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REVIEW ARTICLE

Efficacy of low-level laser for treatment of cancer oral mucositis: a systematic review and meta-analysis

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Abstract

Review effectiveness of low-level laser therapy (LLLT) in the curative treatment of oral mucositis (OM) in patients receiving cancer therapy. A systematic review with meta-analysis was performed using Medline, Embase, and Cochrane Library databases according to PRISMA guidelines, to identify randomized controlled trials (RCT) on OM in patients during and/or after cancer therapy and in which the therapeutic approach was LLLT, with wavelengths between 632 and 970 nm. We considered grade of OM as a dichotomous variable (such as an improvement or not in severe OM on the seventh day of therapy), with the analysis of subgroups of adult patients or children and adolescents and as a continuous variable with determination of the time for the complete resolution and the subgroup analysis occurred with the strata of the samples by treatment only with chemotherapy or chemotherapy and radiotherapy. This paper's protocol was registered a priori at https://www.crd.york.ac.uk/PROSPERO. We found five RCT (total of 315 patients) with adequate methodology. LLLT was effective, presenting a 62% risk reduction of severe mucositis on the seventh day of evaluation (RR = 0.38 [95% CI, 0.19–0.75]). When we analyzed subgroups, RR was 0.28 (95% CI 0.17–0.46) in the adult studies and 0.90 (95% CI, 0.46–1.78) in the studies with children and adolescents. We demonstrated a mean reduction of 4.21 days in the time of complete resolution of OM (CI − 5.65 to − 2.76) in favor of LLLT. There is moderate evidence that LLLT is effective in resolving OM lesions in adult patients undergoing cancer therapy. LLLT demonstrates potential for decreasing the resolution time of OM lesions by approximately 4.21 days.

Keywords Low-level light therapy · Low-level laser therapy · Oral mucositis · Cancer therapy · Therapeutics

Introduction

Oral mucositis (OM) is an inflammatory condition of the mucosa that presents with erythema, ulceration, hemorrhage, edema, and pain. It is one of the main complications of patients on cancer therapy, with several nutritional limitations and the ability to cause secondary infections and fever [1]. Often, due to its morbidity, antineoplastic treatment must be altered or suspended, interfering with tumor control and patient survival [2].

The incidence of OM varies according to the type of cancer as well as the type of cancer therapy. With the use of chemotherapy drugs, mucositis is observed in 5 to 15% of cases, but this incidence may be much higher with some drugs such as daunorubicin and etoposide (incidence of 26%), cytarabine (incidence of 37.5%) and the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen (incidence above 40%) [3, 4]. Chemotherapy regimens generally appear to induce oral mucosal lesions over a short and acute period, usually 4 to 7 days after the start of treatment with a peak incidence at 2 weeks [5]. The control of local infection and maintenance of oral mucosa integrity are essential factors for quality treatment, with less pain and nutritional reestablishment in patients potentially debilitated by the underlying disease [6, 7].

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Patients with head and neck cancer treated with radiotherapy have 65% mucositis rates, and even higher rates, 75 to 85%, are found in those subjected to bone marrow transplantation with chemo- and radiotherapy [4, 8].

Patients with hematological malignancies are more likely to develop OM than those with solid tumors, and those with acute leukemia, non-Hodgkin's lymphomas, and undifferentiated nasopharyngeal carcinomas are the most at risk. Children undergoing chemotherapy have OM on average on the tenth day (± 6.8) of treatment in more than 50% of cases. Although it is resolved on the seventh day (± 3.1), more than 67% of the patients show concomitant neutropenia [5].

Acute leukemia results from the malignant transformation of primitive hematopoietic cells, followed by clonal proliferation and consequent accumulation of these transformed cells. The deficiencies of hematopoiesis in the bone marrow, with the replacement of normal cells by immature cells that accumulate (classifying acute leukemia according to the hematopoietic lineage affected in myeloid and lymphoid leukemias), result in a functional deficiency of the bone marrow that, consequently, is clinically expressed by anemia, bleeding, infections, and hyperviscosity syndrome. Mucositis in these patients may have clinical consequences both in nutritional aspects, due to difficulty or inability to use the oral route, as well as in pain, in the incidence of secondary infections and in the difficulty of continuing adequate cancer therapy [1, 5].

