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Photobiomodulation in Pain Control in Diseases of the Oral Cavity: Overview (Evidence Map) and Its Implementation in Integrative Complementary Medicine

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Abstract

Objective: To assess the evidence available and knowledge gaps in photobiomodulation (PBM) for oral facial pain.

Background data: Effective identification of a noninvasive resource for oral facial pain such as PBM may mitigate the risks of invasive therapeutic resources.

Methods: Nine electronic databases were searched for systematic reviews reporting oral facial pain outcome for PBM. The 3iE (International Initiative for Impact Evaluation) evidence gap map methodology with the tableau was used to graphically display the parameters analyzed in the research.

Results: Several wavelengths within the range of infrared were used in 37.6% of the studies, accompanied by the 32.4% in the red range. The quality of the effect was positive in 61.4% of the studies, whereas the impact degree was low, according to the measurement tool used to assess systematic reviews 2 (AMSTAR 2), in 60.2%.

Conclusions: Despite the positive potential of PBM in the treatment and control of pain in diseases of the oral cavity, complete information on dosimetry in published studies with PBM is still lacking, making it difficult to reproduce the results found.

Keywords: pain, photobiomodulation therapy, evidence-based dentistry, dentistry integrative, evidence map

Introduction

OROFACIAL PAIN, IN MOST CASES, is a chronic pain that affects the quality of life and can be limiting to the daily routine of people who suffer from this pathology. Its diagnosis and management can be challenging, as it involves

complex histories, pathophysiology, and psychosocial comorbidities such as depression and anxiety.¹

Photobiomodulation (PBM) has been available to a health care professional with accessible training as an important adjunct to conventional treatments for pain conditions.^{2–5} PBM using low-power lasers is safe, more accessible in

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terms of cost and benefit, and noninvasive nonpharmacological therapy with numerous forms of indication in the various health specialties. It has attracted more attention owing to its unique advantages in analgesia, biostimulation, and the absence of adverse effects. However, there are three main concerns regarding PBM: incomplete and inaccurate irradiation parameters, incorrect dose calculation, and the misuse of light property terminology.⁶ There is still no consensus in the scientific literature about the ideal protocols for the application of PBM for pain since we are faced with great variability in the wavelength used, dosage employed, pulse repetition rate, number of applications, and treatment duration.^{7,8} Evidence maps are a useful method with the dual function of synthesizing available evidence on a specific topic and identifying knowledge gaps. They use graphical representations (or dynamic representations, through interactive online databases), which facilitate the interpretation of results (Supplementary Data).

Although biophotonics, through PBM, meets some resistance in its use in dentistry, many studies confirm its positive effects. Thus, this article aims to perform an evidence map on the effectiveness of PBM in dentistry with focus on pain.

Materials and Methods

This Overview (Evidence Map) is based on systematic reviews and summarizes interventions and health outcomes related to PBM therapy in pain. Systematic reviews provide a reliable process that summarizes the best available evidence. We report the method and results according to a minimal evidence-based set of items for reporting studies in systematic reviews and meta-analyses (PRISMA) guidelines^{9,10} and the International Initiative for Impact Evaluation (3iE) Evidence Gap Methodology.^{1,11} This evidence map was supported by a technical expert panel of librarians, practitioners, policymakers, and researcher content experts.¹

Data sources

The systematic review studies were tracked in the largest number of national and international databases, such as PubMed/PMC, PubMed/MEDLINE, LILACS, MOSAIC, Embase, Scopus, Google Scholar, Web of Science, and thesis bank. A search in gray literature in thesis bank, Google Scholar, and repositories, in general, is necessary to exclude the risk of publication bias, which favors the publication of studies with positive results or rejects studies that presented unfavorable results. The search started in March 2020 until May 2020 (updated until March 2021), and at the end of the characterization, it ended with six researchers who specialized in the theme and developed the research strategy. A search strategy was developed, using the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCS) terms for PBM, low-level laser, low-level laser therapy (LLLT) and pain, and orofacial pain.

Inclusion criteria

- Systematic reviews on PBM in pain interventions.
- Systematic reviews as reviews with or without meta-analyses with humans, for any age group.
- All participants of all ages and all genders regardless of health status.
- Studies in any language.

