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REVIEW ARTICLE

Is photobiomodulation therapy effective in reducing pain caused by toxicities related to head and neck cancer treatment? A systematic review

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Abstract

Photobiomodulation therapy (PBMT) has been considered an effective method for preventing and managing certain cancer-related toxicities in head and neck cancer (HNC) patients treated with radiotherapy and chemotherapy. However, the potential effects of PBMT on pain control and analgesia resulting from these toxicities is still controversial. The aim of this systematic review was to compile available evidence of the effects of PMBT on pain control and reduced use of analgesics in HNC patients. We searched three indexed databases: MEDLINE/PubMed, Embase, and Scopus. The databases were reviewed up to and including December 2018. Only human clinical studies in English language were selected. Information was only available for mucositis and radiodermatitis. Fifteen out of 1112 studies met the inclusion criteria (14 for oral mucositis (OM) and 1 for radiodermatitis). From the 14 studies involving the prevention and treatment of OM, 10 had the study subjects compared to a placebo group. Of these 10 studies, all but 1 showed statistically significant difference related to pain control favoring the PBMT group. The study that compared PBMT with other treatment modality showed better results in pain control with PBMT. It appears that PBMT application frequency and potency impact on pain control. The only study involving the prevention and treatment of radiodermatitis was compared to placebo arm and showed statistically significant difference related to pain control favoring the PBMT group. Seven studies compared the need of analgesic medication between PBMT and placebo groups. Of these, five studies showed that the use of analgesic medication was significantly higher in the placebo group. The current evidence supports that PBMT is effective in pain control resulting from OM and radiodermatitis and may also reduce the need for analgesics. The evidence is not yet available of the effects of PBMT in other HNC treatment-related toxicities.

Keywords Photobiomodulation therapy · Pain · Systematic review · Head and neck cancer

Introduction

Tumors arising from the head and neck are among the five most common malignant neoplasms worldwide [1]. Contemporary treatment modalities are associated with acute and long-term morbidity and impairment of patients' quality of life (QoL) [2], including oral mucositis (OM), dysphagia, radiation-induced dermatitis, local and systemic infections, radiation caries, nutritional problems, and osteoradionecrosis. [3].

Photobiomodulation therapy (PBMT) is the current technical term that refers to a treatment modality that uses different light sources such as low-level laser therapy (LLLT), light-emitting diodes (LEDs) and broad-band light to improve tissue repair and reduce pain and inflammation wherever the beam of light is applied. Over 700 randomized clinical trials have been published on PBMT to treat patients with a variety of diseases and conditions in sports injury, arthritic joints, neuropathic pain, back and neck pain, and cancer treatment-related toxicities [4].

PBMT has now been used worldwide as part of the arsenal of tools in the supportive care of cancer patients. PBMT is used for prevention and treatment of side effects such as OM, lymphedema, peripheral neuropathy, and radiodermatitis, not only in HNC but also in complications associated with the treatment of

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other types of cancer [5–10]. Although there is robust evidence that PBMT can be effectively used in the prevention and treatment of some toxicities such as OM, the information available about pain control has not been evaluated.

The challenge of pain control in oncology and complications of cancer therapy is increasing as a result of the large number of cancer treatment protocols being developed. Furthermore, the current opioid crisis has leaded the scientific community to search for different pain control protocols. This has been recognized by the International Association for the Study of Pain's Declaration of Montreal 2010 [11]. Despite good results with analgesic drugs, side effects can become a problem. Therefore, other therapies are under investigation for treatment of the inflammatory pain. In view of this complex scenario, the need for the development of a technique to control pain with minimal or no side effect, PBMT has been evaluated as a promising tool [12].

The aim of the present systematic review was to evaluate the current literature addressing the possible effects of PBMT in pain control when used with the goal of preventing and/or treating complications related to HNC antineoplastic therapies.

Materials and methods

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol for this systematic review was registered in the International Prospective Register of Systematic Review (PROSPERO) database (registration number CRD42018115503) to avoid duplicate publications of systematic reviews and to enable comparison among methods as they are reported in the review protocol.

Inclusion criteria

Only human clinical studies (retrospective and prospective) that assessed information about pain control resulting from the use of PBMT to treat or prevent cancer treatment toxicities were included.

Exclusion criteria

Case–control studies, cohort studies, case reports, case series, animal studies, in vitro studies, letters to editors, editorials, review articles, commentaries, monographs, conference abstracts, unpublished data, studies published in a language other than English, and studies without information about pain assessment were excluded.