Treatment of OM involves multidisciplinary evaluation for an adequate care of the oral mucosa. In this regard, opioid analgesics, specific oral hygiene protocols, antimicrobial agents, anti-inflammatory medications, cytoprotective agents (such as amifostine, sucralfate, misoprostol), biological response modifying substances or physical therapies (cryotherapy and laser therapy) may be used. Low-level laser therapy (LLLT) is a phototherapy that can stimulate tissue regeneration, reduce inflammation, and control pain [2, 9–11].

The treatment is called low-level because the light used is of low intensity when compared to other types of laser therapy, such as for ablation or cutting and coagulation. This type of laser treatment stimulates cellular activity, leading to the release of growth factors by macrophages, proliferation of keratinocytes, population increase, and degranulation of mast cells and angiogenesis. In this way, LLLT accelerates the wound healing process partly by reducing the duration of acute inflammation, resulting in faster repair [10, 12].

These effects of LLLT on the oral mucosa have been described in studies with the use of prophylactic laser, which found a good effectiveness in reducing the risk of OM as well as pain related to mucosal lesions [6, 12]. However, the use of LLLT as a curative treatment for mucositis still lacks robust evidence. Only a few systematic reviews have addressed the issue, and moreover, LLLT with therapeutic aspect was not approached as the central object of evaluations [6, 11]. The aim of this study was to review the effectiveness of LLLT in the curative treatment of OM in patients undergoing cancer therapy.

Materials and methods

Search strategy

The review of the literature consisted in the search for randomized controlled trials (RCTs) in the Medline, Embase, and Cochrane Library databases and gray literature (conference abstracts and non-indexed sources) using the MeSH terms according to the analysis of the criteria of the PICO framework questions (P: population, patients with OM; I: intervention, laser therapy; C: comparison, no intervention; O: outcome, grade of OM [outcomes not addressed in the literature search]), with the following problem question from this analysis: "what is the effectiveness of LLLT in the treatment of OM in patients undergoing cancer therapy?" MeSH terms, keywords, and other "free" terms related to mucositis and LLLT were used with Boolean operators (OR, AND) for the search. The search strategy included only terms related to or describing intervention such as LLLT, mucositis, radiotherapy, chemotherapy, chemotherapy and radiotherapy, and cancer, and is available in Fig. 1.

We developed the protocol of this systematic review following the parameters of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and the review was registered a priori at the PROSPERO site (https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017077920).

Inclusion criteria

We included studies of the type (a) RCT, where (b) the diagnosis was of OM caused in patients during and/or after cancer therapy, and where (c) the therapeutic approach for the oral mucosa was with LLLT with wavelengths between 632 and 970 nm. There was no language restriction in the search, and studies from 1992 (date of the first paper suggesting a potential benefit from LLLT for oral mucositis [13]) to 2017 were included.

Exclusion criteria

We excluded studies whose therapeutic approach was based only on prophylaxis of OM, those in animal models, and also those in which only histological and cytological samples were investigated. Irrelevant articles were excluded at different levels (title, abstract, or full article) based on these exclusion criteria.

Fig. 1 The search strategy

Mucositis

("Mucositis"[Mesh] OR "Mucositis" OR Mucositides OR "Stomatitis"[Mesh] OR "Stomatitis" OR Stomatitides OR "Oral Mucositis" OR "Oral Mucositides" OR Oromucositis OR Oromucositides) OR

('mucosa inflammation'/exp OR 'mucosa irritation' OR 'mucositis' OR 'Mucositides' OR 'Oromucositis' OR 'Oromucositides' OR 'stomatitis'/exp OR 'cancrum oris' OR 'denture sore mouth' OR 'denture stomatitis' OR 'mouth epithelium inflammation' OR 'mouth inflammation, ulcerative' OR 'mouth inflammation, ulcerous' OR 'mouth mucosa inflammation' OR 'noma' OR 'oral inflammation, ulcerative' OR 'recurrent stomatitis' OR 'stomatitis prothetica granulomatosa' OR 'stomatitis ulcerativa' OR 'stomatitis ulcerosa' OR 'stomatitis virus' OR 'stomatitis, denture' OR 'stomatitis, ulcerative' OR 'stomatitis, ulcerous' OR 'ulcerative mouth inflammation' OR 'ulcerative oral inflammation' OR 'ulcerative stomatitis' OR 'ulcerous mouth inflammation' OR 'ulcerous oral inflammation' OR 'ulcerous stomatitis')

