Photobiomodulation in Oral Surgery: A Review

Sepanta Hosseinpour, DDS, MPH, PhD Student,¹ Jan Tunér, DDS,²
and Reza Fekrazad, DDS, PhD, FLD, FICD^{3,4}

Abstract

Objective: This article presents a review of current data on the applications of photobiomodulation (PBM) in the field of oral and maxillofacial surgery (OMFS), to guide future research.

Background data: Photobiomodulation therapy (PBMT) has been reported to be effective for various post-operative conditions, including pain relief, improvement of mastication, neurosensory recovery, and wound healing. There is a need for identifying the therapeutic irradiation windows for these conditions, based upon the available literature.

Materials and methods: All original articles related to PBM for oral surgery in MEDLINE (NCBI PubMed and PMC), EMBASE, Scopus, Cochrane library, Web of Science, and Google Scholar were reviewed until December 2018.

Results: Forty-six clinical trials were included in this study. These trials were categorized into three different types of PBM applications. After reviewing all these studies, the most effective physical properties for PBM pain reduction after tooth extraction were as follows: wavelength 650–980 nm; power 4–300 mW; and energy density 3–85.7 J/cm². PBMT at 660–910 nm with 4–500 mW power and 2–480 J/cm² energy density was effective for decreasing facial swelling. At the same wavelength and power range with 4–106 J/cm² energy density, PBM was effective for alleviating trismus after tooth extraction.

Conclusions: Most papers suggested that PBM seemed to be effective in reducing pain, swelling, and trismus after third molar tooth extraction, neurosensory and nerve recovery after mandibular ramus osteotomy. The heterogeneity of the standardization regarding the parameters of laser calls for caution in interpretation of these results. However, this evidence-based review regarding the best protocols for OMFS applications can be beneficial for both future research and clinical applications.

Keywords: low-level laser therapy, photobiomodulation, oral and maxillofacial surgery, oral surgery

Introduction

AFTER THE ADVENT OF MEDICAL LASERS, numerous applications in many fields of medicine have been reported. Nowadays, low-powered lasers are viewed as an integral part of various therapeutic modalities.^{1–4} Therefore, it becomes pivotal to understand and know the mechanisms and rationale of photobiomodulation (PBM) to apply it more efficiently.

The use of PBM in oral and maxillofacial surgery (OMFS) has seen a substantial increase in various postoperative

purposes, including pain relief, improvement of mastication, neurosensory recovery, and wound healing.

Short time modulation of inflammation and acute pain relief with PBM have been demonstrated.^{5–8} PBM causes a biological impact by absorption of its photons by tissues and cellular structures.⁹ In addition, expected therapeutic impacts arise from this interaction. For instance, relief of acute pain, acceleration of the healing process, and muscle relaxation are all results from enhanced cellular energy and alterations in cellular membrane permeability. PBM favors

¹School of Dentistry, Oral Health Centre, The University of Queensland, Brisbane, Australia.

²Private Practice, Swedish Laser Medical Society (SLMS), Stockholm, Sweden.

³Radiation Sciences Research Center, Laser Research Center in Medical Sciences, AJA University of Medical Sciences, Tehran, Iran.

⁴International Network for Photo Medicine and Photo Dynamic Therapy (INPMPDT), Universal Scientific Education and Research Network (USERN), Tehran, Iran.

the hyperpolarized state, directly over primary nerve endings, inhibiting transmission of painful stimuli to the central nervous system.¹⁰ PBM also promotes rapid effects in reducing the level of pain and inflammatory mediators such as prostaglandin E2, interleukin 1 (IL1), tumor necrosis factor, and cyclooxygenase 2 (COX-2).^{11,12}

A number of studies have demonstrated that PBM has an impact on the management of pain and swelling.^{5,13–18} Ferrante reported that PBM is useful for pain reduction after impacted third molar surgery.¹⁹ In an animal study, it has been shown that PBM could reduce pain intensity, inflammation, and immunological reactions; while in human studies some factors including the type of disease, surgery, and laser-related variables influence the outcome of PBM.²⁰ A study by Sanz-Moliner et al.²¹ demonstrated that PBM can diminish pain and reduce swelling compared with a control group in patients with severe chronic periodontitis who underwent flap surgery. Several studies have reported an impact of PBM on postoperative complications, pain, neurosensory recovery, and wound healing. Due to the discrepancy between reported investigations, the current systematic review aims to comprehensively review all available documents on the current applications of PBM in the field of OMFS.

Materials and Methods

Protocol and eligibility criteria

This review is organized and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²²

Types of studies. All *clinical trials*, which administered PBM in oral and maxillofacial field as a therapeutic approach and reported the results of PBM with reasonable account of the used light parameters. *In vivo* and *in vitro* studies, systematic and literature reviews, letter to editors, and theses were omitted.

Types of participants. All types of animal models (such as rats and primates) and high-level laser therapy (such as carbon dioxide laser) were excluded and only clinical studies were included.

Types of interventions. Studies investigating PBM in the field of OMFS, including relief of acute/chronic pain, loss of movement, masticatory malfunction, trismus, wound healing, and other therapeutic goals, were included. Studies that did not primarily investigate therapeutic PBM in OMFS or related to the surgical procedures such as incision or removal of tissues were excluded.

Types of outcome measures. These included level of pain in extraction socket or related trigger points, mandibular mobility, patients' anxiety related to pain, neurosensory recovery, and masticatory muscle's tenderness reported by any of the following tests: visual analog scale (VAS), 3dMD face photogrammetric, edema scales, or 2-point discrimination test.

Information sources

MEDLINE (NCBI PubMed and PMC), EMBASE, Scopus, Cochrane library, Web of Science, and Google Scholar

were the information sources. Moreover, a hand search was performed specifically in the following journals; *Lasers in Medical Science*, *Journal of Photochemistry and Photobiology B*, *Photomedicine and Laser Surgery*, *Tissue Engineering: Part A*, *Lasers in Surgery and Medicine*, and *Journal of Dental Research*.

Search strategy

An electronic search was conducted in PubMed from January 1990 to December 2018, limited to English language publications. Published papers on PBM in oral surgery (pain control, edema, neurosensory recovery, etc.) were found using the following keywords alone or ensemble: ("Laser Therapy"[Mesh] OR "Low-Level light Therapy"[Mesh] OR "low-intensity laser therapy"[Mesh] OR "Laser Phototherapy"[Mesh] OR "Photobiomodulation Therapy"[Mesh] OR "Low-Level Laser Irradiation"[Mesh]) AND ("Surgery, Oral"[Mesh] OR "Oral surgical procedures"[Mesh] OR "osteotomy"[Mesh] OR "tooth extraction").

In addition, manual search of the articles in the selected journals was carried out.

