ISSNe 2178-1990

10.35699/2178-1990.2024.51137

ARQUIVOS EM ODONTOLOGIA

Effect of low-level laser therapy in the treatment of oral mucositis in patients with head and neck cancer: a scoping review

Maria Gabriella Apolinário Xavier[1] | Victória Gonçalves de Queiroz[1] | Milena Lima da Silva[1] | Yorhan Hansley da Silva Medeiros[2] | Maria de Lourdes Neves de Moura[3] | Lucas Nascimento Ribeiro[4] | Marianne de Vasconcelos Carvalho[1,4] | Stefânia Jeronimo Ferreira[1,3]

[1] School of Dentistry, University of Pernambuco, Arcoverde, Pernambuco, Brazil
[2] Bacharelor of Agronomy, Universidade Federal Rural de Pernambuco, Brazil
[3] Postgraduate Program in Health and Social and Environmental Development, University of Pernambuco, Garanhuns, Pernambuco, Brazil
[4] Postgraduate Program in Dentistry – FOP/UPE, Recife, Pernambuco, Brazil

Aim: This article aims to evaluate, using the best sources of evidence, the contribution of low-level lasers in treating oral mucositis in patients with oral cancer.

Methods: This review, including the entire process of the selection of studies and preparation of results, complied with the PRISMA-ScR protocol guidelines. At the end of the predefined analyses (title, abstract, and full text), 02 studies were included that correctly fit the eligibility criteria. These were published in 2015 and 2019 and were classified according to level II of the Agency for Healthcare of Research and Quality (AHRG). After critically reading the study, the common topics addressed in this scoping review were defined.

Results: Two works brought considerations about the laser therapy protocol, the use of the visible red wavelength, and energy densities between 3 and 4 J/cm². In addition, positive correlations were identified between painful symptoms and nutritional status with oral mucositis, as low-level laser therapy reduced pain and weight loss and improved the nutritional quality of cancer patients.

Conclusion: Photobiomodulation proved effective in treating mucositis at higher degrees. Scientific evidence on this topic is still being developed, but it will be promising and valid if more research is conducted.

Uniterms: lasers; therapeutics; stomatitis; mouth neoplasms; radiotherapy.

Data envio: 05/02/2024
Data aceite: 14/05/2024

INTRODUCTION

Oral mucositis is characterized as an inflammation that has a higher incidence in patients treated with radiotherapy for oral and oropharyngeal cancer. If left untreated, it can induce severe clinical consequences such as infectious conditions, the need for parenteral nutrition, intravenous analgesia, and antineoplastic therapy interruption[1-4].

According to Maria, Eliopoulos, and Muanza[2], the pathophysiology of oral mucositis still needs to be fully understood. However, it is already known that reactive oxygen species (ROS) initiate the entire inflammatory cascade, releasing TNF-α, IL-1 β, and IL-6 and, consequently, an oral mucosa exhibiting erythema in the early stages that may progress to ulcerations and infections. In addition, no standard scale classifies the disease. Therefore, classifications were created, related to: 1) the presence of erythema or ulceration (WHO Scale), 2) anatomical site of the appearance of the oral lesion (National Cancer Institute – NCI), and 3) ulceration quantity/dimension (Oral Mucositis Assessment Scales – OMAS)[4,5].

Photobiomodulation (PBM) has shown excellent results in treating mucositis in cancer patients. The low-level laser will act on benign cells, dissociating the nitric oxide, increasing the production of ATP, and, as a result, the synthesis of DNA, RNA and proteins; according to Rupel

Corresponding author:
Maria Gabriella Apolinário Xavier
Department of Dentistry, University of Pernambuco – Arcoverde campus. CEP 56505-045, Arcoverde, Pernambuco, Brazil
E-mail: gabriella17xavier@gmail.com

et al.[6] the action of the low-level laser occurs on the chromophore c oxidase, the main source of reactive oxygen species, which stimulate the reduction of cyclooxygenase-2 (COX-2) levels and neutrophilic infiltrate in the wound, leading to ulcer healing. Four stages well summarize the mechanism of action of PBM: primary effects, through the absorption of photonic energy by the chromophore c oxidase; side effects, changes in ATP, nitric oxide, and reactive oxygen species (ROS); tertiary effects, gene transcription and cell signaling and quaternary effect, indirect and/or distant effects[7-9]. However, with the wide variety of protocols and parameters to be analyzed, it is necessary to clarify dosimetry and effectiveness of therapy in the prevention/treatment or just in the treatment of mucositis, that is, when it is already installed in the oral cavity.