Search strategy

Electronic and systematic searches of scientific studies that evaluated the effect of PBMT in cancer patients for prevention and/or treatment of toxicities induced by antineoplastic therapies were conducted without restriction in publication year (last search December 10th 2018). MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com/login), and Scopus (https://www.scopus.com) were screened. The following keywords were used: "low-level laser therapy," "photobiomodulation," "oral mucositis," "lymphedema," "radiodermatitis," and "radiation-induced dermatitis." Multiple synonyms, abbreviations, and related keywords for each of these terms were used for searching, linked in independent strategies by the Boolean operator "AND." All publications presented in these databases containing a combination of controlled pre-defined Medical Subject Headings (MeSH) and free terms related to PBMT in HNSCC, using Boolean operators ("OR," "AND") to combine searches, were retrieved. The process was repeated in each database to ensure that any relevant result was not missed during the identification phase, adapted to the rules of syntax of each electronic database. Additional manual searches were conducted by reading the reference lists from all selected studies to detect other potentially eligible reports that could meet the inclusion criteria. Furthermore, key authors/co-authors were identified among the included studies, which allowed for verification of extra database searches filtered by author/co-author name.

Study selection

All titles were systematically organized in the Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, USA). The titles were verified, and the duplicates excluded. Later, titles and abstracts were screened and read completely for possible inclusion on the qualitative synthesis of this review. The studies were classified into the following categories: duplicated, other language than English, in vitro, animal studies, and without information about pain. The studies assessed for eligibility were reviewed in detail using the full-text version, by two independent reviewers (ARSS and MPP). The studies that omitted relevant methodological information were also excluded from the current review. When discrepant ratings occurred between the reviewers, a final decision was made by a third reviewer in order to achieve consensus.

Data extraction

Methodological information extracted from included studies were (1) first author and year of publication, (2) size of sample, (3) study type, (4) methods of pain analysis, (5) treatment design, (6) information about analgesic medication, and (7) outcomes.

Risk of bias assessment

To assess the risk of bias, eight methodological aspects were verified according to Cochrane Handbook for Systematic Reviews of Interventions: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, blinding of all-cause mortality, incomplete outcome data (short term), incomplete outcome data (long-term), and selective reporting. If item was present in the selected article, it was judged as "low risk of bias" (green circle). If the item was not presented in the selected article, the paper was judged as "high risk of bias" (red circle). If this information was not available, the paper was classified as "undefined risk of bias" (yellow circle) (Table 1).

Data analysis

Due to a great variation of the PBMT protocols used in the included studies, it was not possible to perform a meta-analysis. The present systematic review presented a detailed qualitative synthesis of the results from the included studies.

Results

Search and study selection

A total of 1112 potentially relevant records were identified from the databases. A flow diagram that summarizes the selection process of the studies is shown in Fig. 1. After the first review process, 523 studies were eliminated due to duplication. After the removal of duplicates, 574 studies were excluded because they did not meet the inclusion criteria. Of these, 502 were excluded because information about pain was not available, 33 were excluded because they were animal studies, 33 were in vitro studies, 4 were conference abstracts, and 2 were in other language than English. In the end, 15 studies fulfilling the inclusion criteria were included in the present systematic review. All the included studies evaluated the pain modulation induced by PBMT for prevention and treatment of toxicities induced by cancer.

Study characteristics

The main characteristics of the included studies are presented in Table 1. Of the 15 [6, 7, 13–25] included studies, 14 [7, 13–25] evaluated the effects of PBMT on OM in HNC patients and 1 [6] study on radiodermatitis in HNC patients. Of the 15 included studies, 8 [16–19, 22–25] were conducted in Brazil, 5 [7, 14, 15, 20, 21] in India, 1 [13] in France, and 1 [6] in China. These studies were published between 1999 and 2018.

Ten [7, 13–15, 18, 20–24] out of 14 OM studies were designed with a placebo group. Besides, 1 [16] study was designed with three different PBMT protocols; 2 [19, 25] studies compared two different PBMT protocols and 1 [17] study compared PBMT with aluminum hydroxide (AH) suspension (310 mg/5 mL). The only study that evaluated the PBMT in the prevention and treatment of radiodermatitis was designed with a placebo arm [6].

When taken together all 11 [6, 7, 13–15, 18, 20–24] OM and radiodermatitis studies based on placebo groups, it was possible to observe lower pain scores in the PBMT study arms. In addition, the study that compared three different laser protocols detected that patients submitted to low-power laser therapy showed higher levels of OM-related pain when compared to patients submitted to the combination of high- and low-power lasers [16]. The other 2 [19, 25] studies that compared two different laser protocols showed that a higher energy density is better to control OM-related pain and that the combination of red and infrared PBMT approaches reduced the prescription of analgesic drugs. PBMT was also considered more efficient to control pain secondary to OM than AH oral rinse [17].

