

Influence of low-level laser on oral mucositis treatment in young cancer patients undergoing chemotherapy: a systematic review

Influência do laser de baixa intensidade no tratamento da mucosite oral em pacientes jovens com câncer em tratamento quimioterápico: uma revisão sistemática

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ABSTRACT

Perform a systematic review of the literature to seek scientific evidence on the effect of low-level laser therapy on duration, degree and pain of chemotherapy-induced oral mucositis in young patients with cancer. Methods: A bibliographic search was performed using the PubMed, Scopus and Web of Science databases to identify relevant scientific studies, found through the descriptors "laser therapy", "phototherapy", "oral mucositis", "pediatric patient" and "children" to evaluate this association. Information regarding the degree of mucositis, pain associated with patients, toothbrushing and laser were analyzed characteristics. Results: Of the nine studies, one did not obtain significant results on the healing action of LLLT on oral mucositis and of the eight remaining studies, 83.3% showed significant evidence of a decrease in the degree of oral mucositis and consequently its duration. With regard to pain, 100% of the studies confirmed its decrease. Conclusion: Low-level laser therapy is considered an efficient instrument for the treatment of oral mucositis on young patients with cancer due to its analgesic, anti-inflammatory and healing effects.

Indexing terms: Child. Laser therapy. Phototherapy. Stomatitis.

RESUMO

Realizar uma revisão sistemática da literatura para buscar evidência científica sobre o efeito da terapia a laser de baixa intensidade sobre a duração, grau e dor da mucosite oral induzida pela quimioterapia em pacientes jovens oncológicos. Realizou-se uma pesquisa bibliográfica utilizando as bases de dados PubMed, Scopus e Web of Science para identificar estudos científicos relevantes, encontrados através dos descritores "laser therapy", "phototherapy", "oral mucositis", "pediatric patient" e "children", que avaliassem esta associação. Foram analisadas informações referentes ao grau de mucosite, a dor associada aos pacientes, a escovação e as

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características do laser. Dos nove estudos incluídos, um não obteve resultados significativos sobre a ação cicatrizante da LLLT na mucosite oral e dos oito estudos restantes, 83,3% mostraram evidências significativas na diminuição do grau da mucosite oral e, conseqüentemente, na duração da mesma. Com relação a dor, 100% dos estudos comprovaram sua diminuição. A laserterapia de baixa intensidade é considerada um instrumento eficiente para o tratamento da mucosite oral em pacientes oncológicos jovens devido aos seus efeitos analgésicos, anti-inflamatórios e cicatriciais.

Termos de indexação: Crianças. Terapia a laser. Fototerapia. Estomatite.

INTRODUCTION

Oral mucositis (OM) is an inflammatory condition that affects a large number of patients undergoing chemotherapy [1,2] and its severity may vary as a result of several factors, such as the dose of cytotoxic drug administered, as well as the nutritional status, age and degree of oral hygiene of the patient [3].

Although OM is a prevalent complication in patients undergoing chemotherapy, there is no standard treatment for it, which is mainly conservative [4].

Children and adolescents undergoing antineoplastic treatment are even more likely to develop this condition, with an incidence of 50 to 80% in pediatric patients. This can be explained by the greater speed of cell mitosis in young people and due to the intense chemotherapy regimens to which they are submitted [5,6].

The clinical symptoms of OM often appear seven days after the start of chemotherapy treatment and mainly affect the sites of the oral cavity corresponding to the lateral part of the tongue and floor of the mouth, with ulceration present in most lesions [7].

Therefore, it is common for children to experience pain, discomfort, difficulty in chewing and swallowing [8], and as a consequence some patients may be forced to receive enteral or parenteral nutrition and in some cases may have their cancer treatment interrupted due to the debilitating condition caused by OM [1,2].

Taking into account the importance of OM and its negative consequences on cancer treatment and patient comfort, it is pertinent to search for ways to alleviate and even prevent it from happening. Among the possible treatments, the use of low-level laser therapy has been suggested to relieve symptoms and it seems to promote the healing of wounds caused by the condition, in addition to having an analgesic and anti-inflammatory effect [9].