Study selection and data extraction

Two independent experienced reviewers analyzed all retrieved articles based on their keywords, titles, and abstracts. After initial assessment, included studies were analyzed based on their full text and in the case of disagreement between two reviewers, a third expert person was involved to resolve it by discussing. All steps were performed based on the PRISMA statement.

Data items

Data were summarized as follows: (1) author and year of publication; (2) laser properties, including laser type, wavelength, power, and energy density; (3) therapeutic purposes; (4) sample size; (5) treatment protocol and location of laser application; (6) method of evaluation; (7) follow-up period; and (8) outcomes of study.

Results

Study selection

Fifty articles were retrieved from Medline and 67 articles from other databases, and one study from hand search (Fig. 1—PRISMA flow chart). A total of 118 articles were initially screened by two independent reviewers, and 40 studies were excluded due to duplication and unrelated keywords according to our study design. After exclusion of nonrelevant articles, the full texts of 78 studies were evaluated. Within these studies, 32 of them were excluded since they were review studies, case reports, or did not report laser properties. Finally, 46 studies were selected and analyzed in this systematic review. All these studies are summarized in Tables 1–3.

Therapeutic applications of PBM in OMFS; protocols and benefits

Pain, edema, and trismus

After tooth extraction. Thirty-three clinical trials were included according to the inclusion criteria, investigating the

FIG. 1. Study design flow chart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

impact of PBM on pain/swelling/trismus after tooth extraction (Table 1). In all these studies, the third molar was the extracted tooth except in one study conducted on premolar's extraction sockets.²³ PBM effectively reduced post extraction pain as shown in 16 studies^{5,6,13,15–19,24–31} compared with placebo. In these studies, wavelengths ranged from 650 to 980 nm. In addition, powers were between 4 and 300 mW, and energy densities were between 3 and 85.7 J/cm². The outcomes were evaluated by VAS, 3dMD face photogrammetric, maximum mouth opening, and facial distance measuring. PBM was applied both extraorally and/or intraorally. Nonsignificant impact of PBM on pain relief in comparison with placebo was observed in 10 articles.^{23,32–40} Eight of these latter studies applied ~810 nm diode lasers^{23,34–40} with various powers (30–500 mW) and energy densities (2–60 J/cm²).

Facial swelling was assessed in 24 clinical trials.^{5,13–19,24–26,28–31,33,34,37–43} Among these studies, 10 articles represented significant decrease in facial swelling after PBM application (wavelength: 660–910 nm; power: 4–500 mW; energy density: 2–480 J/cm²) compared with placebo.^{13–19,31,41–43}

Twenty studies assessed the impact of PBM on postoperative trismus.^{5,13,14,16,17,19,24–26,28–31,33,34,37–39,42,43} The wavelengths between 660 and 980 nm with power between 4 and 300 mW and 4–106 J/cm² energy density were reported as significant in reducing postoperative trismus in comparison with placebo.^{13,14,16,19,31,42,43} In general, extraoral irradiation offered better results, especially for edema.

After orthognathic and minor oral surgeries. One clinical trial investigated pain and swelling after orthognathic surgery,⁴⁴ and another one on secondary palatal operation.⁴⁵ One article reported the impact of PBM on mouth opening after orthognathic surgery and surgically assisted rapid maxillary expansion (SARME).⁴⁶ In total, 112 patients participated in these studies. The wavelengths ranged between 660 and 985 nm with 20–2000 mW power and 5–100 J/cm² energy density. The outcomes were evaluated by distance measurements and VAS. PBM in all studies was significantly

effective compared with placebo. In addition, PBM in orthognathic cases was more effective than SARME cases for enhancing maximum mouth opening after 21 days.⁴⁶

Neurosensory recovery. Neurosensory recovery was assessed in nine studies; six studies after mandibular ramus osteotomy,^{47–52} and three of them after various oral surgeries^{53–55} (Table 2). Six studies represented a wide range of effective PBM parameters for nerve recovery after mandibular ramus osteotomy (wavelength: 632–830 nm; power: 20–100 mW; energy density: 2–32 J/cm²).^{47–52} In addition, three other studies showed positive impact of PBM on inferior alveolar nerve (IAN) paresthesia after various oral surgeries such as orthognathic surgery.^{53–55} de Oliveira et al.,⁵⁴ in a 3-year retrospective study, reported that gallium, aluminum, arsenide (GaAlAs) diode 808 nm at 100 mW and 100 J/cm² was more effective than placebo in treating IAN paresthesia.

Other applications. In five articles, investigators used PBM after oral surgical procedures^{23,56–59} for applications other than those previously mentioned (Table 3). In three studies, GaAlAs diodes were used,^{23,56,57} in one study a gallium arsenide diode⁵⁹ and in one (60 Monea) a red light-emitting diode (LED) was used. The wavelengths ranged from 620 to 904 nm with 100–270 mW power and 46–180 J/cm² energy density. In total, 299 patients had participated in these studies. Saliva immunoglobulin A (IgA) and lysosome level, neovascularization, bone and wound healing, and the level of inflammatory and osteogenic markers were analyzed by radial immunodiffusion method, immunohistochemistry, VAS, real-time polymerase chain reaction, and radiographic evaluations. All studies found PBM as an effective treatment modality in comparison with placebo, except in the study of Paschoal and Santos-Pinto.²³ These authors applied 830 nm diode laser for wound healing and pain relief after premolar tooth extractions, and indicated nonsignificant impact of PBM after 15 days.

TABLE 1. PHYSICAL CHARACTERISTICS, STUDY DESIGN, AND MAIN OUTCOMES OF PHOTOBIO-MODULATION ON POSTOPERATIVE ORAL SURGICAL PROCEDURES' COMPLICATIONS (PAIN, EDEMA, AND TRISMUS) IN INCLUDED CLINICAL TRIALS