Thirteen [7, 13, 14, 16–25] out of 15 included studies used a visual analogue scale and 2 [6, 15] studies used a numeric analogue scale to measure pain. Pain related to the cancer treatment toxicities was assessed daily in 8 [6, 15, 16, 18–20, 23, 24] studies, weekly in 4 [7, 13, 14, 21] studies, twice a week in 2 [17, 25] studies, and fortnightly in 1 [22] study.

Seven [7, 15, 20–23, 25] studies compared the need of analgesic medication between study groups. Of these, 6 [7, 15, 20–23] compared laser and placebo groups and 4 [7, 20, 21, 23] studies showed a significant reduction in the needs of analgesics prescription for the PBMT groups. The other 2 [15, 22] studies did not show statistically significant differences between laser and placebo groups and 1 [25] study observed that high laser energy reduced analgesics prescriptions when compared to the low-energy laser strategy. Eight [6, 13, 14, 16–19, 24] studies did not evaluate the patterns of analgesic prescriptions.

Risk of bias

Thirteen (86.6%) [6, 7, 13, 14, 16, 18–25] studies were considered to have low risk of bias for random sequence generation, 8 (53.3%) [7, 13, 14, 19–22, 25] for allocation concealment, 9 (60%) [7, 13, 19–25] for blinding of participants and personnel, 8 (53.3%) [7, 13, 14, 19–22, 24] for blinding of outcome assessment, 12 (80%) [7, 13–17, 19–21, 23–25] for blinding all-cause mortality, 15 (100%) [6, 7, 13–25] for incomplete outcome data (short term), 14 (93.3%) [6, 7, 13–15, 17–25] for incomplete outcome data (long term), and 15 (100%) [6, 7, 13–25] for selective outcome reporting. One

Table 1 Baseline characteristics of studies included in the systematic review

Study	Sample size	Study type	Method of pain analysis	Treatment design	Information about analgesics	Outcomes
Bensadoun et al., 1999 [13]	30 patients divided into 2 groups: LEL ($n = 15$); and placebo ($n = 15$)	Oral mucositis—multicenter phase III randomized study	Visual Analogue Scale. Evaluated weekly during the RT	He–Ne. Wavelength 632.8 nm. Daily during the 7 weeks of RT	No associated anti-inflammatory or other mucositis treatment was authorized. Prescription of analgesics was allowed, but not during the 2 days before evaluation each week	The frequency of severe pain (grade 3) was 23.8% without LEL, falling to 1.9% with LEL
Mayia et al., 2006 [14]	50 patients divided into 2 groups: laser group ($n = 25$); and placebo group ($n = 25$)	Oral mucositis—randomized clinical trial	Visual Analogue Scale. Evaluated weekly during the RT	He–Ne laser. Wavelength 632.8 nm and output of 10 mW). The laser therapy was given from day 1 till the completion of radiotherapy	Control group patients were given oral analgesics, local application of anesthetics, 0.9% saline and povidine wash during the course of radiotherapy	The result showed a significant difference in pain and mucositis ($p < 0.001$) between the two groups
Arora et al., 2008 [15]	24 patients divided into 2 groups. G1: Laser group ($n = 12$); G2: placebo group ($n = 12$)	Oral mucositis—comparison between groups prospective controlled study	Numeric Rating Scale. Evaluated daily during the RT	He–Ne laser. Wavelength 632.8 nm and output of 10 mW, average energy density of 1.8 J/cm^2. Irradiations daily before RT	For beginning and pursuing the step I and step II analgesia, the differences were not statistically significant in the 2 groups. (According to the World Health Organization [WHO] analgesic ladder)	The difference between the laser and control groups was statistically significant ($p = 0.033$)
Simões et al., 2009 [16]	39 patients divided into 3 groups. G1: low-power laser ($n = 16$); G2: combined high- and low-power lasers ($n = 9$); and G3: low-power laser ($n = 14$)	Oral mucositis—comparison between low- and high-/low--power lasers	Visual Analogue scale. Evaluated daily during the RT	Low-power laser: InGaAlP laser (660 nm/40 mW/6 J cm^2/0.24 J per point). High-power LT: GaAlAs laser (808 nm, 1 W/cm^2). G1: irradiations three times a week; G2: irradiations three times a week; G3: irradiation once a week	Without information	Significant increase in the pain on the last RT session in the G3. The other two groups presented similar degree of pain that were maintained in the same levels from the beginning of the LT to the end of the RT
Lima et al., 2010 [17]	25 patients divided into 2 groups: G1: patients received LLLT ($n = 12$); G2: patients received aluminum hydroxide ($n = 13$)	Oral mucositis—prospective, comparative and nonrandomized study	Visual Analogue Scale. Evaluated twice a week during the RT	LLLT: 830 nm, 15 mW, 12 J/cm^2) daily from the 1st day until the end of RT before each sessions during 5 consecutive days, AH: 310 mg/5 mL, 4 times/day, also throughout the duration of RT, including weekends	The use of concomitant anti-inflammatory and/or analgesic was allowed in both groups	Lower mean pain scores were observed in the laser group during the whole RT treatment, except in the 33rd RT session. A statistically significant difference was observed only in the 13th RT session, in which the LLLT group presented important mean pain reduction compared to the AH group

