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Low-intensity laser-assisted antimicrobial photodynamic therapy and intravascular laser irradiation of blood in oncology: systematic review and a brief report

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ABSTRACT

Oncological patients may present with difficult-to-resolve oral lesions that impair their quality of life, and laser therapy can help these patients. This study sought to present a systematic review of the use of intravascular laser irradiation of blood (ILIB) and antimicrobial photodynamic therapy (aPDT) for oncological patients. Furthermore, it provides a brief report on a patient with laryngeal cancer who experienced cytotoxic symptoms such as oral mucositis and oral candidiasis while receiving aPDT and ILIB. A systematic search of PubMed, Scopus, Embase, Cochrane, Lilacs, Web of Science, Scielo, and Gray Literature was conducted, with no year or language restrictions, for primary clinical studies that used ILIB and aPDT to treat oral manifestations in oncological patients. In the brief report, aPDT was administered within the first five days, and ILIB was used for persistent lesions and pain. The review included five clinical studies. They included case reports, retrospective studies, randomized clinical trials, and non-randomized clinical trials. ILIB therapy combined with aPDT has been shown to reduce pain and promote faster healing when compared to not using ILIB. In our brief clinical case, healing was accelerated while pain and infectious inflammatory processes were reduced in the oral cavity. This neutralization of oral toxicity by combining aPDT and ILIB improved overall health, resulting in rapid healing of the oral lesions. The combination of aPDT and ILIB may be an effective therapy for the rapid recovery of oral lesions among cancer patients. More research is needed to better understand the effects of ILIB in oncology patients.

Key words: cancer, laser therapy, low-intensity light therapy, intravascular laser irradiation of blood.

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Introduction

Head and Neck Cancer (HNC) constitutes an important group of malignancies, with laryngeal cancer being a subset.[1,2] Conventional treatment options include surgery, radiotherapy, and/or chemotherapy.[1] Among these options, radiotherapy is predominantly favored, primarily because surgery is often deemed impractical due to anatomical limitations associated with certain types of head and neck cancer.[2] Despite that, it can cause side effects that manifest in the oral cavity of these patients, which may interfere with their quality of life.[1]

Oral Mucositis (OM), is a common side effect in patients with head and neck cancer undergoing radiotherapy, with or without concurrent chemotherapy.[1] It manifests erythema, edema, and ulceration following radiation therapy or chemotherapy for cancer treatment. Once installed, OM presents symptoms such as pain, speech disorders, and odynophagia, thereby compromising patients' quality of life.[1] Additionally, these patients are susceptible to developing oral candidiasis (OC), which can escalate into a fungal and opportunistic infection if left untreated and has a high incidence in patients undergoing head and neck radiotherapy (RT).[2] Failure to diagnose and treat these oral complications can compromise the patient's systemic condition, necessitating discontinuation of cancer treatment or an undesirable hospitalization.[3]

Antimicrobial Photodynamic Therapy (aPDT) has emerged as a promising approach.[4,5] The typical parameters for low-intensity laser usage include a red laser diode emitting light at a wavelength of 660 nanometers in a precise and continuous manner. The beam has a diameter of 0.25 cm, a power output of 100 mW, and an irradiation time of 3 seconds per point. This setup generates a fluence of 1.2 J/cm² over the entire length of the lesion, with a uniform spacing of 1 cm between points.[4,6] The antimicrobial effect of aPDT is based on the principle that visible light activates a non-toxic photosensitizer molecule, which generates reactive oxygen species that kill microorganisms through an oxidative burst.[6] The increase of pathogens resistant to commonly used drugs in the general population underscores the urgent need for antimicrobial approaches capable of efficiently inactivating pathogens without inducing resistance.[7]

Similarly, Intravascular Laser Irradiation of Blood (ILIB), currently performed transcutaneously and minimally invasive, has contributed to preventing the appearance of lesions in different regions of the body and can be used to treat various diseases.[8] In addition to its analgesic effects, ILIB also demonstrates spasmolytics, and sedative properties.[9] ILIB facilitates the absorption of red wavelength light by the blood, thereby increasing the person's metabolism through the stimulation of mitochondrial components.[10] Furthermore, it influences the synthesis of the enzyme superoxide dismutase, the primary physiological protein regulating the body's oxidative system. Superoxide dismutase inhibits the action of reactive oxygen species (ROS) and protects cells by combating free radicals.[8,10] The literature describes the use of low-intensity laser therapy parameters targeting the radial or carotid artery using a 660-nanometer red laser with an optical power of 100 mW and continuous exposure for 10 minutes.[11-14]

Evidence in the literature portraying the use of ILIB for the treatment of OM and OC is scarce. Therefore, our objective is to present a systematic review addressing the critical question: Is ILIB an effective therapy for treating oral manifestations in oncological patients? Additionally, we provide a brief report of an oncological patient presenting with oral manifestations of OM and OC, where aPDT combined with ILIB was utilized to treat lesions in the oral cavity.

