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Original article

**Laser therapy in oral mucositis control:
a meta-analysis[☆]**

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A B S T R A C T

Objective: To perform a systematic review and meta-analysis of the effectiveness of laser therapy (LT) in the prevention of oral mucositis (OM) in patients undergoing oncotherapy.

Methods: A search was conducted in the MEDLINE, LILACS, and Cochrane databases using the keywords “laser therapy” and “oral mucositis” in order to perform this systematic review and meta-analysis. The case-control studies included were submitted to odds ratio (OR) analysis, whose cut-off for statistic calculation was OM grade ≥ 3 . Calculations were performed with the BioEstat program, release 5.0, using DerSimonian-Laird’s random effects statistical analysis.

Results: In this systematic review, twelve studies were included; the meta-analysis of seven of them demonstrated that LT in patients undergoing oncotherapy is approximately 10 times more effective in the prevention of OM grade ≥ 3 than in patients without laser treatment (OR: 9.5281; 95% CI: 1.447-52.0354; $p = 0.0093$).

Conclusion: The data demonstrated the significant prophylactic effect of OM grade ≥ 3 in patients undergoing LT. Further studies, with larger sample sizes, are needed for better evaluation of LT’s prophylactic effect on OM grade ≥ 3 .

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Laser terapia no controle da mucosite oral: um estudo de metanálise

R E S U M O

Objetivo: Realizar uma metanálise da eficácia da laser terapia (LT) na prevenção da mucosite oral (MO) em pacientes submetidos à oncoterapia.

Métodos: Foi realizada uma busca nas bases de dados MEDLINE, LILACS e Cochrane, utilizando as palavras-chave “laser therapy” e “oral mucositis”. Os estudos de caso-controle incluídos foram submetidos à análise do *odds ratio* (OR), cujo ponto de corte para a estatística foi MO

Palavras-chave:

Laser terapia

Mucosite oral

Prevenção

Metanálise

[☆] Study conducted at the Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil.

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grau ≥ 3 . Os cálculos foram realizados com o programa BioEstat 5.0, utilizando a análise estatística de Efeito Aleatório de DerSimonian-Laird.

Resultados: Doze estudos foram incluídos na revisão sistemática. A metanálise de sete deles evidenciou que a LT em pacientes submetidos à oncoterapia é aproximadamente 10 vezes mais eficaz na prevenção de MO grau ≥ 3 do que em pacientes sem o tratamento com laser (OR: 9,5281; intervalo de confiança de 95% 1,447-52,0354, $p = 0,0093$).

Conclusão: Esses dados demonstraram efeito profilático significativo de MO grau ≥ 3 nos pacientes submetidos à LT. Estudos com maior tamanho amostral são necessários para melhor avaliação do efeito profilático de MO grau ≥ 3 por LT.

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Introduction

Many patients with cancer are submitted to an initial therapy by radiotherapy (RT), surgery and chemotherapy (CT). RT is usually the treatment of choice in cases involving the head and neck, where the irradiation field involves the oral mucosa and salivary glands.¹ Alone or combined with CT, RT has a good clinical response in the treatment of stage I and stage II cancer. However, cancer therapy is closely related to the location of the tumor, its staging, its histological type, as well as the patient's status.²

Additionally, in cases of malignant and non-malignant hematological diseases, severe immunodeficiency, and bone marrow aplasia, one of the recommended treatments is hematopoietic stem cell transplantation³ (HSCT). Therefore, bone marrow transplantations require the continuous use of a conditioning regimen responsible for myeloablation, in order to create space in the recipient's bone marrow.⁴ Therefore, immunosuppression and destruction of neoplastic cells are other effects of high doses of CT drugs, whether or not combined with RT.

Mucosal inflammation is a frequent acute complication in patients with malignancies undergoing oncotherapy. Among patients with head and neck cancer treated with RT, 90% to 97% have some degree of oral mucositis⁵ (OM). Literature indicates that the incidence of OM, in any degree, associated with oncotherapy for HSCT varies between 76.3% and 89%.⁶ However, some risk factors appear to be implicated in the pathogenesis of OM, such as the location of the radiation field, preexisting dental disease, poor oral hygiene, low saliva production, compromised immune function, and focus of local infection.^{7,8}

The toxicity produced by the treatment causes alterations that manifest as mucositis, in light of its action on cells with high mitotic activity.⁹ Thus, there is an intense mucosal involvement, with a decrease in the capacity to overcome the natural exfoliation process, and consequent inflammation and edema.

