	$10^{-13} – 10^{-10}$
	Photomechanical interactions	$10^{12} – 10^{15}$	$10^{-12} – 10^{-9}$
	Photoablation	$10^{8} – 10^{11}$	$10^{-9} – 10^{-7}$
	Photothermal interactions	$10^{2} – 10^{7}$	$10^{-5} – 10^{0}$
LLLT	Photochemical and photobiostimulatory interactions	$10^{-3} – 10^{0}$	$10^{1} – 10^{3}$

receptive cells and tissues to initiate light-induced chemical reactions such as photobiostimulation or photobiomodulation. The interaction with target tissues converts light energy of the laser into heat energy (photothermal reaction), resulting in photoablation and consequent breakdown of the tissue. The high-power laser triggers photomechanical interaction which then gives rise to rupture of the tissue; therefore, high-level laser is used for photoablation, photothermal, and photomechanical interaction (Table 1). In contrast, the low-level laser is used for photochemical effects on the tissues. LLLT employs red and infrared light to promote wound healing process of soft tissues, as well as to reduce inflammatory response and associated pain by its photochemical effects on cells (Table 2).[1]

The cellular effect of LLLT

The cellular mechanism of LLLT

The main cellular effects of LLLT are dependent upon the absorption of wavelengths of red and infrared light that activates the electron respiratory chain in mitochondrial membranes. The photon of the laser is absorbed in cytochrome, generating single oxygen free radicals which increase its cellular energy by elevating ATP synthesis. These responses from nitric oxide (NO) leads to the alteration of cell activity by increasing cell membrane permeability to calcium and other ions.

Table 2. Physical Characteristics of the Low-level Laser Therapy (LLLT)

Light source	Visible (generally red) or near-infrared light generated from a laser or light emitting diode (LED) system
Wave length	600–1000 nm
Power	10–500 mW
Intensity (power density)	5–50 mW/cm^2 (for stimulation and healing)
Dose (energy density)	1–20 J/cm^2

Furthermore, this laser may also affect RNA and DNA synthesis and therefore have an effect on cell proliferation, release of the growth factors, an increase in collagen synthesis by fibroblast, change in nerve conduction, and release of the neurotransmitter.[2]

The effects of the LLLT particularly on osteoblasts, osteoclasts, and fibroblasts are more of interest in regards to orthodontic tooth movement (Table 3).

Osteoblast

Dörtbudak et al.[3] described the biostimulatory effect of LLLT on osteoblasts *in vitro* while reporting an increased bone matrix production by irradiation of a pulsed diode soft laser. While some studies demonstrated an increase in DNA replication and proliferation of the osteoblasts *in vitro* in response to LLLT stimulation,[4,5] others demonstrated temporarily triggered G2/M arrest on the cell cycle of the osteoblast and promoted osteoblast differentiation and osteogenesis.[6] Furthermore, Grassi et al.[7] reported that LLLT augmented the osteogenic potential of growth-induced cells and further stimulated the rate of growth and differentiation of the human osteoblast-like cells.

Osteoclast

Unlike the effects of LLLT on osteoblasts, its effects on osteoclasts are not clear. Aihara et al.[8] applied Ga–Al–As semiconductor laser on rat osteoclast precursor cells *in vitro*, and demonstrated that LLLT facilitated differentiation and activation of osteoclasts via RANK expression.

Macrophage colony-stimulating factor (M-CSF) is essential for osteoclastogenesis to stimulate not only osteoclast precursor cells but also mature osteoclasts. Yamaguchi et al.[9] presented that LLLT increased the velocity of tooth movement via

