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Review article

Efficacy of low-level laser therapy for preventing and treating oral mucositis in pediatric oncology patients: A meta-review

Eficacia de la terapia con láser de baja potencia en la prevención y tratamiento de la mucositis oral en pacientes oncológicos pediátricos: una meta-revisión

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ABSTRACT

This meta-review analyzed four major studies (published between 2021 and 2023) that evaluated photobiomodulation therapy for oral mucositis in pediatric oncology patients. The analysis included 3,314 patients across 154 studies, examining wavelengths (620-970 nm) and power settings (0.005-3.2 W). Results showed significant mucositis severity reduction (RR = 0.35, 95%CI 0.25-0.45), high treatment adherence (91%, 95%CI 88.30-93.70), and notable pain reduction [SMD = -0.85, 95%CI -1.20-(-)0.50]. Using WHO classification systems, positive outcomes were demonstrated across chemotherapy, radiotherapy, and HSCT treatments, supporting PBM's effectiveness in pediatric oncology settings.

Keywords: Photobiomodulation therapy; Oral mucositis; Pediatrics; Oncology; Low-level light therapy.

RESUMEN

Esta meta-revisión analizó cuatro estudios principales (2021-2023) que evaluaron la terapia de fotobiomodulación para la mucositis oral en pacientes oncológicos pediátricos. El análisis incluyó 3.314 pacientes en 154 estudios, examinando longitudes de onda (620-970 nm) y configuraciones de potencia (0,005-3,2 W). Los resultados mostraron una reducción significativa en la severidad de la mucositis (RR = 0,35; IC95% 0,25-0,45), alta adherencia al tratamiento (91%; IC95% 88,30-93,70) y una notable reducción del dolor (DME = -0,85; IC95% -1,20-(-)0,50). Utilizando los sistemas de clasificación de la OMS, se demostraron resultados positivos en tratamientos de quimioterapia, radioterapia y TCMH, respaldando la efectividad de la TFB en entornos oncológicos pediátricos.

Palabras clave: terapia por fotobiomodulación; mucositis oral; pediatría; oncología; terapia por luz de baja intensidad.

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INTRODUCTION

Oral mucositis (OM) represents one of the most severe and debilitating complications associated with non-surgical antineoplastic treatments, such as chemotherapy and radiotherapy.[1-3] This acute inflammatory process affects the gastrointestinal tract mucosa, particularly in the oral cavity, characterized by erythema, edema, painful ulcerations, dysphagia, and odynophagia, among other symptoms that significantly compromise patients' quality of life.[4-6]

The pathophysiology of OM is complex and multifactorial, beginning with direct DNA damage to mucosal cells caused by antineoplastic agents, followed by the formation of reactive oxygen species, which triggers alterations in the immune response, induces cellular apoptosis and tissue injury, and ultimately progresses to mucosal ulceration in the presence of proinflammatory substances.[8,9] The World Health Organization (WHO) scale represents one of the most widely used tools in clinical practice for evaluating OM severity, which assesses OM in 5 grades, from grade 0 to grade 4. However, other scales evaluate multiple variables, allowing for a more detailed assessment.[10] This condition requires a multidisciplinary approach as it can result in serious complications, such as secondary bacterial and fungal infections, due to the disruption of mucosal barriers and immunosuppression secondary to oncological treatment.[11]

In the pediatric population, the incidence of OM is alarmingly high, with reports indicating that between 52% and 80% of children undergoing antineoplastic treatment present some degree of this complication.[12-16] Unlike the adult population, pediatric patients have unique characteristics that make them prone to this condition, such as faster cell regeneration, an immature immune system, and greater susceptibility to therapy-associated toxicity.[17-19] These factors, combined with poor oral hygiene practices and inadequate nutritional status, increase the risk of severe OM development, which can lead to high morbidity, impair adequate nutrition, require intensive analgesic management, prolong hospital stays, delay oncological treatments, and significantly increase healthcare costs.[20-26]

Currently, there is no universally effective prophylactic treatment for OM, and clinical management focuses on symptom palliation and prevention of secondary infections. Traditional therapeutic strategies include the use of analgesics, anti-inflammatory agents, antibiotics, antifungals, cryotherapy, and strict oral hygiene measures.[27-29] However, these interventions are limited in preventing OM occurrence or accelerating oral lesion healing.[11,30] In this context, photobiomodulation (PBM), especially low-level laser therapy (LLLT), has emerged as a promising option for OM management.[31-34]

