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Review

Photobiomodulation Therapy in Oral Medicine: A Guide for the Practitioner with Focus on New Possible Protocols

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Abstract

Photobiomodulation (PBM) is the term to define the wide range of laser applications using low-energy densities and based on photochemical mechanisms where the energy is transferred to the intracellular mitochondrial chromophores and respiratory chain components. In literature, a great number of works are reported showing the advantages of PBM use in many oral diseases such as recurrent aphthous stomatitis, herpes infections, mucositis, and burning mouth syndrome. Different factors may explain the increasing reported use of PBM in oral medicine: the absence of side effects, the possibility of safely treating compromised patients such as oncologic patients, the possibility of a noninvasive approach not associated with pain or discomfort, and the possibility of performing short sessions. The review's aim is to describe the possible applications of PBM in oral medicine, giving practitioners simple guide for practice together with the information of a new treatment possibility ''at home'' performed by the patient himself under supervision.

Keywords: photobiomodulation, low-level laser therapy, oral medicine, home use

Introduction

Photobiomodulation Therapy (acronym: PBM) is the universally recognized term to define the wide range of laser applications with low parameters, taking finally the place of a lot of definitions such as ''Low Level Laser Therapy'' (acronym: LLLT), ''Biostimulation'' or ''soft laser'' or ''cold laser,'' mostly used in the 70s and 80s[1–3]; this term was added in 2015 as MeSH term of the National Library of Medicine's controlled vocabulary thesaurus.[4]

The father of PBM is Endre Mester, the Hungarian physician, who first observed in the 60s the effects of a ruby laser (wavelength of 694.3 nm) on animal models he used to understand the presence or not of a carcinogenic effect for laser used at low-energy densities (1 J/cm^2); Mester performed studies on the effect of laser phototherapy on healing processes and tissue repair in animal, on phagocytosis of bacteria by leukocytes, on synthesis of hemoglobin, and healing of ulcerative lesions not responding to conventional therapies.[5,6]

The scientific interest around PBM is due to its different properties in terms of stimulation of both wound healing (mucosa, skin, tendon …) and repair (bone, cartilage, and dentin) as well as on pain and inflammation.

On the basis of its effects, PBM is defined by Anders et al. as ''a form of light therapy that utilizes nonionizing forms of light [.....], a non-thermal process involving endogenous chromophores eliciting photo-physical and photochemical events at various biological scales. This process results in beneficial therapeutic outcomes including but not limited to the alleviation of pain or inflammation, immunomodulation, and promotion of wound healing and tissue regeneration.''[4]

Mechanisms of action

PBM is based on a photochemical mechanism where the energy is transferred to the intracellular mitochondrial chromophores that are light-absorbing molecules such as endogenous porphyrins and respiratory chain components such as cytochrome c oxidase capable of transferring the absorbed laser energy to the mitochondria; at this level, laser energy is converted into metabolic energy by the respiratory chain with the production of adenosine triphosphate (ATP).[7,8]

The primary photoacceptors of PBM for visible light are the mitochondrial respiratory chains, while those of infrared light are the calcium channels located at the cellular membrane.[9,10]

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The light absorption by the components of the respiratory chain causes short-term respiratory chain activation and the oxidation of nicotinamide adenine dinucleotide (NADH), causing changes in both mitochondrial and cytoplasmic redox states. The electron transport chain activation leads to an increase in the electrical potential of the mitochondrial membrane and the ATP reserve, the cytoplasm alkalization,[11–14] and finally, the activation of nucleic acid synthesis.[11]

Tina Karu in the article she wrote in 2012[15] about the primary and secondary mechanisms of laser PBM on cells identified at least five primary mechanisms:

1. The acceleration of electron transfers in the respiratory chain attributed to the changes in redox properties.[15]
2. The conversion of energy into heat defining the increase in chromophore temperature in a transient way.[15]
3. The so-called singlet-oxygen hypothesis where singlet oxygen acts as free radical influencing the formation of ATP and the transmembrane proton gradient at the mitochondrial level.[15–17]
4. The so-called superoxide anion hypothesis where superoxide anions may be reabsorbed by mitochondria functioning as the source of electrons for the oxidative adenosine di-phosphate (ADP) phosphorylation under physiological conditions, but also causing multiple secondary responses such as an increase in Ca^{++} alkalization of the cytoplasm and activation of Ca^{++} ATPase.[15]
5. The so-called NO hypothesis in which laser irradiation could reverse the partial inhibition of the catalytic center by NO and finally increase the O_2 binding and respiration rate.[15–18]