In essence, low-level laser therapy holds promise in mitigating the morbidity associated with oral mucositis and enhancing the quality of life for cancer patients[2,10]. This therapeutic approach can potentially expedite the wound healing process, yielding superior outcomes, and could be integrated into the cancer treatment regimen[10,12]. Hence, this study aims to unearth the most compelling evidence supporting the efficacy of low-level laser therapy in managing oral mucositis in patients with oral and oropharyngeal cancer.

METHODOLOGY

PROTOCOL AND REGISTRATION

The methodology of the present article followed the guidelines of the PRISMA-ScR[12,13] protocol, which presents the recommended items for systematic reviews and extension of meta-analyses and scoping reviews. Subsequently, with the completion of the protocol, it was registered on June 6, 2023 in the Open Science Framework (https://osf.io/yudre/).

ELIGIBILITY CRITERIA

The inclusion and exclusion criteria determined the studies included in this scoping review. Therefore, publications on laser therapy's effects in treating oral mucositis in patients with oral and oropharyngeal cancer were selected. In addition, articles published between 2010 and 2021 in English, Portuguese, and Spanish, and classified as randomized clinical trials, were also included. Thus, cohort studies, case-control studies, case reports/series, *in vitro* studies, theses, expert opinions, and congress abstracts were excluded from this scoping review.

DATABASE

The following databases were used to search for the abovementioned articles: PUBMED, VHL (Virtual Health Library), Web of Science, SciELO, Scopus, and EMBASE.

SEARCH STRATEGY

The following search key was created using Boolean descriptors and operators: ("radiotherapy") AND ("mucositis") AND ("mouth cancer" OR "oropharynx cancer" OR "oral cancer") AND ("photobiomodulation" OR "laser therapy") AND ("treatment"). To formulate the PICO strategy, the following terms were used: P (researched population) - patients diagnosed with oral mucositis resulting from radiotherapy for oral and oropharyngeal cancer; I (intervention) – use of photobiomodulation; C (comparison) – a control group that received placebo, no treatment, or other interventions; O (conclusion/outcome) – beneficial effects of the treatment. From this, the final question of our study was: "Is low-level laser therapy able to treat mucositis in patients with oral and oropharyngeal cancer treated with radiotherapy?".

SELECTION OF EVIDENCE SOURCES

According to the eligibility criteria, the researchers (MGAX and VGQ) independently evaluated the titles and abstracts and, later, the full texts of each selected article. A third researcher (SJF) analyzed possible cases of disagreement between the first two researchers. The final agreement of 0.99 was obtained using the intra- and inter-examiner Kappa agreement test. Rayyan software was used to remove duplicates and read titles and abstracts.

DATA ITEMS

As the research advanced, a flowchart was developed based on the PRISMA-ScR guidelines (PRISMA 2020 flowchart), which aims to systematize all the steps of the methodology, thus portraying the total number of studies found in all databases up to the final sample after application of the selection criteria (Figure 1). Some aspects will be predetermined to be analyzed in each study included in this scoping review: Authors, year and journal of publication, the sample of patients and their specificities, randomization, laser therapy protocol used, results, and critical evaluation of the evidence (Table 1).

CRITICAL APPRAISAL OF CURRENT SOURCES OF EVIDENCE

The critical evaluation of the selected studies methodological design was performed using the Agency for Healthcare of Research and Quality (AHRG) classification[14], which, through six levels, categorizes research by the quality of scientific evidence into I- Systematic review or meta-analysis of multiple trials randomized clinical trials; II- Individual studies with experimental designs; III- Study with quasi-experimental design as a study without randomization with a single pre- and post-test group, time series or case-control; IV- study with non-experimental design, such as a descriptive correlational and qualitative research; V- case evidence or experience report and systematic review of descriptive and qualitative studies; and VI- Studies based on expert opinion.

