Decade Long Survey of Low-level Laser Therapy/ Photobiomodulation (LLLT/PBM) Therapy for Oral Mucositis Treatment

Hyun Seok Ryu^{1,2}
Celine Abueva¹
Phil-Sang Chung^{1,3}
Seung Hoon Woo^{1,3}

¹Beckman Laser Institute, Cheonan, Korea

²Interdisciplinary Program for Medical Laser,
Dankook University, Cheonan, Korea

³Department of Otorhinolaryngology-Head and
Neck Surgery, Dankook University College of
Medicine, Cheonan, Korea

Low-level laser therapy or photobiomodulation (LLLT/PBM) therapy has been widely applied to enhance and accelerate the recovery of oral mucositis. This study investigates the documented effect of LLLT on oral mucositis caused by chemotherapy. This review appraises 6 animal studies and 12 clinical studies published in the Pubmed database during the past 10 years, related to the application of LLLT for the treatment of mucositis. Despite varied parameters and diverse conditions, the assessed articles indicate that application of LLLT on oral mucositis using near-infrared wavelengths is prophylactic, reduces pain, and enables a rapid recovery. Various combined treatments were also identified among the published papers, which further establishes the efficacy of LLLT as a viable treatment.

Key words

Oral mucositis; Low-level laser therapy; Photobiomodulation therapy; Chemotherapy

Received April 5, 2021

Accepted June 7, 2021

Correspondence

Seung Hoon Woo
Department of Otorhinolaryngology-Head and
Neck Surgery, Dankook University College of
Medicine, 119 Dandae-ro, Dongnam-gu,
Cheonan 31116, Korea
Tel.: +82-41-550-1781
Fax: +82-41-550-7837
E-mail: lesaby@hanmail.net

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INTRODUCTION

Oral mucositis (OM) is a common condition experienced by patients who underwent chemo and radiation therapy for head and neck cancers. It is identified as one of the general complications (40%) of concern in many types of chemotherapy drugs.^{1,2} More than 90% of patients with head and neck cancer who received chemo and radiotherapy develop oral mucositis.^{3,4} Aside from chemo and radiotherapy, approximately 80% of the patients who received hematopoietic stem cell therapy (HSCT) have also been found to develop OM.

The patients suffering from OM usually complain of pain in the mouth characterized by an inflamed collapsed mucous membrane which potentially progresses into ulcers.⁵ Functional damage to the oral cavity by OM can cause speech and eating disorders. Thus, this condition negatively impacts the patients' quality of life affecting nutrition, ability to communicate, and introducing the risk for secondary infection which can interfere with the cancer treatment.⁶ Progressive ulcer formation increases the risk of pain and sepsis by increasing bacterial and fungal infections.⁷ Additional treatments to relieve their symptoms are prescribed to patients with OM. Recommended treatments include local antimicrobial agents, vitamins, and mouthwash for gargle (Fig. 1). However, these treatments do not result in considerable alleviation of OM in afflicted patients.^{8,9} Although articles emphasizing the importance of preventing mucosal inflammation through oral and hygienic management have been published a clear-cut strategy to reduce the incidence of OM in cancer patients is yet to be established.

On the other hand, several authors have found that low-level laser therapy/photobiomodulation (LLLT/PBM) potential for mitigating oral inflammation.¹⁰⁻¹³ The emission

wavelength used in LLLT/PBM therapy is within the red to near-infrared range (630 to 830 nm) of the electromagnetic spectrum and an average power density between 5 and 150 mW/cm² which does not extreme heat effects because of their low power used and large exposure area. Low-level laser therapy works by regulating certain cellular metabolic processes of the tissues exposed to light energy. Light energy is absorbed by the cytochromes and porphyrins within the mitochondria, which promotes cell activation, cell proliferation, and differentiation, and triggers an acceleration of the regeneration process.¹⁴⁻¹⁷ Dispersed elevated temperature results in cellular bio-stimulation and aids in the reduction of pain and inflammation in affected tissues. These effects help with cell nutrition and promote the development of dense micro-vascularization within local connective tissue leading to accelerated wound healing and reduced swelling.¹⁸⁻²⁰ These mechanisms are particularly useful for alleviating OM symptoms by prompting pathways that control inflammation and pain.²¹⁻²⁵ Treatment of OM with LLLT/PBM aims to prevent or reduce inflammation and promote cellular metabolism.²⁶⁻²⁸

