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Low-level laser therapy dosimetry most used for oral mucositis due to radiotherapy for head and neck cancer: a systematic review and meta-analysis

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ABSTRACT

Dosimetry for low-level laser therapy (LLLT) depends on several parameters, such as target tissue type, lesion type and laser equipment used. This study aimed to determine the most used LLLT dosimetry for the treatment and prevention of oral mucositis (OM) resulting from radiation therapy (RT) in head and neck cancer patients (HNCP). This research was conducted according to the PRISMA guidelines using the PICO framework. After extensively searching PubMed, Web of Science, Embase, Scopus, BVS and Cochrane Library databases, we found 130 records and selected 7 studies, involving 363 HNCP with an average age of 60.6 years who received RT. Briefly, sites affected by tumors were the following: oral cavity (170), oropharynx (91), throat (42), larynx (32), nasopharynx (11), hypopharynx (9), and in 8 cases, sites were not reported. These studies used several classifications for OM (RTOG/EORTC, WHO, NCI-CTC) and pain (NRS, VAS and modified VAS). These various researchers performed the LLLT punctual application of different forms using several protocols making analysis difficult. However, LLLT was effective regardless of the parameters used (632.8 nm to 685 nm, 1.8 J/cm^2 to 3.0 J/cm^2, 10 mW to 60 Mw, 0.8 J to 3.0 J). The meta-analysis showed a better results with preventive LLLT 660 nm, 3.8 J/cm^2, 15 mW; 0.15 J compared to preventive LLLT 660 nm, 1.3 J/cm^2, 5 mW; 0.05 J (OMS: $p = 0.03$; NCI-CTC: $p = 0.027$). We conclude that there is, as of yet, no evidence of better laser dosimetry being more effective. Thus, randomized clinical trials to determine which doses of LLLT are most appropriate for treating and preventing OM due to RT are lacking and should be further investigated.

1. INTRODUCTION

The curative effects of radiation therapy are caused by direct or indirect damage to the DNA of cells. When irreparable DNA damage is generated, the cell stops performing cell division, losing its proliferative potential. So if all the cells lose this potential proliferation in the patient, he or she would be considered cured. This creates a partial reduction in the potential proliferation of cancer, which will be in stasis or regression, and can grow back if the cells regain their proliferative potential. The damage to the proliferative potential is not limited to cancer cells but also affecting healthy cells (Ray-Chaudhuri et al., 2013).

Most head and neck cancer patients will need to undergo radiotherapy as a primary treatment or as a complement to surgery or in combination with chemotherapy. In order to estimate the dose of radiation required, one must take into account the location, type of malignancy and whether radiotherapy will be implemented with another type of treatment (Vissink et al., 2003).

Patients diagnosed with head and neck cancer often experience acute or late reactions to antineoplastic therapy. Acute reactions will occur during treatment and will have their remission weeks to months after their conclusion, whereas chronic or late reactions can occur months and years after the end of treatment. Hyperfragmentation of radiotherapy has reduced the onset of chronic complications, but has increased the severity of acute ones (Fischer and Epstein, 2008).

Some of the most frequent acute complications for the face and oral cavity are the following disorders: oral mucositis, pain, dysphagia, infections, salivary alterations, dysgeusia and dermatitis. On the other hand, the most common oral chronic complications are the following: hyposalivation and xerostomia, mucosal infections, dysgeusia, dental demineralization, progression of periodontitis, bone necrosis, mucocutaneous and muscle fibrosis, dysphagia, trismus, lymphedema, dermatitis and voice and speech alterations. Among the few measures of care available, low-level laser therapy (LLLT) or light therapy has been shown to be a promising treatment in the prevention and treatment of oral mucositis (Zecha et al., 2016).

LLLT includes effects that are analgesic, anti-inflammatory, edema reduction,

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minimizing pain and biostimulation. Notably, laser therapy does not have a direct curative effect and effectively favors the tissue repair of the injured region through cellular biostimulation (Lins et al., 2010).

There is evidence to suggest that the efficacy of LLLT treatment varies greatly with respect to both the applied energy and power density used. The response to LLLT changes with wavelength, irradiance, time, pulses, and perhaps even coherence and polarization. Treatment with LLLT should cover an adequate area of the lesion, and there is an important consideration about how long to irradiate with the laser. Dosimetry in LLLT is highly complex. The large number of interrelated parameters shows that there has not yet been a comprehensive study that examined the effect of the various parameters individually. The considerable degree of complexity means that the choice of parameters often depends on the preference or personal experience of the practitioner, rather than the consensus statement of a guideline (Chung et al., 2012). Thus, this systematic review aimed to determine which LLLT dosimetry was the most recommended, for the treatment and prevention of oral mucositis due to radiotherapy in head and neck cancer patients.

2. METHODS

2.1. REGISTRATION AND PROTOCOL

This study followed the protocols established in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) and the protocol was recorded in the International Prospective Register of Systematic Reviews-PROSPERO (CDR42017080523).

2.2. RESEARCH INFORMATION AND SEARCH STRATEGY

Descriptors (MeSH and DeCs) for the search strategy were controlled and defined according to the PICO strategy: 1) Population: patients with oral mucositis due to radiotherapy in the treatment of head and neck cancer; 2) Intervention: low-level laser therapy; 3) Comparison: placebo group, group that received no therapy or received various LLLT protocols; 4) Outcome: the most used dosimetry of LLLT for the prevention or treatment of oral mucositis.

The survey of all the records included in this review was conducted using the following databases: PubMed, Web of Science, Embase, Scopus, BVS and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials- CENTRAL). The search strategy included terms related to “Low-Level Light Therapy”, “Oral Mucositis”, “Head and Neck Neoplasms”, and “Radiotherapy”. These terms were combined using Boolean operators (OR/AND) and adapted to use in each of the bibliographic databases, in combination with specific filters. The strategy used was the following: (Low-Level Light Therapy OR Laser Phototherapy OR Laser Therapy, Low-Power OR Low-Level Laser Therapy OR Low-Power Laser Irradiation OR Low-Power Laser Therapy OR Photobiomodulation Therapy OR Biostimulation, Laser OR Irradiation, Low-Power Laser OR Laser Irradiation, Low Power OR Laser Therapies, Low-Level OR Laser Therapies, Low-Power OR Laser Therapy, Low Level OR Laser Therapy, Low Power OR Light Therapies, Low-Level OR Light Therapy, Low-Level OR Low Level Laser Therapy OR Low Level Light Therapy OR Low Power Laser Irradiation OR Low Power Laser Therapy OR Low-Level Laser Therapies OR Low-Level Light Therapies OR Low-Power Laser Therapies OR Photobiomodulation Therapies OR Phototherapy, Laser OR Therapies, Low-Level Light OR Therapies, Photobiomodulation OR Therapy, Low-Level Light OR Therapy, Photobiomodulation OR Laser Therapy, Low-Level OR Laser Biostimulation OR Laser Irradiation, Low-Power OR LLLT) AND (Stomatitis OR Mucositis, Oral OR Oromucositis OR Mucositides, Oral OR Oral Mucositides OR Oromucositides OR Stomatitides OR Oral Mucositis OR Mucositis OR Mucositides) AND (Head and Neck Neoplasms OR Cancer of Head OR Cancer of Neck OR Cancer of the Head OR Cancer of the Head and Neck OR Cancer of the Neck OR Head Neoplasms OR Head, Neck Neoplasms OR Neoplasms, Head OR Neoplasms, Head and Neck OR Neoplasms, Neck OR Neck Neoplasms OR Cancer of Head and Neck OR Head and Neck Cancer OR Head Cancer OR Neck Cancer) AND (Radiotherapy OR Radiotherapy, Targeted OR Targeted Radiotherapy OR Chemotherapy, Adjuvant OR Adjuvant Drug Therapy OR Adjuvant Chemotherapy OR Drug Therapy, Adjuvant).

In addition, gray literature (list of references, manual search, Open Gray and digital library of theses and dissertations-Brazilian Institute for Information in Science and Technology) was searched. There was no restriction of language or year of publication in this systematic review.

2.3. ELIGIBILITY CRITERIA

The present systematic review included studies in radiotherapy induced oral mucositis patients who had undergone treatment of head and neck cancer, studies that used a control LLLT placebo group, no therapy or who received several LLLT protocols and studies whose experimental group (intervention) were treated with LLLT.

Studies were excluded if the patients presented other oral complications due radiotherapy, were treated with chemotherapy, underwent stem cell transplantation, studies with high power laser therapy and studies whose control group received some type of topical therapy.