Although there is still no well-defined protocol for the use of laser therapy, its use has been considered tolerable and accessible, even if it is necessary daily [10]. Therefore, the present study seeks to clarify these benefits of using laser therapy in young patients during cancer treatment and to standardize the laser variables for the treatment of OM.

METHODS

According to the statement of preferred reporting items for systematic reviews and meta-analyses (PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses - www.prisma-statement.org), this systematic review was performed with the purpose of finding potential studies related to the proposed topic.

PICO Question

The PICO strategy (P - participants/population, I - intervention, C - comparison or control, O - study outcome) was used to answer the clinical question at issue: does low-power laser have therapeutic action in young patients undergoing cancer chemotherapy treatment? Considering the strategy factors presented in table 1.

Table 1. Description of the PICO QUESTION.

Participants (P)	Young patients with oral mucositis undergoing cancer chemotherapy.
Intervention (I)	Low level laser.
Comparison (C)	Patients not exposed to low-level laser therapy.
Outcome (O)	Sensory and cicatricial characteristics of the oral mucosa.

Search criteria

The literature relevant to the topic was reviewed using the PubMed-Medline, Scopus and Web of Science databases to identify relevant studies, without year limitation and language restriction, published until January 2023.

The MeSH and non-MeSH descriptors were based on the DeCS (Health Sciences Descriptors). The uniterms or keywords were defined by reading articles on the subject and the search strategy was submitted to test/evaluation of the result/retest in order to establish the best configuration. The group of uniterms was combined with Boolean operators "AND" and "OR" in order to refine the search results. The search strategy used in the different databases is shown in table 2.

Table 2. Databases and search strategies.

Data base	Search strategy
Web of Science Scopus Pubmed - Medline	(("laser therapy" OR phototherapy) AND "oral mucositis" AND ("pediatric patient" OR children))

Eligibility criteria

Primary studies with young patients, aged from 10 months to 18 years, being diagnosed with any type of cancer undergoing chemotherapy treatment who had OM and who were treated with low-level laser were selected, including epidemiological and observational studies that followed the descriptors:

- Population: young patients with OM undergoing chemotherapy cancer treatment;
- Intervention: low-level laser;
- Control: patients not exposed to low-level laser therapy;
- Outcome: sensitive and cicatricial alterations of the oral mucosa.

Exclusion criteria were: studies on the prophylactic action of laser; studies on high power laser; studies with patients undergoing bone marrow transplantation; studies with patients undergoing radiotherapy or radiotherapy and chemotherapy; case reports; literature reviews; theses; dissertations; and those not consistent with the question of the study.

Selection of studies

Two examiners responsible for the search and evaluation of the studies were calibrated according to the eligibility criteria using 10% of the articles obtained with the application of the search strategy. The studies were independently pre-selected by two examiners using the EndNote X7.5® software (ClarivateAnalytics, Philadelphia, USA), removing

duplicate results and evaluating the titles and abstracts of the articles. If there was insufficient information for an inclusion or exclusion decision at this stage, the full text would be obtained and evaluated.

Subsequently, the pre-selected articles were read in full by the two examiners and the inclusion and exclusion criteria were evaluated independently. Any disagreements were discussed and re-examined until consensus was reached.

Data extraction

For each selected study, two reviewers independently collected quantitative and qualitative data, such as: author, year of publication, type of study, sample size, degree of OM, proposed scale for pain and degree of mucositis, oral hygiene habits; and laser characteristic: wavelength, power and energy density. The data extracted from the articles were organized in a Table in Microsoft Office Excel 2010 software (Microsoft Corporation, Redmond, WA, USA).