In addition to the aforementioned mechanisms, cell membrane light-sensitive receptors are involved in the mechanism of absorption of laser light; these receptors are mainly ion channels able to allow the entrance into the cell of calcium that, together with reactive oxygen species, cyclic AMP and NO, may provoke the activation of transcription factors responsible for cell proliferation and differentiation processes[14] and, finally, of long-lasting results even after a relatively brief exposure.[19]

Secondary mechanisms for PBM are characterized by the activation of different intracellular signaling pathways, and regulate nucleic acid synthesis, protein synthesis, enzyme activation, and cell cycle progression; several transcription factors are regulated by changes in the cellular redox state, for example, the redox factor-1 (Ref-1)-dependent activator protein-1 (AP-1), the nuclear factor κB (NF-κB), p53, activating transcription factor/cAMP-response element-binding protein (ATF/CREB), hypoxia-inducible factor (HIF)-1α, and HIF-like factor[20,21] and also the recently described extracellular latent growth factor complex TGF-β1.[22]

The activation of this wide range of factors is responsible for the so-called tertiary effect that, linked to proliferation and migration of cells and protein synthesis, could be identified as responsible for the systemic effect.[21]

Primary reactions to PBM occur in the irradiation zone, but a secondary systemic response related to the transport of photoproducts such as prostaglandins, enkephalins, endorphins, mediated by the lymphatic system and with a persistent effect for several hours or weeks, is thought possible.

For effects of PBM reported on brain damage cases where laser application was not direct, different hypotheses have been described: the stimulation of mast cells and macrophages on the downregulation of proinflammatory cytokines and the upregulation of anti-inflammatory cytokines, and also the irradiation of bone marrow stem cells.[14]

This is the main reason why it is important in the design of experimental studies and in the interpretation of results to consider the use of protocols in which there is an internal control (e.g., irradiation of even structures).[23]

The many biological effects of PBM are attributed to parameters such as wavelength, power density, and fluence. However, despite the monochromatic characteristic of laser light being considered of importance to the responses, nonmonochromatic light such as the LED light may also cause similar biological effects.[24] PBM produces a change in cellular redox potential in the direction of increased oxidation and, since different cells, under certain growth conditions, have different redox states, the effects of PBM can vary considerably from tissue to tissue. Cells that are in a more ''stressed'' state (e.g., low intracellular pH) have a high potential to respond to PBM, whereas cells in the optimal redox state respond weakly or do not respond at all to treatment.[21,25]

The most accredited theory attributes to PBM a mechanism by which a particle of light acts as only a trigger for some changes in cellular metabolism. In the cell, there are, in fact, processes of signal transduction and amplification such as changes in the parameters of cellular homeostasis; light photons are absorbed by the primary photoacceptors and this changes the physiological mechanism of existing cellular regulation, which would explain the need for relatively small intensities and doses to determine its effect.[25] The universality of the effects of lasers/LED used at low power and the possibility of using different wavelengths for irradiation are correlated to the fact that primary photoacceptors are ubiquitous in the cells; it seems, moreover, that the magnitude of the effects of biostimulation laser also depends on the physiological state of the cell at the time of irradiation, which is why the response of tissue in vivo (and in some ways also in vitro) to PBM would seem directly related to stress conditions,[25–27] characterized by an inhibitory concentration of NO.[19]

In the field of PBM, it is defined as ''therapeutic window'' the range of wavelengths useful and usable for this type of application; this window is located between 600 and 1150 nm on the basis of the fact that absorption and diffusion of light in tissues depend on wavelengths and tissue chromophores: wavelengths below 600 nm would be too much absorbed by hemoglobin, those above 1150 nm from water in tissues.[28]

Laser Parameters in PBM

Contrary to what happens with other kinds of laser application, in the field of PBM, there are no real parameters' homogeneity used, especially with respect to power density and fluence, as well as dosimetry.[29] Too low doses may have no effect (subclinical), those too high cause little or no effect until an inhibitory effect (overdose).[28] PBM seems to require fluences between 0.05 and 10 J/cm^2; fluences greater than 10 J/cm^2 are related to a bioinhibitory effect, the biomodulatory effect seems greater for exposure times from 30 to 120 sec[29–31] and even scientific literature describes irradiation times until 7000 sec.[29]