Materials and Methods

The methodology was defined following the PRISMA guidelines (Preferred Systematic Reviews and Meta-Analysis Report) and registered in the International Prospective Registry of Systematic Reviews (PROSPERO) under registration CRD42022351003. The case report followed the Declaration of Helsinki. The patient agreed and signed the Consent Form.

The literature search was conducted in 7 databases and gray literature. The review's question was: "Is ILIB an effective therapy for treating oral manifestations in oncological patients?". The flow diagram was used as the strategy design.

Literature research

A search was performed in PubMed, Scopus, Embase, Cochrane, Lilacs, Web of Science, Scielo, and Gray Literature, as well as a manual search of the reference lists of the included studies, with no year or language restriction. The first phase established an investigation to de-

fine MeSH (Medical Subject Headings) terms to ensure high sensitivity and accuracy, and researchers tracked abstract and publication titles. The MESH terms used in searches across all databases were: ILIB or " intravascular laser irradiation of blood, "intravascular photobiomodulation" or "intravenous laser therapy," or "intravascular blood irradiation" or "intravascular laser irradiation" or "intravascular laser phototherapy" or "irradiation of blood" AND aPDT or "antimicrobial photodynamic therapy" or "antibacterial photodynamic therapy" or "photodynamic therapy" or laser or "low-intensity light therapy" or photochemotherapy AND "oral manifestation" or "oral lesions" or "oral complications" or candidiasis or stomatitis or laceration or erosion or vesicle or "traumatic lesions" or infections or "pemphigus vulgaris" or "lichen planus" or aphthous or xerostomia or "bullous lesions" or pemphigus or candidal or "bacterial infections" or mucositis or "mucosal pain" or "taste dysfunction" or fibrosis or Osteoradionecrosis AND "oncological patients" or radiotherapy or chemotherapy or oncological or cancer or tumor.

Eligibility criteria

Based on titles and abstracts, articles describing ILIB or the combination of ILIB with aPDT and photobiomodulation therapy (PBMT) as a treatment for oral manifestations of oncological patients were included in this review. Inclusion criteria were defined using the PICOS strategy (Population, Intervention, Comparison, Outcome, and Study Type) (Table 1). The exclusion criteria were studies that evaluated the use of aPDT for the treatment of oral cavity lesions without the association of ILIB. Articles assessing ILIB for conditions other than those involving the oral cavity were also excluded. Review studies, editorials, or opinion articles were likewise excluded.

Selection and quality assessment of relevant studies

Articles selected according to the criteria were retrieved in PDF format, numbered, and randomly distributed among three researchers. The researchers manually reviewed the reference list to retrieve publications not previously found in the database search aiming to enhance the sensitivity and quality of the review. A consensus meeting was held to discuss divergences after evaluating the quality of publications and guaranteeing the validation of the articles.

Data extraction

Articles included in the study were randomly assigned to researchers for data collection. The authors utilized a table to extract pertinent information from the articles, encompassing author and year, study location, study type, objectives, patient demographics (sex and age), sample size, diagnosis, oral cavity manifestations, and ILIB and aPDT/PBMT laser protocol details. This included laser parameters, application location and duration, and case outcomes. Subsequently, the collected data were individually evaluated, and each literature issue was documented in separate rows of the table.

Results

Selection and heterogeneity of studies

In the first phase, 4,293 articles were identified in the databases, and after removing the duplicates, 46 articles remained for reading the title and abstract. Upon evaluation of all records, 17 articles were selected and read. Following the application of the inclusion and exclusion criteria, five

Table 1. PICOS strategy with inclusion criteria using research.

PICOS strategy	
P	Oncological patients with oral manifestations
I	Use of ILIB as a single therapy or associated with aPDT/PBMT for healing or remission of lesions in the oral cavity of cancer patients
C	Oncological patients who did not use the ILIB, or used only aPDT/PBMT
O	The use of ILIB or the association of ILIB + aPDT provide rapid healing in lesions in the oral cavity or oral manifestations in oncological patients
S	Blinded randomized clinical trials, randomized clinical trials, case reports

PICO, population-intervention-control-outcome-study type; ILIB, intravascular laser irradiation of the blood.; aPDT, antimicrobial photodynamic therapy; PBMT, photobiomodulation therapy.

papers were ultimately included, as shown in the infographic (Figure 1).

