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Does laser photobiomodulation prevent hyposalivation in patients undergoing head and neck radiotherapy? A systematic review and meta-analysis of controlled trials

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ABSTRACT

Introduction: Head and neck radiotherapy can cause hypofunction of the salivary glands. Many studies report that laser photobiomodulation (PBM) is able to minimize radiation-induced hyposalivation, yet there is no consensus about its effects.

Objective: To carry out a meta-analysis of controlled clinical trials that used PBM to prevent radiation-induced hyposalivation. Methods: A systematic search was performed through Embase, Medline/PubMed, Cochrane, EBSCO, Scopus, LILACS and Web of Science databases. The strategy included comparisons of the effect of PBM with placebo/clinical follow-up on unstimulated and/or stimulated salivary flow in patients undergoing head and neck radiotherapy.

Results: Six clinical trials were included, five of which were used for meta-analysis. Evidence was observed between the use of PBM and increased unstimulated salivary flow (MD 0.20 mL/min, 95 % Cl 0.10−0.30, $I^2 = 96$ %, $p < 0.00001$) and in stimulated salivary flow (MD 0.27 mL/min, 95 % CI 0.08−0.46, $I^2 = 95$ %, $p < 0.00001$).

Conclusion: PBM appears to minimize radiation-induced hyposalivation.

1. Introduction

Saliva is a complex fluid composed mainly of water, electrolytes (sodium, potassium, magnesium, calcium, bicarbonate, phosphate and others), enzymes, proteins and nitrogenous components such as urea and ammonia (Pedersen et al., 2018; Kubala et al., 2018). Due to its composition, saliva is important for the maintenance of oral health, playing a fundamental role in lubrication and protection in the oral cavity, as well as assisting in dental integrity by the des and remineralization process. It has antimicrobial activity and aids in taste and digestion (Humphrey and Williamson, 2001). Under normal circumstances, it is estimated that an individual produces an average of 0.3−0.4 ml/min of unstimulated saliva and 2 mL/min of stimulated saliva (Kubala et al., 2018; Proctor, 2016). Hyposalivation is considered when salivary flow is less than 0.1 mL/min (Pedersen et al., 2018; Humphrey and Williamson, 2001; Ericsson, 1959) for unstimulated saliva and 0.7 mL/min for stimulated saliva (Pedersen et al., 2018; Ericsson, 1959). Sometimes salivary dysfunctions may be accompanied by symptoms of dry mouth, called xerostomia. The presence of xerostomia is not predictive of hyposalivation, since both conditions can manifest themselves, independently of each other. Nevertheless, the greater the hyposalivation, the greater the patient's tendency to manifest xerostomia (Pedersen et al., 2018; Humphrey and Williamson, 2001).

Radiotherapy is a cancer treatment modality that uses the emission of ionizing radiation to treat malignant neoplasms. Usually, for head and neck tumors, the radiation distributed at the tumor site varies between 50 and 70 Gy, divided into daily doses of 1.8–2 Gy (Chambers et al., 2004). The antineoplastic mechanism occurs by the direct damage on DNA structure or indirectly, through the production of free radicals that act on DNA integrity, especially in cells with high mitotic potential (Baskar et al., 2014). Although salivary gland cells have low turnover, these structures are highly sensitive to radiotherapy (Norberg and Lundquist, 1989; Konings et al., 2005). The exact reason for this sensitivity is not yet clear (Konings et al., 2005; Abok et al., 1984; Pinna et al., 2015). It is possibly related to multiple mechanisms of action, such as

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damage to membrane receptors (Konings et al., 2005), changes in the expression of aquaporins (Araujo et al., 2018) and dysregulation of cytoplasmic granules (Abok et al., 1984). However, activation of p53 transcription induced by DNA damage appears to play a key role in acinar cell radiosensitivity. The accumulation of the p53 protein activates the up-regulated modulator of apoptosis (PUMA) and Bcl-2-associated X protein (Bax) target genes (Avila et al., 2009; Grundmann et al., 2009). These genes have a pro-apoptotic effect, resulting in a decrease in the number of acinar cells in a dose-dependent relationship (Cheng et al., 2011; Acauan et al., 2015). Permanent changes may be evidenced with doses higher than 30 Gy (Chambers et al., 2004).

Since salivary glands are often within the radiation portal, patients develop hyposalivation and xerostomia. It is estimated that about 80–93 % of patients undergoing head and neck radiotherapy will develop some degree of xerostomia (Pinna et al., 2015; Jensen et al., 2010 a). Usually, these patients complain of difficulty in oral lubrication that could lead to some oral disorders, such as dysphagia, dysgeusia and burning sensation. Due to the low amounts of enzymes and immunoglobulins present in the oral mucosa, these individuals are more susceptible to the development of oral infections such as candidiasis and dental caries (Pinna et al., 2015). In addition, patients often report worsening quality of life due to radiation-induced hyposalivation (Jensen et al., 2010 a).

To date, there is no effective treatment for radiation-induced xerostomia and hyposalivation. Although some alternatives, such as the use of muscarinic agonists and amifostine, demonstrate beneficial results in the treatment of xerostomia and hyposalivation, they have side effects that are poorly tolerated by patients (Ma et al., 2019). Furthermore, preventive methods for radiation-induced salivary gland dysfunction have no proven evidence (Jensen et al., 2010 b). Thus, few recommendations are available for protection of glandular function during radiotherapy.

Among the preventive modalities of radiation-induced xerostomia and hyposalivation, laser photobiomodulation (PBM) has gained prominence because it is a non-toxic treatment, painless and well accepted by patients (Lopes C de et al., 2006; Simões et al., 2010a; Oton-Leite et al., 2013; Campos et al., 2009; Saleh et al., 2014; Gonnelli et al., 2016a; Palma et al., 2018; Libik et al., 2017; Palma et al., 2017; González-Arriagada et al., 2018). It is a modality that converts the photon energy into biological stimuli. The exact mechanism of action of PBM on living tissues is still unclear, however evidence has suggested that complex IV of the respiratory chain, also known as cytochrome c oxidase, is a photoceptor of light at the red/infrared wavelength (Karu, 1989). In this way, laser irradiation on tissues would cause an excitation of cytochrome c oxidase, leading to increase in electron flow in the respiratory chain, accelerating the synthesis of adenosine triphosphate (ATP) (Karu, 1989; Farivar et al., 2014; Hamblin and Demidova, 2006). As a consequence of ATP accumulation, there is a change in cell metabolism associated with a higher production of cAMP and a higher intra-cell concentration of Ca^{2+} secondary to the activation of ATP-dependent ion pumps. In addition, the change in the redox state caused by laser radiation also appears to increase a transient production of reactive oxygen species (ROS). This brief increase in ROS is sufficient to activate the nuclear factor kappa B (NF-kB), a protein complex that plays an important role in the immune response, inflammation and apoptosis (Hamblin and Demidova, 2006; AC-H et al., 2009). In this way, PBM is able to stimulate tissue repair, increase DNA and RNA synthesis, pain relief, anti-inflammatory control and prevent apoptosis (Karu, 1989; Mussttaf et al., 2019).