The parameters that determine more evident clinical effects, as reported by the literature data, are in the range of fluences of 1–10 J/cm^2, but values between 1 and 5 J/cm^2 and 10 J/cm^2 are also acceptable. Different studies reported applied doses until 100 J/cm^2, even if for the highest parameters inhibitory effects are reported, confirming the Arndt–Schultz law.[29,31] The biological effect of PBM has been related not only to variables such as wavelength, power, and fluence density but also to the cell cycle phase and irradiation time.[9,29,32] Most part of the ''stimulating'' wavelengths are in the field of visible light (380–780 nm), which is also demonstrated in studies using He-Ne lasers (632.8 nm in most cases) and diode lasers (wavelengths varying from 630 nm to about 940 nm).[29]

The timing for irradiation with respect to the healing time of the bone tissue must also be included among the variables; it seems that, when performed in the initial phase of bone healing, cell organs are more sensitive to PBM.[33]

Safety and Contraindications

Thanks to the use of parameters characterized by low-energy density, PBM can be considered free of possible side effects, but instead with higher parameters correlated to damage and tissue destruction.[20,34]

In literature, pregnancy is reported as a contraindication for the use of laser when treatment may be performed on the abdominal area with high doses, resulting in this way only a theoretical contraindication to PBM protocols. Considering it prudent to avoid high doses at the pregnant uterus, however, there is no scientific evidence to support the risk of irradiation of areas distant from the gravid uterus.[20]

Some researchers have indicated the periocular area and the presence of circulatory or vascular disorders as contraindications for laser treatment,[20,34] while additional contraindications are considered to be hypersensitivity to sunlight, epilepsy, exposure of the retina, hyperthyroidism, the presence of infected wounds, and chest treatment with pacemakers in situ.[35]

Considering the potential of proliferative stimulation, the application of PBM protocols directly on potentially or certainly malignant lesions in the past was not recommended as safe.[34]

Irradiation at sites different from the primary tumor localization cannot be correlated with the potential effect of tumor stimulation, as in the protocols applied in the treatment of radiotherapy/chemotherapy-induced oral mucositis.[35]

Recently, Ottaviani et al. showed, based on the consideration that experiments on the effect of laser light on cultured cells are not representative of the in vivo condition, in an in vivo study on mice, laser light may be able to reduce tumor progression, stating that PBM is a safe procedure in multi-modal anticancer protocols in humans.[36]

Effects of PBM

The photochemical reactions at the base of PBM can define three different clinical effects, namely the stimulation of healing, the anti-inflammatory effect, and the painkilling action.[37]

Stimulation of wound healing

In vitro and in vivo studies on animals and humans have demonstrated the efficacy of PBM in promoting physiological effects such as DNA synthesis, neoangiogenesis, keratinocyte, fibroblast, and endothelial cell proliferation, maturation and migration, collagen synthesis and deposition, activation of macrophages, revascularization and contraction of the wound by means of myofibroblast transformation and neurogenesis.[38,39]

Anti-inflammatory effect

PBM may increase the activity of macrophages and neutrophils, with a specific and preferential modality for some mediators of inflammation; PBM is able to modulate cytokine release by decreasing the tissue levels of TNF-α and increasing the levels of IL-1β, to regulate inflammation-induced angiogenesis, and to act on endothelial cells.[40]

PBM inhibits the catabolic mediators of inflammation such as inhibitors for collagen synthesis and cell proliferation, reduces the influx of neutrophils to the level of inflamed tissue, and stimulates the production of anti-inflammatory metabolites such as cyclooxygenase-1 (COX-1) and COX-2.

PBM also seems to contribute to the reduction of edema.[41]

Analgesic-painkiller effect

The mechanism underlying the pain relief by PBM has not yet been fully clarified and is probably quite complex: one of the most accredited hypotheses is related to the increase of nociception threshold with neural block, specifically with inhibition of type A fibers and C mediated by alteration of axonal flow or by inhibition of neural enzymes. Further, there appears to be an increase in the production of endorphins as changes in opioid receptors. PBM can also mimic the effects of anti-inflammatory drugs by attenuating the level of prostaglandins-2 and by inhibiting COX-2.[42]

PBM defines the reduction of acute and chronic pain through a conduction block and an alteration of nociceptors A-delta and C, with action at the level of the central nervous system through ascending and descending transmission.[41] In fact, PBM is able to modulate peripheral nervous system signaling, defining at the central nervous system level, the pain modulation effect.[43]

PBM "at home" and recent application of PBM in medicine: new scenarios for PBM?