All studies were carried out in Brazil. They were case reports in the literature,[11,12] retrospective studies,[13] randomized clinical trials,[14] and non-randomized clinical trials,[15] and were published between 2019 and 2022 in English and Portuguese. One hundred seven cancer patients (53 women and 54 men) with a mean age of 58 years were submitted to the therapeutic protocol of ILIB and aPDT/PBMT to control manifestations in the oral cavity. These patients were diagnosed with breast cancer,[11,12,13] Head and Neck Cancer, Breast Cancer Gastric Adenocarcinoma, Non-Hodgkin's Lymphoma, Liposarcoma, Kidney Cancer, Pancreatic Cancer, Rectal Cancer, Colon Cancer, Gastric Adenocarcinoma, Lung Cancer[15] and solid tumors.[14] The main manifestations in the oral cavity were dysgeusia,[11,13] lingual paresthesia,[12] and mucositis.[14,15] The objectives of these studies were to portray the use of ILIB for the treatment of dysgeusia,[11,13] mucositis,[14,15] and lingual paresthesia[12] to evaluate the efficacy of the ILIB and test its use for the carotid[12,13] or radial artery[11,14,15] in these patients (Table 2). The general characteristics of studies and diagnosis of the patients are detailed in Table 3 and Table 4.

Laser protocol

The ILIB application site was the radial artery[11,14,15] and carotid artery.[12,13] The laser parameters used were consistent across all studies, with a wavelength of 660 nm ± 10 nm. Power: 100 mW ± 20%, changing power values over time. The energy varies from 30J,[15] 60J,[11,13,14] and 90J,[12] and application times from 5 minutes,[15] 10 minutes,[13] 15 minutes,[11,12] and 30 minutes,[14] the outcomes portrayed are that there was a reduction of lesions in the first days with their subsequent total healing (Table 5).

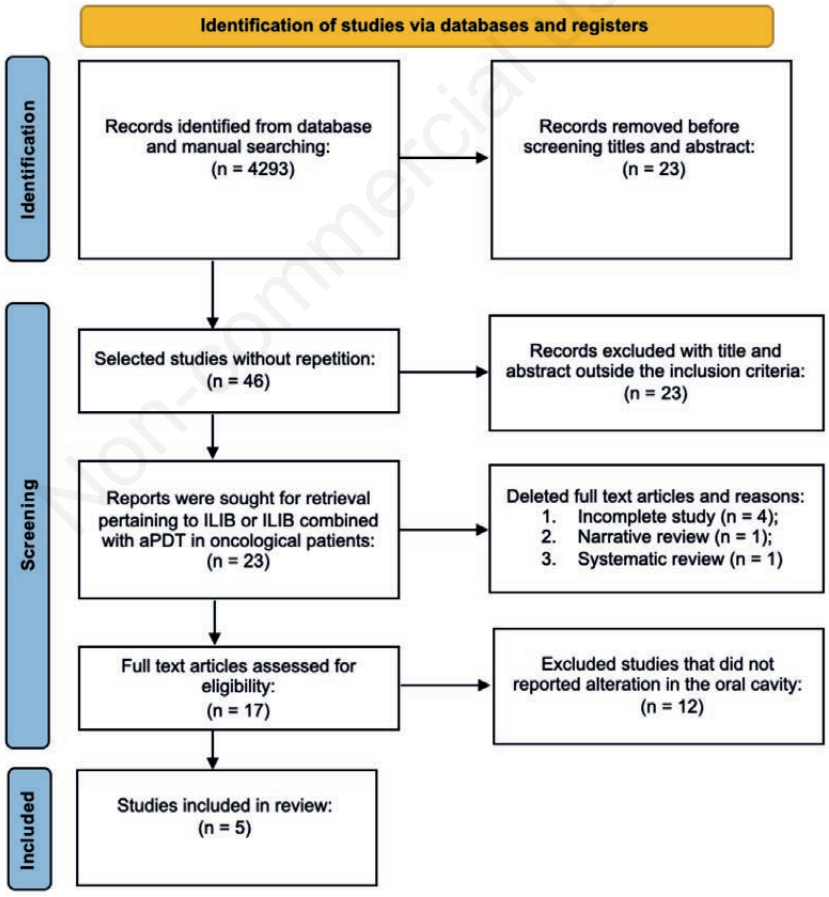

Figure 1. Literature search flow diagram and selection criteria adapted from PRISMA (Preferred report items for systematic reviews and meta-analysis).

Table 2. ILIB dosimetry parameters for the case report. The ILIB therapy was used on the fifth day of treatment.