Application of PBM after tooth extraction										
Laser properties										
Studies	Type	Wavelength (nm)	Power (mW)	Energy density (J/cm ²)	Therapeutic purpose	Sample size (n)	Location and treatment protocol	Method of evaluation	Follow-up period	Authors' conclusion
Asutay et al. ⁵	GaAlAs diode	810	300	4	Pain, trismus, swelling	45	Extraoral, IPMM, NM.	VAS, MO, 3dMD face photogrammetric	7 Days	PBM vs. placebo ↓ pain, NS FS NS trismus
Koparal et al. ²⁴	GaAlAs diode	810	300	4	Pain, swelling, trismus	45	Extraoral, IPMM, immediately after extraction, and day 2.	VAS, MO, 3dMD face photogrammetric	7 Days	PBM vs. placebo ↓ pain, NS FS NS trismus
Tuk et al. ³²	InGaAIP diode laser	660	198	67.5	Pain during local anesthetic injection	163	Maxillary third molar extractions: the posterior superior alveolar nerve, and injection points. Mandibular third molar extractions: the buccal nerve, and injection points. Immediately before extraction.	Heart rate, sweat response, questionnaire	0	PBM vs. placebo NS trismus PBM vs. placebo NS pain
Ratesian et al. ²⁵	GaAlAs diode	980	300	18	Pain, swelling, trismus	44	Intraoral on two points of vestibular and lingual of surgery site, and extraoral IPMM, immediately after extraction and day 1.	VAS, FDM, MO	1 Week	PBM vs. drug therapy ↓ pain, NS FS NS trismus
Petrini et al. ²⁶	GaAlAs diode	980	300	NM	Pain, swelling, trismus	45	Extraoral IPMM, intraoral lingual and buccal sides, immediately after extraction and day 1.	VAS, FDM, MO	7 Days	PBM vs. drug therapy ↓ pain, NS FS NS trismus
Kahraman et al. ²⁷	GaAlAs diode	830	100	3	Pain	60	Intraoral and extraoral IPMM, immediately before and after extraction.	VAS	1 Week	Intraoral PBM vs. extraoral PBM ↓ pain
Hamid ⁶	GaAlAs diode	810	100	32.86	Pain	30	Intraoral at three points occlusal, buccal, and lingual, immediately after extraction.	VAS	7 Days	PBM vs. placebo ↓ pain
Farhadi et al. ³³	NM	550	100	5	Pain, swelling, trismus	24	Extraoral, IPMM, immediately after extraction.	VAS, FDM, MO	7 Days	PBM vs. placebo NS pain, NS FS NS trismus
Alan et al. ²⁸	GaAlAs diode	810	300	4	Pain, swelling, trismus	15	Extraoral, IPMM, immediately after extraction and day 2.	VAS, MO, 3dMD face photogrammetric	7 Days	PBM vs. placebo ↓ pain, NS FS NS trismus
Eroglu et al. ²⁹	NM	940	NM	4	Pain, swelling, trismus	35	Extraoral, IPMM, Immediately after extraction.	VAS, FDM, MO	7 Days	PBM vs. placebo ↓ pain, NS FS NS trismus
Eshghpour et al. ³⁰	InGaAIP diode	660	200	85.7	Pain, swelling	40	Angle of the mandible, and the lower border of the mandible. Immediately, 2, 4 days after extraction.	VAS, edema coefficient equation	7 Days	PBM vs. placebo ↓ pain, NS FS NS trismus

(continued)

TABLE 1. (CONTINUED)

Application of PBM after tooth extraction						
Studies	Laser properties			Therapeutic purpose	Sample size (n)	Location and treatment protocol
	Type	Wavelength (nm)	Power (mW)	Energy density (J/cm^2)		
Landucci et al. ¹³	GaAlAs diode	780	10	7.5	90	Six points intraoral to the socket, six points extraoral on IPMM, and masseter muscle, immediately after extraction.
Pedreira et al. ³⁴	GaAlAs diode	808	NM	2	24	Six points intraoral to the socket, six points extraoral on IPMM, and masseter muscle. Immediately after extraction and every day for 7 days.
Sierra et al. ¹⁴	InGaAlP/GaAlAs diode	660, 808	100	106	60	Four points intraoral to the socket, four points extraoral on IPMM, and masseter muscle. Immediately after extraction.
Pol et al. ⁵³	InGaAlP/GaAs diode	904, 650	8–500, 70	NM	25	Directly to the socket. Immediately after extraction, and on days 1 and 2.
Elbay et al. ³⁵	GaAlAs diode	810	300	4	37	Three points intraoral to the socket. Immediately after extraction.
Abdel-Alim et al. ¹⁶	GaAlAs diode	830	4	NM	80	Extraoral IPMM. Immediately after extraction, and on days 2–4.
Fabre et al. ¹⁷	InGaAlP diode	660	35	5	10	Four points intraoral to the socket. Immediately after extraction and on days 1–4.
Merigo et al. ¹⁸	InGaAlP/GaAs diode	650, 910	NM	480, 31	59	Intraoral and extraoral. Two hours after extraction.
Sierra et al. ³⁶	NM	660, 808	100	106	60	Four points intraoral to the socket, four points extraoral on IPMM, and masseter muscle. Immediately after extraction.
Kazancioglu et al. ³¹	GaAlAs diode	808	100	4	60	Extraoral IPMM. Immediately after extraction and on days 1, 3, and 7.
Ferrante et al. ¹⁹	NM	980	300	NM	15	Two points intraoral to the socket, extraoral IPMM. Immediately after extraction and on day 1.

(continued)

TABLE 1. (CONTINUED)

<i>Studies</i>	<i>Laser properties</i>				<i>Therapeutic purpose</i>	<i>Sample size (n)</i>	<i>Location and treatment protocol</i>	<i>Method of evaluation</i>	<i>Follow-up period</i>	<i>Authors' conclusion</i>
	<i>Type</i>	<i>Wavelength (nm)</i>	<i>Power (mW)</i>	<i>Energy density (J/cm²)</i>						
López-Ramírez et al. ³⁷	GaAlAs diode	810	500	5	Pain, swelling, trismus	20	Directly to the socket. Immediately after extraction.	VAS, FDM, MO	7 Days	PBM vs. placebo NS pain, NS FS NS trismus
Paschoal and Santos-Pinto ²³	GaAlAs diode	830	100	60	Wound healing and pain	14	Three points intraoral to the socket. Immediately after extraction and on days 1–3.	Visual inspection of photographs, VAS	15 Days	PBM vs. placebo NS pain, NS healing
Amarillas-Escobar et al. ³⁸	NM	810	100	4	Pain, swelling, trismus	30	One point intraoral to the socket, six points extraoral. Immediately after extraction and on days 1–3.	VAS, FDM, MO	7 Days	PBM vs. placebo NS pain, NS FS NS trismus
Aras and Güngörmüş ⁴³	GaAlAs diode	808	100	4	Swelling, trismus	48	Intraoral to the socket, extraoral IPMM. Immediately after extraction.	Amin and Laskin method for FS, MO	7 Days	Extraoral PBM vs. intraoral PBM ↓ FS (extraoral) ↓ trismus (extraoral)
Aras and Güngörmüş ⁴²	GaAlAs diode	808	100	4	Swelling, trismus	32	Extraoral IPMM. Immediately after extraction.	Amin and Laskin method for FS, MO	7 Days	PBM vs. placebo ↓ FS ↓ trismus
Markovic and Todorovic ⁴¹	GaAlAs diode	637	50	4	Swelling	120	Directly to the socket. Immediately after extraction.	FDM	1 Day	PBM vs. placebo ↓ FS (synergistic effect with dexamethasone)
Roynedal et al. ³⁹	NM	830	40	NM	Pain, swelling, trismus	25	One dosage, NM.	VAS, custom-made instrument for FS, MO	7 Days	PBM vs. placebo NS pain, NS FS NS trismus
Fernando et al. ⁴⁰	NM	830	30	NM	Pain, swelling	64	Directly to the socket. Immediately after extraction.	VAS, swelling scale	7 Days	PBM vs. placebo NS pain, NS FS