Many studies have focused on PBM as a possible treatment for salivary gland dysfunction. Studies in animal models suggest that PBM may increase salivary flow (Simões et al., 2008), increase protein content in parotids (Simões et al., 2009a), modulate antioxidant systems (Ibuki et al., 2013; Simões et al., 2010b; Campos et al., 2014), regulate glycemic control in salivary glands (Ibuki et al., 2013; Simões et al., 2009b), reduce lipid accumulation in this tissue (de Castro et al., 2018) and increase myoepithelial cell proliferation (Uzêda-e-Silva et al., 2017). Human studies have shown that PBM is able to decrease xerostomia symptoms during chemotherapy (Arbabi-Kalati et al., 2013), increase unstimulated salivary flow in patients with medically induced hyposalivation (Terlević Dabić et al., 2016) and reestablish some degree of salivary flow in patients with idiopathic xerostomia (Lončar et al., 2011).

Due to its biological effects, PBM is used as an auxiliary method to treat the side effects of head and neck radiotherapy (Campos et al., 2009). This modality is well established, especially in the treatment of mucositis, demonstrating noticeable effects on pain and reduction of tissue damage (Oberoi et al., 2014; Zadik et al., 2019). However, its effects on salivary flow are not yet well understood. Although many studies show promising results in increasing salivary flow, these effects also present controversy among authors (Saleh et al., 2014; Palma et al., 2017). Therefore, the aim of this study was to conduct a systematic review and meta-analysis of controlled clinical trials to assess whether PBM used concomitantly with head and neck radiotherapy has the ability to prevent salivary gland hypofunction.

2. Methods

2.1. Selection of articles

This study was previously reviewed and registered on the PROSPERO platform under registration number CRD42019139620.

We conducted a systematic review of studies that evaluated the effect of PBM on salivary hypofunction to clarify the following question: "Can PBM prevent head and neck radiotherapy-induced hyposalivation?" Therefore, a systematic literature search was performed according to the PRISMA guidelines, using the following databases: Embase, Medline/PubMed, Cochrane, EBSCO, Scopus, LILACS and Web of Science. The search strategy was elaborated on the PubMed platform and adapted to the other databases, using the following mesh terms: “Low-level Laser Therapy,” "Radiotherapy," "Hyposalivation," "Xerostomia," "Hypersalivation," "Saliva" and "Salivary Glands". Synonyms of the mesh terms were also included to broaden the literature search.

The following PICO question was established:

Population – Patients undergoing head and neck radiotherapy.

Intervention – PBM.

Control – Sham laser, laser of different wavelengths, clinical follow-up or drug monitoring.

Outcome – Average stimulated and/or unstimulated salivary flow rate.

No filters related to the date of publication of the studies were added. The last search was made on July 4, 2020.

EndNote X7 software was used for article selection. The analysis of titles and abstracts of the studies was performed by two independent evaluators. Cases of disagreement between peers were resolved by the decision of a third evaluator. Included studies were reviewed from the reading of the full article, also independently by both reviewers and the third reviewer in case of disagreements.

2.2. Inclusion and exclusion criteria

Controlled clinical trials that used PBM prophylactically for glandular hypofunction induced by head and neck radiotherapy were selected. Studies should include at least PBM dose, wavelength, method and frequency of assessment of hyposalivation, substance or technique used as a control and average salivary flow over at least two analysis periods: before or until the third radiotherapy session and at the end of radiotherapy treatment.

Studies that used patients diagnosed with diabetes, Sjögren’s syndrome or collagen diseases were excluded.

2.3. Outcome assessment

The primary outcome of this review was the average salivary flow expressed in ml/min. We considered studies that evaluated both stimulated and unstimulated salivary flow by the spitting method (Navazesh, 1993). For stimulated saliva samples, only studies using masticatory or taste salivary stimuli were selected.

Secondary outcomes included symptoms of xerostomia and salivary composition. In the first case, the symptom should be expressed by score using at least one of the following questionnaires: "Treatment Emergent Symptom Scale" (TESS), Visual Analog Scale (VAS) and Xerostomia Inventory (XI).

2.4. Data extraction

Two authors working independently screened the abstract and title of the research results. The differences were resolved by consulting a third author. All potentially relevant articles were investigated by reading the full text. If there was a difference of opinion, the third author was consulted and made the final decision. The Kappa coefficient was used to evaluate the agreement between the two evaluators during the title and abstract classification and in the reading of the full studies.

Data extraction was also performed by the two independent evaluators. The divergences of results were discussed and resolved by agreement between the evaluators. The following data were collected: study title, study author, year of publication, study design, age and gender of participants, definition of control group, mean and standard deviation of salivary flow rate, mean of xerostomia score, mean values of salivary components, salivary flow evaluation frequency, xerostomia evaluation frequency, salivary composition evaluation frequency, type of laser used, spot size, irradiation points, energy per point, energy per session, power, dose, wavelength, mode of application, exposure time, and periodicity of PBM applications. In case of missing data in the studies, the corresponding author was contacted to retrieve such information.

2.5. Risk of bias

The risks of bias in the studies included were assessed according to the criteria of the Cochrane Manual for the Development of Systematic Intervention Reviews version 5.1.0 (Higgins et al., 2019), using the Review Manager software (RevMan) version 5.3. This tool is divided into two parts of judgment for each study, where seven domains are presented: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. In the first step, each domain is classified according to the judgment of risk of bias in "high risk," "low risk" or "unclear risk." The second part refers to the descriptive judgment of the authors in each domain. The judgments were made by two evaluators. Disagreements were resolved by discussion between the evaluators.

2.6. Meta-analysis

The association between PBM and outcomes was evaluated using meta-analysis. Relative effect was assessed by mean difference (MD) using the inverse variance method and assigning 95 % confidence intervals. For the analysis, the means of the stipulated effects of the studies and their respective standard deviations were used. High heterogeneity was explored using group divisions. Chi-square (χ^2) and I-square (I^2)

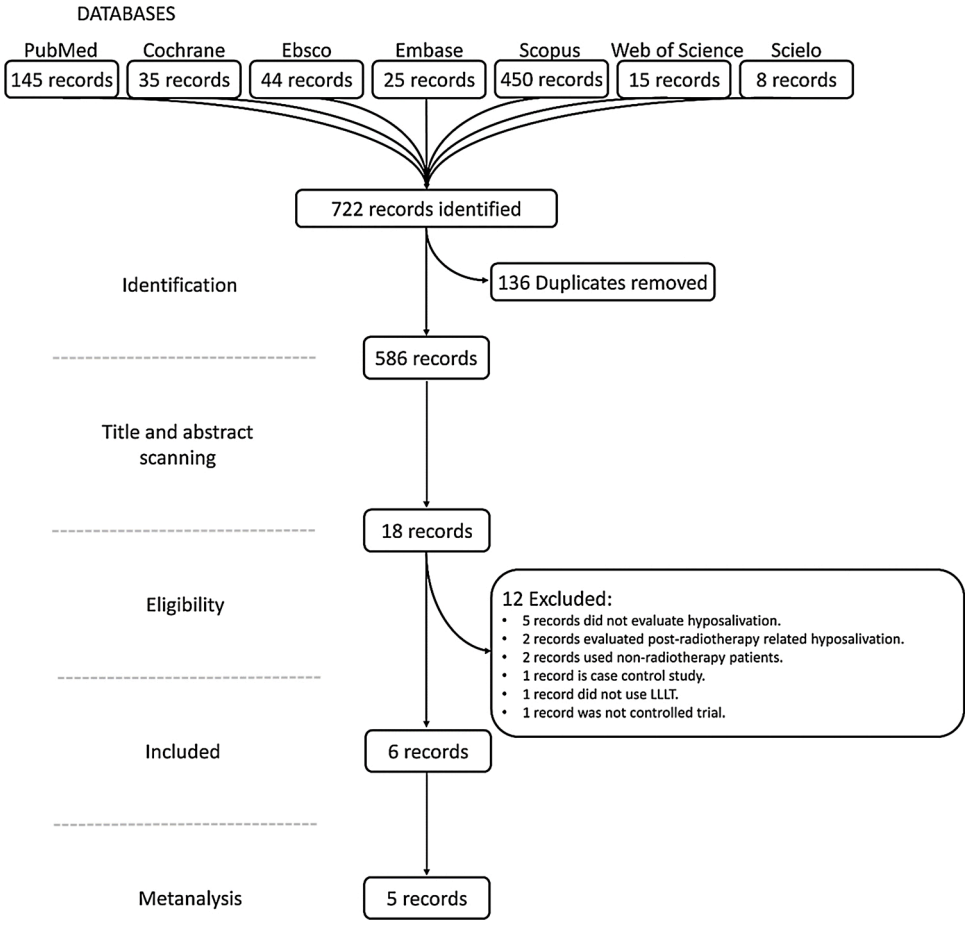

Fig. 1. Flowchart of the systematic review and meta-analysis according to the PRISMA guidelines.

