REVIEW

IS THE PHOTOBIOMODULATION THERAPY EFFECTIVE IN CONTROLLING POST-SURGICAL SIDE EFFECTS AFTER THE EXTRACTION OF MANDIBULAR THIRD MOLARS? A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives
The extraction of third molars is one of the most performed surgical procedures in oral and maxillofacial surgery. Pain, oedema, and trismus are the most frequently complications related in the surgical postoperative period. The literature has indicated PBM as a potential adjuvant method to reduce these complications. The aim of this review and meta-analysis is evaluate the PBM, as an optimal method to improve patient experience and minimize postoperative morbidity. Additionally, we seek to determine which wavelength, site, and frequency of application are most effective.

Methods
This review was registered in PROSPERO (CRD42023429966) and followed PRISMA guidelines. The search was carried out in the main databases, PubMed/MEDLINE, Cochrane Library, Embase, Scopus, and Lilacs, including reviews in the most important journals in the area of oral surgery and laser applied to oral surgery. In addition, all article references and also gray literature were reviewed. After the studies selection, the relevant data was collected. All the studies were randomized controlled trials and the patients were allocated into two groups: active PBM and inactive PBM. The statistical analysis was carried out using Stata v.16, and the methodological quality and risk of bias were assessed by the Jadad scale and RoB 2.0, respectively.

Results
Where included 22 studies and 989 subjects, to all with a minimum follow-up of 7 days. Pain and oedema showed statistically significant results in favor to the active PBM group. Especially when laser applied in infrared mode, for pain and oedema at 48 h, MD = -1.80 (CI95% -2.88, -0.72) $I^2 = 92.13\%$ and MD = -1.45 (CI95% -2.42, -0.48) $I^2 = 65.01\%$, respectively. The same is not true for trismus at 48 h, MD = 0.07 (CI95% -0.06, 0.21) $I^2 = 3.26\%$. The meta-analysis also presented results in respect of laser site of application and number of PBM sessions.

Conclusions
PBM with infrared laser, in a combination intraoral and extraoral application, in one session in the immediate postoperative period, has been shown to be effective to achieve the objectives of reducing pain and oedema after third molar extraction.

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INTRODUCTION

The extraction of third molars is one of the most performed surgical procedures in oral and maxillofacial surgery.[1,2]The first days of the postoperative period are marked by an intense inflammatory response, which is associated with short-term postoperative pain, facial oedema, and trismus, which affects the quality of life of patients.[2-4]

Winter[5] and Pell and Gregory[6] created systems to classify third molars in relation to their position in the mandibular bone, with the intention of facilitate the analysis of surgical difficulty. Other aspects like the duration of the surgery and the technique used,[1] patient's trust in the surgeon who performs the surgery,[3] skill and expertise of the surgeon,[1] the preoperative oxidative stress[7] and pericoronitis[8] are factors to influences postoperative outcome, and in a certain way predict the surgical prognosis of a third molar extraction.

The most varied resources are used to reduce complications in the surgical postoperative period, and thus provide more comfort to patients. Antibiotics[9,10] and anti-inflammatories prescription,[11] cryotherapy,[12] kinesio taping,[12] platelet-rich fibrin,[13] ozone therapy, and finally the objective of the current review, photobiomodulation (PBM) with low-power laser.[14]

Increasingly, in routine dental practice, there is a demand to use less invasive methods that help to reduce discomfort and provide rapid tissue healing. The literature has indicated PBM as a potential adjuvant method to achieve these objectives but has a wide variety of application protocols. This review and meta-analysis aim to evaluate PBM, with low-power laser, as an optimal method to improve patient experience and minimize postoperative morbidity. If so, we seek to determine which wavelength, site, and frequency of application are most effective in maximizing the effect of PBM therapy.

MATERIAL AND METHODS

Register Protocol

This review was carried out following the PRISMA guidelines[15] and according to the PICOS method[16]: Patients with indication to extract both lower wisdom teeth presenting the same classification (split mouth), or one lower wisdom tooth in the same classification as the other study participants (parallel). Classification as determined by the authors of the study (P = Patient); PBM with laser in the immediate post-surgical period (I = Intervention); laser inactive (C = Comparison); reduction in postoperative discomfort (O = Outcome); Randomized clinical trial (S = study design). It has been duly registered with PROSPERO (CRD42023429966).

Selection Criteria, Sources of Information and Research

A bibliographic search was carried out using keywords (with the appropriate Boolean operators), in the main databases, PubMed/MEDLINE, Cochrane Library, Embase, Scopus, and Lilacs, including reviews in the most important journals in the area of oral surgery and laser applied to oral surgery. In addition, all article references and also gray literature were reviewed in order to identify relevant studies, which compared the use of PBM in reducing postoperative discomfort with a control group (Supplementary 1). The search includes the period between the first records found in the database until June 2023. When necessary, we contact the authors of the studies to clarify missing information or data.

Inclusion Criteria

(1) Randomized clinical trials (RCT) studies; (2) Studies that used active soft laser application as a study group and the inactive laser as a control group; (3) Studies with patients with indication for extraction of one mandibular wisdom teeth, or extraction of both wisdom teeth, who were in a similar position;[5,6] (4) Studies in all languages were included.

Exclusion Criteria

(1) Studies that are clinical cases or case series; (2) Studies that have in the control group, any treatment other than the inactive laser, or that the application protocol of the non-active laser is not the same as the protocol used for the study group.

Study Selection

Two independent researchers, GCVC and PVAV, carried out the study selection in two stages. The first included an analysis of titles and abstracts of the articles found in the search. Studies not related to the topic of interest were eliminated, that is, texts that did not deal with PBM as a treatment for post-extraction discomfort of lower third molars. In the second stage, the full texts of eligible studies were analyzed to verify whether they met the eligibility criteria. A careful analysis of the references of eligible articles was also done to verify studies that were not detected in the main search strategy. Excluded studies were recorded separately, along with the reasons for exclusion (Supplementary 2).

Data Collection Process

The full articles were read by both investigators (GCVC and PVAV) who collected the data (in duplicate), to prevent measurement bias. A third researcher (FFVS) acted as a mediator in case of discrepancy or lack of agreement. The degree of agreement between the two researchers reached a Cronbach's alpha of 0.93.[17]

Study Variables

The following data was extracted from each study: first author; year of publication; country; study design; sample size; gender; average age; wavelength of laser; site of application; number of PBM sessions; variable of interest and time of evaluation of each variable of interest (follow-up).