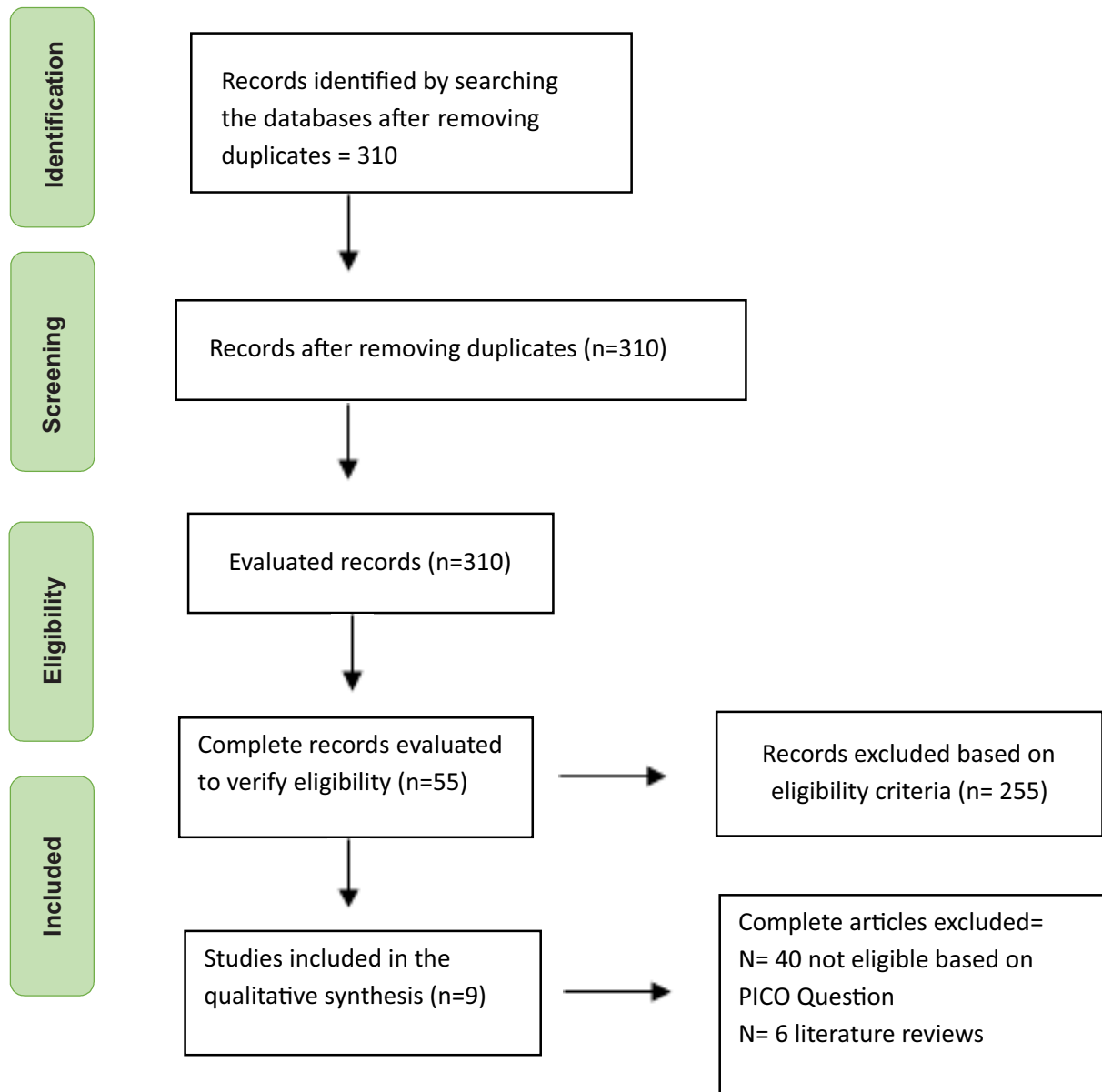


Figure 1. PRISMA flowchart.

Note: Flowchart of the systematic review, according to the PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analysis).

RESULTS

Selection of studies

Based on the search strategy used, 310 potentially relevant records, excluding duplicates, were identified. After reviewing titles and abstracts, 255 studies were excluded as they did not meet the eligibility criteria. Of the 55 studies retained for detailed review, 46 were excluded because they did not fit the PICO question, in terms of intervention and research participants. Thus, nine studies were included. Figure 1 summarizes the article selection process according to the PRISMA flowchart.