were calculated to assess the heterogeneity of the studies, and values greater than 50 % were considered having substantial heterogeneity. In these cases, the random effect was used. The high heterogeneity among studies were explored by using subgroups meta-analysis.

2.7. Quality of evidence

Quality of evidence was assessed using the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) system, as recommended in the Cochrane Manual for the Development of Systematic Intervention Reviews version 5.1.0 (Higgins et al., 2019). This tool allows the evaluation of the quality of each outcome according to a 4-level rating: very low, low, moderate and high. The initial classification of the quality of evidence is generated according to the study design (randomized controlled trial or observational study) and may be reduced according to methodological limitations (risk of bias), inconsistency, indirect evidence, inaccuracy and publication bias, or may be increased depending on magnitude of effect, dose-response gradient and residual confounders. The evaluation was performed independently by two evaluators using the GRADEpro program. In cases of disagreement, a third reviewer was consulted for resolution. The reason for the quality reduction due to each factor is described in the table footer.

3. Results

3.1. Literature search

A total of 722 studies were found in the databases, of which 136 were duplicate articles, resulting in a total of 586 studies. After the titles and abstracts were read by the evaluators, 568 studies were excluded because they were not associated with the theme. Of the 18 studies evaluated in full, 12 were excluded due to the following reasons: 2 studies (Saleh et al., 2014; Palma et al., 2017) were performed on patients who had already completed head and neck radiotherapy; 5 studies (Moraes et al., 2009; Oton-Leite et al., 2012, 2015; Gautam et al., 2015; da C. Lino et al., 2011) did not evaluate salivary flow; 1 study (González-Arriagada et al., 2018) was a retrospective case-control study; 1 study (Bossi et al., 2016) did not use PBM; 2 studies (Vidović Juras et al., 2010; Brzak et al., 2018) used patients who were not irradiated in the head and neck region; and 1 study was not controlled (Simões et al., 2010a). Finally, 6 studies (Lopes C de et al., 2006; Oton-Leite et al., 2013; Gonnelli et al., 2016a; Libik et al., 2017; Gonnelli et al., 2016b; Louzeiro et al., 2020) were selected for this review, 5 (Lopes C de et al., 2006; Oton-Leite et al., 2013; Libik et al., 2017; Gonnelli et al., 2016b; Louzeiro et al., 2020) of which were included for meta-analysis (Fig. 1). The agreement between authors during the classification of titles and abstracts was considered intermediate (K = 0.75), and during the reading of the full articles, it was classified as perfect (K = 1).

3.2. General characteristics of the studies

Of the six studies included, five were available in English and one in Portuguese (Lopes C de et al., 2006). Only two studies (Oton-Leite et al., 2013; Louzeiro et al., 2020) were described as a randomized controlled trial. The study sample ranged from 21 (Libik et al., 2017; Louzeiro et al., 2020) to 60 participants (Lopes C de et al., 2006) and no sex restrictions were observed (Table 1). In three studies (Gonnelli et al., 2016a, b; Louzeiro et al., 2020), the red and infrared wavelengths were used for intra and extraoral applications, respectively, while the others used only the red wavelength. The modalities used in the control groups included pharmacological treatment based on 0.15 % benzydamine hydrochloride mouthwash (Libik et al., 2017), sham laser (Oton-Leite et al., 2013; Louzeiro et al., 2020) and clinical follow-up (Lopes C de et al., 2006; Gonnelli et al., 2016a, b).

A detailed description of the characteristics of the PICO strategy and information on the type of laser used, dosimetry and frequency of

Table 1
General characteristics of the studies.

Author/ year	Age	Nº of subjects in experimental/ control group	Criteria for evaluation of salivary conditions	Frequency of assessment of salivary flow rate
Lopes C de et al., 2006	28–88	31/29	Stimulated (acid stimulation) and unstimulated salivary flow rate.	At day 1, at the end and after 30 days of radiotherapy treatment.
Oton-leite et al., 2013	30–81	30/30	Stimulated (acid stimulation) and unstimulated salivary flow rate.	1 week before starting radiotherapy, and after 15 and 30 sessions of radiotherapy.
Gonnelli et al., 2016a		13/10	Stimulated (acid stimulation) and unstimulated salivary flow rate.	After the first session of radiotherapy/ chemotherapy and 30 after days the end of treatment.
Gonnelli et al., 2016b	35–74	17/10	Unstimulated salivary flow rate.	Before radiochemotherapy, at the 15th radiotherapy session, after the last radiotherapy session, and at 30 and 90 days after the end of cancer treatment.
Libik et al., 2017	–	11/10	Xerostomia Inventory. Unstimulated salivary flow rate.	Before the first radiotherapy/ radiochemotherapy session, and after the 15th session and the last session.
Louzeiro et al., 2020	48–74	10/11	Simulated (mechanical stimulation) and unstimulated salivary flow rate. Unstimulated and stimulated salivary pH. Visual analog scale of xerostomia. Treatment emergent symptom scale. Stimulated salivary concentration of total proteins, calcium, sodium, potassium and chloride. Catalase and amylase activity of stimulated saliva.	Before the first radiotherapy/ radiochemotherapy session, at the 15th radiotherapy session, after the last radiotherapy session and after 60 days of cancer treatment.

Table 2
Characteristics of the studies according to PICO question.