Years of in vitro studies, in vivo studies, and clinical trials have provided a significant amount of useful information on LLLT/PBM application.²⁹ A wide range of parameters including wavelength, power, energy density, irradiation duration, and continuity is essential for its effectiveness and safety.³⁰ Despite evidence in favor of LLLT/PBM as a therapeutic option, a clear established treatment protocol is yet to be established due to the considerable range of parameters to be considered.^{24,31-34} This study aimed to conduct a review of published studies from the past ten years that affirm the positive effects of LLLT/PBM therapy on OM induced by chemotherapy and/or radiotherapy.

Fig. 1. Recommended treatment types for oral mucositis management.

MATERIALS AND METHODS

The author searched the PubMed database for papers from the last 10 years using the keywords "low-level laser therapy"/"photobiomodulation"/"LLLT"/"PBM" and "Oral mucositis" and "chemotherapy". A total of 18 papers have been reviewed, including human and other species studies related to keywords. Systematic reviews and meta-analyses were excluded. The author selected and prepared papers related to this content, such as research topics, titles, and methods.

RESULTS

A total of 18 relevant articles were obtained from the PubMed database of which 6 involved animal experiments; 4 studies used hamsters and the rest used Sprague Dawley rats (Table 1). The wavelength used for the treatment of oral mucositis ranged from 660 nm to 940 nm, and various treatments were used at the same time. The animal experiments indicated that the use of LLLT as a prophylactic and application of LLLT at low doses significantly improves its efficacy as a treat-

ment.³⁵⁻³⁸ Simultaneous application of dual wavelengths showed better results than using a single wavelength.³⁹ In a comparison between LLLT and photodynamic therapy (PDT) treatment using indocyanine green (ICG), ICG has been found to possibly accelerate the effects provided by LLLT.⁴⁰ From the 12 clinical studies, 8 utilized LLLT/PBM while the remaining 4 made use of photosensitizers or other treatment groups (Table 2). Application of LLLT/PBM as either a prophylactic against OM before chemo and/or radiotherapy or as a treatment for OM have been conducted and results indicated that it was effective in preventing OM, OM grade reduction, and OM pain management.⁴¹⁻⁴⁷ Lesion reduction was also observed in studies combining LLLT/PBM treatment with photosensitizers though to a lesser extent.^{48,49} This combination was recommended to reduce the OM grade, shorten the recovery period,⁵⁰ and if an infection was suspected.⁴⁹ There were also cases where there was no statistically significant difference in pain reduction and OM.^{51,52}

DISCUSSIONS

This study aimed to review articles published in the past

Table 1. Data of selected animal studies

Author (year)	Title	Therapy protocol	Result
Freire et al. ³⁵ (2014)	LED and laser photobiomodulation in the prevention and treatment of oral mucositis: experimental study in hamsters	Laser (GaInPAI, 660 nm, 40 mW, 4.8 J/cm ²) LED (670 nm, 150 mw, 4 J/cm ²)	Preventive treatment is better than therapeutic treatment in the case of chemotherapy mouth mucosa
Campos et al. ³⁶ (2016)	Comparative study among three different phototherapy protocols to treat chemotherapy-induced oral mucositis in hamsters	InGaAlP diode laser (660 nm, 40 mW, 6 J/cm ²) LED (635 nm, 120 mW, 1.2 J/cm ²) GaAlAs high power diode laser (defocused, 808 nm, 1.0 W, 10 J/cm ²)	LLLT and LEDs reduced the severity of OM and were more effective in wound healing than high-power laser therapy
Bayer et al. ³⁷ (2017)	Comparison of laser and ozone treatments on oral mucositis in an experimental model	Diode laser (940 nm, 1W, 7.14 J/cm ²) Ozone generator (80% oxygen, 120 s)	Both laser and ozone therapies have effects, but laser therapy is more effective
Cotomacio et al. ³⁸ (2017)	Dosimetric study of photobiomodulation therapy in 5-FU-induced oral mucositis in hamsters	Diode laser (660 nm, 40 mW) Group: L1 (6 J/cm ² , 6 s, 1 point), L2 (25 J/cm ² , 25 s, 1 point), L3 (24 J/cm ² , 6 s, 4 point)	Low energy density was the most effective treatment effect, but depending on the application and treatment area, it could interfere with OM treatment
Thieme et al. ³⁹ (2020)	Comparison of photobiomodulation using either an intraoral or an extraoral laser on oral mucositis induced by chemotherapy in rats	Group: Intraoral (InGaAlP, 660 nm, 100 mW, 6 J/cm ²), Extraoral (pulse diode laser, 810 nm + 980 nm, 2 W, 6.11 J/cm ² , 12.22 J/cm ²)	The protocols of intraoral and extraoral irradiation have positive effect but the most effective protocol is the extraoral 6.11 J/cm ²
Alinca et al. ⁴⁰ (2019)	Comparison of the efficacy of low-level laser therapy and photodynamic therapy on oral mucositis in rats	Group: LLLT (Diode laser, 810 nm, 0.3 W, 18.75 J/cm ²) Photodynamic therapy (Indocyanine green + LLLT (Diode laser, 810 nm, 0.3 W, 18.75 J/cm ²))	Comparison of PDT and LLLT resulted in PDT leading to more growth factors. ICG also promoted the LLLT effect in the study