LLLT utilizes specific wavelengths of light (typically between 630 and 900 nm) to stimulate biological processes at the cellular level, including fibroblast proliferation, collagen synthesis, and modulation of the inflammatory response, with no significant reported adverse effects.[35-38] The mechanism of action is based on the absorption of light energy by intracellular chromophores, leading to increased adenosine triphosphate (ATP) production and the generation of reactive oxygen species.[39-41] These changes activate intracellular signaling pathways that promote tissue repair, angiogenesis, and pain reduction through modulation of neuronal excitability and endogenous endorphin release.[42] Scientific evidence suggests that LLLT not only reduces OM severity but may also prevent its occurrence when used prophylactically in patients undergoing oncological treatments, particularly those receiving radiotherapy in the head and neck region.[43-45]

This study aimed to systematically review existing literature on the efficacy of low-level laser therapy in preventing and treating oral mucositis in pediatric oncology patients.

METHOD

Protocol

A systematic literature review was conducted to assess the effectiveness of low-level laser therapy in preventing and treating oral mucositis in pediatric oncology patients, specifically evaluating application parameters, therapeutic efficacy, and clinical outcomes. This systematic review was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[46] standards and was registered with PROSPERO (CRD42024599982).

PICO strategy

Based on the PICO strategy,[47] the following question was formulated: What is the efficacy of low-level laser therapy for preventing and treating oral mucositis in pediatric oncology patients?

Participants: Pediatric oncology patients (0-18 years) receiving chemotherapy, radiotherapy, or hematopoietic stem cell transplantation**.** Intervention**:** Low-level laser therapy (LLLT)/Photobiomodulation (PBM). Comparison**:** Standard care or placebo/sham treatment**.** Outcomes: Incidence and severity of oral mucositis, pain levels, healing time, treatment adherence, and quality of life during cancer treatment.

Information sources and search strategy

The keywords used in the databases (PubMed, ScienceDirect, ClinicalKey, Ebscohost) to select reviewed publications were "low-level laser therapy," "oral mucositis," "pediatric patient," and "children." The Boolean search strategy used the combination ("low-level laser therapy") AND "oral mucositis" AND ("pediatric patient" OR children). The search focused exclusively on open-access articles published between 2019 and 2024.

Eligibility criteria

The rationale for including mixed-population studies: Given the limited number of systematic reviews that focus exclusively on pediatric populations, studies with mixed demographics were included if they provided extractable pediatric subgroup data or if pediatric patients comprised a substantial portion (>30%) of the study population.

Inclusion criteria: The meta-review included systematic reviews and meta-analyses published between 2019 and 2024 that evaluated the use of Low-Level Laser Therapy (LLLT)/photobiomodulation therapy for the prevention and/or treatment of oral mucositis in pediatric oncology patients (0-18 years) with hematological cancers or solid tumors who were undergoing chemotherapy, radiotherapy, or hematopoietic stem cell transplantation.

Exclusion criteria: This meta-review excluded systematic reviews that focused exclusively on adult populations. However, systematic reviews that included mixed populations (pediatric and adult patients) were included if they provided separate analysis or subgroup data for pediatric patients (0-18 years) or if pediatric patients represented a significant portion of the study population. Studies were also excluded if they involved noncancer patients, patients not at risk of developing oral mucositis due to their cancer treatment, were published before 2019 or after 2024, or were not available as open-access publications. Additionally, single-arm experimental studies, case reports, case series, and narrative reviews were excluded from the analysis.

Data collection process

Two primary observers conducted the research, with a third observer serving as a mediator to resolve any discrepancies. The selection process involved reviewing titles and abstracts, as well as examining eligible full-text studies. Data extraction utilized a pilot-tested, standardized form that documented authors' information, study characteristics, and methodological approaches. The form captured LLLT intervention parameters (wavelength, power output, energy density, treatment duration), population characteristics, and clinical outcomes based on WHO mucositis classification. Effectiveness was assessed through pain levels, healing time, and treatment adherence.

Quality assessment of studies and risk of bias

Two researchers independently evaluated the literature and thoroughly reviewed the original texts. In case of evaluation discrepancies, a third researcher acted as a mediator. Differences in evaluation scores were discussed until a final consensus score was agreed upon, using the Joanna Briggs Institute (JBI) checklist.[48]

Heterogeneity assessment and data synthesis

The study did not include primary studies, analytical observational studies, or randomized clinical trials, resulting in a limited number of studies. This document is a review of other reviews, also known as a meta-review. Consequently, the assessment of heterogeneity, I-squared statistics, and similar metrics do not apply in this context and should be omitted from the analysis.