Table 1 (continued)

Study	Sample size	Study type	Method of pain analysis	Treatment design	Information about analgesics	Outcomes
Zanin et al., 2010 [18]	72 patients divided into 2 groups: laser group ($n = 36$); and placebo group ($n = 36$)	Oral mucositis—prospective study	Visual Analogue Scale. Evaluated daily during the RT	Diode laser (660 nm, power 30 mW, spot size 2 mm, energy 2 J per point. Irradiation twice a week, during the RT	Without information	Patients in control group presented increasing indexes of pain from weeks 1 to 4 ($p = 0.008$), remaining constant to week 7 ($p = 0.44$), whereas patients in laser group reported absence of pain during the entire cancer treatment ($p = 0.05$)
Carvalho et al., 2011 [19]	70 patients divided into two low-level laser therapy groups: G1 ($n = 35$) and G2 ($n = 35$)	Oral mucositis—a double-blind randomized study	Visual Analogue Scale. Evaluated daily during the RT	Group 1: (660 nm/15 mW/3.8 J/cm^2/spot size 4 mm^2). Group 2: (660 nm/5 mW/1.3 J/cm^2/spot size 4 mm^2). Applications were realized daily, 5 consecutive days per week, starting on the first day of RT	Without information	Up to the fifth day of evaluation, no patient in group 1 complained of oral pain, but in group 2, two patients reported pain. The highest pain scores occurred during the third week in both groups. Importantly, the mean intensity of pain was always higher for group 2 ($p = 0.004$)
Gautam et al., 2012 [20]	221 patients divided into 2 groups: laser group ($n = 111$); and placebo group ($n = 110$)	Oral mucositis—a triple blinded randomized controlled trial	Visual Analogue Scale. Evaluated daily during the RT	632.8 nm, power 24 mW, dosage 3.0 J/point, total dosage/session 36–40 J, spot size = 1 cm^2. Irradiations were performed prior to RT daily	Lesser number of patients required WHO steps analgesics (I, II, and III) in laser than placebo group. Also, mean duration of step III analgesia required was significantly lower in the placebo group	Average pain scores were consistently lower in laser than placebo group patients ($p < 0.0001$)
Gautam et al., 2012 [21]	110 patients divided into 2 groups: laser group ($n = 55$); and placebo group ($n = 55$)	Oral mucositis—a randomized controlled trial	Visual Analogue Scale. Evaluated weekly during the RT	He–Ne laser, 632.8 nm, 24 mW, ED = 3.5 J/cm^2. Application daily during the RT	Incidence of opioid analgesics use in laser and placebo group patients was 7% and 21%, respectively ($p < 0.001$)	Mean pain scores and patients experienced severe pain was consistently lower in laser than placebo group patients. Duration of severe oral pain experienced was also less in laser than placebo group
Gouvea de Lima et al., 2012 [22]	75 patients divided into 2 groups: laser group ($n = 37$;) and placebo group ($n = 38$)	Oral mucositis—a phase III randomized study	Visual Analogue Scale. Evaluated at weeks 2, 4, and 6 of RT	660-nm wavelength gallium aluminum-arsenide, 10-mW laser, with a spot size of 4 mm^2. The patients underwent LLLT applications daily before	The use of concomitant analgesic medication was similar between the LLLT and placebo arms (54% vs. 50% for nonsteroidal anti-inflammatory drugs	The proportion of patients presenting with severe pain remained similar between the LLLT and placebo arms throughout week 2 (5 of 37 patients in the LLLT arm

Table 1 (continued)