ILIB	
Wavelength λ (nm)	660
Power (mW)	80
Operation mode	Continuous
Polarization	Random
Spot diameter (mm)	8.0
Spot area (cm^2)	0.50
Irradiance (mW/cm^2)	160
Fluence (J/cm^2)	144.0
Duration of each session (s)	900
Radiant energy per session (J)	72
Application technique	Contact (spot)
Location	Radial artery of the wrist
Number of sessions during therapy	10

ILIB, intravascular laser irradiation of the blood.

Table 3. Characteristics of the studies selected in the review regarding the location of the cases, type of studies, and objectives.

Study characteristics			
Author and year	**Local**	**Study design**	**Objectives**
Pacheco *et al.*, 2019 [11]	Cancer Hospital of Ribeirão Preto, Brazil	Case report	Use the low intesity laser in the oral cavity and in the radial artery of the wrist for the treatment of dysgeusia
Pacheco *et al.*, 2020 [12]	Cancer Hospital of Ribeirão Preto, Brazil	Case report	To present a clinical case of topical and systemic photobiomodulatory Treatment of lingual paresthesia Caused by long-term use of tamoxifen in a breast cancer patient
Pacheco *et al.*, 2019 [13]	Cancer Hospital of Ribeirão Preto, Brazil	Retrospective study	The purpose of this study is to categorize a transdermal anatomical location in the primitive carotid artery for the use of modified Intrasvacular laser irradiation of blood
Lima *et al.*, 2022 [14]	Public Hospital of São Paulo State, Brazil	Randomized clinical trial	To evaluate the efficacy of ILIB 30' and ILIB 60' protocols on side effects on the gastrointestinal tract (nausea, vomit, diarrhea and constipation) and on hematopoietic tissue (thrombocytopenias, neutropenias and hemoglobin)
da Silva and Pinheiro, 2021 [15]	Oncology department of Hospital PUC Campinas, Brazil	Non-randomized clinical trial	To assess the clinical application of intravascular laser irradiation of blood, photodynamic therapy, and photobiomodulation therapy in mucositis in cancer patients

ILIB, intravascular laser irradiation of the blood.

Table 4. Characteristics of the studies selected in the review regarding the number of people, sex, mean age, diagnosis, and reported oral manifestations.

Author and year	**Patient characteristics**			
	Number of patients per group/sex	**Middle age**	**Diagnosis**	**Oral alteration**
Pacheco *et al.*, 2019 [11]	1 female	63	Multifocal invasive right breast carcinoma	Dysgeusia
Pacheco *et al.*, 2020 [12]	1 female	60	Invasive left breast carcinoma	Lingual paresthesia
Pacheco *et al.*, 2019 [13]	16 female	NR	Breast cancer	Dysgeusia
Lima *et al.*, 2022 [14]	53 (15 female and 38 male)	54	Solid tumors	Oral mucositis
da Silva and Pinheiro, 2021[15]	36 (20 female and 16 male)	55	Head and neck cancer, breast cancer, gastric adenocarcinoma, non-Hodgkin's lymphoma, liposarcoma, kidney cancer, pancreatic cancer, rectal cancer, colon cancer, gastric adenocarcinoma, lung cancer	Oral mucositis

NR, not reported.

Table 5. Characteristics of the studies selected in the review regarding the ILIB and aPDT or PBMT laser protocol. Reported laser parameters, site and the total time of application, and the outcome of therapy.