2.4. SELECTION STUDY AND DATA COLLECTION PROCESS

The records obtained in the databases after applying the search strategy were compiled in EndNote Web reference manager, for storing the references and excluding duplication of studies. Initially, two independent reviewers (B.M.S. and A.C.S.P.) selected articles by titles and abstracts according to all the eligibility criteria described above. Subsequently, potentially eligible studies were included in the second phase for full text reading (articles and theses), which also included titles and abstracts that did not present sufficient information for direct inclusion. Disagreements were resolved through discussion with a third independent reviewer (P.S.S.S.).

2.5. SYNTHESIS AND PRESENTATION OF DATA

The included studies were independently examined and relevant information was extracted to assess the quality of each study and extract data. The details of the included studies are shown in Table 1. Finally, only the information available in these articles was considered for research for this study.

2.6. STATISTICAL METHODS

Meta-analysis was performed to investigate the data from the multiple included studies. The Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA) was used, with p-value of < 0.05 considered significant. The heterogeneity of the results will be explored using an analysis of subgroups. In addition, the random effect of data will be taken into account.

2.7. RISK OF BIAS IN INDIVIDUAL STUDIES

The Cochrane Collaboration tool was used to assess the risk of bias in included studies. Two independent reviewers performed the qualitative evaluations of the selected trials. During data selection and quality assessment, all discrepancies between reviewers were resolved through discussion and, if necessary, by consulting a third reviewer.

3. RESULTS

3.1. RESEARCH AND SELECTION OF STUDIES

A total of 208 records were found and placed into the EndNote Web reference manager to remove duplicate articles, obtaining 120 articles, 10 articles from the gray literature, yielding a total of 130 articles that were submitted to the eligibility criteria. Of these studies, 39 articles were selected in the first phase of reading the title and abstract, 28 were excluded because they did not meet the eligibility criteria, and the remaining 11 articles needed a complete evaluation of the text for full consideration. Out of these 11 articles, 4 studies were excluded due to non-compliance with the eligibility criteria: more specifically, 3 of these studies used local therapies in the control group (Arun Maiya et al., 2006; Fernandes, 2012; Kelner, 2006), and 1 study did not have a control group (de Paula, 2011). In the end, we included only seven studies for this systematic review which were carried out in India (Arora et al., 2008; Gautam et al., 2015), France (Bensadoun et al., 1999), and Brazil (Carvalho et al., 2011; Carvalho, 2015; Oton-Leite et al., 2012; Oton-Leite et al., 2013), and published from 1999 to 2015. Details are shown in Fig. 1.

3.2. TYPES OF STUDIES

In the present study, it was possible to compare the overall results of the present study with the other studies (Arora et al., 2008) and randomized clinical studies (Gautam et al., 2015; Bensadoun et al., 1999; Carvalho et al., 2011; Oton-Leite et al., 2013). The samples for comparison consisted of studies in which head and neck cancer patients underwent radiotherapy (RT) and had oral mucositis (OM) due to antineoplastic therapy.

Table 1
Details of included studies (in alphabetical order).

Author/ Year	Sample	Age (mean)	Location of tumour	Therapy antineoplastic			Intervention (G1) /use	Control (G2)	Sample collection time
				Type	Total dose (Gy)	Time (week)			
Arora et al. (2008)	24 11 G1 13 G2	55 - 59	G1: 3 buccal mucosa, 1 lower lip, 5 tongue, 2 hard palate. G2: 5 buccal mucosa, 3 tongue, 2 hard palate, 2 floor of the mouth, 1 retromolar trigone.	RT	66 Gy, 33 fractions	6,5	LLLT + Analgesics /Prev and C.	Analgesics	April 2005 to March 2006
Bensadoun et al. (1999)	30 (26 M, 4 F). 15/G	36 - 78 (60,4)	G1: 6 OF, 5 OC, 4 H F. G2: 7 OF, 5 H F, 3 OC.	RT	65 Gy, fractions of 2 Gy/day	7	LLLT + Analgesics /Prev.	Analgesics + Laser placebo	September 1994 to March 1998
Carvalho et al. (2011)	70 (46 M, 4 F). 35 G1 (8 P) 35 G2 (8 P)	G1: 22 - 94 (56,2) G2: 35 - 79 (58,1)	G1: 24 OC (12 tongue, 3 buccal, 2 palate, 1 trigone, 1 gingiva, 4 floor, 1 lip), 11 OF. G2: 25 OC (11 tongue, 4 buccal, 4 palate, 1 trigone, 1 gingiva, 4 floor), 10 OF.	RT and/or CT	≥ 4000 cGy	6	LLLT + Analgesics /Prev and C. (5 mW; 1,3 J/cm^2)	LLLT + Analgesics /Prev. and C. (15 mW; 3,8 J/cm^2)	February 2008 to December 2009
Carvalho, (2015)	73 (56 M, 17 F). 23 G1 (2 P) 23 G2 (3 P) 27 G3 (3 P)	29 - 79 (55,8)	G1: 7 OC (4 tongue, 1 palate, 1 retromolar, 1 gingiva), 13 OF, 3 NF. G2: 10 OC (3 tongue, 2 mucosa jugal, 1 palate, 2 retromolar, 1 gingiva, 1 floor of the mouth), 10 OF, 3 NF. G3: 10 OC (3 tongue, 1 buccal mucosa, 1 palate, 1 retromolar, 3 gingiva, 1 tongue e gingiva), 12 OF, 5 NF.	RT and/or CT	≥ 60 - 72 Gy. 1,62 - 2,12 Gy /day	7 to 8	LLLT + Analgesics /C. (25 mW; 6,3 J/cm^2 and 15 mW; 3,8 J/cm^2)	LLLT + Analgesics /Prev. (15 mW; 3,8 J/cm^2)	January 2013 to December 2014.
Gautam et al. (2015)	46 (39 M, 7 F). 23 G1 (1 P) 26 G2 (2 P)	64 - 78. G1 (71,57) G2 (69,67)	G1: 11 OC (6 tongue, 4 buccal mucosa, 1 alveolus), 11 OF. G2: 13 OC (4 tongue, 7 buccal mucosa, 2 alveolus), 11 OF.	RT	66 Gy, fractions of 2 Gy/day	6,5	LLLT + Analgesics /Prev.	Analgesics + Laser placebo	September 2009 to March 2012
Oton- Leite et al. (2012)	60 (49 M, 11 F). 30 G1 30 G2	> 18. G1: 8 ≥ 60, 22 < 60. G2: 11 ≥ 60, 19 < 60.	G1: 9 OC, 9 Fx, 10 L, 2 U. G2: 10 OC, 12 Fx, 6 L, 2 U.	RT and/or CT	60 – 70 Gy, fractions of 2 Gy/day	6 to 7	LLLT + Analgesics /C.	Analgesics + Laser placebo	September 2008 to November 2009
Oton- Leite et al., (2013	60 (49 M, 11 F). 30 G1 (2 P) 30 G2 (2 P)	> 18. 30 - 81 (56,1)	OC, Px, L, U.	RT and/or CT	50 – 70 Gy, fractions of 2 Gy/day	5 to 7	LLLT + Analgesics /Prev.	Analgesics + Laser placebo	Not reported

Abbreviations: (G) Group; (M) Men; (F) Women; (P) Loss of patients during the study; (OC) Oral cavity; (HF) Hypopharynx; (NF) Nasopharynx; (OF) Oropharynx; (Fx) Pharynx; (L) Larynx; (U) Unknown; (Prev) Preventive Laser Therapy; (T) Treatment; (RT) Radiotherapy; (CT) Chemotherapy; (LLLT) Low-level laser therapy; (OM) Oral mucositis; (WHO) World Health Organization; (VAS) Visual analogue scale; (without) Weeks; (RTOG / EORTC) Radiation Therapy Oncology Group / European Organization for Research & Treatment of Cancer; (NRS) Numeric Rating Scale; (NCI-CTC) National Cancer Institute's Common Toxicity Criteria.

3.3. NUMBER AND CHARACTERISTICS OF THE SAMPLE

The sample collected by the studies included in this systematic review was composed of 363 head and neck cancer patients who received RT, 277 men and 86 women, with a mean age of approximately 60.6 years. The sites most affected by the tumor were the oral cavity with 170 cases, oropharynx 91 cases, hypopharynx 9 cases, nasopharynx 11 cases, pharynx 42 cases, larynx 32 cases and in 8 cases, the sites were not reported (Table 1).

The diagnosis and/or treatment of patients' primary tumors were carried out at Kasturba Medical College, Manipal, India (Arora et al., 2008), Center Antoine-Lacassagne, Nice, France, Marseilles (Institut Paoli-Calmettes) and Reims (Institut Jean-Godinot) (Bensadoun et al., 1999), Hospital AC Camargo, São Paulo, Brazil (Carvalho et al., 2011; Carvalho, 2015), Hospital Manipal University, Manipal, Karnataka, India (Gautam et al., 2015) and Araújo Jorge Hospital, Cancer Combat Association of Goiás, Goiania, Brazil (Oton-Leite et al., 2012; Oton-Leite et al., 2013).