Data analysis and outcome measures

The analysis strategy was determined considering the following standardized outcome measures. Primary outcome (treatment efficacy): Risk ratios (RR) with 95% confidence intervals for mucositis severity reduction. Secondary outcomes: Pain reduction: Standardized mean difference (SMD) with 95% confidence intervals. Treatment adherence: Proportions with 95% confidence intervals.

Ethical considerations

Considering that this study employs retrospective documentary research techniques and methods and does not perform any intervention or modification in biological, physiological, psychological, or social variables to study participants - including review of medical records, interviews, questionnaires, and others that do not identify or deal with sensitive aspects of their behavior - it is considered a risk-free study, according to resolution 008430 of 1993 of the Ministry of Health of Colombia.[49]

RESULTS

Study characteristics

A comprehensive analysis was conducted on four systematic reviews, comprising 154 studies with a total of 3,314 participants. Patel et al.[50] contributed the most extensive dataset, examining 1,830 patients across 107 studies. Hafner et al.[52] followed with a substantial analysis of 929 patients from 15 studies, while Lai et al.[51] evaluated 256 patients across 26 studies. Cruz *et al*.[53] completed the dataset with a focused meta-analysis of 299 patients from 6 studies.

It is essential to note that although our inclusion criteria focused on pediatric populations, some of the selected systematic reviews (notably Patel *et al*.[50]) included mixed populations comprising both adult and pediatric patients. These studies were included because they provided valuable subgroup analyses for pediatric patients and represented the most comprehensive evidence available for LLLT in pediatric oncology mucositis management. The demographic distribution across studies revealed that 38.70% of patients in the Patel et al. study were pediatric, providing substantial pediatric-specific data for analysis.

Table 1. Study characteristics and patient demographics.

Author	Study type	Patients	Age	Cancer type	Treatment type	Primary outcome (95%CI)
Patel *et al*.[50]	Systematic Review	1830 (107 studies)	6-84 years (61.30% adult and 38.70% pediatric)	61.30% solid tumors, 38.70% hematological	Chemotherapy radiotherapy HSCT	RR = 0.35 (0.25-0.45) for mucositis severity reduction
Lai *et al*.[51]	Systematic Review	256 (26 studies)	0-23 years and adults	Various (osteosarcoma ALL unspecified)	HSCT and chemotherapy	RR = 0.42 (0.31-0.53) for severe mucositis prevention
Hafner *et al*.[52]	Systematic Review	929 (15 studies)	0-18 years	ALL and other pediatric cancers	Chemotherapy	RR = 0.65 (0.55-0.75) for healing time improvement
Cruz *et al*.[53]	Systematic Review & Meta-analysis	299 (6 studies)	Children and adolescents	Not specified	Chemotherapy and HSCT	SMD = -0.85 [-1.20-(-)0.50] for pain

Note: ALL = Acute Lymphoblastic Leukemia. HSCT = Hematopoietic Stem Cell Transplantation. N/A = Not Available/Not Applicable. *Mixed populations were included when pediatric subgroup data was available or when pediatric patients comprised >30% of the study population.

Patient demographics

The demographic distribution across studies revealed a broad age spectrum ranging from 0 to 84 years. Patel *et al*.[50] provided the most detailed demographic analysis, reporting a population distribution of 61.30% adults and 38.70% pediatric patients, with a gender breakdown of 66.70% male and 33.30% female. Their study also documented a diverse cancer type distribution, with 61.30% solid tumors and 38.70% hematological

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magnificence. Complementing this broad spectrum, Hafner *et al*.[52] focused on pediatric populations aged 0-18 years, whereas Lai *et al*.[51] (2021) included both pediatric patients (0-23 years) and adults in their analysis.

Table 2. Technical specifications and outcomes.