	Laser protocol ILIB			Laser protocol aPDT/PBMT			Outcome
Author and Year	**Parameter**	**Region of the application**	**Application time**	**Parameter**	**Region of the application**	**Application time**	
Pacheco *et al.*, 2019[11]	Wavelenght: 660 nm±10 nm. Power: 100 mW±20%. Energy: 60 J	Radial artery of the wrist	15 minutes, 2 times for week for 2 months	Wavelenght: 660 nm. Power: 100 mW± 20%. Energy: 1 J and 2 J on the back.	Bilateral salivary glands (parotid, sublingual and submandibular), and in the lingual region (lateral border)	90 s	The patient returned for the normal and nutritional tasks with some success after the 1st application and the taste returned completely after 14 sessions progressively
Pacheco *et al.*, 2020[12]	Wavelenght: 660 nm±10 nm. Power: 100 mW±20%. Energy: 90 J	Primitive carotid artery	15 minutes, 3 times a month	Wavelenght: 660 nm±10 nm. Power: 100 mW±20%. Energy: 2 - 3 J	Total back extension of the tongue (9 points distancing 1.5 cm), larger salivary glands in the sublingual, parotid (3 points, 1 point per gland) and left submandibular and bottom region of left vestibule	350 s, 3 times a month	Complete remission of the lingual paresthesia
Pacheco *et al.*, 2019[13]	Wavelenght: 660 nm±10 nm. Power: 100 mW±20%. Energy: 60 J	Primitive carotid artery	10 minutes, 1 time a week fot 7 months	Treatment not performed	Treatment not performed	Treatment not performed	Cancer patients treated with personalized protocols associated with the carotid region reduce the health-disease process related to morbidities as a consequence of the dysgeusias and imbalance of the oral microbiome
Lima *et al.*, 2022[14]	Wavelenght: 660 nm±10 nm. Power: 100 mW±20%. Energy: 60 J.	Radial artery	ILIB 30': 30 minutes daily for 10 consecutive weekly days; ILIB 60': 60 minutes with 5 applications (10 days with 48h between each application)	Treatment not performed	Treatment not performed	Treatment not performed	Transcutaneous laser therapy, using both ILIB 30' and ILIB 60' protocols, was effective
da Silva and Pinheiro, 2021[15]	Wavelenght: 660 nm±10 nm. Power: 100 mW/cm^2±20%. Energy: 30 J.	Radial artery	5 minutes, 1 time weekly, for 5 months	aPDT: Curcumin photosensitivity solution, blue LED, Wavelenght: 468 nm. Power: 1200 mW±20% and PBMT: Wavelenght: 660 nm±10 nm. Power: 100 mW±20%. Energy: 1 J	26 points were irradiated for 10 s at each point: one point at each commissure labial (2 points), three points in the upper labial mucosa, three points in lower lip, three stitches on each side of the buccal mucosa (6 stitches), three stitches in each lateral edge of the tongue (6 stitches), two stitches on the floor of the tongue, two stitches on the belly of the tongue and two stitches on the soft palate	aPDT: 5 minutes and PBMT: 260s, 1 time, weekly for 5 months	There was a reduction in the degrees of oral mucositis (p=0.0277)

ILIB, intravascular laser irradiation of blood; aPDT, antimicrobial photodynamic therapy; PBMT, photobiomodulation therapy, X, absent data.

Three of the selected studies in this paper used previously or concomitantly PBMT[11,12,15] and aPDT[15] for the therapy. The laser parameters were Wavelength: 660 nm. Power: 100 mW ± 20%. The energy used in each article was different, ranging from 1 to 3J per point (Table 5). Three of the selected studies in this paper also utilized PBMT previously or concomitantly,[11,12,15] and aPDT[15] for therapy. The laser parameters for these treatments were consistent with a wavelength of 660 nm and a power of 100 mW ± 20%. The energy applied varied between 1 to 3J per point (Table 5).

Brief report

A 68-year-old female patient attended Ribeirão Preto Cancer Hospital Fundação SOBECCan, with severe lesions in the OM and OC, on the tongue and along the entire length of the lips (Figure 2), as a result of radiotherapy (RT) to treat laryngeal cancer. The patient presented with a severe inflammatory-infectious condition in the oral cavity, resulting in compromised nutrition and immunosuppression. The initial treatment was aPDT, where the photosensitizing agent was applied with a sterile syringe with 0.01% methylene blue (Chimiolux - DMC) to the entire linguistic region, lower lip, and bilateral lip commissure (Figure 3). The pre-irradiation time was 5 minutes of tissue interaction with a solution before laser application. Then, a low-power laser was applied punctually with a red laser wavelength of 660 nm ± 10 nm and; a red laser emission power of 100 mW ± 20% of power (DMC - São Carlos - Brazil). Nine points were irradiated across the entire tongue, 6 points on the lip, 1 point on each lip commissure (Figure 4A and B), 6 Joules of energy per point until covering the entire area of the clinical lesion, totaling 17 minutes per visit. The parameters used in laser treatment were defined according to the protocol described in the hospital over the years.[11-13] On the 5th day, there was a significant improvement in OM, but the OC presented resistance in the tongue and commissures. The patient still had pain. Thus, on the 6th day, the use of ILIB on the radial artery of the wrist was associated (Figure 4C). The laser parameter for ILIB is in Table 2. The vital signs (Blood Pressure, Oxygen Saturation, and heart rate) were monitored during all sessions. There was an acceleration of the final healing process of the oral lesions on the 10th day and a complete reduction in pain and infectious inflammatory processes in the tongue, lower lip, and bilateral lip commissure (Figure 5).