Table 3. Summary of the Studies on the Cellular Effects of LLLT *In Vitro*

No.	First Author (Publication Year)	Cell Culture	Laser Type	Wave Length	Power, Time	Dose (J/cm²)	Result
Osteoblast							
1	Dörtbudak[3] (2000)	Rat femora	Diode laser	690 nm	21 mW, 60 s	1.6	Increase cell growth
2	Yamamoto[4] (2001)	Mouse calvaria	Diode laser	830 nm	500 mW, 20 min	7.64	Increase DNA replication and gene expression
3	Fukuhara[6] (2006)	Rat calvaria	Diode laser	905 nm	150 s	1.25	Arrest G2/M of cell cycle
4	Pires Oliveira[5] (2008)	Mouse bone	Diode laser	830 nm	50 mW, 36 s	3	Increase mitochondrial activity
Osteoclast							
5	Aihara[8] (2006)	Rat bone	Diode laser	810 nm	50 mW 1 min 3 min 6 min 10 min	9.33 27.99 55.98 93.30	Stimulate osteoclast formation
6	Yamaguchi[9] (2007), Fujita[11] (2008)	Rat bone	Diode laser	810 nm	50 mW, 3 min	27.99	Increase M-CSF, c-fms expression
7	Xu[12] (2008)	Rat calvaria	Diode laser	650 nm	2 mW 1 min 5 min 10 min	0.23 1.14 2.28	Downregulate RANKL:OPG mRNA ratio
Fibroblast							
8	Soudry[13] (1998)	Human gingival fibroblasts	Helium–neon laser	632.8 nm	10 mW, 10 min	1.2	Growth acceleration Increase of cell division
9	Saygun[14] (2008)	Human gingival fibroblasts	Diode laser	685 nm	25 mW, 140 s 1 cm²	24	Increased the proliferation of human gingival fibroblasts and release of bFGF, IGF-1, and IGFBP3
10	Frozanfar[15] (2013)	Human gingival fibroblasts	Diode laser	810 nm	50 mW, 32 s 0.4 cm²	4	Increase in proliferation and collagen I gene expression

stimulating the expression of M-CSF and its receptor system (colony stimulating factor-1 receptor; c-fms) in the Wistar rats. The follow-up study[10] in the same specie asserted that the expression of MMP-9, cathepsin K, and integrin α (v)β3 increased with application of LLLT which may help to increase the rate of tooth movement. Fujita et al.[11] observed, as well, that LLLT *in vitro* promoted the differentiation and activation of osteoclasts due to increased c-fms gene expression and RANK/RANKL. However, Xu et al.[12] have shown that LLLT indirectly inhibited osteoclast differentiation by downregulating the RANKL: OPG mRNA ratio in osteoblasts and promoting proliferation and differentiation of osteoblasts, thus contributing to bone remodeling.

Fibroblast

It has been shown that LLLT *in vitro* increases the proliferation of human gingival fibroblast (HGF), and the expression of collagen type I, basic fibroblast growth factor (bFGF), insulin-like growth factor-1 (IGF-1), and receptor of IGF-1 (IGFBP3) in HGF.[13–15]

Animal studies of LLLT

There are various animal studies on the effects of LLLT on orthodontic tooth movement. Among these studies, nine studies were conducted in rats[9–11,16–21] and two studies in dogs.[22,23] The studies that did not offer data on the velocity of tooth movement with control and/or placebo group were excluded. The animal studies offer vast arrays of evidence on the effect of laser on orthodontic tooth movement (Table 4).

In 2000, Kawasaki and Shimizu[16] published the first investigation ever conducted to find the effect of LLLT on tooth movement in animals in 2000. They described the effect of LLLT on tooth movement by applying a mesial force of 10 g with a closed coil spring on the upper left first molar in rats. Ga–Al–As diode laser with a wavelength of

Table 4. Summary of the Studies on Effect of LLLT on the Tooth Movement in Animal Subjects