Associated with a directly harmful effect on the mucous cells, pro-inflammatory cytokines play a role in the worsening of initial mucosal lesions. Tumor necrosis factor- α (TNF- α) and interleukin-1 β , interleukin-11, and interleukin-6 appear to play an important role in tissue damage associated with oncotherapy.¹⁰ According to the literature,¹¹ there are four

stages in the mucosal lesion process: (1) white patches, with intra- and extracellular edema; (2) appearance of erythematous areas in mucosa, in addition to dysphagia; (3) raised areas of the superficial layers of the mucosa, with reddish borders and re-covered by serofibrinous pseudomembrane, (4) when erythematous areas or areas with pseudomembrane are not re-covered in time, there is a loss of mucous lining, increase of the pain, and fever can occur, and oncotherapy interruption becomes necessary.

The inflammatory picture causes pain and discomfort, with impairment of speech, deglutition, and feeding, and ulcerating lesions can lead to dehydration and poor nutrition. Furthermore, the ulcerations bring a high risk of microbial invasion, causing predisposition to local or systemic infections.¹² The increased severity of OM may cause fever, infection risk, need for total parenteral nutrition, need for intravenous analgesics, and mortality during the first 100 days.¹³

The severity of OM is commonly assessed by the Oral Toxicity Scale, a graduated scale established by the World Health Organization (WHO). This scale contains criteria such as the presence of erythema and ulceration, local pain, and deglutition capacity. When the score is 0 no abnormality has been detected; the presence of erythema without need for treatment characterizes a score of 1; a score of 2 indicates the presence of painful symptoms with no need for analgesics, with difficulty in feeding; a score of 3 indicates painful ulceration requiring the use of analgesics and preventing feeding; finally, a score of 4 indicates necrosis requiring parenteral nutrition.¹⁴

Another form of assessment that can be used to evaluate OM is the Toxicity Criteria recommended by the National Cancer Institute (NCI), which establishes grade 0 in the absence of OM; grade 1 when there are painless ulcers, erythema, or mild pain in the absence of ulcers; grade 2 in the presence of painful erythema, edema, or ulcers, but feeding or swallowing is possible; grade 3 in the presence of painful erythema, edema, or ulcers when there is need of parenteral nutrition; grade 4, in case of severe ulcerations or need for parenteral nutrition or prophylactic intubation; and grade 5, in case of death-related toxicity.¹³ Among other scales used to classify the severity of OM, the Radiation Therapy Oncology Group (RTOG) scale must be cited, which also evaluates, in general, oral toxicity derived from the cancer treatment used.¹³ The Oral Mucositis Index (OMI) is another tool used in the classification of OM.¹⁵ In 1996,

Tardieu et al. created the Quantitative Scale of Oral Mucositis by HSCT, used in some articles to assess OM.¹⁶

Despite a considerable range of studies performed in the last ten years regarding the prevention of OM due to cancer treatment, preventive measures have yet to be established for mucosal inflammation due to oncotherapy.¹⁷ The literature has recorded the use of over 20 preventive measures for oral mucositis caused by oncotherapy,¹⁸ of which the following may be cited: cryotherapy, chlorhexidine gluconate, oral hygiene, glutamine, benzydamine, sucralfate, vitamin E, and rinsing the mouth with salt and soda.^{19,20} However, there is a scarcity of scientific evidence regarding the clinical usage of agents such as benzydamine and cryotherapy.²⁰ Currently, OM prevention is predominantly based on palliative care (oral rinses, anti-inflammatory drugs, and oral hygiene) and prevention of secondary infections.