3.4. TYPES OF INTERVENTIONS

All studies considered LLLT as an intervention. The control groups of the studies were: no therapy plus analgesic administration (Arora et al., 2008), placebo laser plus administration of analgesic (Gautam et al., 2015; Bensadoun et al., 1999; Oton-Leite et al., 2012; Oton-Leite et al., 2013) and in 2 studies several parameters of LLLT were used plus administration of analgesic. In particular, one study compared 2 parameters of LLLT (preventive LLLT: energy density of 3.8 J/cm^2 and 1.3 J/cm^2) (Carvalho et al., 2011) and another study compared 3 parameters of LLLT (curative LLLT: 3.8 J/cm^2; preventive LLLT: 3.8 J/cm^2 and 6.3 J/cm^2). The curative LLLT started when patients presented OM Grade 2, until the last RT session. The preventive LLLT started since the first day of RT until the end of treatment (Carvalho, 2015).

There were different protocols for LLLT application, performed as follows: 9 points in the posterior third of the jugal mucosa, soft palate and anterior tonsils (Bensadoun et al., 1999); 6 points in the buccal mucosa, dorsum and belly of the tongue, mucosa lab and the palate of the mouth and palate (Arora et al., 2008); 12 points in the belly and lateral border of the tongue, labial mucosa, jugal mucosa, floor of the mouth and palate (Gautam et al., 2015); 59 points, on the left and right jugal mucosa (8 points on each side), internal mucosa of the upper and lower lip (3 points), palatine folds (2 points), lateral border of the tongue (10 points on each side) (Oton-Leite et al., 2013); and in the labial commissure (1 point), the dorsum of the tongue (8 points), soft palate (3 points); in 4 anatomical sites of the buccal mucosa with a distance of 1 cm between them (linea alba of the right and left jugal mucosa, vermilion of the inferior and superior lips, bottom of superior and inferior groove and commissures, belly and lateral border of the right tongue and left and right and left side floor of the mouth) (Carvalho et al., 2011; Carvalho, 2015). None of the included studies applied LLLT in the tumor area. Additionally, patients and operators used specific protective eyewear.

3.5. SEVERITY OF ORAL MUCOSITIS

The severity of OM was assessed using several methods. Two studies evaluated the score of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC), with the defined following scores: 0 none, 1 erythema of oral mucosa, 2 patchy mucositis (< 0.5 mucosa), 3 confluent fibrinous mucositis (> 0.5 mucosa), 4 ulceration, necrosis or hemorrhage (Arora et al., 2008; Gautam et al., 2015). Two studies evaluated OM according to the WHO classification, being considered grade 0 to 4. Grade 1, soreness; grade 2, erythema, ulcers, can eat solids; grade 3, confluent ulcers, requires liquid diet only (Bensadoun et al., 1999; Oton-Leite et al., 2012).

Three studies used two classifications, the National Cancer Institute's Common Toxicity Criteria National Cancer Institute (NCI-CTC) and World Health Organization (WHO). The NCI uses the following classifications: grade 0, none; grade 1, erythema of the mucosa; grade 2, focal pseudomembranous reaction (areas and/or areas generally ≤ 1.5 cm in diameter and non-contiguous); grade 3, confluent pseudomembranous reaction (zones and/or contiguous areas, generally > 1.5 cm in diameter); grade 4, necrosis or deep ulceration may include bleeding not induced by minor trauma or abrasion (Carvalho et al., 2011; Carvalho, 2015; Oton-Leite et al., 2013).

3.6. PAIN

Several classifications were used to assess patient pain. One study evaluated pain using a numeric rating scale (NRS), with scores ranging from 0 to 10, with

0 equal to no pain and 10 equal to maximum pain. In addition, additional analgesic medication according to the WHO analgesic ladder was also recorded. Three steps were considered in this case, Step I, II and III. Step I refers to the ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief; Step II refers to the addition of tramadol (weak opioid) for pain relief; and Step III refers to the use of morphine (strong opioid) to relieve pain (Arora et al., 2008).

Four studies evaluated pain using the visual analogue scale (VAS), following the WHO criteria. More specifically, a score 0 indicates no pain; a score 1 to 3, mild pain; a score 4 to 7, moderate pain; and a score 8 to 10, intense pain - with a 10 indicating maximum pain tolerable (Gautam et al., 2015; Carvalho et al., 2011; Carvalho, 2015; Oton-Leite et al., 2013).

Another study evaluated the modified VAS according to the following: grades 1 and 2 are combined and noted as grade 1 (mild pain), grades 3 and 4 are noted as grade 2 (moderate pain), grades 5 thru 7 are noted as grade 3 (severe pain), and grades 8 thru 10 are noted as grade 4 (worst possible pain) (Bensadoun et al., 1999).

3.7. OUTCOMES - EFFECTS OF INTERVENTIONS

3.7.1. THE MOST USED LLLT PARAMETERS

The studies investigated included two types of LLLT: Helium-Neon-He-Ne (Arora et al., 2008; Gautam et al., 2015; Bensadoun et al., 1999) and Gallium aluminum–arsenate-InGaAIP (Carvalho et al., 2011; Carvalho, 2015; Oton-Leite et al., 2012; Oton-Leite et al., 2013). The most used wavelengths were: 632.8 nm (Arora et al., 2008; Gautam et al., 2015; Bensadoun et al., 1999), 660 nm (Carvalho et al., 2011; Carvalho, 2015) and 684 nm (Oton-Leite et al., 2012; Oton-Leite et al., 2013). The energy density was 1.8 J/cm^2 (Arora et al., 2008), 2.0 J/cm^2 (Bensadoun et al., 1999; Oton-Leite et al., 2012; Oton-Leite et al., 2013), 3.0 J/cm^2 (Gautam et al., 2015), 3,8 J/cm^2 (Carvalho et al., 2011; Carvalho, 2015), 1,3 J/cm^2 (Carvalho et al., 2011) and 6,3 J/cm^2 (Carvalho, 2015). Further details regarding LLLT parameters are given in Table 2.

3.7.2. GRADE OF ORAL MUCOSITIS

The groups in the included studies will be named Group 1 (G1) for the group of patients who received LLLT and Group 2 (G2) for the control group, none of whom therapy (NT), placebo laser (LLLT-) and different laser parameters (LLLT, G2/G3).

Two studies evaluated OM during the 7 weeks of RT through the RTOG / EORTC, found that G1 patients presented less severe degrees of OM than those of G2, with a statistically significant difference (NT: Arora et al., 2008; LLLT-: Gautam et al., 2015). A study showed a significant difference from the second to the seventh week ($p = 0.004$; 0.000; 0.029; 0.031; 0.019; and 0.045, respectively) (Arora et al., 2008). Another study found that the progression of OM in G1 (LLLT: 632.8 nm; 3.0 J/cm^2) was slower than in G2 (LLLT-) and in the last weeks of RT G1 showed grade of OM less severe ($p = 0.016$) (Gautam et al., 2015). In both studies, none of the G1 patients required parenteral nutrition.

Two studies evaluated OM according to the WHO classification and both found statistically significant differences favorable to the G1 group compared to G2 ($p = 0.01$; $p = 0.002$ Oton-Leite et al., 2012). In one study the mean degree of OM during the 7 weeks of RT, were significant at the fourth and seventh week. There was more severe OM in both groups in the fifth week of RT (G1: 632.8 nm, 2.0 J/cm^2) (Bensadoun et al., 1999). Another study reported that RT was temporarily suspended 25/30 patients in G2 (92% for severe oral mucositis and 8% for dermatitis). A feeding tube was used before and during RT in 3/30 patients in G1 (685 nm, 2.0 J/cm^2) and 7/30 patients in G2. Three patients in each group had feeding tubes before initiating treatment (Oton-Leite et al., 2012).

Three studies evaluated OM through two classifications (NCI-CTC and WHO). One of them evaluated the OM three-stage, initial, intermediate and final of the RT, comparing the LLLT (G1: 685 nm; 2.0 J/cm^2) with the placebo laser (G2), in the intermediate and final evaluations, the scores in both classifications were significantly lower in G1 compared to G2 ($p < 0.001$). For NCI-CTC, there was a tendency to progressively increase the severity of OM in G2, but this effect was less pronounced in G1. According to the WHO scale, mean values of the OM were more pronounced at the intermediate stage in both groups than at the initial and final stages (Oton-Leite et al., 2013) (Table 3).