de Rezende et al. ⁴⁶	GaAlAs diode	780	100	100	Mouth opening after orthognathic and SARME surgery	82	Eight points overlying the masseter muscle, two preauricular points, two over the jugulodigastric lymph nodes, and two over the submandibular lymph nodes, immediately after surgery and every 24 h for 3 days.	MO	21 Days	PBM application in orthognathic vs. SARME surgery ↑ MO (orthognathic surgery)
Ezzat et al. ⁴⁵	GaAlAs diode laser	980	2000	35	Pain, swelling in secondary palatal operation	20	Surgical site. Immediately after surgery.	VAS, edema scale	7 Days	PBM vs. placebo ↓ pain, ↓ FS
Gasperini et al. ⁴⁴	InGaAlP/GaAlAs	660, 780	20, 70	5, 70	Pain, swelling after orthognathic surgery	10	Eight points in the mandibular ramus and body. Immediately after surgery and on days 1–3.	VAS, Carrillo's formula for swelling	30 Days	Combined PBM vs. placebo ↓ pain, ↓ FS

FDM, facial distance measuring; FS, facial swelling; GaAlAs, gallium, aluminum, arsenide; GaAs, gallium arsenide; GO-CA, Gonion-Contos; GO-PO, Gonion-Pogonion; GO-SN, Gonion-Subanal; InGaAlP, indium, gallium, aluminum, phosphide diode laser; IPMM, insertion point of the masseter muscle; MO, maximum mouth opening; NM, not mentioned; NRS, numerical rating scale; NS, not significant; OHIP-14, oral health impact profile; PBM, photobiomodulation; PRS, pain rating scale; SARME, surgically assisted rapid maxillary expansion; TR-GO, Tragus-Gonion; VAS, visual analog scale.

TABLE 2. PHYSICAL CHARACTERISTICS, STUDY DESIGN, AND MAIN OUTCOMES OF PHOTOBIMODULATION ON NEUROSENSORY RECOVERY AFTER ORAL SURGICAL PROCEDURES IN INCLUDED CLINICAL TRIALS

Application of PBM after third molar extraction									
Studies	Laser properties			Therapeutic purpose	Sample size (n)	Location and treatment protocol	Method of evaluation	Follow-up period	Authors' conclusion
	Type	Wavelength (nm)	Power (mW)						
Application of PBM in inferior alveolar nerve paresthesia due to various oral surgeries Pol et al. ⁵³ de Oliveira et al. ⁵⁴ Przeres et al. ⁵⁵	GaAs diode	904	200	Recovery of the inferior alveolar nerve	57	Once a week, 10 sessions, extraoral.	2PDT, thermal test, VAS	6 Months	PBM vs. placebo Effective
	GaAlAs diode	808	100	Neurosensory recovery	125	One to two times a week, 10 sessions, intra- and extraoral.	Recovery of sensitivity in the affected nerve area	3 Years retrospective study	PBM vs. placebo Effective
	GaAlAs diode	830	50	Recovery of paresthesia after orthognathic surgery	6	Two times a week, 12 sessions, extraoral.	Mechanical (deep and shallow) and thermal (cold) sensitivity	6 Weeks	PBM vs. placebo Effective
Application of PBM after mandibular ramus osteotomy Guarini et al. ⁴⁷	GaAlAs diode	810	100	Neurosensory recovery	42	Eight sessions, intraoral, 1, 2, 3, 5, 10, 14, 21, and 28 days after surgery.	2PDT, VAS	2 Years	PBM vs. placebo Effective
Mohajerani et al. ⁴⁸	GaAlAs and HeNe	810, 632.8	NM	Neurosensory recovery	20	Six sessions, intra- and extraoral, 1, 3, 7, 14, 60, and 180 days after surgery.	BSDT, 2PDT, VAS	180 Days	PBM vs. placebo Effective
Gasperini et al. ⁴⁹	InGaAlP/GaAlAs diode	660, 789	20, 60	Neurosensory recovery	10	NM, extraoral, 24, 48, 72 h and every 2 days.	2PDT, thermal discrimination	60 Days	PBM vs. placebo Effective
Führer-Valdivia et al. ⁵⁰	GaAlAs diode	810	100	Neurosensory recovery	17	Three times a week, 10 sessions, intra- and extraoral.	VAS, 2PDT, thermal discrimination	6 Months	PBM vs. placebo Effective
Miloro and Repasky ⁵¹	GaAlAs diode	810	70	Neurosensory recovery	6	Five sessions, intra- and extraoral, 6 and 24 h and 2, 3, 4, and 7 days postoperative.	BSDT, 2PDT, VAS	28 Days	PBM vs. placebo Effective
Khullar et al. ⁵²	GaAlAs diode	820	70	Neurosensory recovery	13	Twenty sessions, extraoral.	VAS, Semmes-Weinstein monofilaments, termotester	20–63 Days	PBM vs. placebo Effective

2PDT, 2-point discrimination test; BSDT, brush stroke directional discrimination test; HeNe, Helium-Neon.

TABLE 3. PHYSICAL CHARACTERISTICS, STUDY DESIGN, AND MAIN OUTCOMES OF PHOTOBIO-MODULATION ON VARIOUS THERAPEUTIC PURPOSES AFTER ORAL SURGICAL PROCEDURES IN INCLUDED CLINICAL TRIALS

Studies	Laser properties				Therapeutic purpose	Sample size (n)	Location and treatment protocol	Method of evaluation	Follow-up period	Authors' conclusion
	Type	Wavelength (nm)	Power (mW)	Energy density (J/cm^2)						
Dostalova et al. ⁵⁶	GaAlAs diode	830	270	46	Saliva sIgA and lysozyme level	213	Extraction socket, immediately after extraction, and on day 3.	Radial immunodiffusion method	3 Days	PBM vs. placebo Effective
Halon et al. ⁵⁷	GaAlAs diode	820	200	6	Postextraction neovascularization in HIV ⁺ patients	27	Extraction socket, immediately after extraction, and on day 5.	CD34 immunohistochemistry	6 Days	PBM vs. placebo Effective
Monea et al. ⁵⁸	LED	620	NM	NM	Bone healing in extraction socket	35	Extraoral, once a day for 21 days.	Radiographic evaluation	120 Days	PBM vs. placebo Effective
Paschoal and Santos-Pinto ²³	GaAlAs diode	830	100	60	Wound healing and pain	14	Extraction socket, immediately after extraction, and on days 1–3.	Visual inspection of photographs, VAS	15 Days	PBM vs. placebo NS pain, NS healing
Mozzati et al. ⁵⁹	GaAs diode	904	200	180	The level of inflammatory and osteogenic markers	10	Extraction socket, immediately after extraction, and on days 3 and 5.	RT-PCR	7 Days	PBM vs. placebo Effective

LED, light-emitting diode; RT-PCR, real-time polymerase chain reaction; sIgA, salivary level of immunoglobulin A.