Some studies, however, suggest other prophylactic measures, acting on the biological mechanisms involved in each phase of OM, such as the use of low-intensity laser.¹²

Laser therapy (LT) is known to stimulate biological effects, such as elimination of pain and inflammatory modulation. The ability to modulate a variety of metabolic events through photophysical and biochemical processes explains the effects of this therapy.^{21,22} The laser energy is absorbed only by a thin layer of surrounding tissue beyond the point affected by the radiation. For this reason, the use of lasers with low penetration power is currently recommended, with wavelengths of 640 nm to 940 nm, which should be used immediately after the lesion occurs.²³ For comparison, the visible red light-emitting diode has less penetration power, being more suitable for tissue repair, while the diode with longer wavelength, which emits infrared laser, has a greater capacity to penetrate, being more indicated for analgesia. Low-intensity lasers increase cell metabolism by stimulating mitochondrial activity,²⁴ acting as analgesic, anti-inflammatory, and reparative agents in mucosal lesions.²⁵ They cause several biological events, such as epithelial and fibroblast proliferation as well as maturation, transportation, and transformation of fibroblasts into myofibroblasts.²⁶

There are also cell and vascular alterations that depend, among other factors, on the laser wavelength. These include production of collagen, elastin, and proteoglycans; revascularization; wound contraction; increased phagocytosis by macrophages; and increased proliferation and activation of lymphocytes and higher tensile strength, accelerating the healing process.

Helium-neon (He-Ne) and gallium-aluminum-arsenic (Ga-Al-As) lasers have shown good results when used in cases of OM caused by oncotherapy. Although studies have suggested a significant role of LT in the treatment of OM due to oncotherapy,²⁷ further studies are necessary to assess the efficacy of prophylactic LT use at low doses in severe inflammation of the oral mucosa.

Considering the need for further studies on the use of LT in patients with OM caused by oncotherapy, this study aimed to perform a systematic review and meta-analysis of the effectiveness of LT in preventing the development of OM ≥ 3 in patients undergoing cancer treatments.

Methods

Search strategy

From January to February of 2012, a search was performed in the LILACS, MEDLINE, and Cochrane electronic databases, with no restriction regarding the year of publication of the articles. The following key words used were in all databases: "laser therapy" and "oral mucositis", aiming at standardizing the research. Initially, three researchers analyzed the titles and abstracts of studies listed in the databases. Then, the studies selected after evaluation of their abstracts were further analyzed by the researchers. Based on this assessment, the studies were submitted to the inclusion and exclusion criteria for the meta-analysis.

Criteria for inclusion and exclusion of studies

Considering the expected statistical analysis, studies were included when (1) the patients had a diagnosis of OM caused by oncotherapy, during or after treatment; (2) the treatment of the oral mucosa was performed with low-intensity laser, whose wavelength was set between 632 and 1,064 nm; and (3) the study design consisted of a randomized trial with a control group.

Data collection and study quality

The relevant data for the study were extracted by three researchers using a standardized form. The form was created based on the identification of the most relevant data for the study, containing information about the authors, year of publication, country of origin, and study design.

The data on the population of each study were also analyzed: sample, type of cancer, type of oncotherapy, gender, age of patients and controls, as well as the type of treatment used for the control group. The wavelength applied through the LT (in nm), type of laser used, laser power (in mW), dose (in J/cm²), irradiation time (in seconds), and number of sessions per week were also included in the standardization. To assess the methodological quality, the studies included in the analysis were analyzed according to the Jadad scale.²⁸

Statistical analysis

For the analyzed data, a meta-analysis was performed using BioEstat release 5.0, using DerSimonian-Laird's random effect analysis method, considering the heterogeneity of the studies. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated for each study individually and then for the combination of the selected studies. Only p-values < 0.05 were considered significant. To assess the effectiveness of LT prophylactic capacity, the presence of OM ≥ 3 at the end of LT was used as cutoff in all of the scales; this is the grade of OM in which painful ulcerations are observed, requiring the use of

Table 1 – Preliminary data from the included studies.