Exclusion criteria

We excluded systematic reviews that did not have pain as an outcome being treated with PBM.

Procedure

Eight independent literature reviewers screened the systematic review search output blinded at the software Rayyan.¹² Citations deemed potentially relevant by at least five reviewers and unclear citations were obtained as full text. Full-text publications were screened against the specified inclusion criteria by six independent reviewers; disagreements were resolved through discussion. This process is given in the PRISMA flow diagram^{10,13} (Fig. 1).

We applied the measurement tool used to assess systematic reviews 2 (AMSTAR 2)¹⁰ to analyze the quality (high, moderate, low) of the included systematic reviews. From each included systematic review, we extracted the intervention PBM in pain and the main health outcomes that were summarized across included studies. We retrieved data about population, treatment effect (positive, potentially positive, mixed findings, negative) estimates for health outcomes, and systematic review characteristics.

Titles were checked and duplications were first excluded in the Rayyan tool. Subsequently, they were systematically transferred and organized in a spreadsheet, designed with columns to record information on the methodologies and dosimetry of each study, which were obtained and read in full, filling the worksheet items, and undergoing a second check.

Data synthesis

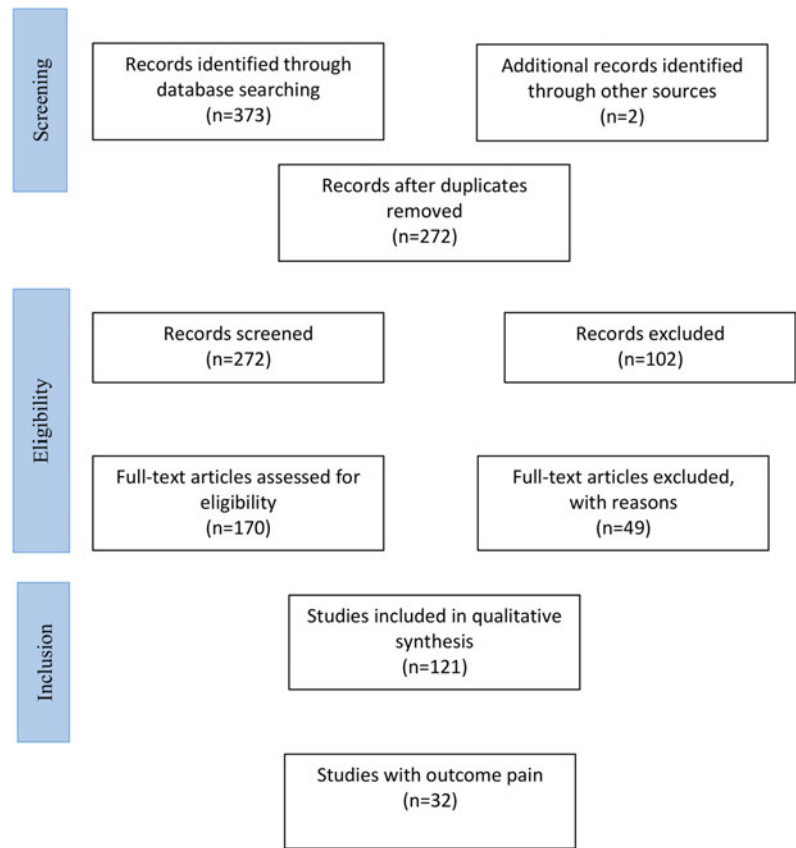
We developed a characterization matrix to synthesize the findings. This matrix included: number, reviewer's name, name of an article; Interventions; Interventions Group; Outcomes; Outcomes Group; Effect; Population; Database ID; Focus Country; Publication Country; Publication Year; Type of Review; Review Design; Study Design; Confidence Level (AMSTAR 2), link to the full text, and citation of authors. Systematic review outcomes were drafted by one reviewer and discussed in the review team, also the matrix was discussed in two workshops organized by Regional Library of Medicine (BIREME).¹⁴ The Latin American and Caribbean Centre for Health Sciences Information, also known by its original name, Regional Library of Medicine (BIREME), is a specialized center of the Pan American Health Organization World Health Organization PAHO/WHO). We organized the Evidence Map considering outcomes, effects, and level of confidence of the included systematic reviews. In a second moment, those reviews that presented the primary pain outcome were selected for this study.