Low Level Laser Therapy

("Low-Level Light Therapy"[Mesh] OR "Low-Level Light Therapy" OR "Low Level Light Therapy" OR "Low-Level Light Therapies" OR "Photobiomodulation Therapy" OR "Photobiomodulation Therapies" OR "LLLT" OR "Low-Level Laser Therapies" OR "Low-Power Laser Therapy" OR "Low Power Laser Therapy" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Laser Phototherapy") OR

('low level laser therapy'/exp OR 'endoscopic laser therapy' OR 'laser biostimulation' OR 'laser therapy' OR 'laser therapy, low-level' OR 'laser treatment' OR 'low energy laser therapy' OR 'low energy laser treatment' OR 'low intensity laser therapy' OR 'low intensity laser treatment' OR 'low level laser treatment' OR 'low level light therapy' OR 'low power laser therapy' OR 'low power laser treatment' OR 'low-level light therapy')

Randomized Controlled Trial

(clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR

('crossover procedure'/exp AND [embase]/lim OR ('prospective study'/exp AND [embase]/lim) OR ('follow up'/exp AND [embase]/lim) OR ('placebo'/exp AND [embase]/lim) OR ('clinical trial'/exp AND [embase]/lim) OR ('single blind procedure'/exp AND [embase]/lim) OR ('double blind procedure'/exp AND [embase]/lim) OR('randomization'/exp AND [embase]/lim) OR ('controlled clinical trial'/exp AND [embase]/lim) OR ('randomized controlled trial'/exp AND [embase]/lim)).

Two examiners (FA and JW) performed the search independently in the electronic database. Articles that appeared in more than one database were considered only once. The form of data extraction was developed by the authors and the results were synthesized according to the parameters presented in Table 1. In this extraction, the mentioned inclusion and exclusion criteria were considered, as well as the ethical aspects and the presence of clinically important outcomes and objects in this review. When some data were missing from the original work, the authors of these articles were contacted to obtain this information. Agreement on inclusion of studies among reviewers was assessed using the kappa test. The agreement strength was defined as light (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or near perfect (0.81 to 1.00).

Risk of bias

We used the Cochrane Collaboration tool to access the potential risks of bias in randomized clinical trials. This tool systematizes the following domains for internal validation: selection bias, performance bias, detection bias; attrition bias, and reporting bias [14]. We evaluated the following sources of bias related to these domains: randomization, allocation concealment, blinding of participants and personnel, incomplete

Table 1 Characteristics of included studies and laser therapy parameters

First author (year)	Country	No. of patients	Age group	Groups/ wavelength (nm)	Power (mW)	Spot size (cm^2)	Energy density (J/cm^2)	Irradiation time (s)	Days of application	Outcome	Classification scale of mucositis
Amadori (2016)	Italy	125	Children	Laser (830) × control	150	1	4.5	30	4	gOM(−)/pain(+)	WHO
Gobbo (2017)	Italy	101	Adults	Laser (970) × control	250	1	6	30	4	gOM(+)/pain(+)/use of analgesic(−)/neutrophila(−)	WHO
Kuhn (2009)	Brazil	21	Children	Laser (830) × control	100	0.06	4	56	5	Days (+)/gOM(+)	NCI CTCS
Kuhn (2007)	Brazil	34	Adults	Laser (830) × control	100	0.06	4	54	5	Days (+)/gOM(+)	NCI CTCS
Genot-Klastersky (2008)	Belgium	36	Adults	Laser (*) × control	*	1.2	2 (mean)	33 (mean)	21 (mean)	gOM(+)	EORTCS

*Laser therapy was performed with a scanning laser combining a visible laser of 100 mW and infrared laser with 50, 250, and 500 mW;

(+) positive effect on outcome

(−) negative effect on outcome

gOM, grade of oral mucositis; *WHO*, World Health Organization; *NCI CTCS*, Scale of Common Toxicity Criteria of National Cancer Institute; *EORTCS*, Scale of European Organization for Research and Treatment of Cancer

outcome data, blinding of outcome assessment, and selective outcome reporting.

It is a two-part tool, addressing the related domains, each one includes one or more specific entries in a "Risk of bias" table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry.

Methodological quality

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to assess the quality of the evidence and the strength of the recommendations in health. This system provides explicit criteria for rating the quality of evidence (classifies in one of four levels—high, moderate, low, and very low) that include study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect. The classification was performed independently and blindly by two researchers/authors (FA and JW) and there was a consensus among the researchers about the scores. Disagreements between researchers/authors at this stage were resolved with analysis of a third author (MEZC) [15].