LED, light-emitting diode; LLLT, low-level laser therapy; OM, oral mucositis; PDT, photodynamic therapy; ICG, indocyanine green.

Table 2. Data of selected human studies

Author (year)	Title	Therapy protocol	Result	Anticancer therapy
Antunes et al. ⁴¹ (2013)	Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation	InGaAlP diode (660 nm, 100 mW, 4 J/cm ²)	LLLT improved grade 3-4 OM in HNSCC patients receiving chemoradiation therapy to grade 2 or grade 0-1. LLLT was effective in preventing Grade 3-4 OM	Chemoradiation
Silva et al. ⁴² (2015)	The impact of low-level laser therapy on oral mucositis and quality of life in patients undergoing hematopoietic stem cell transplantation using the oral health impact profile and the functional assessment of cancer therapy-bone marrow transplantation questionnaires	InGaAlP diode (660 nm, 40 mW, 4 J/cm ²)	The severity of OM by chemotherapy in patients receiving HSCT was reduced by using LLLT, but there was no improvement in the quality of life	Chemotherapy and/or radiotherapy
Amadori et al. ⁴³ (2016)	Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study	DioBeam 830 diode laser (830 nm, 150 mW, 4.5 J/cm ²)	The difference in OM grades reduction in LLLT was not statistically significant. However, the LLLT treatment group had a pain reduction effect	Chemotherapy
Antunes et al. ⁴⁴ (2017)	Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis	InGaAlP diode (660 nm, 100 mW, 4 J/cm ²)	In the group that treated LLLT before chemotherapy treatment, the use of opioid decreased, and OM grade was also found to be lower than the control group	Chemoradiation
Medeiros-Filho et al. ⁴⁸ (2017)	Laser and photochemotherapy for the treatment of oral mucositis in young patients: Randomized clinical trial	LLLT: InGaP (660 nm, 100 mW, 4 J/cm ²) PCT: InGaP (660 nm) & AsGaAl (808 nm), 100 mW, 4 J/cm ² , 0.005% Methylene Blue	Treatment combining PCT and LLLT is more effective in reducing severity and lesion size of OM than treatment with LLLT only	Chemotherapy
Rozza-de-Menezes et al. ⁵¹ (2018)	Behaviour and prevention of 5'fluorouracil and doxorubicin-induced oral mucositis in immunocompetent patients with solid tumors: a randomised trial	Chlorhexidine: 0.12%, mouth wash twice a day Triclosan: 0.03%, mouth-wash twice a day LLLT: 660 nm, 4 J/cm ²	Despite the lack of statistical significance, treatment with IOCP and LLLT showed positive results to prevent OM	Chemotherapy
Gobbo et al. ⁴⁵ (2018)	Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT	Eltech K-Laser (660 and 970 nm-combined, 3.2 W, 36.8 J/cm ²)	A statistically significant difference in OM grade and self-reported pain persisted through day 11	Chemotherapy
Ribeiro da Silva et al. ⁴⁹ (2018)	Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy	PDT: diode laser (660 nm, 100 mW, 107 J/cm ² , 0.01% Methylene Blue) LLLT: diode laser (660 nm, 100 mW, 35 J/cm ²)	PDT and LLLT could be used for OM treatment in pediatric/adolescent patients because there is no significant difference in treatment outcome. However, the authors recommend using PDT in case of infection	Chemotherapy
Noirit-Esclassan et al. ⁴⁶ (2019)	Photobiomodulation with a combination of two wavelengths in the treatment of oral mucositis in children: The PEDIAL-ASE feasibility study	Diode laser phototherapy system (635 nm & 815 nm, 150 mW, 4 J/cm ²)	External and internal applications through a combination of two wavelengths showed no association between HEDEN mucosa scores and hematological recovery, but improved HEDEN mucosa scores without hematological recovery and alleviated OM-related pain	Chemotherapy and/or radiotherapy