SUMMARY OF RESULTS

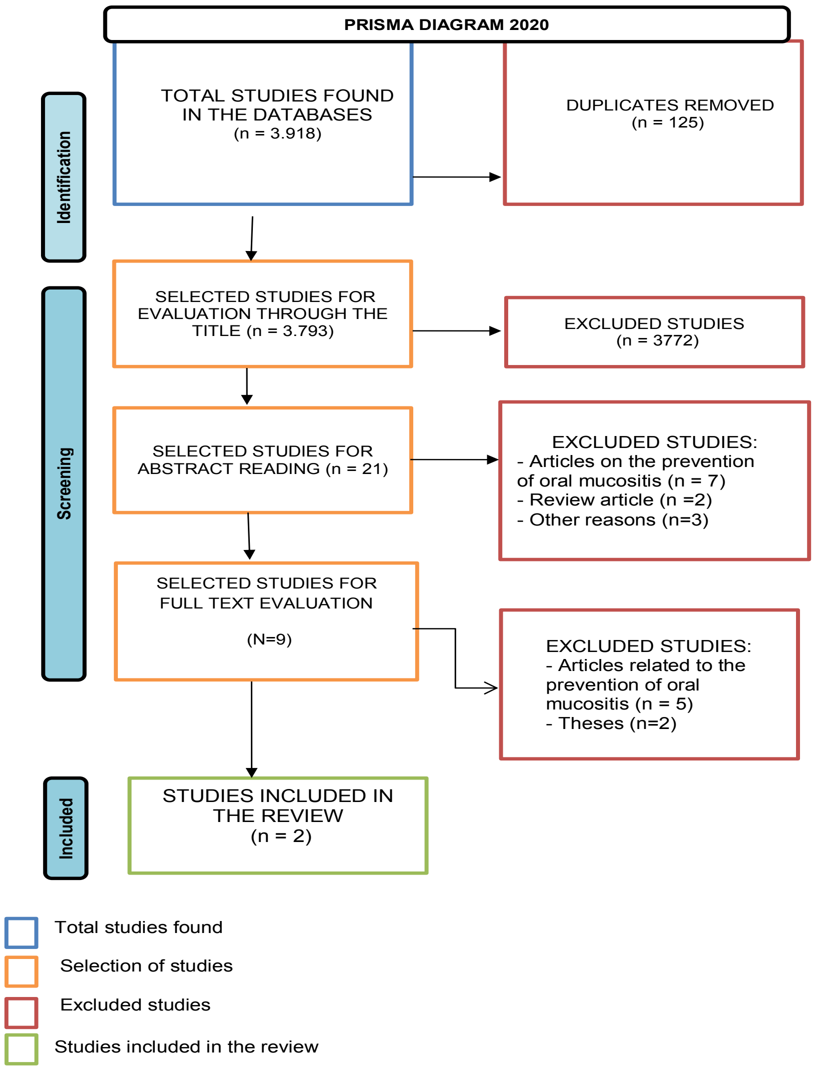
This scoping review will present and discuss all scientific evidence from randomized clinical trials present in the databases, referring to the effects of low-level laser therapy in the treatment of oral mucositis in patients treated with radiotherapy.

RESULTS

SELECTION AND CHARACTERIZATION OF SOURCES OF EVIDENCE

According to the criteria applied in the step-by-step of this scoping review, 02 studies were included that correctly fit what had been predetermined in the methodology of this research. No studies were included through manual search (Figure 1).

Figure 1. Flowchart of the search in the databases – BASED ON PRISMA 2020.



RESULTS OF THE CRITICAL INDIVIDUAL ASSESSMENT OF THE SOURCES OF EVIDENCE

According to the AHRG classification[14], carried out to critically evaluate the included studies, 100% of the works correspond to level II of scientific evidence, that is, individual studies with experimental designs. For the selection of randomized clinical trials, it was recommended that the studies approach the same methodological design. That is, they should focus on treating mucositis with low-power laser in patients with head and neck cancer. Studies that used only prophylactic lasers were excluded. Furthermore, research that addressed other methodologies, such as cohort, case-control, and cross-sectional studies, was also removed.