Discussion

Pain, edema, and trismus

In this systematic review including 33 studies, PBM was used for the treatment of postoperative major complications such as pain, edema, and trismus in various oral surgeries such as tooth extraction, maxillary expansion, and orthognathic surgeries. The review revealed that most of these studies (18 of 30 articles assessing pain) demonstrated a positive impact of PBM on pain, especially during the first days; whereas some investigations reported nonsignificant results. In addition, it was concluded that PBM seems to be effective in enhancing maximum mouth opening by 4–5 mm 7 days after surgery. However, performing an evidence-based decision based on these studies is difficult due to their study design heterogeneity and contradictory findings. For example, Amarillas-Escobar et al.³⁸ reported no significant differences in the level of pain, facial swelling, and trismus between irradiated and placebo groups (810 nm; 100 mW; 4 J/cm²). On the contrary, in a similar study (808 nm; 100 mW; 4 J/cm²), Kazancioglu et al.³¹ demonstrated a significant reduction in all three variables, not only in comparison with the placebo group but also compared with ozone therapy after 7 days. In addition, Aras and Güngörmüş, in two separate studies in 2010⁴³ and 2009,⁴² observed that PBM (808 nm; 100 mW; 4 J/cm²) significantly reduced pain and trismus, especially after extraoral applications. In contrast, López-Ramírez et al.³⁷ revealed that 810 nm diode laser with 5 J/cm² energy density had no beneficial impact on facial swelling, trismus, and pain.

Farhadi et al.³³ reported that 550 nm PBM adjuvant treatment is not clinically helpful for decreasing pain, swelling, and trismus. The authors concluded that administration of analgesics and antibiotics may play the most imperative role and camouflage the impact of PBM in these cases. Further, the low penetration rate of 550 nm might be considered. In similarity to this study, other investigations reported no evidence of difference between PBM and placebo groups.^{23,32–40} In these negative studies, various medications have been prescribed. For instance, López-Ramírez et al.³⁷ recommended 750 mg amoxicillin (every 8 h for 7 days) and ibuprofen (every 8 h for 2 days). Moreover, patients in the study by Amarillas-Escobar et al.³⁸ received amoxicillin (750 mg), acetaminophen (500 mg), and ketorolac (30 mg for severe pain).

In contrast to these results, other investigations stated a significant impact. Eshghpour et al.³⁰ designed a split-mouth randomized controlled trial, conducted on 40 patients with similar bilateral impacted mandibular third molars. In the laser-treated side, patients received 660 nm (200 mW) intraoral and 810 nm (200 mW) extraoral irradiation. All patients were advised to receive amoxicillin (500 mg) and ibuprofen (400 mg). Their findings represented significantly lower pain and swelling after 7 days. In addition, all these disagreements observed between various findings in clinical trials could be attributed to the various administrated wavelengths, powers, energy densities, and location of irradiation (intraoral vs. extraoral). Moreover, received medications before or after oral surgical procedures may play a significant role in the outcomes of the trials.

Neurosensory recovery

Nine clinical trials were included in this section, all of them reporting PBM as an effective therapeutic approach for

neurosensory recovery. Some oral and maxillofacial surgical procedures can cause injuries to various nerve tracts, especially the IAN.^{60–62} Bilateral sagittal split osteotomy (BSSO) in mandibular ramus is one of the most critical procedures for IAN injuries.^{52,63,64} Mohajerani et al.⁴⁸ and Guarini et al.⁴⁷ demonstrated that 810 nm diode laser can effectively enhance neurosensory functions after 6 months and 2 years. Gasperini et al.⁴⁹ revealed the effectiveness of PBM after BSSO, accelerating the recovery period on the irradiated side. This study reports an 86% improvement in VAS scores and a 96% improvement in brush stroke at 2 months postoperatively. Moreover, the present systematic review found three articles,^{53–55} which demonstrated the effectiveness of PBM during or shortly after oral and maxillofacial surgical procedure in reducing pain and enhancing neural function in paresthesia. The investigation by Pol et al.⁵³ showed that the sensitivity of the lower lip and chin in all patients to the laser-treated side as well as to the placebo side was improved. However, the recovery on the laser-treated side was faster. This suggests an accelerating impact of PBM on the neural healing process. These findings were in agreement with de Oliveira et al.⁵⁴ and Prazeres et al.⁵⁵ Although promising, the actual effect of PBM administration is difficult to determine due to the multifactorial essence of PBM.

Other applications

This analysis found that the application of PBM was not limited to postoperative pain, edema, and neurosensory injuries. In fact, five clinical studies were included in this systematic review,^{24,56–59} evaluating other potential impacts of PBM after oral and maxillofacial surgeries. Dostalova et al.⁵⁶ observed that PBM application after tooth extraction has an immunological impact. The investigators reported that there is a positive relationship between salivary level of IgA and lysozyme after 830 nm laser irradiation performed directly to the extracted tooth socket. IgA is an antibody that plays an important role in mucosal immunity. In addition, lysozyme is responsible for anti-Gram-positive bacterial resistance. These findings confirmed a positive immunological impact of PBM, which can support the healing process.

In a study by Halon et al.,⁵⁷ 820 nm PBM application in HIV-positive patients showed significant enhancement in neovascularization. The authors concluded that the positive effect of PBM is not dependent on CD4⁺ lymphocytes. Monea et al.⁵⁸ also showed that 620 nm LED extraoral PBM application for 21 days can effectively improve bone healing after 60 days. Bone extraction samples before the placement of implant demonstrated a promotion and maturation of osteoblasts.

Collagen fibers as an important part of bone formation matrix are increased after PBM administration. In agreement with this clinical finding, Posten et al.⁶⁵ demonstrated that PBM can induce proliferation of human gingival fibroblasts and expression of collagen type I gene *in vitro*.