Table 2. Continued

Author (year)	Title	Therapy protocol	Result	Anticancer therapy
Legouté et al. ⁵² (2019)	Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: results of a randomised, triple blind, multicentre phase III trial	He-Ne laser HETSCHL® (658 nm, 100 mW, 4 J/cm ²)	No difference in pain and OM	Chemoradiotherapy
Marín-Conde et al. ⁴⁷ (2019)	Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: prospective randomized controlled trial	Diode laser (940 nm, 0.5 W, 83.3 J/cm ²)	photobiomodulation with LLLT reduces the incidence and severity of mucositis in patients treated with radiotherapy and/or chemotherapy	Chemoradiotherapy
Pinheiro et al. ⁵⁰ (2019)	Photobiomodulation therapy in cancer patients with mucositis: a clinical evaluation	PBM-T : low-intensity laser (660 nm, 100 mW, 142 J/cm ²) PDT : blue LED (468 nm, 1200 mW, 5 min), curcumin (1.5 g/L)	PBM-T and PBM-T+PDT treatments for OM showed that the PBM-T+PDT group had a short recovery period and a decrease in the grade of OM, but there is no statistically significant difference	Chemotherapy and/or radiotherapy

HNSCC, head and neck squamous cell carcinoma; PCT, photochemotherapy; HEDEN, Hétéro Evaluation Douleur Enfant.

decade to verify the effect of LLLT/PBT treatment on the recovery of chemotherapy-induced oral mucositis. Six animal studies were reviewed for the treatment of chemotherapy-induced oral mucositis and 12 human studies were reviewed for the treatment of chemotherapy and/or radiotherapy-induced oral mucositis. Both animal and human studies used near-infrared wavelengths (600–1100 nm) for LLLT/PBM treatments and demonstrated it was effective for tissue recovery and pain reduction for oral mucositis. Results from previous studies on inflammation reduction and pain relief through LLLT were confirmed^{3,31,53} and the majority of the recent studies involved combination treatment rather than LLLT alone. The combined treatment was carried using a complex wavelength or coupled with PDT. The complex wavelength was applied by using two or more different wavelengths at the same time while a photosensitizer was used for experiments using PDT combined with LLLT/PBM. Clinical studies demonstrated that tissue recovery was promoted through the combined PDT and LLLT treatment however number of cases was insufficient thus no significant results were obtained.^{48–50}

In summary, studies using the near-infrared wavelength laser and applying various parameters are in progress and LLLT has the potential to lessen pain, reduce lesions, and promote wound healing as a prophylactic treatment as well as a remedy for mucositis caused by chemical and/or radiation therapy. However, studies on the prevention of mucositis are insufficient, and treatment mechanisms and treatments are not well defined, making

relevant clinical techniques difficult to establish. Continued investigations involving a wider range of wavelength, varied parameters, and considerable sample size are needed for further consolidation for relevant information regarding the usability of LLLT/PBM for oral mucositis.

CONFLICT OF INTEREST

Seung Hoon Woo is the Editor-in-Chief of the journal but was not involved in the review process of this manuscript. Celine Abueva and Phil-Sang Chung are editorial board members of the journal but were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

FUNDING

None.

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How to cite this article: Ryu HS, Abueva C, Chung PS, Woo SH. Decade long survey of low-level laser therapy/photobiomodulation therapy (LLLT/PBM) for oral mucositis treatment. *Med Lasers* 2021;10:138-145. <https://doi.org/10.25289/ML.2021.10.3.138>