Study	Sample size	Study type	Method of pain analysis	Treatment design	Information about analgesics	Outcomes
				each fraction and during all RT sessions	and 8% vs. 8% for opioids, respectively)	and 5 of 38 patients in the placebo), week 4 (8 of 37 and 8 of 38, respectively) and 6 (8 of 37 and 8 of 38, respectively)
Antunes et al., 2013 [23]	94 patients divided into 2 groups. laser group ($n = 47$ patients) and placebo group ($n = 47$)	Oral mucositis—prospective, randomized, double-blind, placebo-controlled phase III trial	Visual Analogue Scale. Evaluated daily during the RT	InGaAlP (660 nm–100 mW–1 J–4-J/cm^2). LLLT was applied daily before every single fraction of RT	LLLT patients used fewer opioid analgesics ($p < 0.001$) throughout the treatment	Patients in the LLLT group had less severe oral pain, with significant intergroup differences
Oton Leite et al., 2013 [24]	60 patients divided into 2 groups. laser group ($n = 30$ patients); and placebo group ($n = 30$)	Oral mucositis—a double-blinded randomized study	Visual Analogue Scale. Evaluated daily during the RT	InGaAlP diode laser: 685 nm, 35 mW, 2 J/cm ^{2} and a spot laser of 0.028 cm^2. The energy delivered was 0.8 J per point of application. The first session was performed a week before the beginning of RT and the following sessions occurred daily, until the end of the treatment	Both groups received antifungal and/or analgesic medications when needed	Significant between-groups differences occurred in the intermediary and final evaluations ($p < 0.01$)
Gautam et al., 2015 [7]	46 patients divided into laser group ($n = 22$) and placebo group ($n = 24$) groups	Oral mucositis—randomized placebo-controlled trial	Visual Analogue Scale. Evaluated once a week during the RT	Helium–neon laser: 632.8 nm, 24 mW, power density of 0.024 W/cm^2, beam aperture diameter = 0.6 mm, beam spot size = 1 cm^2, energy density of 3.0 J/cm^2	Lesser number of patients required supplement opioid analgesics in laser (8.3%) than the placebo (35.7%) group	There were significantly lesser number of patients who experienced severe oral pain ($p = 0.023$) in laser than placebo at the end of RT. There was statistically significant difference in the duration severe oral pain ($p = 0.028$) between the two groups
Soares et al., 2018 [25]	42 patients divided into 2 groups: group 1: 660- and 808-nm LLLT ($n = 20$); and group 2: 660 nm LLLT ($n = 22$)	Oral mucositis—a parallel, single-blind, two-arm controlled study	Visual Analogue Scale. evaluated twice a week during RT	Group 1: both 660- and 808-nm wavelengths (300 J/cm^2, 9 J of total energy, 100 mW, spot size 3 mm^2. Group 2: only 660-nm wavelength (300 J/cm^2, 9 J of total energy, 100 mW, spot size 3 mm^2. Both treatments were performed twice a week	Group 1 significantly reduced analgesics prescription in comparison to group 2 Without information	No significant differences between groups 1 and 2 were observed according to pain scale. However, the combination of red and infrared LLLT reduced the prescription of the analgesics drugs

Table 1 (continued)

Study	Sample size	Study type	Method of pain analysis	Treatment design	Information about analgesics	Outcomes
Zhang et al., 2018 [6]	60 patients divided into 2 groups: laser group ($n = 30$); placebo group ($n = 30$)	Radiodermatitis—randomized, placebo-control study	Numerical rating scale. Evaluated daily during the RT	The irradiation time was 10 min, 2 times/day, the lampshade was 15–20 cm from the wound surface, and the wound temperature was 30 °C		There was a significant difference in the occurrence of skin pain at the end of second, third, and fourth weeks between the two groups ($p < 0.05$), but there was no significant difference at the end of fifth and sixth weeks between the two groups ($P > 0.05$)

LEL low-energy laser, *He–Ne* helium–neon, *LLLT* low-level laser therapy, *LT* laser therapy, RT radiotherapy, *InGaAlP* aluminum gallium indium phosphide, *AH* aluminum hydroxide, *GaAlAs* gallium aluminum-arsenide

(6.6%) [17] study was considered to have high risk of bias for random sequence generation, 3 (20%) [16, 17, 24] for allocation concealment, 2 (13.3%) [15, 16] for blinding of participants and personnel, 3 (20%) [16, 24, 25] for blinding of outcome assessment, 3 (20%) [6, 18, 22] for blinding all-cause mortality, 1 (6.6%) [16] for incomplete outcome data (long term), and no studies for incomplete outcome data (short term) or selective outcome reporting. In relation to unclear risk of bias, 1 (6.6%) [15] study was considered for random sequence generation, 4 (26.6%) [6, 15, 18, 23] studies for allocation concealment, 4 (26.6%) [6, 14, 17, 18] studies for blinding of participants and personnel, 4 (26.6%) [6, 15, 17, 18] studies for blinding of outcome assessment, and no studies for blinding all-cause mortality, for incomplete outcome data (short term), for incomplete outcome data (long term), and for selective outcome reporting (Fig. 2).