Table 1. Synthesis of articles included in the scope review.

RESULTS					
AUTHORS, YEAR, AND PERIODIC OF PUBLICATION	**SAMPLE OF PATIENTS**	**RANDOMIZATION**	**PROTOCOL USED**	**OBSERVED RESULTS**	**CRITICAL ANALYSIS EVIDENCE**
LEGOUTÉ et al. (2019) Radiation Oncology	83 patients with head and neck cancer were treated with concurrent chemoradiotherapy (CRT) or radiotherapy alone, aged between 18 and 75 years.	42 patients were randomly assigned to the active laser group (group A) and 41 to the placebo control group (group B).	- HETSCHL He-Ne laser (lambda: 658nm, output: 100mW, and energy density: 4J/cm²). -1 session/day, 5 times/week. There could also be an interval of 1 or 2 days. - Irradiation point: 1cm² - Intraoral irradiation at the first visible signs of lesions.	Overall, participants treated with LLLT (laser or placebo) had excellent laser tolerance during sessions (91%). However, there was no significant difference between the groups between the time the lesions appeared and the evolution to a degree greater than or equal to 3. Regarding the analysis of pain and nutritional status, there was also no significant difference in the values presented.	II
GAUTAM et al. (2015) Journal of photochemistry and photobiology. B, Biology.	This study involved 46 patients over 60 years of age recently diagnosed with head and neck cancer and had radiotherapy treatment involving at least 2/3 of the oral cavity.	This is a randomized, double-masked, group placebo- and laser-controlled study. Randomization occurred through a computerized table of random numbers. Patients and testers were blinded.	- He-Ne laser, 632.8nm, output power: 24 mW, energy density: 3 J/cm², total dose/ session: 36 J/ 5 sessions. - Irradiation point: 1 cm² - 12-point irradiation (6 on each side of the oral cavity)	The group irradiated with low-level laser showed lower severity and duration of oral mucositis lesions, and used fewer opioid analgesics when compared to the placebo group. In addition, the need for parenteral nutritional support was also lower in the laser group.	II

SUMMARY OF RESULTS

CONSIDERATIONS ABOUT THE USED PROTOCOL OF LASER THERAPY

The dosages used by Gautam et al.[15] and Legouté *et al*.[16] were quite similar, as the energy density was 3J/cm² and 4J/cm², respectively. Regarding the wavelength, the authors defined the red length to be applied to patients, and Gautam et al.[15] administered 632.8 nm, and Legouté et al.[16] 658 nm. The irradiation points were 1 cm², but for Gautam et al.[15] and Legouté et al.[16], the irradiation time was 125s and 40s, respectively. The maximum dose/session defined by Gautam et al.[15] was 36J, 5x a week; it had already pre-defined 12 anatomical sites where the laser would be irradiated. In the case of Legouté et al.[16], the anatomical points were not previously defined; therefore, there was no maximum dose per session, and the laser would be used in places where the lesions were visible.

CORRELATION BETWEEN THE TREATMENT OF ORAL MUCOSITIS AND PAINFUL SYMPTOMS REPORTED BY PATIENTS

In the study by Gautam et al.[15], patients allocated to the laser group reported less intense and severe pain scores than those in the placebo group. According to the Visual Analogue Scale, in patients in which laser therapy was applied, the maximum score found was 4; on the other hand, the maximum evaluation presented in the placebo group was 5.79; in addition, pain related to severe mucositis was reported by 8.3% of the patients who used lasers and by 50% of the patients in the placebo group. Consequently, fewer patients in the laser group needed to use opioid analgesics[16].

For Legouté et al.[16], 42.8% of the patients in both groups had moderate or severe pain according to the Visual Analogue Scale; in addition, 83.1% (69 people) used analgesics – 33 in the laser group and 36 in the placebo group. Thus, there was no statistical difference in the per-protocol analysis of the groups. With the use of laser therapy, a decrease was observed in reports of pain with scores 4-6 on the scale and an increase in scores 0 and 1-3. In the information provided by patients in the placebo group, increased pain levels of 4-6 and 7-10 were observed[16].