Data extraction

Data extraction was done individually by two examiners (FA and JW) to search for the following variables for each included study: principal investigator (s) of publication, country of publication, year of publication, sample demographics, characteristics of LLLT (wavelength, power, spot size, energy density, irradiation time, days of application), main results/outcomes, improvement of oral mucositis on the seventh day of treatment, time needed for resolution of OM, characteristics of the underlying disease, and type of cancer therapy.

Data synthesis

The data listed from the five original articles selected were combined in this study for meta-analysis. For the primary outcome, grade of OM, we considered grade of OM as a dichotomous variable (such as an improvement or not in severe OM, with effect determined on the seventh day of therapy) and the data were synthesized using relative risk (RR) as a measure of effect with 95% confidence interval (CI). RR less than 1 indicates that LLLT is better than placebo in the curative treatment of OM (protecting oral mucosa or alleviating OM). In this evaluation, we proceeded to the analysis of subgroups in studies carried out with adults or children and adolescents.

The duration of oral mucositis can indicate a delay in the onset and rate of resolution of oral mucositis lesions and thus can be used to represent the efficacy of treatment oral mucositis. For this outcome (days for complete resolution of

mucositis lesions), the time for the complete resolution of mucositis was determined, obtaining the mean time and standard deviation (in days) in the groups with and without LLLT. For this evaluation, we performed subgroup analysis, dividing the strata of the samples by treatment of cancer with chemotherapy alone or chemotherapy and radiotherapy.

This review also addressed the role of LLLT in pain relief related to OM and the presence of adverse events associated with therapy.

The meta-analysis was performed using the program Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre) [16]. The I^2 method was used to assess the statistical heterogeneity among studies in each analysis. Heterogeneity was considered statistically significant if p value was < 0.1. If $I^2 \leq 25$, the studies were regarded homogeneous, the $I^2 > 25$ and < 75 classified the studies as having moderate heterogeneity and $I^2 \geq 75$ with high heterogeneity. When faced moderate or high heterogeneity, we performed the analysis in subgroups.

Results

Literature search and exclusion procedure

The review of the literature revealed 303 scientific papers on OM and LLLT. After the first analysis, when the 303 articles were then transferred to the reference management software that removed duplicate articles to reduce the number to 265 articles, the articles were assessed by the inclusion/exclusion criteria at different levels of exclusion (title (n.:183), abstract (n.:70)) and yielded a total of 12 were listed as potentially relevant, keeping focus on the object of this study. Of these, seven were excluded (full-article level) and five were evaluated qualitatively (Fig. 2).

The reasons for exclusion at this stage were as follows: study without randomization [17], study design not clinical trial [18], without placebo control group [19, 20], control without OM as the study factor [21], data presented only as medians [22], and study with duplicate data included [23]. After the qualitative evaluation, five were included in the final quantitative analysis, with articles published between 2007 and 2017, consisting of a total of 317 patients [4, 24–27]. The kappa index estimating agreement between the reviewers was 0.826 (0.71 to 0.93) with $p < 0.001$. The inclusion and exclusion procedures are described in the flowchart (Fig. 2).

The authors of two studies [24, 27] were contacted to provide information and data on this review (three contacts per author from January to March 2018). These data and those collected directly from the studies are summarized in Table 1. The World Health Organization classification for OM was used in two studies from Italy included in the analysis, the classification of the National Cancer Institute (version 2.0) in two studies from Brazil, and the scale of the European Organization for Research and Treatment of Cancer in one study from Belgium (Table 1).

There was a slight variation in the type of laser, wavelength, energy released, and duration of irradiation used in the studies. The wavelengths varied between 830 and 970 nm with power that oscillated according to each protocol of use between 50 and 500 mW. Except for one study [4], the energy density ranged from 4 to 6.5 J/cm^2 and the days of LLLT application were between 4 and 5 days. Table 1 also shows the outcomes as dichotomous variables and, with the exception of one paper [27], the other four studies showed a positive effect on the grade of OM outcome [4, 24–26]. Two studies positively assessed LLLT for pain reduction [24, 27] and two studies identified a decrease in the number of days with OM (outcome brought here as "days") [25, 26] (Table 1).