General characteristics of the studies

Table 3 presents detailed information on the descriptive characteristics of the included studies, such as authors, year of publication, type of study, sample size, OM assessment scale and associated pain, degree of mucositis, oral hygiene habits; and laser characteristics, such as energy density, wavelength and power. Among the articles included, there are seven clinical trials [4,11-16] and two pilot studies [17,18].

Sample sizes in the studies ranged from 16 to 85 patients, aged between 10 months and 18 years. To assess the degree of OM, seven studies [11-14, 16-18] used the World Health Organization (WHO) scale, while only two studies [4,15] used the toxicity criteria recommended by the National Cancer Institute (NCI).

Patients' pain measurements were based on studies by Cauwels and Martens [17]; Amadori et al. [11]; Guimaraes et al. [14]; Mohamed et al. [15]; Reyad et al. [16] on the Visual Analog Scale (VAS). On the other hand, the study by Ribeiro da Silva et al. [18], the Children's International Mucositis Evaluation Scale (ChIMES) was used, while in the study by Gobbo et al. (2018), the analysis was performed using the Numeric Rating Scale (NRS) and, in one of the studies, pain measurement was not addressed [4].

The toothbrushing habit was guided by six of the included studies [4,11,15-18]. Two studies did not report encouraging toothbrushing [13,14] and only one of the articles did not include an assessment of oral health status in study design [12,15,16].

Table 3. Baseline characteristics of the included studies.

1 of 2

Author (year)	Study design	Sample size	Proposed rating scale		Degree of oral mucositis	Laser feature			Hygiene incentive	Clinical outcome
			Oral mucositis	Pain		Wavelength (nm)	Power (mW)	Energy density (J)		
Kuhn et al. [4]	Randomized clinical trial	18	NCI	No rate	Greater than or equal to 2	830	100	4	Yes	Laser therapy, in addition to oral hygiene, may shorten the duration of chemotherapy-induced OM.
Cauwels and Martens [17]	Pilot study	16	WHO	EVA and FACE	1,2,3 and 4.	830	150	Degree 1 - 2 Degree 2 - 4 Degree 3 - 6 Degree 4 - 8	Yes	Reduction in the severity and duration of mucositis, in addition to pain relief.

Table 3. Baseline characteristics of the included studies.

Author (year)	Study design	Sample size	Proposed rating scale		Degree of oral mucositis	Laser feature			Hygiene incentive	Clinical outcome
			Oral mucositis	Pain		Wavelength (nm)	Power (mW)	Energy density (J)		
Amadori et al. [11]	Clinical trial	85	WHO	EVE	Greater than or equal to 2	830	150	4.5	Yes	No significant result in reducing the degree of mucositis, but pain relief.
Ribeiro da Silva et al. [18]	Pilot study	29	WHO	CHI-MES	Greater than 1	660	100	35	Yes	Pain reduction and wound healing.
Gobbo et al. [12]	Randomized clinical trial	75	WHO	NRS 0-10	3 and 4	660 to 970	320	36.8	No	Safe, viable and effective treatment for children, as it accelerates mucosal recovery and reduces pain.
Tomažević et al. [13]	Clinical trial	42	WHO	No rate	Degree 3 and 4	810	A-250 B-500 C-250	(A) 3- 8.8 (B) 4- 15.5 (C) 3- 4.4 4- 7.75	No report	LLLT is an acceptable means of treating chemotherapy-induced MO in pediatric patients.
Guimaraes et al. [14]	Clinical trial	40	WHO	EVE	-	660	100	3.6	No report	Findings suggest that LLLT has therapeutic effects on OM.
Mohamed et al. [15]	Clinical trial	30	NIC	EVE	Greater than or equal to 2	870	60	Average from 5 to 150	Yes	LLLT decreases the prevalence, discomfort, and severity of OM.
Reyad et al. [16].	Clinical trial	44	WHO	EVE	1,2,3,4	980	1.5	4.5	Yes	The use of LLLT, along with conventional treatment, was effective in reducing pain and healing OM lesions in children undergoing chemotherapy. It was also safe and applicable to children.