Discussion

The high efficacy of aPDT has resulted in its growing interest among the scientific community. This therapy has demonstrated effectiveness against t multidrug-resistant microorganisms,[4,5] with a low tendency to induce drug resistance.[7,16,17] Moreover, it exhibits lower toxicity.

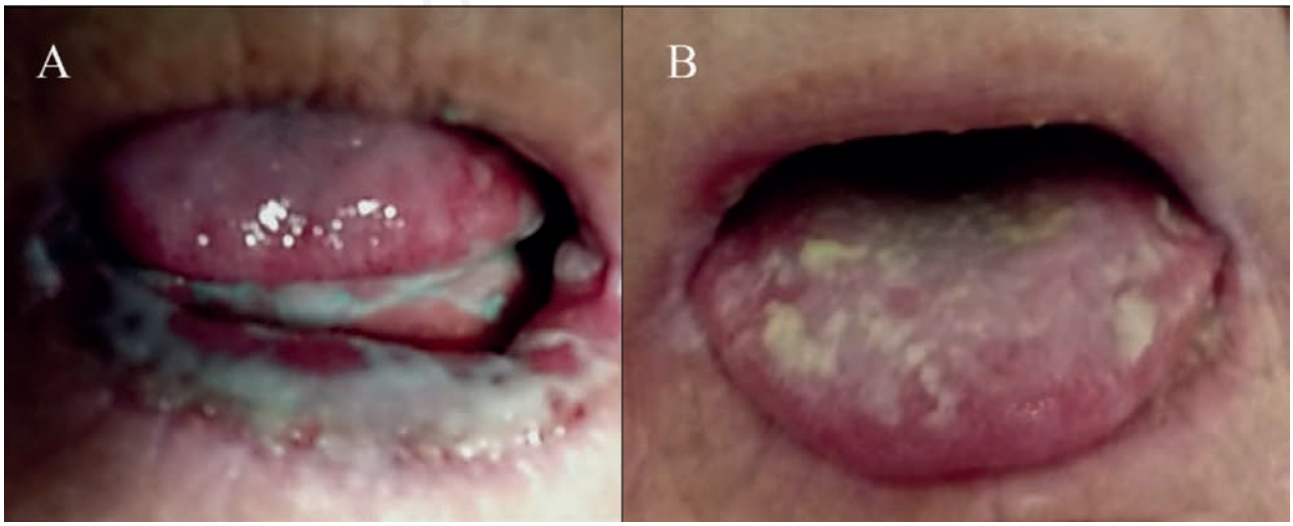

Figure 2. Oncological patient with severe oral mucositis lesions and oral candidiasis along the lips (A) and tongue (B).

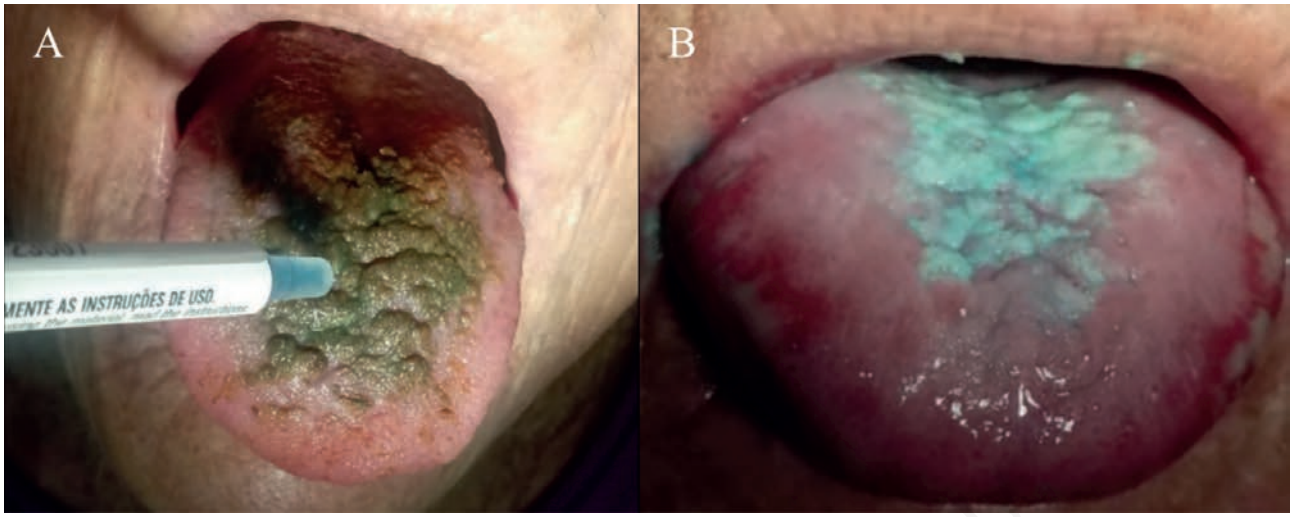

Figure 3. Treatment with aPDT using a sterile syringe with 0.01% methylene blue on the tongue (A), lips, and labial commissure (B).