One study compared two parameters of LLLT, G1 LLLT (3.8 J/cm^2) and G2 LLLT (1.3 J/cm^2). According to the WHO classification, G1 patients had a longer average time to present OM grade 2 (13.5 days) and grade 3 (23.6 days) than G2 patients (grade 2: 9.8 days; $p = 0.005$ and grade 3: 17,1 days, $p = 0.014$). According to NCI, similar data were observed, with no statistically significant difference ($p = 0.498$). In the weekly evaluation, according to the WHO classification, the G2 presented a mean significantly higher OM than G1 at weeks 2 ($p = 0.019$), 3 ($p = 0.005$) and 4 ($p = 0.003$), only 1 patient G1 presented OM grade 4 (fifth week of RT) and in G2 there were 6 patients (22.2%). According to the NCI classification, there were statistically significant differences between the two groups at weeks 2 ($p = 0.009$) and 4 ($p = 0.013$), favorable for G1 that presented lower OM. The NCI classification presented a higher percentage of grade 3 when compared to the WHO classification (Carvalho et al., 2011).

Another study compared 3 types of LLLT parameters, two groups of preventive LLLT (G1: 3.8 J/cm^2, 15 mW, G2: 6.3 J/cm^2, 25 mw) and one of curative LLLT (G3: 3.8 J/cm^2; 15mw). According to the WHO and NCI classifications, the percentage of patients who presented grade 1 was greater for G1 than

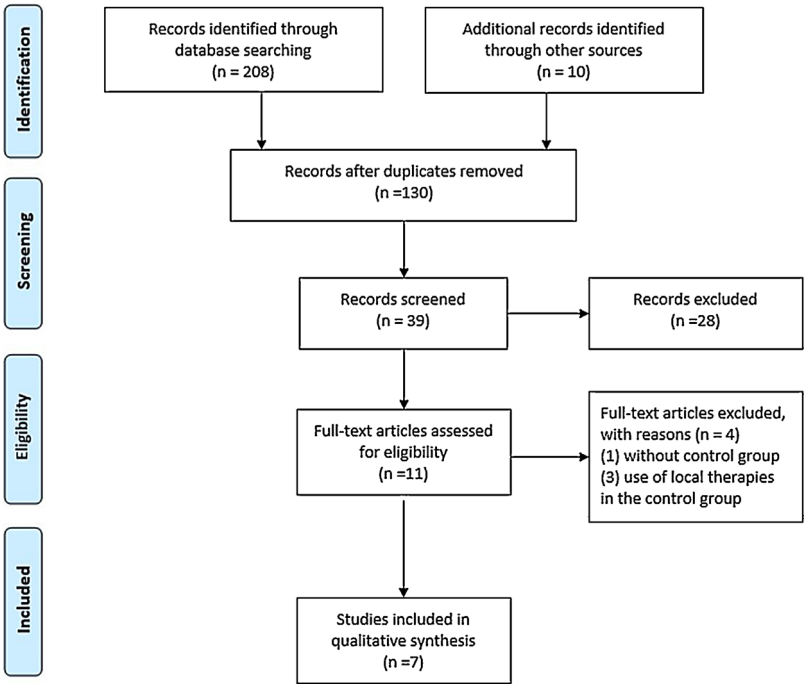


Fig. 1. Flow diagram of studies included in the qualitative analysis.

Table 2
Low-level laser therapy (LLLT) parameters used in included studies.

Author/ Year	Type of laser	Wavelength (nm)	Power (W)	Time (s)	Total energy (J)	Energy density (J/cm^2)	Power density (W/cm^2)	Area (cm^2)	Application method	Number sessions	Manufacturer
Arora et al. (2008)	He-Ne, Prev., C.	632,8 nm	10 mW = 0,010 W	300 s	3 J	1,8 J/cm^2	0,0059 W/cm^2	1,67 cm^2	Punctual (12)	31 sessions	Electro care Ltd, Laser 2001, Chennai, India
Bensadoun et al. (1999)	He-Ne	632,8 nm	60 mW = 0,060 W	300 s, 33 s /p	1,98 J	2 J/cm^2	0,06 W/cm^2	1 cm^2	Punctual (9)	35 sessions	Fradama (Geneva, Switzerland)
	He-Ne	632,8 nm	25 mW = 0,025 W	720 s, 80 s /p	2 J	2 J/cm^2	0,025 W/cm^2	1 cm^2	Punctual (9)	35 sessions	Fradama (Geneva, Switzerland)
Carvalho et al. (2011)	InGaAIP- Prev.	660 nm	15 mW = 0,015 W	10 s /p	0,15 J	3,8 J/cm^2	0,375 W/cm^2	0,04 cm^2	Punctual 4 / area	35 sessions	MMOptics Ltda, São Carlos-SP, Brasil
	InGaAIP- Prev.	660 nm	5 mW = 0,005 W	10 s /p	0,05 J	1,3 J/cm^2	0,125 W/cm^2	0,04 cm^2	Punctual 4 / area	35 sessions	MMOptics Ltda, São Carlos-SP, Brasil
Carvalho, (2015)	InGaAIP- C.	660 nm	15 mW = 0,015 W	10 s /p	0,15 J	3,8 J/cm^2	0,375 W/cm^2	0,04 cm^2	Punctual 4 / area	35 sessions	Twin Flex® (GaAlAs – MM Optics)-SP, Brasil
	InGaAIP-Prev.	660 nm	15 mW = 0,015 W	10 s /p	0,15 J	3,8 J/cm^2	0,375 W/cm^2	0,04 cm^2	Punctual 4 / area	35 sessions	Twin Flex® (GaAlAs – MM Optics)-SP, Brasil
	InGaAIP-Prev.	660 nm	25 mW = 0,025 W	10 s /p	0,25 J	6,3 J/cm^2	0,625 W/cm^2	0,04 cm^2	Punctual 4 / area	35 sessions	Twin Flex® (GaAlAs – MM Optics)-SP, Brasil
Gautam et al. (2015)	He-Ne, Prev.	632,8 nm	24 mW = 0,024 W	125 s /p	3 J	3 J/cm^2	0,024 W/cm^2	1 cm^2	Punctual 6 / area	35 sessions	Electro care Ltd, Laser 2001, Chennai, India
Oton- Leite et al. (2012)	InGaAIP- C	685 nm	35 mW = 0,035 W	25 s /p	0,8 J	2 J/cm^2	1,25 W/cm^2	0,028 cm^2	Punctual (59)	31 to 36 sessions	Theralase, DMC equipments Lta, São Carlos-SP, Brasil
Oton- Leite et al. (2013)	InGaAIP-Prev.	685 nm	35 mW = 0,035 W	25 s /p	0,8 J	2 J/cm^2	1,25 W/cm^2	0,028 cm^2	Punctual (59)	26 to 36 sessions	Theralase, DMC equipments Lta, São Carlos-SP, Brasil

Abbreviations: (He-Ne) Helium-Neon, (InGaAIP) Gallium aluminum-arsenate, (p) Point, (Prev) Preventive LLLT, (C) Curative laser therapy.

grades 2 and 3. To achieve OM grade 2, the G1 took an average of 16.7 days compared to G2 and G3, which took an average of 10.5 days, taking a significant longer time ($p < 0.001$). According to the WHO classification the days it took to present mucositis grade 3, in G1 was 23.5 days, in G2 22.1 days and in G3 20.5 days. According to NCI, the data were similar (mean G1: 24.0, G2: 19.5, G3: 18.3 days), there was no statistically significant difference between the groups in both classifications (WHO, $p = 0.547$, NCI, $p = 0.344$). In the evaluation during 8 weeks of OM according to the WHO, G2 and G3 presented averages above G1 in all weeks of RT. There was a statistically significant difference in G2 compared to G1 (both preventive laser) at week 2, 3 and 5 ($p < 0.001$, 0.042 and 0.007, respectively). On the other hand, G3 compared to G1 showed significant difference at weeks 2, 3, 4, 5 and 7 ($p = 0.002$, 0.006, 0.006, 0.013 and 0.046, respectively). No significant differences were found between the G2 and G3 from week 1 to week 7. The results according to the NCI scale were very similar to the WHO reported results. None of the groups presented OM Grade 4 in both scales (Carvalho, 2015).

3.7.3. EVALUATION OF THE PAIN

One study reported that there was a need for analgesic pain medication according to the WHO analgesic ladder (Step I and II) in all patients. There were no statistically significant differences between G1 (LLLT: 632.8 nm; 1.8 J/cm^2) and G2 (NT). However, pain, according to NRS, increased gradually and was higher at the end of RT (7 weeks), the difference was statistically significant ($p = 0.033$). The highest pain intensity in G1 was in the sixth week of RT and in G2 in the seventh week (Arora et al., 2008).