One of the main practical problems related to PBM is the necessity for short sessions, but with a frequency of two or three times/week, in some cases even daily.[44] To allow the patients to have their treatment without going to the therapist, recently, there appeared in the market a new family of devices that, due to their classification as class II American National Standard Institute (ANSI), may be used directly by patients themselves without the need for protective goggles in a very simple way, thanks to the presetted parameters; size and cost are reduced and the risk of side effects and contraindications is absent, nevertheless, evaluation of the patients by a specialist is mandatory.[45]

At home, laser use has been described, for example, for temporomandibular disorders (TMD), using preset devices and therapies set by the therapist, limiting the discomfort of repeated appointments and obtaining good results in terms of pain [assessed through an appropriate visual analog scale (VAS)] at 1 and 2 weeks from start of PBM applications.[46]

Some case reports were also described for the treatment of neurological face diseases, also related to an intraosseous implant for prosthetic rehabilitation.[47]

Beyond head and neck fields, at home, PBM has been used for skin wounds with healing difficulties,[48] for retinal thickness in diabetic patients,[49] and for the improvement of cognitive function.[50,51]

PBM is currently proposed in the literature as a therapeutic possibility for serious neurological conditions such as trauma-induced brain injury, stroke, spinal cord injury, and degenerative diseases of the central nervous system; this is based on stimulatory effects for angiogenesis and neurogenesis and with noninvasive applications in transcranial mode.[52]

PBM has also been correlated with the upregulation of brain-derived neurotrophic factor (BDNF), contributing to a decrease in dendrite atrophy and the loss of cells in Alzheimer's disease; in fact, this is related, in its progression, to the reduction of the BDNF in the hippocampus, which plays a critical role in the dendrite survival and growth.

The PBM has demonstrated, both in vitro and in vivo, the regulatory capacity of neuronal function paving the way for the effects of its application in this pathology treatment.

Other promising fields of application are related to Parkinson's disease and amyotrophic lateral sclerosis.

Intravenous or intravascular irradiation in PBM protocols through an optical fiber inserted in a vascular canal, generally a vein of the forearm has been proposed in the literature based on the hypothesis that the therapeutic effect is conveyed through the circulatory system. The feasibility of endovascular irradiation for the treatment of cardiocirculatory pathologies was presented by the *American Heart Journal* in 1982[53] and developed mainly in Asia (including Russia) to improve blood flow and its transport activities, that is, ''normalizing'' the lipids in the blood (low-density lipoprotein, high-density lipoprotein, and cholesterol), making the platelets less subject to ''aggregation,'' decreasing the probability of clot formation, and activating the immune system (dendritic cells, macrophages, and lymphocytes).

PBM has been widely used for the treatment of several oral diseases, including radiotherapy/chemotherapy-induced oral mucositis, herpetic lesions, and bullous and erosive ulcerative diseases, and it has been described also as therapy on other kinds of diseases such as granulomatous diseases nonresponding to conventional treatments.[54]

PBM in Oral Medicine

PBM in the control of pain and nerve complications after surgery

The postextraction intra- and/or extraoral application of PBM protocols realized mostly with diode lasers in visible and near infrared (NIR) spectrum of light (from 660 to 940 nm) is reported in the literature in randomized controlled trial (RCT) studies as effective already in the early postoperation phases (first and third day) (Table 1).

Mainly, the described effect for PBM on third molar postextraction site or on postflap surgery site is linked to the reduction of pain, swelling, and trismus in PBM groups compared with the control groups.[55–61]

One study on postextraction PBM in HIV patients reported a more important increase in angiogenesis in a single irradiation PBM group than in the nonirradiated control group.[62]

A systematic review of the publications related to surgery of the lower third molar, one of the most morbid oral surgical procedures, analyzed the effect of PBM protocols on pain, edema, and postoperative trismus, reporting significant effects, particularly on the latter.[63]

PBM protocols are also reported in the literature in case of iatrogenic damage of the lingual nerve and of the inferior alveolar nerve correlated to the lower third molar surgery, with results in terms of complete recovery or clinical improvement in cases of anesthesia, hypoesthesia, and paraesthesia. The effect in this type of application would seem, from the in vitro studies present in the literature, correlated to an increase in the production of collagen with a concomitant decrease of the cicatricial outcomes.[64,65]

PBM in periodontology and implantology

The application and effects of PBM protocols in periodontology are currently the subject of a wide and articulated discussion. The rationale for the application of this laser approach to periodontal therapy, through in vitro and in vivo studies, would be the acceleration of healing processes through the stimulation of cell proliferation and differentiation demonstrated, for example, on fibroblasts as well as on periodontal ligament cells with stimulation of the production of inflammatory cytokines.[27] Clinical studies have also shown the acceleration of the healing process induced by PBM after mucogingival surgery, as well as after scaling and root planning sessions, and the reduction of gingival inflammation in patients classically more at risk, for example, patients with diabetes mellitus.[66]