Methodological quality and risk of bias

The methodological quality was considered good or high for the included studies, considering that some additional information from the authors (unpublished) was necessary for the composition of the evaluation. Our analysis demonstrated the majority of studies with adequate allocation concealment and blinding of outcome evaluators. There was no decrease in quality, but there was some concern with the possibility of selection bias (allocation concealment) in some studies [25, 26]. In this way, overall risk of bias was considered low. By identifying only five studies in this systematic review, although we searched several research sources, there was clearly the risk of publication bias. On evaluating the quality of the evidence, we found the evidence regarding the outcomes to be moderate [4, 24–27] (Fig. 3).

Effect on oral mucositis severity

There was a 62% decrease in the risk of severe OM (OM with grade ≥ 2) in patients who received LLLT compared to the control group (95% CI 0.16 to 0.75, $p < 0.05$). Of the 158 patients who underwent the LLLT intervention, only 25 still had OM with grade ≥ 2 at the time of reevaluation (seventh day of course of OM). In the control group, with 157 patients, 60 had OM with grade ≥ 2 (Fig. 4).

In view of the heterogeneity demonstrated ($I^2 = 57\%$), we carried out the analysis in subgroups, considering studies carried out in adults (three studies with 171 patients, $I^2 = 0\%$) and in children/adolescents (two studies with 144 patients, $I^2 = 0\%$), with $I^2 = 86.6\%$. Thus, LLLT in the treatment of OM in adults was effective with a RR of 0.28 (95% CI 0.17 to 0.46); however, in the studies with children, there was no demonstration of this same effect with RR of 0.90 (95% CI 0.46 to 1.78) (Fig. 4).

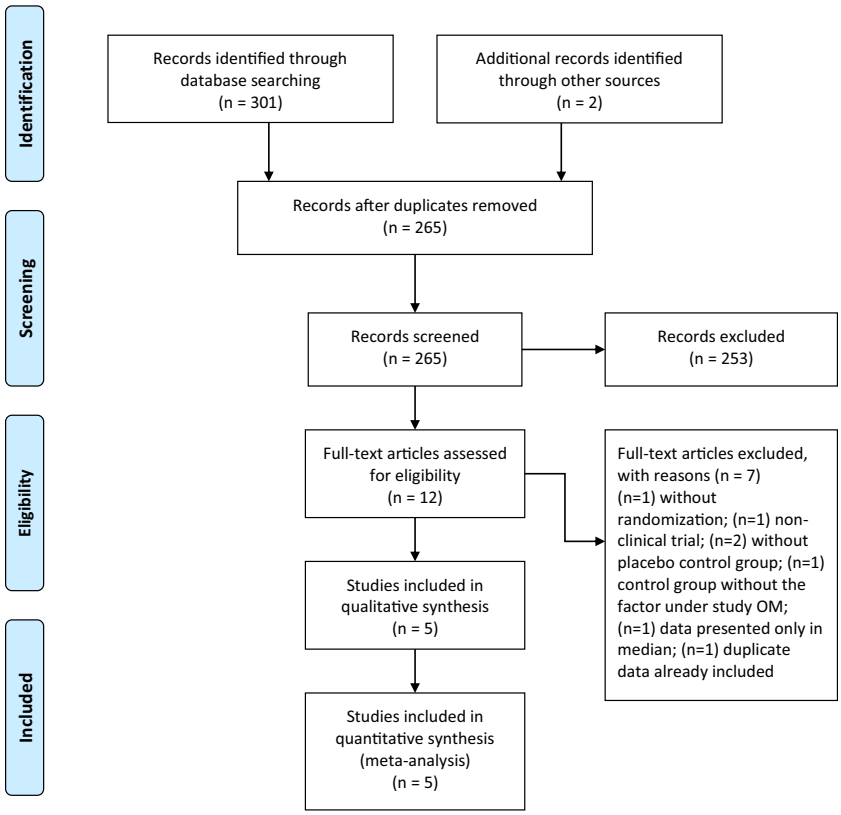

Fig. 2 Flowchart of identification to selection of articles

Effect on the duration of oral mucositis

In two studies, it was possible to extract data referring to the time in days for the complete resolution of mucositis (I^2 = 56% and $p < 0.05$), and we found a mean reduction of 4.21 days (95% CI − 5.65 to − 2.76) in favor of the use of LLLT (Fig. 5) [25, 26]. Figure 5 displays the results in three strata of these two studies with subgroup analysis, due to the demonstrated heterogeneity, considering OM in patients undergoing chemotherapy (two strata, $n = 43$ patients, $I^2 = 0\%$) and undergoing chemo- and radiotherapy (one stratum, $n = 12$ patients), with $I^2 = 76.2\%$. In the group on chemotherapy, there was a reduction in the time of complete resolution of 3.55 days on average (95% CI − 4.68 to − 2.42; $p < 0.05$), and in the group on chemo- and radiotherapy, the reduction was of 5.7 days on average (95% CI − 7.42 to − 3.98, $p < 0.05$) [25, 26]. None of the studies listed reported side effects or adverse events related to LLLT, further indicating that laser therapy was well tolerated by patients [4, 24–27].