N	Author	Year	Country	Study design	Sample	Neoplasia	Oncotherapy
1	Cowen et al. ²⁹	1997	France	Prospective	30	ALL, AML, MM, NHL	CT
2	Bensadoun et al. ³⁰	1999	France	Prospective	30	Head and neck	RT
3	Arun-Maiya et al. ³¹	2006	India	Prospective	50	Head and neck	RT
4	Cruz et al. ³²	2007	Brazil	Prospective	59	Leukemia/Lymphoma: 35 Solid tumors: 25	CT
5	Schubert et al. ³³	2007	Brazil	Prospective	70	Leukemia/Lymphoma	CT
6	Abramoff et al. ³⁴	2008	Brazil	Prospective	22	Osteosarcoma ALL	CT
7	Kuhn et al. ³⁵	2008	Brazil	Prospective	23	Head and neck	RT
8	Chor et al. ³⁶	2009	Brazil	Prospective	34	HSCT	CT
9	Khoury et al. ³⁷	2009	Brazil	Prospective	22	ALL, AML, CML, MDS, SAA	CT
10	Gouvêa de Lima et al. ³⁸	2010	Brazil	Prospective	75	Head and neck	CT + RT
11	Carvalho et al. ³⁹	2011	Brazil	Prospective	70	Head and neck	Sur + CT: 26 Sur + RT + CT: 13 RT: 4
12	Silva et al. ⁴⁰	2011	Brazil	Prospective	42	Leukemia/Lymphoma	CT

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CT, chemotherapy; HSCT hematopoietic stem cell transplant; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RT, radiotherapy; SAA, severe aplastic anemia; Sur, surgery.

analgesics and preventing feeding.¹¹ The determination of this criterion is justified by the painful symptoms, food restriction, and discontinuation of treatment in the presence of severe inflammation of the mucosa.

Results

A literature search disclosed 149 studies with keywords “oral mucositis” and “laser therapy”. Forty-one studies considered potentially relevant were selected for detailed evaluation of the inclusion and exclusion criteria. Of these, five were review articles, four were case studies, four addressed LT only as a therapeutic measure, four did not have a control group, and two did not include oncotherapy in the analysis. In addition, two studies did not address LT and two were article comments and were excluded.

The final sample consisted of 12 prospective randomized studies, published between 1997 and 2011, with a total sample of 527 patients. The total number of patients undergoing LT included in the 12 studies was 276, whereas the control group consisted of 251 patients. Among the patients in the sample, the overall frequency of head and neck cancer was 47%, whereas 53% of the patients in the sample were treated for hematological malignancies (Table 1).

Study description

Of the articles included, two studies^{29,30} were performed in France, one in India,³¹ and nine studies were conducted in Brazil.³²⁻⁴⁰ All studies included in the analysis were case-control studies, and three of them^{31,34,39} reported prospective follow-up. Among the selected studies, it is unclear whether there were methodological differences in patient

assessment, with varying inclusion criteria in the sample. In seven studies,^{31,32,34-37,40} at the beginning of the experiments, the group undergoing LT and the control group did not present OM. Four studies^{29,30,33,38} did not report the status of the oral mucosa at the beginning of their study.

Regarding the type of oncotherapy, in three studies^{30,31,36} patients were treated with RT alone, while in six others^{29,33,34,36,37,40} CT was the only anticancer treatment. One study subdivided the sample submitted to oncotherapy into a group treated with CT for HSCT, and a group where CT was the conventional treatment of solid tumors.³² Another article described the treatment of their patients restrictively with combined CT and RT.³⁸ Similarly, other authors³⁹ used four types of combinations of treatments that included surgery, CT, and RT.

Regarding demographic data, the group of patients submitted to LT consisted mostly of males.^{30,32,35,37-40} The mean age of patients undergoing LT was ≥ 50 years in four studies^{30,31,38,39} and among controls, in four as well.^{30,31,38,39} Two of the studies included in the analysis consisted of pediatric patients only.^{32,34}

The WHO scale was used in four studies,^{30,37,39,40} whereas the NCI oral toxicity scale was used in three.^{32,34,38} One study³³ assessed OM through the OMI¹⁵; however, this same study established a degree of comparison between the OMI and the scale recommended by WHO; thus, the numbers based on the latter were used by the present study. One study³⁹ used the WHO and NCI scales, finding similar results, and the NCI classification showed a higher percentage of grade 3 OM than the WHO scale. Two studies^{29,36} evaluated OM using the Tardieu classification.¹⁶

The measure used for OM prevention in the control groups showed a significant variation. Eight studies^{30,33-36,38-40} used placebo laser, and one study³⁹ used in the control group the same laser as in the study group, but with lower potency and

Table 2 – Results of included studies.

