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Research Article

Photobiomodulation on Oral Mucosal Lesions- A Systematic Review

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Abstract

Background: Photo Biomodulation Therapy (PBMT) previously known as Low Level Laser Therapy is a therapeutic modality that uses red or near-IR light to treat the oro-mucosal lesions by the process of stimulation, healing, regeneration. It is used in the treatment of various pathologies, including several oral disease conditions and complications of oral cancer treatments. However, the results from PBMT varies significantly in various articles.

Aim of the study: To assess the significance of PBMT in the treatment of various oral mucosal lesions and complications of oral cancer treatment.

Research question: Can PBMT be used as a significant tool in the long-term therapeutics?

Materials and Methods: With the Medline, Cochrane and Medknow database (English literature) taken as reference, 20 articles that have undergone Randomized Control Trial was selected for the study after having met the criterion for Systematic Review.

Result: Photo biomodulation therapy is an important and significant tool to treat oral mucosal lesions.

Keywords: Photo Biomodulation; Cytochrome C Oxidase; ROS; ATP; NO

Introduction

LASER (light amplification by stimulated emission of radiation) was first discovered by Theodore H. Maiman in 1960 [1]. The term Photo biostimulation was coined by Endre Mester following his observation of the effects of low dose laser treatments on stimulation of wound healing [1]. Later, it was also noted that along with stimulation, light therapy may also modify certain deleterious processes, such as inflammation or pain, and thereby the term photo biomodulation (PBM) was established. Currently, PBM includes a broad range of nonionizing light sources such as lasers, Light-Emitting Diodes (LEDs), and broadband visible light in the visible and near infrared spectrum at very low, non-thermal doses. PBM stimulates both positive tissue processes such as wound healing, regeneration, and immune responses and negative tissue processes such as inflammation, pain, and aberrant immune responses. PBM is also used for the management of Oral Mucositis which is caused as a complication of oral cancer treatment [3].

Aim of the study

To assess the significance of PBMT in the treatment of various oral mucosal lesions and complications of oral cancer treatment.

Research Question

Is the current popular concept of PBMT significant in the long-term therapeutics?

Materials and Methodology

Although numerous researches and studies have been carried out with this regard so far, but there still exists an aorta of doubt about significance and therapeutic effects of PBMT in long term. With Cochrane collaboration taken as reference along with other scientific libraries such as Medline and Medknow, about 35 research/Study articles were selected having undergone Randomized Controlled Trial (RCT). Out of these 20 articles were screened and finally selected for our study based on the inclusion and exclusion criterion as discussed below.

The following table includes the list of finally selected 20 articles which were included in our study

SL No	Title of study	Author	Year
1	Photobiomodulation Therapy in Oral Mucositis and Potentially Malignant Oral Lesions: A Therapy Towards the Future	Reem Hanna, Snehal Dalvi., *et al*.	2020
2	Photobiomodulation safety in cancer patients: *In vivo* data. Support". *Care Cancer* 28 (2020): 3003-3006.	Bensadoun R and Epstein JB	2020
3	Evidence-based management of oral mucositis". *JCO Oncology Practice* (2020)	Lalla J	2020
4	Applications of Photobiomodulation Therapy in Oral Medicine-A Review	Mohamed Faizal Asan, G Subhas Babu, Renita Lorina Castelino, KumudaRao and Vaibhav Pandita	2021
5	Accelerated burn wound healing with Photobiomodulation therapy involves activation of endogenous latent TGF-β1. Scientific reports.	Khan I, Rahman SU, Tang E, Engel K, Hall B, Kulkarni AB, Arany PR.	2021
6	Photobiomodulation therapy in the treatment of a palatal ulcer	Chinam N, Vaidya A, John TT	2021