Further, as shown by different in vitro studies, PBM increases bone formation by stimulating the proliferation and differentiation of osteoblasts, evidenced by higher levels of alkaline phosphatase activity, mRNA expression for osteopontin, osteocalcin, bone sialoprotein, and the presence of calcified nodules. These studies have led to further research on the application of PBM in traditional implantology, with the advantage of faster and greater osseointegration thanks to better proliferation and attack by fibroblasts and osteoblasts to titanium surfaces.[67,68]

Matarese et al. in their recent RCT showed that PBM associated with conventional treatment of scaling and root planning improved clinical parameters such as probing depth and clinical attachment loss significantly more than conventional treatment alone, maintaining the result until 1 year of follow-up;[69] similar results were reported by Mokeem in a recent systematic review.[70]

PBM and recurrent aphthous stomatitis

Case reports and RCT in single- and double-blind reported positive effects resulting from the application of PBM protocols in clinically identifiable recurrent aphthous stomatitis (RAS) with minor forms; published protocols generally use diode lasers in the visible and NIR spectrum, with different delivery methods but always below 10 J/cm^2 per application session.[71]

Table 1. Parameters and Main Effects of Photobiomodulation Therapy in Oral Medicine Conditions and Diseases

Oral disease/condition	*Wavelengths*	*Energy density J/cm²*	*Laser PBM sessions/treatment protocol*	*Effects*
Postsurgical pain control[55–63]	Visible 660 nm[59,60]	5[59,60]	8–30 sec—CW—intra/extraoral—multiple treatments (three to four sessions in the first week after surgery)[75,76]	Reduction of pain, edema, and trismus
	He-Ne 632.8 nm[63]	10[63]	Multiple treatments[63]	
	650 nm[61]	31[61]	15 min—CW—intra/extraoral—multiple treatments[61]	
	NIR 810 nm[55,59,63]	4–10[55,59,63]	40 sec—CW—single dose[55]	
	—	6[62]	30 sec—intra/extraoral—multiple treatments[59,63]	
	820 nm[62]	4[63]	intraoral—multiple treatments (5 consecutive days)[62]	
	830 nm[63]	31[61]	10 min—intra/extraoral—multiple treatments—(three sessions until the third day after surgery)[63]	
	910 nm[61]	20[56]	15 min—PW—intra/extraoral—multiple treatments (three sessions until the first day after surgery)[61]	
	940 nm[56]		CW—single dose[56]	
	980 nm[57]		180 sec—intra/extraoral—single dose[57]	
Nerve complications after surgery[64,65]	NIR	4.9[64]	CW—multiple treatments (three times/week)[64]	Improvement of sensitivity and reduction of anesthesia/paraesthesia
	830 nm[64]	95.31[65]	270 sec—CW—multiple treatments (days 1-2-3-5-10-14-21-28 after surgery)[65]	
Periodontitis[50–54]	Visible 635 nm[68]	4.5[68]	90 sec[68]	Reduction of PD and CAL
	670 nm[66]	—	14 min—multiple treatments (5 consecutive days)[66]	
	NIR 810 nm[69]	24–84[69]	20 sec/tooth—PW—single treatment[69]	
	830 nm[68]	8.75[68]	25 sec[68]	
Recurrent aphthous stomatitis[71–76]	Visible 450 nm[76]	17[76]	60 sec—CW[76]	Reduction of healing time
	635 nm[76]	36[76]	30 sec—CW[76]	Reduction of pain
	658 nm[71]	27[71]	CW—80 sec—multiple treatments[71]	Improvement of quality of life
	670 nm[71]	3[71]	PW—2–3 min—multiple treatments[71]	Decreased recurrence
	NIR 808 nm[76]	50[76]	CW—60 sec[76]	
	809 nm[72]	6.3[72]	80 sec—PW—multiple treatments (three times every other day)[72]	
	810 nm[70–73]	6[73]	30 sec—multiple treatments (days 1-3-7)[73]	
	940 nm[70]	24.84[70]	20–30 sec[70]	
	980 nm[70]	13.5[70]	20 sec[70]	
	2078 nm[75]	94.3[70]	30 sec[70]	
		5[91]	PW—20 sec—single treatment[75]	

(*continued*)

TABLE 1. (CONTINUED)