N	Author	OM scale	OM prevention control	Laser therapy		Control	
				G < 3	G ≥ 3	G < 3	G ≥ 3
1	Cowen et al. ^{a,b}	Tardieu	—	—	—	—	—
2	Bensadoun et al. ^a	WHO	Placebo	—	—	—	—
3	Arun-Maiya et al.	WHO	Oral analgesics Anesthetics 0.9% saline solution Antiseptics	25	0	0	25
4	Cruz et al. ^b	NCI	—	26	2	28	3
5	Schubert et al. ^x	OMI	Placebo	—	—	—	—
6	Abramoff et al.	NCI	Placebo	11	0	10	1
7	Kuhn et al.	WHO	Placebo	11	0	5	7
8	Chor et al. ^c	Tardieu	Placebo	—	—	—	—
9	Khoury et al.	WHO	Mouthwash	12	0	5	5
10	Gouvêa de Lima et al.	NCI	Placebo	29	8	29	9
11	Carvalho et al. ^a	WHO/NCI	Placebo	—	—	—	—
12	Silva et al. ^b	WHO	Mouthwash	21	0	15	6
Combined total				135	2	92	107

G < 3, OM grade < 3; G ≥ 3, OM grade ≥ 3; Tardieu, Quantitative scale of oral mucositis associated with autologous bone marrow transplantation (Tardieu et al., 1996), daily index of mucositis (DIM); WHO, Oral Toxicity Scale of the World Health Organization (1979); NCI, Toxicity Scale of the National Cancer Institute; RTOG, Oral Toxicity Scale of the Radiation Therapy Oncology Group; OMI, Oral Mucositis Index.

^aDisclosed only the means of OM grades at the end of the study.

^bThere was no treatment for the control group.

^cDisclosed only the p-value in results.

dose. Conversely, the other placebo-controlled studies used the same laser device as the group submitted to LT, but the device was turned off during the use in the control group. One study³¹ used a combination of oral analgesics, anesthetics, 0.9% saline solution, and antiseptics as prophylactic tools in the control group. Information regarding the type of prophylactic measure chosen for the control group, the type of scale used to assess OM, and the cutoff used in the present study are shown in Table 2.

Regarding LT, five studies^{33-36,38} used only the Ga-As-Al laser, four studies^{29-31,39} used the He-Ne laser, one study⁴⁰ used only indium-gallium-aluminum-phosphorus (In-Ga-Al-P) laser, and another³⁷ used two types of lasers on alternate days, one emitting red visible light (660 nm [In-Ga-Al-P]) and another infrared (780 nm [Ga-Al-As]) on alternate days. One article³² did not report the type of laser used in patients undergoing CT. Only one study³³ subdivided the group submitted to LT with Ga-Al-As into two smaller groups: a subgroup submitted to a wavelength of 650 nm, with a 2 J dose and 40 mW power, and another submitted to 780 nm, with a 2 J dose and 60 mW power.

Four of the 12 studies did not observe losses in their samples,^{29,30,31,34} whereas three did not describe losses during the experiments.^{36,37,38} Two patients in one study³³ died from complications related to OM. In one study,³⁹ eight patients were excluded from the sample. Another study³² started with a sample of 62 patients, two of whom were excluded for not following the protocol established by the authors. Furthermore, at the end of the experiments, the researchers³² evaluated only 59 of the 60 patients included, providing no justification for the procedure. One study intended to evaluate 30 patients, but

only 23 completed the treatment with LT. Moreover, without giving any justification, the authors³⁵ did not include patient number 12 in the sample reported in the publication. Another study⁴⁰ intended to evaluate 56 patients; however, 14 subjects were excluded for not meeting the criteria established for inclusion in the experiment.