Several signaling pathways participate in bone formation as a complicated process.^{66,67} PBM can effectively alter RUNX-2 expression.^{68–73} Moreover, it increases the electrons' availability in the catalytic center of COX. Previous studies measured expression of COX-2 by IHC analysis^{72,74,75} and found higher expression of COX-2, especially

first days after surgery.^{74,75} It has been suggested that expression of COX-2 can be beneficial for bone healing. In early stage of bone formation, COX-2 is associated with the maturation of osteoblasts and modulating differentiation genes.^{76–78} In this regard, Mozzati et al.⁵⁹ investigated PBM impacts on IL-1b, IL-6, IL-10, and COX-2 in a split-mouth designed study on 10 healthy individuals after similar tooth extractions. The investigators demonstrated that 904 nm diode laser with 200 mW power and 180.5 J/cm² energy density can significantly impede the expression of inflammatory markers.

Consensus conclusions and future direction

In the included studies, the physical properties of the most effective PBM parameters for pain reduction after tooth extraction were as follows: wavelength, 650–980 nm; power, 4–300 mW; and energy density, 3–85.7 J/cm². PBM application at 660–910 nm with 4–500 mW power and 2–480 J/cm² energy density was effective for decreasing facial swelling; and at the same wavelength and power range with 4–106 J/cm² energy density it was effective for alleviating trismus after tooth extraction. We identified several wavelengths ~800 nm, ±30 nm. It is unclear if these are physically verified by the investigators, or due to diode quality variations. Nor have we been able to verify a biological difference of a specific wavelength in this narrow spectrum. In addition, PBM has been applied successfully for nerve recovery after mandibular ramus osteotomy (wavelength: 632–830 nm; power: 20–100 mW; energy density: 2–32 J/cm²). The use of PBM can prove to be an effective tool in the management of a wide variety of conditions with greater efficiency than is currently possible. The great variation in light parameters seen in positive as well as negative studies urges future researchers to look for the optimal application when it comes to parameters such as dose, energy, time of illumination, and number of sessions. Due to the heterogeneity of the studies and parameters, we were not able to perform a quantitative analysis of the data.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

There was no funding provided for this article.

References

- Madhumathi D, Kumar M. Low-level laser therapy in oral and maxillofacial surgery—A review. *Drug Invention Today* 2018;10:685–691.
- Xu G-Z, Jia J, Jin L, Li J-H, Wang Z-Y, Cao D-Y. Low-level laser therapy for temporomandibular disorders: a systematic review with meta-analysis. *Pain Res Manag* 2018;2018:4230583.
- Moskvin VS, Apolikhin IO. Effectiveness of low level laser therapy for treating male infertility. *Biomedicine* 2018;8:e108.
- Zokaee H, Zahmati AHA, Mojrian N, Boostani A, Vaghari M. Efficacy of low-level laser therapy on orofacial pain: a literature review. *Adv Hum Biol* 2018;8:70.
- Asutay F, Ozcan-Kucuk A, Alan H, Koparal M. Three-dimensional evaluation of the effect of low-level laser therapy on facial swelling after lower third molar surgery: a randomized, placebo controlled study. *Nigerian J Clin Pract* 2018;21:1107–1113.
- Hamid MA. Low-level laser therapy on postoperative pain after mandibular third molar surgery. *Ann Maxillofac Surg* 2017;7:207–216.
- Dawdy J, Halladay J, Carrasco-Labra A, Araya I, Yanine N, Brignardello-Petersen R. Efficacy of adjuvant laser therapy in reducing postsurgical complications after the removal of impacted mandibular third molars: a systematic review update and meta-analysis. *J Amer Dent Ass* 2017;148:887.e884–902.e884.
- Balevi B. Efficacy of adjuvant laser therapy in reducing postsurgical complications after the removal of impacted mandibular third molars: a systematic review update and meta-analysis. *J Evid Based Dent Pract* 2018;18:162–164.
- Farivar S, Malekshahabi T, Shiari R. Biological effects of low level laser therapy. *J Lasers Med Sci* 2014;5:58–62.
- Carroll JD, Milward MR, Cooper PR, Hadis M, Palin WM. Developments in low level light therapy (LLLT) for dentistry. *Dent Mater* 2014;30:465–475.
- Bjorndal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RAB. Low-level laser therapy in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. *Photomed Laser Surg* 2006;24:158–168.
- Hosseinpour S, Fekrazad R, Arany PR, Ye Q. Molecular impacts of photobiomodulation on bone regeneration: a systematic review. *Prog Biophys Mol Biol* 2019; Apr 17. [Epub ahead of print]; DOI:10.1016/j.pbiomolbio.2019.04.005.
- Landucci A, Wosny A, Uetanabaro L, Moro A, Araujo M. Efficacy of a single dose of low-level laser therapy in reducing pain, swelling, and trismus following third molar extraction surgery. *Int J Oral Maxillofac Surg* 2016;45:392–398.
- Sierra SO, Deana AM, Bussadori SK, et al. Choosing between intraoral or extraoral, red or infrared laser irradiation after impacted third molar extraction. *Lasers Surg Med* 2016;48:511–518.
- Pol R, Ruggiero T, Gallesio G, et al. Efficacy of anti-inflammatory and analgesic of superpulsed low level laser therapy after impacted mandibular third molars extractions. *J Craniofac Surg* 2016;27:685–690.
- Abdel-Alim HM, Abdel-Dayem H, Mustafa ZA, Bayoumi A, Jan A, Jadu F. A comparative study of the effectiveness of immediate versus delayed photobiomodulation therapy in reducing the severity of postoperative inflammatory complications. *Photomed Laser Surg* 2015;33:447–451.
- Fabre HS, Navarro RL, Oltramari-Navarro PV, et al. Anti-inflammatory and analgesic effects of low-level laser therapy on the postoperative healing process. *J Phys Ther Sci* 2015;27:1645–1648.
- Merigo E, Vescovi P, Margalit M, et al. Efficacy of LLLT in swelling and pain control after the extraction of lower impacted third molars. *Laser Ther* 2015;24:39–46.
- Ferrante M, Petrini M, Trentini P, Perfetti G, Spoto G. Effect of low-level laser therapy after extraction of impacted lower third molars. *Lasers Med Sci* 2013;28:845–849.
- Fekrazad R, Chiniforush N, Bouraima SA, et al. Low level laser therapy in management of complications after intra oral surgeries. *J Lasers Med Sci* 2012;3:135.
- Sanz-Moliner JD, Nart J, Cohen RE, Ciancio SG. The effect of an 810-nm diode laser on postoperative pain and tissue response after modified Widman flap surgery: a pilot study in humans. *J Periodont* 2013;84:152–158.