Oral disease/condition	*Wavelengths*	*Energy density J/cm²*	*Laser PBM sessions/treatment protocol*	*Effects*
Herpes infections[61–66]	Visible			Reduction of healing time
	660 nm[81]	—	—	Reduction of pain
	NIR	5[79]	CW—80 sec—multiple treatments (three irradiations)[79]	Decreased recurrence
	830 nm[78]	4.5[80]	Multiple treatments (one session/week)[80]	Reduction of drug (and costs)
	780 nm[79,80]	3.8[81]	CW—multiple treatments (10 sessions)[81]	
	870 nm[82]	4.5[82]	PW—multiple treatments (daily until healing)[82]	
Oral mucositis[67–70]	Visible		PW—7 min 30 sec—multiple treatments (4 consecutive days)[85]	Reduction of healing time
	660 nm[85]	36.8[85]		Reduction of pain
	630–685 nm[84]	3–4[84]		Reduction of drug (and costs)
	NIR		CW and PW—intra and extraoral—multiple treatments[84]	Improvement of quality of life
	970 nm[85]			Possible use in prevention protocols
	780–830 nm[84]			
Ulcer-erosive lesions	Visible		CW—multiple treatments (two times/week)[88]	Reduction of healing time
OLP	630 nm[88]	1.2[87]	CW—multiple treatments (2/week until healing)[93]	Reduction of pain
Pemphigus/pemphigoi[87–95]	660 nm[94]	4[91,93]	CW—multiple treatments (every other day for 4 weeks)[94]	
	NIR	4[92]	30 sec—multiple treatments (three times/week)[87]	
	810 nm[87,95]	2[94]	3.73 sec—CW—multiple treatments (1/week until healing)[91]	
	980 nm[91,93]	5[95]	PW—multiple treatments (2/week until healing)[92]	
	904 nm[92]		30 sec—multiple treatments[87]	
			40 sec—multiple treatments (7 days)[95]	
Burning mouth syndrome[80–85]	Visible		10 sec—multiple treatments (10 sessions in 10 weeks)[100]	Reduction of pain/burning sensation
	660 nm[100]	1.5[98]		
	NIR	6[99]		
	800 nm[98]	20[100]	PW—70 sec—multiple treatments (once/day for 3 weeks)[98]	
	790 nm[99]	10[101]	CW—10 sec/point—multiple treatments[99]	
	980 nm[101]		10 sec/point—multiple treatments (2/week for 5 weeks)[101]	
TMD[86,87]	808 nm[46]	3.2[46]	PW—15 min—single treatment[46]	Reduction of pain
Orthodontics[88,89]	830 nm[104]	4[104]	28 sec—single and multiple treatments[104]	Reduction of pain
				Faster tooth movement
Pulp treatment[105–107]	632–660 nm[105,106]	2–4 J/cm² [105–107]	10 sec[105]	Clinical and radiological improvement of success rate
	970 nm[107]		135 sec[106]	

CAL, clinical attachment loss; CW, continuous wave; NIR, near infrared; OLP, oral lichen planus; PBM, photobiomodulation; PD, probing depth; PW, pulsed wave; TMD, temporomandibular disorders.

Albrektson et al. described the improvement of pain (on a VAS) with an 809 nm laser at 6.3 J/cm^2 fluence immediately after laser treatment, at 1 and 2 days, with an improvement of daily activities (minor difficulties during feeding, phonation, and brushing phases) in a significant way for laser-treated patients compared with control ones.[72]

With a similar protocol (810 nm laser at 6 J/cm^2 fluence), Jijin et al. described a significant reduction of pain 3 days after treatment with a reduction of ulcer size in the laser group.[73]

An improvement of pain on VAS at 1, 4, and 7 days after treatment was described by Tezel et al. with Nd:YAG laser (1064 nm) at 2 W–20 Hz[74] and by Yilmaz et al. with an Er,Cr:YSGG used without water but only with air spray at 5 J/cm^2 fluence.[75]

Recently, Rocca et al. published a study comparing different wavelengths in a visible (450 and 635 nm) and NIR spectrum (808 and 2940 nm); among the four wavelengths, the 635 nm diode was the device obtaining the earliest effect reducing the pain already during the treatment and maintaining it at low level immediately after the laser application and at 3 and 7 days after treatment.[76]

In their recent systematic review on this topic, Han et al. reported a significant effect for PBM in reducing pain and improving healing of RAS without any kind of side effect or complication, even if the weakness of evidence requires more long-term RCT.[71]

PBM and herpes infections

The exact mechanism of antiviral PBM effect is still unknown. Zupin et al. hypothesized, in a recent work, that the irradiation performed with blue laser may result in a direct inhibitory effect in the virus itself rather than in the virus inside the cell[77]; Donnarumma et al. reported an effect for PBM on HSV-1 replication and on modulation of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, antimicrobial peptide HBD2, chemokine IL-8, and the immunosuppressive cytokine IL-10, identifying an action on the final stage of HSV-1 replication with a control action on viral spread from cell to cell.[78]