CORRELATION BETWEEN THE TREATMENT OF ORAL MUCOSITIS AND NUTRIONAL STATUS/WEIGHT LOSS OF PATIENTS

The studies by both authors evaluated the nutritional status of patients. According to Legouté et al.[16], about 54.1% of the subjects had a weight loss of greater than 5%, and 17.6% had a weight loss of greater than 10%; the authors found no significant difference between the groups. For Gautam et al.[15], the laser group lost less weight (2.5kg) than the placebo group (5.57kg); in addition, interruption of radiotherapy treatment was necessary for 14.3% of patients in the placebo group and no patients in the laser group.

EFFICACY OF THE PROPOSED TREATMENT

According to the results published by Gautam et al.[15], severe mucositis and oral pain lasted less time in the laser group, around 10 days. By contrast, in the placebo group, both lasted for approximately 16 days. The evolution of the degree of oral mucositis was evaluated weekly. From the third week onwards, some cases of severe mucositis (grade 3) were recorded, but with the use of the laser, the cases fell to grades 1 and 2 or remained in grade 3, with no evolution to 4. The opposite occurred with the placebo group, since from the fourth week onwards, some cases of severe mucositis (grade 3) were observed, and in the subsequent weeks, there were progressions to grade 4[16].

Another fact that calls attention, even if it is not statistically significant, was the identification of mucositis grade ≥ 2 in 81.9% of the patients (no difference between laser and placebo groups). However, in 63.2% of the cases, the lesions remained with the same grade mentioned above; that is, they did not progress to grades ≥ 3[16].

DISCUSSION

Low-power lasers have gained significant recognition in stomatology, for which some research has aimed to evaluate the effectiveness of laser therapy in preventing and treating oral mucositis in cancer patients. In general, many articles related to the topic mentioned above were obtained. However, as this scoping review aimed to analyze only the results of photobiomodulation in treating oral mucositis, some studies were left out of the eligibility criteria because they focused only on preventing inflammation.

In the stages of reading the abstract and full text of the articles, it was identified that the authors used the term treatment, referring to the prophylactic treatment of mucositis and not to the actual treatment of the lesions, that is, from the moment they were clinically visible. As examples, one can cite the works of Oton-Leite et al.[17] and Marín-Conde et al.[18], in which laser sessions were begun together with radiotherapy. This characteristic reflects the more preventive nature of the studies. In addition, the authors depicted many other issues, such as the frequency of appearance and severity of lesions, than the treatment itself.

Regarding the included studies, both articles presented methodological differences, such as the laser therapy protocol used. Gautam et al.[15] presented their results with an initially prophylactic and later treatment perspective. On the other hand, Legouté et al.[16] only exposed the results of treating oral lesions. From the analysis of these two studies, it can be suggested that combining protocols brings more efficiency to the therapy.

Considering analyzing low-level laser therapy in oral mucositis, La Torre and Alfaro[19] concluded that photobiomodulation therapy has beneficial anti-inflammatory and analgesic effects on tissues, such as activation of microcirculation and angiogenesis, thus stimulating cell growth and accelerating healing. It is suggested that wavelengths between 640 and 990 nm, with visible red light, induce tissue repair through low-energy light interaction at a few Joules per square centimeter in affected areas.

10.35699/2178-1990.2024.51137

According to Zecha et al.[20], the ideal energy density that should be used in laser therapy is 2-3 J per point to cover the entire involved area. The wavelengths can vary between 633-685 nm or 780-830 nm and can be administered two to three times a week or even daily. Merigo et al.[21] did not disclose the ideal energy density; they only reported that the laser should be used with a power density of 5 to 150 mW/cm² once or twice weekly for 30-60 seconds. Only one survey clarified the weekly irradiance. For Soares et al.[22], 300J/cm² reduced the worst degree of mucositis in the study.

In the randomized clinical trials included in this review, the weekly irradiation doses did not exceed 200J/cm², both lasers being in the visible red wavelength. Even though the surveys have reported satisfactory results, these results may have been negatively influenced by the total density, since the values were lower than those used by Soares and collaborators[22]. In addition, the dose variation between studies generates a concern: The absence of a single and well-established protocol for safely using photobiomodulation.