The proposed categorization of studies can vary according to the researcher's focus and the research being sought and this map is the first whose search for studies can be replicated and reorganized according to the outcome. Thus, those studies with the outcome pain were separated and analyzed.

Results

We identified 121 citations of which 32 unique systematic reviews (references) met the criteria for inclusion in the Overview of PBM in dentistry and with an analysis of the

FIG. 1. Flow diagram of the information flow through the different phases of the systematic review. The PRISMA.¹⁰



outcome pain. Most of the reviews were published in 2011 and 2020. We note that 62.5% of studies involving pain as one of the primary outcomes were published in 2017.

The complete list of references and the interactive evidence map can be accessed in the Traditional, Complementary, and Integrative Medicine (MTCI) Virtual Health Library, available at: <https://public.tableau.com/profile/bireme#!/vizhome/laserterapia-pt/evidence-map>.¹⁴

Study design

Studies included were designed as systematic reviews of randomized controlled clinical trials (78.4%) and non-randomized controlled studies (12.5%); follow-up studies were ~5.7%.

Population

The systematic reviews included analyzed data from the following population. In most systematic reviews (36.8%) it was not reported in the text. In 24.2% of the studies, it was composed of adults and adolescents, followed by the adult population in general (10.9%). Individuals with cancer comprised 7.0%, children 2.7%, adolescents, diabetic patients, and smokers all comprised 2.5% or less.

Countries

In the evaluation of countries included in systematic reviews, where pain was present as the primary outcome, we observed that 46.6% did not inform the location of the primary studies and that 53.4% were divided between

countries in five continents, where groups are researching specifically on the topic of PBM and pain in oral cavity diseases. Brazil and Italy appear isolated as the country of primary studies included with 4.5% of the studies.

Outcomes and effects

Always based on the specific outcome of pain, we observed that 37.6% of studies use the infrared wavelength, followed by 32.4% of studies that use therapy in the red wavelength. The 121 studies showed 67 outcomes in total divided into major groups: dentin hypersensitivity (21.6%), orthodontics (18.2%), orofacial pain and temporomandibular disorders (TMD) (11.4%), surgery (10.2%), recurrent aphthous stomatitis (10.2%), endodontics (4.5%), mucositis (3.4%), lichen plan (3.4%), burning mouth syndrome (3.4%), herpes simplex (2.3%), complications of chemotherapy and radiotherapy (1.1%), and the topic of PBM in dentistry (10.2%) with studies of various dental within a single systematic review.

As for the degree of impact of the studies (high, moderate, and low), according to the evaluation of the impact of systematic reviews of AMSTAR 2 questionnaire, the following results were obtained: 60.2% were analyzed as low, 30.7% high, and 9.1% moderate.

For the assessment of the action potential of the effects, they were classified as: positive 61.4%; positive potentials 27.3%; inconclusive/mixed 9.1%; no effect 1.1%; and negative 1.1%.

We can observe, as the evaluation of the review design, that most are of effectiveness (38.6%), safety and effectiveness (20.5%), and cost-effectiveness (2.3%).

Lack of investigation

Most reviews have dosimetry limitations. Most systematic reviews indicate wavelength, mode of delivery, energy per point, and in some, exposure time. In most reviews, data such as power, irradiation time, beam area (on the surface of the skin or test culture), energy density, pulse repetition rate parameters, anatomical location (skin color, target location, i.e., depth below the skin), number of sessions, and the interval between sessions are also important. They are minimum parameters necessary for a scientific study to be possible for reproduction and also prevent the definition of better standardized protocols.¹⁵

Discussion

The main difficulties for the inclusion of complementary integrative practices in health in the MTCI are related to the scientific proof of these therapies, as well as the qualification of professionals trained to use safe and effective clinical protocols for these.¹ The purpose of this study was to survey systematic reviews that use PBM therapy in the treatment of diseases of the oral cavity, evaluating the degree and quality of evidence based on the development of a map of clinical evidence on the use of this therapy.