			Laser					Application			
No	*First Author (Publication Year)*	*Animal*	*Laser type*	*Wave Length*	*Power, Time*	*Dose (J/cm^2)*	*Total Energy (J)*	*Irradiation Interval*	*Applied Tooth*	*Force (g)*	*Result Velocity*
1	Kawasaki[16] (2000)	24 Rats 6 Weeks old	Diode laser	830 nm CW	100 mW, 3 min 0.0028 cm^2	6000/Point 18,000/Session 234,000/13 Days	18/Point 54/Session 702/13 Days	Once a day Total 13 days	Upper 1st molar (3 points)	10	Increase 1.3 fold
2	Yamaguchi[9] (2007)	50 Rats 6 Weeks old	Diode laser	810 nm CW	100 mW, 3 min 0.0028 cm^2	6000/Point 18,000/Session 144,000/8 Days	18/Point 54/session 432/8 Days	Once a day Total 8 days	Upper 1st molar (3 points)	10	Increase
3	Fujita[11] (2008)	75 Rats 6 Weeks old	Diode laser	810 nm CW	100 mW, 3 min 0.0028 cm^2	6000/Point 18,000/Session 144,000/8 Days	18/Point 54/Session 432/8 Days	Once a day Total 8 days	Upper 1st molar (3 points)	10	Increase
4	Yoshida[17] (2009)	60 Rats 6 Weeks old	Diode laser	810 nm CW	100 mW, 2.5 min 0.0028 cm^2	4500/Point 18,000/Session 162,000/9 Days	13.5/Point 54/Session 486/9 Days	Once a day for 7, 13, and 20 days	Upper 1st molar (4 points)	10	Increase
5	Gama[19] (2010)	30 Rats 12 Weeks old	Diode laser	790 nm CW	40 mW, 2.5min 0.03 cm^2	20/Session	0.6/Session	2 Day interval for total 19 days	Upper 1st molar (4 points, 3 intra, 1 extra)	40	No effect
6	Marquezan[20] (2010)	36 Rats 12 Weeks old	Diode laser	830 nm CW	100 mW, 3min 0.003 ncm^2	6000 Point 18,000/Session	18/Point 54/Session	Once a day Total 7 days	Upper 1st molar (4 points)	41	No effect
7	Yamaguchi[10] (2010)	50 Rats 6 Weeks old	Diode laser	810 nm CW	100 mW, 3 min 0.0028 cm^2	6000/Point 18,000/Session 144,000/8 Days	18/Point 54/Session 432/8Days	Once a day Total 8 days	Upper 1st molar (3 points)	10	Increase
8	Duan[21] (2012)	44 Rats 6 Weeks old	Diode laser	830 nm CW 830 nm PW	180 mW, 4 s 0.2 cm^2 90 mW, 8 s 0.2 cm^2	3.6/Point 10.8/Session 32.4/3 Days	18/Point 54/Session 162/3 Days	Days 0,1,2 Total 3 days	Upper 1st molar (3 points)	10	Increase
9	Altan[18] (2012)	38 Rats10 Weeks old	Diode laser	820 nm CW	100 mW, 30 s, 108 s 0.03 cm^2	343.9/Point 1717.2/Session 95.5/Point 477/Session	3/Point 15/Session 10.8/Point 54/Session	Days 0,1,2 Total 9 days	Upper incisors (5 points)	20	No effect
10	Goulart[23] (2006)	18 Dogs	Diode laser	780 nm CW	70 mW, 3 s 0.04 cm^2	5.25/Session 35/Session	0.21/Session 1.4/Session	Every 7 days Total 9 weeks	1st Molar (1 point)	85	Increase
11	Kim[22] (2009)	12 Dogs	Diode laser	808 nm PW	76.3 mW, 20 s 0.0013 cm^2	41.7/Point 333.6/Session	0.052/Point 0.42/Session	Every 3 days Total 8 weeks	Upper 2nd premolar (8 points)	150	Increase

830 nm at power of 100 mW was applied in the manner of continuous wave by placing the optical fiber tip in contact with the mesial, buccal, palatal side of the gingiva of the tooth for three minutes respectively (9 min in total, 35.3 W/cm^2) for 12 days. The irradiation protocol was based on previous studies that demonstrated osteogenic effects of the laser on rats after maxillary expansion[16] and during bone healing process in tooth extraction socket.[24] The study reported a 1.3-fold increase in tooth movement in the irradiation group, as well as a significant increase of bone formation on the tension side, and an increase in the number of osteoclasts on the pressure side.

Majority of studies[9,10,17–21] conducted afterwards were on rats within the age of 6–12 weeks. All of the studies targeted on the upper first molars, except for one study, which focused on maxillary incisors.[18] While 10 g of force is applied with closed coil springs in majority of these studies, a larger force of 20–41 g was applied on others.[18–20] In most cases, Ga–Al–As diode laser emitting a wavelength of 780–830 nm in the infrared light domain was commonly used.

Most of these studies conducted on animals[9–11,16–20] used continuous wave laser. A recent study by Duan et al.[21] in 2012 aimed to look at the differences in the rate of tooth movement when using the continuous wave laser compared to the pulsed wave laser. The study announced that there were no significant differences between both types of lasers. Both lasers led to faster tooth movement in comparison to the control group. Later on, the study conducted by Kim et al.[23] employed pulsed wave laser on beagle dogs which demonstrated an accelerated effect on the rate of tooth movement.