Effect on pain relief

It was possible to assess the effect of LLLT on pain relief in two studies [24, 27]. One study evaluated the improvement of pain in adult patients with mucositis with statistically significant results in favor of LLLT ($p < 0.006$). In this study, the results of the pain score decreased from 8 points on average in both groups (following a 0-to-10 numeric pain rating) to 1 in the LLLT group and to 2.5 in the sham group on the 7-day evaluation [24].

In another study, with children, the initial score was smaller for both groups, only 4 points on the pain scale. On the seventh day of treatment, the LLLT group had a score of 0 and the control group had a score of 1, also showing statistical significance ($p < 0.0005$) [27].

Adverse events

There were no reports of adverse events in the use of LLLT in the treatment of patients with OM [4, 24–27].

Discussion

Our meta-analysis showed that LLLT improves severe OM and is effective in treating this clinical condition in adult patients undergoing cancer therapy. Despite the well-established role of laser therapy in the prevention of OM, with about nine times more efficacy than the non-application of LLLT, its role in curative treatment still lacked more robust evidence [28, 29]. This treatment strategy brought a positive consequence to the resolution of OM in adult patients. In this way, we can

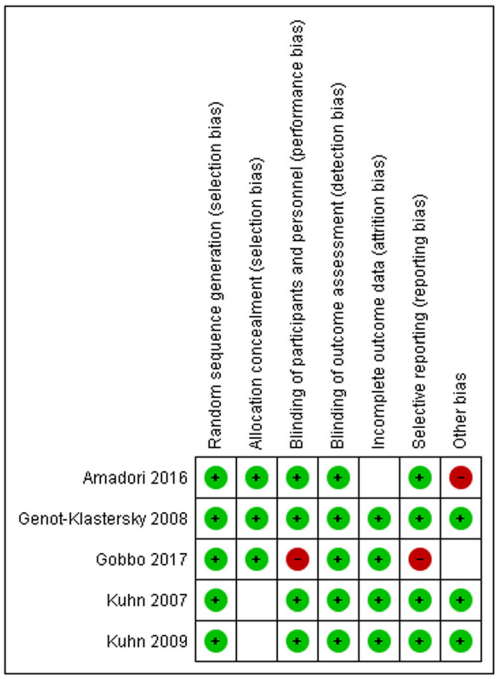

Fig. 3 Summary of review methods: assessment of reviewers/authors on each methodological aspect (presenting the quality of each item in the included studies)

infer that the LLLT has a potential of use both for the reduction of OM cases and for the resolution of those that escaped the prognostic effect. Thus, we could increase the indications of use of the technology and qualified the assistance to these patients.

In general, the risk of bias in the studies was classified as moderate by the GRADE system. Most of the studies presented adequate allocation concealment and blinding of outcome assessors. There was no reduction in quality; although there was some concern about the possibility of allocation concealment in some studies, the overall risk of bias was considered low. Of the five studies analyzed, only three were clear about allocation concealment, and in two, this evaluation was not possible. These findings could be associated with more exaggerated effects of laser treatment. However, the clinical trials that reported adequate allocation concealment were studies with greater weight in the analysis. Another point was the potential publication bias, where the limited number of RCTs of five led us to lower the degree of evidence.

Laser energy, when used at wavelengths ranging from 632 to 970 nm, as referred to in this systematic review, is usually absorbed by a thin layer of tissue under the point of application, in this case, the OM lesion. Effects related to increased mitochondrial activity and cellular metabolism as a whole are reported, as well as analgesic and anti-inflammatory capacity when applied to mucosal surfaces [30]. Considering the current knowledge and biological plausibility in using LLLT as prophylaxis for OM, this systematic review focused on the resolution of OM in curative treatment. OM resolution was evaluated both as a dichotomous variable (such as an improvement in or not of severe MO, with evaluation of the effect on the seventh day of therapy) and in the determination of the time in days needed for complete resolution of mucositis in the groups with and without LLLT.