Statistical analysis

Due to a lack of methodological uniformity in included studies, a meta-analysis of obtained results was not feasible. Therefore, the results are descriptively summarized in this review.

Discussion

In terms of mechanisms, PBMT is believed to have a photochemical effect on the oral mucosae cells. Apparently, a core mechanism of action develops in the mitochondrial cellular level, where light is absorbed in cytochrome c oxidase, a key protein involved in cell metabolism that when stimulated by light can provide an anti-inflammatory effect as well as analgesia. These molecular and cellular events have been described in a variety of cell types, such as fibroblasts, lymphocytes, osteoblasts, stem cells, and smooth muscle cells) [26–28]. These primary reactions stimulate a cascade of secondary reactions at cellular level involving intracellular signaling and leading to stimulation of cytokine reactions, release of growth factors [29, 30], increased metabolism, and, therefore, cell proliferation [31–33]. Because of the benefits related to stimulation of tissue regeneration, inflammation reduction, and pain control, PBMT has been increasingly used in the management of toxicities related to cancer treatment [34].

Based on this systematic review, it appears that PBMT represents a safe method for pain reduction and control. It also seems to reduce the need for analgesic medication during the treatment of HNC patients. Prevention and treatment of OM with PBMT comprised the majority of the studies selected in this review, since only one study involved radiodermatitis.

Opioids are the most powerful drugs used to treat severe pain. However, their use is hampered by side effects such as respiratory depression, nausea, clouding of consciousness,