Unlike most studies[9–11,16,17,21] that demonstrate an accelerated speed of tooth movement in rats by laser irradiation, the investigations by Altan et al.,[18] Gama et al.,[19] and Marquezans et al.[20] announced that there were no significant differences in the rate of tooth movement against the control group. Two main differences in these investigations were the application of laser on older aged (70–120 days old) rats and application of heavier orthodontic forces. This demonstrated the possibility that response to laser irradiation could differ depending on the age and force.

The split-mouth double-blind study in dogs conducted by Goulart et al.[23] looked at the effect of laser on the speed of orthodontic movement in accordance with the dosage of irradiation (5.25 J/cm^2 and 35.0 J/cm^2 irradiation groups). The 5.25 J/cm^2 dosage group showed an accelerated orthodontic movement while the 35.0 J/cm^2 group retarded it. They hypothesized that the lower dosage has an anti-inflammatory effect while higher dosage retarded orthodontic movement as a result of intensifying repair process in the tissues. Such postulation signals that there is a possibility to control the rate of tooth movement by regulating the modality of laser treatment.

In our previous investigation[22] with beagle dogs, animals were exposed to surgically assisted stimulation (corticision) and/or LLLT. The results of this study demonstrated a 2.08-fold increase in the LLLT group associated with cellular activation (Figs. 1 and 2) when compared to a 2.23-fold increase in the rate of tooth movement in the group exposed to corticision. However, in the group where LLLT was combined with corticision, the movement was rather inhibited when compared with the control. We concluded that LLLT may predominantly activate healing process of surgical defect rather than facilitate tooth movement.

Clinical studies of LLLT

The results of the animal studies implied that the rate of tooth movement would be enhanced with a proper amount of energy whereas inhibitory effect appeared with overdose and the tooth movement would receive no effect from an insufficient amount of energy.[24,25] Table 5 illustrates the human studies that (1) used the suitable type and wavelength of laser for biostimulation, (2) suggested a clear LLLT application protocol, (3) presented a difference in tooth movement rate, and (4) met the conditions set forth for randomized controlled trial (RCT)/split-mouse design including control and/or placebo group.

Cruz et al.[26] carried out the first investigation to examine the effect of LLLT on orthodontic tooth movement in humans. Extraction of the upper first premolar was followed by retraction of the canine with 150 g of force in eleven patients of both genders from ages 12 to 18 years. It was a split-mouth study applying Ga–Al–As diode laser with a wavelength of 780 nm in a continuous wave form, and the irradiation totaled up to 2.0 J (5 J/cm^2, irradiated 10 times for 10 s). The study

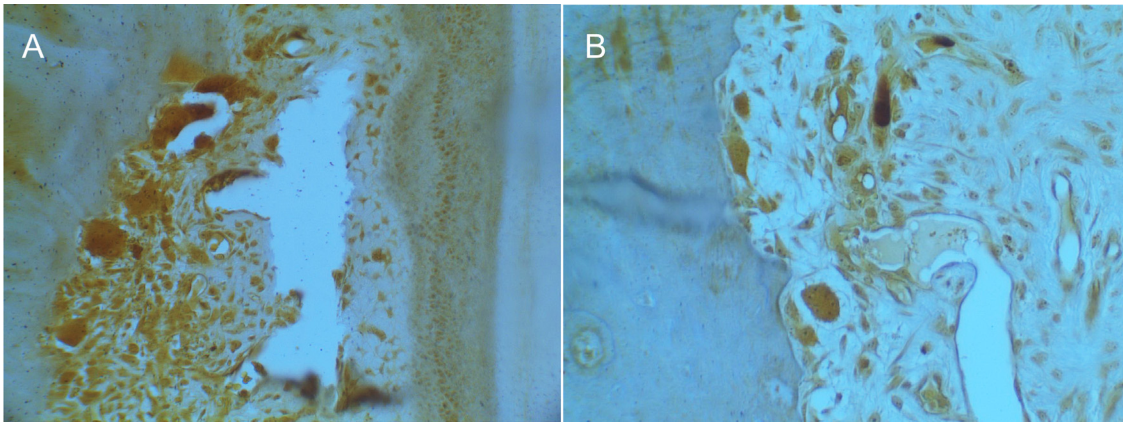

Figure 1. Effects of LLLT on multinucleated cells at 8th week in Beagle dogs [Tartrate resistant acid phosphatase (TRAP) staining, ×400]. (A) In the LLLT group, there is an increase in numbers of TRAP-positive multinucleated osteoclasts lining the resorbed alveolar bone surface on the compression side. (B) Control group. (Color version of figure is available online.)