The PBM protocols applied to the oral manifestations of herpes infections and, particularly, of recurrences (HSV-1) are justified by the stimulation of wound acceleration with a simultaneous pain reduction, both key factors in the labial recurrences that are often painful and characterized by slow healing processes. These aspects should be associated with the stimulation action of the patient's immune response, reported for PBM.[78]

In an RCT literature, and mainly based on the use of diode lasers in the visible or NIR spectrum, the application is performed by points, with doses below 10 J/cm^2 and in the different phases, from prelude to the crusty lesion stage. The described results are positive for reduction of pain symptoms, healing times with better comfort for the patient also from an aesthetic point of view, and recurrence reduction; the explanation for these results is hypothetically related to the immune system modulation effects.[79–81]

The use of PBM appears advantageous in the management of herpetic infections, not only due to the complete absence of side effects but also to the undoubted advantages that are derived, such as drug therapy use limitation, cost reduction, and viral resistance mechanism inhibition, with all due clinical implications especially in immune-compromised patients. Honarmand et al. in a study comparing, for the treatment of herpetic lesions, laser PBM, acyclovir, and placebo found a significant reduction of recovery time and a faster pain decrease in the laser PBM group.[82]

Encouraging results are reported for this type of approach in the preventive treatments of recurrent herpes in patients who suffer from it in a recurrent way.[80]

PBM and mucositis

An important toxic effect, identified with the term ''Mucositis,'' afflicts, with an important deterioration in the quality of life, patients treated for oncological problems with radiotherapy and/or chemotherapy approaches and with hematopoietic stem cell transplantation.

The PBM approach in this disease, reported by the Cochrane review, has been introduced to improve symptomatology, stimulating at the same time faster healing of the oral lesions, helping to quickly restore a normal diet and limiting the discontinuation of the primary disease therapeutic protocol.[83]

The studies in the literature describe particularly encouraging effects in the reduction of pain symptomatology evaluated by means of a VAS and good compliance by patients; in a patient already systemically and locally compromised in the orofacial region, it is essential that any type of therapy has minimal or no side effects, as is the case with PBM.[84]

A recent multi-center study on the use of PBM on degree three to four oral mucositis in chemotherapy-treated children reported an acceleration of mucosal recovery and a reduction of pain in laser PBM-treated patients compared with the placebo group, describing PBM as a safe, feasible, and effective treatment. The risk/benefit ratio is particularly favorable to PBM because, with a small size device, it is possible to obtain a reduction in hospitalization days, and hence costs, with an improvement of the phonatory, swallowing, and chewing capacity.[85]

Parameters for the treatment of oral mucositis are basically defined by a wavelength range of 600–1000 nm within the red and NIR spectrum of light (He-Ne laser, different diode lasers, Nd:YAG laser,...) with a power density between 5 and 150 mW/cm^2 and an application time of 30–60 sec per point, one or two times/week.[86]

PBM and ulcer-erosive diseases

Oral lichen planus (OLP) is an inflammatory disease that can be particularly symptomatic especially in atrophic and erosive types. Several drugs have been used with dissimilar results, but most treatments are based on the use of immunomodulatory drugs, especially topical corticosteroids.

In a recent study, Mutafchieva et al. described the efficacy of PBM on symptomatic atrophic-erosive OLP in reducing pain and stimulating healing using a diode laser (810 nm) with parameters 0.5 W, 30 sec, and 1.2 J/cm^2, three times weekly for a month.[87]

Mirza et al. compared PBM performed with a 660 nm diode laser at 1.5 J/cm^2 per session two times/week with corticosteroid therapy and concluded that PBM may be effective in the treatment of erosive-atrophic forms of OLP in adult patients.[88]

Hoseinpour Jajarm et al. and Al-Maweri et al. with their recent systematic reviews concluded that PBM may be an alternative to corticosteroids for treating OLP, allowing avoiding the adverse effects associated with the pharmacological method.[89,90]

PBM particularly performed in the NIR spectrum (980 nm) with fluence in the order of 4 J/cm^2 has been described as a useful treatment for OLP not responding to traditional therapies with a pain reduction, evaluated through appropriate VAS, and injury reduction.[91,92]