Four studies evaluated pain via the VAS for pain. Two studies found that G1 (LLLT) presented less pain than in G2 (LLLT-), the difference was statistically significant ($p < 0.01$). One of the studies reported that this difference was from the third week of RT (VAS > 7) ($p = 0.028$). The highest intensity of pain in G1 (632.8 nm; 3.0 J/cm^2) was in the sixth week of RT and in G2 in the fifth week (Gautam et al., 2015). The other study, G1 (685 nm; 2.0 J/cm^2) and G2 showed more intense pain in the intermediate stage than in the initial and final stages (Oton-Leite et al., 2013). In the study that comparing 2 parameters of LLLT (G1: 660 nm; 3.8 J/cm^2, G2: 660 nm; 1.3 J/cm^2). In G1, no patient complained of pain until the fifth day, contrary to G2. In both groups, in the fifth week there was greater intensity of pain, however, the mean intensity of pain was always greater for G2 ($p = 0.004$) (Carvalho et al., 2011). The study comparing 3 parameters of LLLT (preventive laser: G1: 660 nm; 3.8 J/cm^2; 15 mW, G2: 660 nm; 6.3 J/cm^2; 25 mW, laser curative: G3: 660 nm; 3,8 J/cm^2; 15 mW), indicated that in G3 there were complaints of pain on the third day, in G2 on the fourth day and in G1 on the seventh day. Pain intensity was lower in G1 when compared to G2 and G3 ($p = 0.002$). G2 presented less pain when compared to G3; however, there was no significant difference between the groups (Carvalho, 2015).

One study reported pain using a modified VAS for pain which indicated that the preventive use of LLLT (G1) significantly reduced pain during the 7 week period of RT compared to G2 (LLLT-) ($p = 0.025$). The mean degree of pain was 1.8 ± 0.3 for G1 and 2.04 ± 0.22 for G2. The highest intensity of pain in both groups was in the fourth week of RT (Bensadoun et al., 1999).

In the case of studies comparing LLLT with NT or placebo laser, LLLT produced positive results when compared to control groups regardless of parameters used, having wavelength ranges from 632.8 nm to 685 nm, the energy density of 1.8 J/cm^2 to 3.0 J/cm^2, power from 10 mW to 60 mW and total power from 0.8 to 3.0 J. Comparison of LLLT parameters was possible only in 2 studies, where there were better results with LLLT parameters with a wavelength of 660 nm, energy density 3.8 J/cm^2, power 15 mW and total energy of 0.15 J compared to the wavelength of 660 nm, energy density 1.3 J/cm^2, power 5 mW and total energy of 0.05 J and the values of the wavelength 660 nm, energy density 6.3 J/cm^2, power 25 mW, total energy of 0.25 J, with the preventive laser. In the curative LLLT, the parameters were 660 nm; 3.8 J/cm^2; 15 mW, in which there were no positive results when compared to the first parameter of preventive LLLT (660 nm, 3.8 J/cm^2, 15 mw) (Carvalho et al., 2011; Carvalho, 2015). Thus, preventive LLLT was effective with the reported parameters, but studies are still needed to determine which are the most adequate LLLT parameters in the treatment of OM.

3.8. META-ANALYSIS

The meta-analysis was conducted with two studies (Carvalho et al., 2011; Carvalho, 2015). Both studies evaluated the effect of two and three parameters of LLLT for OM due to RT for head and neck cancer, respectively, using two scales, the WHO and NCI-CTC (Carvalho et al., 2011: preventive LLLT 15 mW; 3,8 J/cm^2 and 5 mW; 1,3 J/cm^2. Carvalho, 2015: preventive LLLT 15 mW; 3,8 J/cm^2 and 25 mW; 6,3 J/cm^2 - curative LLLT 15 mW; 3,8 J/cm^2).

Within the parameters of LLLT evaluated, preventive LLLT 15 mW; 3.8 J/

Table 3
Details of included studies (in alphabetical order), respect to oral mucositis and pain assessment in the different periods. (*p*-value in the weeks that there was a statistical difference).