7	Safety and efficacy of Photobiomodulation therapy in oncology: A systematic review.	Bensadoun RJ, Epstein JB, Nair RG, Barasch A, Raber-Durlacher JE, Migliorati C, Genot-Klastersky MT, Treister N, Arany P, Lodewijckx J, Robijns J.	2020
8	Photobiomodulation therapy for oral mucositis management in head and neck cancer patients undergoing radiotherapy	JA Pacheco	2021
9	PBMT for the management of recurrent aphthous stomatitis in children: clinical effectiveness and parental satisfaction	Elena Bardellini, Federica Veneri., *et al*.	2020
10	Treatment of mucous membrane pemphigoid with low-level laser therapy". *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology* 129.1 (2020):e26.	Gomes IO, De Morais HO, Chagas WP., *et al.*	2020
11	Retrospective evaluation of the safety of low-level laser therapy/photobiomodulation in patients with head/neck cancer". *Support Care Cancer* 28.7 (2020):3015-3022.	Genot-Klastersky M, Paesmans M, Ameye L., *et al.*	2020
12	Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: Prospective randomized controlled Trial". *International Journal of Oral and Maxillofacial Surgery* 48.7 (2019):917-923.	Marı´n-Conde F, Castellanos-Cosano L, Pacho?n-Iban˜ ez J, Serrera- FigalloMA, Guti_errez-P_erez JL and Torres-Lagares D	2019
13	Photobiomodulation therapy in the treatment of oral mucositis, dysphagia, oral dryness, taste alteration, and burning mouth sensation due to cancer therapy: A case series". *International Journal of Environmental Research and Public Health* 16.22 (2019):4505.	El Mobadder M, Farhat F, El Mobadder W and Nammour S	2019
14	Tumor safety and side effects of photobiomodulation therapy used for prevention and management of cancer treatment toxicities-a systematic review	Depaul Paglioni M., *et al.*	2019
15	Efficacy of low-level laser therapy in management of recurrent herpes labialis: A systematic review". *Lasers in Medical Science* 33.7 (2018):1423-1430.	Al-Maweri SA, Kalakonda B, AlAizari NA., *et al*.	2018
16	Variation of energy in photobiomodulation for the control radiotherapy induced oral mucosities: a clinical study in head and neck cancer patients	Guedes CD., *et al*.	2018
17	Efficacy of low-level laser therapy in management of symptomatic oral lichen planus: A systematic review". *Lasers in Medical Science* 32.6 (2017): 1429-1437.	Al-Maweri SA, Kalakonda B, Al-Soneidar WA, Al-Shamiri HM, Alakhali MS and Alaizari N	2017
18	Mechanisms and applications of the anti-inflammatory effects of photobiomodulation	Michael Hamblin	2017
19	Efficacy of low-level laser for treatment of cancer oral mucositis:A systematic review and meta-analysis	Anschau F, Webster J and Capra MEZ	2019
20	Photobiomodulation or low-level laser therapy	Michael R Hamblin	2016

Table a

Result

PBMT is an important and significant tool that can be used in the treatment of oral mucosal lesions

Discussion

LASER (light amplification by stimulated emission of radiation) are intense beams produced by stimulated emission of radiation from a light source. Miaman was the first who introduced laser application in dentistry in 1960 [1] and its hard and soft tissue application. Albert's theory of spontaneous and simulated emission of radiation describes three characteristic features of lasers as follows

- Monochromatic, i.e., all the waves have the same energy and frequency
- Coherent, which describes all the waves of light to be in phases related to each other in speed and time
- Collimated ensuring parallelism of the waves (low beam divergence

Laser can interact with biological tissues in four different mechanisms

- Reflection
- Scattering
- Absorption
- Transmission

According to tissue applicability or according to the wavelengths and the risk associated with laser application, lasers are classified into

Soft/Athermic/Cold	Hard/Thermic/Surgical
CO2	CO2 (10.6 μ)
He-Ne	Er: YAG
Diode	Er, Cr: YSGG
GaAs (830 nm)	Argon
	Nd: YAG

Table b

The effects of photo biomodulation therapy (PBMT) on the lased tissue can be described in the following steps.

As the cell is exposed to laser, the red (600-700 nm) to near-infrared (760-900) photonic energy is absorbed by the chromophores including cytochrome c oxidase which increases its activity. Cytochrome C Oxidase (CCO) is the mitochondrial enzyme which is responsible for oxygen consumption in electron transport chain in cellular bioenergetics. CCO absorbs photonic energy resulting in the release of the adenosine triphosphate (ATP), dissociation of nitric oxide (NO) and modulation of reactive oxygen species (ROS) [3].

The increased production of ATP stimulates the fibroblasts, promotes collagen formation, increases the cells ability to fight infection and accelerates the healing process. The modulation of ROS activates transcription factors causing cellular repair and healing. The dissociation of nitric oxide, a potent vasodilator from cytochrome c oxidase increases circulation, decreases inflammation and enhances the transport of oxygen and immune cells throughout the tissues.