DISCUSSION

There is no standard therapy for OM and it can be treated in different ways: with supportive therapies, basic oral care, light oral washes, analgesics, cryotherapy, antibiotics, mucosal protectors, inflammatory agents and antibiotics [4]. Several authors already accept the therapy low-level laser therapy (LLLT) as a reducing factor for mucositis and associated pain reduction [1,19], in addition to being well-established in the prevention of OM with about nine times more effectiveness than non-application [20]. Studies carried out on LLLT have the main focus on cancer patients [4].

The mechanism of laser therapy has not yet been completely elucidated, but even so it is believed that a modulation of several metabolic processes occurs through the conversion of energy emitted by the laser into useful energy for the cell. Photoreceptors absorb certain wavelengths [19,21] causing various cascade reactions in the cellular respiratory chain, producing energy. Allied to cell proliferation and protein synthesis [19], LLLT promotes tissue repair [19,21]. Besides, there is an anti-inflammatory effect from the laser linked to the reduction in the expression of inflammatory procytosines and an analgesic effect due to the production of endogenous opioids, which reduce free radicals and alter the conduction of nerve impulses [19].

When a laser's energy is used at wavelengths between 632 to 970 nm, it is usually absorbed by a thin layer of tissue at the point of application, which is the OM lesion. Thus, the increase in mitochondrial activity and cellular metabolism as a whole, as well as the analgesic and anti-inflammatory capacity of laser therapy when applied to the mucosa, are some of the reported effects [22].

Research carried out by Antunes et al. [23] investigated the clinical effects of LLLT in preventing and reducing the severity of a conditioning-induced OM in HSCT patients. Among the patients in the group who underwent LLLT therapy, 95% had mucositis at a degree less than or equal to 2 and 63% had degrees between 0 and 1. In the control group, 32% had OM at a degree less than or equal to 2.

In a study conducted by Gobbo and his collaborators in 2018, the authors concluded that photobiomodulation (PBM) is safe, feasible and effective and should be introduced as standard therapy for pediatric patients affected by oral mucositis, since children and adolescents did not experience side effects, adverse reactions or any difficulty in administering PBM for the treatment of OM [12]. However, research on treatment with PBM in this population is scarce, due to the low incidence of cancer compared to adults, in addition to the lack of universally accepted instruments for the evaluation of OM in children, young people and also in adults [2,24].

LLLT has been studied in the areas of Medicine and Dentistry. However, published trials are difficult to compare due to the lack of protocol standardization and large variations in the tested wavelengths [25].

Barasch and Peterson [26] used the LLLT prophylactically in 20 cancer patients, who received the laser on the right or on the left of midline. The contralateral side served as a control. OM and pain scores were significantly lower on the treated side ($P < 0.05$).

Although studies have mentioned that the prophylactic use of laser can reduce the severity of OM, its performance on pain and the ability to swallow are controversial. A study conducted by Cruz et al. [27] sought to evaluate the role of LLLT in prophylaxis in a group of children with cancer over five days and there was no evidence of benefit when optimal dental care was provided [27].

The appearance of OM lesions is a complex process that begins earlier the painful symptoms and which, through good hygiene of the oral cavity, controls the symptoms and even restores the immune function, directly collaborating to reduce the degree of mucositis [1,4,17,28]. The toothbrushing habit was guided by 57.1% of the included studies [4,11,17,18] and only one of the articles did not encourage this habit [12].

However, it was not possible to establish a positive correlation between the habit of oral hygiene and the improvement in OM lesions among the studies included in this review.

CONCLUSION

The study showed that the use of low-level laser therapy in OM in young cancer patients is promising and beneficial, as it was able to promote pain relief and accelerate its resolution, in addition to being feasible and well tolerated. Even so, it is important to mention that there are limitations due to the lack of consensus among studies on the wavelength to be used since there is no standardized protocol, requiring further research in this regard.

Collaborators

GS Diniz, Project management, writing, reviewer and editing. LMF Felício, data analysis and interpretation. JP Guimarães, supervision.

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