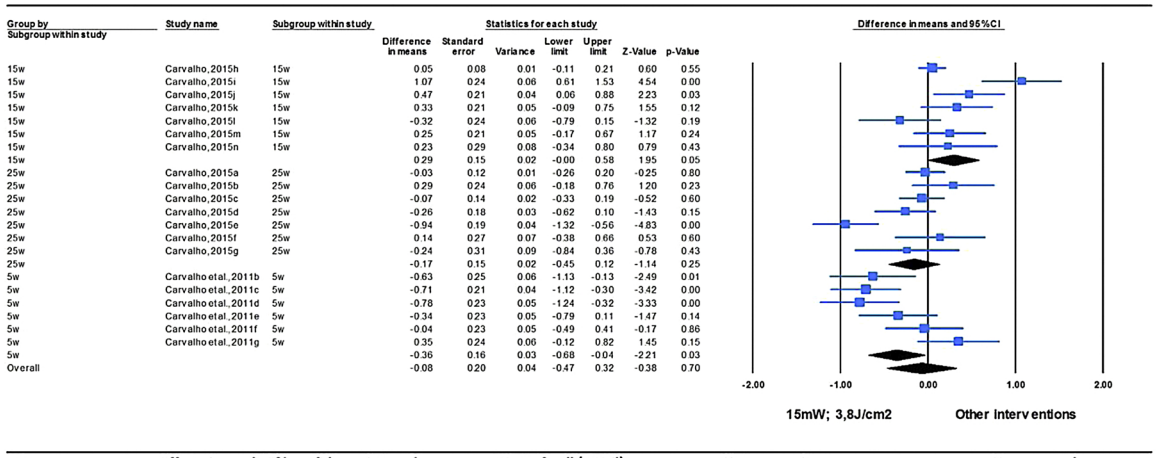
Author/ Year	Application of LLLT	Scales	P value in the weeks that there was statistical difference	Evaluation of the degree of oral mucositis			Evaluation of pain intensity	
Arora et al. (2008)	Daily before RT. Close to the fabric, not in contact.	OM: RTOG/ EORTC	- OM: (*p* value for weeks)	LLLT+ (n = 11)	LLLT- (n = 13)	-	LLLT+	LLLT-
		Pain: NRS	2 0.004	- Data: number of cases	- Data: number of cases		1 0,818 ± 1,41	1 0,569 ± 1,20
			3 0.000	1 G0 (11), G1(0), G2(0), G3(0), G4(0)	1 G0 (13), G1(0), G2(0), G3(0), G4(0)		2 1,509 ± 2,26	2 1,846 ± 1,73
			4 0.029	2 G0 (5), G1(6), G2(0), G3(0), G4(0)	2 G0 (0), G1(7), G2(6), G3(0), G4(0)		3 2,182 ± 1,81	3 3,369 ± 0,92
			5 0.031	3 G0 (0), G1(9), G2(2), G3(0), G4(0)	3 G0 (0), G1(0), G2(6), G3(5), G4(2)		4 2,563 ± 1,78	4 4,584 ± 1,29
			6 0.019	4 G0 (0), G1(4), G2(4), G3(3), G4(0)	4 G0 (0), G1(0), G2(4), G3(4), G4(5)		5 3,090 ± 1,65	5 4,969 ± 1,29
			7 0.045	5 G0 (0), G1(0), G2(6), G3(5), G4(0)	5 G0 (0), G1(0), G2(2), G3(6), G4(5)		6 3,563 ± 1,97	6 5,200 ± 1,37
			- Pain:	6 G0 (0), G1(0), G2(6), G3(5), G4(0)	6 G0 (0), G1(0), G2(2), G3(5), G4(6)		7 3,363 ± 2,16	7 5,307 ± 1,49
			P = 0.033	7 G0 (0), G1(0), G2(6), G3(5), G4(0)	7 G0 (0), G1(0), G2(2), G3(7), G4(4)			
Bensadoun et al. (1999)	Daily, 5 days for week, before RT.	OM: WHO	*p* value for weeks	LLLT+ (n = 15)	LLLT- (n = 15)	-	LLLT+	LLLT-
		Pain: VAS	- OM:	- Data: mean and standard deviation	- Data: mean and standard deviation		1 0,33 ± 7,0	1 0,13 ± 0,25
			4 0.01	1 0,8 ± 0,67	1 0,6 ± 0,63		2 1,06 ± 0,7	2 1,53 ± 0,63
			5 0.01	2 1,4 ± 0,63	2 1,8 ± 0,4		3 1,2 ± 0,59	3 2,06 ± 0,59
			6 0.0025	3 1,8 ± 0,56	3 2,2 ± 0,52		4 1,73 ± 0,45	4 2,66 ± 0,48
			7 0.01	4 2,06 ± 0,25	4 2,66 ± 0,48		5 1,66 ± 0,81	5 2,4 ± 0,51
			1 to 7 0.01	5 2,26 ± 0,59	5 2,86 ± 0,35		6 1,26 ± 0,59	6 2,33 ± 0,49
			- Pain:	6 1,8 ± 0,35	6 2,4 ± 0,5		7 1,13 ± 0,74	7 2,0 ± 0,0
			2 0.05	7 1,66 ± 0,48	7 2,26 ± 0,45		1 to 7: 1,8 ± 0,3	1 to 7: 2,04 ± 0,22
			3 0.01					
			4 0.001	1 to 7: 1,7 ± 0,26	1 to 7: 2,1 ± 0,26			
			5 0.01					
			6 0.001					
			7 0.001					
			1 to 7 0.025					
Carvalho et al. (2011)	Daily, 5 days for week, before RT.	OM: NCI-CTC and WHO	- OM (*p* value for weeks)	LLLT+ Prev: 15 mW; 3,8 J/cm^2 (n=27)	LLLT+ Prev: 5 mW; 1,3 J/cm^2 (n = 27)	-	LLLT+: 15 mW; 3,8 J/cm^2	LLLT+: 5 mW;
		Pain: VAS	WHO /NCI	- Data: mean and standard deviation	- Data: mean and standard deviation			1,3 J/cm^2
			2 0.019 / 0.009	WHO / NCI-CTC	WHO / NCI-CTC		The mean intensity of pain was always higher for LLLT+ 5 mW; 1,3 J/cm^2	
			3 0.005 /	1 0.00 ± 0.00 / 0.00 ± 000	1 0.11 ± 0.42 / 0.11 ± 0.42			
			4 0.003 / 0.013	2 0.78 ± 0.93 / 0.78 ± 0.93	2 1.41 ± 0.93 / 1.56 ± 1.09			
			- Pain	3 1.59 ± 0.97 / 1.74 ± 1.10	3 2,30 ± 0.47 / 2.33 ± 0.48			
			p = 0.004	4 1.52 ± 0.85 / 1.63 ± 0.97	4 2.30 ± 0.87 / 2.33 ± 0.88			
				5 1.85 ± 0.82 / 1.93 ± 0.87	5 2.19 ± 0.88 / 2.22 ± 0.89			
				6 2.15 ± 0.72 / 2.15 ± 0.77	6 2.19 ± 0.96 / 2.26 ± 0.98			
				7 2.35 ± 0.61 / 2.44 ± 0.62	7 2.00 ± 0.79 / 0,12 ± 0.86			
Carvalho, (2015)	Daily, 5 days for week, before RT.	OM: NCI-CTC and WHO	- OM	LLLT+ C: 15 mW; 3,8 J/cm^2 (A) (n=21)	LLLT+ Prev: 15 mW; 3,8 J/cm^2 (B) (n=20)	LLLT+ Prev: 25 mW; 6,3 J/cm^2 (C) (n=24)	Two Groups (B and C) showed a significantly higher mean of pain than the Group A.	
		Pain: VAS	A x B 0,001	- Data: mean and standard deviation	- Data: mean and standard deviation	- Data: mean and standard deviation		
			A x C 0,001	WHO / NCI-CTC	WHO / NCI-CTC	WHO / NCI-CTC		
			B x C NS	1 0,05 ± 0,22 / 0,05 ± 0,22	1 0,10 ± 0,31 / 0,10 ± 0,31	1 0,13 ± 0,45 / 0,13 ± 0,45		
				2 0,43 ± 0,75 / 0,43 ± 0,75	2 1,50 ± 0,76 / 1,55 ± 0,83	2 1,21 ± 0,83 / 1,21 ± 0,83		
			- Pain	3 1,38 ± 0,87 / 1,38 ± 0,87	3 1,85 ± 0,37 / 2,00 ± 0,56	3 1,92 ± 0,50 / 2,21 ± 0,72		
			P = 0,002	4 1,62 ± 0,74 / 1,62 ± 0,74	4 1,95 ± 0,61 / 2,00 ± 0,65	4 2,21 ± 0,59 / 2,25 ± 0,61		
				5 1,67 ± 0,86 / 1,67 ± 0,86	5 1,35 ± 0,67 / 2,45 ± 0,69	5 2,29 ± 0,62 / 2,46 ± 0,66		
				6 2,10 ± 0,54 / 2,10 ± 0,54	6 2,35 ± 0,81 / 2,35 ± 0,81	6 2,21 ± 0,93 / 2,38 ± 0,97		
				7 2,06 ± 0,57 / 2,06 ± 0,57	7 2,29 ± 0,99 / 2,36 ± 1,01	7 2,53 ± 0,72 / 2,59 ± 0,71		
				8 2,33 ± 0,58 / 2,03 ± 0,58	8 3,00 ± 0,00 / 1,50 ± 2,12	8 2,60 ± 0,89 /2,60 ± 0,89		

(*continued on next page*)

Table 3 (*continued*)

Author/ Year	Application of LLLT	Scales	P value in the weeks that there was statistical difference	Evaluation of the degree of oral mucositis			Evaluation of pain intensity	
Gautam et al. (2015)	Daily, 5 days for week, before RT. < 1 cm of tissue.	OM: RTOG/ EORTC Pain: VAS	- OM p < 0.05 - Pain p < 0.05	LLLT+ (n = 22) - Data: number of cases 1 G0(22), G1(0), G2(0), G3(0), G4(0) 2 G0(15), G1(7), G2(0), G3(0), G4(0) 3 G0(6), G1(11), G2(2), G3(3), G4(0) 4 G0(2), G1(2), G2(14), G3(4), G4(0) 5 G0(0), G1(4), G2(15), G3(3), G4(0) 6 G0(0), G1(6), G2(13), G3(3), G4(0) 7 G0(0), G1(6), G2(12), G3(4), G4(0) Severe OM: 18,2%	LLT- (n = 24) - Data: number of cases 1 G0(24), G1(0), G2(0), G3(0), G4(0) 2 G0(4), G1(17), G2(3), G3(0), G4(0) 3 G0(0), G1(8), G2(16), G3(0), G4(0) 4 G0(0), G1(2), G2(15), G3(7), G4(0) 5 G0(0), G1(2), G2(10), G3(9), G4(3) 6 G0(0), G1(2), G2(10), G3(7), G4(5) 7 G0(0), G1(1), G2(9), G3(9), G4(5) Severe OM: 58,3%	-	- Data: mean of pain scores. LLLT+ 1 0,0 2 0,83 3 2,0 4 3,67 5 3,83 6 4,08 7 4,0 Severe pain: 8,3%	- Data: mean of pain scores. LLLT- 1 0,21 2 2,14 3 3,86 4 5,21 5 5,93 6 5,79 7 5,79 Severe pain: 50%
Oton- Leite et al. (2012)	Daily, 5 days for week, before RT. 1º 1 week after.	OM: WHO	- OM p = 0.002	LLLT+ (n = 30) - Data: number of cases Interruption of RT due OM = 5/30	LLLT- (n = 30) - Data: number of cases Interruption of RT due OM = 23/30	-	Not reported	Not reported
Oton-Leite et al. (2013)	Daily, 5 days for week, before RT. 1º 1 week after. 2 mm of tissue.	OM: NCI-CTC and WHO Pain: VAS	- OM WHO / NCI-CTC Initial: 0,69/0,75 Intermediary: < 0.001 / < 0.001 Final: < 0.001 / < 0.001 - Pain Initial: 0.006 Intermediary: < 0.001 Final: < 0.001	LLLT+ (n = 30) - Data: mean (and median) NCI-CTC Initial: 2.07 (2.00) Intermediary: 2.15 (2.00) Final: 2.12 (2.00) WHO Initial: 1.46 (1.00) Intermediary: 1.92 (2.00) Final: 1.50 (1.00)	LLLT- (n = 30) - Data: mean (and median) NCI-CTC Initial: 2.10 (2.00) Intermediary: 2.80 (3.00) Final: 2.95 (3.00) WHO Initial: 1.50 (1.00) Intermediary: 3.00 (3.00) Final: 2.95 (3.00)	-	LLLT+ - Data: mean (and median) Initial: 1.90 (2.00) Intermediary: 4.92 (5.00) Final: 2.88 (3.00)	LLLT+ - Data: mean (and median) Initial: 3.33 (3.00) Intermediary: 8.32 (9.00) Final: 7.64 (8.00)

Abbreviations: (OM) Oral mucositis; (RT) Radiotherapy; (LLLT+) Low-Level Laser Therapy; (LLLT-) Laser placebo; (WHO) World Health Organization; (NCI-CTC) National Cancer Institute's Common Toxicity Criteria National Cancer Institute; (RTOG/EORTC) Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer; (VAS) Visual Analogue Scale; (NRS) Numeric Rating Scale; (G) Degree of oral mucositis; (Prev) Preventive LLLT; (C) Curative LLLT; (NS) No significant. Number 1 to 8: referred to weeks evaluated.



Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number weeks	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed																
15w	7	0,18	0,006	0,00	0,06	0,31	2,93	0,00	23,47	6	0,00	74,43	0,10	0,09	0,01	0,32
25w	7	-0,15	0,007	0,00	-0,28	-0,02	-2,29	0,02	22,78	6	0,00	73,66	0,09	0,08	0,01	0,31
5w	6	-0,37	0,09	0,01	-0,56	-0,19	-3,95	0,00	17,71	5	0,00	71,77	0,14	0,12	0,01	0,37
Overall	20	-0,05	0,04	0,00	-0,13	0,03	-1,19	0,23	91,97	19	0,00	79,34	0,14	0,07	0,00	0,37
Random																
15w	7	0,29	0,15	0,02	-0,00	0,58	1,95	0,05								
25w	7	-0,17	0,15	0,02	-0,45	0,12	-1,14	0,25								
5w	6	-0,36	0,16	0,03	-0,68	-0,04	-2,21	0,03								
Overall	20	-0,08	0,20	0,04	-0,47	0,32	-0,38	0,70								

Fig. 2. Effect of LLLT for oral mucositis due to radiotherapy for head and neck cancer, according to the WHO scale.

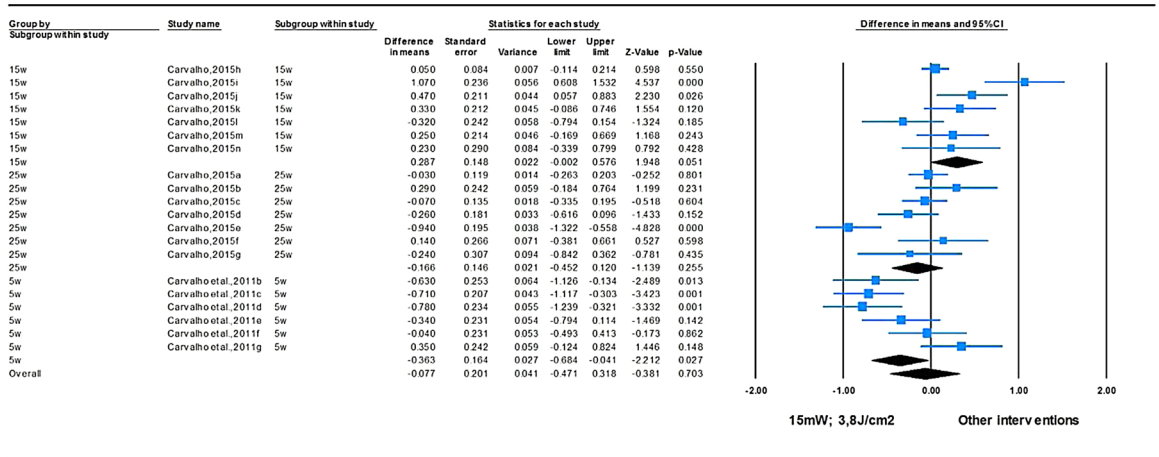
cm^2 was the parameter that was repeated in both studies, enabling the meta-analysis. This parameter was compared to the other LLLT parameters (preventive LLLT 5 mW; 1.3 J/cm^2 and 25 mW; 6.3 J/cm^2; treatment LLLT 15 mW; 3.8 J/cm^2). Due to the heterogeneity of the results, a subgroup analysis was performed and the values of the random effect were considered (Fig. 2 and 3).

In the overall analysis, there was no statistically significant difference between preventive LLLT 15 mW; 3.8 J/cm^2 compared to the other parameters evaluated (OMS: p = 0.70; NCI-CTC: p = 0.703) (95% confidence interval: -0,47 to 0,32; heterogeneity: Q = 91.97, I^2 = 79.34%).

In the analysis of subgroups, the result shows a lower degree of MO with preventive LLLT 15 mW; 3.8 J/cm^2 compared to 5 mW, 1.3 J/cm^2, with a statistically significant difference (OMS: p = 0.03; NCI-CTC: p = 0.027) (Carvalho et al., 2011). In relation to the other subgroups there was no statistically significant difference (Treatment LLLT 15 mW; 3.8 J/cm^2 - OMS: p = 0.05; NCI-CTC: p = 0.051; preventive LLLT 25 mW; 6.3 J/cm^2 - OMS: p = 0.25; NCI-CTC: p = 0.255). Thus, the finding of the severity of OM according to the WHO and NCI-CTC scales was similar.

3.9. QUALITY ANALYSIS OF STUDIES

The present study applied the Cochrane Collaboration tool that evaluates the risk of biases for the included studies, with six domains addressed. In the first domain, which uses random sequence generation, 80% of the included studies had low risk of bias and 20% risk of uncertain bias. While in the second domain, concealment of allocation, studies had approximately 30% low risk of bias and 70% of risk of uncertain bias, due to insufficient data for the judgment



Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number weeks	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed																
15w	7	0,183	0,062	0,004	0,061	0,306	2,934	0,003	23,465	6	0,001	74,430	0,104	0,092	0,009	0,32
25w	7	-0,153	0,067	0,004	-0,284	-0,022	-2,288	0,022	22,781	6	0,001	73,662	0,094	0,080	0,006	0,30
5w	6	-0,374	0,095	0,009	-0,559	-0,188	-3,947	0,000	17,713	5	0,003	71,772	0,137	0,121	0,015	0,37
Overall	20	-0,049	0,041	0,002	-0,129	0,032	-1,190	0,234	91,968	19	0,000	79,341	0,137	0,068	0,005	0,37
Random																
15w	7	0,287	0,148	0,022	-0,002	0,576	1,948	0,051								
25w	7	-0,166	0,146	0,021	-0,452	0,120	-1,139	0,255								
5w	6	-0,363	0,164	0,027	-0,684	-0,041	-2,212	0,027								
Overall	20	-0,077	0,201	0,041	-0,471	0,318	-0,381	0,703								

Fig. 3. Effect of LLLT for oral mucositis due to radiotherapy for head and neck cancer, according to the NCI-CTC scale.

of concealment of allocation. In performance biases (blinding of participants and personnel) and detection (blinding of outcome assessment), they had 70% of low bias risk, and approximately 15% of high risk of bias and 15% of uncertain bias. While friction bias (incomplete outcomes) and reporting (selective reporting) were presented at 60% and 70% of low risk of bias, and 40% and 30% of risk of uncertain bias, respectively (Fig. 2). The Cochrane Collaboration summary (Fig. 3) in its general aspect shows that all studies in one or more domains had low risk of bias, but no study was completely bias free. Of these studies, one had high risk of bias in two domains, and two domains with risk of bias in two domains, and two domains with risk of uncertain bias.

4. DISCUSSION

There are several studies in the literature, including systematic reviews and meta-analyzes, with significant evidence that LLLT reduces the risk of oral mucositis (OM), the severity of OM, and the duration of oral ulcerations (Bjordal et al., 2011; Oberoi et al., 2014; He et al., 2018; Mengxue et al., 2018). Another aspect well reported in the literature is the reduction of severe pain, a decrease in the overall mean pain scores, a decrease for the need for opioid use and unplanned radiotherapy interruptions (Bjordal et al., 2011, Migliorati et al., 2013; Oberoi et al., 2014). However, there has not been a systematic review comparing the various parameters of LLLT that define the dosimetry in the studies. For the most part, this is due to the difficulty of finding all the data and homogeneous parameters. In order to compare LLLT parameters, it is necessary to consider the clinical aspects and the type of equipment used (Freitas and Simões, 2015). A study was able to establish the proper wavelength of LLLT (Lalla et al., 2014). However, other parameters such as frequency of doses, power used, energy density have not yet been established, and these factors may influence the results of the studies (Rampini et al., 2009; Bjordal et al., 2011; Lalla et al.,2014).

In this study we were able to group only information about dosimetric parameters related to the equipment. Furthermore, the grade of OM and the evaluation of pain was described. Heterogeneity exists in the type of LLLT used in the studies included in the present investigation (He-Ne and InGaAIP). Also the laser manufacturer varied as well with four studies using lasers manufactured in Brazil (Theralase and MMO), two studies using lasers manufactured in India (Electro care) and one study using a laser made in Geneva (Fradama). This fact made it difficult to standardize data since the various laser devices provide parameters that may vary according to the manufacturer (Fukuda and Malfatti, 2008). Overall, analysis of the results showed that the mean number of sessions was 33 and all studies used the LLLT point application. Only two studies gave information about how the laser tip was used. That is, whether the laser tip was leaning against the tissue, and could modify the penetration of light into the tissue according to the wavelength parameter of the equipment (Freitas and Simões, 2015).