The primary outcome measure is pain referred by the visual analogue scale-VAS (0-10) where "0" represents the minimum pain and "10" is the maximum pain, and the secondary outcome measures are oedema by facial measurement in millimeter (mm), and trismus by measuring the mouth opening obtained between the edges of the upper central incisor and the lower central incisor with a millimeter scale (mm).

Methodological Quality and Risk of Bias

The methodological quality of the included studies was carried out using the Jadad scale,[18] which, based on five questions, evaluates three aspects of clinical trials; randomization, blinding, and description of loss to follow-up. In three of the questions Yes = 1 or No = 0, in two questions described and appropriate = 1, not described = 0, or described but inappropriate = -1. The final score is given on a scale from 0 (minimum) to 5 (maximum), classifying studies with a final score <3 as low quality.

The risk of bias was evaluated according to the RoB 2.0 tool[19] made up of fixed domains of bias, five in total. Each one being responsible for evaluating bias regarding an aspect of the clinical trials evaluated: the randomization process, deviation from the intended intervention, incomplete outcome data, measurement of outcomes, description of outcomes. The concept can be assigned to each of the questions; yes, probably yes, no, probably no, and no information. In the end, a risk of bias analysis is carried out through algorithms that map the responses and classify them as: low risk, some concerns, or high risk. Again, both analyses were conducted independently by each of the two researchers, and in case of disagreement, the third researcher acted as mediator.

Egger's statistical test was also performed to check for the presence of publication bias. In this test, when the intercept of the regression is zero, it suggests that there is no publication bias, while the further away from zero the results are, the greater the publication bias. Finally, a sensitivity analysis of the studies was carried out with the removal of outliers identified from a visual analysis.

Statistical Analysis

Variables from comparable studies were collected and an analysis was performed with Stata, v.16. The statistically significant results of the quantitative analysis were expressed in mean differences (MD) with a 95% confidence interval (CI) and are presented in Forest Plot graphs.

Heterogeneity was analyzed using the I^2 statistic. The values corresponding to 25%, 50%, and 75% point to low, moderate, and high heterogeneity, respectively.[20] When the observed heterogeneity was moderate or high, a 95% prediction interval (PI) analysis was performed, in order for the clinician to be more confident in adopting the conclusions to treat their patients.[21]

RESULTS

Initially, we detected 26.273 potential studies. After evaluating the studies according to the protocol described above and as illustrated by the PRISMA diagram (Figure 1), 22 were incorporated into this systematic review and meta-analysis. All studies were RCT, however, the studies designs varied, 13 presented a split-mouth design[4,22-33] and 9 presented a parallel design.[14,34-41] The Table 1 shows the basic characteristics of the studies included in this review.

A total of 989 subjects participated in the 22 studies, all with a minimum follow-up of 7 days. The PBM protocols used were very variable in terms of the wavelength used (red, infrared, or both), the site (intra, extraoral, or both), and the number of sessions. In addition, several other co-interventions were used in the studies. Such as prophylactic antibiotic therapy, analgesia and/or non-steroidal anti-inflammatory drugs in the postoperative period.[4,14,22,23,25-27,29-31,33-38,40]

The studies carried out by Aras et al.,[35] Koparal et al.[38] and Bianchi de Moraes et al.[40] had their data analyzed twice and Ahrari et al.[24] three, because they used different protocols for the intervention with PBM, and therefore presented more than one study group.

Photobiomodulation Efficacy

A meta-analysis was performed to determine if there was a statistically significant difference when comparing the results of the active PBM and inactive PBM groups. It was hypothesized that active PBM would be effective in reducing postoperative discomfort after the extraction of lower molars. The null hypothesis was that the administration of active PBM has no effect on postoperative discomfort.

Pain

The pain was evaluated at five postoperative moments: immediately, on the first day (24 h), on the second day (48 h), on the third day (72 h), and after seven days (7 d).

Eighteen studies[14,23-33,36-41] were allocated into two subgroups determined according to the study design, parallel or split mouth. In the immediate postoperative period, as expected, the pain did not present a statistically significant difference for either group, MD = -0.13 (CI95% -0.28, 0.03) I^2 = 71.97% (Figure 2). At all subsequent postoperative moments, the null hypothesis was rejected since pain was always less in the active PBM group, in both subgroups. At 24

Table 1. Detailed descriptive summary of all studies included in the systematic review and meta-analysis. Gender: men (m), women (w); Wavelength (nm) of laser: 550-660 (red), 780-980 (infrared); Time of evaluation of each variable of interest (follow-up): 0 = immediate postoperative (pain) or preoperative/baseline (oedema and trismus), 24 h = 24 hours, 48 h = 48 hours, 72 h = 72 hours, 7 d = 7 days.