Study quality

Study assessment were performed according to the Jadad scale,²⁸ showing similar methodology validations. Eight studies were considered as high quality,^{29,30,32-35,38,39} three were classified as moderate quality,^{31,37,40} and one as low quality.³⁶

Meta-analysis

Only seven of the 12 studies included in this review provided sufficient data to classify successes (OM grade < 3) and failures (OM grade ≥ 3). The meta-analysis was performed based on the seven articles listed,^{31,32,34,35,37,38,40} with a total sample of 293 patients. The combined OR of the studies was 9.5, with $p = 0.0093$, contained in a 95% CI 1.447-52.0354, whose lower limit was > 1. The results rejected the null hypothesis and demonstrated that the effectiveness in preventing OM grade ≥ 3 by LT is approximately 10 times (OR: 9.5) higher than in those individuals not treated with LT ($p = 0.0093$).

The forest plot chart shows the analysis of the LT effect on the prevention of OM grade ≥ 3, compared with no treatment. Results to the right show the values of studies favorable to LT;

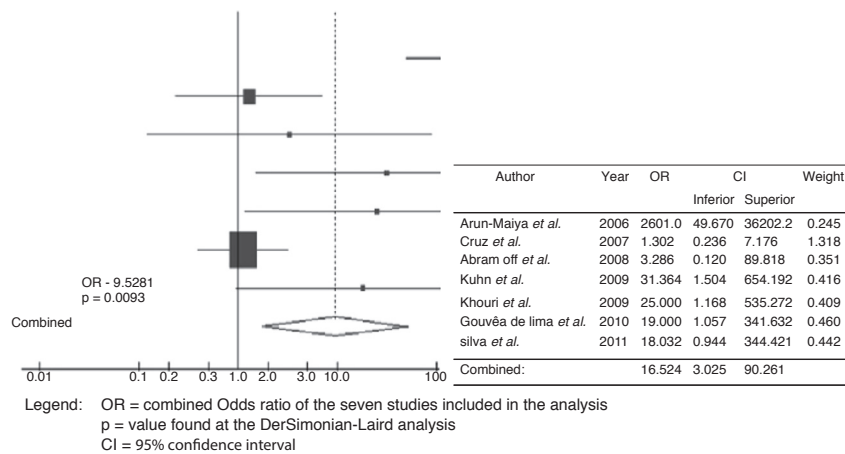


Fig. 1 – Forest plot chart of the studies included in the random effect analysis and combined odds ratio and odds ratio of the included studies.

the combined effect was represented by the diamond shape (Fig. 1). The heterogeneity test applied in the DerSimonian-Laird analysis was significant ($p = 0.0018$), statistically demonstrating the effect of LT on the prevention of OM grade ≥ 3 . The Chi-squared analysis of the heterogeneity of the seven studies included in the meta-analysis^{31,32,34,35,37,38,40} showed $p = 0.0006$, with six degrees of freedom, which was significant, indicating the existence of heterogeneity among the studies and justifying the choice of the DerSimonian-Laird test.

All studies included in this meta-analysis investigated the possibility of adverse effects associated with LT. None of the included studies demonstrated any side effects resulting from their experiments.²⁹⁻⁴⁰

Discussion

The use of low-intensity laser in the oral cavity is capable of preventing the occurrence of OM grade ≥ 3 in patients undergoing oncotherapy, and, in individuals undergoing LT, this prophylaxis is approximately nine times more effective than the absence of LT in the control group (OR: 9.52). These results differ from some literature data; for instance, among the 12 studies included in this study, three did not observe, in a general manner, the effectiveness of LT in OM prevention in patients undergoing anticancer therapy.^{32,36,38}

After a systematic review aiming to combine studies in a meta-analysis, it was observed that the studies were not identical regarding the effect of prevention of OM grade ≥ 3 by LT. Consequently, the differences were investigated and the alternative found for the heterogeneity was to use DerSimonian-Laird's random effect analysis. This test considers not only the existence of the variation within each study included, but also the differences among the studies. It can be inferred that the random effects model does not consider the studies as identical, but admits that a probability distribution establishes an association between the studies. Through sensitivity analysis, the heterogeneity among the

meta-analysis studies was demonstrated, which can be attributed to methodological differences and to the different prophylactic measures used in the control group. Thus, the present study sought to reduce biases as much as possible, which could affect result interpretation and quality, using the criteria discussed below.