Author/year	Population	Intervention	Definition of control group	Main outcome (mean salivary flow rate)
Lopes C de et al., 2006	Patients under radiotherapy	PBM	Clinical follow-up	Decrease of mean stimulated and unstimulated salivary flow rate was observed at the end and after 30 days of radiotherapy in the control group ($p < 0.001$), whereas the laser group did not show statistically significant changes in the same periods. The laser group displayed a significantly higher mean stimulated and unstimulated salivary flow rate at the end and after 30 days of radiotherapy compared with control group ($p < 0.001$).
Oton-leite et al., 2013	Patients under radiotherapy	PBM	Sham laser	Both laser group and control group showed a significant decrease in stimulated and unstimulated salivary flow rate ($p < 0.001$). This decrease was more pronounced in the control group, showing a statistical difference for unstimulated ($p = 0.002$) and stimulated ($p = 0.004$) salivary flow rate for the intermediate period and for the final period ($p < 0.001$).
Gonnelli et al., 2016a	Patients under radiochemotherapy	PBM	Clinical follow-up	Higher mean stimulated ($p = 0.0131$) and unstimulated ($p = 0.0143$) salivary flow rate was observed in the laser group compared with the control group at 30 days after the end of radiotherapy.
Gonnelli et al., 2016b	Patients under radiochemotherapy	PBM	Clinical follow-up	A significantly higher mean value of unstimulated salivary flow rate was observed in the laser group compared with control group after the 15th radiotherapy session ($p = 0.0159$), after the last radiotherapy session ($p = 0.0149$) and 30 days after radiotherapy ($p = 0.0239$).
Libik et al., 2017	Patients under radiochemotherapy	PBM	Benzidamine mouthwash 0,15 %	Both control and laser group showed a decrease in unstimulated salivary flow rate after the 15th radiotherapy session ($p < 0.05$). Besides, the laser group showed a partial recovery of salivary secretion after the last radiotherapy session and a significantly higher mean unstimulated salivary flow rate compared with control group ($p < 0.05$).
Louzeiro et al., 2020	Patients under radiochemotherapy	PBM	Sham laser	Both laser group and control group showed a significant decrease in unstimulated salivary flow rate after the last radiotherapy session ($p < 0.05$), and decrease in the stimulated salivary flow after the 15th radiotherapy session ($p < 0.05$). No significant difference was observed between the groups during and after radiotherapy ($p > 0.05$).

application of each study are available in Tables 2 and 3, respectively.

3.3. Effect of photobiomodulation on salivary flow rate

3.3.1. Unstimulated salivary flow

Five records reported an association between PBM and a higher salivary flow rate (Lopes C de et al., 2006; Oton-Leite et al., 2013; Gonnelli et al., 2016a; Libik et al., 2017; Gonnelli et al., 2016b) and one study reported no association (Louzeiro et al., 2020). Differences in effect between the laser group and placebo could be assessed at different times throughout the radiotherapy treatment. At baseline, no statistical difference between PBM and control were observed in the five studies ($p > 0.05$). However, after the 15th session of radiotherapy, Oton-Leite et al. (2013); Gonnelli et al. (2016a), (2016b) and Libik et al. (2017) observed an increased salivary flow capacity in the laser group compared to the control ($p = 0.004$, $p = 0.0159$ and $p < 0.05$, respectively). This difference was also described in the last radiotherapy session by Lopes et al. (Lopes C de et al., 2006) ($p < 0.001$), Oton-Leite et al. (2013) ($p < 0.001$), Gonnelli et al. (2016a) ($p = 0.0143$), Gonnelli et al. (2016b) ($p = 0.0149$) and Libik et al. (2017) ($p < 0.05$), and 30 days after the end of radiotherapy by Lopes et al. (Lopes C de et al., 2006) ($p < 0.001$) and Gonnelli et al. (2016b) ($p = 0.0239$). However, after 60 days, (Louzeiro et al., 2020) did not observe differences between the groups ($p = 0.301$), and neither did Gonnelli et al. (2016b) after 90 days ($p = 0.3798$) (Table 2).

3.3.2. Stimulated salivary flow

Four records evaluated the effect of PBM on stimulated salivary flow (Lopes C de et al., 2006; Oton-Leite et al., 2013; Gonnelli et al., 2016a; Louzeiro et al., 2020). At baseline, one study (Louzeiro et al., 2020) reported a significantly higher salivary flow rate in the control group than the laser group ($p = 0.029$), while in the other three studies no difference could be noticed between the groups ($p > 0.05$). In this same study, no significant difference between groups was observed in the 15th radiotherapy session ($p = 0.591$), the last radiotherapy session ($p = 0.980$) and after 60 days ($p = 0.900$). However, in the study by Oton-Leite et al. (2013), the laser group showed significantly higher flow compared to the control group ($p = 0.002$) at the 15th radiotherapy session. At the end of treatment, a higher salivary flow in laser group was also noted in the studies by Lopes C de et al. (2006) ($p < 0.001$), Oton-Leite et al. (2013) ($p < 0.001$) and Gonnelli et al. (2016a) ($p = 0.0131$) and after 30 days of radiotherapy in the study by Lopes C de et al. (2006) ($p < 0.001$).

3.4. Effect of photobiomodulation on xerostomia

Xerostomia was evaluated by Libik et al. (2017), through the XI instrument, and by Louzeiro et al. (2020), through the TESS and VAS instruments. Worsening of symptoms was observed in laser and control groups at the 15th radiotherapy session and the end of treatment in both studies ($p < 0.05$), and after 60 days in the study by Louzeiro et al. (2020) ($p < 0.05$). No significant difference between the groups was observed in any period of the studies ($p > 0.05$).

3.5. Effect of photobiomodulation on sialochemical changes

Sialochemical changes were assessed only in the study by Louzeiro et al. (2020). In this study, stimulated and unstimulated salivary pH were evaluated at baseline, 15th session, last session and after 60 days of radiotherapy. Also, concentration of calcium, sodium, potassium, chloride, total proteins and catalase and amylase activity were evaluated in stimulated salivary samples following the same periods of evaluation. PBM showed a significant increase in unstimulated salivary pH at the last radiotherapy session compared to the control group ($p = 0.037$). On the other hand, both control and laser groups showed a significant increase in chloride at the last radiotherapy session ($p < 0.001$) and after 60 days of treatment ($p = 0.015$), and a decrease in amylase activity was observed at the last radiotherapy session ($p < 0.05$) compared to baseline. No significative differences between laser and control groups were observed regarding salivary composition and enzymatic activity ($p > 0.05$).

3.6. Meta-analysis

Comparative analyses of unstimulated salivary flow are shown in Fig. 2. PBM had a significant effect on increasing salivary flow compared

Table 3
Laser therapy parameters of the studies.

Author/ year	Laser type	Spot size (cm^2)	Points of application	Energy per point (J)	Energy per session (J)	Power (mW)	Dose (J/ com^2)	Λ (nm)	Mode of application	Time of exposure per point (s)	Frequency of application
Lopes C de et al., 2006	Diode (InGaAlP)	0.04	3 points on each parotid gland; 1 point on each submandibular gland; 2 points on each buccal mucosa; 2 points on the floor of the mouth; 2 points on tongue; 1 point on each tonsillar pillar; 1 point on the uvula.	2.03	38.57	35	50.75	685	Punctual, in contact mode	58	Daily, concomitantly with radiotherapy treatment.
Oton-Leite et al., 2013	Diode (InGaAlP)	0.028	8 points on each buccal mucosa; 3 points on each labial mucosa; 2 points on palatine folds; 10 points on each tongue edge; 8 points on the dorsum of the tongue; 3 points on the soft palate; 2 points on the mouth floor; 1 point on each labial commissure.	0.8	47.2	35	2	685	Punctual, in noncontact mode, 2 cm away from the surface	25	Starting daily a week before radiotherapy starts and before each radiotherapy session until the end of treatment.
	Diode (GaAlAs)		6 points extraorally on each parotid gland; 2 points extraorally on each submandibular gland.	0.152	2.432	15	3.8	780		10	
Gonnelli et al., 2016a	Diode (InGaAlP)	0.04	2 point on sublingual glands; 3 points on each buccal mucosa; 3 points on each labial mucosa; 3 points on the palate; 1 point on the dorsum of the tongue; 2 points on each lateral border of the tongue; 1 point on each tonsillar pillar.	0.4	9.6	40	10	660	Punctual, in contact mode	10	3 times a week for a total of 21 sessions.
	Diode (GaAlAs)		6 points extraorally on each parotid gland; 2 points extraorally on each submandibular gland.	0.152	2.432	15	3.8	780		10	
Gonnelli et al., 2016b	Diode (InGaAlP)	0.04	3 points on each buccal mucosa; 3 points on each labial mucosa; 2 points on the hard palate; 1 point on the soft palate; 1 point on the dorsum of the tongue; 2 points on each lateral border of the tongue; 1 point on each tonsillar pillar; 2 point on the floor of the mouth.	0.4	9.6	40	10	660	Punctual, in contact mode	10	3 times a week for a total of 21 sessions.
Libik et al., 2017	He-Ne	NS	Buccal mucosa bilaterally; upper and lower lips; hard palate; soft palate; dorsum of the tongue; tongue edges; floor of the mouth; tonsillar pillar bilaterally (numbers of points not specified).	NS	NS	30	5.16 or 6.3	630	Punctual, in contact mode	NS	Daily before RT-CT session until the end of treatment
			Parotid gland and submandibular gland extraorally (numbers of points not specified).				2.5 or 3.8				
Louzeiro et al., 2020	Diode (AsGaAl)	0.028	6 points extraorally for each parotid gland; 3 points extraorally for submandibular glands bilaterally; 2 points intraorally on anterior region of mouth floor.	0.7	15.4	40	25	810	Punctual, in contact mode	17.5	3 times a week, concomitantly with radiotherapy treatment.
	Diode (InGaAlP)		1 point on each labial commissure; 8 points on	0.28	22.4	40	10	660		7	