The lack of unanimity on laser therapy protocols can be cited as a factor that makes it challenging to conduct research in the area, given that large treatment centers need appropriate guidelines to submit cancer patients to clinical trials. However, even without well-established protocols, some authors recorded the specificities most used in low-level laser treatment. For example, according to Globbo et al.[23], the visible red wavelength (632-660 nm) was mainly used in their review articles; the points were irradiated for at least 30 seconds, 3 to 5 times a week. The values mentioned above are identical to those used by Mobadder et al.[24], that is, 635 nm with 3J/cm² for 30 s and Carvalho et al.[25] with 660 nm and 3.8 j/cm².

The two authors evaluated painful symptoms. According to Gautam et al.[15], the laser group had a better outcome, as the patients, in addition to reporting less pain, also used a smaller amount of analgesics. This fact can be explained by the direct action of low-level laser on inflammatory mediators found in saliva, all of which was demonstrated by Oton-Leite et al.[26], who showed in their results a considerable reduction in the levels of IL-6 (interleukin-6) and FGF (Fibroblastic Growth Factor). It was also concluded that IL-1b (interleukin-1b), EGF (Epidermal Growth factor) and VEGF (Vascular Endothelial Growth Factor) showed a slight decrease.

Clinical trials applied the Visual Analogue Scale, an effective instrument to subjectively measure patients' pain and make a good correlation with clinical scores[27]. For Legouté et al.[16], the reported scores ranged from 0 to 10, with a tendency to reduce these soon after the last laser therapy session. This means that the laser was effective in reducing pain, as there was an increase in the initial levels of the scale and a decrease in stages of more advanced pain in the intervention group.

In agreement with the results of this article, a systematic review showed that photobiomodulation showed significant relevance in the treatment of mucositis compared to the placebo group, as it was effective in controlling pain and reducing the use of analgesics[28]. Soares et al.[22] also confirmed this premise, since the decrease in the degree of mucositis by the action of the laser was directly proportional to the reduction in drug prescriptions. Furthermore, the administration of systemic drugs was ineffective in the research by Ling and Larsson[29], as the pain and severity of mucositis remained unchanged even after using the drugs.

Individuals who experienced less weight loss and better nutritional status were included in the laser group. Thus, it was found that low-level lasers can positively impact the morbidity of cancer treatment, the patient's quality of life, and the costs associated with the side effects of the therapy[10,11,30]. In this sense, one can observe the importance of laser therapy in multidisciplinary treatment, given that patients with oral cancer are highly prone to developing malnutrition. Laser therapy can reduce weight loss and prevent a reduction in Body Mass Index (BMI)[31,32].

Other interesting data related to the nutritional indexes of the patients were the dietary changes, which can be explained by the progression of the inflammatory lesions of mucositis, since swallowing solid and often liquid foods becomes impossible. Thus, the need for parenteral support was lower in the laser group than in the placebo group[15].

Regarding the effectiveness of the proposed treatment, oral mucositis lesions, classified as severe, regressed more quickly in the laser group. Concomitantly with this, patients reported less pain during this process. Furthermore, the laser will act precisely to reduce reactive oxygen species and pro-inflammatory cytokines[6]. Hence, the treatment proved effective in both studies because even if the patients were not completely cured of the inflammation, they were not as advanced as in the placebo groups. Thus, the stagnation of the lesion at an initial level is also a characteristic of successful treatment.

10.35699/2178-1990.2024.51137

The main limitations of this research were related to the selection of studies compatible with the eligibility criteria pre-established in the methodology. We only searched for research that reported treating mucositis with low-level laser when the lesions were already installed, not with the laser's preventive action. This resulted in the exclusion of research that did not present both approaches.

CONCLUSIONS

In short, photobiomodulation helps treat the side effects of radiotherapy and chemotherapy, thus improving patient's quality of life. With the high heterogeneity of laser therapy parameters and protocols, this review instigates some important questions for the management of oral mucositis. Furthermore, difficulties related to the patient's lack of adherence to treatment and the complexity of the location of the lesions make low-level laser relatively inaccessible to the general population.