22. Moher D, Shamseer L, Clarke M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
23. Paschoal MAB, Santos-Pinto L. Therapeutic effects of low-level laser therapy after premolar extraction in adolescents: a randomized double-blind clinical trial. *Photomed Laser Surg* 2012;30:559–564.
24. Koparal M, Ozcan Kucuk A, Alan H, Asutay F, Avci M. Effects of low-level laser therapy following surgical extraction of the lower third molar with objective measurement of swelling using a three-dimensional system. *Exp Ther Med* 2018;15:3820–3826.
25. Raiesian S, Khani M, Khiabani K, Hemmati E, Pouretzad M. Assessment of low-level laser therapy effects after extraction of impacted lower third molar surgery. *J Laser Med Sci* 2017;8:42–45.
26. Petrini M, Ferrante M, Trentini P, Perfetti G, Spoto G. Effect of pre-operative low-level laser therapy on pain, swelling, and trismus associated with third-molar surgery. *Med Oral Patol Oral Cir Bucal* 2017;22:e467–e472.
27. Kahraman SA, Cetiner S, Strauss RA. The effects of transcutaneous and intraoral low-level laser therapy after extraction of lower third molars: a randomized single blind, placebo controlled dual-center study. *Photomed Laser Surg* 2017;35:401–407.
28. Alan H, Yolcu Ü, Koparal M, Özgür C, Öztürk SA, Malkoç S. Evaluation of the effects of the low-level laser therapy on swelling, pain, and trismus after removal of impacted lower third molar. *Head Face Med* 2016;12:25.
29. Eroglu CN, Keskin Tunc S. Effectiveness of single session of low-level laser therapy with a 940 nm wavelength diode laser on pain, swelling, and trismus after impacted third molar surgery. *Photomed Laser Surg* 2016;34:406–410.
30. Eshghpour M, Ahrari F, Takallu M. Is low-level laser therapy effective in the management of pain and swelling after mandibular third molar surgery? *J Oral Maxillofac Surg* 2016;74:1321–1322.
31. Kazancioglu HO, Ezirganli S, Demirtas N. Comparison of the influence of ozone and laser therapies on pain, swelling, and trismus following impacted third-molar surgery. *Lasers Med Sci* 2014;29:1313–1319.
32. Tuk JGC, van Wijk AJ, Mertens IC, Keles Z, Lindeboom JAH, Milstein DMJ. Analgesic effects of preinjection low-level laser/light therapy (LLLT) before third molar surgery: a double-blind randomized controlled trial. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2017;124:240–247.
33. Farhadi F, Eslami H, Majidi A, et al. Evaluation of adjunctive effect of low-level laser Therapy on pain, swelling and trismus after surgical removal of impacted lower third molar: a double blind randomized clinical trial. *Laser Ther* 2017;26:181–187.
34. Pedreira AA, Wanderley F, Sa M, et al. Thermographic and clinical evaluation of 808-nm laser photobiomodulation effects after third molar extraction. *Minerva Stomatol* 2016; 65:213–222.
35. Elbay ÜŞ, Tak Ö, Elbay M, Uğurluel C, Kaya C. Efficacy of low-level laser therapy in the management of postoperative pain in children after primary teeth extraction: a randomized clinical trial. *Photomed Laser Surg* 2016;34: 171–177.
36. Sierra SO, Deana AM, Bussadori SK, et al. Effect of low-intensity laser treatment on pain after extraction of impacted mandibular third molars: a randomised, controlled, clinical trial. *Br J Oral Maxillofac Surg* 2015;53:996–1000.
37. López-Ramírez M, Vélchez-Pérez MÁ, Gargallo-Albiol J, Arnabat-Domínguez J, Gay-Escoda C. Efficacy of low-level laser therapy in the management of pain, facial swelling, and postoperative trismus after a lower third molar extraction. A preliminary study. *Lasers Med Sci* 2012;27:559–566.
38. Amarillas-Escobar ED, Toranzo-Fernández JM, Martínez-Rider R, et al. Use of therapeutic laser after surgical removal of impacted lower third molars. *J Oral Maxillofac Surg* 2010;68:319–324.
39. Roynesdal A, Björnlund T, Barkvoll P, Haanaes H. The effect of soft-laser application on postoperative pain and swelling: a double-blind, crossover study. *Int J Oral Maxillofac Surg* 1993;22:242–245.
40. Fernando S, Hill C, Walker R. A randomised double blind comparative study of low level laser therapy following surgical extraction of lower third molar teeth. *Br J Oral Maxillofac Surg* 1993;31:170–172.
41. Markovic A, Todorovic L. Effectiveness of dexamethasone and low-power laser in minimizing oedema after third molar surgery: a clinical trial. *Int J Oral Maxillofac Surg* 2007;36:226–229.
42. Aras MH, Güngörmüş M. The effect of low-level laser therapy on trismus and facial swelling following surgical extraction of a lower third molar. *Photomed Laser Surg* 2009;27:21–24.
43. Aras MH, Güngörmüş M. Placebo-controlled randomized clinical trial of the effect two different low-level laser therapies (LLLT)—intraoral and extraoral—on trismus and facial swelling following surgical extraction of the lower third molar. *Lasers Med Sci* 2010;25:641–645.
44. Gasperini G, de Siqueira IR, Costa LR. Does low-level laser therapy decrease swelling and pain resulting from orthognathic surgery? *Int J Oral Maxillofac Surg* 2014;43: 868–873.
45. Ezzat AE, EL-Shenawy HM, El-Begermy MM, Eid MI, Akel MM, Abbas AY. The effectiveness of low-level laser on postoperative pain and edema in secondary palatal operation. *Int J Pediatr Otorhinolaryngol* 2016;89:183–186.
46. de Rezende RA, Silva DN, Frigo L. Effect of GaAlAs low-level laser therapy on mouth opening after orthognathic surgery. *Lasers Med Sci* 2018;33:1271–1277.
47. Guarini D, Gracia B, Ramirez-Lobos V, Noguera-Pantoja A, Sole-Ventura P. Laser biophotomodulation in patients with neurosensory disturbance of the inferior alveolar nerve after sagittal split ramus osteotomy: a 2-year follow-up study. *Photomed Laser Surg* 2018;36:3–9.
48. Mohajerani SH, Tabeie F, Bemanali M, Tabrizi R. Effect of low-level laser and light-emitting diode on inferior alveolar nerve recovery after sagittal split osteotomy of the mandible: a randomized clinical trial study. *J Craniofac Surg* 2017;28:e408–e411.
49. Gasperini G, de Siqueira ICR, Costa LR. Lower-level laser therapy improves neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy: a randomized crossover clinical trial. *J Cranio-Maxill Surg* 2014;42: e130–e133.
50. Führer-Valdivia A, Noguera-Pantoja A, Ramírez-Lobos V, Solé-Ventura P. Low-level laser effect in patients with neurosensory impairment of mandibular nerve after sagittal split ramus osteotomy. Randomized clinical trial,