(*continued on next page*)

Table 3 (*continued*)

Author/ year	Laser type	Spot size (cm^2)	Points of application	Energy per point (J)	Energy per session (J)	Power (mW)	Dose (J/ com^2)	Λ (nm)	Mode of application	Time of exposure per point (s)	Frequency of application
			upper labial mucosa; 8 points on lower labial mucosa; 12 points on each buccal mucosa; 12 points on hard palate; 4 points on soft palate; 6 points on each tongue edge; 6 points on ventral surface of the tongue; 4 points on mouth floor.								

NS = Not specified or not informed.
Λ = Wavelength.

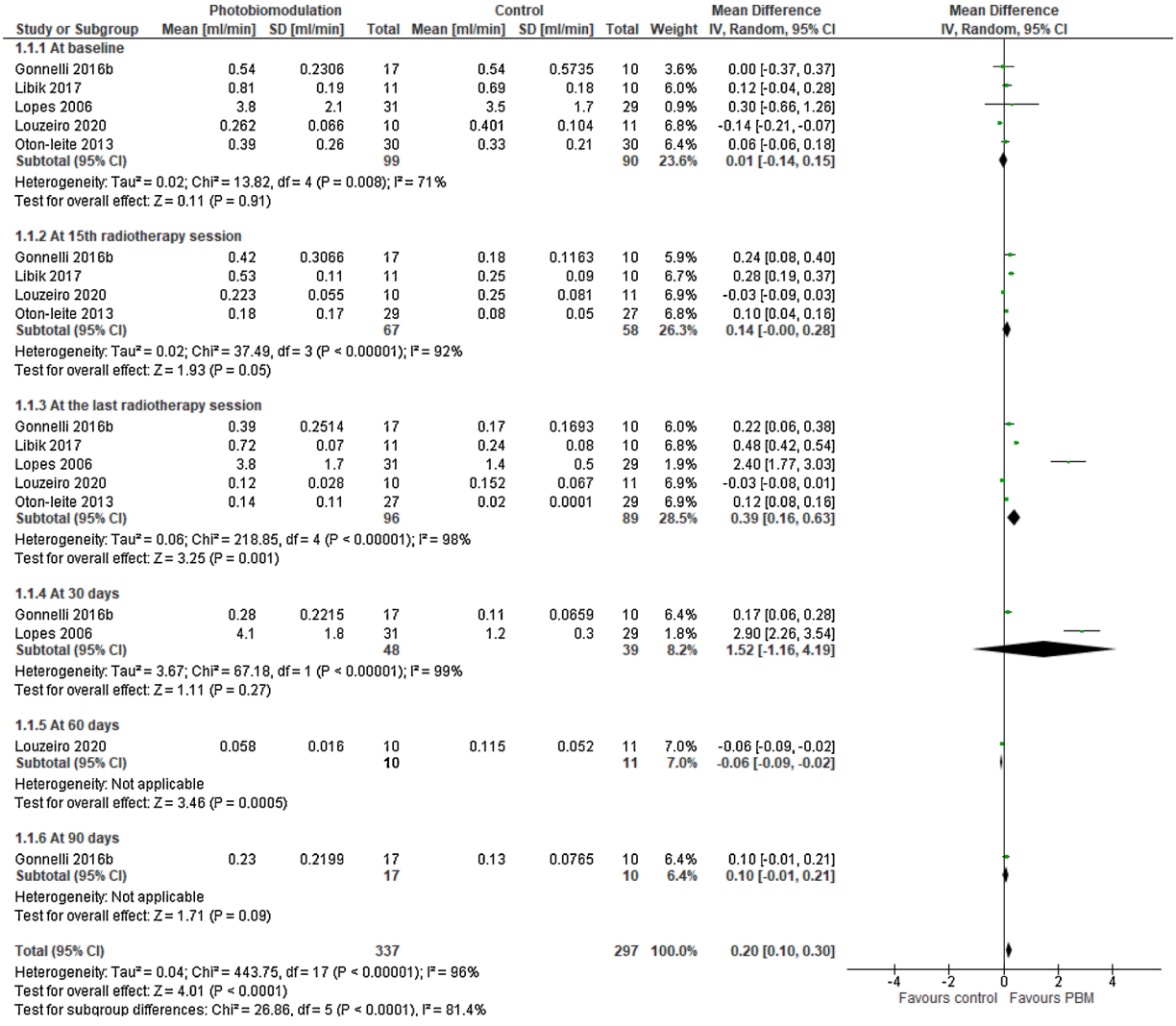

Fig. 2. Forest plot of unstimulated salivary flow rate.

to controls, with a mean difference of 0.20 mL/min (CI 0.10−0.30, $p <$ 0.00001). However, the study results showed high heterogeneity ($I^2 =$ 96 %). Analyzing the times individually (baseline, 15th session, final session and 30 days after radiotherapy), no significant changes were observed between the laser and control groups at baseline (MD 0.01, 95 % CI -0.14−0.15, $I^2 = 71$ %, $p = 0.91$), at 15th radiotherapy session (MD 0.14, 95 % CI 0.00−0.28, $I^2 = 92$ %, $p = 0.05$) and after 30 (MD 1.52, 95 % 95 % CI -1.16−4.19, $I^2 = 99$ %, $p = 0.27$). Significant differences were observed after the last radiotherapy session in favor of the intervention (MD 0.39, IC 0.16−0.63, $I^2 = 98$ %, $p < 0.00001$).