Author	Laser specifications	Clinical results	Who classification	Study quality
Patel *et al*.[50]	620-750 nm variable power and duration	Significant reduction in severe oral mucositis with cryotherapy (RR 0.49) and laser (RR 0.13)	Yes	11/11
Lai *et al*.[51]	Multiple types: HeNe (632.80 nm) AsGaAI (685 nm) LED (670 nm) various powers	Varied results from no significant differences to reduced incidence and severity. 91% treatment adherence	Yes	10/11
Hafner *et al*.[52]	Diode laser 660-970 nm; LED 660 nm; 0.005-3.20 W; 2-107 J/cm²	PBM was effective in reducing oral mucositis severity and pain	Yes	10/11
Cruz et al.[53]	Diode laser 630-904 nm; 2-4 J	PBM was effective in reducing oral mucositis severity compared to control groups	Yes	9/11

Note: PBM, Photobiomodulation (light therapy treatment); RR, Risk Ratio (statistical measure); WHO, World Health Organization

Technical specifications

The technical parameters across studies demonstrated significant variation in laser technologies and applications. For example, Patel *et al*.[50] utilized wavelengths ranging from 620 to 750 nm with variable power and duration settings. Lai *et al*.[51] expanded the technical scope by implementing multiple laser types, including HeNe (632.80 nm), AsGaAI (685 nm), and LED (670 nm) systems. Hafner *et al*.[52] employed diode lasers (660-970 nm) and an LED (660 nm) in their applications, with precise power settings ranging from 0.005 to 3.20 W and energy densities from 2 to 107 J/cm². Cruz *et al*.[53] focused on diode laser applications in the 630-904 nm range, with delivery specifications of 2-4 J.

Clinical outcomes

Clinical outcomes demonstrated significant therapeutic benefits across all studies using standardized WHO classification systems. Analysis of primary outcomes revealed:

Treatment efficacy

Overall mucositis severity reduction RR = 0.35 (95%CI 0.25-0.45).[50] Severe mucositis prevention: RR = 0.42 (95%CI 0.31-0.53).[51] Healing time improvement: RR = 0.65 (95%CI 0.55-0.75).[52] Secondary outcomes: Pain reduction: SMD = -0.85 [95%CI -1.20-(-)0.50].[53] Treatment adherence: 91% (95%CI 88.30-93.70).[50]

These standardized measures demonstrate consistent effectiveness across various aspects of PBM therapy in diverse populations, ranging from children to adults, including specific findings in pediatric patients[52] and those undergoing HSCT.[51] The findings were particularly robust in chemotherapy-induced mucositis,[53] with Risk Ratios below 1.0 indicating beneficial treatment effects across all patient subgroups.

Treatment applications

The analysis revealed diverse applications of PBM therapy across various cancer treatment modalities. Patel *et al*.[50] examined the broadest applications, including chemotherapy, radiotherapy, and HSCT. Lai *et al*.[51] explicitly focused on HSCT and chemotherapy applications, while Hafner *et al*.[52] concentrated on chemotherapy applications in pediatric patients. Cruz *et al*.[53] rounded out the treatment spectrum by evaluating the applications of chemotherapy and HSCT in pediatric populations. This comprehensive examination across various treatment modalities and patient populations provides robust evidence supporting the effectiveness of PBM in multiple therapeutic contexts.

Quality assessment summary

Studies were evaluated using the JBI 11-criteria tool, with scores ranging from 9/11 to 11/11. Patel *et al*.[50] achieved the highest score (11/11), while two studies scored 10/11,[51,52] and Cruz *et al*.[53] scored 9/11. Strengths included transparent methodology, appropriate statistical analysis, and validated assessment tools. The main limitations were the lack of multiple reviewer assessment descriptions and evidence grading. Overall, studies demonstrated good methodological quality with acceptable bias levels, supporting reliable findings despite limitations.

DISCUSSION

This systematic review demonstrates significant evidence supporting photobiomodulation (PBM) therapy, specifically low-level laser therapy (LLLT), for managing oral mucositis in pediatric oncology patients. Analysis of four key systematic reviews encompassing 3,314 patients across 154 studies revealed consistent positive outcomes, with Risk Ratios consistently favoring treatment (RR = 0.35, 95%CI 0.25-0.45 for mucositis severity reduction), significant pain reduction (SMD = -0.85, 95%CI -1.20-(-)0.50), and high treatment adherence (91%, 95%CI 88.30-93.70).

The current analysis expands significantly on existing evidence. While Moskvin *et al*.[54] demonstrated success using LLLT with 904 nm wavelengths in preventive protocols, achieving a reduction in oral mucositis episodes with no reported complications, our analysis confirms similar outcomes across various wavelength ranges and treatment protocols. Fiwek *et al*.[55] provided valuable insights into dosing parameters, demonstrating efficacy with laser parameters of 635 and 980 nm combined wavelengths, which complements our findings on protocol standardization needs.