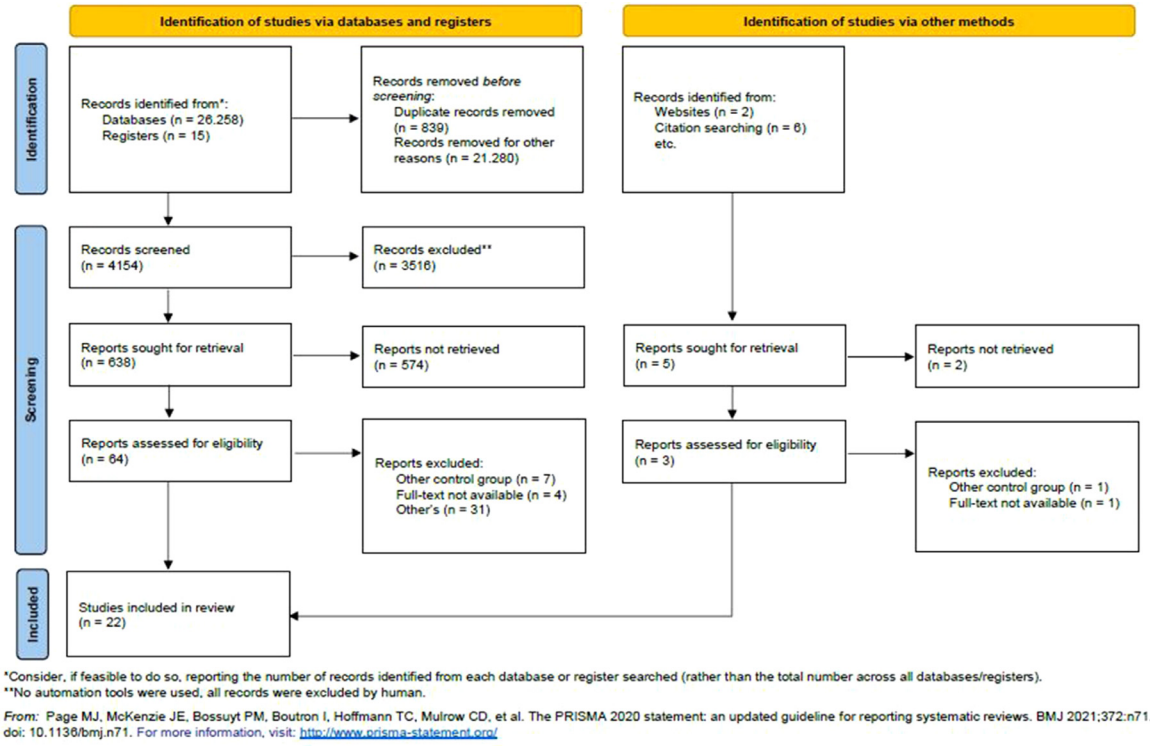
First author/year	Country	Study design	Sample size	Gender (M/W)	Range age	Wavelength (nm)	Aplication site	Number of sessions	Variable of interest	Follow-up
Ahrari F et al. 2020	Iran	Split mouth	40	22/18	18-65	660, 810, 660 + 810	Intraoral	2	Pain	24 h, 48 h, 72 h, 7 d
Alan et al. 2016	Turkey	Split mouth	15	-	17-29	810	Extraoral	2	Pain, Oedema, Trismus	0, 48 h, 7 d
Aras et al. 2009	Turkey	Parallel	32	11/21	18-27	808	Intraoral + Extraoral	1	Oedema, Trismus	0, 48 h, 7 d
Aras et al. 2010	Turkey	Parallel	48	14/34	18-27	808	Intraoral, Extraoral	1	Oedema, Trismus	0, 48 h, 7 d
Asutay et al. 2018	Turkey	Parallel	30	14/16	17-29	810	Extraoral	1	Pain, Trismus	0, 48 h, 7 d
Bianchi de Moraes et al. 2020	Brazil	Parallel	57	12/45	-	660	Intraoral	3	Pain, Oedema, Trismus	0, 24 h, 48 h, 72 h, 7 d
Eroglu et al. 2016	Turkey	Split mouth	35	20/15	not reported	940	Extraoral	1	Pain, Oedema, Trismus	48 h, 7 d
Farhadi et al. 2017	Iran	Parallel	48	24/24	18-35	550	Intraoral + extraoral	1	Pain, Oedema, Trismus	0, 24 h, 7 d
Ferrante et al. 2013	Italy	Split mouth	30	15/15	18-30	980	Intraoral + Extraoral	2	Oedema, Trismus	24 h, 7 d
Kazancioglu et al. 2014	Turkey	Parallel	60	32/28	18-25	808	Extraoral	4	Pain, Trismus	0, 24 h, 48 h, 72 h, 7 d
Koparal et al. 2018	Turkey	Parallel	45	18/27	16-27	810	Extraoral	1, 2	Pain, Oedema	0, 48 h, 7 d
Landucci et al. 2016	Brazil	Split mouth	22	11/11	17-28	780	Intraoral + Extraoral	1	Pain, Oedema, Trismus	0, 48 h, 7 d

(*continued on next page*)

Table 1 (*continued*)

First author/year	Country	Study design	Sample size	Gender (M/W)	Range age	Wavelength (nm)	Aplication site	Number of sessions	Variable of interest	Follow-up
López-Ramírez et al. 2012	Spain	Split mouth	20	9/11	18-37	810	Intraoral	1	Trismus	0, 48 h, 7 d
Momeni E et al. 2022	Iran	Split mouth	25	11/14	18-40	940	Extraoral	1	Pain, Trismus	0, 24 h, 48 h, 72 h, 7 d
Momeni et al. 2021	Iran	Split mouth	25	10/15	18-40	940	Intraoral	1	Pain, Oedema, Trismus	0, 24 h, 48 h, 72 h, 7 d
Pol et al. 2016		Split mouth	25	7/18	16-24	910 + 635	Intraoral	3	Pain, Oedema	0, 24 h, 48 h, 7 d
Raiesian et al. 2017	Iran	Split mouth	44	22/22	18-44	980	Intraoral + Extraoral	2	Pain, Oedema	24 h, 7 d
Salem et al. 2020	Saudi Arabia	Parallel	50	0/50	30-45	660	Intraoral	1	Pain, Oedema, Trismus	0, 24 h, 48 h, 7 d
Santos et al. 2020	Brazil	Split mouth	32	14/18	-	780	Intraoral	1	Pain, Oedema	0, 24 h, 48 h, 72 h,
Sigaroodi AK. et al. 2023	Iran	Split mouth	32	18/14	17-35	808	Intraoral + extraoral	2	Pain, Trismus	0, 24 h, 48 h, 72 h, 7 d
Singh et al. 2019	India	Split mouth	25	14/11	18-40	830	Intraoral + Extraoral	4	Pain, Oedema, Trismus	0, 48 h, 72 h, 7 d
Thorat S et al. 2022	India	Parallel	30	-	18-35	980	Intraoral + Extraoral	2	Pain, Trismus	0, 24 h, 48 h, 72 h, 7 d

Figure 1. Flow diagram of literature search. Diagram according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. *Consider, if feasible to do so, reporting the number of records identified from each database or register search (rather than the total number across all database/registers). **No automation tools were used, all records were excluded by human. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement an updated guideline for reporting systematic reviews. BMJ 2021;372;n71, doi:10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.rog/



h and 72 h postoperatively, the meta-analysis revealed a statistically significant difference for the active PBM group, although, in the subgroup analysis, the parallel group did not present a statistically significant difference at 24 h, MD = -0.91 (CI95% -1.92, 0.10) $I^2 = 88.05\%$. (Figure 3A) and at 72 h, MD = -1.44 (CI95% -3.36, 0.48 $I^2 = 92.15\%$. (Figure 3c). At 48 h and 7 d postoperatively, a statistically significant difference was also observed for the active PBM group at 48 h, MD = -1.46 (CI95% -2.43, -0.50) $I^2 = 90.87\%$. (Figure 3B) and at 7 d, MD = -0.88 (CI95% -1.16, -0.61 $I^2 = 67.03\%$ (Figure 3D) in this case, both subgroups agreed with this result.