In this study, 32 reviews were selected within 11 pathologies of the oral cavity: dentinal hypersensitivity,¹⁶⁻¹⁹ recurrent aphthous stomatitis,²⁰⁻²² complications of chemotherapy and radiotherapy (lymphedema),²³ endodontics,^{24,25} herpes simplex,²⁶ burning mouth syndrome,²⁷ lichen planus of the oral mucosa,^{28,29} oral surgery,^{30,31} oral mucositis,^{32,33} orofacial pain^{34,35} and orthodontics.³⁶⁻³⁸ Two systematic reviews were a compilation of studies with different conditions of diseases of the oral cavity, which were treated with PBM and had primary outcome pain.³⁹

Due to a methodological issue of the Tableau public^{14,40} tool, which requires the use of capital letters and numbers, it was necessary to divide the outcomes into the main group, which gave rise to the categories that were classified according to the search terms searched. in DeCS-MeSH, descriptors in Health Sciences in dentistry. This gave rise to the outcome group in which the selected oral cavity pathologies were the ones with the highest number of primary outcomes in the analysis of general data in the evidence map.

All systematic reviews that were included met the inclusion criteria and were assessed for impact index, according to the analysis of the AMSTAR 2 questionnaire, both for the overall evidence map and for the primary outcome pain. In reviews considered of high impact,^{26,30,38,41} the following information was presented: Patient, Intervention, Comparison, and Outcomes (PICO) question, a primary and secondary outcome, inclusion criteria, indication of the search for comprehensive terms, number of duplicate articles and reasons for exclusion, a technique for analysis of the risk of bias, location of the pathology and treated area, countries of origin of the research of the selected studies, risk of bias with "n" of the studies, analysis of pain intensity reported in the studies, and placebo intervention group, in which the literature was systematically evaluated for identify and suggest effective and safe protocols for pain management in dental diseases and the use of PBM.

The presence of these data facilitates the identification of protocols, as well as the effectiveness of therapy in specific

diseases of the oral cavity. On the contrary, lack of this information makes not only the use of this therapy difficult but also allows the selected articles to receive low rankings in the study. Other authors present the importance of these criteria in their studies. In a review by Hamblin,⁴² the author underlined that the lack of dosimetry parameters not only makes the application difficult but also reduces the reliability of the study.^{10,18,19}

For studies that specifically evaluated the outcome of "pain for herpes," PBM showed efficacy, and the most used wavelengths were between 630 and 780 nm.³⁰ Although photodynamic therapy in cases of contaminated lesions such as those caused by herpes does not have pain control as the primary outcome, the use of this technique promotes local disinfection.⁴⁴ Thus, there are favorable conditions for tissue repair and pain control, as infection zones lead to the release of inflammatory and nociceptive mediators, which act as the body's defense mechanism against pathogens,⁴² making tissue repair difficult. Studies that considered burning mouth syndrome and lichen planus used lasers with wavelengths between 630 and 980 nm.^{32,33,43} As for mucositis, wavelengths between 632 and 970 nm^{37,38} were used.

The mechanism of action of PBM in pain reduction has not been fully elucidated. Some studies attribute its analgesic effect to four different mechanisms: inhibitory effects on nerve depolarization (especially C fibers), activation of mediators oriented to pain stimuli, control of adenosine triphosphate (ATP) production, and reduction of prostaglandin levels.³³ Scientific systematic review articles included in this study that showed >50% of positive or potentially positive effects in the general analysis of oral cavity diseases, included in the evidence map, as well as selected articles that had pain as a primary outcome, are listed within these promising effects on pain control.³¹

de Oliveira et al⁴⁵ declare that, when considering the specific outcome of pain in selected studies, most studies are effective in modulating the painful process in the use of PBM therapy,^{16,36} or that this modulation is part of its effects, considering other actions as anti-inflammatory and tissue repair.^{25,46}

An important methodological fact is to know for whom the PBM will be indicated, with a specific item found in the characterization matrix referring to the type of population evaluated. It was observed that most works do not specify for which population PBM will be offered. This is a problem and may be related to the low level of impact of review studies. This was a finding present in most systematic reviews, in the specific analysis for the primary outcome of pain, and in the general map, which can make it difficult to understand to which audience this therapy is aimed at.^{18,31,36,47}