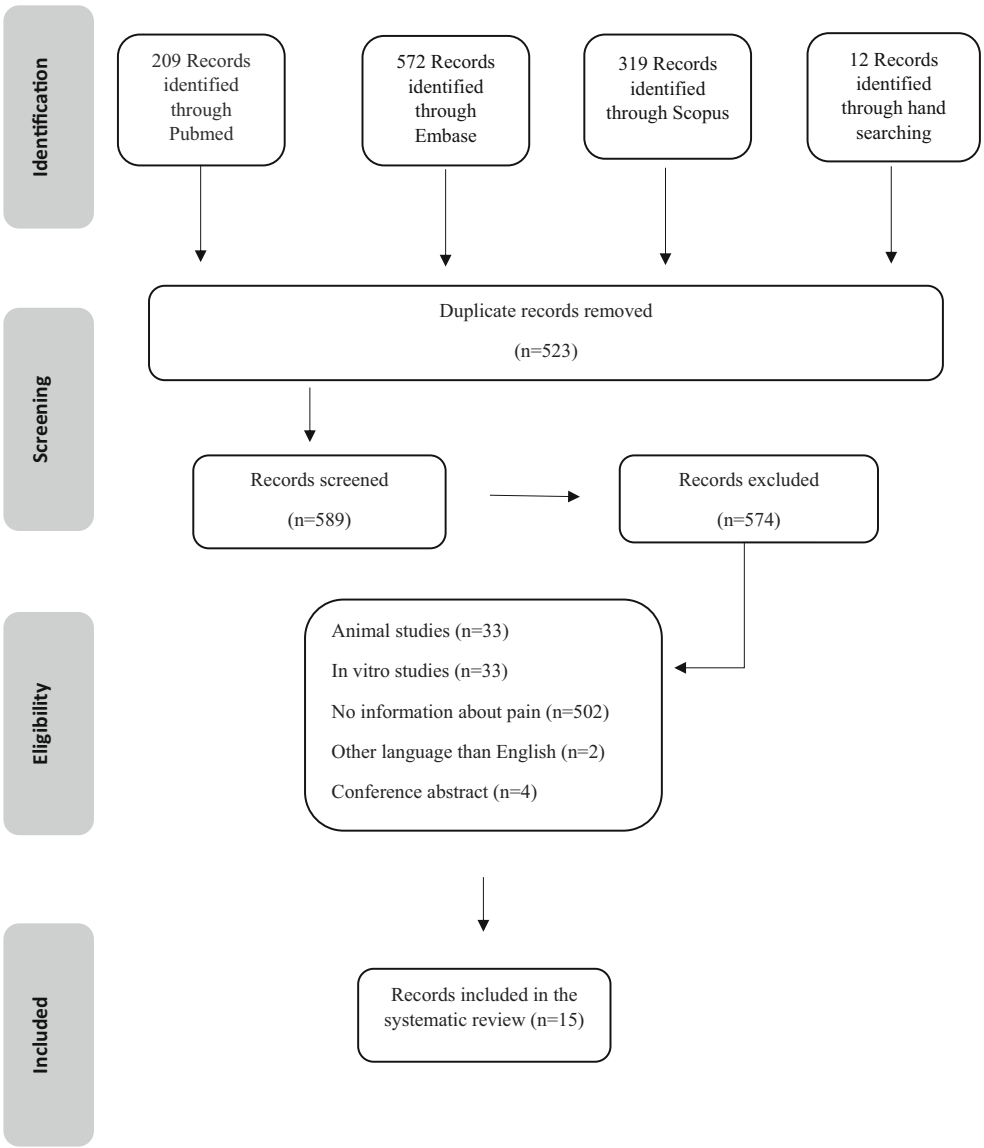

Fig. 1 The selection process of the studies

constipation, addiction, and tolerance [35]. The prescription of opioids has also been affected by the current opioid crisis worldwide. Thus, alternative ways to control pain are being investigated.

PMBT has been widely used to prevent and control OM. Because a large part of the pain in the head and neck area present during the treatment of the HNC patients is associated with OM, the prevention or the reduction of severity of this oral complication could indirectly affect pain control. The mechanisms of action of PBMT in OM have been attributed to anti-inflammatory and analgesic effects of the laser light such as increased local vascularity and reepithelialization of tissue, transformation of fibroblast into myofibroblasts leading to mucosal healing [36]. The PBMT mechanism involved in pain control can be due to the release of endorphin and encephalin or due to cell membrane depolarization, blocking the nervous impulse and fast axonal flow [37]. Chow et al. [13], provided recent evidence through a combination of a clinical trial and experimental data that the mechanisms of pain control with PBMT use may be related to the inhibition of nerve function in vivo, in situ, ex vivo, and in culture. The animal studies using noxious stimuli indicated nociceptor-specific inhibition. Additional data provided direct evidence of local conduction block, leading to inhibited translation of pain centrally. These changes are reversible with no side effects or nerve damage [38].

One of the most common and debiting toxicities related to HNC treatment is the OM, which occurs in nearly all patients receiving head and neck radiation therapy [38–40]. It presents as erythema and/or ulceration of the oral mucosa and is typically very painful, requiring opioid analgesics, impairing nutritional intake and QoL [34].

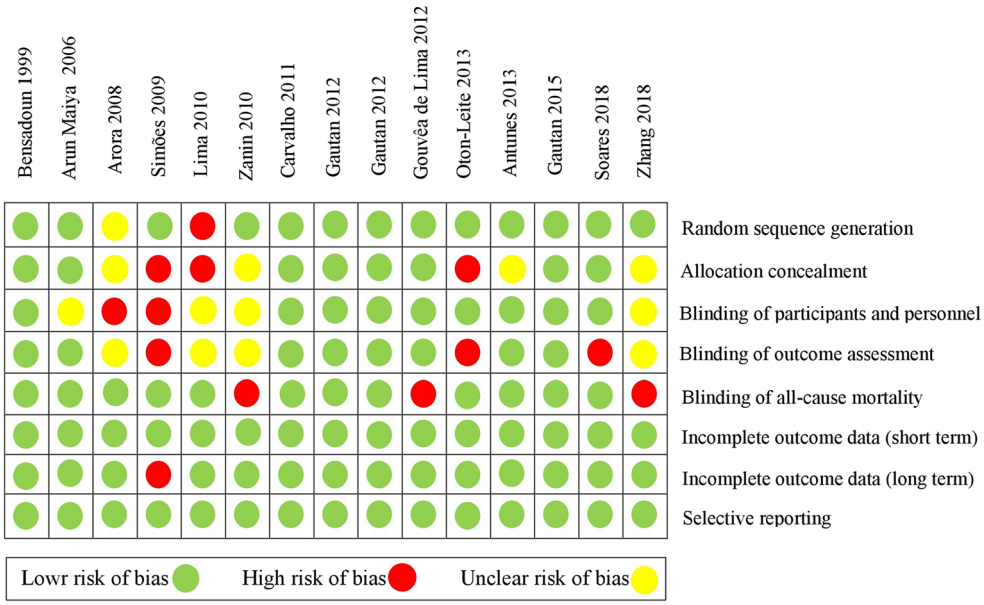

Fig. 2 Risk of bias of the selected articles. If the item was present in the selected article, it was judged as "low risk of bias" (green circle). If the item was not presented in the selected article, the paper was judged as "high risk of bias" (red circle). If this information for the corresponding item was not available in the article, the paper was classified as "undefined risk of bias" (yellow circle)