Subsequent analyses were performed with studies with similar methodology (red wavelength or red + infrared wavelength PBM) to remove possible confounders. These analyses included the 15th and last radiotherapy sessions (Figs. 3 and 4). The combination of extraoral

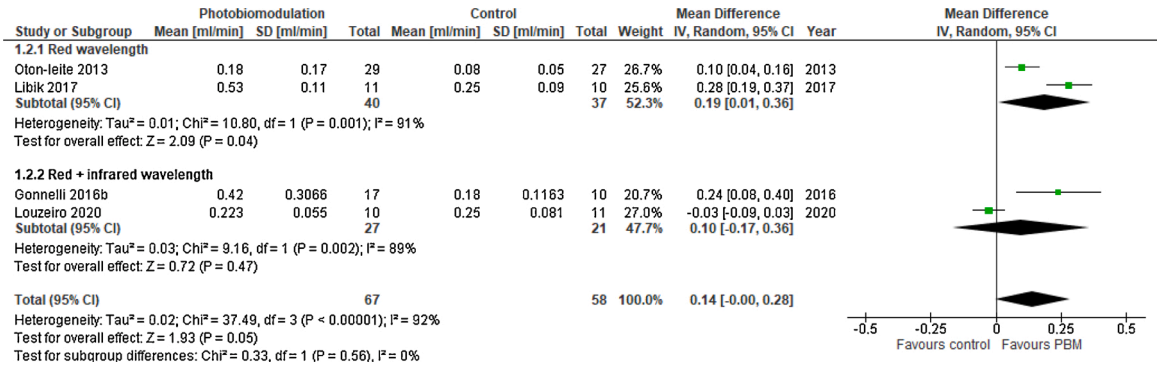

Fig. 3. Forest plot of unstimulated salivary flow rate at 15th radiotherapy session.

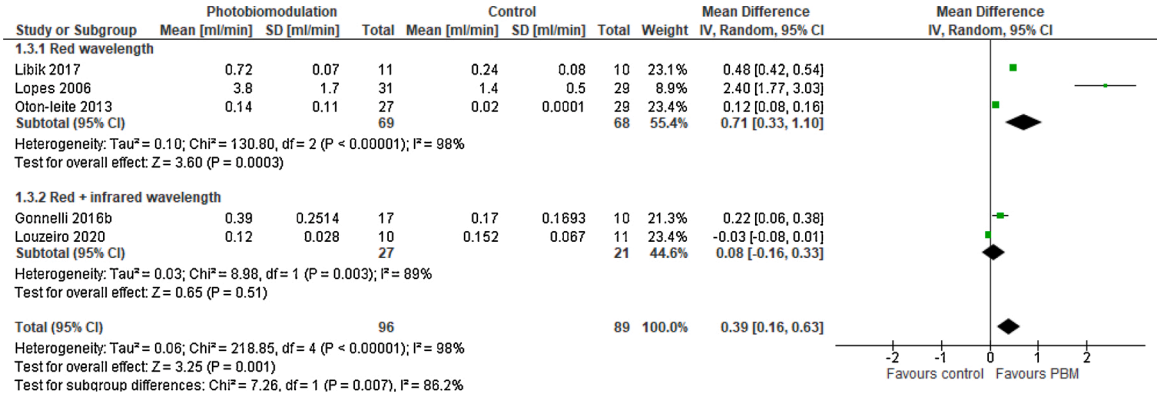

Fig. 4. Forest plot of unstimulated salivary flow at final radiotherapy session.

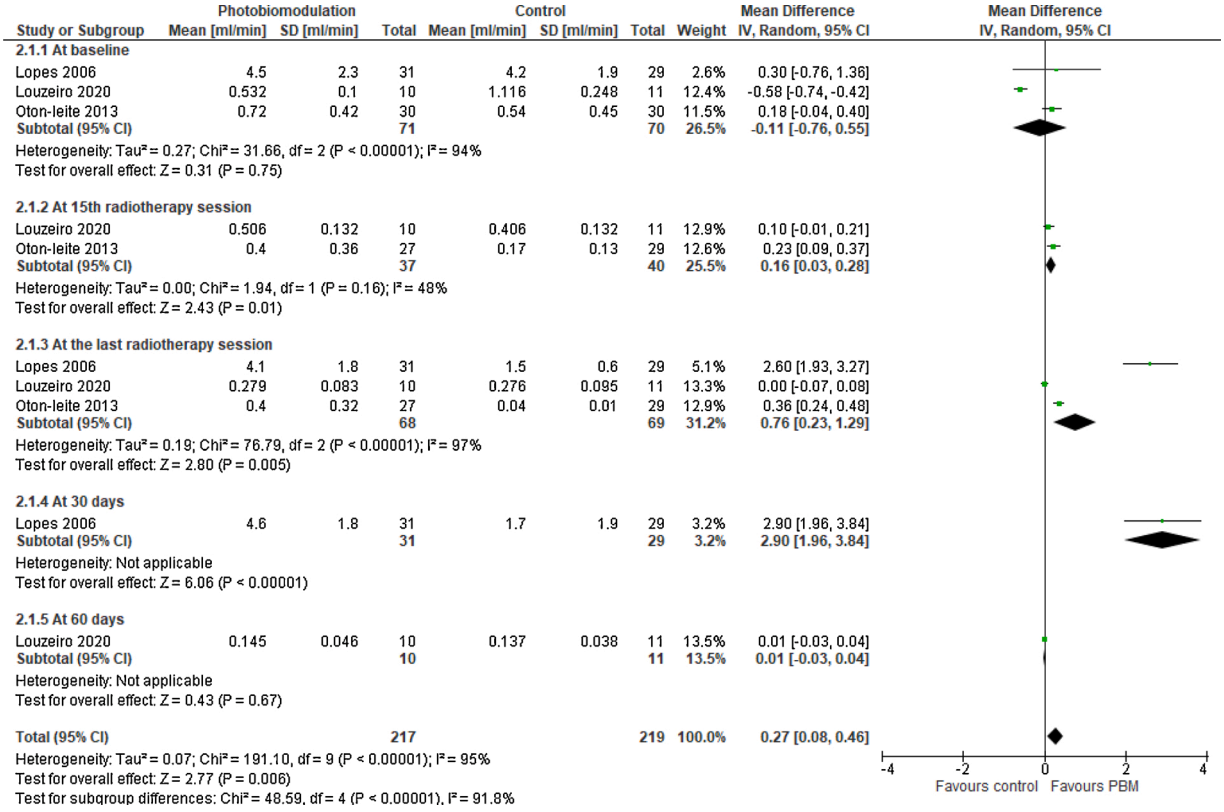

Fig. 5. Forest plot of stimulated salivary flow rate.

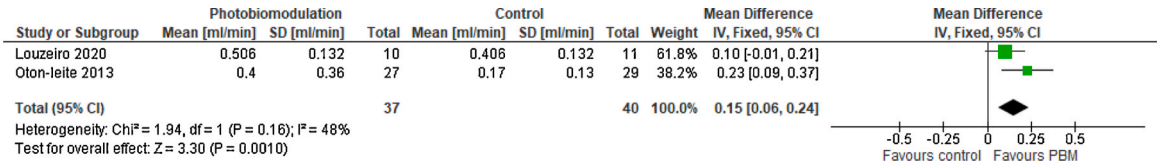

Fig. 6. Forest plot of stimulated salivary flow rate at 15th radiotherapy session.

infrared and red intraoral laser showed no significant differences with the control group at the 15th radiotherapy session (MD 0.10, 95 % CI -0.17−0.36, $I^2 = 89$ %, $p = 0.47$) and nether the last radiotherapy session (MD 0.08, 95 % CI -0.16−0.33, $I^2 = 89$ %, $p = 0.47$). The red wavelength laser, in other hand, showed an increased salivary flow rate compared to controls at the 15th radiotherapy session (MD 0.19, 95 % CI 0.01−0.36, $p = 0.04$), and even higher at the last radiotherapy session (MD 0.71, 95 % CI 0.33–1.10, $p = 0.0003$), although both periods showed great heterogeneity ($I^2 = 91$ % and $I^2 = 98$ %, respectively).