The tertiary effects specifically effect on the cell membrane and nucleus, which control gene transcription, intracellular signalling pathway and subsequently cell proliferation, migration, apoptosis, promotion of growth factor production, antioxidant response, and stimulation of cell repair and inflammation [3]. PBMT helps in pain elimination by inhibiting A- delta and C fibres. The release of pain mediators from injured tissues will be inhibited by PBMT along with the increase in the acetylcholine esterase activity. PBMT improves bone healing by accelerating stem cell differentiation into osteoblasts by activating transcription factors and also through increasing calcium transport during bone formation. PBMT also found to be helpful in increasing bone mineralisation. Angiogenesis is also promoted as PBM acts on the regulation of Vascular endothelial growth factor (VEGF) and Hypoxia induced factor1 alpha (HIF-1alpha).

The quaternary effects of PBMT are the distant, systemic effects associated with the tissues that have not absorbed the photonic energy. But they can still be affected indirectly by the secretions of the cells that have absorbed the laser light [3]. These effects are still under research.

Treatment dose

Arndt-Schultz Law governs the bio stimulatory and inhibitory effects of lasers. According to the Arndt-Schulz Law, weak stimuli will excite physiological activity, moderate stimuli will inhibit and strong stimuli will retard physiological activity. This is also called the biphasic dose response [1]. Therefore, PBMT uses low level doses approximately less than 10 J/cm^2 for stimulating cell repair and higher dose i.e., above 10 J/cm^2 for cell ablation.

Dose or Fluence is a laser parameter of the power output, application time and optical footprint within the tissues.

DOSE = ENERGY/IRRADIATION AREA [1]

The depth of treatment target site, the target tissues and the type of tissues must be taken into consideration. Factors affecting this are wavelength and photon intensity. Variations in the wavelength results in varied absorption into tissues. If photon intensity is low, sufficient absorption of the photons will not occur and the desired result will not be attained. If the photon intensity is too high, the photon energy will be transformed to excessive heat in the target tissue which causes undesirable effects. So optimum photon intensity is needed for optimum desired results. Most of the studies has been in agreement that 1-5J is the optimal power density for proliferation.

Indications

Oral mucosal lesions

Recurrent aphthous stomatitis (RAS) is a very common clinical condition producing painful ulcerative lesions in the oral cavity. PBMT is effective in the pain relief and healing of these lesions when used with a diode laser of 645 nm wavelength, power 100mw onto the lesion of spot size 1cm^2 for a duration of 30sec per cm^2 and energy density 10J/cm^2 used in continuous mode for 3 consecutive days [1]. PBMT with a diode laser of 940nmused in noncontact mode for 30-45 seconds with a pause for 10-20 seconds and a total of 2 minutes in a single session has shown faster reduction of pain and healing of ulcers. Some of the studies have shown that PBMT is also helpful in prevention of recurrent aphthous stomatitis in children [5].

Oral lichen planus (OLP) is a common, idiopathic, chronic, inflammatory, mucocutaneous disorder associated with cell-mediated immune system dysfunction. Clinically it is classified into reticular, papular, plaque-like, erosive, atrophic, and bullous. A range of therapeutic approaches are used with steroids typically being used as standard treatment. However, patients frequently present relapses after treatments discontinuation, develop resistance to corticosteroid therapy as well as secondary candidiasis. Low-level laser therapy (LLLT) is considered to have biostimulatory, anti-infective, and anti-ablation effects and has been proposed as a potential alternative treatment. PBM twice a week. during 1 month (8 sessions) with laser of wavelength 660+/-10nm; power 100mW; radiant energy 177J/cm2; 5sec exposure time per point and 0.5 J of energy per point is found to be effective as corticoid therapy in treating oral lichen planus. The number of points will be variable according to the lesion size. Erosive lichen planus is mainly treated by a 630 nm low-level laser for 10 sessions a month with the power of 1.5 J/cm2. PBMT with red diode lasers helps in analgesic effect in the patients without causing any significant side effects [12].