AUTHOR CONTRIBUTIONS

This study was designed by: Maria Gabriella Apolinário Xavier: Research design, acquisition, analysis, data interpretation, scientific writing and necessary corrections; Victoria Gonçalves de Queiroz, Milena Lima da Silva, Maria de Lourdes Neves de Moura and Yorhan Hansley da Silva Medeiros: Obtaining, analyzing, interpreting and translation data; Lucas Nascimento Ribeiro, Marianne de Vasconcelos Carvalho and Stefânia Jeronimo Ferreira: Research, analysis, data interpretation, writing and critical analysis.

CONFLICT OF INTEREST

None declared.

ETHICS

There was no need for approval by the ethics committee.

SOURCE OF FUNDING

None declared.

ORCID

Maria Gabriella Apolinário Xavier https://orcid.org/0000-0002-4624-5762
Victória Gonçalves de Queiroz https://orcid.org/0009-0000-7507-300X
Milena Lima da Silva https://orcid.org/0000-0002-2650-4456
Yorhan Hansley da Silva Medeiros https://orcid.org/0000-0002-4984-295X
Maria de Lourdes Neves de Moura https://orcid.org/0000-0003-0749-6451
Lucas Nascimento Ribeiro https://orcid.org/0000-0002-9284-749X
Marianne de Vasconcelos Carvalho https://orcid.org/0000-0002-6815-5696
Stefânia Jeronimo Ferreira https://orcid.org/0000-0001-6656-6435

REFERENCES

1. Barasch A, Epstein JB. Management of cancer therapy-induced oral mucositis. Dermatol Ther. 2011;24(4):424-31.
2. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Front Oncol. 2017;7:89.
3. Martins JOL, Borges MMF, Malta CEN, Carlos ACAM, Crispim AA, Moura JFB, et al. Risk factors for oral mucositis during chemotherapy treatment for solid tumors: a retrospective STROBE-guided study. Med Oral Patol Oral Cir Bucal. 2022;27(4):e319-29.
4. Rodríguez-Fuentes ME, Pérez-Sayáns M, Chauca-Bajaña LA, Barbeito-Castiñeiras G, Molino-Bernal MLP, López-López R. Oral microbiome and systemic antineoplastics in cancer treatment: a systematic review. Med Oral Patol Oral Cir Bucal. 2022;27(3):e248-56.
5. Pulito C, Cristaudo A, La Porta C, Zapperi S, Blandino G, Morrone A, et al. Oral mucositis: the hidden side of cancer therapy. J Exp Clin Cancer Res. 2020;39:210.
6. Rupel K, Zupin L, Colliva A, Kamada A, Poropat A, Ottaviani G, et al. Photobiomodulation at multiple wavelengths differentially modulates oxidative stress in vitro and in vivo. Oxid Med Cell Longev. 2018;2018(1):6510159.
7. Henriques ACG, Ginani F, Oliveira RM, Keesen TSL, Barboza CAG, Rocha HAO, et al. Low-level laser therapy promotes proliferation and invasion of oral squamous cell carcinoma cells. Lasers Med Sci. 2014;29(4):1385-95.