The most commonly used LLLT parameters were the following: wavelength from 632.8 nm to 685 nm, energy density from 1.8 J/cm^2 to 3.0 J/cm^2, power from 10 mW to 60 mW and total energy from 0.8 to 3.0 J A total energy between 0.8 and 3.0 J is related to the regeneration and modulation of surface-skin and mucosal inflammation (Hamblin et al., 2013), thus reducing the overall risk of severe mucositis and other measures of OM severity in patients undergoing radiation therapy for head and neck cancer.

Another factor of heterogeneity for the results were the classification scales of the degree of mucositis and pain. In the evaluation of OM with the RTOG / EORTC scale of the Arora et al., 2008, the LLLT parameters had better results in the first weeks of RT compared to the study by Gautam et al., 2015. According to the WHO classification, the LLLT protocols from the studies of Bensadoun et al. 1999 and Oton-Leite et al., 2012 reduced the severity of OM, with no difference between the studies. The studies of Carvalho et al. 2011 and Carvalho, 2015 used two classifications of OM grade (NCI-CTC and WHO); LLLT protocols were InGaAIP-Preventive (Twin flex-MMO), 660 nm, 15 mW, 10 s, 0.15 J, 3.8 J/cm^2, 0.375 W/cm^2 and 0.04 cm^2 area. Both studies showed a postponement of grade 2 and grade3 severity of OM. In the same studies preventive LLLT was effective with the reported parameters above (Figs. 4 and 5).

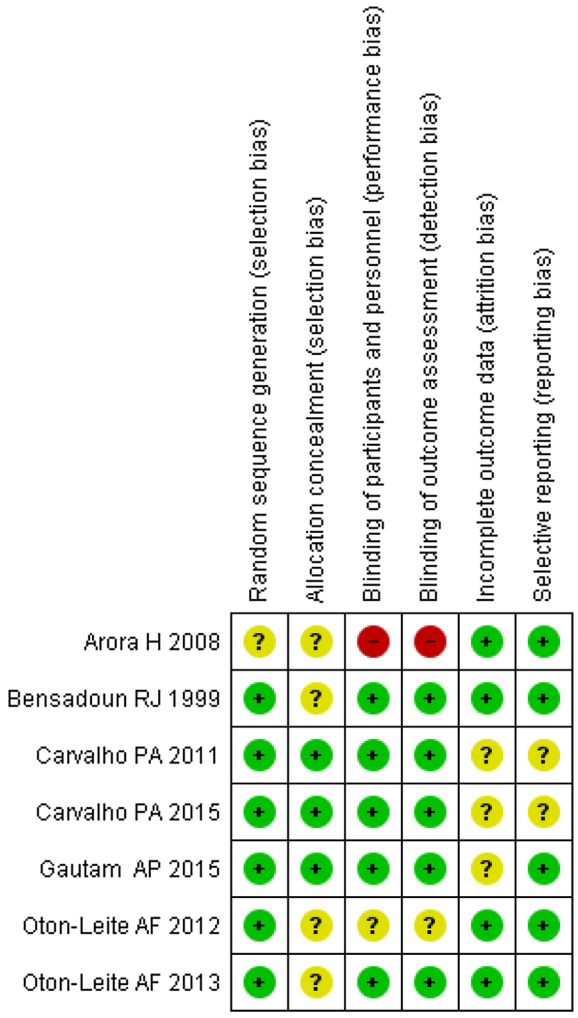


Fig. 5. Bias risk of included studies.

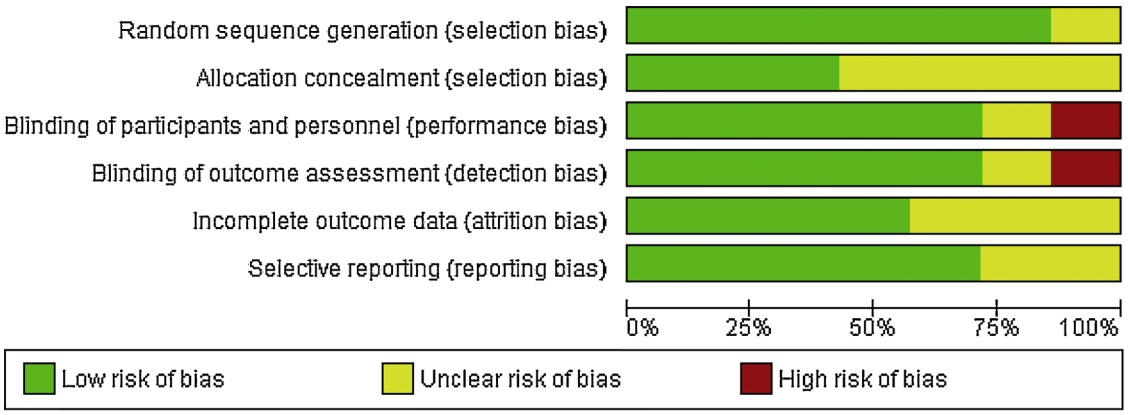


Fig. 4. Bias risk percentages of included studies.

On the other hand, regarding the pain of patients evaluated via the Visual Analogue Scale (VAS), most studies with several LLLT protocols reported analgesia. One factor that made it difficult to analyze the included studies was the heterogeneity in the classification of OM and pain with several scales used. Therefore, it is encouraged that future researches describe the greater amount of information of the LLLT parameters used in the studies, since this will help to have a better standardization of the protocols.

The bias risk in general was favorable (low risk of bias) in the six domains that encompass evaluation of selection bias, performance bias, detection bias, friction bias, reporting bias and others bias, with percentages of 80%, 30%, 75%, 75%, 60% and 75%, respectively. Judgment is subjective, and each outcome must be judged separately (Hamblin et al., 2013). However, in relation to the selection bias, regarding the second domain, in the concealment of the allocation, only 70% of the studies had a risk of uncertain bias because they did not clarify how concealment of the allocation was performed (*e.g.* random list of a computer or sealed and opaque envelope). In the performance and detection biases, during blinding, there was a study that reported the difficulty of blinding, which may alter the outcome of the expected result. Information such as lack of allocation concealment and lack of blinding were related to exaggerated treatments (Jørgensen et al., 2016). The randomized clinical trial is a type of study very prone to bias, either by the arbitrariness of the investigators in the selection of the sample and the measurement of the analyzed variables, or in the difficulty in the control of other factors that may influence the clinical outcome (Higgins and Green, 2011).

Most studies included in this systematic review have used laser prophylaxis for OM with good results. However, there is still no enough evidence of which parameter is best for the treatment of OM because there is little evidence of studies comparing different LLLT parameters (Bensadoun et al., 1999; Arora et al., 2008; Carvalho et al., 2011, Oton-Leite et al., 2012; Oton-Leite et al., 2013; Carvalho, 2015; Gautam et al., 2015). In addition, another limiting factor was the lack of standardization in the grade of OM, evaluation of the pain and the form of description of the data in the included studies, making it difficult to perform a meta-analysis. Therefore, the findings of this systematic review encourage future studies to compare different LLLT parameters in multicentric studies, the use of standardized scales, description of data specifying the mean and standard deviation of the degree of OM and evaluation of pain, to determine which LLLT parameters are most adequate. Thus, further studies comparing different LLLT parameters for the treatment and prevention of OM in individuals receiving radiotherapy in the head and neck region are recommended.

5. CONCLUSIONS

LLLT was effective regardless of the parameters used compared to studies whose control group was a placebo or no therapy. The wavelength ranges were from 632.8 nm to 685 nm, the energy density from 1.8 J/cm2 to 3.0 J/cm^2, power from 10 mW to 60 mW and total power from 0.8 to 3.0 J. In the studies where it was possible to compare 2 or 3 parameters of LLLT, there were better results with the parameters of preventive LLLT 660 nm, 3.8 J/cm^2, 15 mW; 0.15 J compared to preventive LLLT 660 nm, 1.3 J/cm^2, 5 mW; 0.05 J (OMS: p = 0,03; NCI-CTC: p = 0,027) and 660 nm, 6.3 J/cm^2, 25 mw, 0.25 J (OMS: p = 0,25; NCI-CTC: p = 0,255) and treatment LLLT 660 nm, 3.8 J/cm^2;15 mW; 0.15 J (OMS: p = 0,05; NCI-CTC: p = 0,051).

Conflict of interest

There are no conflicts of interest.

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