Similarly, PBM also demonstrated an increase in stimulated salivary flow compared to controls (MD 0.27, 95 % IC 0.08−0.46, $p < 0.00001$, Fig. 5), but with high heterogeneity ($I^2 = 95$ %). No differences were observed during the baseline period (MD -0.11, 95 % CI -0.76−0.55, $p = 0.75$, $I^2 = 94$ %). Significant differences can be observed in favor of PBM at the 15th radiotherapy session (MD 0.15, 95 % IC 0.06−0.24, $p = 0.0010$, Fig. 6) with low heterogeneity ($I^2 = 48$ %), and at the last radiotherapy session (MD 0.76, 95 % IC 0.23–1.29, $p = 0.005$, Fig. 5), however with high heterogeneity ($I^2 = 97$ %).

When analyzing the last radiotherapy session individually, no significant effect was seen using the red wavelength laser compared to controls (MD 1.45, 95 % CI -0.74−3.65, $p = 0.19$, Fig. 7), and there was also substantial heterogeneity ($I^2 = 98$ %).

3.7. Risk of bias classification

In general, there was a predominance of low risk of bias among the seven domains presented (57 %) (Fig. 8). Areas with the highest risk of bias included: random sequence generation reported by two studies (33.33 %); blinding participants reported in three studies (50 %); and allocation concealment, not reported in any study. Blinding of outcomes was at low risk in four of the studies (66.67 %), and in three studies (50 %), the authors reported that the published study included all outcomes present in the protocol. All six studies were at low risk for the "incomplete outcome data" and "other bias" domains (Fig. 9).

3.8. Quality of evidence

Table 4 summarizes the quality of evidence. Both stimulated and unstimulated salivary flow of low-quality of evidence. This result was due to potential risk of bias, inconsistency of results and possibility of publication bias due to high heterogeneity.

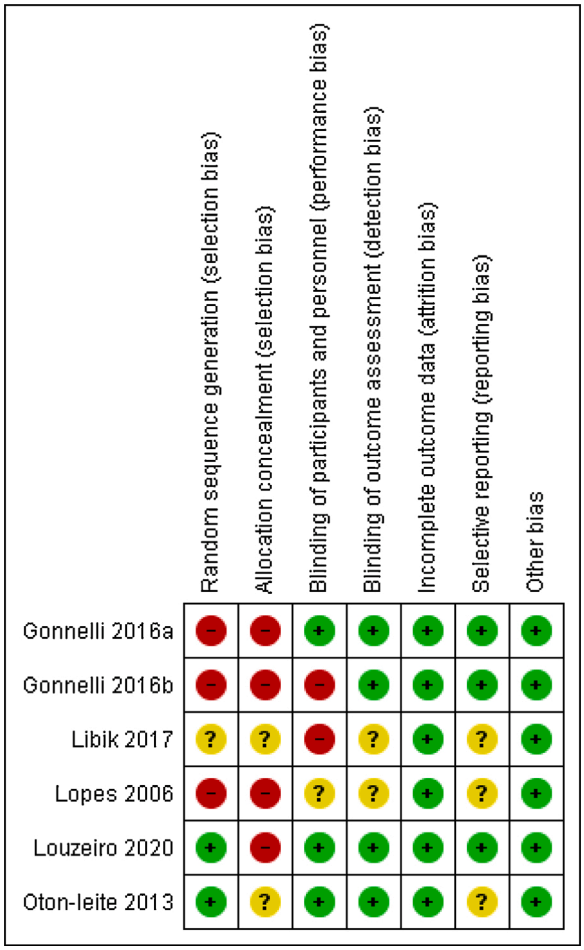

Fig. 8. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

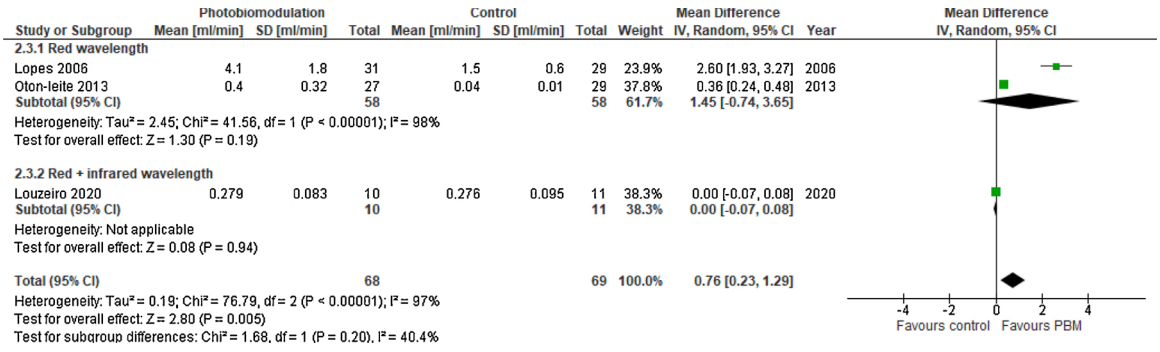

Fig. 7. Forest plot of stimulated salivary flow rate at final radiotherapy session.

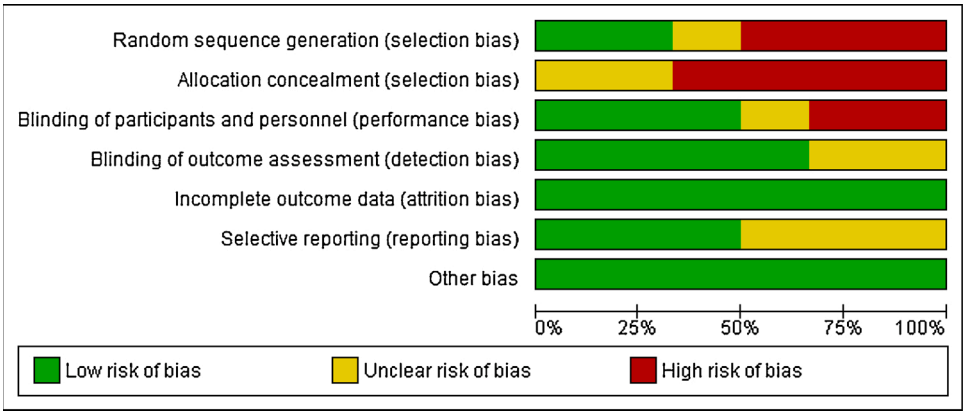

Fig. 9. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

4. Discussion

It seems that regular and continuous applications of PBM have the ability to gradually and linearly increase salivary flow capacity in the glands (Lončar et al., 2011). The exact mechanism by which PBM stimulates salivary flow during its application is unclear. In animal models, Uzêda-e-Silva et al. (2017) observed that euthyroid rats showed greater proliferation of myoepithelial cells after PBM. This evidence suggests that PBM can modulate the functional capacity of the glandular parenchyma, inducing salivary production throughout treatment.

PBM, at red or infrared wavelengths, has been suggested to increase cytochrome c oxidase activity in the mitochondrial respiratory chain, leading to a higher concentration of Ca^{2+} and cAMP (Karu, 1989). These molecules are important transducers of intracellular signals, regulating cellular metabolism. In salivary gland acini, Ca^{2+} and cAMP are essential mediators in the transcription of stimuli for salivary synthesis. The parasympathetic system acts on muscarinic receptors, inducing increased intracellular concentrations of Ca^{2+}, which increases the salivary flow with more fluid characteristics (Turner and Sugiya, 2002; Porcheri and Mitsiadis, 2019). The sympathetic system interacts with beta-adrenergic receptors, which stimulate the synthesis of cAMP, also increasing salivary flow, although with greater amounts of protein in its composition (Proctor, 2016). In this way, the increase in intracellular concentration of Ca2+ and cAMP related to PBM could lead to an increase in salivary flow.