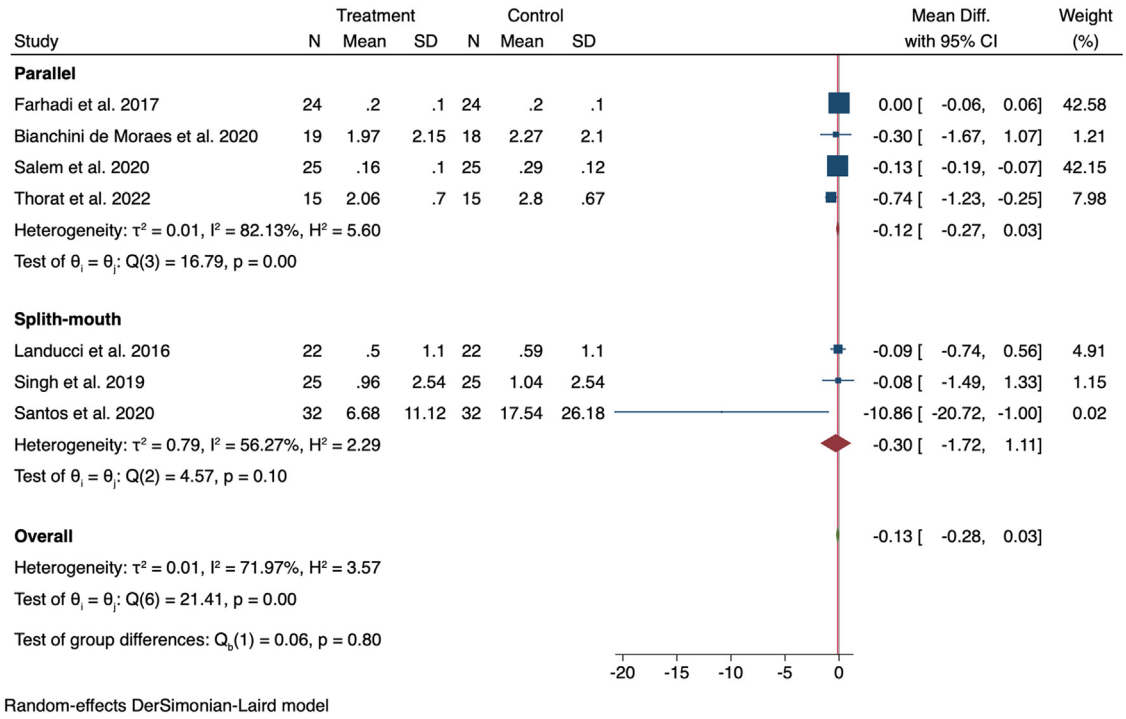
Continuing with the evaluation of pain, but now through a meta-regression regarding the active PBM group when the red laser, infrared laser, or both were applied. Although a high heterogeneity was identified, the studies that applied laser in infrared mode presented less pain at all postoperative moments, especially at 48 h, MD = -1.80 (CI95% -2.88, -0.72) $I^2 = 92.13\%$ (Figure 4).

Another meta-regression verified the difference between applying the laser intraoral, extraoral, or both, in the 48 h follow-up. The results present extraoral and extraoral plus intraoral applications, MD = -1.92 (CI95% -3.66, -0.18) $I^2 = 94.69\%$ and, MD = -1.24 (CI95% -22.43, -0.50) $I^2 = 0.00\%$, respectively, where the pain was less at all postoperative moments (Figure 5). Finally, the application of the laser in just one session or two/more sessions presented quite similar results, 72 h: MD = -2.87 (CI95% -5.13, -0.61) $I^2 = 81.15\%$ and, MD = -1.31(CI95% -2.37, -0.25) $I^2 = 84.97\%$ respectively (Figure 6).

Oedema

Oedema was evaluated at 3 moments: preoperative (baseline), 48 h, and 7 d postoperatively. Fourteen studies[4,26-31,33-36,38-40] were allocated into the two subgroups. At 48 h postoperatively, the null hypothesis was rejected, since the active PBM group presented less oedema than the in-

Figure 2. Forest plot results of the parallel and split mouth subgroups, in the immediate postoperative, for pain outcome. The results show to the left of the centre line (point 0) concern the study group value (PBM active), and those on the right the control group (PBM inactive).



active PBM group, although, in the subgroup analysis, only the split-mouth presented a statistically significant difference at 48 h, MD = -1.16 (CI95% -2.09, -0.24) $I^2 = 63.30\%$ (Supplementary 3A). At 7 d postoperatively the split-mouth and the parallel subgroups presented a statistically significant difference, MD = -1.28 (CI95% -2.54, -0.01) $I^2 = 87.10\%$, and MD = -1.85 (CI95% -3.63, -0.08) $I^2 = 66.47\%$ (Supplementary 3B), respectively.