The PEDIALASE feasibility study by Noirrit-Esclassan *et al*.[56] introduced an innovative approach using two wavelengths (635 and 815 nm) with both extra- and intraoral applications, demonstrating excellent tolerance and significant pain reduction. This observation aligns with the current findings regarding the importance of application technique and wavelength selection. Additionally, Cruz *et al*.[53] corroborated these outcomes through their systematic review and meta-analysis of 299 pediatric patients, showing consistent effectiveness in reducing oral mucositis severity compared to control groups.

Current evidence suggests that the efficacy of LLLT varies based on several factors, including wavelength selection (ranging from 620 to 970 nm), power output (150 to 1500 mW), and energy density (4.50 to 26.80 J/cm^2). The technical specifications documented by Fiwek *et al*.[55] suggest that lower energy densities may be equally effective while improving patient comfort, particularly in pediatric populations.

Importantly, our analysis reveals LLLT's effectiveness even in cases of neutropenia, a finding supported by Moskvin et al.[54], who reported successful outcomes regardless of white blood cell counts. This finding suggests that LLLT's healing mechanisms may operate independently of immune system recovery; however, further research is needed to understand this relationship fully.

Protocol standardization and clinical implementation

The analysis of technical specifications across the reviewed studies reveals significant heterogeneity in treatment protocols, which presents both challenges and opportunities for clinical implementation. The wavelength ranges (620-970 nm) demonstrate that multiple spectral bands can achieve therapeutic effects, with red light (630-670 nm) and near-infrared light (810-904 nm) being the most employed ranges in pediatric populations.

Power output specifications varied considerably, from low-power LED systems (0.005 W) to higher-power diode lasers (3.20 W). However, energy density appears to be the more critical parameter, with effective treatments reported in the range of 2-107 J/cm². For pediatric applications, lower energy densities (2-26.80 J/cm²) may be preferable to ensure patient comfort and compliance while maintaining therapeutic efficacy.

Treatment frequency and duration protocols also showed variation, ranging from daily applications during high-risk periods to three times weekly maintenance protocols. The optimal approach appears to depend on the specific cancer treatment modality, with more intensive protocols recommended for patients undergoing conditioning regimens for HSCT.

Future clinical guidelines should establish standardized protocols specifically for pediatric populations, taking into account factors such as age-appropriate application techniques, optimal wavelength selection based on oral anatomy, and energy density adjustments for different mucositis severity grades.

The limitations acknowledged across studies include heterogeneity in technical parameters, treatment protocols, and outcome measures. Future research should focus on establishing standardized protocols specifically for pediatric populations, emphasizing optimal wavelength combinations and application techniques that are tailored to this population.

CONCLUSIONS

Multiple systematic reviews support the substantial effectiveness of low-level laser therapy in managing oral mucositis in pediatric oncology patients. With consistently positive outcomes and high treatment adherence rates, LLLT shows significant potential as a standard prophylactic treatment in clinical practice. The documented wavelength ranges proved effective across various cancer treatments. While technical parameters vary significantly between studies, the consistent reduction in mucositis severity (RR = 0.35, 95%CI 0.25-0.45) and pain (SMD = -0.85, 95%CI -1.20-(-0.50) underscores LLLT's clinical value in pediatric oncology care. The evidence supports the use of wavelengths ranging from 620 to 970 nm, with energy densities of 2 × 10^7 to 2 × 10^10 J/cm², proving effective across different treatment modalities.

Future research priorities should include (1) establishing age-specific treatment protocols for pediatric populations, (2) determining optimal wavelength and energy density combinations for different cancer treatment types, (3) developing standardized application techniques suitable for pediatric patients, and (4) conducting direct comparison studies between different laser parameters to establish evidence-based clinical guidelines for routine implementation in pediatric oncology centers.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

JPR participated in study conceptualization and design, data collection, statistical analysis, literature review, manuscript drafting, and final approval.
MGR participated in study conceptualization and design, data collection, statistical analysis, literature review, manuscript drafting, and final approval.
MNR conducted data collection, statistical analysis, manuscript drafting, and final approval.
JLLG conducted data collection, statistical analysis, manuscript drafting, and final approval.
FSP conducted data collection, statistical analysis, manuscript drafting, and final approval.
GGR conducted data collection, statistical analysis, manuscript drafting, and final approval.
ADC participated in study design, instrument validation, manuscript drafting, and final approval.

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