Evidence points out that PBM provides radioprotection to cells by altering the cellular redox state. Laser therapy is able to briefly induce the generation of ROS, activating mechanisms to regulate oxidative stress damage in response. NF-kB is one of the main factors responsible for cell regulation in cells under oxidative stress, capable of inducing wound healing, tissue regeneration, analgesia, anti-inflammatory and anti-apoptotic effect (Farivar et al., 2014; AC-H et al., 2009; Zecha et al., 2016). Given this, Karu (Karu et al., 1994) demonstrated that PBM is able to accelerate the repair of cells subjected to gamma radiation. Because of these effects, PBM is widely used in the management of complications from radiotherapy (JAEM et al., 2016), and is currently recommended by the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) as a preventive measure for radio and chemo-induced mucositis (Zadik et al., 2019). On the other hand, the use of laser therapy on active tumors should be avoided, due to the risk of possible stimulation of the malignant cells (Bamps et al., 2018).

There is still no consensus regarding these effects of PBM on the salivary glands, however our meta-analysis, despite a low-quality of evidence, demonstrated that PBM is able to minimize radiation-induced hyposalivation relative to controls. This positive effect of PBM could be seen, at the 15th radiotherapy session and, to a greater extent, at the end of radiotherapy, suggesting a dose-effect relationship.

The included studies used different methods in laser applications. Half of the studies used an association of the intraoral red laser with an extraoral infrared laser over the major salivary glands (Gonnelli et al., 2016a, b; Louzeiro et al., 2020), while another half of the studies used laser at the red wavelength alone (Lopes C de et al., 2006; Oton-Leite et al., 2013; Libik et al., 2017). Still, only two study (Gonnelli et al., 2016b; Louzeiro et al., 2020) using infrared application could be included in our meta-analysis.

Due to these methodological differences, a subsequent meta-analysis was performed using studies with different wavelength. In these analyzes, the red wavelength showed a greater tendency to increase unstimulated salivary flow than the association between the red and infrared wavelength, especially at the 15th radiotherapy session and last radiotherapy session. These results contradict the findings of the study by Brzak et al. (2018), in which the unstimulated salivary flow had a higher response to infrared wavelength applications, possibly related to greater tissue penetration capacity. The data from this meta-analysis might suggest that the red laser has a greater effect on the salivary flow than the association of wavelengths. On the other hand, the low number of infrared laser studies, associated with the low sampling obtained result in a high heterogeneity of the studies. Although these results reinforce the positive effect of PBM on salivary flow, the high heterogeneity obtained prevents further comparison about the effect of different wavelengths on salivary flow.

In addition, not all laser therapy parameters have the same biomodulator effect. The biomodulatory effect of laser therapy depends on the absorption of the light by a chromophore. Each chromophore has an affinity for a specific range of light wavelength. In this way, it will only absorb the photon with a wavelength within its absorption spectrum (Hamblin and Demidova, 2006). However, even with a compatible wavelength, the cellular effect varies in intensity according to the amount of energy supplied. Low doses are insufficient to initiate a biological effect, while excessive doses demonstrate a bioinhibitory effect (Huang et al., 2009). In view of this, the high heterogeneity of the outcome observed can be explained by the different PBM protocols used in the studies.

Regarding the effect of PBM on xerostomia, only Libik et al. (2017) and Louzeiro et al. (2020) evaluated this outcome. As they used different methods of xerostomia analysis, the meta-analysis could not be performed on this outcome. Despite this, the two studies showed no significant differences compared to controls. It is noteworthy that a study did not demonstrate significant effects of PBM in relation to salivary flow. According to Dawes (1987), xerostomia occurs when unstimulated salivary flow decreases by about 40–50 %, which represents most of the included studies (Oton-Leite et al., 2013; Gonnelli et al., 2016a; Libik et al., 2017; Gonnelli et al., 2016b; Louzeiro et al., 2020). Some case reports (Campos et al., 2009; El Mobadder et al., 2018) and an uncontrolled study (Simões et al., 2010a) have reported that PBM was able to

Table 4
Quality of evidence assessment using GRADE system.

PBM compared to placebo/control for radiation induced hyposalivation Bibliography:											
Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With photobiomodulation	Relative effect	Risk with control	Risk difference with photobiomodulation
Unstimulated salivary flow rate											
634 (5 RCTs)	serious [a]	serious [b]	not serious	not serious	publication bias strongly suspected dose response gradient [c]	⊕⊕◯◯ LOW	297	337	–		MD **0.2 higher** (0.1 higher to 0.3 higher)
Stimulated salivary flow rate											
436 (3 RCTs)	serious [a]	serious [b]	not serious	not serious	publication bias strongly suspected dose response gradient [c]	⊕⊕◯◯ LOW	219	217	–		MD **0.27 higher** (0.08 higher to 0.46 higher)

CI: Confidence interval; **MD:** Mean difference.
Explanations.
[a] Some bias rise doubts about viability of results.
[b] Methodological differences imply a high heterogeneity of the studies. This heterogeneity cannot be explained even with subgroup analyzes.
[c] There is a small number of clinical trials and a substantial heterogeneity in results. Some of these had a limited number of participants.

decrease xerostomia in patients undergoing head and neck radiotherapy. In view of these studies, the possibility of improvement in xerostomia after PBM should not be totally ruled out.

In this systematic review, the effect of PBM on sialochemical changes was assessed by only one study (Louzeiro et al., 2020). In this study, PBM was able to increase unstimulated salivary pH. A similar effect was also reported by Palma et al. (2017) in previously irradiated patients. Nevertheless, the mechanism by which PBM is able to increase salivary pH is not known. According to Louzeiro et al. (2020) there is a possibility that PBM could modify buffer activity by changing the concentration of salivary bicarbonate, however; this analysis has not yet been carried out by any study. An uncontrolled study (Simões et al., 2010a) showed that intraoral red laser therapy performed 3 times a week has a greater tendency to reduce the amount of total protein in the unstimulated saliva in relation to week applications, although no analysis was performed between groups to infer this difference. To date, there is no evidence that PBM is able to minimize changes in salivary components caused by radiotherapy.

The present review had several limitations regarding the results obtained: 1) some potential risks of bias among the included studies generated uncertainty about their reliability; 2) there was no methodological standardization among the studies, and different forms of PBM application or outcome analysis were found; 3) this methodological difference along with the small number of studies reflected a high heterogeneity of results; and finally, 4) the low quality of evidence found calls for interpretation of findings with caution.

In conclusion, the results obtained from this meta-analysis show that the use of PBM concomitantly with radiotherapy can minimize radiation-induced hyposalivation; however, the low quality of evidence and the high heterogeneity of the studies generate uncertainty regarding the viability of these results. This review is expected to serve as a guide for further studies to explore more standardized methodologies and obtain more accurate results.

CRediT authorship contribution statement

Gabriel Campos Louzeiro: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Project administration, Funding acquisition. **Dieni da Silveira Teixeira:** Methodology, Validation, Investigation, Writing - review & editing. **Karen Cherubini:** Validation, Writing - review & editing. **Maria Antonia Zancanaro de Figueiredo:** Validation, Writing - review & editing. **Fernanda Gonçalves Salum:** Conceptualization, Methodology, Validation, Writing - review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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