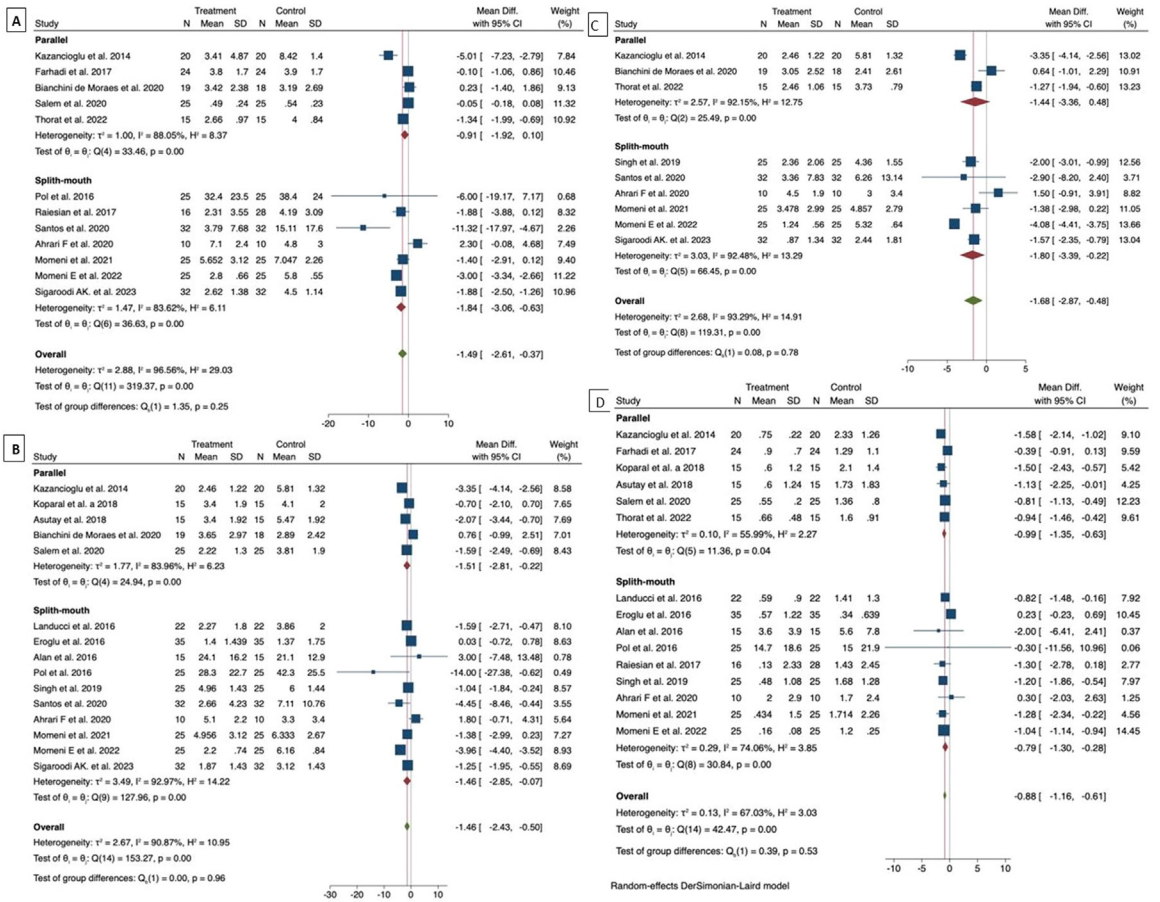
Still evaluating the oedema, but through a meta-regression, it was verified that in the studies in which the infrared laser was applied, the study group presented a statistically significant difference when comparing the results of 48 h and 7 postoperative days, MD = -1.45 (CI95% -2.42, -0.48) $I^2 = 65.01\%$ (Supplementary 4A) and, MD = -1.82(CI95% -3.04, -0.60) $I^2 = 86.20\%$ (Supplementary 4B), respectively. When verifying the difference between the laser application sites, none of the groups (intraoral, extraoral, or a combination of both) presented a statistically significant difference at 48 h (Supplementary 5A). At 7 d, the studies that applied intraoral plus extraoral, were the only ones that presented a statistically significant difference, MD = -1.96 (CI95% - 3.09, -0.83) $I^2 = 61.16\%$ (Supplementary 5B). Regarding the number of laser applications, the studies that applied only one session presented a statistically significant difference for active PBM while the group that applied two sessions or more did not. The results for only one laser session at 48 h, MD = -1.78 (CI95% -3.01, -0.55) $I^2 = 80.16\%$ (Supplementary 6A) and 7 d, MD = -1.95 (-3.34, -0.56) $I^2 = 85.42\%$ (Supplementary 6B), respectively.

Trismus

Trismus was evaluated in eighteen studies,[4,14,22,23,25-28,31,33-41] at 3 moments: preoperative (baseline) and 48 h and 7 d postoperative. At baseline, as expected, trismus did not present a statistically significant difference for either of the two groups, MD = 0.07 (CI95% -0.06, 0.21) $I^2 = 3.26\%$ (Supplementary 7A). At the postoperative moments 48 h (Supplementary 7B) and 7 days (Supplementary 7C), no statistically significant difference was observed for either group.

The same occurred in meta-regression. No statistically significant difference was verified at 48 h when comparing the results of wavelength (Supplementary 8), application sites (Supplementary 9), and the number of laser applications (Supplementary 10).

Figure 3. Forest plot results of the parallel and split mouth subgroups, for pain outcome. (A) At 24 h postoperative. (B) At 48 h postoperative. (C) At 72 postoperative. (D) On the 7th postoperative day.



Prediction Interval

The results of the prediction interval analysis (Supplementary 11), reports that the benefits of using PBM in the postoperative period can vary among positive, null and negative,[21] as the prediction interval presented values that included zero in 100% of the analyses performed.