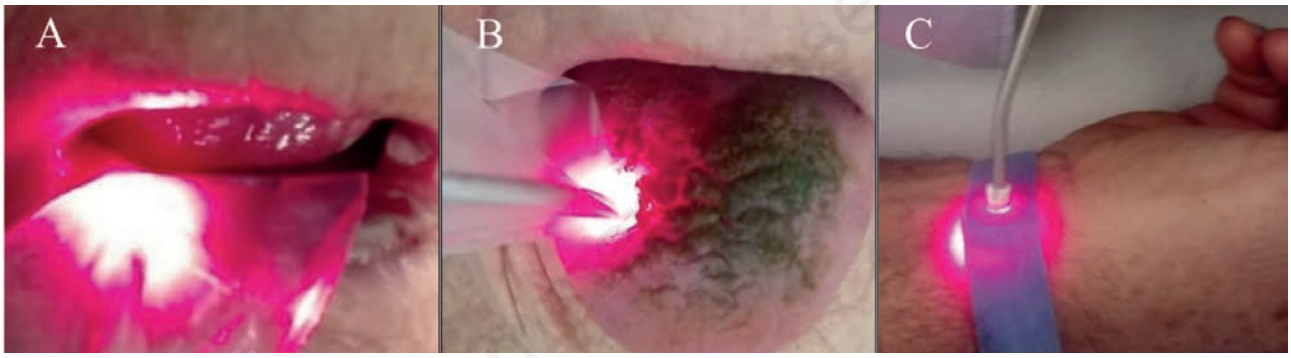

Figure 4. Points of irradiation on the lips (A), tongue (B), and radial artery of the wrist (C).

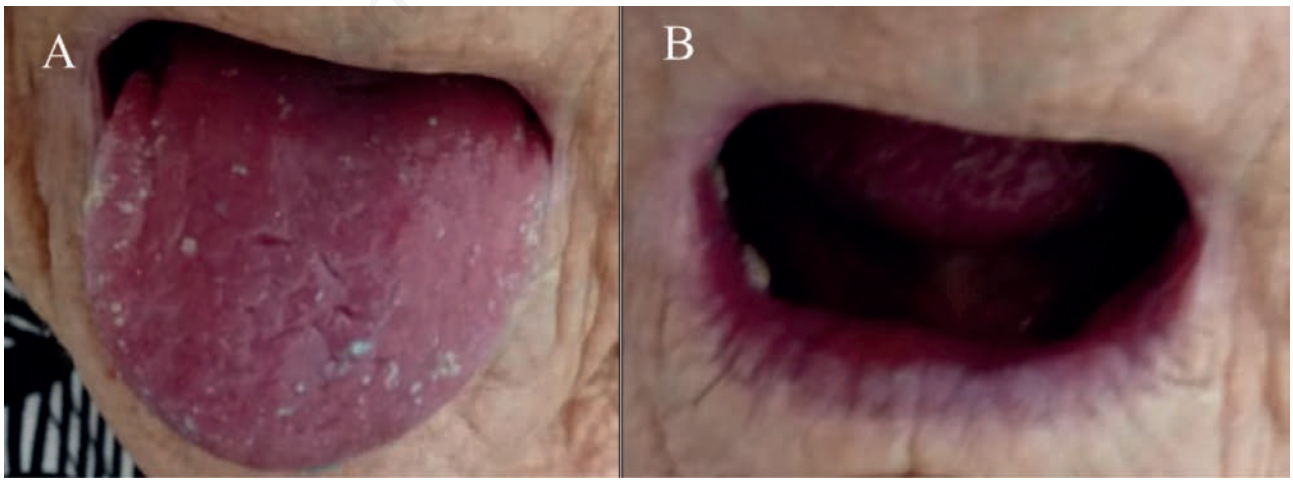

Figure 5. Complete reduction of infectious-inflammatory processes in the tongue (A), lower lip, and bilateral labial commissure (B).