Herpes labialis is a viral infection caused by herpes simplex virus-1 primarily affecting lips. PBMT uses an infrared diode laser operating in a wavelength of 780 nm for 80 seconds, focusing at four points over the herpetic lesion. A dose of 5 J/cm2 for one point is given for 3 consecutive days. Complete relief of symptoms and scabbing is noticed after the treatment. One of the studies proved that antimicrobial photodynamic therapy (aPDT) along with PBM help in the resolution of herpes simplex labialis, oral lesions of patients affected by COVID-19 [25]. Garcez., *et al.* (2021)used a protocol of 03 sessions of aPDT (660nm diode laser + methylene blue) on the lips and tongue, every 24 hours to control contamination, followed by PBMT (low power laser, 100 mW, 2 J/point) for the lips, tongue and oral mucosa for four additional sessions every 24 hours, in ulcerative lesions, hemorrhagic crusts, petechiae and erythematous lesions in patients with COVID-19.The vesicle phase of herpes simplex is highly contagious, here aPDT acts as an alternative to decontaminate and pass to the crust phase after 24 hrs. PBM accelerates tissue healing, reducing the time to remission of the lesion in the crust phase. It is thus the exact identification of clinical stage of herpes important for the proper treatment to be initiated. Some studies have shown that PBMT using lasers within

a wavelength between 632.8 nm and 870 nm, power of 5-80 mW, and 2.04-48 J/cm2 is successful in the management of the recurrent herpes [15]. In another study which included 2 phases of PBM was found to be useful in the reduction in frequency and severity of recurrences. Phase 1 used diode low power laser with wavelength of 660nm-808nm; fixed power of 100mW; energy 1-9 J; area of 0.09cm2 was used for 10 sessions with an interval of 48 hrs between them [24]. After 6 months, Phase 2 treatment was done for 5 sessions [24].

Burning mouth syndrome

Burning Mouth Syndrome (BMS) is a painful condition with a complex etiology and diverse clinical presentation characterised by a burning sensation or pain in the oral mucosa. PBMT has been used as one of the treatment modalities in BMS. Diode lasers comprising gallium-aluminium-arsenide (GaAlAs) in a wavelength of (infrared) 830 nm, indium-gallium-aluminium-phosphide (InGaAlP) in a wavelength of (red) 685 nm, and energy of about 2-5 J per point is used for irradiating sites for about a period of 4-10 weeks [13]. PBMT also reduces the levels of proinflammatory cytokines in saliva such as tumor necrosis factor-alpha and interleukin-6. PBMT acts on the neural impulse conduction and inhibit pain mediators resulting in the analgesic effect. PBM, in particular, red laser protocols, is helpful in pain reduction and improvement of quality of life of burning mouth syndrome patients.

Vesiculobullous disorders

PBMT is of great significance in the management of oral lesions of vesiculobullous disorders like pemphigus and pemphigoid. Lasers of about a wavelength of 660-780 nm and a dose of 8J/cm^2 is targeted at the lesions per point and done twice weekly which resulted in the symptomatic relief and regression of the lesions [6]. Photobiomodulation therapy has been found to be useful in the regression of oral ulcers associated with toxic epidermal necrolysis [22].

Paraesthesia

Paraesthesia of the inferior alveolar nerve is one of the commonly occurred condition after any surgical procedure of the mandible. PBMT with in a wavelength of about 808-830 nm, 70-200 mW targeting the affected area with an energy dose of about 10 J/cm2 per point three times per week for 10-16 sessions has been used for the management of post-operative paraesthesia [19,20]. PBM presented with positive effects on neurosensory recovery in patients suffering from Inferior alveolar nerve injury. PBM therapy was more helpful in patients with shorter duration of paraesthesia. Some studies have found that trigeminal nerve injuries can be effectively treated by PBMT with a wavelength of 800-810 nm, 0.2 W, 12J/cm^2, 12J per point for a time period of 60 seconds in an area of 1cm^2 in continuous mode on 1, 5 ,10 and 14 days after surgery [21].

Oral mucositis

Oral mucositis is the inflammation of the oral mucosal membrane. This is also seen as a side effect of chemo and radiotherapy in cancer patients. According to some studies, lasers with a wavelength of 632-970 nm and an energy dose of 4J/cm^2 has been effective in the management of oral mucositis [12]. Using PBMT directly over an active tumor is not recommended by North American Association for photo biomodulation therapy due to the risk of transformation and stimulation of active cancer cells. But some of the recent studies have proved that PBMT does not affect the survival, time to local recurrences, and disease-free survival of patients treated with radiotherapy.

Conclusion

PBMT has been an effective therapeutic modality in the management of several oral mucosal lesions and oral complications occurring during cancer therapy. Henceforth more research have to be carried on the newer applications of PBMT in dentistry along with the accurate standardization of the wavelength, dosage, and treatment duration for different disorders.

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