Quality Assessment

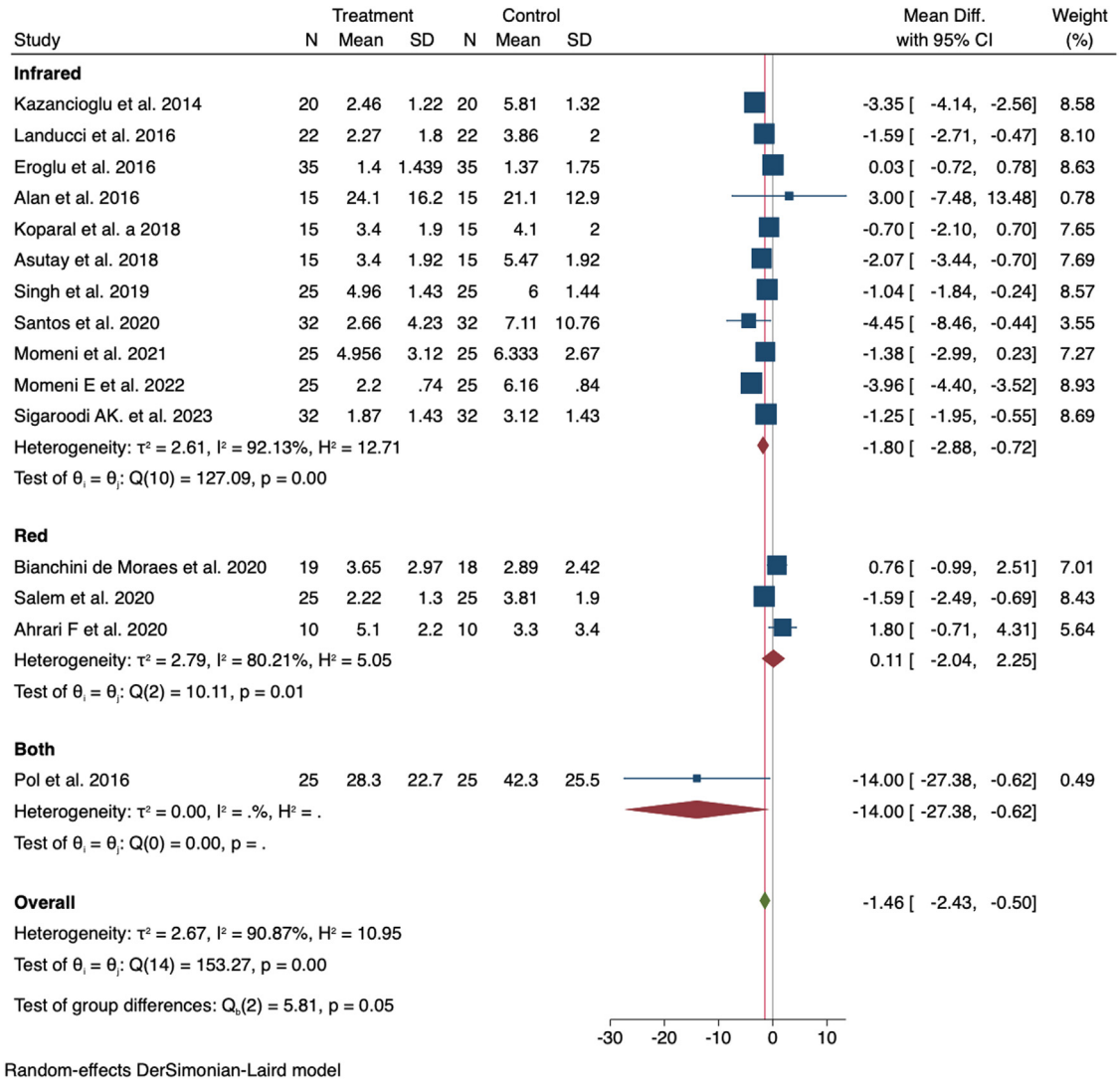
For such evaluations, the 22 studies included in the meta-analysis were considered. Regarding methodological quality, 68% of the selected studies were considered to be of low quality since only 7 of the studies presented a final score ≥ 3.[22,24,25,31-33,40] The detailed scoring and classification of the studies are presented in Table 2. Regarding the Risk of bias, all studies described adequate randomization. The final analysis found a moderate risk since only one study[30] did not record "*some concerns*" as a general bias. Detailed results of each study and risk of bias plot are illustrated in Figure 7.

Publication bias was calculated in those studies where 7-day postoperative data were available, applying Egger's method,[41] and resulted in no publication bias for the three outcomes: pain, oedema and trismus, with *P*-values of $P = .6881$, $P = .1043$ and $P = .5849$ respectively.

DISCUSSION

PBM is a safe therapeutic modality, known for more than two decades.[42] There are various types of laser devices with different characteristics.[43] The laser, which is included in a wavelength of low-energy visible light to near-infrared radiation, has a penetration capacity of 4 mm to 8 mm depth, which corresponds mainly to tissues such as the skin or oral mucosa.[44] Its high affinity for hemoglobin, melanin, and water, which is composed of enormous frequency and depth, facilitates its absorption and action in blood vessels, lymphatics, and nerves.[43] Due to the depth of such structures, it is assumed that the greatest effectiveness of the PBM occurs

Figure 4. Meta-regression forest plot comparing to results obtained by infra-red, red and red + infrared (both) laser application, for pain outcome, at 48 h postoperative.



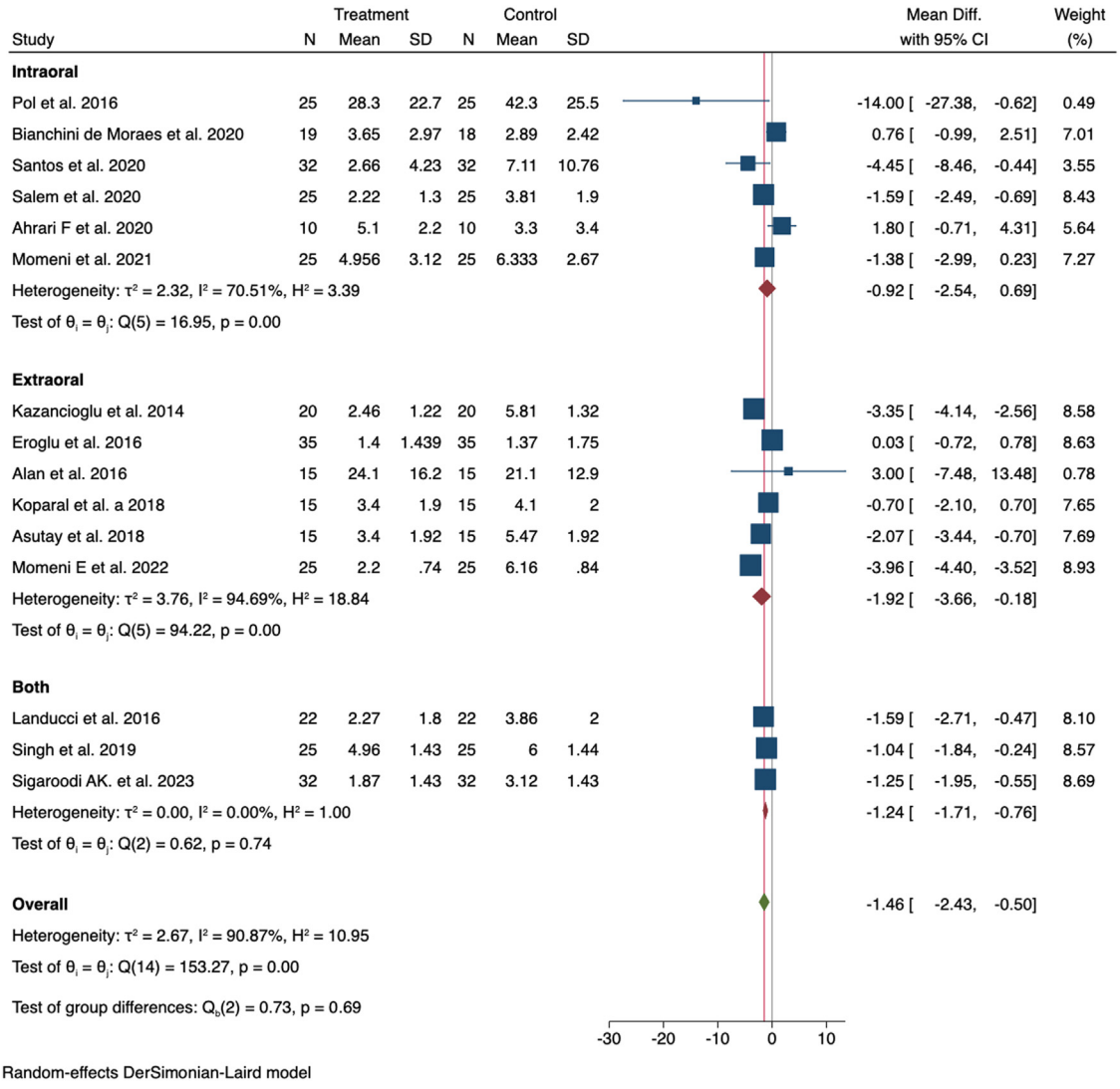
when the infrared wavelength is used,[44] whose electromagnetic spectrum ranges from 780 nm to 980 nm, and when the applications are carried out by a larger diameter probe since the diameter of the probe is directly proportional to the volume of irradiated tissue.[43]