- controlled by placebo. *Med Oral Patol Oral Cir Bucal* 2014;19:e327–e334.
51. Miloro M, Repasky M. Low-level laser effect on neurosensory recovery after sagittal ramus osteotomy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;89:12–18.
 52. Khullar SM, Emami B, Westermarck A, Haanes HR. Effect of low-level laser treatment on neurosensory deficits subsequent to sagittal split ramus osteotomy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;82:132–138.
 53. Pol R, Gallesio G, Riso M, et al. Effects of superpulsed, low-level laser therapy on neurosensory recovery of the inferior alveolar nerve. *J Craniofac Surg* 2016;27:1215–1219.
 54. de Oliveira RF, da Silva AC, Simoes A, Youssef MN, de Freitas PM. Laser therapy in the treatment of paresthesia: a retrospective study of 125 clinical cases. *Photomed Laser Surg* 2015;33:415–423.
 55. Prazeres LDKT, Muniz YVS, Barros KMA, de Martinez Gerbi MEM, Laureano Filho JR. Effect of infrared laser in the prevention and treatment of paresthesia in orthognathic surgery. *J Craniofac Surg* 2013;24:708–711.
 56. Dostalova T, Kroulikova V, Podzimek S, Jelinková H. Low-level laser therapy after wisdom teeth surgery: evaluation of immunologic markers (secretory immunoglobulin A and lysozyme levels) and thermographic examination: placebo controlled study. *Photomed Laser Surg* 2017;35:616–621.
 57. Halon A, Donizy P, Dziegala M, Dobrakowski R, Simon K. Tissue laser biostimulation promotes post-extraction neoangiogenesis in HIV-infected patients. *Lasers Med Sci* 2015;30:701–706.
 58. Monea A, Beresescu G, Tibor M, Popsor S, Antonescu DM. Bone healing after low-level laser application in extraction sockets grafted with allograft material and covered with a resorbable collagen dressing: a pilot histological evaluation. *BMC Oral Health* 2015;15:134.
 59. Mozzati M, Martinasso G, Cocero N, et al. Influence of superpulsed laser therapy on healing processes following tooth extraction. *Photomed Laser Surg* 2011;29:565–571.
 60. Bhat P, Cariappa K. Inferior alveolar nerve deficits and recovery following surgical removal of impacted mandibular third molars. *J Maxillofac Oral Surg* 2012;11:304–308.
 61. Nguyen E, Grubor D, Chandu A. Risk factors for permanent injury of inferior alveolar and lingual nerves during third molar surgery. *J Maxillofac Oral Surg* 2014;72:2394–2401.
 62. Gülicher D, Gerlach K. Sensory impairment of the lingual and inferior alveolar nerves following removal of impacted mandibular third molars. *Int J Oral Maxillofac Surg* 2001;30:306–312.
 63. Bagheri SC, Meyer RA, Khan HA, Wallace J, Steed MB. Microsurgical repair of the peripheral trigeminal nerve after mandibular sagittal split ramus osteotomy. *J Oral Maxillofac Surg* 2010;68:2770–2782.
 64. Bagheri SC. Microsurgical repair of the peripheral trigeminal nerve after mandibular sagittal split ramus osteotomy. *J Oral Maxillofac Surg* 2008;66:34.
 65. Posten W, Wrona DA, Dover JS, Arndt KA, Silapunt S, Alam M. Low-level laser therapy for wound healing: mechanism and efficacy. *Dermatol Surg* 2005;31:334–340.
 66. Hoffmann A, Gross G. BMP signaling pathways in cartilage and bone formation. *Crit Rev Eukar Gene* 2001;11:23–45.
 67. Yang J, Andre P, Ye L, Yang Y-Z. The Hedgehog signaling pathway in bone formation. *Int J Oral Sci* 2015;7:73–79.
 68. Wang Y, Huang Y-Y, Wang Y, Lyu P, Hamblin MR. Photobiomodulation (blue and green light) encourages osteoblastic-differentiation of human adipose-derived stem cells: role of intracellular calcium and light-gated ion channels. *Sci Rep* 2016;6:33719.
 69. Tim CR, Bossini PS, Kido HW, et al. Effects of low-level laser therapy on the expression of osteogenic genes during the initial stages of bone healing in rats: a microarray analysis. *Lasers Med Sci* 2015;30:2325–2333.
 70. Magri AMP, Fernandes KR, Assis L, et al. Photobiomodulation and bone healing in diabetic rats: evaluation of bone response using a tibial defect experimental model. *Lasers Med Sci* 2015;30:1949–1957.
 71. Park JB, Ahn S-J, Kang Y-G, Kim E-C, Heo JS, Kang KL. Effects of increased low-level diode laser irradiation time on extraction socket healing in rats. *Lasers Med Sci* 2015;30:719–726.
 72. Tim CR, Pinto KNZ, Rossi BRO, et al. Low-level laser therapy enhances the expression of osteogenic factors during bone repair in rats. *Lasers Med Sci* 2014;29:147–156.
 73. Patrocínio-Silva TL, de Souza AMF, Goulart RL, et al. The effects of low-level laser irradiation on bone tissue in diabetic rats. *Lasers Med Sci* 2014;29:1357–1364.
 74. Matsumoto MA, Ferino RV, Monteleone GF, Ribeiro DA. Low-level laser therapy modulates cyclo-oxygenase-2 expression during bone repair in rats. *Lasers Med Sci* 2009;24:195–201.
 75. Tim CR, Bossini PS, Kido HW, et al. Effects of low level laser therapy on inflammatory and angiogenic gene expression during the process of bone healing: a microarray analysis. *J Photochem Photobiol B Biol* 2016;154:8–15.
 76. Sato Y, Arai N, Negishi A, Ohya K. Expression of cyclooxygenase genes and involvement of endogenous prostaglandin during osteogenesis in the rat tibial bone marrow cavity. *J Med Dent Sci* 1997;44:81–92.
 77. Forwood M. Inducible cyclo-oxygenase (COX-2) mediates the induction of bone formation by mechanical loading in vivo. *J Bone Miner Res* 1996;11:1688–1693.
 78. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. *J Clin Invest* 2002;109:1405–1415.

Address correspondence to:
 Reza Fekrazad, DDS, PhD, FLD, FICD
 Radiation Sciences Research Center
 Lasers Research Center in Medical Sciences
 AJA University of Medical Sciences
 Flat No. 12, Mooj Building
 First Behestan, Pasdaran Street
 Tehran 1946883893
 Iran

E-mail: rezafekrazad@gmail.com

Received: June 12, 2019.
 Accepted after revision: July 27, 2019.
 Published online: November 21, 2019.