8. Zecha JAEM, Raber-Durlacher JE, Nair RG, Epstein JB, Sonis ST, Elad S, et al. Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Support Care Cancer. 2016;24(6):2781-92.
9. Hanna R, Dalvi S, Benedicenti S, Amaroli A, Sălăgean T, Pop ID, et al. Photobiomodulation therapy in oral mucositis and potentially malignant oral lesions: a therapy towards the future. Cancers (Basel). 2020;12(7):1949.
10. Antunes HS, Herchenhorn D, Small IA, Araújo CMM, Viégas CMP, Ramos GA, et al. 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. Oral Oncol. 2017;71:11-5.
11. Oton-Leite AF, Castro ACC, Morais MO, Pinezi JCD, Leles CR, Mendonça EF. Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. Head Neck. 2012;34(3):398-404.
12. Aromataris E, Munn Z, editors. JBI manual for evidence synthesis. Adelaide: The Joanna Briggs Institute; 2020.
13. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467-73.
14. Stetler CB, Morsi D, Rucki S, Broughton S, Corrigan B, Fitzgerald J, et al. Utilization-focused integrative reviews in a nursing service. Appl Nurs Res. 1998;11(4):195-206.
15. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Guddattu V. Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. J Photochem Photobiol B. 2015;144:51-6.
16. Legouté F, Bensadoun R, Seegers V, Pointreau Y, Caron D, Lang P, et al. 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. Radiat Oncol. 2019;14:83.
17. Oton-Leite AF, Elias LSA, Morais MO, Pinezi JCD, Leles CR, Silva MAGS, et al. Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy. Spec Care Dentist. 2013;33(6):294-300.
18. Marín-Conde F, Castellanos-Cosano L, Pachón-Ibañez J, Serrera-Figallo MA, Gutiérrez-Pérez JL, Torres-Lagares D. Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: prospective randomized controlled trial. Int J Oral Maxillofac Surg. 2019;48(7):917-23.
19. La Torre F, Alfaro C. Terapia de laser de baja potencia en mucositis oral. Rev Estomatol Hered. 2016;26(1):47-55.
20. Zecha JAEM, Raber-Durlacher JE, Nair RG, Epstein JB, Elad S, Hamblin MR, et al. Low-level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 2: proposed applications and treatment protocols. Support Care Cancer. 2016;24(6):2793-805.
21. Merigo E, Rocca J, Pinheiro ALB, Fornaini C. Photobiomodulation therapy in oral medicine: a guide for the practitioner with focus on new possible protocols. Photobiomodul Photomed Laser Surg. 2019;37(11):669-80.
22. Soares RG, Farias LC, Menezes ASS, Silva CSO, Tabosa ATL, Chagas PVF, et al. Treatment of mucositis with combined 660- and 808-nm-wavelength low-level laser therapy reduced mucositis grade, pain, and use of analgesics: a parallel, single-blind, two-arm controlled study. Lasers Med Sci. 2018;33(8):1813-9.
23. Gobbo M, Merigo E, Arany PR, Bensadoun R, Santos-Silva AR, Gueiros LA, et al. Quality assessment of PBM protocols for oral complications in head and neck cancer patients: part 1. Front Oral Health. 2022;3:945718.
24. El Mobadder M, Farhat F, El Mobadder W, Nammour S. Photobiomodulation therapy in the treatment of oral mucositis, dysphagia, oral dryness, taste alteration, and burning mouth sensation due to cancer therapy: a case series. Int J Environ Res Public Health. 2019;16(22):4505.
25. Carvalho PAG, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA. Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral Oncol. 2011;47(12):1176-81.
26. Oton-Leite AF, Silva GBL, Morais MO, Silva TA, Leles CR, Valadares MC, et

al. Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers Surg Med. 2015;47(4):296-305.

27. Chaitanya N, Muthukrishnan A, Karunakar P, Himani M, Allam N, Jain N. Assessment of oral mucositis during concurrent chemoradiation of head and neck cancers using patient-reported measurement scale. South Asian J Cancer. 2018;7(1):46-8.
28. Paglioni MP, Alves CGB, Fontes EK, Lopes MA, Ribeiro ACP, Brandão TB, et al. Is photobiomodulation therapy effective in reducing pain caused by toxicities related to head and neck cancer treatment? A systematic review. Support Care Cancer. 2019;27:4043-54.
29. Ling IS, Larsson B. Individualized pharmacological treatment of oral mucositis pain in patients with head and neck cancer receiving radiotherapy. Support Care Cancer. 2011;19(9):1343-50.
30. González-Arriagada WA, Ramos LMA, Andrade MAC, Lopes MA. Efficacy of low-level laser therapy as an auxiliary tool for management of acute side effects of head and neck radiotherapy. J Cosmet Laser Ther. 2018;20(2):117-22.
31. Camargo DAP, Delfín LN, Ñamendys-Silva SA, Mendoza ETC, Méndez MH, Gómez AH, et al. Estado nutricional de los pacientes con cáncer de cavidad oral. Nutr Hosp. 2013;28(5):1458-62.
32. Melo AS, Andrade CL, Dantas JBL, Medrado ARAP, Martins GB, Lima HR, et al. Impact of photobiomodulation for oral mucositis on body weight and BMI of patients with head and neck cancer. Support Care Cancer. 2022;30:4897-904.