Obtaining a better result when the infrared laser is applied is confirmed in the results of the studies that used this wavelength. The authors report a decrease in pain[23,25,26,31,37,38,41] and oedema.[4,31,34] In contrast, studies that used a wavelength in the red range for pain[24,36,39,40] and for oedema,[36,40] or a combination of the two wavelengths,[29] do not report significant results in favor to PBM, corroborating the result of this meta-analysis.

Another factor to consider when discussing the reason for the greater effectiveness of the PBM when the infrared wavelength is used is the location of the application. Studies that have an intraoral approach apply PBM around the dental element, which corroborates better healing,[24,39] but not necessarily a reduction in pain[24,29,33,40] and oedema.[29,33,35,40] Studies that carry out an extraoral application[14,23,37,38] or a combination of both,[4,25,26,31,34,41] generally have the application of PBM performed closer to the anatomical structures of interest and thus more successful results.

The role of PBM in cell metabolism has been demonstrated, where the increase in the production of ATP, favors the restoration of neuronal membranes and the reduction of

Figure 5. Meta-regression forest plot to results obtained by intraoral, extraoral and intra + extraoral (both) laser application, for pain outcome, at 48 h postoperative.

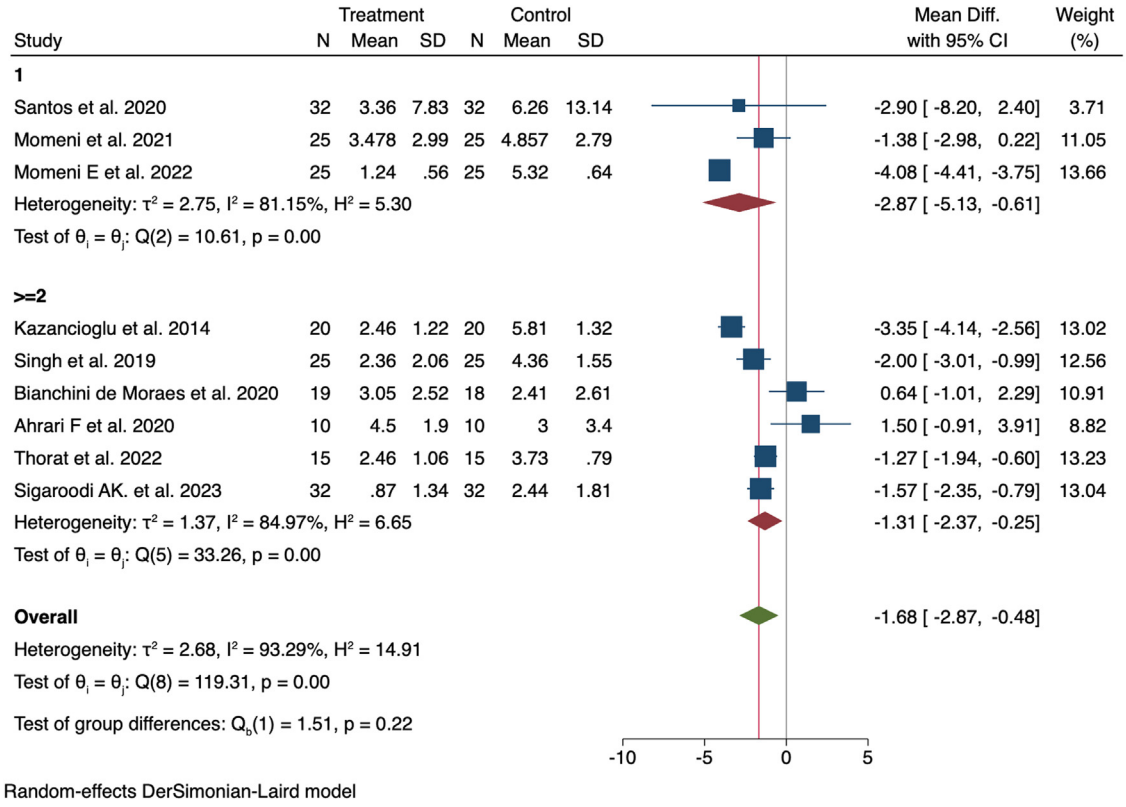


pain transmission.[42,45] Its effect on modulating the inflammatory response is also known, by acting on the synthesis of prostaglandins and other inflammatory cytokines, on apoptosis induced by tissue stress, in addition to favoring vascular perfusion of tissues, and thus favoring lymphatic drainage.[42,43,45] Such mechanisms clarify how PBM can achieve a reduction in pain and oedema when applied in the surgical field.[14,23,25,26,31,34,37,41]

Pain and oedema are consequences of surgical aggression and, therefore, an innate mechanism of the organism to indicate that something is not right and thus activate the process that leads to the repair of the damaged cells. Again, the better result of the infrared laser compared to the red one would be justified, based on its greater penetration capacity.