The literature review was broad and comprehensive, seeking to reduce publication bias by not restricting the language, by including studies published in scientific journals with lower scientific visibility, and by including studies with negative results on the efficacy of LT in preventing OM grade ≥ 3 in patients undergoing oncotherapy. The selection of studies, which was performed in accordance with the criteria of study design (case-control), of OM diagnosis, and LT as the only way of preventing oncotherapy-induced OM grade ≥ 3 , sought to reduce the heterogeneity of the included studies, while encompassing the clinical situation proposed by the project question ("iss low-intensity LT effective in controlling oncotherapy-induced OM grade ≥ 3 ?").

The use of a standardized form, created at a meeting prior to the data collection, in addition to the participation of three researchers to extract the data, contributed to bias reduction at the data collection stage. After the stages of searching and collecting data from the studies, seven of the 12 articles included in the systematic review were selected. The sensitivity analysis, through the chi-squared test, demonstrated the presence of heterogeneity. Thus, taking into account the clinical and methodological differences of the included studies, DerSimonian-Laird's random effect test was chosen to calculate the combined OR, as suggested by the literature.⁴¹

Research has¹³ evidenced that an increase in OM severity can present systemically as fever, risk of infection, total parenteral nutrition dependence, intravenous analgesic use, and mortality during the first 100 days. Therefore, the confirmation of the prophylactic effects of LT corroborating the large number of studies conducted in this area in the past 20 years would be a method to reduce the limitation to

oncotherapy. Literature reports^{42,43} that the tumor site can be better controlled with the use of LT, and there may be increased survival in cancer patients, as well as improvement in their quality of life.

Regarding the remission of painful symptoms, only two studies^{32,38} included in the meta-analysis showed no evidence of pain relief with the use of LT. It should be noted that one of these studies³⁸ reported the interruption of treatment of oncological patients in the placebo group as a possible limitation of the study related to its findings. The other studies^{31,34,35,37,40} showed evidence of decrease in painful symptoms, as well as control in the progression of OM.

Recently, a meta-analysis⁴⁴ was performed on the effects of low-intensity LT in oncotherapy-induced OM, whose combined OR results were similar to those found in the present study ($p < 0.0001$, and combined chi-squared analysis of 32.93). The inclusion criteria used in that meta-analysis, however, were very comprehensive, which probably resulted in its greater heterogeneity. Another recent meta-analysis⁴⁵ included studies that assessed the effect of LT, sucralfate, and benzydamine hydrochloride in the treatment of OM in patients undergoing oncotherapy, including CT, RT, or both procedures. Of the therapies studied, only LT appeared to reduce severe mucositis. It should be noted that, as in the present study, the meta-analyses on LT included different samples concerning age, different modalities of cancer treatment, different laser characteristics, therapeutic dose, and mucositis grade scales.

The current study did not consider demographic factors when analyzing the effectiveness of LT in preventing OM grade ≥ 3 , as they do not appear to influence the final result. The present systematic review with meta-analysis showed evidence of moderate to high efficacy of low-intensity LT in the prophylaxis of oncotherapy-induced OM. One limitation to the present study may be the lack of studies exclusively on prevention of oncotherapy-induced OM by low-intensity LT. In general, the scientific studies were methodologically acceptable, but heterogeneous prophylactic procedures, as well as doses, may have caused the conflict. Furthermore, the small number of patients reported in the literature accounts for an important limitation imposed on the present study.

Conclusion

According to the results obtained from the statistical analysis shown in this meta-analysis, it is clear that LT, when applied to patients undergoing oncotherapy, is effective in controlling OM grade ≥ 3 . Studies have demonstrated the importance of severe OM prevention during the course of oncotherapy, stressing, in practice, the limitations imposed by OM grade ≥ 3 , which may even lead to treatment discontinuation.

Regarding the use of low-intensity laser, factors such as wavelength, dose, duration of irradiation, power, and number of sessions have remarkable influence on the outcome of prevention, which may explain the varied results among studies and their heterogeneity.

Although a large number of studies have been performed on OM prevention in cancer patients, there is still little

published scientific evidence capable of establishing the use of LT in clinical practice on a large scale. For a more accurate evaluation of the prophylactic effect of OM grade ≥ 3 by LT in patients undergoing some kind of oncotherapy, further studies are needed, with larger sample sizes.

Conflicts of interest

All authors declare to have no conflicts of interest.

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