Through the production of ROS, aPDT can inactivate bacteria,[17] fungi, and viruses.[18] Additionally, ILIB enables the elimination of hypoxia and normalization of tissue metabolism, promoting increased ATP synthesis and normalizing cell membrane potential.[8,10]

In the present case, following the application of aPDT, the patient experienced a reduction in oral cavity lesions exacerbated by the ionizing radiation of the RT, but this was insufficient due to the severity of the lesions. The selection of the red laser for aPDT is due to the greater affinity of this wavelength with the chosen methylene blue solution. The same wavelength was used in ILIB to provide a systemic photobiomodulation effect promoting the improvement of the immune system, and pain control, and inhibiting the action of ROS. This comforting action aids in cancer treatments.[19-24]

The improvement became more pronounced with the association of ILIB in the radial artery of the wrist within 05 days of treatment. Xu *et al.*[19] found that only low-intensity lasers with wavelengths between 630-670 nm can enhance blood oxygen transport, and more than 50 types of diseases can be treated using this method. In our study, ILIB enhanced the antioxidant enzyme system with an antitoxic effect and stimulation of the immune response, in addition to stabilizing blood pressure, oxygen saturation, and heart rate.[20,21]

The techniques complement each other synergistically, with PDT playing a leading role in controlling microbiota, thereby promoting oral cavity decontamination.[6-7] Conversely, systemic application of ILIB laser favors blood homeostasis, and pain control, and improves the immune system.[9-13,23-24] A recent study demonstrates that ILIB can also promote a reduction in blood pressure and heart rate among oncological patients.[25]

Our review identified five studies that evaluated ILIB as a therapeutic protocol for oral cavity manifestations in cancer patients.[11-15] Consistent with our brief report, these studies suggest that the use of ILIB alone or associated with PBMT or aPDT, results in improved prognosis with rapid healing of the lesions and enhancement of the patient's systemic condition. It is important to emphasize that the therapeutic protocol should be individualized, considering the systemic condition, location, and clinical presentation of oral lesions. For optimal intervention, a multidisciplinary team should monitor and discuss the best protocol for each patient.[22]

It is essential to consider monitoring during the ILIB treatment, as we realize that each patient, regardless of the protocol used, with 15 minutes like our report, or with 30 and 60 minutes as in work by Lima *et al.*[14] presents a similar photoresponse. While some patients quickly benefit from the treatment, others may need time and more incredible energy for the same response.

Therefore, the treatment of OM and OC in the oral cavity, utilizing aPDT associated with transcutaneous ILIB in the radial artery of the wrist, played a critical role in the patient's recovery process. The synergy of topical aPDT and systemic antimicrobial irradiation – ILIB - is suggested to have high efficacy and low toxicity. Despite the results achieved, it is recommended that further studies in larger samples be carried out so that they can contribute to the prevention and control of OM and OC in patients irradiated by head and neck radiotherapy.

The main limitation of this study is the absence of an analysis regarding the quality of the articles included in the review. The exploratory nature of this study resulted in the identification of preliminary studies on the topic through the review process. In this case, formal assessment of study quality may be less pertinent or even discouraged in such contexts. Also, a single case was included. It is important to conduct further studies with larger samples that are representative of the population. Even so, the five articles included in this review and the report of this case unanimously showed improvement in patients. We have seen that both aPDT and ILIB treatments can help, as palliative care is associated with traditional therapies. Thus, this article may encourage other multidisciplinary treatment teams to use these treatments.[11-15]

The treatment of OM and OC in the oral cavity, utilizing the combined techniques of aPDT and ILIB in the radial artery of the wrist, is crucial for facilitating the rapid recovery of the patient. The synergy between aPDT and ILIB suggested to offer high efficacy and low toxicity in addressing oropharyngeal disorders in patients undergoing RT irradiation. Therefore, aPDT with ILIB may serve as a viable alternative for treating OM and OC in oncological patients with clinical application.

Conclusions

The current literature suggests that the use of aPDT with ILIB may be an effective therapy for the rapid recovery of oral lesions and cytotoxic symptoms in oncological patients. Laser therapies have proven effective in treating patients with mucositis and oral candidiasis undergoing radiotherapy.

Contributions

All authors participated in designing the protocol. First, JAP and EVV designed the study. KFM and JAP then did the literature search. JAP, KFM selected the studies and extracted the relevant information, then assessed and confirmed by the senior authors. All authors then participated in synthesizing the data. JAP, EVV, HP, SLP, and BT also wrote the first draft of the paper. JAP, HP, BT, and SLP provided critical guidance on the analysis and overall direction of the study. JAP made a clinical case. JAP, EVV, and KFM wrote the brief report. All authors critically revised successive drafts of the paper and approved the final version.

Conflict of interest

The authors declare no conflicts of interest.

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Ethical approval

All procedures performed in studies involving human participants followed the ethical standards of the institutional and national search committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Consent was obtained from the patient for the publication of this report and any accompanying images.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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