was conducted in reference to the animal experiment by Luger et al.[27] which aimed to determine the optimum dose of laser, expecting 10 times of 5 J/cm^2 of laser irradiation to deliver a more uniform energy to tooth, rather than 60 J/cm^2 which is the dosage for healing a fractured tibia in rats. The study reported that the rate of tooth movement was accelerated by 34% in the experimental group.

More researches followed thereafter to examine the effect of laser on tooth movement on human subjects.[28–31] Most of the studies adopted Ga–Al–As diode laser emitting a wavelength of 780–810 nm of infrared light, and performed comparative measurements through split-mouth study with 150 g of retraction force on the canine after extracting of the upper first premolar. All the studies demonstrated that the application of laser accelerated the velocity of tooth movement; however, there appeared to be no significant difference between the laser and the control group in the study conducted by Limpanichkul et al.[28] The design of the study was identical to the study by Cruz et al.,[26] with the only difference of adopting 18.4 J (25 J/cm^2, eight times of irradiation for 23 s). The authors proclaimed that such a result sprung from insufficient laser dose to accelerate the tooth move-

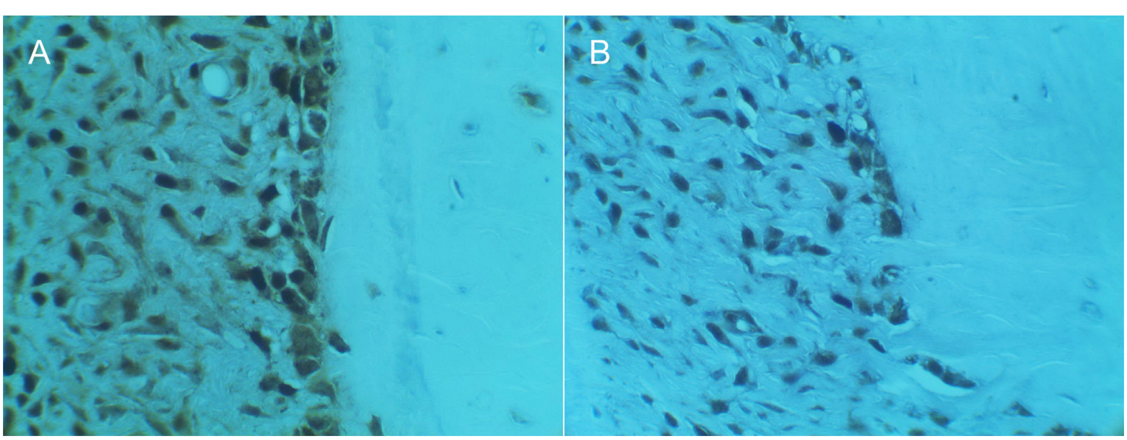

Figure 2. Effects of LLLT on PCNA-positive cells at 8th week in beagles [Proliferating cell nuclear antigen (PCNA) staining, ×400]. (A) In the LLLT group, there is an increase in numbers of hyperchromatic proliferative PCNA-positive cells on the tension side: osteoblasts lining the newly formed bone surface and fibroblasts in the periodontal ligament. (B) Control group. (Color version of figure is available online.)