A systematic review and meta-analysis [35] published in 2011 based on 11 randomized controlled trials in HNC patients treated with chemotherapy and/or radiotherapy concluded that there was consistent evidence that PBMT applied with doses of 1–6 J per point reduced OM prevalence, severity, and pain duration. The present systematic review evidenced similar results. Ten of the 14 selected OM studies addressing the effect of PBMT on pain resulting from OM compared study subjects with a placebo group. All these 10 studies showed in the placebo groups increased severity and duration of OM and a significant higher mean score of pain [7, 13–15, 18, 20–24].

Simões study was designed with three different protocols of PBMT (the protocols involved either low-power laser once or three times a week or association of high-/low-power lasers three times a week) [16], and Soares et al.'s study [25] compared two different PBMT protocols (using the combination of red and infrared and only red PBMT)—both applied with the same frequency (twice a week). Both studies showed that fractioned PBMT could lead to more detectible effects related to pain control than one-time irradiation, no matter the wavelength.

One study demonstrated that PBMT significantly decreased OM-related pain outcomes when compared to AH topical use [17]. There is evidence that AH promote mucus production and local production of prostaglandin, increasing blood flow, mitotic activity, and surface migration of cells, thus providing binding of epithelial growth factors and basic fibroblastic growth factors to tissues. Despite these benefits, some authors indicated this drug only in the absence of other resources such as PBMT [34, 41].

Other common toxicity related to radiotherapy for HNC is the radiation-related dermatitis or radiodermatitis. It is a skin reaction to radiation therapy characterized by erythema, dry or moist desquamation, and even ulceration [42]. The condition impacts adversely not only in cosmetics, function, and QoL [43, 44] but also on treatment outcomes; radiation schedules may be interrupted especially in patients who develop secondarily infected dermatitis [45]. The prevention and treatment remains a challenge and there is no evidence-based standard approach for the prevention and treatment of radiation dermatitis, although several medications have been proposed such as topical agents, dressings, and radioprotectors [46]. For the treatment of radiodermatitis, based on the effects of PBMT on the epidermis and dermis (reduced inflammation and improved wound healing) and on the shared similarities in pathobiology with OM, it seems reasonable to assume that PBMT may reduce the prevalence and/or severity of radiation dermatitis [47, 48].

The only study founded regarding the effects of PBMT on pain related to radiodermatitis on HNC patients showed that the control group presented higher score of pain in the second, third, and fourth weeks of treatment [6]. Despite the lack of information about the effect of PBMT in pain control of HNC patients, several phase III studies in breast cancer patients treated with PBM showed promising results in relation to prevention, treatment, and reduction of patients' symptoms [48, 49].

Only 7 studies specifically evaluated the need of analgesic medication associated with OM pain control [7, 15, 20–23, 25]. Six of these studies suggested that PBMT seems to be efficient in reducing the need for pain medications, while 1 study did not show significant decrease pain in patients submitted to PBMT; however, this study showed unplanned radiation therapy interruptions due to severe OM in 6 patients in the placebo arm and none in the PBMT arm, indicating a negative impact in terms of pain outcomes [50].

Conclusions

To our knowledge, this is the first systematic review designed to evaluate the body of evidence regarding the efficacy of PBMT on pain control and reduction in the use of analgesics due to toxicities caused by HNC treatment. In spite of the scarce literature available, it appears that PBMT should be considered effective in reducing pain and the need for analgesic medication in patients undergoing HNC treatment. Considering the current epidemic of narcotic overdose, finding alternative ways to control pain is a must. Further randomized clinical trials should be conducted to assess the efficacy of PBMT in the management of HNC treatment toxicities other than OM and radiodermatitis. The small number of studies that fulfilled the inclusion criteria was the primary limitation of this systematic review. Another significant limiting factor of this study is the lack of standardization for PBMT protocols available in the pertinent literature, which makes it difficult to establish comparisons between clinical studies.

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Compliance with ethical standards

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

Control of the data The authors have full control of all primary data and agree to allow the journal to review our data if requested.

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