Some case reports and case series have reported the efficacy of PBM in the treatment of other mucous/cutaneous diseases such as pemphigus vulgaris and pemphigoid of mucous membranes. The application of PBM associated or not to the traditional topical therapies may improve the pain and the clinical signs without complications or side effects; this point represents an aspect that must not be underestimated together with patient compliance also linked to the chronic appearance of these diseases.[93–95]

PBM and burning mouth syndrome

Burning mouth syndrome (BMS) is a complex chronic disorder characterized by discomfort in the particularly complex orofacial district regarding diagnosis and treatment.[96]

Recently, PBM has been suggested in the literature for the treatment of some patients suffering from BMS.[97,98] Many studies are based on diode laser applications with wavelengths from the visible light (660 nm) to the NIR light spectrum with total fluence within the 20 J/cm^2 per session and protocol of one to two sessions/weeks until 12 weeks of treatment:[98–100] the sessions described last about 10 min, this factor is particularly important for patient compliance, they do not involve any pain or side effect, and in none of the treated cases have they defined symptom worsening. The assessment of the reported symptomatology assessed by VAS was positive for pain reductions in most of the patients treated with the maintenance of the result up to a year of follow-up.[98–100]

Arduino et al. realized a randomized pilot study on PBM versus clonazepam (actually one of the best treatments for BMS) in patients with BMS performing laser treatments with a 980 nm laser at 10 J/cm^2 weekly for 5 weeks with a follow-up of 12 weeks and comparing the results of this group with a group of patients treated for 21 days with clonazepam 2 mg tablets three times/day. Results in favor of the PBM group was significant particularly at 8 weeks of follow-up with a reduction of pain, anxiety, and quality of life.[101]

PBM and temporomandibular joint disorders

TMD are a set of dysfunctional models concerning the temporomandibular joints and chewing muscles with an incidence on about a 1/3 of the general population; the etiology of pain in this type of patients has not yet been clearly understood.

Among the described therapeutic procedures, PBM protocols have recently been proposed by literature to reduce pain intensity and improve maximum mouth opening in patients with acute and chronic TMD, who do not respond to other treatments. The data are reported in the literature for which the PBM approach is probably more effective for the treatment of joint dysfunctions with respect to problems related to masticatory muscles.[46–102]

The analgesic effect of PBM acts at different levels and with different mechanisms; this effect can be explained by the increased level of beta-endorphins in spinal liquor, increased urinary excretion of glucocorticoids, inhibitors of beta-endorphin synthesis, the increased pressure pain threshold through a complex electrolyte mechanism at the level of nerve fibers, decreased release of histamine and acetylcholine, reduced bradykinin synthesis, increased ATP production, improved local microcirculation, and reduced lymphatic flow edema.[102]

PBM in orthodontics

The application of PBM in the orthodontic field has seen, in recent years, an increased scientific production, initially with in vivo studies in the animal and then with clinical studies aimed at investigating the laser protocol application effect at low energy on the dental element movement acceleration with a simultaneous analgesic potential.[103] The stimulation effect of the proliferation and cell differentiation involved in bone metabolism, in particular osteoblasts and osteoclasts, is the basis of the results obtained, similarly to the maxillary and mandibular level, on the reduction of the time needed to finalize orthodontic therapy. This type of application, free from side effects, especially on the periodontium, defines a beneficial effect in the carious disease prevention strategy and the pain symptom simultaneous improvement often related to the active orthodontic movement phases.[104]

Studies in the literature, in particular, for protocols at different times of PBM administration (weekly, every other day, with monthly cadenced doses) report more striking effects for low fluence values (between 5 and 8 J/cm^2) compared with values above 20 J/cm^2.[103]

PBM treatments for pulp healing

PBM has been proposed also for the application on pulp treatment procedures. Fernandes et al.[105] described the improvement in radiographical success rate at different times of evaluation until the 18-month follow-up by adding PBM to calcium hydroxide, Also, Ansari et al.[106] reported similar results by adding PBM to a calcium-enriched mixture. Kuo et al.[107] compared diode application and sodium hypochlorite reporting positive results without a significant statistical difference.

Conclusions

Modern dentistry treatment success is created by ''minimally invasive dentistry'' that limits aggressive approaches in operative interventions as well as respects the patient's comfort and level of pain.

One factor that explains the increase of PBM in oral medicine is related to low-cost devices now available for patients without side effects. These devices provide compromised patients (i.e., oncologic patients) with noninvasive approaches that eliminate pain, offer short sessions, and have less discomfort.

The devices provide additional solutions for chronic issues by offering self-administered sessions of PBM done by patients at home under doctor supervision, and this opens the door for new perspectives within the PBM field.

Author Disclosure Statement

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