Although the LLLT application protocols varied among the studies in this systematic review, four studies used a similar LLLT application strategy at one point of the OM lesion and

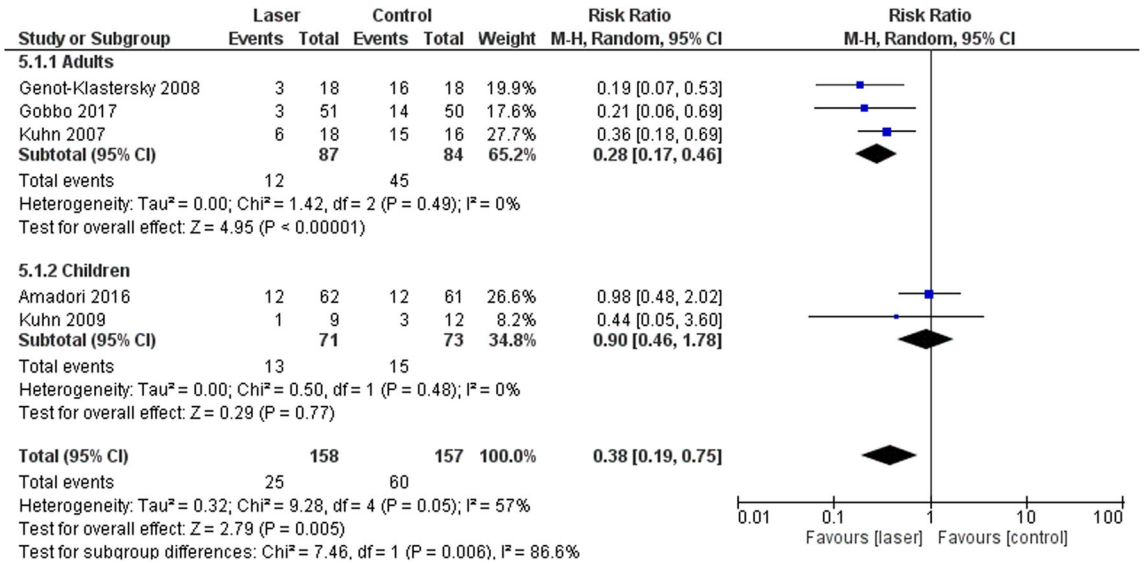

Fig. 4 Forest plot demonstrating the results of the meta-analysis of the curative treatment of patients with oral mucositis using low-level laser therapy. The plotted results on the left side indicate the effects favoring low-level laser therapy, while those on the right indicate the effects favoring the control group (placebo). The analysis was done per subgroup (adults and children). Events: patients who still had OM with grade ≥ 2 after treatment

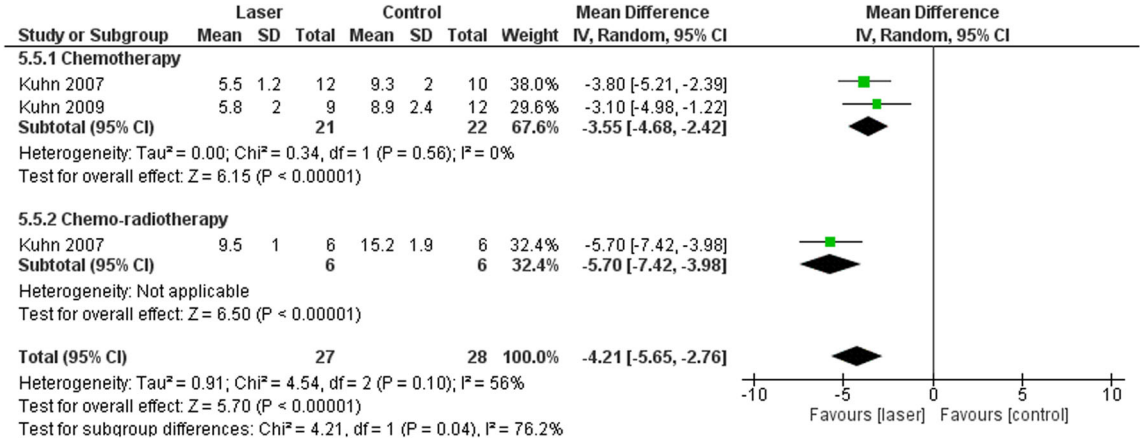

Fig. 5 Forest plot demonstrating the results of the meta-analysis of the curative treatment of patients with oral mucositis using low-level laser therapy (according to time for complete cure). The plotted results on the left side of the graph indicate the effects favoring low-level laser therapy, while those on the right indicate the effects favoring the control group (placebo). The analysis was done per subgroup (chemotherapy and chemo- and radiotherapy). Events: days needed for complete cure of OM after treatment