The analysis of the pain outcome was only possible after the construction of the evidence map, obtained from 121 systematic review articles, published in recognized journals for 13 years and 1 month, from February 2008 to March 2021. Articles were reviewed, and an assessment of the records of PBM therapy parameters related to the joint use of PBM application methods was performed. A variety of parameters were observed in these studies, with consequent variation in dosimetry, in addition to methodological deficiencies, a factor that prevents the replication of many studies.^{34,36,46,48}

Few studies indicate the summary of laser parameters that should be observed in all articles for publications with minimally structured and standardized topics, such as type

of study [e.g., randomized clinical trials (RCTs)], sample size/groups/control/randomization/blinding, laser emission wavelength, delivery system, emission mode, device calibration, target tissue/lesion, distance from tissue tip, irradiated “spot” size, irradiance, total energy, irradiation time, irradiation frequency movement tip/covered area, number of sessions, and time between sessions.

The evaluation of the type of review and the design of the studies included and evaluated in systematic reviews is a factor that can influence the degree of impact of the studies, as well as how they will be analyzed by the scientific community. Systematic reviews were the chosen scope in this study, but systematic reviews associated with meta-analyses were also found, considered more complex studies, with more details and more information,^{23,25,29,31,32,37} often requiring professional training for this specific work.

There is a strong World Health Organization (WHO) recommendation on strategies focused on helping health authorities to find solutions that provide a broader vision of improving the health and empowerment of patients through the safe and effective use of MTCI, with product regulation, practices, and professionals until the year.^{7,44}

The advancement of this research brings scientific reading based on evidence, through data that make up the evidence map on the clinical effectiveness of PBM in oral health. On the contrary, the lack of detailed dosimetry information and some methodological issues compromise the quality of some scientific studies. This makes it difficult to include PBM as an integrative and complementary therapy in the treatment and control of pain in oral cavity diseases, despite the positive effects and positive potential, proven efficacy, and effectiveness.

Future approaches with information from appropriate protocols, prioritizing dosimetry, and well-defined methodologies, will be important for decision making in several areas. From the academic environment, pointing out existing gaps will guide in future scientific research. Even public management helps managers regarding health actions that need to be reinforced and implemented with PBM.

Conclusions

The construction of the evidence map on the application of PBM for pain made it possible to verify that even with so much research in this area, it is important that the scientific community carry out research with well-designed methodologies to be reproduced. In addition, dental specialists now have a useful tool to demonstrate to public managers the importance of implementing PBM in public health systems with an integrative and complementary practice.

Authors' Contributions

This article has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. We have read and understood your journal's policies, and we believe that neither the article nor the study violates any of these. There are no conflicts of interest to declare. Each author's contribution is listed hereunder.

R.C.: Conceptualization (lead), investigation (equal), design of methodology (equal) and writing original draft (equal). A.D.N.L.: Investigation (equal), design of methodology, writing (equal) original draft (equal), final approval

of the version (lead). M.C.D.d.M. and P.N.L.d.M.: Design of methodology (equal), writing original draft (equal) and formal analysis (equal). L.F.K.: Investigation (equal), writing original draft (equal). R.d.F.Z.L.: Writing original draft (equal) and formal analysis (lead). G.M.N.: Writing—review and editing (equal). R.F.C.d.M.: Writing—original draft (supporting) and writing—review and editing (equal). Y.M.E.e.S.: Formal analysis (equal) and writing—original draft (supporting). R.M.L.: Conceptualization (equal), writing—review and editing (lead).

Acknowledgments

The authors thank the Brazilian Ministry of Health in partnership with the Latin American and Caribbean Center on Health Sciences Information BIREME—PAHO—WHO and the Brazilian Academic Consortium of Integrative Health for developing Therapies Evidence Gap Maps Complementary.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this study.

Supplementary Material

Supplementary Data

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Received: March 14, 2022.

Accepted after revision: July 18, 2022.

Published online: October 10, 2022.