This meta-analysis showed quite similar results when the number of PBM sessions was considered, one or two or more, this is justified when considering that acute inflammation is a short-term process.[46] That is, it begins immediately after the injury has occurred and follows the irritative, vascular, exudative, degenerative, and reparative phases. This entire process takes from minutes to a few days.[46] Once PBM modulates the inflammatory process, the phases occur at a more accelerated rate,[47] and it is expected that signs such as pain and oedema will disappear more quickly.

Figure 6. Meta-regression forest plot comparing to results obtained by only session[1] and two/more sessions (>=2) laser application, at 72 h postoperative, for pain outcome.



This would also explain why in some studies the oedema at 24 h was greater in the study group than in the control group.[4,30,39] One session immediately after the surgical procedure[26,33,34,36,38,39] is enough to accelerate all the signaling, the following sessions 48 h or 7 d[4,27,29,30,40] after surgery are unjustified for this purpose.

Regarding the results obtained for trismus, probably no significant difference was observed between the active PBM and inactive PBM groups, and very exceptional between the laser groups because no study applied a protocol for the temporomandibular joint. It is true that, the post-surgical trismus may be due to facial oedema, trauma to the chewing muscles or the articular structure, caused by a long mouth-opening period.[48]

The present review included RCTs with parallel study design, where a second patient is a control and split mouth, where the patient is your own control. We tried to follow the recommendations of Lesaffre et al.[49] and carried out data extraction according to the study design and, above all, we paid attention to the importance of carrying out one of subgroup analyses. So, the first sequence of meta-analyses focused on checking the effectiveness of treatment according to the type of study design (Figures 2, 3, 7 and 11). This was a novelty presented by our review, as previous reviews have not reported separating subgroup analyses according to study design or even provided any explanation of the importance of doing this. In the subgroup analysis, we didn't find results with statistically significant differences, and the heterogeneity observed was > 50%. We then proceeded to consider the results of both study designs, and to evaluate the results by subgroups according to other variables, in order to use as many studies as possible in the meta-analysis, avoiding the possibility of missing information in the literature.[50]

Would be expected, given all the exposed above, that applying the PBM in the postoperative period of an extraction performed without complications would lead to a reduction in pain during all postoperative days, an oedema already presents in the first 24 postoperative hours, but reduced and of considerable regression or already absent at 72 h, in addition to a practically non-existent lockjaw. However, not all

Table 2. Classification of the assessment of study quality according to the Jadad scale.

Study	Score according to the answer					Total score
	1. Was the study described as randomized? Y = 1, N = 0	2. Was the method of randomization appropriate? A = 1, N = 0, I = -1	3. Was the study described as double-blind? Y = 1, N = 0	4. Was the method of blinding appropriate? A = 1, N = 0, I = -1	5. Was there a description of withdrawals and dropouts? Y = 1, N = 0	
Ahrari et al. 2020	1	1	1	0	0	3
Alan et al. 2016	1	0	0	0	0	1
Aras et al. 2009	1	0	0	0	0	1
Aras et al. 2010	1	0	0	0	0	1
Asutay et al. 2018	1	0	1	0	0	2
Bianchi de Moraes et al. 2020	1	1	1	0	1	4
Eroglu et al. 2016	1	1	0	0	0	2
Farhadi et al. 2017	1	0	1	-1	0	1
Ferrante et al. 2013	1	0	0	0	0	1
Kazancioglu et al. 2014	1	0	0	0	0	1
Koparal et al. 2018	1	0	0	0	0	1
Landucci et al. 2016	1	0	0	0	1	2
López-Ramírez et al. 2012	1	1	1	1	1	5
Momeni et al. 2022	1	1	0	0	0	2
Momeni et al. 2021	1	1	1	1	0	4
Pol et al. 2016	1	1	0	0	0	2
Raiesian et al. 2017	1	0	0	0	0	1
Salem et al. 2020	1	0	1	-1	1	2
Santos et al. 2020	1	0	1	0	1	3
Sigaroodi et al. 2023	1	0	1	1	1	4
Singh et al. 2019	1	1	1	0	0	3
Thorat et al. 2022	1	0	0	0	0	1

studies presented such results. This may be due to factors such as, for example, the variability of protocols of the included studies, and this reflects high heterogeneity, as detected in the meta-analysis. Furthermore, due to the high heterogeneity detected, we are concerned about the reliability of the results obtained in this meta-analysis and therefore, we proceed to perform the calculation of the prediction interval (PI)[21] presented in Supplementary 11. Contrary to the results obtained in the meta-analyses, it reported results including the null effect in all the analyses performed to verify the effectiveness of the use of PBM in controlling all the side effects after the third molar extraction.

Figure 7. Classification of the assessment (graph and summary) by Cochrane risk of bias tool for randomized trials (RoB 2.0).

This result highlights the necessity and importance of conducting new studies that include a larger sample size and less variability in the PBM protocols used.

Limitations

The main limitations of this systematic review and meta-analysis arise from the problems with heterogeneity in the clinical and methodological factors exposed in the studies and also from the diversity of measurement results, and their definitions. In an attempt to reduce heterogeneity, the studies were divided into subgroups of wavelength applied, the site of application of the PBM, or the number of sessions applied. Still, heterogeneity <50% was rarely observed. Another important limitation observed is related to the methodological quality since more than 50% of the included studies presented low quality and the risk of bias which was moderate in twenty-one studies and high in one study.

CONCLUSION

PBM with infrared laser, in extraoral application or a combination intraoral and extraoral application, in one session in the immediate postoperative period, has been shown to be effective as a complementary method to routine care, to achieve the objectives of reducing pain and oedema after third molar extraction. Such results should be interpreted with caution, as the prediction intervals presented results including expected, null and opposite effects to significance for pain reduction, oedema and trismus. However, the heterogeneity found with respect to the amount of energy applied and the standardization of laser parameters requires caution in the interpretation of these results. Therefore, studies that follow similar, if not the same, protocols are necessary to obtain a more consistent and significant result.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jebdp.2024.101983.

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