reported similar wavelengths (830 and 970 nm) with energy density ranging from 4 to 6.5 J/cm^2, considered as adequate when the laser therapy strategy is curative [7]. Only one study used the laser scanning strategy and an energy density of 2 J/cm^2, which despite being the recommended dose only for OM prophylaxis protocols, showed promising results in favor of LLLT [4].

We have identified two groups of patients in this systematic review with different estimates of the OM treatment benefit with LLLT. Adult patients demonstrate a clear benefit in using LLLT as a treatment strategy for OM. However, in the studies with children, there was no demonstration of this same effect. At this point, it is important to note that although there were only two studies in children, the total number of individuals ($n = 144$) was close to that in the adult studies ($n = 171$). Although a systematic review study reported a possible beneficial effect of LLLT in children [31], other LLLT prognostic evaluation studies did not demonstrate this association [32, 33]. The lack of effect of LLLT in this group may be due to different factors such as (i) spontaneous cure observed by pediatricians and dentists, which occurs most frequently in OM in children undergoing oncotherapy, especially when children or their caregivers are educated and follow stricter oral hygiene protocols; (ii) different protocols for LLLT use (number of sessions/application time/energy density) that should be modulated differently for children; (iii) absence of risk factors for oral lesions in children; (iv) less severe OM lesions at the beginning of treatment; (v) chemotherapy medications other than those of adults; (vi) different doses (usually minor) of chemotherapeutic agents and/or radiotherapy [1, 3, 5, 32]. These discordant results make us think of the need for new studies evaluating this association between children and the treatment of OM.

Two studies identified a decrease in the mean time for the course of OM. Analysis of this outcome, i.e., days for complete resolution of OM, showed that LLLT was an effective treatment against mucositis lesions with a reduction of approximately 4.21 days. In these two studies, we identified three strata in which it was possible to analyze subgroups: patients undergoing chemotherapy (two strata, $n = 43$ patients) and undergoing chemo- and radiotherapy (one stratum, $n = 12$ patients). In the group on chemotherapy, there was a reduction in the time needed for complete resolution, i.e., 3.55 days on average, and in the group undergoing chemo- and radiotherapy, the mean reduction was 5.7 days.

The biological pathways for the induction of OM may be slightly different between chemotherapy and radiotherapy. Chemotherapy induces OM more acutely with an onset between the fourth and seventh days with a peak incidence in the second week. On the other hand, radiation-induced OM is usually dose-dependent and typically begins with a cumulative dose of 15 Gy, around the tenth day, peaking at 30 Gy, remaining for weeks [34]. In this way, we can assume that in view of more punctual radiotherapy in the oral cavity tissue, direct treatment with LLLT can restore the damage more quickly. However, we also need to remember the different cytotoxic actions between the various chemotherapeutic agents, which may influence the LLLT and decrease the resolution time of OM.

In terms of LLLT adverse events in the treatment of patients with OM, there were no reports of incidents or complications arising from the use of laser therapy.

From the properties of laser therapy in the selective inhibition of peripheral pain receptors [7, 12], two studies addressed the reduction of pain through visual analog scales and the results were favorable to LLLT with reduction of pain related to OM [24, 27]. However, the initial pain scores were twice as high in the study with children compared to the study with adults, which is why we did not evaluate these results together. The evidence identified in this systematic review regarding

OM pain in patients undergoing cancer therapy is the effectiveness of LLLT in reducing pain.

We conclude that there is moderate evidence that LLLT is effective in resolving OM lesions in adult patients undergoing cancer therapy. Although, there is not enough evidence to point out effectiveness in the curative treatment of OM in children. LLLT demonstrates potential for decreasing the resolution time of OM lesions by approximately 4.21 days. There are limitations to this conclusion related to the potential risk of bias (allocation concealment) and to the fact that we found few RCTs in the literature, specifically addressing this curative aspect of LLLT, which has led to have a lower robustness of results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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