Table 5. Summary of the Effect of LLLT on the Tooth Movement in Human Subjects

No	First Author (Publication Year)	N	Laser: Laser type	Laser: Wave length	Laser: Power, Time	Laser: Dose (J/cm^2)	Laser: Total Energy (J)	Application: Irradiation Interval	Application: Applied Tooth	Application: Force (g)	Result: Velocity
1	Cruz[26] (2004)	11	Diode laser	780 nm	20 mW, 10 s 0.04 cm^2	5/Point 50/Session	0.2/Point 2.0/Session	4 Days of each month	Canine	150	Increase 34% (2 mo)
2	Limpanichkul[28] (2006)	12	Diode laser	860 nm	100 mW, 23 s 0.09 cm^2	25/Point 200/Session	2.3/Point 18.4/Session	First 3 days of each month	Canine	150	No effect (3 mo)
3	Youssef[29] (2008)	15	Diode laser	809 nm	100 mW, 10/20/10 s	No information	8.0/Session	0,3,7,14 Days	Canine	150	2× Increase (6 mo)
4	Sousa[30] (2011)	13	Diode laser	780 nm	20 mW, 10 s 0.04 cm^2	5/Point 50/Session	0.2/Point 2.0/session	0,3,7 Days of each month	Canine	150	2× Increase (4 mo)
5	Genc[32] (2013)	20	Diode laser	808 nm	20 mW, 10 s 0.28 cm^2	0.71/Point 7.1/Session	0.2/Point 2.0/session	0,3,7,14,21,28 Days	Upper lateral incisors	80	20–40% Increase (1 mo)

ment. Upon considering the results of previous investigations, the "18.4 J" of energy that Limpanichkul et al.[28] applied was found to be higher than the "2.0–8.0 J" range of energy levels other studies had applied to demonstrate an enhanced tooth movement in human subjects.

In the study by Youssef et al.,[29] a double-fold increase in the rate of tooth movement was observed when 8.0 J Ga–Al–As diode laser was irradiated while reducing 70% of accompanying pain during tooth movement. Unlike the designs in other previous studies, Genc et al.[31] measured the velocity of orthodontic tooth movement and nitric oxide levels in the gingival crevicular fluid (GCF) when retracting the maxillary lateral incisor with 80 g of orthodontic force. This study applied 2.0 J (0.71 J/cm^2, 10 times of irradiation, for 10 s each) laser, and observed a 20–40% significant acceleration of orthodontic tooth movement. However, they reported no statistically significant changes in the nitric oxide level of GCF during orthodontic treatment.

Putting together the previous clinical studies, Ga–Al–As diode laser of 780–810 nm wavelength irradiation was found to accelerate the velocity of orthodontic tooth movement when a continuous wave of 5–20 J/cm^2, 2.0–8.0 J was applied by contacting the tip of the laser to the gingival surface (Fig. 3). The optimum dose of laser energy required to facilitate the tooth movement in human subject appeared to be different against the dose recommended in animal subjects.

Figure 3. Clinical application of low-level laser therapy around the target tooth to be moved. Four irradiation points at the labial surface, two points on the mesial and two points on the distal, and another four points at the lingual surface turned out to be effective in accelerating tooth movement. (Color version of figure is available online.)

Discussion

The effect of LLLT on accelerating tooth movement is still controversial in animal studies as well as in clinical trials for human subjects. Although a majority of the findings demonstrated positive effects in expediting tooth movement,[9–11,16,17,21–23,26,29–31] several other reports announced a zero effect or even an inhibitory effect.[18–20,28]

The effects of the laser poses variant results depending upon the wavelength, power, spectral area, dose, application frequency, and exposure time of the laser. The wavelength is presumably not the decisive factor of facilitating tooth movement amongst the physical configurations of the laser[32]; however, it is rather predominantly attributable to the total energy dose exposed to the subject.

The Arndt–Schulz rule is a claimed law concerning the effects of drugs or poisons in various concentrations. It states that for every substance small doses stimulate, moderate doses inhibit, and large doses kill. It is relevant to set up the optimal level of the laser dosage towards the therapeutic window, since an excessive dosage may inhibit the effect of tooth movement with insufficient amount leading to no effect. Both animal studies and clinical trials for human subjects which employ the laser approach may imply such a rule to be valid regarding the energy density and dose.

Several issues of LLLT usage still need to be resolved such as high cost laser equipment of which the burden could be imposed on patients, a long duration of time consumed while applying the laser leading to a lengthy chair time, and a requirement for trained human resources. It is imperative for further well conducted prospective clinical trials to determine a "gold standard" for clinical application of LLLT.

Conclusion

Understanding the characteristics and limitations of the biostimulation caused by LLLT would lead to broader clinical implications in orthodontics in addition to the control of tooth movement rate.

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